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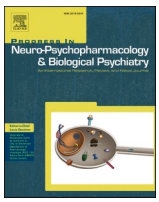

Premorbid functioning in schizophrenia spectrum disorders with comorbid substance use: A systematic review

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ABSTRACT

Premorbid functioning has been related with several clinical features and prognosis of schizophrenia spectrum disorders. Comorbidity with substance use is highly prevalent and usually hinders clinical improvement in this kind of psychiatric disorders. This systematic review analyzes the differences in the premorbid functioning of subjects with a schizophrenia spectrum disorder with substance use (SSD+, dual psychosis) or without it (SSD-). A systematic review (PRISMA guidelines), including search in electronic databases (MEDLINE, Web of Science, and Cochrane Library), was performed. 118 published works were considered of which only 20 met our inclusion criteria. Although there is a great variability in methodologies, diagnoses included, and substances used, studies using the Premorbid Functioning Scale to assess the academic and/or social domains found that SSD+ subjects had a poorer academic but better social premorbid functioning than those with SSD-. Current evidence is not conclusive, so additional studies are required to integrate intervening factors in order to clarify the clinical implications of premorbid functioning to improve the course and therapeutic response of patients.

1. Introduction

Persons affected with Schizophrenia Spectrum Disorders (SSD) usually show poor premorbid functioning before the onset of the illness. Premorbid functioning refers not only to premorbid intelligence quotient (IQ), but also to the individual's psychosocial functioning in educational, occupational, social and interpersonal relation areas before the onset of the psychotic symptomatology (Addington and Addington, 2005; Cannon-Spoor et al., 1982). This poor premorbid functioning has been related with an earlier onset age of illness, longer duration of untreated psychosis, more positive and negative psychotic symptomatology, cognitive impairment, and neuropsychological deficits in SSD (Addington and Addington, 2005; Amoretti et al., 2016; MacBeth and Gumley, 2008). Moreover, poorer premorbid functioning is a predictor of poor clinical outcome and psychosocial functioning (Levine et al., 2010; Lyngberg et al., 2015; Schimmelmann et al., 2008), an effect that has been described in first-episode psychosis (FEP), as well as in subjects with chronic schizophrenia and clinical high risk (CHR) of psychosis (Addington and Addington, 2008; Morcillo et al., 2015). Some studies have also found gender differences: males affected with schizophrenia tend to show poorer premorbid functioning compared to schizophrenic females (Bailer et al., 1996), a finding also observed in CHR (Salokangas et al., 2014).

Authors have studied premorbid functioning across developmental stages (childhood, early and late adolescence, and adulthood), either as a one-dimension or as a non-unitary construct. When a non-unitary construct is considered, it usually differentiates between two main dimensions, social and academic, and sometimes also includes a focus on clusters according to the developmental pattern (stable or deteriorating), or relating to the global premorbid adjustment, whether in schizophrenic, FEP or CHR subjects (Addington and Addington, 2005; Allen et al., 2001, 2005; Barajas et al., 2013; Larsen et al., 2004; Lyngberg et al., 2015).

Social and academic functioning were associated with several variables and patterns of impairment related to clinical aspects of psychotic spectrum disorders. The social dimension was associated with

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symptomatology factors such as severity of negative symptoms (Allen et al., 2001, 2005; Barajas et al., 2013; Larsen et al., 2004), mainly the avolition factor (Bucci et al., 2018). The academic dimension was associated with neurocognitive impairment in different cognitive domains (Allen et al., 2001; Cannon et al., 1997; Rannikko et al., 2015), with heterogeneous results (Larsen et al., 2004; Gónzalez-Blanch et al., 2008; Rabinowitz et al., 2007a, 2007b). Cluster analysis suggested that the deteriorating social course in the subjects studied showed an increase in social inhibition and negative symptoms after the onset of the illness. This deterioration in the social domain was associated to a greater prevalence of the clinical subtype of schizophrenia that meets the criteria for the deficit syndrome (Haim et al., 2006; Horton et al., 2015; Monte et al., 2008).

Furthermore, reduced intellectual functioning is associated with SSD (David et al., 2008; Mortensen et al., 2005; Sorensen et al., 2010) and FEP (Barder et al., 2015). This premorbid IQ deficit is related to how cognitive abilities develop along the age periods, which could affect the resilience to the disorder (Akiyama et al., 2016). In contrast, a better cognitive reserve might lead to lesser clinical severity and better neurocognitive functioning after the onset of the psychotic disorder (Herrero et al., 2020).

Comorbidity with a substance use disorder (SUD) has also been studied in SSD, due to a high prevalence of 30–66% worldwide (Hunt et al., 2018; Torrens et al., 2015). Dual diagnosis (DD) increases the severity of other disorders, impairing social and community functioning, and clinical evolution (Buhler et al., 2002; Mauri et al., 2017). Some authors have described a relationship between substance use and greater prodromal symptoms (Compton et al., 2009), with longer duration of untreated psychosis (Broussard et al., 2013) and a poorer premorbid functioning (including IQ). DD also seems related to greater neurocognitive deficits, a more erratic and deteriorating course of SSD, and fewer probabilities of symptomatic remission (Mahoney 3rd. et al., 2017; San et al., 2007). In contrast, a better premorbid functioning may predict symptomatic remission at one year of treatment for both SSD+ and SSD- (Caton et al., 2006). Moreover, good premorbid functioning has also been associated with better short-term outcomes in a subgroup of FEP without antipsychotic medication, although comorbid cannabis use impaired the prognosis in this group (Conus et al., 2017).

It therefore appears that premorbid functioning can predict the prognosis and clinical course of people with dual diagnosis. This fact is of great clinical relevance, mainly at the time of making the selection of clinical treatment (Hatzimanolis et al., 2020). However, few studies have addressed this topic, despite the fact that the analysis of premorbid functioning in SSD+ *vs.* SSD- could be of notable clinical importance.

The main purpose of this systematic review is to assess potential differences in premorbid functioning between SSD+ and SSD- groups. With this aim, we have analyzed and structured the early-course clinical and social factors in SSD+ and SSD- and assessed their impact on the course of the illness.

2. Materials and methods

The search, selection and critical assessment of the relevant works was performed and reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009; Urrútia and Bonfill, 2010).

2.1. Search strategy and data sources

We conducted the data search through the computerized databases MEDLINE, Web of Science, and the Cochrane Library, using the following keywords: "Substance-related disorders, substance use", "Schizophrenia, schizophrenia spectrum disorders", and "Premorbid functioning". During the selection process, some papers that had not appeared in the initial search were identified. These were equally assessed by the two investigators and those who met the inclusion criteria were added.

2.2. Study selection criteria

The inclusion criteria for the articles were: a) published from January 1990 to December 2019, b) written in English, c) full text available on-line, d) studying premorbid functioning, e) comparing SSD+ and SSD-, and f) with human subjects. The exclusion criteria were as follows: a) Studies that only consider participants without an SSD diagnosis and b) not assessing any early clinical and social factors previous to psychosis onset. The search was carried out for a minimum period of 25 years. The decision to start it in 1990 was due to the fact that on this date the clinical importance of dual pathology began to be considered, with pioneering publications on this topic.

Two of the authors performed the search and selection of articles independently and blindly, and any discrepancies were resolved by consensus between both authors (GP and AA).

Our review focuses on comparing premorbid functioning in SSD+ and SSD- subjects. Additionally, we have also reviewed some articles from our search that did not meet our inclusion criteria, but which provided interesting data to assess the relations among premorbid functioning, clinical variables and substance use, a topic to be further explored in future research.

2.3. Risk of bias assessment

In our review, there is a great heterogeneity of research designs, because few of them have focused their attention on determining the differences in premorbid functioning between SSD + and SSD-. In fact, most consist of cross-sectional studies originating from larger studies that have general objectives of analyzing different variables related to the functioning of schizophrenic patients, including premorbid functioning, or longitudinal studies that investigate premorbid functioning in the field of its possible relationship with clinical characteristics of schizophrenic patients. Although there are published criteria to establish the quality of the different types of studies included in the review (Higgins and Green, 2008), in our case their assessment would only obey a description of the quality of the study according to its own objective, but most of the time it would not be related, nor would it be relevant to the object of the review. For this reason, although it is recommended to evaluate the risk bias, it has not been carried out, because it is not considered essential (Arksey and O'Malley, 2005) and because no paper has been excluded for quality reasons.

3. Results

3.1. Articles overview

Fig. 1 shows a flowchart of our article selection process. The initial search retrieved 118 articles, of which we excluded 66 for being redundant. Then we excluded another 46 that did not meet our selection criteria. 20 papers were finally included in this review (marked with asterisks in references). We took into account the possible existence of confounding factors across studies, considering the following data from each paper: a) sex, b) SUD features, c) premorbid IQ, d) premorbid social functioning, e) premorbid academic functioning, and f) other premorbid factors. Table 1 presents the main results for the studies selected, together with other characteristics such as sample size, SSD, SUD features, and premorbid academic, social and IQ functioning. However, a meta-analysis could not be carried out due to the high heterogeneity found across the studies in key methodological aspects such as age, sex, and psychiatric diagnosis, among others.

