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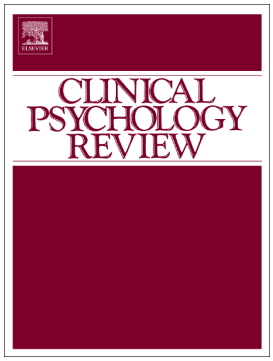

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Predictors of functional recovery in first-episode psychosis: A systematic review and meta-analysis of longitudinal studies

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Running title: Predictors of functioning in FEP

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Abstract

Background: Three out of four first-episode psychosis (FEP) patients achieve clinical remission following treatment. Unfortunately, functional recovery lags behind symptomatic remission, and many individuals with FEP remain socially isolated with poor functional outcomes.

Aims. To systematically compile and analyse predictors of functional recovery in FEP.

Method. Systematic review and meta-analysis of peer-reviewed, longitudinal studies reporting predictors of functioning, with a minimum 12-month follow-up and at least 80% of participants diagnosed with FEP.

Results. Out of 2,205 citations, 274 articles were retrieved for detailed evaluation resulting in 50 eligible studies (N=6,669). Sociodemographic, clinical, physical and neuroimaging variables had little impact on long-term functioning. Conversely duration of untreated psychosis (DUP), most cognitive variables, and concurrent remission of positive and negative symptoms were independently related to functional recovery.

Conclusions. These findings strongly support the rationale for early intervention in FEP. Novel treatments targeting cognitive deficits may improve functional outcomes in FEP.

Word-count: 151/200

Keywords: first-episode psychosis, functioning

Introduction

Around 75% of first-episode psychosis (FEP) patients achieve symptomatic remission following antipsychotic treatment (Cassidy, Norman, Manchanda, Schmitz, & Malla, 2010; Lieberman et al., 1993; Tohen et al., 2000). Unfortunately functional recovery lags behind clinical remission and many individuals with FEP remain socially isolated with poor functional recovery (Lieberman et al., 1993). While clinical remission was long considered the critical treatment goal, there is now growing widespread interest in addressing functional

recovery from the perspective of researchers, clinicians and consumers (Alvarez-Jimenez et al., 2016). Indeed, the onset of psychosis usually results in a downward spiral of loneliness and detachment from community and peers, discontinuation of hobbies and school, and impairment in work-related activities directly impacting long-term wellbeing (Penn, Waldheter, Perkins, Mueser, & Lieberman, 2005). Not surprisingly, functional recovery (i.e., engagement with vocational and educational pathways) is the treatment outcome (Iyer, Mangala, Thara, & Malla, 2010) most valued by FEP patients (Iyer, Mangala, Anitha, Thara, & Malla, 2011).

Identifying risk factors for poor functional recovery may help to identify FEP patients at higher risk of poor long-term functioning. Targeting direct, more intense treatment resources towards such cohorts may assist to offset long-term impairment and improve functional trajectory. Similarly, the identification of modifiable risk factors affecting functional outcomes will inform the development of novel targeted treatments designed to address such mechanisms and thus improve functional recovery.

Identifying robust predictors of functional recovery in FEP is essential to advance the field. It is thought that the first 3-5 years post diagnosis may constitute a critical period in shaping long term outcome (Birchwood, Todd, & Jackson, 1998; Crumlish et al., 2009). Hence, evaluating the impact of potential predictors up to this 5-year window is especially important. Furthermore, maintenance of functional improvements is important to determine whether meaningful recovery is achieved, with studies recommending a follow-up period of at least 15 months (Kane, Leucht, Carpenter, & Docherty, 2003). Thus, analysis of longitudinal studies (with a follow-up of at least 12 months) are needed to effectively assess long-term functional recovery as opposed to shorter-term periods that are typically used to assess remission (Kane et al., 2003). To date there have been no meta-analytic studies undertaken on long-term recovering in FEP patients. Restricting studies to a homogenous cohort of FEP patients (where individuals fall under the same stage of illness), is essential to identifying salient (i.e., modifiable) predictors of long term-functioning for this group. As such, the aim of this study was to conduct a rigorous evaluation of the available evidence for predictors of functional outcome in FEP from longitudinal studies with a minimum 12-month follow-up. This is both overdue and essential to identify patients at high risk of poor functional recovery, and to inform novel approaches to early interventions.

Method

Data sources

Electronic systematic searches employing Cochrane methodology, from inception until March 2016, were performed to find relevant English language reports from the following databases: Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, CINAHL, EMBASE, ISI Information Social Science & Humanities proceedings, ProQuest Dissertations & Theses (PQDT) and Conference Proceedings Citation Index (CPCI). The abstracts, titles and index terms of studies were searched using combinations of relevant keywords (see Supplementary Information). Additional articles were identified by hand-searching the references of retrieved articles and reviews. Authors were contacted for studies without online access.

Study selection

Considered for inclusion were longitudinal or prospective studies examining sociodemographic, clinical, psychological, biological or treatment predictors of functioning, which comprised at least 80% of participants with a FEP using either DSM (APA, 1994) or ICD (WHO, 1992) criteria (Álvarez-Jiménez, Hetrick, González-Blanch, Gleeson, & McGorry, 2008; Álvarez-Jiménez, Parker, Hetrick, McGorry, & Gleeson, 2011; Alvarez-Jimenez et al., 2012). A wide-ranging definition of FEP was considered including both non-affective psychoses (i.e., schizophrenia spectrum and other psychotic disorders) and affective psychoses (i.e., bipolar disorder, or major depressive disorder with psychotic features). FEP was based on baseline status and when the threshold for the diagnosis was first met (i.e., presence of a psychotic symptom for the first time, consisting of hallucinations, delusions, disorganized behaviour or disorder of thinking) reaching adequate severity for at least 7 days, with <12 weeks of lifelong antipsychotic medication (Larsen, McGlashan, & Moe, 1996; van der Gaag et al., 2013). Non-English language articles, retrospective studies, studies with a follow-up period <12 months and studies with n<30 were excluded. Three reviewers (M.P., O.S-E. and S.R.) independently assessed all potentially relevant articles for inclusion. Cases of conflict were resolved through discussion with other authors.

Overall functioning was broadly defined including one or more of the following: 1) Global functioning as measured by standardized measures (e.g., GAF, SOFAS); 2) Social functioning or social connectedness as measured by standardized measures (e.g., SFS); 3) Quality of Life as measured by standardized measures (e.g., QoL scale, WHOQoL-Bref); and

4) Individual definitions of functioning covering one or more of the following areas: vocational functioning, educational functioning, degree of independence and social functioning.

Data extraction

Data were extracted on all the predictors considered for analysis for each study. Two reviewers (O.S-E. and M.P.) independently extracted relevant data, including study and participant characteristics, functioning criteria and measurement, and predictors examined. Standardized data extraction forms were used. Any discrepancies were resolved by consensus.

Assessment of methodological quality

Two of the reviewers (O.S-E. and S.R.) rated each study on 4 domains of methodological quality (Downs & Black, 1998; Hackett, Hons, & Anderson, 2005), including: reporting and external validity (i.e., representativeness and generalizability of the predictive model); internal validity (i.e., risk of bias of the model), statistical validity (i.e., quality of the models reported), and quality of functioning measurement (assessed against the criteria put forward by Liberman (2002) (Liberman, Kopelowicz, Ventura, & Gutkind, 2002) as well as expert consensus guidelines (Kane et al., 2003) (e.g., occupational functioning, peer relationships and independent living)).

Data analysis

Pooled functioning rates were estimated with Comprehensive Meta-Analysis Software, Version 2.2 (Borenstein, Hedges, Higgins, & Rothstein, 2006). When the same outcome was evaluated with different scales or domains within the same study, we retained one measure corresponding to a pre-established order (Borenstein, Hedges, Higgins, & Rothstein, 2009; Fusar-Poli et al., 2015) (see Supplementary Information; Method).

The majority of effect sizes reported in the studies were in the form of correlations (*r*). Therefore, associations of predictors of functioning were estimated by using Pearson correlations (*r*). Although only two studies are needed to perform a meta-analysis (Valentine, Pigott, & Rothstein, 2010), effect sizes were pooled for predictors analysed in 4 or more studies reporting data in a usable format in order to provide a more reliable information and not to compromise statistical power (Cooper, 2003) . We used Fisher's *r*-to-*z* conversion for

variance stabilization and normalization (Borenstein et al., 2009) and transformed all the outcomes to *r* scale. Due to the considerable heterogeneity in adjustment for potential confounders across studies, we used unadjusted data when available, for primary analysis (Alvarez-Jimenez et al., 2012; Glass, McGaw, & Smith, 1981). When *Betas* from regression analysis were provided, we employed the mathematical transformation proposed by Peterson and Brown (Peterson & Brown, 2005) to derive an approximation to *r* from the corresponding *Beta*. When conversion was not possible, authors were contacted for the provision of the necessary data (see Supplementary Information; Method). We pooled the effect sizes using random-effects models accounting for within-study error and variation in the true effects across studies (Borenstein et al., 2009).

