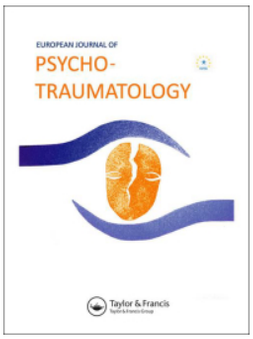

European Journal of Psychotraumatology

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/zept20

Childhood trauma and substance use underlying psychosis: a systematic review

Esther Setién-Suero, Paula Suárez-Pinilla, Adele Ferro, Rafael Tabarés-Seisdedos, Benedicto Crespo-Facorro & Rosa Ayesa-Arriola

To cite this article: Esther Setién-Suero, Paula Suárez-Pinilla, Adele Ferro, Rafael Tabarés-Seisdedos, Benedicto Crespo-Facorro & Rosa Ayesa-Arriola (2020) Childhood trauma and substance use underlying psychosis: a systematic review, European Journal of Psychotraumatology, 11:1, 1748342, DOI: 10.1080/20008198.2020.1748342

To link to this article: https://doi.org/10.1080/20008198.2020.1748342

EUROPEAN JOURNAL OF PSYCHOTRAUMATOLOGY
2020, VOL. 11, 1748342
https://doi.org/10.1080/20008198.2020.1748342

REVIEW ARTICLE

OPEN ACCESS Check for updates

Childhood trauma and substance use underlying psychosis: a systematic review

Esther Setién-Suero[a,b,c*], Paula Suárez-Pinilla[a,b,c*], Adele Ferro[d], Rafael Tabarés-Seisdedos[b,e,f], Benedicto Crespo-Facorro [a,b,c,g†] and Rosa Ayesa-Arriola[a,b,c†]

[a]University Hospital Marqués de Valdecilla, Department of Psychiatry, School of Medicine, University of Cantabria, Santander, Spain; [b]CIBERSAM, Biomedical Research Network on Mental Health Area, Madrid, Spain; [c]IDIVAL, Valdecilla Biomedical Research Institute, Santander, Spain; [d]Department of Pathophysiology and Transplantation, Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [e]Department of Medicine, University of Valencia, Valencia, Spain; [f]Department of Psychiatry, INCLIVA Health Research Institute, Valencia, Spain; [g]Department of Psychiatry, School of Medicine, University Hospital Virgen del Rocio, University of Sevilla, Biomedical Research Institute (IBIS), Sevilla, Spain

ABSTRACT

Background: Schizophrenia spectrum disorders (SSD) are mental diseases caused by a combination of genetic susceptibility and a number of environmental factors. Among these factors, the role of traumatic events suffered in childhood, as well as that of substance use, have been of particular research interest.

Objectives: To conduct a systematic review to clarify whether there is an interaction between childhood trauma and substance use related to the diagnosis or symptoms of SSD. It was also the objective of this review to collate the associations that may exist between the three variables of the study (trauma, substance use and psychosis).

Methods: We conducted a systematic search resulting in 240 articles. We considered all of the original articles that explored childhood trauma and substance use in patients suffering from SSD.

Results: Twenty-three articles were selected for this review. Several of the reviewed papers found associations between childhood trauma and substance use with SSD, as well as interactions between trauma and drug use on SSD.

Conclusions: The results suggest that childhood trauma and substance use may be present at the basis of psychosis. This double hit on the pathogenesis could have clinical implications, since each of these impacts could be considered a window of opportunity for the primary prevention of SSD.

Revisión sistemática sobre la relación entre trauma infantil, consumo de sustancias y psicosis

Introducción: Los trastornos del espectro de la esquizofrenia (SSD) son enfermedades mentales que parecen estar provocadas por una combinación de múltiples factores genéticos y ambientales. Entre los factores ambientales desencadenantes, el papel de los eventos traumáticos sufridos en la infancia y el consumo de sustancias resultan de particular interés para la investigación.

Objetivos: Aclarar si existe una interacción entre el trauma infantil y el uso de sustancias relacionadas con el diagnóstico o los síntomas de las SSD. También fue el objetivo de esta revisión cotejar las asociaciones que pueden existir entre las tres variables del estudio (trauma, consumo de sustancias y psicosis).

Métodos: Se realizó una búsqueda sistemática que resultó en 240 artículos. Consideramos todos los artículos originales que exploraron el trauma infantil y el consumo de sustancias en pacientes que presentaban trastornos psicóticos.

Resultados: 23 artículos fueron seleccionados a los efectos de esta revisión. Varios de los artículos revisados encontraron asociaciones entre el trauma infantil y el consumo de sustancias con SSD, además de interacciones entre trauma y consumo en los trastornos psicóticos.

Conclusiones: El doble impacto que representan el trauma en la infancia y el consumo de sustancias en la patogénesis de la enfermedad podría tener implicaciones clínicas por la ventana de oportunidad que supone la intervención en estos factores en la prevención primaria de los trastornos psicóticos.

思觉失调患者的童年创伤和药物滥用：系统综述

背景：精神分裂症谱系障碍（SSD）是由遗传易感性和许多环境因素共同导致的精神疾病。在这些因素中，童年遭受的创伤事件以及药物滥用的作用引起了特别的研究兴趣。

ARTICLE HISTORY

Received 27 August 2018
Revised 9 March 2020
Accepted 10 March 2020

KEYWORDS

Childhood trauma; substances use; cannabis use; psychosis; schizophrenia

PALABRAS CLAVE

Trauma infantil; consumo de sustancias; consumo de cannabis; psicosis; esquizofrenia

关键词

童年创伤; 药物滥用; 大麻使用; 思觉失调; 精神分裂症

HIGHLIGHTS

- Schizophrenia is caused by a combination of genetic susceptibility and a number of environmental factors. Traumatic events suffered in childhood, as well as substance use, have been of particular interest.
- Our results reveal a positive association between traumatic experiences in childhood and drug use and their interaction with schizophrenia spectrum disorders.
- Detecting cases of childhood trauma, as well as cases of trauma associated with substance use, could be useful for the primary prevention of some psychiatric diseases such as psychosis.

CONTACT Esther Setién-Suero setiensuero@hotmail.com Unidad de Investigación Psiquiatría, IDIVAL, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla, SN. 39008, Santander, Spain

*These authors contributed equally to this work
†These authors jointly supervised this work. All authors have significantly contributed to this work.
Supplemental data for this article can be accessed here.

