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Systematic review and meta-analysis on predictors of prognosis in patients with schizophrenia spectrum disorders: An overview of current evidence and a call for prospective research and open access to datasets

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ABSTRACT

Background: Schizophrenia spectrum disorders (SSD) have heterogeneous outcomes. If we could predict individual outcome and identify predictors of outcome, we could personalize and optimize treatment and care. Recent research showed that recovery rates tend to stabilize early in the course of disease. Short- to medium-term treatment goals are most relevant for clinical practice.

Methods: We performed a systematic review and meta-analysis to identify predictors of outcome ≤1 year in prospective studies of patients with SSD. For our meta-analysis risk of bias was assessed with the QUIPS tool.

Results: 178 studies were included for analysis. Our systematic review and meta-analysis showed that the chance of symptomatic remission was lower in males, and in patients with longer duration of untreated psychosis, more symptoms, worse global functioning, more previous hospital admissions and worse treatment adherence. The chance of readmission was higher for patients with more previous admissions. The chance of functional improvement was lower in patients with worse functioning at baseline. For other proposed predictors of outcome, like age at onset and depressive symptoms, limited to no evidence was found.

Discussion: This study illuminates predictors of outcome of SSD. Level of functioning at baseline was the best predictor of all investigated outcomes. Furthermore, we found no evidence for many predictors proposed in original research. Possible reasons for this include the lack of prospective research, between-study heterogeneity and incomplete reporting. We therefore recommend open access to datasets and analysis scripts, enabling other researchers to reanalyze and pool the data.

1. Introduction

Psychotic disorders have heterogeneous outcomes, some patients make a full recovery while others continue to experience severe symptoms and impairment. However, currently we are unable to predict the outcome for individual patients. If we could predict individual outcome and identify (modifiable) predictors of psychosis, we could personalize and optimize treatment and care.

Symptomatic remission, functional improvement and personal recovery are seen as different outcomes for schizophrenia spectrum disorders. Symptomatic remission is defined as an absent to mild symptom intensity level, where these symptoms do not influence an individual's behavior (Andreasen et al., 2005). Schizophrenia spectrum disorders are often accompanied by impairment on various aspects of individual, social and societal functioning. Although the importance of functional recovery has been acknowledged by patients, their loved ones and healthcare professionals for many years, there is no consensus about criteria for functional recovery (Lahera et al., 2018). Personal recovery is about having a personally meaningful and contributory life and identities that are beyond patienthood (Chan et al., 2018). It represents a process rather than an outcome, containing elements of connectedness, hope and optimism, identity, meaning and empowerment (van Weeghel et al., 2019).

How and to what extent symptomatic remission, functional improvement and personal recovery are related to each other is still a subject for research. Symptomatic remission is associated with a higher level of functioning, but is no guarantee of an adequate level of function or quality of life (Lambert et al., 2010). In a study examining individuals who achieved both symptomatic and functional recovery, 25 % of those individuals did not achieve adequate personal recovery (Lambert et al.,

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2006). On the other hand, criteria for either symptomatic or functional recovery were not met in 8 % of individuals who reported adequate personal recovery (Lambert et al., 2006).

For personal recovery, there is only a small to moderate negative correlation with symptom severity and a small to moderate correlation with functional recovery (Van Eck et al., 2018). The small correlations between different outcome domains support separate predictor analysis for each outcome.

Many studies have attempted to identify predictors of outcome in schizophrenia spectrum disorders.

The following predictors of symptomatic remission have been identified by a review of Lambert et al. (2010): better premorbid adjustment, better functioning at baseline, lower psychopathology or illness severity at baseline, shorter duration of untreated psychosis (DUP), early improvement in symptoms and functioning during treatment and medication adherence (Lambert et al., 2010) As possible predictors of symptomatic remission female gender and no substance abuse at baseline were identified (Lambert et al., 2010).

For symptomatic relapse, a systematic review and meta-analysis by Alvarez-Jimenez et al. (2012) showed a 2–4 fold increase in relapse rate in patients with poorer premorbid adjustment, medication non-adherence, persistent substance use disorder and a family environment with high expressed emotion (Alvarez-Jimenez et al., 2012). Relapse rates were hardly influenced by clinical and demographic variables (Alvarez-Jimenez et al., 2012). Prior hospitalization was one of the strongest predictors of future hospitalization (Chi et al., 2016).

For functional improvement, a systematic review and meta-analysis by Santesteban-Echarri et al. (2017) showed that better functioning over time was predicted by shorter DUP, shorter duration of untreated illness, better cognitive function and less positive and negative symptoms (Santesteban-Echarri et al., 2017). Functional outcome was hardly influenced by general sociodemographic, clinical and physical variables (Santesteban-Echarri et al., 2017).

However, there is increasing evidence that for the various domains of functional improvement, the strength of the associated variables differs. For example, cognitive function appears to be an important predictor of independent living and vocational functioning. Nevertheless, cognition is not an important predictor of social functioning defined as interpersonal functioning (e.g. initiating, accepting and maintaining social contacts, effectively communicating) (Strassnig et al., 2015), while negative symptoms are (Kalin et al., 2015). For personal recovery, predictors are self-esteem, hope, negative symptoms and affective symptoms (Best et al., 2020; Law et al., 2014).