In the case of premorbid functioning, no specific criterion has been selected *a priori*, and the studies have been chosen independently of the option used to evaluate it. *A posteriori*, the type of measurement has been considered, since this has been a variable of interest in the organization

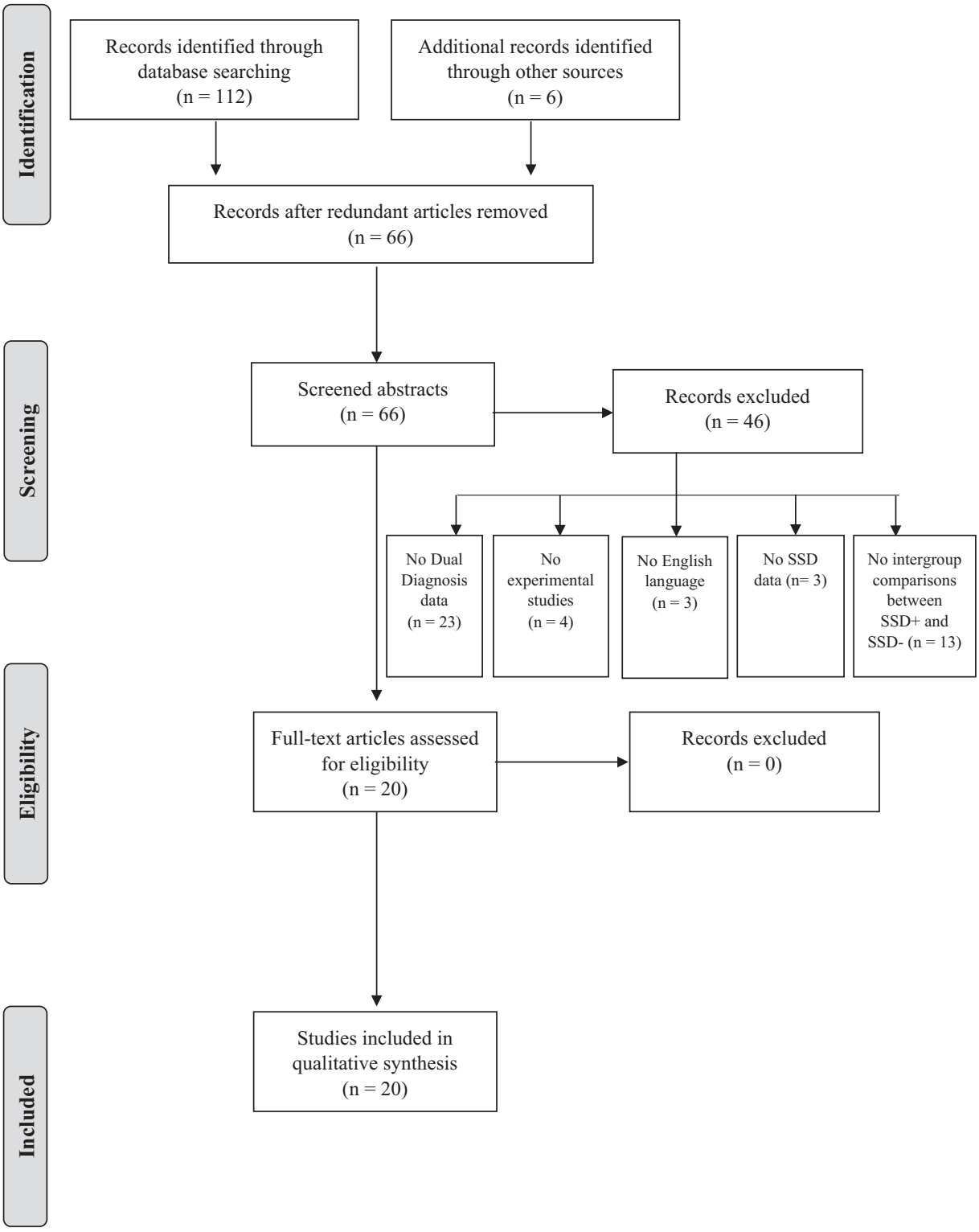

Fig. 1. Articles selection flowchart.

of the information collected and useful both for the description and for the presentation of the information in the manuscript.

Thus, most of the publications used the Premorbid Adjustment Scale (PAS), or a variation of it, to compare premorbid functioning between SSD+ *vs.* SSD- (Cannon-Spoor et al., 1982; Rabinowitz et al., 2007a, 2007b; Van Mastrigt et al., 2004). Fourteen of these used one version of the PAS; in 11 of these, the PAS was used as the only measure of premorbid adjustment (Arndt et al., 1992; Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Ringen et al., 2008, 2013; Van Mastrigt et al., 2004; Wade et al., 2005; Weibell et al., 2019), although two of them completed their analysis with a measure of premorbid IQ (Leeson et al., 2012; Rodríguez-Sánchez et al., 2010), a third one added a measure of premorbid cognitive functioning (Sevy et al., 2001), and a fourth one included a measure of general premorbid functioning using the Global Functioning Scale (GAF) (Rabinowitz et al., 1998). Four works used IQ as the only premorbid measure (Benaiges et al., 2013; Coulston et al., 2007; DeRosse et al., 2010; Ferraro et al., 2013). Finally, one study (Salyers and Mueser,

Table 1
Main features of papers included in the review that used the Premorbid Adjustment Scale (PAS) as a measure of premorbid functioning.

Authors	Sample	SUD data	Premorbid data	Main results
Dixon et al. (1991)	*N* = 83 inpatients. Age: 18–65 yr. Gender: No data provided Psychiatric disorder (SCID-I): Schizophrenia: 68 Schizoaffective: 12 Schizophreniform: 3	Drug or alcohol abuse or dependence (DSM-III criteria): 40 (21 polyconsumers). No abuse or dependence: 43; Dependence: 64; Abuse: 12 Type of drug: Alcohol: 21; Cannabis: 26; Cocaine: 14; Stimulants: 19; Hallucinogens: 5; Sedative-hypnotics: 3; Other: 2 Recent abusers (SUD 6 months prior assessment): 29; Past abusers (SUD in remission): 11.	Premorbid social and academic adjustment in the 4 age periods by PAS (data showed only for the early and late adolescence period).	Drug abusers showed better social and worse academic adjustment in both early and late adolescence. Differences disappear when only diagnosis of schizophrenia is considered. No differences between groups in childhood or adulthood developmental stages. No differences in clinical symptoms between the two groups at admission.
Arndt et al. (1992)	*N* = 131 selected from several larger studies (outpatients). Age: 31.54 ± 8.94 yr. Gender: 93 males, 38 females Psychiatric disorders (DSM-III criteria; no data available on the n of each diagnosis): Schizophrenia, Schizophreniform.	Modified abuse criteria (DSM-II) for drug abusing diagnostic. Pathological use: 64 (34 polyconsumers). Non-drug users: 67 Type of drug: Alcohol: 50; Cannabis: 42; Stimulants: 15; LSD: 4	Premorbid psychosocial adjustment in two age periods: age 6 to 12, and age 13 to 21 assessed with a modified version of PAS. Psychosocial adjustment with 3 common items for both periods of age (withdrawal, peer relationships, interest) and one item, plus (socio-sexual adjustment) Dispersion data no showed.	Better premorbid adjustment for pathological drug use in all drugs considered, except for the LSD group. Specific study of polyconsumption suggests this finding is due mainly to alcohol, and to a lesser extent to cannabis. More males than females used drugs. Without differences in any clinical factor studied except for duration of hospitalization, which was shorter in pathological drug users.
Rabinowitz et al. (1998)	*N* = 541 inpatients Age: 15–60 yr. Gender: 299 males, 242 females Psychiatric disorder (SCID-I): Bipolar with psychotic features: 153 Schizophrenia spectrum: 224 Major depressive with psychotic features: 99 Non-organic psychosis: 65	SUD (SCID-I): No lifetime abuse or dependence: 289 In remission: 154 (97 full; 57 partial; Mild abuse or dependence: 31; Moderate to severe abuse or dependence: 67 60% polyconsumers	Premorbid social and academic adjustment in the four age periods assessed with the PAS (data not provided). GAF used to assess the best month in the year prior to baseline interview (data not provided).	No significant differences found between abusers and non-abusers. The 'moderate to severe current abuse or dependence' group had stated their abuse or dependence several years prior to psychosis onset. For females, it was related to an earlier onset of psychotic illness (6 years before). For both genders, it was related to more antisocial behavior. The bipolar disorder group had the highest prevalence of SUD.
Sevy et al. (2001)	*N* = 118 FEP inpatients from a larger study. Age: 26 ± 6 yr. Gender: 61 male, 57 female Psychiatric disorder (Research Diagnosis Criteria, RDC): Schizophrenia: 83 Schizophreniform-manic: 9 Schizophreniform-depressed: 26	History of substance abuse or dependence: Positive: 27; negative: 91 No history of substance abuse or dependence: 91 Main type of drug: Alcohol: 12; Cannabis: 12; Cocaine: 3; Polyconsumers: 9	Premorbid social adjustment in the four different age periods assessed with the PAS (see Table 2) Premorbid cognitive functioning assessed by means of a constructed scale with test of general knowledge, vocabulary and reading skills.	No differences in PAS scores between those with a history of substance use and those with no substance use. Patients with a history of substance use showed higher premorbid cognitive functioning. No differences in other clinical characteristics, age of onset of psychosis and level of symptoms.
Salyers and Mueser (2001)	*N* = 404 inpatients from a large study treated with fluphenazine. Age: 29.5 ± 7.5 yr. (18–55 yr.) Gender: 270 males, 134 females. Psychiatric disorder: Schizophrenia: 314 Schizoaffective and Schizophreniphorm: 90	Assessment of level of history of drug-related problems with a 5-points Likert scale. History minimum of three months of substance use: 404 Frequency of drug use: No/Low alcohol: 236; Alcohol only: 127; Drug use: 41	Premorbid functioning assessed with a single 3-point Likert item (1-very well to 3-poorly) reflecting the level of premorbid problems. No/Low alcohol: 1.6 ± 0.7 Alcohol only: 1.5 ± 0.7 Drug use: 1.3 ± 0.6	The groups did not differ in the level of premorbid problems. Drug use group had the earliest age at first hospitalization compared with the two other groups and, more hospital admission compared with the no/low alcohol use group. Group of no/low alcohol showed greater level of negative symptoms and worse social functioning.
Van Mastrigt et al. (2004)	*N* = 357 inpatients and outpatients. Age: 24 ± 8.03 yr. Gender: 238 males, 119 females Psychiatric disorder (SCID-I): Schizophrenia: 131 Schizophreniform: 133 Psychotic disorder no specified: 61 Brief psychotic disorder: 14 Substance-induced psychotic disorder: 8	Severity of substance use (Case Manager Rating Scale for Substance Use Disorder; CMRS): none, mild, moderate and sever/extremely sever. Substance use: 159 No substance use: 198 Type of drug: Alcohol: 36; Cannabis: 51; Other drugs: 10; Alcohol + cannabis: 31; Alcohol + other drugs: 31.	Premorbid functioning assessed with the PAS (domains or age periods not specified; data not provided).	No differences were observed among groups regarding premorbid functioning or psychotic symptom level. Users of cannabis or cannabis + alcohol were younger and had an earlier age of onset than non-users and those who used alcohol + other drugs or those of the other drugs. Alcohol and cannabis use was related to more positive symptoms. Men showed higher level of alcohol and cannabis consumption.