目的：本系统综述想要阐明童年创伤与药物滥用之间是否存在与SSD的诊断或症状相关的相互作用。目的还有总结三个变量（创伤，药物滥用和思觉失调）之间可能存在的关联。
方法：我们进行了系统搜索，共检索到240条文章，其中考虑了所有探讨SSD患儿的童年创伤和药物使用的原始文章。
结果：共有23篇文章被纳入。一些已纳入论文中报告了童年创伤与SSD药物滥用之间，以及创伤与药物滥用对SSD的交互作用。
结论：童年创伤和药物滥用可能是思觉失调的基础。二者在发病机理中的共存可能具有临床意义，因为这些影响中的每一个都可以被视为预防SSD的机会窗口。

1. Introduction

Schizophrenia spectrum disorders (SSD) are mental diseases caused by a combination of environmental factors and genetic susceptibility (Bernardo et al., 2017; Pelayo-Teran, Suarez-Pinilla, Chadi, & Crespo-Facorro, 2012; van Os, Kenis, & Rutten, 2010). However, the fact that a considerable percentage of identical twins are discordant regarding disease expression confirms a complex pattern of heritability for SSD. Studies suggest a genetic-environment interaction in which some genetic factors influence the onset of psychosis but different environmental experiences may moderate this susceptibility (Cannon, Kaprio, Lonnqvist, Huttunen, & Koskenvuo, 1998; Gottesman, 1994; Kendler, 1983; Kringlen, 2000; Mrazek, 1994). For these reasons, non-genetic factors should be widely considered in the pathogenesis of SSD (Torrey, Bartko, & Yolken, 2012; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005).

The role of suffering from early trauma as socio-environmental risk for developing SSD has reached a particular research interest. Trauma models of mental disorders have emphasized the effects of stress, particularly during the early stages of life, as a key factor in their subsequent development (Cassidy, 2008). A prior history of childhood trauma is associated with increased odds of experiencing perceptual abnormalities in ultra-high-risk (UHR) subjects (young people who are identified as being at high risk of developing a psychotic illness in the near future) (O' Connor, Nelson, Cannon, Yung, & Thompson, 2019) and with the onset of SSD (Matheson, Shepherd, Pinchbeck, Laurens, & Carr, 2013; Morgan & Fisher, 2007; Trotta, Murray, & Fisher, 2015).

Moreover, the abuse of substances with psychoactive properties, such as alcohol, amphetamines, cannabis, cocaine, and hallucinogens, has been associated with a greater risk for psychotic experiences in the general population (Kelleher & Cannon, 2011). Epidemiological and biological studies suggest that cannabis is a component that interacts with other factors in the development of schizophrenia or other psychotic disorders (Castle, 2013). For instance, Caspi and colleagues have suggested the role of the catechol-O-methyltransferase (COMT) gene in the development of SSD when exposed to cannabis (Caspi et al., 2005); Arseneault and colleagues, in a review of studies with well-defined samples, have shown that cannabis use confers an overall twofold increase in the relative risk for later schizophrenia on an individual level, whereas on a population level, the elimination of cannabis use would reduce the incidence of schizophrenia by approximately 8%, assuming a causal relationship (Arseneault, Cannon, Witton, & Murray, 2004). Furthermore, other studies show that cannabis consumption in adolescence may play a role in neurodevelopment processes relevant to SSD, and it may produce changes in the endocannabinoid system (Murray et al., 2017) and dopamine sensitization (D'Souza, Sewell, & Ranganathan, 2009; Volkow, 2016). In any event, the psychosis risk-increasing effects are not explained by only a shared genetic predisposition between SSD and cannabis use (Murray et al., 2017). It is noteworthy that evidence for the causative role of other substances is less systematic, and existing studies were based on only correlations between SSD and substance use (Thirthalli & Benegal, 2006), showing that exposure to several neurotoxic substances during specific sensitive time windows may affect the stages of brain development (Heyer & Meredith, 2017).

There is growing evidence that some of the risk factors for SSD may have a multiplicative effect on diagnoses beyond the associated risk to either factor alone (Pelayo-Teran et al., 2012; Zammit, Lewis, Dalman, & Allebeck, 2010). The 'double hit' theory of the pathogenesis of SSD proposes that the illness may involve an early exposure to any adverse factor that produces a latent vulnerability, and when this vulnerability is manifested, individuals become more susceptible to other stressful events that contribute to the development of SSD (Feinberg, 1982; Maynard, Sikich, Lieberman, & LaMantia, 2001). Hence, some authors have hypothesized that childhood trauma may advance existing gene-environment conceptualizations of the cannabis-psychosis link (Houston, Murphy, Shevlin, & Adamson, 2011), and childhood adversity has been postulated as a key factor to include in analyses investigating associations between cannabis and SSD (Murphy, Houston, Shevlin, & Adamson, 2013).

To date, several reviews have been devoted to the study of risk factors for SSD. Some deal with the relationship between childhood trauma and psychosis (Blacker, Frye, Morava, Kozicz, & Veldic, 2019; Trotta et al., 2015), while others deal with substance

use and psychosis (Martinotti et al., 2012; Parakh & Basu, 2013). Recently, the review by Stilo & Murray was aimed at the study of different non-genetic risk factors for schizophrenia, showing that there is a cumulative effect among environmental risk factors (Stilo & Murray, 2019). However, according to our knowledge, none of the reviews carried out so far thoroughly examines the influence of the relationship between childhood trauma and substance use on schizophrenia spectrum disorders. Therefore, our objective was to conduct a systematic review of the literature to clarify whether there is an interaction between childhood trauma and substance use related to the diagnosis or symptoms of SSD. It was also the objective of this review to collate the associations that may exist between the three variables of the study: trauma, substance use and psychosis.

2. Material and methods

2.1. Comprehensive search of the literature

We followed Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines for the reporting of this systematic review (Moher, Liberati, Tetzlaff, & Altman, 2010). Searches were conducted by two persons independently (one psychologist and one medical doctor) through an electronic search of scientific journals from the Medline database via PubMed and Embase. The following key terms were used for the search: 'childhood trauma OR early trauma OR adverse childhood experience' AND 'substance use OR substance abuse' AND 'psychosis OR schizophrenia'. No restriction was used in the search. We found 231 articles, all of which were published between September 1980 and September 2019. In addition, the reference list of identified studies was also hand-searched to obtain additional articles, and nine articles that met the established inclusion criteria were included.

2.2. Eligibility and study selection

Records were selected if they met the following inclusion criteria: i) were reported articles written in English; ii) explored the relationship between childhood trauma, substance use and schizophrenia spectrum disorders (SSD) (SSD: schizophrenia, schizophreniform disorder, brief psychotic disorder, not otherwise specified psychosis, schizoaffective disorder), not being necessary that they had studied all possible relationships or interactions between the three variables; iii) reported their results quantitatively or qualitatively; and iv) were peer reviewed articles.

Records were excluded if they i) were conducted in animals; ii) were case-series studies, case studies, case reports or experimental or quasi-experimental studies; iii) were reviews or meta-analyses; or iv) were books, comments, conference papers, editorials, letters, theses or related publications. No time restriction was imposed in either the computerized or the manual searches.

The full text of each potentially eligible article was read by two researchers before a final decision was reached about its inclusion in the present review. Articles that contained two samples were included in the review when at least one of them fulfilled the inclusion criteria, taking into account only the sample of interest. We did not consider studies with overlapping samples, which means that a sample of subjects was included only once in this review despite appearing in more than one study.