The previously identified predictors should be interpreted with care because the study designs and results differ significantly. Some studies investigated the same outcome, but investigated different predictors or choose different durations of follow-up. Some studies found different strengths of the association between predictors and outcomes and other studies even reported contradictory directions of the association between predictors and outcomes. Finally, various studies examined cross-sectional data.

In order to obtain more consistent results for predictors of outcome in schizophrenia spectrum disorders and to minimize the risk of recall bias, this review included only studies with a prospective study design. We focused on a duration of follow-up up to one year because a recent meta-analysis on long-term outcome showed that recovery rates tend to stabilize early in the course of disease suggesting that the poor outcome trajectory is already apparent during the early stages of illness, and because short- to medium term treatment goals are most relevant for clinical practice (Lally et al., 2017). Because previous literature showed different predictors for different outcomes, we predefined the most important and best defined outcomes of psychotic disorders (symptomatic remission, symptomatic relapse, functional recovery and personal recovery) and reviewed all possible predictors for each of these outcomes. Meta-analyses on predictors of outcomes performed when enough data is available, otherwise the association is investigated by frequency counts.

This systematic review and meta-analysis will provide an up-to-date overview of all available evidence from prospective research on predictors of predefined outcome measures of psychotic disorders.

2. Methods

2.1. Protocol and registration

The study was registered with PROSPERO (CRD42020162331) and conducted in accordance with PRISMA guidelines (Supplement 1 Checklist).

2.2. Data sources and study selection process

2.2.1. Search

We searched the PubMed, Embase, Cochrane and PsycINFO databases with the search terms ‘psychotic disorders’, ‘predictor’ and ‘outcome’ and their synonyms, to identify relevant literature from their interception dates to September 23, 2022 (Supplement 2 Search strategy).

2.2.2. Inclusion and exclusion criteria

We included studies that prospectively investigated a possible predictor of any outcome for psychotic disorders. We excluded case reports and case series with 20 or fewer included patients because of high risks of selection and publication bias, reduced chance of finding a true effect and reduced likelihood that a significant result reflects a true effect (Button et al., 2013). We included only studies where at least 75 % of patients had a primary psychotic disorder (schizophreniform, schizoaffective, schizophrenia disorders, otherwise specified schizophrenia spectrum disorders and not otherwise specified schizophrenia spectrum disorders), because of presumptive evidence for differences in prognosis between disorders with psychotic symptoms. We excluded studies with a mean duration of follow-up $\geq$14 months. We did not investigate treatment interventions as predictors of outcome because systematic reviews and meta-analysis on these topics are already available (Leucht et al., 2013; Roder et al., 2011).

2.2.3. Study selection

We reviewed all search results by applying the inclusion and exclusion criteria (Fig. 1). For the primary search performed on July 2019, one author (VvD) screened all the abstracts and selected the relevant studies. Any doubts about the article selection were resolved in consensus meetings with the three authors. In September 2022 a search update was performed. To increase efficiency and quality of screening we used the open-source active-learning tool ASReview (https://asreview.nl/, version 1.03) for priority screening. We provided ASReview with the studies (n = 11,377) labeled relevant and irrelevant from the original search as training data. Using these training data, ASReview learned to prioritize the yielded records of our search update automatically. ASReview presents the record that the machine deems most likely to be relevant first. One author (VvD) indicated whether the presented paper was relevant or irrelevant, and the algorithm used this information to retrain. In this way the machine kept learning from every new input. Again, any doubts about the article selection were resolved in consensus meetings with the three authors. At some point an active learning process mostly irrelevant research remains. We used a combination of two predetermined stopping criterions to decide when to stop the screening process. The first was based on the results of our primary search, and used the observed fraction of relevant papers to extrapolate an estimate of relevant papers for the complete set (15,101 papers in complete set * (473 / (10,904 irrelevant papers primary search + 473 relevant papers primary search) = 628 estimated relevant papers) (van Haastrecht et al., 2021). Second, to avoid screening too many irrelevant papers in case this calculation resulted in a gross overestimation of