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Table 1 (*continued*)

Authors	Sample	SUD data	Premorbid data	Main results
Wade et al. (2005)	*N* = 126 inpatient and outpatients. Age: 15-30 yr. 21.5 ± 3.5 yr. Gender: 89 males, 37 females Psychiatric disorder (Royal Park Multidiagnostic Instrument for Psychosis, RPMIP), only FEP: Non-affective psychosis: 81 Affective psychosis: 36 Other Psychosis: 9	Lifetime SUD (Chemical Use, Abuse and Dependence Scale, CUAD): 71% 12 months SUD: 69.8% Lifetime-daily tobacco use: 77%; 12 months daily tobacco use: 76.2%	Premorbid social and academic adjustment in 3 periods of age (no adulthood) by PAS scale (data not shown).	No differences in premorbid functioning were observed between SUD and non-SUD patients. SUD is more prevalent in males and younger age.
Larsen et al. (2006)	*N* = 301 FEP from a large study (84% inpatients). Age: 27.9 ± 9.5 yr. Gender: 178 males, 123 females. Psychiatric disorder (SCID-I): Schizophrenia: 102 Schizophreniform: 58 Schizoaffective: 36 Mood disorder with mood-incongruent psychotic disorder: 36 Delusional disorder: 19 Brief psychosis: 19 Other psychosis: 31	Drug abuse for a period of 6 months prior the start of the treatment (Alcohol and Drug Use Scale): No abuse: 202; Alcohol abuse: 28; Abuse of drugs: 51; Abuse of alcohol and drugs: 19	Premorbid social and academic adjustment in the four age periods evaluated by PAS, (see Table 2).	Drug abuse associated with better scores for premorbid social functioning for both childhood and early adolescence and worse scores for the academic dimension during adolescence. Alcohol and drug abuse had poorer scores for the premorbid academic dimension in three developmental periods as well as fewer years of education as compared to the non-abusers. The drug abuse group was the youngest and had a greater proportion of males.
Ringen et al. (2008)	*N* = 423 outpatients (84%) and inpatients from a large study. Age: 34.3 ± 11.0 yr. Gender: 215 males, 208 females. Psychiatric disorder (SCID-I): Schizophrenia: 187 Schizoaffective: 48 Schizophreniform: 17 Bipolar I: 104 Bipolar II: 60 Bipolar NOS: 7	Frequency of drug use in the last 6 months (interview): Non-user group: 329 High use: 53 Low use: 41 Type of drug (urine samples): Cannabis: 84%; Amphetamines: 22.3%; Cocaine: 14.9%; Ecstasy: 3.2%; Hallucinogens: 4.2%; Kath: 1.1%; GHB: 1.1%.	Premorbid social and academic adjustment only in one age period (Childhood) by PAS (data shown by chart).	High drug users showed poorer childhood premorbid academic functioning than non-users or low drug users in the whole sample (corrected for gender and diagnosis). A high level of psychotic symptoms was observed in high drug use subjects with schizophrenia. Premorbid functioning did not mediate the relationships between current drug use and symptoms load in patients with schizophrenia.
Carr et al. (2009)	*N* = 376 outpatients. Age: 16–50 yr. Gender: 280 males, 96 females Psychiatric disorder (SCID-I); only FEPs: Schizophrenia spectrum: 251 Substance induced: 32 Delusional disorder:9 Mood disorder: 26 Psychosis NOS: 47 Other: 11	SUD (SCID-I) Concurrent SUD: 114 (84 single drug; 30 two drugs) No concurrent SUD: 262 Type of drug: Cannabis: 91; Alcohol: 13; Cocaine: 2; Opiates: 1; Hallucinogens: 1; Polysubstance: 6.	Premorbid social and academic adjustment in 3 age periods (no adulthood) by PAS (see Table 2).	Subjects with concurrent substance use disorder showed a higher social premorbid functioning in the three periods of age (childhood, early adolescent and late adolescent). Subjects with concurrent substance use had a lower score in academic premorbid functioning in early and late adolescence. Group of subjects with concurrent SUD have proportionately more males, an earlier age of psychosis onset and showed a greater number of positive psychotic and anxiety symptoms.
Rodríguez-Sánchez et al. (2010)	*N* = 104 outpatients from a large study. Age: 26 ± 6.1 yr. (15–60 yr.) Gender: 60 males, 44 females. Psychiatric disorder (SCID-I): Schizophrenia: 68 Schizophreniform: 24 Brief psychotic disorder: 8 Psychoses NOS: 4 Healthy controls: 34	No drug dependence (DSM-IV), except nicotine. Presence or absence of cannabis prior to illness onset (verbal report in clinical interview; cannabis positive if at least there was a weekly use frequency during the year previous to program entry) Cannabis users: 47 Cannabis non-users: 57 44.7% used other substances.	Premorbid functioning assessed by PAS (global score in each four-year period for academic and social domains). Users: Childhood: 5.0 ± 2.7 Early adolescence: 7.5 ± 3.1 Late adolescence: 9.8 ± 3.9 Adulthood: 3.7 ± 3.9 Social domain: 0.8 ± 0.7 Academic domain: 2.9 ± 0.9 Non-users: Childhood: 6.3 ± 3.5 Early adolescence: 8.1 ± 3.5 Late adolescence: 8.6 ± 4.3 Adulthood: 4.3 ± 3.9 Social domain: 1.1 ± 0.9 Academic domain: 2.5 ± 1.0 Premorbid IQ was studied (see Table 3).	Differences between groups in premorbid function in the four periods of age of the PAS. Cannabis users had a better premorbid adjustment of social domain during childhood early adolescence and adulthood, and no differences were found in the academic domain. Cannabis users had a lower premorbid IQ. In the group of cannabis users there was a higher percentage of males, they were younger and had an earlier age of illness onset as well as more psychotic positive symptoms than the non-users. Moreover, cannabis users exhibited better attention and executive functions than non-users.

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Table 1 (*continued*)