2.3. Data extraction and analysis

Relevant data from the selected studies were extracted into a pre-defined, structured extraction table. Data extraction was performed by a single researcher for each included study, and a second individual independently verified the extracted information. The variables for each article included in the review were the year of publication, number of participants, type of childhood trauma, type of substance consumed, diagnosis, psychometric instruments employed to assess childhood trauma, type of substance use, type of psychotic disorder, and symptoms. The results of the included articles were synthesized into four sections: the first was about the association between childhood trauma and substance use; the second was about the association between childhood trauma and SSD; the third was about the association between substance use and SSD; and the last was about the interaction between childhood trauma, substance use and SSD.

2.4. Quality assessment

To assess the risk of bias in the different studies, we used the Newcastle-Ottawa Scale (NOS) (Wells et al., 2014). The NOS is an eight-item tool designed to rate methodological aspects of case-control and cohort studies, which includes three domains: study selection, the comparability of cohorts on the basis of the design or analysis, and exposure. The overall score ranges from 0 to 9. Scores <5 were considered low-quality studies (i.e., high risk of bias), scores 5–6 as moderate-quality studies and scores >7 indicated high-quality studies (Stang, 2010).

We used an adapted version of the NOS to evaluate the risk of bias of the cross-sectional studies (Modesti et al., 2016). The three domains included in this scale were study selection, comparability and outcome. The overall score ranges from 0 to 10. Scores <5 were considered low-quality studies, scores 5–6 were considered moderate-quality studies, scores 7–8 were considered good-quality studies, and scores 9–10 were considered high-quality studies (Herzog et al., 2013).

3. Results

Out of the 240 found articles, 164 were selected based on the search criteria after duplicates were removed. Of them, 130 articles were chosen as potentially relevant after excluding articles for different reasons (1 book chapter, 7 articles in different languages, 24 reviews, and 2 letters to editor). Among them, 107 studies were excluded because they did not explore a direct relationship between childhood trauma and substance use, between trauma in childhood and SSD, between substance use and SSD, or among three variables (childhood trauma, substance use and SSD). The final number of studies included in the review was 23 (see Figure 1). Data from all included studies are summarized in Table 1. Among these articles, we found two studies that included several samples in their results (Konings et al., 2012; van Nierop et al., 2016). In one of them (Konings et al., 2012), only one sample was taken into account since the other was included in other study of this review.

3.1. Quality assessment

The methodological quality assessment of each included study was performed according to the NOS tool (see Supplementary Tables 1 and 2). Methodological flaws were found for the selection assessment (5/23), comparability (7/23) and exposure in the case of cohort and case-control studies (1/11) or for the outcome in the case of cross-sectional studies (5/12). Overall, scores ranged from 4 to 9 in the cohort studies and between 5 and 10 in the cross-sectional studies, suggesting moderate- to high-quality studies. One of the studies were classified as having a high risk of bias, ten as moderate risk, and twelve studies as low risk.

3.2. Relationship between childhood trauma and substance use

Of the 23 articles selected for review, 19 (83%) directly analysed the association between the two environmental risk factors for psychosis: childhood trauma and substance use. In 16 of them, a positive association was found between both factors: specifically, in nine studies, childhood trauma was related to the use of different substances (Conus et al., 2010; Cutajar et al., 2010; Haahr et al., 2018; Neria, Bromet, Sievers, Lavelle, & Fochtmann, 2002; Rosenberg, Lu, Mueser, Jankowski, & Cournos, 2007; Schalinski, Fischer, & Rockstroh, 2015; Scheller-Gilkey, Moynes, Cooper, Kant, & Miller, 2004; Tomassi et al., 2017; van Nierop et al., 2016); in five studies, childhood trauma was related to cannabis use

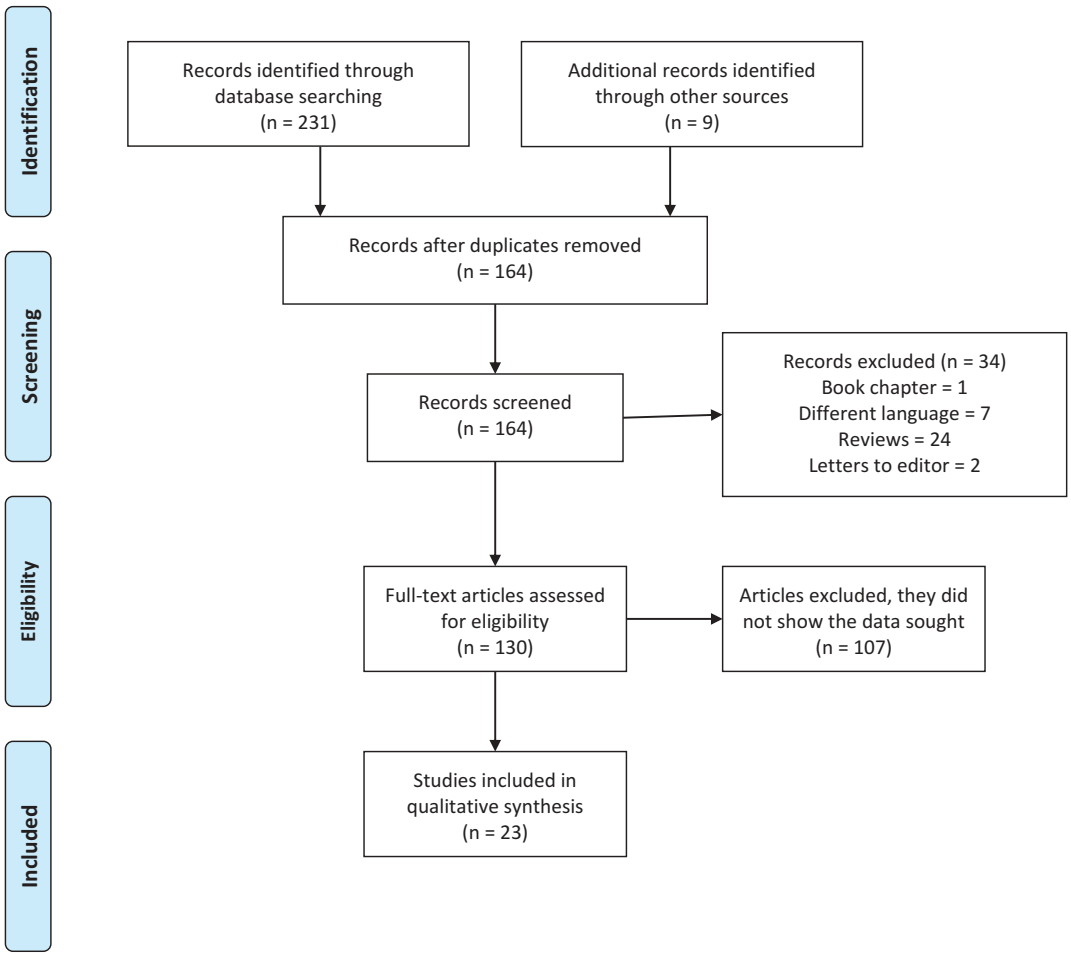

Figure 1. Flow diagram selection of the study process.