Sensitivity analysis

To assess the robustness of our results, when possible, subgroup analyses were performed to examine the differential effects of type of outcome (differentiating: 1) quality of life, 2) domain of functioning and, 3) vocational functioning, relationships or independent living). Thus, we performed a main meta-analysis summarizing all data available "overall functioning" into a single pooled estimate (according to the pre-established order (Borenstein et al., 2009; Fusar-Poli et al., 2015); see Supplementary Information; Method). In order to better understand overall functioning, we also performed subgroup analysis comparing results from measures strictly assessing functioning "domain of functioning" (e.g., studies using GAF, SOFAS, GAS, etc.) vs. quality of live (e.g., studies using QLS, QLI, etc.), vs. study-specific definitions of functioning (only measuring vocational functioning, relationships or independent living). We did not assume a common among-study variance component across subgroups (this is the option RevMan employs). Subgroup analysis by type of outcome was used as a default analysis strategy, with the exception of predictors being assessed by fewer than 5 studies (where subgroups are likely to provide imprecise estimations (Borenstein et al., 2009)). Further sensitivity analyses were also performed to examine statistical heterogeneity, diagnosis, differences in follow-up measurements and the effects of using univariate and multivariate effect sizes on the pooled estimates.

Heterogeneity and publication bias

Heterogeneity was calculated by testing the null hypothesis that the true effect size is the same in all studies using the *Q* statistic (Borenstein et al., 2009). The I^2 statistic explains the percentage of variance in the observed effects due to variance in the true effects. Finally,

publication bias was tested with the Duval & Tweedie (Duval & Tweedie, 2000) trim-and-fill method by entering data in a funnel graph (plot of dispersion between study effect and a measure of study size). A symmetrical inverted distribution of the studies about the mean effect size represented in the funnel indicates absence of publication bias (Borenstein et al., 2009). That is, if publication bias exists, smaller studies are expected to show the biggest effect sizes.

Results

eFigure 1 illustrates the study retrieval and selection strategy (see Supplementary Information). Of the 2,205 citations retrieved a total of 1,931 were excluded on the basis of information available in the abstract. Of these, 274 articles were retrieved and subjected to detailed evaluation, leaving a total of 50 included in the study. Full reference list and reasons for exclusion is available in the Supplementary Information (eTable 4).

Characteristics of the studies included are presented in eTable 1 (see Supplementary Information). Fifty studies involving 6,669 participants were included. In 49 of the 50 included studies, 100% of participants included in the main analysis were identified as FEP. In only one study (Holthausen et al., 2007) 81% of participants were identified as FEP and 19% of participants were referred for a second psychotic episode. Participants' mean age ranged from 15.6 to 43.2 years (mean age of 23.3 years). Twenty studies reported follow-up periods ranging from 12-18 months, 17 included follow-up of 2 to 3 years, 7 included follow-ups of 4-7 years and 6 included follow-ups of more than 7 years. With respect to assessment of overall functioning, 15 studies employed the GAF (or GAS, C-GAF, MIRECC-GAF), 4 studies used the GAF-F, 10 the SOFAS, 10 the QLS, 10 used a definition of vocational functioning, 4 the SCFS, 3 the SFS, 2 a definition of social relations, 2 a definition of independent living, and 1 a definition of disability, 3 the WHO-DAS, and the WQOL, QOL, CAN, GSDS, PSP, SAS and RFS were only employed by one study (some studies used more than one scale of functioning; therefore the number of assessments of functioning is higher than the total number of studies). Twenty-five trials were conducted in Europe (N=2,446), 3 in Asia (N=964), 12 in North America (N=1,487), and 10 in Australasia (N=1,772).

Methodological quality

The quality of the reviewed studies is summarised in eTable 2 (see Supplementary Information). There was variability in the internal and external validity across studies. The

main differences were the inclusion of affective psychosis (28 of 50 studies) compared to non-affective psychosis only. In addition, some characteristics of the population were inconsistently reported (age at onset of psychosis: 20 of 50 studies; comorbidity 31 of 50 studies). Only 17 studies provided research hypotheses and 29 studies provided diagnostic criteria for FEP.

The internal validity of the majority of the studies was weak with a significant lost to follow-up rate (only seven studies had less than a 10% drop-out at follow-up (ranging from no drop-out (Larsen, Moe, Vibe-Hansen, & Johannessen, 2000) to 77.1% drop-out rate (Turner et al., 2015)). Moreover, only 11 studies reported blinding assessment (in relation to previous assessments (Addington, Van Mastrigt, & Addington, 2004; Addington, Young, & Addington, 2003a; Alvarez-Jimenez et al., 2012; Alvarez-Jimenez et al., 2011; Marchesi et al., 2015; Norman et al., 2012; Ross M G Norman et al., 2007), treatment condition at baseline (Allott, Alvarez-Jimenez, et al., 2011), diagnostic condition (Alvarez-Jimenez et al., 2012; Amminger et al., 2011; Harris et al., 2005) and duration of untreated psychosis (DUP) status (Addington et al., 2004, 2003a; Crumlish et al., 2009; Saravanan et al., 2010)). The control variables included in the analyses differed considerably across studies, and important potential predictors of overall functioning such as sex, diagnosis, or premorbid adjustment were only included in half of the multivariate models. Furthermore, colinearity (13 out of 50 studies) and sensitivity and specificity (16 out of 50 studies) were rarely assessed. Only one model (Marino et al., 2015) was externally validated on another published sample to determine if results were comparable to other international FEP programs. Finally, just 22 studies provided precision estimates (i.e., standard deviations or confidence intervals).

There was also variability in the definition and quality of functioning across studies. Although nearly all included vocational functioning (49 out of 50) or relationships (47 out of 50) in their measure of functioning, only half (24 out of 50) included independent living and just seven studies measured subjective quality of life. Finally, among all the functioning measurement 19 studies did not use scales that exclude psychotic symptoms.

Predictors of functioning

eTable 3 (see Supplementary Information) shows baseline variables associated with better overall functioning at follow-up for FEP treatment. For clarity purposes, idiosyncratic predictors measured in only one study were not reported (e.g., general anxiety tension, traditional healer, excitement, self-image, etc. Complete data available upon request). One

hundred and five predictors were analysed across studies, with 38 (36.2%) being assessed in 4 or more studies. Of those, only predictors with useful data from at least 4 studies were considered, and data was extracted and pooled for 29 predictors. The Supplementary Information (Method) provides details on the analysis strategy to account for differences in outcomes, follow-up periods and type of effect sizes reported for each predictor.

Sociodemographic and family variables

Twelve sociodemographic variables were examined, with 7 being assessed in 4 or more studies. Education (15 of 22; i.e. a significant association in 15 of 22 examining this variable) and work history (6 of 9), showed a consistently positive association with overall functioning. Being female (13 of 36) and ethnicity (2 of 5) showed conflicting associations with functioning. Finally, age (2 of 28), family history of psychiatric disorders (0 off 4) and marital status (1 of 4) were not significantly associated with overall functioning (eTable 2).

Summary correlations were estimated for four sociodemographic variables (Fig. 1 significant and eFig. 2 non-significant). There was a significant association between better overall functioning and gender (female) (Alvarez-Jimenez et al., 2012; Faerden et al., 2013; Harrigan, McGorry, & Krstev, 2003; Harris et al., 2005; Jordan et al., 2014; Lappin et al., 2014; Norman et al., 2012; O'Connor et al., 2013; Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004; Tandberg et al., 2011; Turner et al., 2015; Verma, Subramaniam, Abdin, Poon, & Chong, 2012; Wade, Harrigan, McGorry, Burgess, & Whelan, 2007; Wunderink, Nieboer, Wiersma, Sytema, & Nienhuis, 2013) (14 of 36; i.e., data was pooled from 14 out of 36 studies reporting on this variable; r=0.172, 95% CI [0.115-0.208], p<0.000). Heterogeneity was noted (Q=43.124, df=13, p=0.000, I^2=69.854). Subgroup analysis indicated that being female was not associated to a better vocational outcome (p=0.972). Results remained unchanged when domain of functioning (r=0.144, p=0.012) or quality of life (r=0.191, p<0.000) were analysed. Three studies also provided adjusted estimates, one study (Alvarez-Jimenez et al., 2012) controlling for the effects of age of onset, work status, education, premorbid adjustment, negative psychotic symptoms; other study (Faerden et al., 2013) controlling for premorbid adjustment, DUP, positive psychotic symptoms, apathy and verbal memory and learning; and other study (Tandberg et al., 2011) for age. The resulting summary effect remained unchanged after replacing the r (r=0.176, 95% CI [0.121-0.231], p<0.000; Q=43.729, df=13, p=0.000, I^2=70.271).