Authors	Sample	SUD data	Premorbid data	Main results
Compton et al. (2011)	*N* = 109 inpatients from a larger study. Age: 23.1 ± 4.7 yr. (18–40 yr.) Gender: 83 males, 26 females. Psychiatric disorder (SCID-I): Schizophrenia Schizophreniform Schizoaffective Brief Psychotic disorder Delusional disorder Psychotic disorder NOS. No percentage was shown (referred for a description to Compton et al., 2009)	Drug use was obtained inquiring directly about age of initiation of drug intake and frequency of use (annual, weekly, daily). Early adolescence (<15 years) Cannabis users: 49; Cannabis non-users: 60; Nicotine users: 43; Nicotine non-users: 66; Alcohol users: 45; Alcohol non-users: 64 Late adolescence (<18 years) Cannabis users: 77; Cannabis non-users: 32; Nicotine users: 69; Nicotine non-users: 40; Alcohol users: 82; Alcohol non-users: 27	Premorbid social and academic adjustment only in two age period: early adolescence and late adolescence by PAS (see Table 2).	Cannabis users in early adolescence showed better social functioning than non-users. No differences in academic premorbid functioning were found in this group. Similar results were obtained with alcohol, but not for nicotine use No differences in social premorbid functioning between cannabis users and non-users in the late adolescence were found; however, non-users showed better academic premorbid functioning than cannabis, nicotine or alcohol users. No differences in prodromal features between groups who use THC were found. THC was associated with an acute mode of onset. Gender differences in premorbid functioning between groups were not studied.
Leeson et al. (2012)	*N* = 99 inpatients and outpatients. Age: Non-users: 28.29 ± 10.87 yr. Users: 23.42 ± 6.06 yr. Gender: 64 males, 35 females. Psychiatric disorder (Diagnostic Interview for Psychosis- Diagnostic Module; DIP-DM): Schizophrenia: 87 Schizophreniform: 1 Schizoaffective: 11	Semi-structured interview within the DIP-DM. No drug consumed more than a monthly basis at any point of life, except tobacco. Never users: 34 Cannabis-users: 65 (who reported having used the drug throughout their lives).	Premorbid social adjustment in two periods of age, childhood and early adolescence by PAS (see Table 2). Premorbid IQ was studied (see Table 3).	No differences in premorbid social adjustment were observed between groups. Cannabis users showed better premorbid IQ that explains differences in cognitive domains, being better in cannabis users, except for planning. The better premorbid IQ did not explain differences in social functioning and, it is not related with cannabis abstinence. Cannabis users had a younger age at prodromal and psychosis onset.
Ringen et al. (2013)	*N* = 364 from a large study (the same used in 2008). Inpatients and outpatients. Age: 31.2 ± 9.6 yr. (18–65 yr.) Gender: 207 males, 157 females. Psychiatric disorder (SCID-I): Schizophrenia: 278 Schizophreniform: 30 Schizoaffective: 56	Urine cannabis samples: 21 positives, 343 negatives. Diagnosis of abuse/addiction with SCID-E module. Cannabis lifetime diagnosis: 15.7%; Current cannabis: 11.8%; Current alcohol: 10.4%; Current stimulants: 4.4%. Tobacco allowed.	Premorbid social and academic adjustment only in the childhood period by PAS (See Table 2).	Subjects with current use of cannabis had lower premorbid academic functioning. Current differences in cognition are explained by premorbid academic functioning.
Frascarelli et al. (2016)	*N* = 43 inpatients and outpatients. Age: Cannabis users: 36 ± 10.8 yr. Non-users: 43.7 ± 7.3 yr. Gender: 33 males, 10 females. Psychiatric disorder (SCID-I): Psychotic disorder NOS: 14 Schizophrenia: 24 Schizoaffective: 5	Clinical Interview. Cannabis use before the onset of the illness on a daily basis with no combined use of any other substances: 21 yes, 22 not	Premorbid social and academic adjustment in the 4 age periods by PAS (data not shown).	The two groups scored similarly in all the PAS items except for the school adjustment domain relative to the period up to age 11, in which cannabis users showed worse functioning respect nonusers. Cannabis users are younger at onset of illness.
Weibell et al. (2019)	*N* = 195 FEP outpatients Age: 15–65 yr. Gender: 111 males, 84 females. Psychiatric disorder (SCID-IV): Schizophrenia spectrum disorders (Schizophrenia, schizophreniform or schizoaffective disorders): 136 Affective disorders (mood disorder with mood-incongruent psychotic features): 28 Other (delusional disorder, brief psychotic disorder, psychosis-NOS disorder): 31	Substance use: alcohol and drug use scale. No caffeine or nicotine assessment. Nonusers: 106 Stop users: 26 Episodic users: 33 Persistent users: 30 Users and non-users at initiation of the study (no data showed).	Premorbid social and academic adjustment in the childhood and several periods if available by PAS. A change score between childhood and the last available was calculated. Social domain: Non-users: 1.8 Stop users: 1.6 Episodic users: 1.9 Persistent users: 1.9 Academic domain: Non-users: 2.2 Stop users: 2.3 Episodic users:2.5 Persistent users:3.0	Substance users (all) had poorer premorbid academic functioning, and shorter length of education in the baseline score. Substance users were more likely male and younger than non-users.

Abbreviations: DSM: Diagnostic and Statistical Manual of Mental Disorders; SCID: The Structured Clinical Interview for DSM-IV; FEP: First Episode Psychosis; yr.: years; NOS: Not Otherwise Specified; SUD: Substance Use Disorder; IQ: Intelligence Quotient; GAF: Global Assessment of Functioning scale.

2001) assessed premorbid functioning with one single item designed *ad hoc*.

The PAS can assess two dimensions of premorbid adjustment (social and academic) (Larsen et al., 2004; Rabinowitz et al., 2007a, 2007b), and also includes a general section on the maximum functional level reached before SSD onset. Adjustments can be measured for four developmental periods organized in four age groups: childhood (up to 11 years), early adolescence (12 to 15), late adolescence (16 to 18) and adulthood (19 years or older) (see Table 2).

The articles reviewed also showed great heterogeneity in the measurements applied to assess dimensions and developmental stages. In some cases, an overall score was obtained for each dimension, without considering the age group (Rodríguez-Sánchez et al., 2010; Weibell et al., 2019). In other cases, only one of the dimensions was analyzed (Leeson et al., 2012; Sevy et al., 2001), and in most of them results were obtained for only some developmental stages (Arndt et al., 1992; Compton et al., 2011; Dixon et al., 1991; Ringen et al., 2008, 2013; Leeson et al., 2012). Although this may be plausible for the adulthood period, according to the scale's own instructions, it is not recommended in those cases in which the disease appears before age 19.

Finally, many articles indicated only the degree of statistical significance between SSD+ and SSD-, but did not mention the PAS scores obtained, did not specify whether one or two dimensions had been assessed, or what stages of development had been studied (Frascarelli et al., 2016; Leeson et al., 2012; Rabinowitz et al., 1998; Rodríguez-Sánchez et al., 2010; Van Mastrigt et al., 2004; Sevy et al., 2001; Wade et al., 2005; Weibell et al., 2019).

Those works focusing on identifying premorbid cognitive functioning performed an estimation of IQ previous (see Table 3) to the psychosis onset using several standardized instruments such as the

Table 2
Mean ± Standard Deviation (SD) of the Premorbid Adjustment Scale (PAS) scores. Includes only those works which provided the data.

Sample	PAS dimensions	Drug use	Dixon et al. (1991)	Arndt et al. (1992)	Sevy et al. (2001)	Larsen et al. (2006)	Carr et al. (2009)	Leeson et al. (2012)	Compton et al. (2011)	Ringen et al. (2013)
Childhood	Social	Users	–	–	0.97 ± 0.78	OH: 0.9 ± 1.3 D: 0.6 ± 0.9 OH + D: 1.2 ± 1.4	2.4 ± 2.3	2.3 ± 1.0	–	1.6 ± 1.3
		Non-users	–	–	1.24 ± 0.87	1.1 ± 1.1	3.2 ± 2.6	2.2 ± 1.0	–	1.3 ± 1.5
	Academic	Users	–	–	–	OH: 1.8 ± 1.3 D: 1.8 ± 1.1 OH + D: 2.6 ± 1.6	3.5 ± 2.3	–	–	2.7 ± 1.4
		Non-users	–	–	–	1.7 ± 1.3	3.5 ± 2.5	–	–	1.7 ± 1.3
Early adolescence	Social	Users	1.38 ± 1.06	OH: 2.37 C: 2.75 ST: 3.00 H: 2.25	1.41 ± 0.85	OH: 1.3 ± 1.6 D: 0.7 ± 1.0 OH + D: 1.5 ± 1.6	4.0/−3.2	2.3 ± 0.9	1.21 ± 0.85	–
		Non-users	2.17 ± 1.39	4.46	1.33 ± 0.84	1.4 ± 1.3	5.0 ± 3.6	2.5 ± 1.0	1.75 ± 1.27	–
	Academic	Users	2.61 ± 1.42	–	–	OH: 2.4 ± 1.2 D: 2.4 ± 1.2 OH + D: 3.0 ± 1.5	5.0 ± 2.6	–	2.06 ± 0.79	–
		Non-users	1.85 ± 1.31	–	–	2.0 ± 1.3	4.2 ± 2.8	–	1.81 ± 0.96	–
Late adolescence	Social	Users	2.12 ± −1.17	OH: 4.47 C: 4.32 ST: 4.27 H: 4.25	1.86 ± 1.10	OH: 1.7 ± 1.6 D: 1.1 ± 1.2 OH + D: 1.7 ± 1.2	4.2 ± 3.5	–	1.42 ± 1.06	–
		Non-users	2.53 ± 1.60	6.53	1.58 ± 1.05	1.6 ± 1.4	5.8 ± 4.3	–	1.67 ± 0.95	–
	Academic	Users	2.74 ± 1.32	–	–	OH: 2.4 ± 1.1 D: 2.9 ± 1.2 OH + D: 3.2 ± 1.5	6.0 ± 3.0	–	3.48 ± 1.53	–
		Non-users	1.97 ± 1.49	–	–	2.1 ± 1.3	5.1 ± 3.2	–	1.93 ± 1.23	–
Adulthood	Social	Users	–	–	1.93 ± 1.29	OH: 2.2 ± 1.6 D: 1.4 ± 1.3 OH + D: 1.8 ± 1.4	–	–	–	–
		Non-users	–	–	1.80 ± 1.37	1.8 ± 1.5	–	–	–	–
	Academic	Users	–	–	–	–	–	–	–	–
		Non-users	–	–	–	–	–	–	–	–

Abbreviations: OH: Alcohol; C: Cannabis; ST: Stimulants; H: Hallucinogens; D: different drugs.

Table 3
Main features of the papers reviewed that measured premorbid Intelligence Quotient (IQ).