Table 1. Characteristics of the included studies involving patients with SSD.

Authors	Sample	Trauma Assessment	Type of Trauma	Drug Assessment	Type of Drug	Diagnostic Tool	Diagnosis	Symptoms Assessment	Design of studies	Relationship between variables
Arranz et al., 2018	207	CTQ-SF	Emotional, physical and sexual abuse; emotional and physical neglect	Interview designed by authors	Cannabis	DSM-IV	Psychotic disorder	US	Case/Control	+B* +C* +D*
Morkved et al., 2018	57	CTQ-SF	Emotional, physical and sexual abuse; emotional and physical neglect	DUDIT and KKS	Any drug	ICD-10 and SCL-90-R	Psychotic disorder	PANSS/ SCL-90-R	Case/Control	-A +B^
Haahr et al., 2018	191	BBTS	Emotional, physical and sexual abuse	US	Drugs and alcohol	DSM-IV	SSD	PANSS	Cross-sectional	+A
Ajnakina et al., 2018	237	CAECA-Q	Severe sexual abuse, severe physical abuse, separation, and/or loss	AUDIT/CEQ	Cannabis and alcohol	ICD-10	FEP	US	Longitudinal	+A +B^
Tomassi et al., 2017	345	CAECA-Q	Severe sexual abuse, severe physical abuse, separation, and/or loss	Cannabis Experiences Questionnaire	Cannabis, cocaine and heroin	ICD-10	Affective and non-affective psychosis	US	Cross-sectional	+A +B*
van Nierop et al., 2016	532	CTQ-SF	Emotional, physical and sexual abuse; emotional and physical neglect	CIDI	Any drug	DSM-IV	Psychotic disorder	PANSS	Cross-sectional	+A +B^
Duhig et al., 2015	100	CTQ	Emotional, physical and sexual abuse; emotional and physical neglect	Current and lifetime substance use questionnaire	Alcohol, tobacco, cannabis, and other illicit drugs	ICD-10	FEP	PANSS	Cross-sectional	-A
Barrigon et al., 2015	120	US	Emotional neglect, psychological, physical or sexual abuse	CIDI	Cannabis	SCID-I	Psychotic disorder	PANSS	Case/Control	+B* +C* -D*
Schalinski et al., 2015	62	MACE	Emotional, physical and sexual abuse; emotional and physical neglect	ICD-10	Any drug	ICD-10	SSD	PANSS	Longitudinal	+A +B^
Saddichha et al., 2015	409	CTQ	Emotional, physical and sexual abuse; emotional and physical neglect	MINI Plus	Cannabis/ Stimulant	MINI Plus	Psychotic disorder	US	Cross-sectional	+A +C*
Banducci et al., 2014	280	CTQ	Emotional, physical and sexual abuse; emotional and physical neglect	DSM-IV-TR	Alcohol, cannabis, cocaine and opiates	DSM-IV-TR	Psychiatric disorders including psychotic disorder	SCID	Cross-sectional	+A +B^
Ding et al., 2014	189	US	Emotional, physical and sexual abuse	ICD-10	Methamphetamine/ other drugs	MINI-Plus	Meth-associated psychosis	SCID	Cross-sectional	+A +B* +D*
Konings et al., 2012	1636	A question from the parental questionnaire	Unspecified	US	Cannabis	CAPE	Psychotic disorder	CAPE	Longitudinal	-A +D*
Ramsay et al., 2011	61	CTQ-SF	Emotional, physical and sexual abuse; emotional and physical neglect	LSUR	Cannabis/alcohol	DSM-IV	FEP	SAPS/SANS	Cross-sectional	+A +B^ +C^
Houston et al., 2011	7394	Questionnaire "Domestic Violence and Abuse"	Sexual trauma	SCAN	Cannabis	SCAN	General population (Psychosis)	SCAN	Case/Control	+B* +D*

(*Continued*)

Table 1. (Continued).

Authors	Sample	Trauma Assessment	Type of Trauma	Drug Assessment	Type of Drug	Diagnostic Tool	Diagnosis	Symptoms Assessment	Design of studies	Relationship between variables
Cutajar et al., 2010	5365	Child sexual abuse	Child sexual abuse	ICD	Substance abuse	ICD	Axis I (Psychosis)	ICD	Case/Control	+A
Harley et al., 2010	211	K-SADS	Physical and sexual abuse; Domestic violence	K-SADS	Cannabis	K-SADS	General population (Psychosis)	K-SADS	Case/Control	+A +B* +D*
Conus et al., 2010	658	EPFQ	Emotional, physical and sexual abuse	US	Substance use	DSM-IV	FEP	US	Longitudinal	+A
Houston et al., 2008	5877	CIDI	Rape and sexual assault	CIDI	Cannabis	DSM-III-R	General population (Psychosis)	CIDI	Case/Control	-B* -C* +D*
Rosenberg et al., 2007	569	SAEQ/CTS	Emotional, physical and sexual abuse	DALI/SCID	Drugs and alcohol	DSM-IV	SSD	BPRS	Cross-sectional	+A
Compton et al., 2004	18	CTQ	Emotional, physical and sexual abuse; emotional and physical neglect	DSM-IV	Cannabis	DSM-IV	Psychotic disorders	US	Cross-sectional	+A
Scheller-Gilkey et al., 2004	122	CTES	Death of a family member, sexual or physical abuse, exposure to violence and illness or injury	ASI	Drugs and alcohol	US	Schizophrenia	PANSS	Cross-sectional	+A
Neria et al., 2002	426	DSM-III-R (PTSD module)	Any harm or threat to physical integrity	DSM-III-R	Substance abuse	DSM-IV	Psychotic disorders	US	Cross-sectional	+A

Table 1. +: There is relationship; -: There is not relationship; *: Relationship with Diagnosis; ^: Relationship with symptoms or psychotic experiences; A: Relationship between childhood trauma and substance use; B: Relationship between childhood trauma and psychosis; C: Relationship between substance use and psychosis; D: Interaction between childhood trauma, substance use and psychosis; ASI: Addiction Severity Index; AUDIT: Alcohol Use Disorders Identification Test; BBTS: Brief Betrayal-Trauma Survey; CAPE: The Community Assessment of Psychic Experiences; CAECA-Q: Childhood experience of care and abuse-questionnaire; CEQ: Cannabis Experience Questionnaire; CIDI: Composite International Diagnostic Interview; CTES: Childhood Traumatic Events Scale; CTQ: Childhood Trauma Questionnaire; CTQ-SF: Childhood Trauma Questionnaire-Short Form; CTS: Conflict Tacties Scales; DALI: Dartmounth Assessment of Lifestyle Instrument; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, 3rd ed. Rev; DUDIT: The Drug Use Disorder Identification Test; EPFQ: Early Psychosis File Questionnaire; FEP: First Episode of Psychosis; KKS: Norwegian national client mapping system; K-SADS: Schedule for Affective Disorders and Schizophrenia for School-Age Children; LSUR: Lifetime Substance Use Recall; MACE: Maltreatment and Abuse Chronology of Exposure; SAEQ: Sexual Abuse Exposure Questionnaire; SCAN: Schedule for Assessment in Neuropsychiatry; SCID-I: Structured Clinical Interview for DSM; SCL-90-R: Symptoms Check List -90- Revised; SSD: Schizophrenia Spectrum Disorders; US: Unspecified Scale.