Age at study enrolment (Allott, Alvarez-Jimenez, et al., 2011; Faerden et al., 2013; Lappin et al., 2014; Larsen et al., 2000; Meng et al., 2006; Pencer, Addington, & Addington, 2005; Peña et al., 2012; Robinson et al., 2004; Tandberg et al., 2011; Turner et al., 2015; Verma et al., 2012; Wood et al., 2006) (data was pooled from 12 out of 28 studies reporting on this variable) was not significantly associated with overall functioning (r=0.030, 95% CI [-0.055-0.114], p=0.489) with no heterogeneity observed across studies (Q=14.139, df=12, p=0.292, I^2=15.126). One study accounted for 96.6% of the weight for the functioning subgroup and 57.96% of the weight for the overall sample (Verma et al., 2012). After exclusion of one study (Verma et al., 2012) (in which age was younger and older age), results remained unchanged (r=0.019, p=0.653; I^2=13.079, p=0.288). Results remained unchanged when domain of functioning (p=0.749), quality of life (p=0.445) and vocational functioning (p=0.191) were examined.

Education (Alvarez-Jimenez et al., 2012; Carlsson, Nyman, Ganse, & Cullberg, 2006; Chang et al., 2013; Harrigan et al., 2003; Harris et al., 2005; Norman et al., 2012; Peña et al., 2012; Robinson et al., 2004; Segarra, Ojeda, Pena, et al., 2012; Turner et al., 2015; Verma et al., 2012; Wunderink et al., 2013) (data was pooled from 12 out of 22 studies reporting on this variable) was significantly associated with better overall functioning (r=0.155, 95% CI [0.109-0.200], p<0.000) and no heterogeneity was noted (Q= 13.106, df= 11, p=0.286, I^2= 16.070). Subgroup analysis indicated that education was associated to domain of functioning (r=0.175, p<0.000) and quality of life (r=0.144, p=0.011), however it was not associated with vocational functioning (p=0.956). Two studies provided adjusted estimates, one study (Alvarez-Jimenez et al., 2012) controlling for the effects of age of onset, work status, education, premorbid adjustment, negative psychotic symptoms; and other study (Norman et al., 2012) controlling for socioeconomic status, mode of onset, premorbid adjustment, substance use disorder, DUP, duration of untreated illness, and negative and positive psychotic symptoms. The resulting summary effect remained unchanged after replacing the r (r=0.151, 95% CI [0.106-0.196], p<0.000; Q=13.176, df=11, p=0.282, I^2=16.513).

Duration of work history (Alvarez-Jimenez et al., 2012; Norman et al., 2007; Tandberg et al., 2011; Turner et al., 2015; Wunderink et al., 2013) (data was pooled from 5 out of 9 studies reporting on this variable) was significantly associated with better overall functioning (r=0.306, 95% CI [0.146-0.451], p<0.000) and heterogeneity was noted (Q=13.104, df=4, p=0.011, I^2=69.475). Visual examination of the plot showed an outlier. Exclusion of one study (Turner et al., 2015) which included paid and non-paid jobs

eliminated heterogeneity (Q=3.196, df=3, p=0.362, I^2=6.133) while results remained unchanged (r=0.234, 95% CI [0.141-0.323] p<0.000) Due to significant variability in age in the studies included (ranging from 15.6 to 43.2 years old), age could be a confounding variable since having work experience was not equally possible for all age ranges.

Clinical variables

Twenty-five clinical variables were examined, with 17 being assessed in 4 or more studies. Functioning at baseline (12 of 18; i.e., a significant association in 12 of 18 examining this variables), negative psychotic symptoms (20 of 30), duration of untreated illness (4 of 5), general psychopathology/symptoms severity (6 of 12), DUP (18 of 33), insight (3 of 5) and medication adherence (3 of 8) showed a consistent association with overall functioning. Conversely, diagnosis (9 of 19), duration of prodromal symptoms (2 of 4), positive psychotic symptoms (9 of 26) and total psychotic symptoms (4 of 10) showed conflicting associations with overall functioning. Finally, age at onset (2 of 16), depressive symptoms (2 of 14), substance use disorders (1 of 11), severity of substance use disorder (1 of 4), alcohol use disorder (0 of 5), and type of antipsychotic medication (0 of 4) were not associated with overall functioning (eTable 2).

Summary correlations were estimated for seven clinical variables (Fig. 2 for significant predictors and eFig 3 non-significant). There was no association between overall functioning and age at onset (Allott, Alvarez-Jimenez, et al., 2011; Alvarez-Jimenez et al., 2012; Harrigan et al., 2003; Harris et al., 2005; Jordan et al., 2014; Larsen et al., 2000; Malla, Norman, Manchanda, & Townsend, 2002; Norman et al., 2012; Pencer et al., 2005; Wunderink et al., 2013) (data was pooled from 10 out of 16 studies reporting on this variable; r=0.047, 95% CI [-0.016-0.109], p=0.144) with no significant heterogeneity across studies (Q=9.999, df=10, p=0.441, I^2=0.000). Subgroup analyses did not change the results as age of onset was not significantly associated with domain of functioning (p=0.303) or quality of life (p=0.231). One study (Norman et al., 2012) provided adjusted estimates controlling for the effects of socioeconomic status, mode of onset, premorbid adjustment, substance use disorder, DUP, duration of untreated illness, and negative and positive psychotic symptoms. The resulting summary effect remained unchanged after replacing the r (r=0.053, 95% CI [-0.009-0.116], p=0.095; Q=10.378, df=10, p=0.408, I^2=0.000).

Insight (Alvarez-Jimenez et al., 2012; O'Connor et al., 2013; Pena et al., 2012; Segarra, Ojeda, Zabala, et al., 2012) (data was pooled from 4 out of 5 studies reporting on this variable) was not significantly associated with overall functioning (r=0.036, 95% CI [-0.166-0.236], p=0.728). Evidence of significant heterogeneity was noted (Q=16.177, df=3, p=0.001, I^2=81.455) when using clinical insight as the outcome for O'Connor's study (O'Connor et al., 2013). When clinical insight was replaced by cognitive insight, results and heterogeneity values remained unchanged (r=0.025, 95% CI [-0.197-0.244], p=0.830; Q=19.669, df=3, p=0.000, I^2=84.747). Heterogeneity could be explained by different measures employed to assess insight (a combined measure with the Positive and Negative Syndrome Scale (PANSS) G12 item and the Scale to Assess Unawareness of Mental Disorder (SUMD) (Segarra, Ojeda, Zabala, et al., 2012), the SUMD exclusively (Pena et al., 2012), as part of the assessment with the Royal Park Multidiagnostic Instrument for Psychosis (RPMIR) (Alvarez-Jimenez et al., 2012), and with the Schedule for Assessment of Insight-Expanded (SAI-E) (O'Connor et al., 2013)). Also, the two studies with Spanish populations had more homogeneous results(Pena et al., 2012; Segarra, Ojeda, Zabala, et al., 2012) and differed from the other studies conducted in English Speaking countries (Australia (Alvarez-Jimenez et al., 2012) and the UK (O'Connor et al., 2013)). One study (O'Connor et al., 2013) provided adjusted estimates controlling for the effects of gender, ethnicity and negative psychotic symptoms. The resulting summary effect remained unchanged after replacing the r for both clinical insight (r= -0.012, 95% CI [-0.186-0.162], p=0.894; Q=11.959, df=3, p=0.008, I^2=74.915) and cognitive insight (r=0.003, 95% CI [-0.189-0.195], p=0.976; Q=14.677, df=3, p=0.002, I^2=79.560).

DUP among studies was very variable with large standard deviations suggesting severely skewed distributions (median range from 31.5 (Faerden et al., 2013) to 732 days (Harris et al., 2005)). Two studies (Alvarez-Jimenez et al., 2012; Harris et al., 2005) reported bivariate predictors with four cut-offs for DUP (<1 month, <2 months, <3 months, <12 months). When we included the <1 month DUP cut-off for both studies, longer DUP (Addington, Young, & Addington, 2003b; Alvarez-Jimenez et al., 2012; Carlsson et al., 2006; Del Rey-Mejías et al., 2015; Faerden et al., 2013; Fraguas et al., 2014; Harrigan et al., 2003; Harris et al., 2005; Jordan et al., 2014; Larsen et al., 2000; Malla et al., 2002; Meng et al., 2006; Norman et al., 2012; O'Connor et al., 2013; Peña et al., 2012; Robinson et al., 2004; Tandberg et al., 2011; Wade et al., 2007; Wood et al., 2006; Wunderink et al., 2013) (data was pooled from 20 out of 33 studies reporting on this variable) was significantly

associated with worse overall functioning (r= -0.162, 95% CI [-0.220]-[-0.101], p<0.000) and evidence of significant heterogeneity was noted (Q=61.574, df=19, p=0.000, I^2=69.143) probably due to great variability in DUP duration for each study. When the <12 months DUP was tested, results remained unchanged (r= -0.153, p=<0.000). Subgroup analysis revealed that longer DUP was also associated with domain of functioning (r= -0.171, 95% CI [-0.290]-[-0.047], p=0.007), quality of life (r= -0.161, 95% CI [-0.233]-[-0.087], p<0.000). Conversely, DUP was not associated with relationships (p<0.063) and vocational functioning (p=0.999). Four studies provided adjusted estimates, one study (Tandberg et al., 2011) controlling for the effects of age and gender; one study (Norman et al., 2012) controlling for socioeconomic status, education, mode of onset, premorbid adjustment and substance use disorder; one study (Fraguas et al., 2014) controlling for age at onset, gender and socioeconomic status; and one study (Faerden et al., 2013) controlling for gender and premorbid adjustment. The resulting summary effect remained unchanged after replacing the *r's* (r= -0.144, 95% CI [-0.200]-[-0.087], p<0.000). In total, 64% of the studies examining the relationship between DUP and functioning controlled for confounders (50% for gender, 32% for age or age at onset, 32% for premorbid adjustment, 23% for psychotic symptoms and 18% for diagnosis).