Authors	Sample	SUD data	Premorbid IQ data	Main results
Coulston et al. (2007)	*N* = 76 outpatients Age: 26.4 ± 5.4 yr. (17–45 yr.) Gender: only males Psychiatric disorder (SCID-I): Schizophrenia Schizoaffective disorder: 59 (no data about n of each disorder) Healthy controls: 17	No alcohol or other illicit drug use within 24 h previous to cognitive assessment (urine sample). Lifetime cannabis: abuse/dependence (SCID-I): Criteria: 44; Without criteria: 15 Cannabis abuse/dependence (previous week, urine controls): With dependence: 11; Non-dependence: 7 Cannabis use frequency (one year prior): Low: 34; Medium: 7; High: 11	Comparison of Premorbid IQ (The Shipley Institute of Living Scale-Vocabulary Component; SILS-V) between cannabis users and non-users (data not provided).	No differences between users and non-users in premorbid IQ. However, recent cannabis users (previous week) had a significantly lower estimate of premorbid IQ than the non-users. This is related to a worse performance in short-term memory, planning, organization, and complex information processing. The mean of the estimated IQ for medium frequency users was lower (not significant) than for the other two groups (high and low users), which also had a poorer cognitive performance.
DeRosse et al. (2010)	*N* = 455 outpatients from a larger genetic study. Age: 18–65 yr. Gender: Cannabis users: 153 males, 22 females. Non-cannabis users: 173 males, 107 females. Psychiatric disorder (SCID-IV): Schizophrenia Schizoaffective (no data about n of each disorder)	No recent diagnosis of drug abuse or dependence (within 1 month). 175 with SUD: Cannabis abuse: 51 Cannabis dependence: 124	Premorbid IQ > 70 (Wide Range Achievement Test-Third Edition; WRAT-3, Reading subtest) Cannabis users: 93.36 ± 13.42 No-cannabis users: 92.48 ± 14.07	No premorbid IQ differences between cannabis users and non-users. Cannabis users presented better functioning (GAF) and performance in neurocognitive measures; greater proportion of males.
Rodríguez-Sánchez et al. (2010)	N = 104 FEP outpatients and inpatients from a large study. Age: 26 ± 6.1 yr. (15–60 yr.) Gender: 60 males, 44 females. Psychiatric disorder (SCID-I): Schizophrenia: 68 Schizophreniform: 24 Brief psychotic disorder: 8 Psychoses NOS: 4 Healthy controls: 34	No drug dependence (DSM-IV), except nicotine. Presence of cannabis prior to illness onset clinical interview; cannabis positive if at least there was a weekly use frequency during the year previous to program entry): Users: 47; non-users: 57 44.7% used other substances.	Comparison of Premorbid IQ from Wechsler Intelligence Scale (WAIS-III; estimated from Vocabulary test) between cannabis users and non-users (data not shown)	Cannabis users showed worse premorbid IQ than non-users and controls. In the group of cannabis users there exist a higher % of males, were younger and have an earlier age of illness onset and, more psychotic positive symptoms than the non-users. Moreover, cannabis users have better attention and executive functions than non-users.
Leeson et al. (2012)	N = 99 inpatients and outpatients. Age: Non-users: 28.29 ± 10.87 yr. Users: 23.42 ± 6.06 yr. Gender: 64 males, 35 females. Psychiatric disorder (Diagnostic Interview for Psychosis- Diagnostic Module; DIP-DM): Schizophrenia: 87 Schizophreniform: 1 Schizoaffective: 11	Semi-structured interview within the DIP-DM. Non-users (consumed no more than a monthly throughout life, except nicotine): 34 Cannabis users (consumed the drug throughout life): 65	Comparison of the Premorbid IQ from the Wechsler Test of Adult Reading (WTAR) between drug users and non-users. Non-users: 88.9 ± 11.73 Cannabis users: 95.54 ± 12.79	Premorbid IQ explains differences in cognitive domain, being better in cannabis users, except for planning processing.
Benaiges et al. (2013)	*N* = 95 outpatients Age: 20–60 yr. (37.24 ± 7.62) Gender: only males. Psychiatric disorder (SCID-I): Schizophrenia: 53 Schizoaffective: 7	SUD (SCID-I): SSD+: Cocaine dependence: 30 SSD-: Non-drug dependence: 30 SUD: with cocaine dependence: 35 Abstinent of all type of substances of abuse at least 4 months prior.	Premorbid IQ assessed with the Wechsler Intelligence Scale (WAIS-III) subtest of vocabulary (verbal) and block design (non-verbal) Data showed in *Z*-scores and in graphic mode. Verbal IQ (direct score): SSD-: 40.71 ± 9.22 SSD+: 42.76 ± 6.93 SUD: 43.02 ± 6.60 Non-verbal IQ (direct score): SSD-: 39.32 ± 11.44 SSD+: 34.93 ± 11.10 SUD: 43.02 ± 6.60	No differences were observed in premorbid verbal IQ among groups. SSD- group showed worse non-verbal IQ compared with SUD group.
Ferraro et al. (2013)	*N* = 119 outpatients from a large genetic study of FEP and 160 healthy controls Age: 18–65 yr. (29.6 ± 8.5) Gender: 84 males, 35 females	Lifetime use of drugs. Cannabis Experience Questionnaire: Cannabis use lifetime: 86 (37 only	Comparison of Premorbid IQ with the Wechsler Test of Adult Reading (WTAR) between cannabis users and non-users Users: 91.2 ± 16.5 Non-users: 79.1 ± 11.5	Premorbid IQ was significantly higher in lifetime cannabis users compared with those who had never used.

(*continued on next page*)

Table 3 (*continued*)

Authors	Sample	SUD data	Premorbid IQ data	Main results
		cannabis; 49 cannabis and other drugs)		
	Psychiatric disorder (Operational Criteria Checklist, OPCRIT): Affective psychoses: 33 Non-affective psychoses: 86	Current cannabis use: 34		

Abbreviations: SCID: The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; FEP: First Episode Psychosis; yr.: years; NOS: Not Otherwise Specified; SSD: Schizophrenia Spectrum Disorder; SUD: Substance Use Disorder; GAF: Global Assessment of Functioning scale.

Vocabulary subtest of the WAIS-III (Benaiges et al., 2013; Ferraro et al., 2013; Rodríguez-Sánchez et al., 2010), the Vocabulary component of the Shipley Institute of Living Scale (Coulston et al., 2007), the Wechsler Test of Adult Reading (WTAR) (Ferraro et al., 2013; Leeson et al., 2012) or the Wide Range Achievement Test-Third Edition (WRAT-3, Reading subtest) (DeRosse et al., 2010). One of the studies complemented the IQ estimation also assessing cognitive premorbid functioning by means of a composed score, based on a test of general knowledge which included vocabulary and reading subtests (Sevy et al., 2001).

The different aims of each study may account for the variability found. Only four works had as their main goal to study the premorbid functioning in relation to substance use (Arndt et al., 1992; Compton et al., 2011; Ferraro et al., 2013; Ringen et al., 2008). In contrast, in most of the remaining works, premorbid functioning was included as one more factor to assess along with other clinical variables such as onset age of psychosis, history of hospital admissions, duration of untreated psychosis, or level of psychotic symptomatology (Carr et al., 2009; Dixon et al., 1991; Larsen et al., 2006; Leeson et al., 2012; Salyers and Mueser, 2001; Sevy et al., 2001; Van Mastrigt et al., 2004). Other aims of the works reviewed were to study cognitive functioning in SSD+ and SSD- subjects at the moment of the assessment, and the relation with clinical aspects such as substance use, community functioning or predictive aspects of clinical course (Benaiges et al., 2013; Coulston et al., 2007; DeRosse et al., 2010; Frascarelli et al., 2016; Rabinowitz et al., 1998; Ringen et al., 2013; Rodríguez-Sánchez et al., 2010; Wade et al., 2005).

3.2. Premorbid functioning

Regarding premorbid functioning, most of the works used the PAS, and differentiated between social and academic premorbid functioning. In these studies, differences between SSD+ and SSD- were obtained for the two dimensions of the scale. In such cases, academic adjustment was poorer for SSD+ than for SSD- (Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Ringen et al., 2008, 2013; Weibell et al., 2019). These results were observed in the developmental stages of childhood (Dixon et al., 1991; Ringen et al., 2008, 2013; Weibell et al., 2019), and in early and late adolescence (Carr et al., 2009; Compton et al., 2011; Frascarelli et al., 2016; Larsen et al., 2006).

The results on academic functioning were obtained from subjects who were consuming at the time of the study, who had consumed different types of drugs, or with a comorbid SUD (Carr et al., 2009). The patterns of consumption were also diverse: alcohol and cannabis (Dixon et al., 1991; Ringen et al., 2013; Van Mastrigt et al., 2004), alcohol and other drugs (Larsen et al., 2006), illicit substances (Ringen et al., 2008), and polyconsumption (Weibell et al., 2019). Furthermore, similar results were obtained in substance users who had started consumption before the disorder onset (Salyers and Mueser, 2001) and in cannabis users who had started consuming alcohol or nicotine before age 15 (Compton et al., 2011).

Regarding social functioning, some studies found differences in social premorbid adjustment, although less consistent than those observed in academic functioning. Overall, SSD+ subjects obtained better scores than SSD- in this domain for childhood, early (Compton et al., 2011; Dixon et al., 1991; Larsen et al., 2006; Rodríguez-Sánchez et al., 2010) and/or late (Arndt et al., 1992; Carr et al., 2009) adolescence stages. In contrast, other studies did not find any significant differences in the social domain for childhood, early (Leeson et al., 2012) or late adolescence (Compton et al., 2011). One study extended this observation to the four periods of development assessed by the PAS (Frascarelli et al., 2016). Another study found only a trend for better premorbid social functioning in the SSD+ group (Ringen et al., 2008).