(Ajnakina et al., 2018; Compton, Furman, & Kaslow, 2004; Harley et al., 2010; Ramsay, Flanagan, Gantt, Broussard, & Compton, 2011; Saddichha, Werker, Schuetz, & Krausz, 2015); one study based its analyses on the relationship between trauma and cocaine use (Banducci, Hoffman, Lejuez, & Koenen, 2014); and another investigated the relationship between trauma and methamphetamine use (Ding, Lin, Zhou, Yan, & He, 2014).

The remaining three studies found no significant relationship. One of them based their analyses on the relationship between childhood trauma and cannabis use (Konings et al., 2012), while the other two studied the relationship between trauma and the use of any substance (Duhig et al., 2015; Morkved et al., 2018).

3.3. Relationship between childhood trauma and SSD

Of the total included studies in this review, 13 (57%) discussed the relationship between childhood trauma and SSD. All studies except two (Ajnakina et al., 2018; Schalinski et al., 2015) conducted their analyses cross-sectionally. Eight of these studies showed good methodological quality; in four, the quality was moderate; and one of them was low quality.

There were five studies that showed a positive association between exposure to childhood trauma and the severity of psychotic symptoms (Ajnakina et al., 2018; Banducci et al., 2014; Ramsay et al., 2011; Schalinski et al., 2015; van Nierop et al., 2016). In one of these studies, major methodological flaws were found for the selection and comparability assessment (Schalinski et al., 2015). Three other studies related sexual abuse in childhood with a higher probability of presenting a diagnosis of SSD (Ding et al., 2014; Houston et al., 2011; Tomassi et al., 2017). Barrigon et al. (2015) and Harley et al. (2010) found that the chances of suffering psychosis were 7.3 and 5.2 times higher, respectively, for those who had suffered childhood trauma than for those who had not experienced it, and both works had moderate methodological quality. Additionally, with moderate quality, the Morkved study examined two different patient samples: a sample of patients with SSD and a sample of patients with substance abuse. Although no significant association was found in the first sample, it is worth noting that in the substance abuse sample, there were statistically significant correlations between the psychoticism scale score and the Childhood Trauma Questionnaire (CTQ) score (Morkved et al., 2018). In the study by Arranz et al., using the CTQ scale, they noted that the FEP group was more likely than healthy controls to report higher total scores in the trauma measure (Arranz et al., 2018). In total, twelve studies showed a positive relationship between exposure to childhood trauma and SSD. In contrast to the results described, there was a study that found no relationship between having lived through a traumatic experience in childhood and presenting a psychotic disorder. This last work presented moderate quality in their methodology (Houston, Murphy, Adamson, Stringer, & Shevlin, 2008).

3.4. Relationship between substance use and SSD

Five studies (22% of the total included studies) showed data on the relationship between substance use and SSD, and in four of them, a positive relationship was found between the two. All the included studies in this section evaluated their variables cross-sectionally. Two of them presented good-quality methodology, and three presented moderate-quality methods.

The study carried out by Ramsay et al. (2011) found a positive relationship between cannabis and the severity of psychotic symptoms. The work of Saddichha et al. (2015) examined whether there were differences between those who used cannabis and those who used stimulants with regard to SSD, and they found that cannabis users had higher rates of lifetime SSD than stimulant users. Barrigón et al., found that the odds of developing psychosis were 16.5 times higher for subjects who used cannabis than for those who did not use cannabis (Barrigon et al., 2015). The last two described works that presented a moderate methodological quality. Furthermore, Arranz et al. (2018) detected that the relationship of cannabis use and psychosis depended on the amount consumed; they observed that a severe cannabis smoking pattern was associated with psychosis, while moderate use was not. Finally, contrary to these studies, Houston et al. (2008) found no significant effects of early cannabis use on SSD.

3.5. Interaction between childhood trauma, substance use and SSD

There were seven studies (30% of the total sample) in which analyses were performed to determine the interaction among the three factors: childhood trauma, substance use and SSD. Of these, six were cross-sectional, and one had a longitudinal design. All studies showed NOS scores that suggested moderate to high quality.

All but one study in this section, studied the effect of the interaction between childhood trauma and cannabis use on SSD. On the other hand, Ding et al. (2014) studied the effect of the interaction between childhood trauma and methamphetamine use on the risk of psychosis and found a significant interaction.

In the studies of Harley et al. (2010) and Konings et al. (2012) a significant interaction between childhood trauma and cannabis use was presented in their psychosis model. Two studies found that childhood sexual abuse trauma and cannabis use showed

a significant interaction that contributed to the presence of SSD (Houston et al., 2008, 2011). Both studies introduced socio-demographic variables (sex, age, urbanity, education and employment status) as confounding variables, and the Houston et al. (2011) study also introduced alcohol consumption. In the study by Arranz et al. (2018) the highest levels of exposure to childhood trauma and cannabis use were associated with FEP. Furthermore, the combined effect of risk factors (socio-demographic variables, recent events, childhood trauma and misuse variables) yielded a significant association with psychosis, explaining 49% of its variation.

Finally, it is necessary to highlight that one of the seven studies did not find a significant interaction among the studied variables (Barrigon et al., 2015).

4. Discussion

The main aims of this review were to evaluate whether there is an interaction between childhood trauma, substance use and psychotic disorder diagnosis or psychotic symptoms in patients with SSD and to collate whether there is a relationship among the three studied variables.

The summarized results can lead us to infer that early trauma or maltreatment and substance use play a role in the diagnosis of SSD or in their symptomatic exacerbation. Overall, the quality of the included studies that address this interaction ranges from moderate to high. A significant two-way interaction was found in 86%, showing a positive relationship.

This plausible two-way interaction may be explained in part by the 'two-hit' model of the pathogenesis of SSD. This model proposes that a first factor during early life ('first-hit') disrupts central nervous system (CNS) development. This disruption produces a long-term vulnerability to a 'second-hit' during adolescence or adulthood, leading to the expression of SSD (Feinberg, 1982; Maynard et al., 2001). In the interaction among trauma, substance use, and psychosis, suffering from childhood trauma may be the first impact that could cause changes in the stress responses, modulating neurotransmitter or neuropeptide systems, or the development of a cognitive framework of susceptibility that may confer brain vulnerability to a second impact, such as substance use during adolescence or young adulthood, which could be a precipitating factor for SSD. Whereas an early risk factor may be related to neurodevelopmental disturbances, such as structural and neurochemical abnormalities in the brain (Bak et al., 2005; Ucok et al., 2007), subsequent environmental risk factors acting later may be considered not only as potential aetiological risk factors but also as precipitants for the illness in vulnerable individuals (Dean & Murray, 2005). In the same vein, Scheller-Gilkey and colleagues suggest that the mechanism of physiological adaptation to stress in response to trauma in early life may lead to long-term stress vulnerability, representing the common aetiological pathway in individuals with co-occurring disorders such as schizophrenia and substance abuse (Scheller-Gilkey et al., 2004). Following this trend, animal studies suggest that early and severe stress can create permanent behavioural and hormonal responses to stress in vulnerable animals (Anisman, Zaharia, Meaney, & Merali, 1998). Therefore, stress exposure at an early age might prompt brain dysfunctions that potentially cause a latent vulnerability to CNS disorders.