One study (Alvarez-Jimenez et al., 2012) reported three cut-offs for duration of untreated illness (<6 month, <12 months, <24 months). When we included the <6 month duration of untreated illness, longer duration of untreated illness (Alvarez-Jimenez et al., 2012; Jaracz, Górna, & Rybakowski, 2007; Norman et al., 2012; Turner et al., 2015) (data was pooled from 4 out of 5 studies reporting on this variable) was significantly associated with worse overall functioning (r= -0.251, 95% CI [-0.410]-[-0.078], p=0.005) and no evidence of significant heterogeneity was noted (Q=6.024, df=3, p=0.110, I^2=50.203). Sensitivity analysis for <12 months duration of untreated illness and <24 months duration of untreated illness showed a decrease on the strength of the association with longer duration of untreated illness (r= -0.223, p=0.046 and r= -0.221, p=0.054 respectively). Two studies provided adjusted estimates, one study (Turner et al., 2015) controlling for disorganized symptoms, DUP, work history and baseline functioning; and other study (Norman et al., 2012) controlling for socioeconomic status, education, mode of onset, premorbid adjustment, substance use disorder, DUP, and negative and positive psychotic symptoms. The resulting summary effect remained unchanged after replacing the r for <6 month duration of untreated illness meta-analysis (r= -0.195, p=0.023). However the model was non-significant after

replacing the *r* for <12 months and <24 months duration of untreated illness meta-analyses (*r*= -0.165, *p*=0.108; and *r*= -0.163, *p*=0.119 respectively).

Medication adherence (Allott, Alvarez-Jimenez, et al., 2011; Jordan et al., 2014; Norman et al., 2007; Robinson et al., 2004; Wade et al., 2007) (data was pooled from 5 out of 8 studies reporting on this variable) was not significantly associated with better overall functioning (*r*= -0.035, 95% CI [-0.221]-[-0.152], *p*=0.714) and evidence of significant heterogeneity was noted (*Q*=17.995, *df*=5, *p*=0.003, I^2=72.074). Visual inspection of the graph indicated that one study (Allott, Alvarez-Jimenez, et al., 2011) was an outlier. Exclusion of this study (Allott, Alvarez-Jimenez, et al., 2011) which used the Medication Adherence Rating Scale (MARS) (Thompson, Kulkarni, & Sergejew, 2000) as a rating scale for medication adherence rather than percentage of time taking antipsychotic medication (as the rest of the studies did), maintained results and heterogeneity unchanged (*r*= -0.016, 95% CI [-0.205-0.173], *p*=0.867; *Q*=14.558, *df*=3, *p*=0.002, I^2=79.393).

Positive psychotic symptoms (Addington et al., 2003b; Carlsson et al., 2006; Faerden et al., 2013; Ho, Nopoulos, Flaum, Arndt, & Andreasen, 1998; Meng et al., 2006; Norman et al., 2012; Pencer et al., 2005; Peña et al., 2012; Stouten, Veling, Laan, Van der Helm, & Van der Gaag, 2014; Tandberg et al., 2011; Turner et al., 2015; Verma et al., 2012; Wunderink et al., 2013) (data was pooled from 13 out of 26 studies reporting on this variable) were significantly associated with worse overall functioning (*r*= -0.232, 95% CI [-0.316]-[-0.145], *p*<0.000) and evidence of significant heterogeneity was noted (*Q*=74.587, *df*=11, *p*<0.000, I^2=85.252). There was a great variability of follow-up periods (ranging from 1 to 12 years). The majority of studies measured positive symptoms with the Positive and Negative Syndrome Scale (Kay, Fiszbein, & Opler, 1987) (PANSS), while two studies (Ho et al., 1998; Norman et al., 2012) used the Scale for the Assessment of Positive Symptoms (Andreasen, 1984) (SAPS) and one study (Carlsson et al., 2006) the Brief Psychiatric Rating Sacale (Ventura, Shaner, & Liberman, 1993) (BPRS). Criteria for age at enrolment varied with the majority of studies not restricting to any specific age (usually <65), one study (Meng et al., 2006) including patients between 12-18 years, one study (Verma et al., 2012) only including those between 15-40 years, and one study excluding those between 21-26 in order not to overlap their adolescent (15-40) vs. adult (26-50) categories; criteria for minimal previous treatment was ≤12 weeks for the majority of the studies, while one study (Norman et al., 2012) narrowed the period to ≤4 weeks. Two studies excluded patients with a substance use disorder (Carlsson et al., 2006; Verma et al., 2012). Finally all but three studies (Addington

et al., 2003a; Pencer et al., 2005; Wunderink et al., 2013) included affective disorders in their sample. Nevertheless, there was not a clear trend of the distribution of the data to comprehensively explain heterogeneity from visual inspection of the graph. Subgroup analysis showed that positive psychotic symptoms were associated with domain of functioning (r= -0.202, p=0.007) and quality of life (r= -0.261, p<0.000). However, positive psychotic symptoms were not significantly associated with vocational functioning (p=0.895). Three studies provided adjusted estimates, one study (Faerden et al., 2013) controlling for gender, premorbid adjustment and DUP; one study (Pencer et al., 2005) controlling for premorbid adjustment; and one study (Ho et al., 1998) controlling for psychotic and disorganized symptoms. The resulting summary effect remained unchanged after replacing the r (r= -0.220, p<0.000).

Negative psychotic symptoms (Addington et al., 2003b; Allott, Alvarez-Jimenez, et al., 2011; Alvarez-Jimenez et al., 2012; Carlsson et al., 2006; Chang et al., 2013; Faerden et al., 2013; Ho et al., 1998; Meng et al., 2006; Norman et al., 2012; O'Connor et al., 2013; Pencer et al., 2005; Peña et al., 2012; Tandberg et al., 2011; Turner et al., 2015; Verma et al., 2012; Wood et al., 2006; Wunderink et al., 2013) (data was pooled from 17 out of 30 studies reporting on this variable) were significantly associated with worse overall functioning (r= -0.255, 95% CI [-0.354]-[-0.150], p<0.000) and evidence of significant heterogeneity was noted (Q=178.705, df=17, p=0.000, I^2=90.487). There was a great variability of follow-up periods (ranging from1 to 12 years). The majority of studies measured negative symptoms with the Positive and Negative Syndrome Scale (Kay et al., 1987) (PANSS), while four studies (Allott, Alvarez-Jimenez, et al., 2011; Alvarez-Jimenez et al., 2012; Ho et al., 1998; Norman et al., 2012) used the Scale for the Assessment of Negative Symptoms (Andreasen, 1984) (SANS) and one study (Carlsson et al., 2006) the Brief Psychiatric Rating Sacale (Ventura et al., 1993) (BPRS). Criteria for age at enrolment varied with the majority of studies not restricting to any specific age (usually <65), one study (Meng et al., 2006) including patients between 12-18 years, one study (Verma et al., 2012) only including those between 15-40 years, and three studies including those between 15-25 years (Allott, Alvarez-Jimenez, et al., 2011; Alvarez-Jimenez et al., 2012; Wood et al., 2006). Criteria for minimal previous treatment was ≤12 weeks for the majority of the studies, while one study (Norman et al., 2012) narrowed the period to ≤4 weeks and other study (Alvarez-Jimenez et al., 2012) included a longer period of ≤24 weeks. Two studies excluded patients with a SU diagnosis (Carlsson et al., 2006; Verma et al., 2012). Finally all but five studies (Addington et al.,

2003a; Alvarez-Jimenez et al., 2012; Chang et al., 2013; Pencer et al., 2005; Wunderink et al., 2013) included affective disorders in their sample. Subgroup analysis showed that negative psychotic symptoms were associated with worse domain of functioning (r= -0.320, p<0.000). However, the associations between negative psychotic symptoms and quality of life (p=0.115) and vocational outcome (p=0.690) were not significant. Three studies provided adjusted estimates, one study (Peña et al., 2012) controlling for social functioning at baseline and general psychopathology; one study (Norman et al., 2012) controlling for socioeconomic status, education, mode of onset, premorbid adjustment, substance use disorder, DUP, duration of untreated illness and positive symptoms; and one study (Ho et al., 1998) controlling for psychotic and disorganized symptoms. The resulting summary effect remained unchanged after replacing the r (r= -0.249, p<0.000). Finally, Allot et al. (2011) (Allott, Alvarez-Jimenez, et al., 2011) reported data stratified by group depending on the type of therapy received (Cognitive Behavioural therapy CBT vs. Befriending). Less negative psychotic symptoms were associated with better functioning only in the Befriending group.