Similarly to academic functioning, when assessing social functioning and substance use there was much heterogeneity in substances used and consumption patterns: cannabis (Arndt et al., 1992; Leeson et al., 2012; Rodríguez-Sánchez et al., 2010), alcohol, alcohol and cannabis (Dixon et al., 1991), and in other drug users (Larsen et al., 2006). Likewise, these patterns were also found in cannabis users who had begun cannabis or alcohol consumption prior to age 15 or 18 (Arndt et al., 1992; Compton et al., 2011; Rabinowitz et al., 1998), as well as in mild users of illicit substances (Ringen et al., 2008).

Finally, some works found no differences in premorbid functioning (Rabinowitz et al., 1998; Salyers and Mueser, 2001; Van Mastrigt et al., 2004; Wade et al., 2005). This might be due to methodological differences in how premorbid adjustment was assessed, or to the characteristics of the samples.

3.3. Premorbid IQ

Only seven papers compared premorbid cognitive functioning between SSD+ and SSD-, despite its clinical relevance. These studies focused mostly on cannabis users, but also obtained very heterogeneous results. Two studies found no differences between SSD+ and SSD- (Benaiges et al., 2013; DeRosse et al., 2010), three found a better premorbid cognitive functioning or a higher IQ in the SSD+ subjects, regardless of whether they were past or current users (Ferraro et al., 2013; Leeson et al., 2012; Sevy et al., 2001). One study found a lower premorbid IQ in the SSD+ group (Rodríguez-Sánchez et al., 2010), while another obtained this result only for those subjects with recent, moderate cannabis use (Coulston et al., 2007).

Usually, the different papers analyzed premorbid IQ in SSD+ subjects in relation to their current level of cognitive functioning (Coulston et al., 2007; Ferraro et al., 2013; Leeson et al., 2012; Rodríguez-Sánchez et al., 2010). Regarding higher premorbid cognitive functioning or higher premorbid IQ, two studies found a strong correlation with current IQ or cognitive performance in drug users (Ferraro et al., Leeson et al., 2012), and one study did not find differences when comparing subjects with or without a history of substance use (Sevy et al., 2001). A lower premorbid IQ in SSD+ subjects was related to worse outcomes in working memory performance (Coulston et al., 2007; Rodríguez-Sánchez et al., 2010).

3.4. Analysis of intervening factors

Most of the studies were reviewed taking into account several confounding factors, but some methodological issues did not allow us to explore all of them. Additionally, some differences in experimental design and/or in aims may help to understand the heterogeneity of the results, such as psychiatric diagnosis, clinical characteristics of the samples, drug consumption patterns, and age and sex of the participants.

3.4.1. Psychiatric diagnoses and clinical characteristics of the samples

In the 20 articles reviewed, the psychiatric diagnoses of the participants were very heterogeneous. Moreover, in many of them other diagnoses with psychotic symptomatology were also considered, even though they would not belong in the SSD group, such as affective or delusional disorders (whether alone or comorbid) (Carr et al., 2009; Compton et al., 2011; Ferraro et al., 2013; Larsen et al., 2006; Rabinowitz et al., 1998; Ringen et al., 2008; Van Mastrigt et al., 2004; Wade et al., 2005; Weibell et al., 2019). Some articles also included the diagnosis of non-specified psychosis (Carr et al., 2009; Compton et al., 2011; Ferraro et al., 2013; Frascarelli et al., 2016; Larsen et al., 2006; Rabinowitz et al., 1998; Ringen et al., 2008; Wade et al., 2005; Weibell et al., 2019) or of substance-induced psychotic disorders (Carr et al., 2009; Ringen et al., 2008; Van Mastrigt et al., 2004). Nine works used subsamples of FEP taken from larger studies (Arndt et al., 1992; Compton et al., 2011; Ferraro et al., 2013; Leeson et al., 2012; Rabinowitz et al., 1998; Ringen et al., 2008, 2013; Sevy et al., 2001; Van Mastrigt et al., 2004). Eleven works included only schizophrenia, schizoaffective and schizophreniform disorders (Arndt et al., 1992; Benaiges et al., 2013; Compton et al., 2011; Coulston et al., 2007; DeRosse et al., 2010; Dixon et al., 1991; Leeson et al., 2012; Ringen et al., 2013; Rodríguez-Sánchez et al., 2010; Salyers and Mueser, 2001; Sevy et al., 2001). This multiplicity of diagnoses hinders the comparison among those works that did not analyze premorbid functioning according to diagnostic type, which may have greatly influenced their results. For example, in one study the differences between substance users and non-users disappeared when only the schizophrenic subjects were considered (Dixon et al., 1991).

There were also differences in the level of patient care studied. Most of the works had participants from outpatient units (Benaiges et al., 2013; Carr et al., 2009; Coulston et al., 2007; DeRosse et al., 2010; Ferraro et al., 2013; Rodríguez-Sánchez et al., 2010; Weibell et al., 2019). Some works only included inpatients (Compton et al., 2011; Dixon et al., 1991; Rabinowitz et al., 1998; Salyers and Mueser, 2001; Wade et al., 2005), while others included both types, without exploring the possible differences between the two (Frascarelli et al., 2016; Larsen et al., 2006; Leeson et al., 2012; Ringen et al., 2008, 2013; Sevy et al., 2001; Van Mastrigt et al., 2004). This aspect clearly involves personal, social and clinical course characteristics of the subjects that may be related to their premorbid functioning. Future studies that deepen into it could provide very relevant data in order to improve our knowledge of both severity and prognosis of the clinical disorder as well as the health care level most indicated for the patient.

3.4.2. Substance use characteristics

In general, we found a non-homogeneous assessment of substance use characteristics in the papers selected. Most of them used the clinical criteria for substance use disorders from different versions of the DSM (Benaiges et al., 2013; Carr et al., 2009; Compton et al., 2011; DeRosse et al., 2010; Dixon et al., 1991; Ringen et al., 2013; Rabinowitz et al., 1998; Rodríguez-Sánchez et al., 2010), or were based in DSM criteria, such as the interview in the Diagnosis Interview for Psychosis-Diagnostic Module (DIP-DM) (Leeson et al., 2012). However, one study included only substance abuse (Arndt et al., 1992) while another one only considered the severity of symptoms (Rabinowitz et al., 1998).

Five works used a clinical interview to assess substance consumption (Compton et al., 2011; Ferraro et al., 2013; Frascarelli et al., 2016; Ringen et al., 2008; Rodríguez-Sánchez et al., 2010). There also was great variability in the standardized instruments used: the Alcohol and Drug Use Scale (Larsen et al., 2006; Weibell et al., 2019), the Case Manager Rating Scale for Substance Use Disorders (Van Mastrigt et al., 2004), the Cannabis Experience Questionnaire (Ferraro et al., 2013), the Research Diagnostic Criteria (Sevy et al., 2001), or the Chemical Use, Abuse and Dependence Scale (Weibell et al., 2019). This also yielded great heterogeneity in considering comorbidity, ranging from an objective diagnosis of SUD to near-diagnoses based on several degrees of substance use.

The assessment of the period of substance use also differed widely among studies. Thus, some studies considered current use or previous use to psychosis onset (Compton et al., 2011; DeRosse et al., 2010; Frascarelli et al., 2016; Ringen et al., 2013), others took into account lifetime use (Ferraro et al., 2013; Wade et al., 2005), and still others assessed substance use in the period prior to the study, which ranged from one month to one year (Benaiges et al., 2013; Dixon et al., 1991; Larsen et al., 2006; Leeson et al., 2012; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Salyers and Mueser, 2001; Van Mastrigt et al., 2004; Wade et al., 2005). In other cases, certain types of previous substance consumption were excluded, such as physical drug dependence (Salyers and Mueser, 2001), different withdrawal periods of the substances (Benaiges et al., 2013; Coulston et al., 2007; DeRosse et al., 2010; Larsen et al., 2006), or previous consumption of some specific drug type, such as opiate use for six months (Ringen et al., 2008). However, studies analyzing only one type of drug, mainly cannabis, excluded and controlled for previous consumption of other substances, usually carrying out confirmatory toxicological tests (Coulston et al., 2007; Leeson et al., 2012; Ringen et al., 2013). However, in several studies nicotine and/or caffeine dependence were not controlled for (Benaiges et al., 2013; Leeson et al., 2012; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Wade et al., 2005), since they were not considered confounding variables. Exceptions were one work specifically studying nicotine (Compton et al., 2011), and two others that did not include consumers of these two substances (Coulston et al., 2007; Weibell et al., 2019).

The works also varied greatly in the type of substance studied. Two studies considered all the main type of substances (Dixon et al., 1991; Ringen et al., 2008), others separated cannabis from alcohol, cocaine or stimulants (Carr et al., 2009; Compton et al., 2011; Larsen et al., 2006; Rodríguez-Sánchez et al., 2010; Sevy et al., 2001; Van Mastrigt et al., 2004; Wade et al., 2005), or only contemplated illicit substances (Ringen et al., 2008). Finally, some works considered only one type of substance, mainly cannabis (Compton et al., 2011; DeRosse et al., 2010; Ferraro et al., 2013; Frascarelli et al., 2016; Leeson et al., 2012) or cocaine (Benaiges et al., 2013). None of the 20 works reviewed specifically analyzed a sample of polyconsumers, although this is the most prevalent consumption pattern worldwide (Torrens et al., 2015).