Secondarily, when only the association between early trauma exposure and substance use was explored among the included articles, 84% showed a positive association between early trauma and addictive behaviours. The review included four longitudinal studies, and in three of them, there was a significant relationship between childhood adversity and substance use. All included studies have a quality range from moderate to high, except for a longitudinal study, with poor quality in the comparability domain (Schalinski et al., 2015). These results provide support that both environmental factors are correlated between them, independent of the ulterior development or exacerbation of SSD. In this line, previous reviews have already concluded that there is a positive association between childhood or adulthood trauma and substance use (Kittirattanapaiboon, Srikosai, & Wittayanookulluk, 2017; Konkolÿ Thege et al., 2017; Lijffijt, Hu, & Swann, 2014; Simpson & Miller, 2002), but the timing of the association is still unclear as most of the traumatic experiences are retrospectively self-reported. Therefore, longitudinal well-designed studies about this area are highly recommended to establish robust conclusions.

This review also gives consistency to the already well-known relationship between substance use and the diagnosis of SSD. Overall, 80% of the included articles that address this association support a positive association between the two variables. All studies range from moderate to high quality, but none of the studies have a longitudinal design. However, as seen in previous research in this area (Henquet, Murray, Linszen, & van Os, 2005; Khokhar, Dwiel, Henricks, Doucette, & Green, 2018), cannabis use seems to be involved in the majority of associations. Longitudinal studies based on different types of drugs are encouraged to address this issue.

Finally, a positive association between early trauma and psychosis (the diagnosis of SSD or symptom exacerbation in patients with SSD) was found in 92% of the included studies that addressed this relationship. Two of the positive studies have a longitudinal design, and overall, the quality ranges

from moderate to high, except in a longitudinal study (aforementioned previously), with a low score in the comparability domain. Therefore, our review confirms previous works that highlight the role of trauma and adverse childhood experiences in psychotic symptoms in patients with SSD (Schalinski et al., 2019) and in symptomatic exacerbation in patients with a first episode of schizophrenia (Misiak, Moustafa, Kiejna, & Frydecka, 2016). For future reviews and meta-analyses, subgroup analysis based on the same population type may partially overcome the heterogeneous results in this area.

This review has some limitations that are worth knowing for the interpretation of the current findings. Importantly, several limitations are inherent to each original study, mainly because different risk factors for SSD may be serious confounders (Mrazek, 1994); however, to partially address this limitation, the confounding variables controlled for in the included studies are referred to in the Results section. Furthermore, the existence of uncontrolled variables such as the age of the trauma, the type of trauma and substance, the length of the exposure, or the disease severity could not always be identified in the included articles; this may explain some of the apparent discrepancies across different studies. It is also worth noting that the most used drug among the analysed studies was cannabis; however, some studies also analysed the relationship between childhood trauma and the use of any type of drug. For future research, it seems necessary to design prospective, instead of retrospective, studies with larger sample sizes and follow-up studies of UHR subjects. These studies may give more information about the influence of early adverse events on the start and course of substance use disorders and on the diagnosis and course of SSD. Among the strengths of this work, it is interesting to note that, to the best of our knowledge, this is the first effort to systematically summarize the interaction among childhood trauma, substance use, and SSD.

In conclusion, knowing the relationship between childhood trauma and substance use with SSD and the interaction among the three factors may have an important implication for public health. Detecting cases of childhood trauma, as well as cases of trauma associated with substance use, could be useful for the primary prevention of some psychiatric diseases. Future studies designed in a prospective manner during childhood and adolescence, prior to the appearance of psychotic symptoms, could shed light on the mechanisms underlying the trauma and substance use relationship and clarify their role in brain development and the vulnerability to SSD while identifying potential points of intervention before psychosis onset.

Disclosure statement

No potential conflict of interest was reported by the authors.

ORCID

Benedicto Crespo-Facorro http://orcid.org/0000-0003-0033-7132

References

Ajnakina, O., Trotta, A., Forti, M. D., Stilo, S. A., Kolliakou, A., Gardner-Sood, P., … Fisher, C. (2018). Different types of childhood adversity and 5-year outcomes in a longitudinal cohort of first-episode psychosis patients. *Psychiatry Research*, *269*, 199–206.

Anisman, H., Zaharia, M. D., Meaney, M. J., & Merali, Z. (1998). Do early-life events permanently alter behavioral and hormonal responses to stressors? *International Journal of Developmental Neuroscience*, *16*(3–4), 149–164.

Arranz, S., Monferrer, N., Jose Algora, M., Cabezas, A., Sole, M., Vilella, E., … Sanchez-Gistau, V. (2018). The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis. *Schizophrenia Research*, *201*, 352–359.

Arseneault, L., Cannon, M., Witton, J., & Murray, R. M. (2004). Causal association between cannabis and psychosis: Examination of the evidence. *British Journal of Psychiatry*, *184*, 110–117.

Bak, M., Krabbendam, L., Janssen, I., de Graaf, R., Vollebergh, W., & van Os, J. (2005). Early trauma may increase the risk for psychotic experiences by impacting on emotional response and perception of control. *Acta Psychiatrica Scandinavica*, *112*(5), 360–366.

Banducci, A. N., Hoffman, E., Lejuez, C. W., & Koenen, K. C. (2014). The relationship between child abuse and negative outcomes among substance users: Psychopathology, health, and comorbidities. *Addictive Behaviors*, *39*(10), 1522–1527.

Barrigon, M. L., Diaz, F. J., Gurpegui, M., Ferrin, M., Salcedo, M. D., Moreno-Granados, J., … Ruiz-Veguilla, M. (2015). Childhood trauma as a risk factor for psychosis: A sib-pair study. *Journal of Psychiatric Research*, *70*, 130–136.

Bernardo, M., Bioque, M., Cabrera, B., Lobo, A., Gonzalez-Pinto, A., Pina, L., … Mas, S. (2017). Modelling gene-environment interaction in first episodes of psychosis. *Schizophrenia Research*, *189*, 181–189.

Blacker, C. J., Frye, M. A., Morava, E., Kozicz, T., & Veldic, M. (2019). A review of epigenetics of PTSD in comorbid psychiatric conditions. *Genes*, *10*(2), 140.

Cannon, T. D., Kaprio, J., Lonnqvist, J., Huttunen, M., & Koskenvuo, M. (1998). The genetic epidemiology of schizophrenia in a Finnish twin cohort. A population-based modeling study. *Archives of General Psychiatry*, *55*(1), 67–74.

