Appendix A, supplementary materials:

Systematic search:

**Search string PubMed:** ((schizophrenia[MeSH Terms]) OR (psychotic disorder[MeSH Terms])) AND ((longitudinal studies[MeSH Terms]) OR (long-term)) AND ((cognition[MeSH Terms]) OR (cognition disorders[MeSH Terms])) – **1076 hits**

**Search string Embase**: Schizophrenia.mp OR psychotic disorder.mp AND neurocognition.mp. OR cognition.mp OR cognitive decline.mp AND long-term.mp OR longitudinal stud\* limit to human **– 722 hits**

**Search string PsychInfo**: schizophrenia or psychosis or psychoses or psychotic disorder or schizophrenic disorder AND long-term or longitudinal AND cognition or cognitive function or neurocognition – **1220 hits**

We identified a total of 3018 papers, we deleted 710 duplicates and excluded 2018 based on title alone leaving 290. After reading abstracts we identified 55 papers reporting on longitudinal outcomes of cognition, and we identified 14 papers representing 9 studies that reported on variables associated to level of cognitive functioning after 10 – 25 years. Two studies reported clinical characteristics associated to cross-sectional neurocognitive outcome in first episode psychosis patients, six studies reported clinical characteristics associated to longitudinal changes in neurocognition in first episode patients, and one study reported clinical characteristics associated with changes in neurocognition of chronic schizophrenia patients with a mean age of 55 at study inclusion:

**eTable 1: List of baseline characteristics that have been investigated in association with long-term neurocognitive outcomes:**

|  |  |  |
| --- | --- | --- |
| **Baseline** | **No association** | **Association** |
| Clinical characteristics that have been examined in association with long-term neurocognition in First episode patients (over 10 years) | Age (2), sex, premorbid social functioning, DUP, use of antipsychotic medication1, education, premorbid adjustment, SAPS, SANS, employment, still living with parents, socioeconomic status, diagnosis, substance use, growing up with both parents, diagnosis, living alone, being in a relationship | sex2, DAT\* (duration of psychosis after treatment), premorbid academic functioning2, age at illness onset2, employment status2, early specialized intervention treatment2, finishing highshool2, level of education3\*\*\*\*  negative symptoms4 |
| Clinical characteristics that have been examined in association with change in long-term neurocognition in first episode patients (over 10 years) | Age, vocabulary, DUP(2), DAT education, premorbid adjustment, SAPS, SANS, employment, still living with parents, socioeconomic status, diagnosis, substance use, hospitalization, PANSS | Age5, DUI6\*\*\*, parents history of mental illness6, stable remission\*\*7, DAT\*\*\*\*\*8, Baseline neurocognition9, level of education10, baseline IQ10, age of illness onset10, schizophrenia diagnosis11,5, premorbid IQ12, Cannabis sessaition13\*\*\*\*\*\* symptom severity\*\*\*\*\*\*\*14, |
| Variables associated to change in chronic schizophrenia patients | Symptom levels, global functioning, social functioning, disease insight, substance use | Age1 |

\*Defined as the number of weeks per year with a score of four or higher on PANSS items: P1-delusions, P3-halluciantory behavior, P5-grandiosity, P6-suspiciousness or General scale item 9-unusual thought content. They grouped DAT into three groups of equal numbers of patients termed long, medium and short duration.

\*\*Stable remission in this study was defined as no relapse within the first year after admission

\*\*\* Significant only prior to Bonferroni correction

\*\*\*\* divided into low (up to 8 years) medium (8-12 years) and high (longer than 12 years), and subdivided age into low and high below or above 10 years)

\*\*\*\*\* They defined the three groups (short, medium and long) by dividing them into equal sizes

\*\*\*\*\*\* They used self-reported use of cannabis to divide participants into four groups based on patterns of use: Non-users patients who had never used, b) stop-users, c) episodic users, and d) persistent users. Patients who had only “no-use” measurements during the first 2 years of follow-up were defined as nonusers (NUs). Patients who had used at baseline and then not use for at least two consecutive measurements, i.e.  at 1 and 2 years of follow-up, were defined as stop-users (SUs). Persistent users (PUs) used at all follow-up points, and episodic users (EUs) had various other substance-use patterns.

\*\*\*\*\*\*\* They used SCAN to index symptom severity into 4 groups: 0=absent, 1=mild, 2=moderate, and 3=severe

Selection of predictors of neurocognitive change for our analysis

**Variables associated with poor long-term neurocognition were:**

1) male sex, 2) younger age at illness onset, 3) unemployment, 4) not finishing high-school 5) lower level of education and 6) premorbid academic functioning and 7) not receiving early specialised interventions. We combined not finishing high-school and lower level of education into one variable dividing patients into two groups with above or below 10 years of education.

**Variables associated with changes in neurocognition were**:

1. Age5, 2) Duration of untreated illness6, 3) parents history of mental illness6, 4) stable remission in the first year7, 5) duration of psychosis after treatment initiation8, 6) baseline neurocognition9, 7) level of education10, 8) baseline IQ10, 9) age at illness onset10, 10) a schizophrenia diagnosis11,5, 11) premorbid IQ12, 12) cannabis sessaition13, and 13) indexed symptom severity14.

To match the identified variables, we had to create new variables from our own data. To create a variable expressing symptom remission in the first year, we combined psychotic symptom assessments conducted every three months during the first two years of the OPUS trial. Because they were assessed using SAPS, they covered all three months between every assessment, allowing us to create a variable of continuous remission during the first year following diagnosis for all patients that did not exhibit significant psychotic symptoms following their first admission in the study. The study on cessation of cannabis use used cessation between baseline and the end of their study, which is when they conducted their cognitive tests. For this reason, we did not include baseline cannabis use in our analysis, but the pattern of use during the 10-and 20-year follow-up, which is when we conducted our cognitive testing. Unfortunately, our sample was too small to examine strict cessation of cannabis use, as this only occurred in 4 patients. eTable 2 shows the distribution of patterns of substance use between the 10- and 20-year follow-up. Instead, we have chosen overall substance and alcohol abuse diagnosed using SCAN as a variable in this study.

eTable 2: Patterns of substance use between the 10- and 20-year follow-up, Appendix 1:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No use** | **Continued use** | **Started use** | **Stopped use** |
| Overall alcohol or substance use | 115 (75.2%) | 23 (15%) | 8 (5.2%) | 7 (4.6%) |
| Alcohol use | 132 (86.3%) | 9 (5.9%) | 5 (3.3%) | 7 (4.6%) |
| Cannabis use | 138 (90.2%) | 8 (5.2%) | 3 (2.0%) | 4 (2.6%) |
| Other groups (opioids, cocaine, mixed) | 146 (95.4%) | 1 (0.7%) | 5 (3.3%) | 1 (0.7%) |

We did not have information on parents history of mental illness6, duration of psychosis after treatment initiation8, baseline neurocognition9 and baseline IQ (except it had to be over 70 for inclusion in the study). We also did not have information un duration of untreated illness an chose to use duration of untreated psychosis instead. Because of collinearity between indexed symptom severity and the symptom remission categorical variable we only included stable remission in our analysis, and because of collinearity of premorbid academic functioning and premorbid IQ, we chose only to include premorbid academic functioning in our analysis, as we had more data on this variable.

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