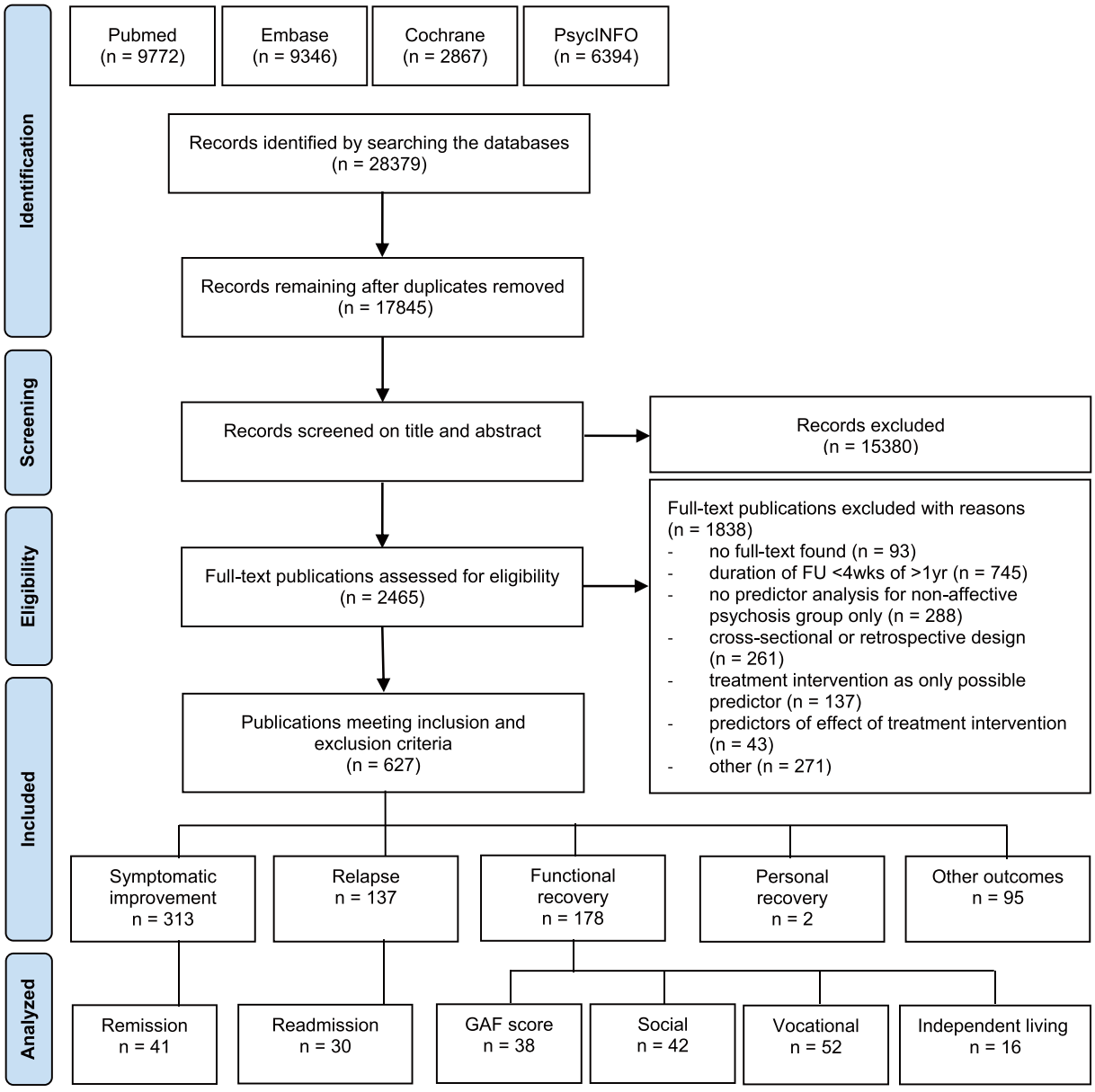

Fig. 1. Study attrition diagram.

relevant papers, we predetermined to stop screening when 300 consecutive reviewed papers were considered irrelevant. We chose 300 as a safe choice, whereas in literature often 50 or 100 is used (Ros et al., 2017).

2.2.4. Assessment of outcome

From the literature we identified four categories of outcome: symptomatic remission, relapse, functional improvement and personal recovery.

We defined symptomatic remission according to the consensus criteria of the Remission in Schizophrenia Working Group (RSWG) (Andreasen et al., 2005). The RSWG consensus criteria consist of symptom criteria and a time criterion of sustained remission during 6 months. Besides studies using the RSWG consensus criteria in total, we also included studies using only the symptom criteria but not the time criterion of sustained remission during 6 months, because many studies had a duration of follow-up of less than six months.

We defined relapse as (re)admission to a psychiatric hospital because this definition is most commonly used and consensus on other relapse criteria is lacking (Gleeson et al., 2010).

As an outcome measure for global functional improvement we used the Global Assessment of Functioning (GAF) scale. We included studies using the traditional GAF scale, as well as studies using the Global Assessment Scale (GAS) (Endicott et al., 1976), Children's Global Assessment of Functioning Scale (cGAS) (Shaffer et al., 1983) or the Modified Global Assessment of Functioning Scale (mGAF) (Hall, 1995). For further analysis, we subdivided functional outcome into vocational outcome, social outcome and independent living, as proposed and executed in previous literature (Harvey, 2013). Because there is no consensus on the definition of functional recovery and on what tool should be used to assess functional recovery all definitions and outcome assessment tools for functional recovery as reported by the included studies were used in our analysis.

Personal recovery is subjective by definition. There is no consensus on the definition of personal recovery and on which instruments should be used to measure it. Therefore, all definitions and outcome assessment tools for personal recovery as reported by the included studies were used in our analysis.

2.2.5. Assessment of possible predictor variables

We analyzed all variables investigated as predictors in the included articles. Only variables investigated twice or more in relation to an investigated outcome measure are reported. Variables measured only ones in relation to an investigated outcome are listed in Supplement 10.

For some possible predictors of prognosis, there is no consensus on definition and/or type of measurement. For example, there are various operational criteria to define 'first episode psychosis' and 'duration of illness' (Breitborde et al., 2009; Murru and Carpiniello, 2018). To create a complete overview of all available information regarding the relation between a predictor and a domain of outcome, for data extraction for this review and meta-analysis we used the definition as applied by the authors of the included studies.