Caspi, A., Moffitt, T. E., Cannon, M., McClay, J., Murray, R., Harrington, H., & Craig, I. W. (2005). Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry*, *57*(10), 1117–1127.

Cassidy, J., & Shaver, P. R. (Eds.). S. P. (2008). *Handbook of attachment: Theory, research, and clinical applications* (2nd ed.). New York: The Guilford Press.

Castle, D. J. (2013). Cannabis and psychosis: What causes what? *F1000 Medicine Reports*, *5*, 1.

Compton, M. T., Furman, A. C., & Kaslow, N. J. (2004). Preliminary evidence of an association between childhood abuse and cannabis dependence among African American first-episode schizophrenia-spectrum disorder patients. *Drug and Alcohol Dependence*, *76*(3), 311–316.

Connor, K. O., Nelson, B., Cannon, M., Yung, A. R, & Thompson, A. (2019). Perceptual abnormalities in an ultra-high risk for psychosis population relationship to trauma and co-morbid disorder. *Early Intervention in Psychiatry*, *13*, 231–240.

Conus, P., Cotton, S., Schimmelmann, B. G., Berk, M., Daglas, R., McGorry, P. D., & Lambert, M. (2010). Pretreatment and outcome correlates of past sexual and physical trauma in 118 bipolar I disorder patients with a first episode of psychotic mania. *Bipolar Disorders*, *12* (3), 244–252.

Cutajar, M. C., Mullen, P. E., Ogloff, J. R., Thomas, S. D., Wells, D. L., & Spataro, J. (2010). Psychopathology in a large cohort of sexually abused children followed up to 43 years. *Child Abuse & Neglect*, *34*(11), 813–822.

D'Souza, D. C., Sewell, R. A., & Ranganathan, M. (2009). Cannabis and psychosis/schizophrenia: Human studies. *European Archives of Psychiatry and Clinical Neuroscience*, *259*(7), 413–431.

Dean, K., & Murray, R. M. (2005). Environmental risk factors for psychosis. *Dialogues in Clinical Neuroscience*, *7*(1), 69–80.

Ding, Y., Lin, H., Zhou, L., Yan, H., & He, N. (2014). Adverse childhood experiences and interaction with methamphetamine use frequency in the risk of methamphetamine-associated psychosis. *Drug and Alcohol Dependence*, *142*, 295–300.

Duhig, M., Patterson, S., Connell, M., Foley, S., Capra, C., Dark, F., … Scott, J. (2015). The prevalence and correlates of childhood trauma in patients with early psychosis. *Australian & New Zealand Journal of Psychiatry*, *49*(7), 651–659.

Feinberg, I. (1982). Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? *Journal of Psychiatric Research*, *17*(4), 319–334.

Gottesman, I. I. (1994). Complications to the complex inheritance of schizophrenia. *Clinical Genetics*, *46* (1Spec No), 116–123.

Haahr, U. H., Larsen, T. K., Simonsen, E., Rund, B. R., Joa, I., Rossberg, J. I., … Melle, I. (2018). Relation between premorbid adjustment, duration of untreated psychosis and close interpersonal trauma in first-episode psychosis. *Early Intervention in Psychiatry*, *12*(3), 316–323.

Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., … Cannon, M. (2010). Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychological Medicine*, *40*(10), 1627–1634.

Henquet, C., Murray, R., Linszen, D., & van Os, J. (2005). The environment and schizophrenia: The role of cannabis use. *Schizophrenia Bulletin*, *31*(3), 608–612.

Herzog, R., Alvarez-Pasquin, M. J., Diaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, A. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health*, *13*, 154.

Heyer, D. B., & Meredith, R. M. (2017). Environmental toxicology: Sensitive periods of development and neurodevelopmental disorders. *Neurotoxicology*, *58*, 23–41.

Houston, J. E., Murphy, J., Adamson, G., Stringer, M., & Shevlin, M. (2008). Childhood sexual abuse, early cannabis use, and psychosis: Testing an interaction model based on the national comorbidity survey. *Schizophrenia Bulletin*, *34*(3), 580–585.

Houston, J. E., Murphy, J., Shevlin, M., & Adamson, G. (2011). Cannabis use and psychosis: Re-visiting the role of childhood trauma. *Psychological Medicine*, *41*(11), 2339–2348.

Kelleher, I., & Cannon, M. (2011). Psychotic-like experiences in the general population: Characterizing a high-risk group for psychosis. *Psychological Medicine*, *41*(1), 1–6.

Kendler, K. S. (1983). Overview: A current perspective on twin studies of schizophrenia. *The American Journal of Psychiatry*, *140*(11), 1413–1425.

Khokhar, J. Y., Dwiel, L. L., Henricks, A. M., Doucette, W. T., & Green, A. I. (2018). The link between schizophrenia and substance use disorder: A unifying hypothesis. *Schizophrenia Research*, *194*, 78–85.

Kittirattanapaiboon, P., Srikosai, S., & Wittayanookulluk, A. (2017). Methamphetamine use and dependence in vulnerable female populations. *Current Opinion in Psychiatry*, *30* (4), 247–252.

Konings, M., Stefanis, N., Kuepper, R., de Graaf, R., Ten Have, M., van Os, J., … Henquet, C. (2012). Replication in two independent population-based samples that childhood maltreatment and cannabis use synergistically impact on psychosis risk. *Psychological Medicine*, *42*(1), 149–159.

Konkolÿ Thege, B., Horwood, L., Slater, L., Tan, M. C., Hodgins, D. C., & Wild, T. C. (2017). Relationship between interpersonal trauma exposure and addictive behaviors: A systematic review. [journal article]. *BMC Psychiatry*, *17*(1), 164.

Kringlen, E. (2000). Twin studies in schizophrenia with special emphasis on concordance figures. *American Journal of Medical Genetics*, *97*(1), 4–11.

Lijffijt, M., Hu, K., & Swann, A. C. (2014). Stress modulates illness-course of substance use disorders: A translational review. *Frontiers in Psychiatry*, *5*, 83.

Martinotti, G., Di Iorio, G., Sepede, G., De Berardis, D., De Risio, L., & Di Giannantonio, M. (2012). Cannabis use and psychosis: Theme introduction. *Current Pharmaceutical Design*, *18*(32), 4991–4998.

Matheson, S. L., Shepherd, A. M., Pinchbeck, R. M., Laurens, K. R., & Carr, V. J. (2013). Childhood adversity in schizophrenia: A systematic meta-analysis. *Psychological Medicine*, *43*(2), 225–238.

Maynard, T. M., Sikich, L., Lieberman, J. A., & LaMantia, A. S. (2001). Neural development, cell-cell signaling, and the "two-hit" hypothesis of schizophrenia. *Schizophrenia Bulletin*, *27*(3), 457–476.