Diagnosis (schizophrenia spectrum disorder) (Amminger et al., 2011; Harrigan et al., 2003; Harris et al., 2005; Robinson et al., 2004; Tandberg et al., 2011; Turner et al., 2015; Wunderink et al., 2013) (data was pooled from 7 out of 19 studies reporting on this variable) was not significantly associated with better overall functioning (r=0.072, 95% CI [-0.073-0.215], p=0.331) and evidence of significant heterogeneity was noted (Q=32.787, df=6, p=0.000, I^2=81.700). Heterogeneity may be explained by the differential way of grouping diagnosis by each study. Some studies (Amminger et al., 2011; Wunderink et al., 2013) included under the category schizophrenia-spectrum disorder: schizophrenia diagnosis, schizophreniform psychosis, schizoaffective disorder, delusional disorder, brief psychotic episode and psychosis not otherwise specified; whilst other studies (Harrigan et al., 2003; Harris et al., 2005; Turner et al., 2015) only included schizophrenia and schizophreniform psychosis under this category; and other study (Tandberg et al., 2011) included schizophrenia, schizoaffective and schizophreniform disorder. Also, some studies classified diagnosis following DSM-II-R criteria while others used the Structured Clinical Interview for the DSM-IV (SCID-I), and one study (Robinson et al., 2004) used the Schedule for Clinical Assessment in Neuropsychiatry (SCAN) matching DSM-IV, where functioning had a greater weight on disorders. One study (Tandberg et al., 2011) provided adjusted estimates controlling for age, gender and DUP. The resulting summary effect remained unchanged after replacing the r (r=0.046, p=0.489). Sensitivity analysis including both schizophrenia

spectrum disorder and schizophrenia diagnoses (Amminger et al., 2011; Carlsson et al., 2006; Harrigan et al., 2003; Harris et al., 2005; Lappin et al., 2014; Robinson et al., 2004; Tandberg et al., 2011; Turner et al., 2015; Wunderink et al., 2013) (data was pooled from 9 out of 19 studies reporting on this variable) showed that diagnosis was not significantly associated with better overall functioning (r=0.088, 95% CI [-0.048-0.220], p=0.203) and evidence of significant heterogeneity was noted (Q=39.827, df=8, p=0.000, I^2=79.913). Heterogeneity could be explained by differences in diagnosis categorization and assessment tools used as mentioned above. Subgroup analyses showed similar results for schizophrenia spectrum disorder (p=0.143) and schizophrenia (p=0.961). One study (Tandberg et al., 2011) provided adjusted estimates controlling for age, gender and DUP. The resulting summary effect remained unchanged after replacing the r (r=0.068, p=0.285). Finally, sensitivity analysis of the impact of affective vs. non-affective psychosis on functioning was not possible due to the lack of available data to be pooled for meta-analysis. Specifically, data was pooled from 4 out of 28 studies reporting on affective psychosis (Del Rey-Mejías et al., 2015; Harris et al., 2005; O'Connor et al., 2013; Verma et al., 2002). However, of these, three studies reported on the category affective psychosis – with schizophrenia or schizophrenia spectrum disorders serving as the reference category (Del Rey-Mejías et al., 2015; Harris et al., 2005; Verma et al., 2002), whereas one study reported on the category non-affective psychosis – with affective psychosis being the reference category (O'Connor et al., 2013). Therefore, diagnostic categories were not comparable.

Premorbid variables

Three premorbid variables (and two sub-variables) were examined, with only one being assessed in 4 or more studies. Premorbid adjustment (20 of 23; i.e., a significant association in 20 of 23 examining this variables) showed a consistently positive association with overall functioning (eTable 2). Summary correlations were estimated for premorbid adjustment (Fig. 3). Poor premorbid adjustment (Addington et al., 2003b; Alvarez-Jimenez et al., 2012; Faerden et al., 2013; Fraguas et al., 2014; Harrigan et al., 2003; Harris et al., 2005; Jordan et al., 2014; Larsen et al., 2000; Lucas, Redoblado-Hodge, Shores, Brennan, & Harris, 2008; Malla et al., 2002; Norman et al., 2012; Pencer et al., 2005; Peña et al., 2012) (14 of 23; i.e., data was pooled from 14 out of 23 studies reporting on this variable) correlated with poorer overall functioning at follow-up (r=0.261, 95% CI [0.311-0.210], p<0.000). Heterogeneity

was noted (Q=45.516, df=13, p=0.000, I^2=71.439). Four studies (Addington et al., 2003b; Faerden et al., 2013; Larsen et al., 2000; Norman et al., 2012) provided categorical measures of premorbid adjustment assessed by the Premorbid Adjustment Scale (PAS) (Cannon-Spoor, Potkin, & Wyatt, 1982) (childhood (up to age 11 years), early adolescence (age 12–15 years), late adolescence (age 16–18 years) and adulthood (age +19 years)) which were combined into one total measure of premorbid adjustment in order to better compare premorbid adjustment with the rest of the studies. Subgroup analysis showed similar results for domain of functioning (r=0.221, p=0.040) and for quality of life (r=0.250, p<0.000). Exclusion of two outlier studies (Norman et al., 2012; Peña et al., 2012) eliminated statistical heterogeneity (I^2=0.000, p=0.849), while results remained unchanged (r=0.251, p<0.000). Three studies provided adjusted estimates, one study (Faerden et al., 2013) controlling for gender; other study (Norman et al., 2012) controlling for education; and other study (Norman et al., 2007) controlling for education and initial capacity for work. The resulting summary effect remained unchanged after replacing the r (r=0.240, p<0.000).

Physical variables

Only two predictors, comorbid somatic illness (Górna, Jaracz, & Rybakowski, 2005; Jaracz et al., 2007) (2 of 2; i.e., a significant association in 2 of 2 studies examining this variable) and body mass index (BMI) (Marino et al., 2015) (0 of 1) were identified in the studies, however, there was not available data to be pooled into meta-analysis.

Cognitive variables

Twelve cognitive variables (and ten sub-variables) were examined, with nine being assessed in 4 or more studies. Of those, visuo-motor skills (4 of 7; i.e., a significant association in 4 of 7 studies examining this variables) showed a consistently positive association with overall functioning. However, general cognitive ability (7 of 15), attention (4 of 9), processing speed (4 of 10), verbal fluency/language (5 of 12), verbal memory, learning (5 of 14), working memory (3 of 9) and nonverbal memory and learning (3 of 10) showed conflicting associations with functioning. Among the remaining variables, few studies provided a consistent association between executive functioning (2 of 10) and functioning (eTable 2).

Summary correlations were estimated for eight cognitive variables (Fig. 4 for significant associations and eFig 4 for non-significant). There was a significant association between overall functioning and general cognitive ability (Bodén, Abrahamsson, Holm, & Borg, 2014; Carlsson et al., 2006; Faerden et al., 2013; Jordan et al., 2014; Lucas et al., 2008; Malla et al., 2002) (7 of 15; i.e., data was pooled from 7 out of 15 studies reporting on this variable; r=0.183, 95% CI [0.074-0.287], p=0.001), with no significant heterogeneity (Q=5.722, df=5, p=0.334, I^2=12.611) (including relationships as the main outcome for two studies (Bodén et al., 2014; Malla et al., 2002)). When independent living was used as the main outcome for those studies (Bodén et al., 2014; Malla et al., 2002), the association between general cognitive ability and functioning remained significant (r=0.116, 95% CI [0.066-0.264], p<0.001; Q=6.423, df=5, p=0.267, I^2=22.149). Subgroup analysis indicated that general cognitive ability was associated with domain of functioning (r=0.194, p=0.006) and there was a trend towards a significant association with relationships (p=0.065). Two studies provided adjusted estimates, one study (Carlsson et al., 2006) controlling for diagnosis, DUP and education; and one study (Bodén et al., 2014) controlling for use of antipsychotic medication. The resulting summary effect remained unchanged after replacing the r (r=0.194, p<0.000) when including relationships and (r=0.176, p=0.002) and independent living as outcomes.