2.3. Quality of evidence

We assessed the quality of the studies used in our meta-analysis with the QUIPS (quality in prognostic factor studies) checklist (Hayden et al., 2006; Riley et al., 2019). The QUIPS checklist covers six areas of potential study bias: study participation; study attrition; prognostic factor measurement; outcome measurement; confounding measurement and account and analysis. For our meta-analysis we extracted raw baseline and outcome data, and therefore risk of bias concerning confounding and analysis in the original study was deemed not relevant for the quality of our evidence. Quality assessment was performed by one author (VvD).

2.4. Data extraction

We created a standardized data extraction form containing 45 fields (Supplement 3 Data extraction form). The extracted data consist of general study information, characteristics of study population, methodological characteristics and results on the associations between investigated variables and outcome measures. The most frequently investigated variables (23 selected variables after data-extraction of the first 20 studies) were implemented in the form, other associations were reported in the fields 'other significant predictors' and 'other non-significant predictors'. All available information on the association between variable and outcome was extracted: (i) the effect size of the association, (ii) the direction, (iii) the statistical significance.

Extraction of raw data from all studies was performed by one author (VvD). When the author was uncertain about the interpretation of the results a second author (HS) was consulted. In consensus meetings, we settled minor differences in judgement. Data extraction of the articles selected for our meta-analysis was checked by a second author (HS). There were, apart from typing errors, no differences in judgement. Because of the few minor typing errors in data-extraction of the articles selected for meta-analysis by the check of the second author, data-extraction for the systematic review has been double checked by the first author.

2.5. Data analysis

2.5.1. Meta-analysis

For our meta-analysis we calculated the effect size from the original data. The associations between a specific variable and outcome were investigated by meta-analysis when at least 5 included studies provided enough data to calculate the effect size. Unfortunately, sufficient information to do so was only available for the outcome measure 'symptomatic remission' defined by RSWG consensus criteria and some variables. For the other outcomes and variables heterogeneous definitions were used or original data were not available.

For the study results with available effect sizes a pooled effect size was calculated using a random effect model. For dichotomous outcomes we reported odds ratios and for continuous outcomes Cohens *d*'s. We performed subanalyses for studies reporting on first episode psychosis (FEP) patients only, and for studies reporting on mixed FEP/non FEP patients. We used R version 4.0.3 (2020-10-10), library 'meta' package (version 4.18-0); scripts available at https://github.com/patterns-in-psychiatry/Systematic-Review-and-Meta-analysis-psychosis-prognosis-predictor.

2.5.2. Systematic review

For our systematic review on symptomatic remission, relapse and functional improvement we report frequency counts based on the direction of effects for the relationship between investigated variables and outcome measures. Our search yielded only 2 studies about predictors of personal recovery in people with schizophrenia spectrum disorders, both measuring a different aspect of personal recovery as outcome (Chan et al., 2018; Dubreucq et al., 2022). Therefore we were not able to analyze predictors of personal recovery in this systematic review.

Results from all statistical methods used in the included studies were considered as equally important for this review. First, we divided associations for each article into significant positive or negative associations ($p < 0.05$), non-significant associations ($p \geq 0.05$) and inconclusive results. We considered an association inconclusive when various ways of measurement of the variable or various statistical methods mentioned in the original article yielded conflicting results regarding the association. We also considered an association inconclusive when articles using the same dataset reported conflicting results regarding the association.

Second, we counted for each variable-outcome combination how many articles reported a significant positive (assigned a score of $+1$) or negative (-1) association, a non-significant association (0) or an inconclusive result ($+0.5$ or -0.5 depending on the direction of the effect). The sum-score divided by the total number of articles yielded a score between -1 and 1 which was used to determine the direction and robustness of the association. Association scores ≤ -0.5 or ≥ 0.5 were labeled as strong negative or positive associations, respectively. An association score ≤ -0.33 but > -0.5 was labeled as a negative association, and an association score ≥ 0.33 but < 0.5 as a positive association. Association scores > -0.33 but < 0.33 were labeled as non-significant (ns).

2.5.3. Overlapping datasets

When articles with overlapping patient populations reported on the same variable and outcome, we used the results of the article with the largest study population and/or longest duration of follow-up for our analysis.

3. Results

The literature search yielded 28,379 studies, of which 17,845 remained after we removed duplicates. After screening the title and abstract on inclusion and exclusion criteria 2465 studies remained of which 627 studies remained after screening on full-text.

For this review we only analyzed the results of studies that reported on at least one of the predetermined outcomes of interest. Of the 627 selected studies, 178 studies met this criterion. Of these 178 studies, 42 reported on symptomatic remission according to the criteria of the RSWG (Andreasen et al., 2005), 29 on readmission, 38 on global functioning measured by GAF scale, 42 on social functioning, 53 on vocational functioning, 16 on independent living and 2 on personal recovery. As mentioned before we were not able to analyze predictors of personal recovery, because our search yielded only 2 studies measuring different aspects of personal recovery. In the Supplementary material we present the references of the 178 articles (Supplement 4 References studies for analysis), their characteristics (Supplement 5 Characteristics studies for analysis) and the characteristics of these studies per outcome domain (Supplement 6 Characteristics studies per outcome domain).