Furthermore, many studies did not analyze the specific relation between drug use and premorbid functioning. Some works grouped subjects according to their current use or non-use of substances (Arndt et al., 1992; Carr et al., 2009; DeRosse et al., 2010; Dixon et al., 1991; Larsen et al., 2006; Leeson et al., 2012; Rodríguez-Sánchez et al., 2010), and some included frequency of use as a measure of severity (Coulston et al., 2007; Rabinowitz et al., 1998; Ringen et al., 2008, 2013; Salyers and Mueser, 2001; Weibell et al., 2019). Other works took into account history of drug use (Leeson et al., 2012) before onset of psychotic symptomatology (Frascarelli et al., 2016), as well as current and prior consumption (Compton et al., 2011). In some cases, the data on consumption were complemented by information from urinalyses (Ringen et al., 2013), length of consumption periods with different levels of severity (Van Mastrigt et al., 2004), or involuntary drug-free periods (Larsen et al., 2006).

All this diversity makes it difficult to establish a direct relationship between substance use patterns and levels of premorbid functioning. Although some studies obtained significant associations (Arndt et al., 1992; Compton et al., 2011; Larsen et al., 2006; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Salyers and Mueser, 2001), no comparable analyses regarding substance use could be performed. Future studies should take into account factors related to substance use characteristics such as diagnosis of SUD, severity of addiction, frequency of use, type of substance, and onset of substance use, in order to clarify their influence on premorbid functioning.

3.4.3. Sex and age

Most of the works reviewed included samples of both women and men, and only two included only male subjects (Benaiges et al., 2013; Coulston et al., 2007). However, only two works carried out direct sex comparisons at the premorbid level between SSD+ and SSD- subjects, but they found no differences in any age period considered (Compton et al., 2011; Frascarelli et al., 2016). In many studies, the SSD+ group had a larger proportion of men compared with the SSD- group (Arndt et al., 1992; Carr et al., 2009; DeRosse et al., 2010; Larsen et al., 2006; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Wade et al., 2005; Weibell et al., 2019). Although this is in correspondence with clinical reality, we cannot affirm that the results may be generalized to both sexes.

Regarding age, in the majority of the studies the SSD+ subjects were younger on average than the SSD- ones (Carr et al., 2009; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Leeson et al., 2012; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Salyers and Mueser, 2001; Van Mastrigt et al., 2004; Wade et al., 2005). Some works found differences in age depending on the severity of substance consumption (Weibell et al., 2019) or the type of substance used, with alcohol users being older on average than illicit drug users (Larsen et al., 2006; Salyers and Mueser, 2001; Wade et al., 2005), cannabis users, or cannabis and alcohol users (Wade et al., 2005).

In the light of these findings, future studies should analyze the possible relations among sex, onset age of substance consumption, type of substances consumed, or pattern and frequency of substance use, in order to assess the contribution of these factors.

3.5. Premorbid functioning and clinical or functional outcomes

In the articles reviewed, assessment of premorbid functioning and/or comorbid substance use aimed to analyze some clinical aspects related to SSD and/or FEP. However, the results obtained varied greatly once more. In some works, the SSD+ subjects had characteristics associated with severe psychiatric disorders, such as more positive symptoms (Carr et al., 2009), mainly in heavier users (Ringen et al., 2008, 2013), a history of more hospital admissions (Salyers and Mueser, 2001), greater presence of family history of positive psychiatric symptoms (Frascarelli et al., 2016), more symptoms of other psychiatric disorders such as antisocial personality disorder (Rabinowitz et al., 1998), an acute onset (Compton et al., 2011), and an earlier onset age of psychosis (Frascarelli et al., 2016; Leeson et al., 2012; Rabinowitz et al., 1998; Rodríguez-Sánchez et al., 2010; Van Mastrigt et al., 2004). Although positive symptoms and other psychotic features are more severe in SSD+ than in SSD- groups, some studies did not find any differences in clinical severity or other psychiatric comorbidities (Coulston et al., 2007; Dixon et al., 1991; Leeson et al., 2012; Rabinowitz et al., 1998; Sevy et al., 2001; Van Mastrigt et al., 2004; Wade et al., 2005).

In relation to negative symptoms, some studies indicate that consumer patients would present to a lesser degree this type of symptoms (Dixon et al., 1991; Salyers and Mueser, 2001; Van Mastrigt et al., 2004), or a tendency to show fewer negative symptoms (Arndt et al., 1992). Some studies suggest a relationship between this symptomatology and the level of substance use, such that SSD + subjects with a higher level of consumption (high-users) would present more negative symptoms than subjects with lower levels of consumption (Leeson et al. ., 2012; Ringen et al., 2008, 2013; Weibell et al., 2019). Finally, longitudinal studies have indicated that drug withdrawal in SSD + subjects leads to a decrease in negative symptoms (Leeson et al., 2012; Rodríguez-Sánchez et al., 2010). However, most of the studies do not identify differences for this type of symptomatology between SSD + and SSD- (Frascarelli et al., 2016; Ferraro et al., 2013; Larsen et al., 2006; Coulston et al., 2007; Rabinowitz et al., 1998; Sevy et al., 2001; Wade et al., 2005).

Over the last years, authors have focused on the cognitive aspects of SSD subjects and the relationship with substance consumption, mainly cannabis. In fact, several studies reviewed showed that SSD+ subjects had better cognitive functioning than the SSD- ones when also considering cannabis (Leeson et al., 2012) or cocaine use (Benaiges et al., 2013). A better cognitive level was usually associated with a better premorbid cognitive and/or social functioning in SSD+ cannabis users (Larsen et al., 2006), especially when onset of substance use came earlier than psychosis onset (Compton et al., 2011; Ferraro et al., 2013).

4. Discussion

To our knowledge, this is the first systematic review on the possible differences in premorbid functioning between SSD+ and SSD- subjects. Although the articles reviewed found differences in premorbid functioning between both groups, it is difficult to systematize such results because very few of the works aimed specifically to compare SSD+ and SSD- subjects. In addition, the methodological differences among the studies, such as the characteristics of the samples (psychiatric diagnoses, substance types, degree of consumption) and how premorbid functioning was assessed (instruments, time periods), makes it difficult to obtain solid conclusions.

Regarding the instruments used to asses premorbid functioning, 16 out of the 20 works measured premorbid adjustment, 15 of which did so by means of some adaptation of the PAS (Arndt et al., 1992; Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Leeson et al., 2012; Rabinowitz et al., 1998; Ringen et al., 2008, 2013; Rodríguez-Sánchez et al., 2010; Sevy et al., 2001; Van Mastrigt et al., 2004; Wade et al., 2005; Weibell et al., 2019), while the other one used only one item designed *ad hoc* (Salyers and Mueser, 2001). Eleven papers analyzed the two domains of the PAS (Arndt et al., 1992; Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Ringen et al., 2008, 2013; Van Mastrigt et al., 2004; Wade et al., 2005; Weibell et al., 2019), whereas three papers assessed only the social domain (Arndt et al., 1992; Leeson et al., 2012; Sevy et al., 2001). Four papers analyzed only premorbid IQ using some standardized instruments (Benaiges et al., 2013; Coulston et al., 2007; DeRosse et al., 2010; Ferraro et al., 2013).

The findings obtained in these papers regarding either one or both domains (academic and social) of the PAS and for the different age periods seem quite consistent. Eight works clearly assessed the academic domain (Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Frascarelli et al., 2016; Larsen et al., 2006; Ringen et al., 2008, 2013; Weibell et al., 2019), finding a poorer premorbid functioning for SSD+ subjects in different age periods, while only one did not obtain any differences between SSD+ and SSD- groups in this domain (Rodríguez-Sánchez et al., 2010). Regarding the social domain, most works reported a better social premorbid functioning for SSD+ subjects in different age periods (Arndt et al., 1992; Carr et al., 2009; Compton et al., 2011; Dixon et al., 1991; Larsen et al., 2006; Rodríguez-Sánchez et al., 2010), although two studies did not find any differences in this aspect (Leeson et al., 2012; Frascarelli et al., 2016), but there did not seem to be any methodological aspect that might explain such contrast. Four papers that studied premorbid functioning (social and academic, or as a global measure) did not find any difference between SSD+ and SSD- subjects (Rabinowitz et al., 1998; Salyers and Mueser, 2001; Van Mastrigt et al., 2004; Wade et al., 2005). These works described the characteristics of their samples, including psychiatric diagnosis, such as affective (Rabinowitz et al., 1998; Van Mastrigt et al., 2004; Wade et al., 2005) *vs.* non-affective (Salyers and Mueser, 2001) psychoses as well as substance use patterns, considering life-time substance use (Salyers and Mueser, 2001; Van Mastrigt et al., 2004; Wade et al., 2005) and severity of drug use (Rabinowitz et al., 1998), also examining if such characteristics might account for the absence of differences. However, these factors were not controlled for in these studies, and the heterogeneity of the samples was similar to the one observed in the previous works that did obtain differences. In this sense, it is also difficult to determine if the methodology used for measuring premorbid functioning had an effect on these findings, since one work used only one Likert-type item designed *ad hoc*

(Salyers and Mueser, 2001), and although the other three used the PAS, they did not detail how it was administered, the dimensions assessed or the scores obtained (Rabinowitz et al., 1998; Van Mastrigt et al., 2004; Wade et al., 2005).