Attention (Faerden et al., 2013; Holthausen et al., 2007; Jordan et al., 2014; Peña et al., 2012; Robinson et al., 2004; Tandberg et al., 2011) was significantly associated with better overall functioning (data was pooled from 6 out of 9 studies reporting on this variable; r=0.216, 95% CI [0.112-0.315], p<0.000) and evidence of significant heterogeneity was noted (Q=14.599, df=5, p=0.012, I^2=65.751). Heterogeneity may be explained by the variability of attention domains measured and different scales used (attention with the Brief Test of Attention (Pena et al., 2012) vigilance with the Digit Span forwards from WAISS-III (Faerden et al., 2013), attention with the d2 Test of Attention (Jordan et al., 2014), attention and inhibition with the Stroop interference score (Holthausen et al., 2007), sustained attention with the index d' of the Continuous Performance Test, Identical Pairs Version (CPT-IP) (Tandberg et al., 2011), and attention measured within a neuropsychological battery (Robinson et al., 2004)). Subgroup analysis showed that attention was not related to domain of functioning (p=0.260) while vocational functioning remained significant (p<0.000).

Working memory (Faerden et al., 2013; Jordan et al., 2014; Malla et al., 2002; O'Connor et al., 2013; Peña et al., 2012) was significantly associated with better overall

functioning (data was pooled from 5 out of 9 studies reporting on this variable; r=0.171, 95% CI [0.084-0.255], p<0.000) and no significant heterogeneity was noted (Q=1.608, df=4, p=0.807, I^2=0.000) when we included one study (Malla et al., 2002) that measured relationships only as outcome. When only taking domain of functioning into account, results remained unchanged (r=0.157, p=0.001). One study (O'Connor et al., 2013) provided adjusted estimates controlling for gender, ethnicity and negative psychotic symptoms. The resulting summary effect remained unchanged after replacing the r (r=0.142, p=0.001).

Verbal fluency/language (Faerden et al., 2013; Malla et al., 2002; O'Connor et al., 2013; Peña et al., 2012; Robinson et al., 2004; Verdoux, Liraud, Assens, Abalan, & Os, 2002) was significantly associated with overall functioning (data was pooled from 6 out of 12 studies reporting on this variable; r=0.167, 95% CI [0.081-0.251], p<0.000), and no significant heterogeneity was noted (Q=1.687, df=5, p=0.981, I^2=0.000). Subgroup analysis revealed that verbal fluency/language was related to domain of functioning (r=0.163, p=0.006). One study (O'Connor et al., 2013) provided adjusted estimates controlling for gender, ethnicity and negative psychotic symptoms. The resulting summary effect remained unchanged after replacing the r (r=0.148, p=0.001).

Verbal memory/learning (Bodén et al., 2014; Faerden et al., 2013; Jordan et al., 2014; Peña et al., 2012; Verdoux et al., 2002) was significantly associated with overall functioning (data was pooled from 5 out of 13 studies reporting on this variable; r=0.145, 95% CI [0.034-0.252], p=0.011), and no heterogeneity was noted (Q=4.713, df=4, p=0.318, I^2=15.132) when including those studies measuring only vocational functioning (Bodén et al., 2014; Verdoux et al., 2002). Subgroup analysis revealed that the association between verbal memory and domain of functioning was significant (r=0.197, p=0.010) while the association was not significant for vocational functioning (p=0.332). Three studies provided adjusted estimates, one study (Faerden et al., 2013) controlling for gender, premorbid adjustment, DUP, positive symptoms and apathy; one study (Bodén et al., 2014) controlling for use of antipsychotic medication; and one study (Jordan et al., 2014) controlling for DUP, medication adherence, age at onset, gender substance use disorder and premorbid adjustment. The resulting summary effect remained unchanged after replacing the r (r=0.118, p=0.013).

Executive functioning (Faerden et al., 2013; Jordan et al., 2014; Malla et al., 2002; Peña et al., 2012; Robinson et al., 2004; Verdoux et al., 2002) was not associated with overall functioning (data was pooled from 6 out of 10 studies reporting on this variable; r=0.064,

95% CI [-0.031-0.157], p=0.188), and no heterogeneity was noted (Q=5.325, df=5, p=0.378, I^2=6.096) when including those studies (Robinson et al., 2004; Verdoux et al., 2002) measuring vocational functioning only. Subgroup analysis showed similar results for domain of functioning (p=0.341), relationships (p=0.812) and vocational functioning (p=0.248).

Processing speed (Bodén et al., 2014; Jordan et al., 2014; Malla et al., 2002; Peña et al., 2012; Stouten et al., 2014) was significantly associated with domain of functioning (data was pooled from 5 out of 10 studies reporting on this variable; r=0.197, 95% CI [0.098-0.292], p<0.000) and heterogeneity was not noted (Q=1.742, df=3, p=0.628, I^2=0.000). Stouten's study (Stouten et al., 2014) reported effect size (*Beta*) was higher than 0.5, and according to Peterson, Brown et al. (Peterson & Brown, 2005) recommendations, these values should not be transformed into correlation. For this reason, Stouten's study was not included in the meta-analysis. One study (Bodén et al., 2014) provided adjusted estimates controlling for use of antipsychotic medication. The resulting summary effect remained unchanged after replacing the r (r=0.197, p<0.000).

Nonverbal memory and learning (Faerden et al., 2013; Jordan et al., 2014; Malla et al., 2002; Peña et al., 2012; Stouten et al., 2014) was not significantly associated with overall functioning (data was pooled from 5 out of 10 studies reporting on this variable; r=0.119, 95% CI [-0.093-0.322], p=0.271), and heterogeneity was noted (Q=23.455, df=4, p=0.000, I^2=82.946) when including relationships as an outcome for Malla's study (Bodén et al., 2014). When independent living was included as the outcome of Malla's study (Bodén et al., 2014), the association remained non-significant. Visual examination of the plot showed an outlier. Exclusion of one study (Stouten et al., 2014), nonverbal memory and learning was significantly associated with domain of functioning (r=0.166, 95% CI [0.066-0.263], p=0.001) and heterogeneity was eliminated (Q=1.567, df=3, p=0.667, I^2=0.000) when including relationships as outcome for Malla's study. One study (Peña et al., 2012) provided adjusted estimates controlling for social functioning at baseline and general psychopathology. The resulting summary effect remained unchanged after replacing the r (r=0.166, p<0.001).

Finally, visuo-motor skills (Bodén et al., 2014; Faerden et al., 2013; Malla et al., 2002; Robinson et al., 2004; Verdoux et al., 2002) were not significantly associated with overall functioning and heterogeneity was not noted (data was pooled from 5 out of 7 studies reporting on this variable; r=0.143, 95% CI [-0.045-0.321], p=0.136; Q=12.018, df=4, p=0.017, I^2=66.716) when pooling all available data regardless of definition of functioning.

When only studies measuring domain of functioning and vocational functioning (Faerden et al., 2013; Robinson et al., 2004; Verdoux et al., 2002) or domain of functioning and relationships (Bodén et al., 2014; Faerden et al., 2013; Malla et al., 2002) or domain of functioning and independent living (Bodén et al., 2014; Faerden et al., 2013; Malla et al., 2002; Verdoux et al., 2002) were included, the association remained non-significant.

Neuroimaging

Twelve neuroimaging variables were examined, with none being assessed in 4 or more studies. Among those variables, grey matter loss (Lappin et al., 2014) (1 of 1; i.e., a significant association in 1 of 1 study examining this variable), superior gyrus volume (Robinson et al., 2004) (total, left and right) (1, 1, and 1 of 1), left frontal NAA/Cr ratio spectropy (Wood et al., 2006) (proton magnetic resonance spectroscopy to provide the ratio of N-acetyl aspartate (NAA) and choline-containing compounds to creatine and phosphocreatine (Cr) (NAA/Cr ratio), a metabolite which is reduced in areas with neuronal loss) (1 of 1) and torque (a composite syntax of cortical asymmetry) (Robinson et al., 2004) (1 of 1) showed a consistently positive association with overall functioning. Cortex volume (Robinson et al., 2004) (total, left and right) (0, 1 and 0 of 1, respectively) and hippocampal volume (Lappin et al., 2014; Robinson et al., 2004) (total, left and right) (1, 0 and 0 of 2, respectively) showed conflicting associations with overall functioning. The whole brain volume (Lappin et al., 2014; Robinson et al., 2004) (0 of 2), lateral ventricular volume (Robinson et al., 2004) (total, left and right) (0, 0 and 0 of 1), third ventricle volume (Robinson et al., 2004) (0 of 1), caudate volume (total, left and right) (0, 0 and 0 of 1), grey matter volume (Lappin et al., 2014) (0 of 1), and left temporal NAA Cr ratio spectropy (Wood et al., 2006) (0 of 1) showed no association with overall functioning (see eTable 2).

Course variables

Eighteen course variables were examined with three being examined in 4 or more studies. Remission of positive symptoms (3 of 4; i.e., a significant association in 3 of 4 studies examining this variable), remission of negative symptoms (4 of 4), and concurrent remission of positive and negative symptoms (5 of 9) were consistently associated with better overall functioning. Days hospitalized (1 of 4) showed a consistent non-significant association with overall functioning.