3.1. Predictors of symptomatic remission by meta-analysis

In the 48 studies on symptomatic remission, we searched for studies that provided enough data on the association between a variable and symptomatic remission to calculate and compare effect sizes. This data was available for 13 variables. For these 13 variables we pooled study results in a random effects model and determined the direction and strength of the associations. Pooled effect sizes with subanalysis for FEP are displayed in Table 1. Forest plots for the association between each variable and symptomatic remission are presented in Supplement 7. Male sex, longer duration of untreated psychosis, higher symptom scores and worse global functioning at baseline were all significantly associated with lower chances on symptomatic remission at follow-up. Results are presented in Table 1. When analyzing studies including FEP patients only the association between positive symptoms and CGI-S scores at baseline with symptomatic remission were not significant anymore.

The quality of evidence of the 30 studies that provided enough information on one or more of the selected variables for meta-analysis was evaluated by the QUIPS tool (Supplement 8 QUIPS-tool). Many articles (67 %) lacked an adequate report of the sample recruitment which is a risk factor for selection bias. Information about participants lost to follow-up was often incomplete (58 %) which is a risk factor for attrition bias. The description of measurements of possible predictors and outcome was in most studies concise but sufficient.

3.2. Predictors of outcome by frequency counts

An overview of the results of frequency counts for each domain is presented in Table 2. More detailed information about the frequency counts for each domain is presented in Supplement 9.

3.2.1. Predictors of symptomatic remission

We analyzed the results of 48 studies reporting on 10,291 patients, that investigated possible predictors of symptomatic remission according to the RSWG criteria (Andreasen et al., 2005). These 48 studies reported on 42 unique datasets (39 studies used unique datasets, 4 studies used one dataset, 3 studies used a second dataset and 2 studies used a third dataset).

Higher chances on symptomatic remission were strongly predicted by history of childhood trauma, less comorbidity, shorter DUP, better premorbid adjustment, living independently, better global functioning, having a first episode psychosis, being in symptomatic remission at baseline, less symptoms, better insight and lower CGI-severity score..

3.2.2. Predictors of relapse defined as (re)admission

We analyzed the results of 29 studies reporting on 10,289 patients. A single study reported results of analysis on 2 separate study populations, which are considered as 2 studies for this review.

Higher chances on readmission were strongly predicted by more previous hospitalizations, worse treatment adherence and more depressive symptoms at baseline.

3.2.3. Predictors of functional improvement

3.2.3.1. Functional improvement: global functioning measured by GAF scale. We analyzed the results of 40 studies, reporting on 5074 patients. The 40 studies reported on 38 unique datasets (2 studies reported on one dataset and 2 other studies on another dataset). A higher GAF score was strongly predicted by non-white/non-native ethnicity, better premorbid adjustment, a higher GAF score, worse neurocognitive functioning and better treatment adherence at baseline.

3.2.3.2. Functional improvement: social functioning. We analyzed the results of 42 studies, reporting on 4562 patients. Better social functioning was strongly predicted by a shorter duration of first hospitalization, better premorbid adjustment, better social functioning, independent living, less general symptoms, better insight and better perception of emotions at baseline.

3.2.3.3. Functional improvement: vocational outcome. We analyzed the results of 53 studies, reporting on 6851 patients. These 53 studies reported on 51 unique datasets (3 studies used the same dataset). From these studies, 20 investigated having work or studying at or during follow-up as a dichotomous outcome, while 31 other studies investigated vocational functioning as a categorical or continuous outcome. Better vocational functioning was strongly predicted by total months of

Table 1
Associations between predictor variables and symptomatic remission according to RSWG.

Variable	All studies				FEP only			
	Studies, n	Patients, n	Effect size[a] [95 % CI]		Studies, n	Patients, n	Effect size[a] [95 % CI]	
			OR				OR	
Sex (male)	26	4095	**0.73**	**[0.64; 0.84]**	14	1685	**0.71**	**[0.58; 0.89]**

Variable	All studies				FEP only			
	Studies, n	Patients, n	Effect size[a] [95 % CI]		Studies, n	Patients, n	Effect size[a] [95 % CI]	
			Cohen's D				Cohen's D	
Age	26	4019	−0.05	[−0.16; 0.06]	14	1787	0.05	[−0.13;0,22]
Duration of illness	8	697	−0.27	[−0.53; 0.00]	1	45	−0.04	[−0.63; 0.55]
Age at onset	10	1663	0.11	[−0.03; 0.26]	5	731	0.19	[−0.01; 0.40]
DUP	5	748	**−0.30**	**[−0.55; −0.04]**	5	748	**−0.30**	**[−0.55; −0.04]**
Years of education	8	654	0.09	[−0.20; 0.38]	6	514	0.09	[−0.27; 0.45]
Depressive symptoms	8	1192	−0.16	[−0.35; 0.03]	5	1034	−0.18	[−0.43; 0.07]
Positive symptoms	24	3084	**−0.28**	**[−0.44; −0.13]**	15	1724	−0.15	[−0.33; 0.03]
Negative symptoms	24	3084	**−0.56**	**[−0.69; −0.44]**	15	1724	**−0.50**	**[−0.64; −0.36]**
General symptoms	14	2145	**−0.43**	**[−0.66; −0.20]**	10	1500	**−0.42**	**[−0.71; −0.13]**
Total symptoms	14	2103	**−0.43**	**[−0.62; −0.23]**	8	1278	**−0.34**	**[−0.57; −0.11]**
CGI-S	6	1542	**−0.37**	**[−0.57; −0.17]**	1	111	−0.18	[−0.56; 0.20]
GAF	6	1017	**0.53**	**[0.28; 0.78]**	2	366	**0.28**	**[0.07; 0.49]**

Abbreviations: DUP = duration of untreated psychosis, CGI-S = clinical global impression – severity scale, GAF = global assessment of functioning scale.