Among the works that compared premorbid IQ in SSD+ and SSD- subjects, five obtained results for either a higher (Ferraro et al., 2013; Leeson et al., 2012; Sevy et al., 2001) or a lower (Coulston et al., 2007; Rodríguez-Sánchez et al., 2010) premorbid IQ in SSD+ subjects, whereas two obtained no differences (Benaiges et al., 2013; DeRosse et al., 2010). The data on premorbid IQ are inconclusive, since there are no known modulating factors affecting IQ (age, years of schooling, severity of symptoms, duration of illness) associated to these works depending on the results obtained.

Some works proposed a hypothesis that could partially account for the opposing results regarding premorbid adjustment in the academic and social domains. One suggested that the better premorbid social functioning of the SSD+ subjects relies on their greater ability to obtain illegal drugs and sustain their consumption (Cunha et al., 2013). Another proposed that this could be due to the SSD+ subjects' greater cognitive reserve (Herrero et al., 2020). This would also be related to better prognosis features and less vulnerability to develop SSD (Arndt et al., 1992; Larsen et al., 2006; Leeson et al., 2012; Petersen et al., 2008). Such findings on better premorbid cognitive or social functioning are in agreement with the vulnerability theory (Ferraro et al., 2013; Leeson et al., 2012; Sevy et al., 2001).

Also, in line with the vulnerability theory, some data suggest that SSD subjects with a worse social premorbid functioning show a greater impairment in cognitive functioning, and more negative psychotic symptomatology after the onset of SSD (Chang et al., 2016; Haim et al., 2006). The latter hypothesis would also relate the lower scores in academic premorbid functioning of SSD+ subjects to some features closely associated to substance use, such as antisocial traits, which have a negative effect on school performance in adolescence (Huber et al., 2016; Schweinsburg et al., 2008). Although one work found a worse premorbid IQ for SSD+ subjects (Rodríguez-Sánchez et al., 2010), another found no association between neurocognitive functioning and premorbid IQ in SSD+ (DeRosse et al., 2010). A cluster study with a heterogeneous sample of psychosis-spectrum patients (Crouse et al., 2018) found that the subjects in the most impaired cluster also had a lower premorbid IQ, a worse cognitive impairment, and higher risk to develop deficits on social functioning and to consume alcohol.

Some authors have postulated the self-medication hypothesis (Khantzian, 1997) to explain the worse academic premorbid functioning in SSD+ subjects. This hypothesis states that SSD+ subjects with a worse premorbid functioning have a greater predisposition for later substance use, seeking to improve their functioning in different domains (DeQuardo et al., 1994). The hypothesis has received little support, since it is well known that chronic substance consumption significantly reduces cognitive functioning. However, no clear relationship has been strongly established so far, since either improvements, impairments or no affectation on cognitive function have been related to drug use in different studies (Thoma et al., 2007; Mallet et al., 2017; Sánchez-Torres et al., 2013; Yücel et al., 2012).

As mentioned above, we cannot rule out that these results are influenced by the great heterogeneity observed in the samples used, regarding both psychiatric diagnoses of the SSD subjects and the characteristics assessed in the substances studied, since most of the works reviewed did not control for these factors. Two studies considered whether psychiatric diagnosis could account for the possible differences in premorbid functioning. One of them (Dixon et al., 1991) found that the differences in premorbid functioning disappeared when only the diagnosis of schizophrenia was considered, while the other one (Ringen et al., 2008) continued to observe them after controlling for the diagnosis. It is known that the analysis of premorbid factors yields different results depending on the psychiatric diagnosis (Chan et al., 2019; Mollon and Reichenberg, 2018; Parellada et al., 2017). Therefore, the diagnosis variable should be controlled for, and the samples should include a sufficient number of patients in order to carry out analyses among the different pathological conditions, in order to further elucidate the influence of diagnosis on premorbid functioning.

The same problem arises regarding the differences in the pattern of substance consumption, since there was great variability in the methods used to assess substance use. The studies differ in how comorbidity was established, whether it was according to SUD clinical diagnostic criteria (Benaiges et al., 2013; Carr et al., 2009; Compton et al., 2011; DeRosse et al., 2010; Dixon et al., 1991; Leeson et al., 2012; Rabinowitz et al., 1998; Ringen et al., 2013; Rodríguez-Sánchez et al., 2010) assessing frequency of consumption (Ferraro et al., 2013; Larsen et al., 2006; Sevy et al., 2001; Van Mastrigt et al., 2004; Weibell et al., 2019), or indicating only severity of consumption (Rabinowitz et al., 1998). In addition, there is also great diversity in how length of consumption periods was assessed, with studies that considered current use (Compton et al., 2011; DeRosse et al., 2010; Frascarelli et al., 2016; Ringen et al., 2013), others that recorded life-time use (Ferraro et al., 2013; Wade et al., 2005), and still others that controlled for abstinence, although with great variability in time periods (Coulston et al., 2007; DeRosse et al., 2010; Ferraro et al., 2013; Larsen et al., 2006). Likewise, the possibility that the type of substance used is contributing to possible differences was not explored in the majority of the studies. One study (Dixon et al., 1991) found differences in premorbid functioning for all the substances considered, while in other studies such effect was found only for cannabis use (Compton et al., 2011; Frascarelli et al., 2016; Ringen et al., 2013; Rodríguez-Sánchez et al., 2010). None of these studies, except for one (Compton et al., 2011), explored consumption of other substances, and this may be another confounding factor. Future studies on premorbid functioning should consider the factors related to substance use, since it is known that they can influence social and cognitive functioning, and they are also predictors of the clinical course of both the addictive and the psychiatric disorder (Bozzarello et al., 2019; Caton et al., 2006; Chan et al., 2019; Conus et al., 2017; Weibell et al., 2019).

It seems that SSD+ subjects have greater severity and worse prognosis, and this is sometimes related to a worse premorbid functioning (Carr et al., 2009; Leeson et al., 2012; Ringen et al., 2013; Rodríguez-Sánchez et al., 2010). However, this is not observed in all cases (Arndt et al., 1992; Coulston et al., 2007; Dixon et al., 1991; Rabinowitz et al., 1998; Salyers and Mueser, 2001; Sevy et al., 2001; Van Mastrigt et al., 2004; Wade et al., 2005). One fact that may underlie the presence or absence of such relationships is the lack of control over the type of patient treatment, such as the inclusion of hospitalized patients, who are usually the most severe ones. Similarly, it is also relevant to study how the relationship between substance use and premorbid functioning affects clinical course, since both factors, alone or combined, have been described as predictors of clinical prognosis, relapses, treatment resistance, and worse social and cognitive functioning in SSD patients (Bozzarello et al., 2019; Buonocore et al., 2018; Carra et al., 2016; Chan et al., 2019; Conus et al., 2017; Dewangan and Singh, 2018; Levine et al., 2010; Monte et al., 2008; Rannikko et al., 2015; Rebetz et al., 2014) and in CHR (Addington and Addington, 2008; Morcillo et al., 2015; Tharbox-Berry et al., 2018). Although factors such as treatment adherence (Caseiro et al., 2012) or other comorbid psychiatric disorders (Barrett et al., 2010; De Haan et al., 2013) may be contributing to the worse clinical course, it seems of great interest to further explore such relationship in future studies.

Furthermore, we should not dismiss the influence of age and sex on the existing premorbid functioning data, since both are closely related to psychiatric diagnoses and to substance consumption in patients with SSD+ (Adan et al., 2017; Hanlon et al., 2017; Thorup et al., 2007). Few of the studies reviewed analyzed the effect of these factors to account for potential differences in premorbid functioning, and their results showed no differences between men and women, nor any effect of age (Compton et al., 2011; Frascarelli et al., 2016; Ringen et al., 2008).

All the data reviewed suggest that premorbid functioning in SSD is

related with the characteristics of the clinical subgroups, and with complex overlapping multifactorial psychopathological processes. This makes it difficult to establish the causal effects, and therefore more longitudinal studies are needed on FEP, CHR and psychotic patients in order to confirm the role of premorbid functioning and substance use. Furthermore, the great variability in intervening factors suggests that, in order to carry out relevant clinical interventions, strategies should be adopted at all levels, ranging from prevention to more direct interventions, while considering at the same time the specific individual factors for each patient, in line with the new approach proposed by precision medicine (Szerman and Peris, 2019). In this regard, the consideration of premorbid functioning in SSD+ and SSD- individuals may be a key element that should be explored in future studies.

5. Conclusions

Although premorbid functioning has been well explored in SSD, its association with substance use is underexplored, with only 20 studies published in the past three decades directly addressing this relationship. It is possible that complex and overlapping multifactorial mechanisms underlying comorbidity, such as pattern of substance use, sociodemographic factors and psychiatric diagnosis, could difficult the direct comparison between groups. It is expected that, in future studies, these factors will be controlled, since they can be of great relevance when establishing the role of premorbid functioning in SSD +, as has been evidenced in the case of psychiatric diagnosis.

Premorbid functioning is a good predictor of clinical course in SSD+ and SSD- patients. In fact, studies that have used standardized tools to measure premorbid functioning, such as PAS, would indicate that the academic dimension would be worse in SSD+ patients than in SSD-, whereas the social dimension would be better in SSD+ than in SSD- subjects. Current available evidence makes it advisable to assess of premorbid functioning in the social and cognitive domains; including such evaluation in intervention protocols, especially for FEP and CHR patients. This inclusion would be of great relevance in clinical practice since the obtained data would benefit therapeutic interventions on SSD+ patients improving both the course of the disorder and their therapeutic response.

Declaration of Competing Interest

None.

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Further-reading

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