Summary of correlations were estimated for three course variables (Fig. 5). Remission of positive psychotic symptoms was significantly associated with overall functioning (data was pooled from 4 out of 4 studies reporting on this variable; r=0.356, 95% CI [0.156-0.528], p=0.001). Heterogeneity was noted (Q=15.127, df=3, p=0.002, I^2=80.167). Heterogeneity could be explained by different follow-up periods of measurement in each study (at 8 months (Alvarez-Jimenez et al., 2012), at 5 years (Norman et al., 2012), remitted at any time point (Cassidy et al., 2010; Jordan et al., 2014)). One study (Jordan et al., 2014) provided adjusted estimates controlling for DUP, medication adherence, age at onset, gender, substance use disorder, verbal memory and remission of negative symptoms. The resulting summary effect showed a stronger association after replacing the r (r=0.331, p=0.004; Q=17.969, df=3, p=0.000, I^2=83.305).

Remission of negative psychotic symptoms was significantly associated with overall functioning (data was pooled from 4 out of 4 studies reporting on this variable; r=0.293, 95% CI [0.067-0.490], p=0.012), with evidence of statistically significant heterogeneity (Q=17.447, df=3, p=0.001, I^2=82.805). Heterogeneity could be explained by the different follow-up periods of measurement in each study (at 8 months (Alvarez-Jimenez et al., 2012), at 5 years (Norman et al., 2012), remitted at any time point (Cassidy et al., 2010; Jordan et al., 2014)). One study (Jordan et al., 2014) provided adjusted estimates controlling for DUP, medication adherence, age at onset, gender, substance use disorder, and verbal memory. The resulting summary effect remained unchanged after replacing the r (r=0.417, p<0.000) and heterogeneity was eliminated (Q=7.447, df=3, p=0.061, I^2=59.366).

Concurrent remission of positive and negative symptoms (Addington et al., 2003b; Alvarez-Jimenez et al., 2012; Cassidy et al., 2010; Chang et al., 2013; Holthausen et al., 2007; Jordan et al., 2014; Marchesi et al., 2015; Marino et al., 2015; Norman et al., 2012) was strongly and significantly associated with overall functioning (data was pooled from 5 out of 9 studies reporting on this variable; r=0.490, 95% CI [0.606-0.354], p<0.000), and heterogeneity was noted (Q=14.978, df=4, p=0.005, I^2=73.293). Heterogeneity was likely to be explained by different follow-up periods of measurement in each study (at 8 months (Alvarez-Jimenez et al., 2012), at 5 years (Norman et al., 2012)at 2 years (Chang et al., 2013), remitted at any time point (Cassidy et al., 2010; Jordan et al., 2014)).

Publication bias

The funnel plot indicated that there was an asymmetry for baseline functioning, diagnosis (schizophrenia spectrum disorder vs. schizophrenia), education, gender (female), insight, nonverbal memory and learning, premorbid adjustment, processing speed, remission of negative symptoms, and a slight asymmetry for attention.

Discussion

The aim of this review and meta-analysis was to systematically examine predictors of long-term functioning in FEP longitudinal studies. Prospective relationships are especially useful for understanding the dynamic association of variables over time, as opposed to baseline or course predictors, and are key in accurately determining long-term functioning. If modifiable risks factors are able to be isolated, they may inform novel preventive interventions. The results of this meta-analysis demonstrated that general sociodemographic, clinical and physical variables have little impact on improving functioning over time in FEP. Although 105 factors were assessed across studies, only cognitive variables (cognitive ability, attention, processing speed, verbal fluency, verbal memory and working memory), being female, education, work history, positive symptoms, negative symptoms, premorbid adjustment, DUP, duration of untreated illness, and remission of positive, negative and joint symptoms were significantly associated with functioning over time after FEP. The results of predictors of functioning in FEP revealed that the existing literature is heterogeneous in the definition and measurement of outcome. However we divided outcome into the most parsimonious definitions of functioning and quality of life in order to disentangle nuanced differences derived from measurement used in each study. To our knowledge, this is the first meta-analysis that compiles quantitative evidence of all possible predictors of long-term functional recovery (at least 12 months follow-up) in a FEP population.

Shorter DUP was associated with better long-term functioning. This is the most relevant clinical finding consistent with previous research (Carbone, Harrigan, McGorry, Curry, & Elkins, 1999; Hill et al., 2012; Larsen et al., 1996), and this association was independent of potential confounding factors, such as premorbid functioning, gender, diagnosis and age at onset of symptoms (Bottlender et al., 2003; Drake, Haley, Akhtar, & Lewis, 2000; Haas, Garratt, & Sweeney, 1998; Hill et al., 2012; Larsen et al., 2000; Loebel et al., 1992). Two systematic reviews examining DUP as a predictor have also found that DUP is an independent predictor of functioning in FEP patients (Marshall et al., 2005;

Perkins, Gu, Boteva, & Lieberman, 2005) with follow ups to 12 months. Although we found a moderate negative correlation, we bridge a gap in the literature given DUP is not universally accepted as a predictor of functional recovery. Some studies have not found such an association (Craig et al., 2000; Beng Choon Ho, Andreasen, Flaum, Nopoulos, & Miller, 2000), probably due to variation in sample size, diagnosis and sample inclusion criteria. While these results are based on longitudinal data and therefore do not imply a causal relationship between DUP and long-term functioning, our findings are consistent with previous studies that manipulated DUP experimentally (e.g., the ongoing STAGES study (Francey et al., 2010)). Specifically, the TIPS project (Joa et al., 2008) showed that targeted information campaigns reduced DUP significantly, which was translated into better GAF scores.

As derived from our results, cognitive impairment may be sharing part of the variance with DUP. FEP patients with longer DUP may have different cognitive performance compared to those with shorter DUP (Penttilä, Jääskeläinen, Hirvonen, Isohanni, & Miettunen, 2014). It could also be an indicator that an insidious onset, with more severe negative symptoms, could lead to longer periods of non-treated psychosis, increasing the overall probability of poor functioning (Morgan et al., 2006; Penttilä et al., 2014). Other variables may be salient, as time to intervention is not the only modifiable factor associated with outcome. For example, quality of treatment seems to also influence outcome (McGorry, Edwards, Mihalopoulos, Harrigan, & Jackson, 1996). A systematic review (Menezes, Arenovich, & Zipursky, 2006) showed that combination therapy was the main predictor of good outcome in FEP, although its relationship seems less robust compared to its association with DUP (Harris et al., 2005). Finally, the debate whether DUP is an epiphenomenon of premorbid functioning still remains a relevant question since both factors usually correlate (Larsen et al., 2004, 2000). Although a third of the studies included in this meta-analysis controlled for the influence of premorbid functioning (Faerden et al., 2013; Harrigan et al., 2003; Harris et al., 2005; Jordan et al., 2014; Larsen et al., 2000; Malla et al., 2002; Norman et al., 2012), more studies controlling for premorbid factors are needed to assess the independent impact of DUP on outcome.

We found similar results after undertaking the sensitivity analysis (with <1 month DUP compared to <12 months DUP), however this comparison was only possible with two studies (Alvarez-Jimenez et al., 2012; Harris et al., 2005) reporting different DUP cut-offs points. A 15-year follow-up study undertaken with a population of patients with

schizophrenia showed poorer functioning among patients with >12 months DUP compared to those with <6 or <1 months (Bottlender et al., 2003; Harris et al., 2005). These results suggest that the association of DUP is maintained in the long term. However, more studies examining different durations of DUP are needed to draw further conclusions regarding the nature of the longitudinal associations between DUP and functioning. Finally, data from two studies (Fraguas et al., 2014; Harrigan et al., 2003) suggested that longer DUP was related to poor long-term functioning among schizophrenia patients but there was not an association among affective patients. Due to the heterogeneity of our data, we did not restrict samples with affective diagnosis; and as such we were unable to test this difference. Although diagnosis may have a moderating effect, it is not supported by our data since it was not related to functioning. Nevertheless, our findings extend previous findings as no previous review has showed quantitative evidence from more than twenty studies for an independent association between shorter DUP and better long-term functioning. DUP can have a significant social impact increasing social isolation, unemployment, stigma and depression in the critical period following illness onset, therefore generating a negative spiral that may affect long-term recovery (Lieberman et al., 1993; Penn et al., 2005). These results have relevant clinical implications addressing the importance of early intervention programs to decrease the length of untreated psychosis. We also found similar results for duration of untreated illness (even after controlling for DUP), supporting the idea that prodromal periods are important; therefore earlier interventions in populations of young people at ultra-high risk for psychosis are recommendable too.

Consistent with previous literature in FEP patients (Malla et al., 2002), premorbid adjustment was a predictor of better overall functioning and all definitions of functioning (domain of functioning, quality of life, vocational functioning and independent living). This indicates that adjustment prior to the onset of illness, probably during adolescence, has implications for long-term functioning after development of psychosis. However, the majority of studies controlled for confounder variables in in order of their chronological development to take into account the independent contributions of each. More than a third of the studies included in the analysis measuring the contribution of DUP controlled for premorbid adjustment, suggesting that each variable had an individual contribution (Larsen et al., 1996; Loebel et al., 1992).