[a] Effect sizes are odd ratio's for binary outcome variables and Cohen's D for continues. For variables that are significantly associated with symptomatic remission according to RSWG effect sizes are displayed in bold.

Table 2
Predictors of frequency counts.

Variable	Symptomatic remission	Relapse	Functional improvement: global (GAF)	Functional improvement: social	Functional improvement: vocational	Functional improvement: independent living
Sex (male)	ns	ns	ns	ns	ns	ns
Age	ns	ns	ns	ns	ns	ns
Ethnicity/race (white or native)	ns	ns	▼▼	ns	ns	
Positive family history for mental illness	ns					
History of childhood trauma	▼▼					
Medical history						
Concomitant (somatic and/or psychiatric) diseases	▼▼					
Age first psychosis	ns	ns	ns		▲	ns
Age at start first antipsychotic treatment	ns					
Age at first hospitalization				ns		
Duration of illness	ns	▲		ns	ns	▼
Duration of untreated psychosis	▼▼	▲	ns	▼	ns	ns
Number of previous hospitalizations	▼	▲▲		ns	ns	
Duration of first hospitalization				▼▼		
Duration of last hospitalization		ns				
Total months of hospitalization					▼▼	
Functioning						
Better premorbid adjustment	▲▲	ns	▲▲	▲▲	ns	
Having friends	ns					
Having a partner/being married (y/n)	ns	ns	ns	ns	ns	
Social functioning at baseline				▲▲		
Household emotional expression/ disturbed family interaction		▲		▼	▼	
Independent living (y/n)	▲▲	ns		▲▲	▲	▲▲
Parental level of education					ns	
Higher IQ	ns	ns	ns		ns	
Years education	ns	ns	ns	ns	ns	ns
Working/studying (y/n)	ns	▼		▲	▲▲	▲▲
Motivation for work					▲▲	
Preceding stressors	ns					
Global Assessment of Functioning (GAF) score	▲	▼	▲▲	ns	ns	
GAF lowest previous year	▲▲					
Social and Occupational Functioning Assessment Scale (SOFAS)	▲▲					
Disability Assessment Schedule (DAS)	ns					
Quality of Life scale	▲					
Current medical situation						
Substance abuse	ns	▲		ns	ns	
BMI	ns					
First episode psychosis (y/n)	▲▲					
Hospitalization (y/n)	ns					
Clinical Global Impression Scale-Severity (CGI-S)	▼▼					
Subjective Well-being under Neuroleptics Scale (SWN)	▲▲					
Treatment adherence	▲	▼▼	▲▲	ns		
Symptoms						
Negative symptoms	▼▼	▲	ns	ns	ns	▼▼
Positive symptoms	▼	ns	ns	ns	ns	ns
General symptoms	▼			▼▼	ns	
Total symptoms	▼▼	ns	ns		▼▼	
Depressive symptoms	ns	▲▲		ns	ns	ns
Symptomatic remission at baseline	▲▲					
PANSS excitement dimension	ns					
PANSS disorganized dimension	▼▼					
PANSS cognitive dimension	▼					
Insight	▲▲	ns	ns	▲▲		
Diagnosis (schizophrenia vs other)	▼				ns	
Schizophrenia subtype (paranoid vs other)	▲					
Neurocognitive functioning						
Verbal learning and memory	ns			ns	ns	ns

(*continued on next page*)

Table 2 (*continued*)

Variable	Symptomatic remission	Relapse	Functional improvement: global (GAF)	Functional improvement: social	Functional improvement: vocational	Functional improvement: independent living
Attention	▲			▲	▲▲	▲▲
Processing speed	▲			▲	ns	▲▲
Working memory/executive functioning	ns		ns	▲	▲	ns
Abstract reasoning					▲▲	▲▲
Composite score	ns		▼▼	ns	▲	▲▲
Verbal fluency	ns					
Social cognition				ns		▲▲
Perception of emotions				▲▲		
Self-stigma					▼▼	

▲(▲) presence or higher score on variable is (strongly) associated with higher chance on outcome. ▼(▼) presence or higher score on variable is (strongly) associated with lower chance on outcome. NS = not significant: ≥67 % of analyzed studies showed no significant association between variable and outcome. Empty cell: association between variable and outcome is ≤1 times investigated in included studies. Only variables investigated in relation to >1 outcome are displayed here.

hospitalization, working/studying and motivation for work, total symptom scores, better neurocognitive functioning (attention and abstract reasoning) and less self-stigma at baseline.

3.2.3.4. Functional improvement: independent living. We analyzed the results of 16 studies reporting on 1991 patients. These 16 studies reported on 14 unique datasets (12 studies used unique datasets, 2 studies used one dataset and 2 other studies used another dataset). Better independent living was strongly predicted by independent living, working/studying, less negative symptoms and better neurocognitive functioning (attention, processing speed, abstract reasoning and composite score) and better social cognition at baseline.