Misiak, B., Moustafa, A. A., Kiejna, A., & Frydecka, D. (2016). Childhood traumatic events and types of auditory verbal hallucinations in first-episode schizophrenia patients. *Comprehensive Psychiatry*, *66*, 17–22.

Modesti, P. A., Reboldi, G., Cappuccio, F. P., Agyemang, C., Remuzzi, G., Rapi, S., & Fuchs, F. D. (2016). Panethnic differences in blood pressure in Europe: A systematic review and meta-analysis. *PloS One*, *11*(1), e0147601.

Moher, D., Liberati, A., Tetzlaff, J., & Altman, D. G. (2010). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *International Journal of Surgery*, *8*(5), 336–341.

Morgan, C., & Fisher, H. (2007). Environment and schizophrenia: Environmental factors in schizophrenia: Childhood trauma–A critical review. *Schizophrenia Bulletin*, *33*(1), 3–10.

Morkved, N., Winje, D., Dovran, A., Arefjord, K., Johnsen, E., Kroken, R. A., & Løberg, E.-M. (2018). Childhood trauma in schizophrenia spectrum disorders as compared to substance abuse disorders. *Psychiatry Research*, *261*, 481–487.

Mrazek, J. (1994). *Reducing risks for mental disorders. frontiers for preventive intervention research*. Institute of Medicine (US) Committee on Prevention of Mental Disorders. Washington, DC: National Academies Press (US).

Murphy, J., Houston, J. E., Shevlin, M., & Adamson, G. (2013). Childhood sexual trauma, cannabis use and psychosis: Statistically controlling for pre-trauma psychosis and psychopathology. *Social Psychiatry and Psychiatric Epidemiology*, *48*(6), 853–861.

Murray, R. M., Englund, A., Abi-Dargham, A., Lewis, D. A., Di Forti, M., Davies, C., & D'Souza, D. C. (2017). Cannabis-associated psychosis: Neural substrate and clinical impact. *Neuropharmacology*, *124*, 89–104.

Neria, Y., Bromet, E. J., Sievers, S., Lavelle, J., & Fochtmann, L. J. (2002). Trauma exposure and posttraumatic stress disorder in psychosis: Findings from a first-admission cohort. *Journal of Consulting and Clinical Psychology*, *70*(1), 246–251.

Nierop, M. V., Bak, M., Graaf, R. D., Have, M. T., Dorsselaer, S. V., & Winkel, R. V. (2016). The functional and clinical relevance of childhood trauma-related admixture of affective, anxious and psychosis symptoms. *Acta psychiatrica Scandinavica*, *133*(2), 91–101. functional and clinical relevance of childhood trauma-related admixture of affective, anxious and psychosis symptoms. *Acta psychiatrica Scandinavica*.

Parakh, P., & Basu, D. (2013). Cannabis and psychosis: Have we found the missing links? *Asian Journal of Psychiatry*, *6*(4), 281–287.

Pelayo-Teran, J. M., Suarez-Pinilla, P., Chadi, N., & Crespo-Facorro, B. (2012). Gene-environment interactions underlying the effect of cannabis in first episode psychosis. *Current Pharmaceutical Design*, *18*(32), 5024–5035.

Ramsay, C. E., Flanagan, P., Gantt, S., Broussard, B., & Compton, M. T. (2011). Clinical correlates of maltreatment and traumatic experiences in childhood and adolescence among predominantly African American, socially disadvantaged, hospitalized, first-episode psychosis patients. *Psychiatry Research*, *188*(3), 343–349.

Rosenberg, S. D., Lu, W., Mueser, K. T., Jankowski, M. K., & Cournos, F. (2007). Correlates of adverse childhood events among adults with schizophrenia spectrum disorders. *Psychiatric Services*, *58*(2), 245–253.

Saddichha, S., Werker, G. R., Schuetz, C., & Krausz, M. R. (2015). Stimulants and cannabis use among a marginalized population in British Columbia, Canada: Role of trauma and Incarceration. *International Journal of Offender Therapy and Comparative Criminology*, *59*(13), 1487–1498.

Schalinski, I., Breinlinger, S., Hirt, V., Teicher, M. H., Odenwald, M., & Rockstroh, B. (2019). Environmental adversities and psychotic symptoms: The impact of timing of trauma, abuse, and neglect. *Schizophrenia Research*, *205*, 4–9.

Schalinski, I., Fischer, Y., & Rockstroh, B. (2015). Impact ofmstsc childhood adversities on the short-term course of illness in psychotic spectrum disorders. *Psychiatry Research*, *228*(3), 633–640.

Scheller-Gilkey, G., Moynes, K., Cooper, I., Kant, C., & Miller, A. H. (2004). Early life stress and PTSD symptoms in patients with comorbid schizophrenia and substance abuse. *Schizophrenia Research*, *69*(2–3), 167–174.

Simpson, T. L., & Miller, W. R. (2002). Concomitance between childhood sexual and physical abuse and substance use problems. A review. *Clinical Psychology Review*, *22*(1), 27–77.

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, *25*(9), 603–605.

Stilo, S. A., & Murray, R. M. (2019). Non-Genetic Factors in Schizophrenia. *Current Psychiatry Reports*, *21*(10), 100.

Thirthalli, J., & Benegal, V. (2006). Psychosis among substance users. *Current Opinion in Psychiatry*, *19*(3), 239–245.

Tomassi, S., Tosato, S., Mondelli, V., Faravelli, C., Lasalvia, A., Fioravanti, G., & Cristofalo, D. (2017). Influence of childhood trauma on diagnosis and substance use in first-episode psychosis. *British Journal of Psychiatry*, *211*(3), 151–156.

Torrey, E. F., Bartko, J. J., & Yolken, R. H. (2012). Toxoplasma gondii and other risk factors for schizophrenia: An update. *Schizophrenia Bulletin*, *38*(3), 642–647.

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: A systematic review and meta-analysis. *Psychological Medicine*, *45*(12), 2481–2498.

Ucok, A., Bikmaz, S., Anisman, H., Zaharia, M. D., Meaney, M. J., & Merali, Z. (2007). The effects of childhood trauma in patients with first-episode schizophrenia. *Acta Psychiatrica Scandinavica*, *116*(5), 371–377.

van Os, J., Kenis, G., & Rutten, B. P. (2010). The environment and schizophrenia. *Nature*, *468*(7321), 203–212.

van Os, J., Krabbendam, L., Myin-Germeys, I., & Delespaul, P. (2005). The schizophrenia envirome. *Current Opinion in Psychiatry*, *18*(2), 141–145.

Volkow, N. D. (2016). Effects of cannabis use on human behavior-reply. *JAMA Psychiatry*, *73*(9), 996.

Wells, G., Shea, B., O'Connell, D. L., Peterson, J., Welch, V., Losos, M., Tugwell, P., Ga, S. W., Zello, G. A., Petersen, J., & Wells, G. A. (2014). *The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis*.

Zammit, S., Lewis, G., Dalman, C., & Allebeck, P. (2010). Examining interactions between risk factors for psychosis. *British Journal of Psychiatry*, *197*(3), 207–211.