4. Discussion

This current meta-analysis and review studied comprehensively examined predictors of up to one year outcome of patients with schizophrenia spectrum disorders. In our meta-analyses we included 48 studies and analyzed 13 variables as possible predictors of symptomatic remission. In our systematic review we analyzed predictors of symptomatic remission (48 studies, 10,291 patients), relapse (29 studies, 10,289 patients), global functioning (40 studies, 5074 patients), social functioning (42 studies, 4562 patients), vocational outcome (53 studies, 6851 patients). We were able to include more studies reporting on many more patients than previously published systematic reviews and meta-analysis about these topics, even though we restricted our inclusion criteria to studies with a prospective study design in order to obtain more consistent results. This meta-analysis and review provides an up-to-date overview of all available evidence from prospective research on predictors of predefined outcome measures of psychotic disorders.

For all investigated outcomes, level of functioning at baseline was the best predictor of outcome. We did not find evidence for many other frequently investigated and proposed predictors of outcome in original research.

4.1. Results of meta-analysis on predictors of symptomatic remission

Our prospective meta-analysis showed that symptomatic remission was predicted by female sex, shorter DUP, less symptoms (positive-, negative-, general- and total symptoms and lower CGI-severity score) and higher GAF-score at baseline. To our knowledge our study is the first meta-analysis on short- to medium- term predictors of symptomatic remission. The results of our meta-analysis are in line with the results of a smaller review without meta-analysis by Lambert et al. (2010), examining 12 prospective studies with a follow-up duration of 12–36 months (Lambert et al., 2010). In addition to our findings, that study identified early symptomatic and functional improvement and lack of substance abuse or remitted substance use at baseline as predictors of symptomatic remission. We were unable to examine early improvement as predictor due to insufficient data.

4.2. Results of systematic review

4.2.1. Symptomatic remission

Our systematic review showed that symptomatic remission was strongly predicted by history of childhood trauma, less comorbidity, shorter DUP, higher level of functioning, first episode psychosis, less severe symptoms and less previous admissions at baseline.

In contrast to results of the meta-analysis by Lambert et al., we found no significant association between substance abuse at baseline and symptomatic remission. A possible explanation might be the differences in follow-up period and in- and outpatient ratio.

4.2.2. Relapse defined as readmission

Our study showed that readmission was most strongly predicted by a higher number of previous hospitalizations, more depressive symptoms and worse treatment adherence at baseline. These findings are consistent with previous research (Chi et al., 2016; Li et al., 2020; Wunderink et al., 2020).

4.2.3. Functional improvement

Our study showed that global functioning by GAF scale was strongly predicted by non-white/non-native ethnicity, better premorbid adjustment, higher GAF score, worse neurocognitive functioning and better treatment adherence at baseline. These findings are in line with a previous systematic review and meta-analysis on prospective predictors of functional improvement (measured by GAF, SOFAS and GAS) (Santesteban-Echarri et al., 2017). While Santesteban Echarri et al. also identified female sex, education and positive and negative symptoms as predictors of global functioning, these variables could not be confirmed as predictors based on our results. This might be explained by differences in study population as Santesteban-Echarri et al. (2017) focused on predictors of long-term prognosis (up to 12 years) in patients with first episode psychosis including affective and non-affective disease. Contrary to the conclusion of the meta-analysis of Immonen et al. we found no evidence for age at onset as a predictor of improvement in global and social functioning (Immonen et al., 2017).

Our study shows that recovery on the subdomains of functional improvement (social functioning, vocational functioning and independent living), is most strongly predicted by the level of functioning in general and in that specific subdomain at baseline. In addition, better social functioning was strongly predicted by shorter duration of first hospitalization, better premorbid adjustment, better insight into illness and lower general symptom scores. The association between negative symptoms and social functioning as found by previous research could not be confirmed by our results (Kalin 2015). Vocational functioning was also strongly predicted by total months of hospitalization, total symptom scores, better neurocognitive function and less self-stigma at

baseline. Independent living was also strongly predicted by less negative symptoms, better neurocognitive functioning and better social cognition at baseline.

4.3. Research gaps

Our research identified several research gaps. First, only a limited number of studies for each outcome met inclusion criteria, despite our broad literature search. We were not able to investigate predictors of personal recovery at all because of lack of available studies that met inclusion criteria on this topic. Second, the selected studies are heterogeneous in study design, study populations, statistical methods used and definition and measurement of predictors and outcome, which limited the possibilities to pool and compare the data. Third, raw data and original test statistics were often unavailable, therefore many predictors of outcome could only be investigated by frequency counts. Fourth, several groups of variables, including genetics, blood-derived variables and neuroimaging, are extensively investigated in relation to outcome of schizophrenia spectrum disorders, but could not be analyzed because most studies were not prospective and/or highly heterogeneous with respect to investigated predictors criteria. Fifth, the classical analysis methods used in the included studies may not be optimal to predict prognosis. It is, for example, unclear which of the predictors identified by these analyses could be combined to improve predictive power, and how this should be done. In addition, it is unclear whether the group-level differences found with these analyses can be used to generate predictions for individuals (Koutsouleris et al., 2016).

4.4. Clinical implications

We conclude that level of functioning at baseline is the most important predictor for each investigated outcome. Therefore, to improve prognosis we should focus on prevention, early detection and intervention to prevent or minimize functional decline. A lack of early treatment in psychosis yields a longer DUP which is an independent predictor for prognosis (Howes et al., 2021).

Traditionally, psychiatry provides reactive healthcare. A patient comes to psychiatric services when the condition is already (sub) chronical and often is marked by comorbidity, complications and impaired levels of functioning. These are all predictors for less effect of treatment and poorer outcome.

To improve outcome in the asymptomatic risk phase, focus should be on the modifiable factors that are related to the development of psychosis, such as harmful parenting styles (Oldehinkel et al., 2006; Thijssen et al., 2017), cannabis use (Di Forti et al., 2019) and trauma (Cunningham et al., 2016; Sallis et al., 2020). Public health interventions are important to decrease the risk of development of psychotic disorders in this stage (Kahn et al., 2015). A second opportunity to prevent psychosis is by detecting and intervening in the prodromal phase, characterized by a decline in cognitive and social functioning, which often precedes the onset of psychotic symptoms by >10 years. A more specific part of the prodromal phase is the Clinical High Risk for Psychosis (CHR-P) state, characterized by psychotic symptoms and/or a family history of psychosis (Fusar-Poli et al., 2020; Bosnjak Kuharic et al., 2019). The CHR-P state is a potent predictor of development of psychosis. A meta-analysis showed a conversion rate to psychosis of 22 % by 1 year and 36 % in 3 years (Fusar-Poli et al., 2012). Interventions to prevent or delay transition to psychosis in CHR-P individuals, such as cognitive behavioral therapy and omega-3 fatty acids, are promising (Bosnjak Kuharic et al., 2019). Even if interventions could only postpone psychosis by a few years, this extra time would enable young adults to finish their education and acquire life skills improving their overall prognosis (Kahn et al., 2015).

Once a psychotic episode has manifested, prognosis might be improved by treatment by early intervention services specifically designed to meet the needs of patients with early-phase psychosis (Correll et al., 2018).

Still, often it is not possible to prevent psychosis or predict the individual prognosis of a patient once psychosis has manifested. Moreover, it is unclear which treatment works for who. With machine learning techniques the predictors identified in the current study may be used to build a tool to predict short- to medium-term prognosis of psychotic illness. Such a prediction tool available for both patient and caregiver provides insight in (modifiable) predictors of psychosis and makes it possible to personalize and optimize treatment and care. This will support shared decision making.

Machine learning techniques may be more suitable to detect (sets of) predictors of outcome, because of (i) their multivariate nature and ability to learn nonlinear relationships and interactions between variables, (ii) the inherent (cross)validation design, and (iii) the possibility to generate individual predictions. However, simply applying complex statistical methods does not guarantee better results (Salazar de Pablo et al., 2021). The use of machine learning techniques requires a large enough sample size, which enables to avoid chance finding and to deal with heterogeneity within and between datasets (Janssen et al., 2018; Schnack and Kahn, 2016; Varoquaux, 2018). Several outcome prediction studies employing machine learning have been recently published, both for short-term outcome (Koutsouleris et al., 2016) and long-term outcome (de Nijs et al., 2021).

4.5. Strengths and limitations

To our knowledge this is the first meta-analysis and systematic review investigating predictors of short- to medium- term outcomes of psychotic disorders including prospective studies only. The study provides an up-to-date overview of the enormous amount of available research on this topic. Our study confirms some of the previously identified predictors, but also shows that for many other proposed predictors in original research evidence is lacking. As discussed above, several research gaps have been identified which enabled us to provide recommendations for future research.

Due to the extensive number of studies published on this research topic it was not possible for us to run each step in the study selection, data-extraction and quality assessment of studies by two authors. Because of the lack of consensus in literature about definitions of our investigated outcomes, we used broad definitions for social functioning, independent living and personal recovery. A narrower definition might have showed more consistent (but possibly statistically non-significant) findings but it could also have led to loosing valuable information about possible associations.

Despite the many studies identified by our search, for most variables and outcomes there was not enough data to perform a meta-analysis. By using raw, univariate data in the meta-analysis possible confounders are not taken into account. To summarize the large amount of heterogeneous and often limited information from the studies in our systematic review we used the method of frequency counts based on the direction of effect. This is a crude method that provides no information on the magnitude of effect and does not account for differences in the relative sizes of the studies (McKenzie and Brennan, 2021). The method we created to calculate a sum-score in order to determine the overall direction and robustness of the association could be criticized as being subjective.

5. Conclusion

In this prospective systematic review and meta-analysis we examined predictors of symptomatic and functional outcome. We found that level of functioning at baseline is the most important predictor for each investigated outcome. Therefore, to improve prognosis we should focus on prevention, early detection and intervention to prevent or minimize functional decline.

For future research on this topic we recommend prospective study

designs and using state-of-the-art analysis methods (such as machine learning) to investigate whether the predictors found at group level can be used to build prognosis prediction tools to personalize and optimize treatment and care for individual patients.. Furthermore, published reports of these studies should provide all the necessary data and results, as well as open access to datasets and analysis scripts, to enable other researchers to use and pool the data. Only then, with shared effort, personalized psychosis prognosis prediction can become reality.

For more information about the psychosis prognosis project see Psychosis Prognosis Predictor (PPP) – Patterns in Psychiatry (patternsonline.org).

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Systematic review and meta-analysis on predictors of short-term prognosis in patients with schizophrenia spectrum disorders: An overview of current evidence and a call for prospective research and open access to datasets.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2023.02.024.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: H. Schnack reports financial support was provided by ZonMw.

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