Sociodemographic variables such as being female (Usall, Ochoa, Araya, & Márquez, 2003), education (Menezes et al., 2006) and work history (Menezes et al., 2006) were

moderately associated with better long-term functioning as has previously been described in the literature. In general, it seems there is a trend for females to score better than males on relevant outcome scales (Larsen et al., 2000). Education and work history correlated with outcome since both variables are part of the definition of functioning and may be part of the trajectory. It may also be the case that these variables generate positive upwards spirals of recovery and can be easily targeted via occupational interventions (Alvarez-Jimenez et al., 2012; Rinaldi et al., 2010).

Six of the nine cognitive variables examined showed a moderate but consistent association with long-term overall functioning. We found that attention had the strongest association with functioning, followed by processing speed, cognitive ability, working memory, verbal fluency and verbal memory. Importantly, not only specific cognitive domains, but also general cognitive ability was associated with functioning, which previous studies failed to demonstrate (Allott, Liu, Proffitt, & Killackey, 2011). Our results are in line with a review reporting that at least one cognitive domain was associated with functioning, especially for longer-term follow-up studies (Allott, Liu, et al., 2011). The cognitive variables more consistently related with outcome were problem solving, verbal language, verbal learning and memory and general cognition (Allott, Liu, et al., 2011). However, they included studies which did not control for other predictors, no more than three studies examined each cognitive domain and different domains of functioning were not assessed. Heterogeneity was not shown in any of the significant results but for attention, where different domains of attention were pooled together, likely explaining the variability. These results strengthen previous findings showing consistent positive associations of cognition with functioning and have important clinical implications. Moreover, interventions such as Cognitive Remediation Therapy (CRT) have been shown to improve psychosocial functioning in FEP patients moderated by the improvement of cognitive functions (Lee et al., 2013; Wykes et al., 2007). Thus, using routinely screenings and comprehensive assessments at an early stage of the illness may help to identify those individuals who are more vulnerable and at increased risk of worse long-term functioning.

Studies of patients with schizophrenia and recent-onset psychosis have consistently shown structural abnormalities in brain asymmetries (see Bartholomeusz et al., 2017 for a review) and functional brain changes (see Mwansisya et al., 2017 for a review). Reduced grey matter volume and increased ventricular volume are now well established findings (Honea, Crow, Passingham, & Mackay, 2005). Moreover, abnormalities in cortical areas

appear to be present at the point of first diagnosis (Shenton et al., 2001). Also, fMRI studies in FEP patients have identified abnormalities in prefrontal regions such the lateral prefrontal and orbital frontal cortex and the left superior temporal gyrus (Mwansisya et al., 2017). However, there is a scarcity of prospective neuroimaging studies in FEP examining the association of these changes with clinical and functional outcomes with retrospective or cross-sectional studies yielding conflicting findings (Wood et al., 2006; Bartholomeusz et al., 2017). Our review identified preliminary evidence of a positive association between hippocampal volume (Lappin et al., 2014), NAA/Cr ratio (Wood et al., 2006), superior gyrus volume, torque (Robinson et al., 2004) and overall functioning; and a negative association between grey matter loss and overall functioning (Lappin et al., 2014). That said, we were unable to pool any of these studies in meta-analysis due to the inconsistency in the neuroimaging variables being measured and study design. Therefore, replication of these studies in other FEP cohorts is needed to establish the role of brain changes as potential predictors of functioning (Díaz-Caneja et al., 2015).

Finally, lower positive, negative and joint psychotic symptoms at baseline were moderately associated with better long-term functioning. However, three course variables, remission of positive, negative joint psychotic symptoms had the strongest significant association with overall functioning. Andreasen and colleagues (2005) suggested employing both positive and negative symptoms simultaneously as criteria for remission and our data confirms this approach, with a large correlation between remission of joint symptoms and overall functioning of 0.5. Although all studies followed consensus remission criteria (Andreasen et al., 2005), overall periods varied among studies which may account for heterogeneity. This could indicate that baseline measures may not be the best predictors of long-term functioning, and further follow-up assessments should be done along the course of the illness. Moreover, there is some evidence that longer DUP periods (1 week compared to 2.72 weeks) were associated with a reduced (i.e., 1.2 times reduced) odds of remission (Petersen et al., 2008). Therefore, shortening DUP periods may be directly correlated with the strongest variable predicting better long-term functioning, remission of joint symptoms. Taken together, these results support the rationale for early intervention in FEP as a key strategy to promote long-term recovery.

Limitations

Some limitations apply. First of all, most of the studies were conducted in high-income countries and developing country of origin has been found a predictor associated with better outcome (Menezes et al., 2006). There was substantial heterogeneity in the characteristics of the studies included such as duration of follow-up (ranging from 1 to 16 years) or diagnosis (28 studies included affective psychosis vs. 28 that did not). Also, there was methodological variation in the operationalization of functioning as numerous scales were used (measuring functioning, quality of life or single definitions of functioning: vocational functioning, relationships and independent living). This resulted in low number of studies with the same variables and outcome categories. Nevertheless, when heterogeneity was present, sensitivity analyses were undertaken to further explain results in a consistent way. Second, the definition of functioning varied greatly across studies. Some studies reported single scores of functioning while others reported separated domains (vocational functioning, relationships, independent living or quality of life). Many of the studies measuring an overall measure of functioning used the GAF measure, which includes symptoms as part of the overall score. Also, the majority of studies did not report a measure of subjective quality of life which may vary greatly from clinician's rating (Harvey & Bellack, 2009). Third, although more than a hundred predictors were analysed, only 38 (36.2%) were assessed in 4 or more studies, and 29 had useful data to pool into meta-analysis. Therefore, our results are limited to what other studies have reported on. Thus, some potentially relevant predictors (potential protective variables) have not been included in the meta-analysis (for example, different type of antipsychotics or doses, psychosocial treatments, personality traits, social support, illicit drug use, particularly cannabis). The systematic review by Menezes et al., (2006) (Menezes et al., 2006) showed that combination therapy (pharmacotherapy and psychosocial therapy) was the main predictor of good outcome in FEP. However we were unable to replicate those results derived from our data. Also, we could not adjust for covariates due to the heterogeneity of covariates the studies used. Fourth, while our results assist in determining the association between different predictors and long term functioning in FEP patients, it only provides supportive but not conclusive evidence. The studies included in the meta-analysis were correlational in design and only experimental designs would be able to ascertain the direction of the association. In addition, it is likely that understanding the dynamic association of variables over time, as opposed to baseline or course predictors, will be key in accurately determining long-term functioning. Furthermore, significant reporting bias was shown, since the majority of studies did not provide statistically non-significant data (i.e., only statistically significant data was available pooled to analysis). Although authors were contacted to reduce

this bias, this limitation should be noted. Finally, the majority of the analyses we performed for each predictor had less than 10 studies, preventing us from properly testing publication bias. Tests for funnel plot asymmetry should not be used if there are less than ten studies in the meta-analysis as is difficult to distinguish real asymmetry from chance. Although significant efforts to identify unpublished data were made, interpretations of our results should be taken with caution due to this limitation. Thus, future studies need to address methodological limitations of the extant research (e.g. measurement/definition of functioning); to focus on the identification of protective factors of functioning; to further control for confounding variables and mediators; to assess the dynamic association of variables over time; and to further study psychological constructs (e.g., perceived social support, self-efficacy) as well as neuroimaging variables as potential protective predictors of functioning over time.

Summary

In summary, based on the available evidence, the results of this meta-analysis demonstrated that general sociodemographic, clinical and physical variables have little impact on improving functioning over time. In contrast, duration of untreated psychosis (DUP), duration of untreated illness and most cognitive variables (cognitive ability, attention, processing speed, verbal fluency, verbal memory and working memory) were moderately, but consistently related to functional recovery. Remission of psychotic symptoms had the strongest correlation with better long term-functioning (Alvarez-Jimenez et al., 2012). This study provides meta-analytic evidence that DUP is likely to be an independent predictor of long-term functioning.

Future directions

Given that DUP is a malleable factor that could be targeted for treatment, our findings support the importance of early intervention for psychosis and ultra-high risk for psychosis as a key strategy to promote long-term functional recovery (Melle, 2008). Early intervention programs targeting vulnerable populations with greater neurocognitive deficits should be a priority given the predictive value of worse functioning over time. This approach could constitute a secondary prevention method which may attenuate active disruption of neurodevelopmental mechanisms (Arango, Fraguas, & Parellada, 2014).

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Contributors

M.P. performed the literature search. M.P., O.S-E., and S.R. independently assessed all potentially relevant articles for inclusion. O.S-E, M.P. independently extracted relevant data. O.S-E., S.R. and M.A-J., rated each study's methodological quality. O.S-E. performed the statistical analysis. O.S-E. and M.P. wrote the first draft of the manuscript. C.G-B., P.M., J.G. and M.A-J contributed to the design, participated in the consensus process, and critically revised the manuscript. All authors contributed to and approved the final manuscript.

Conflict of Interest

Authors have no conflict of interest to disclose.

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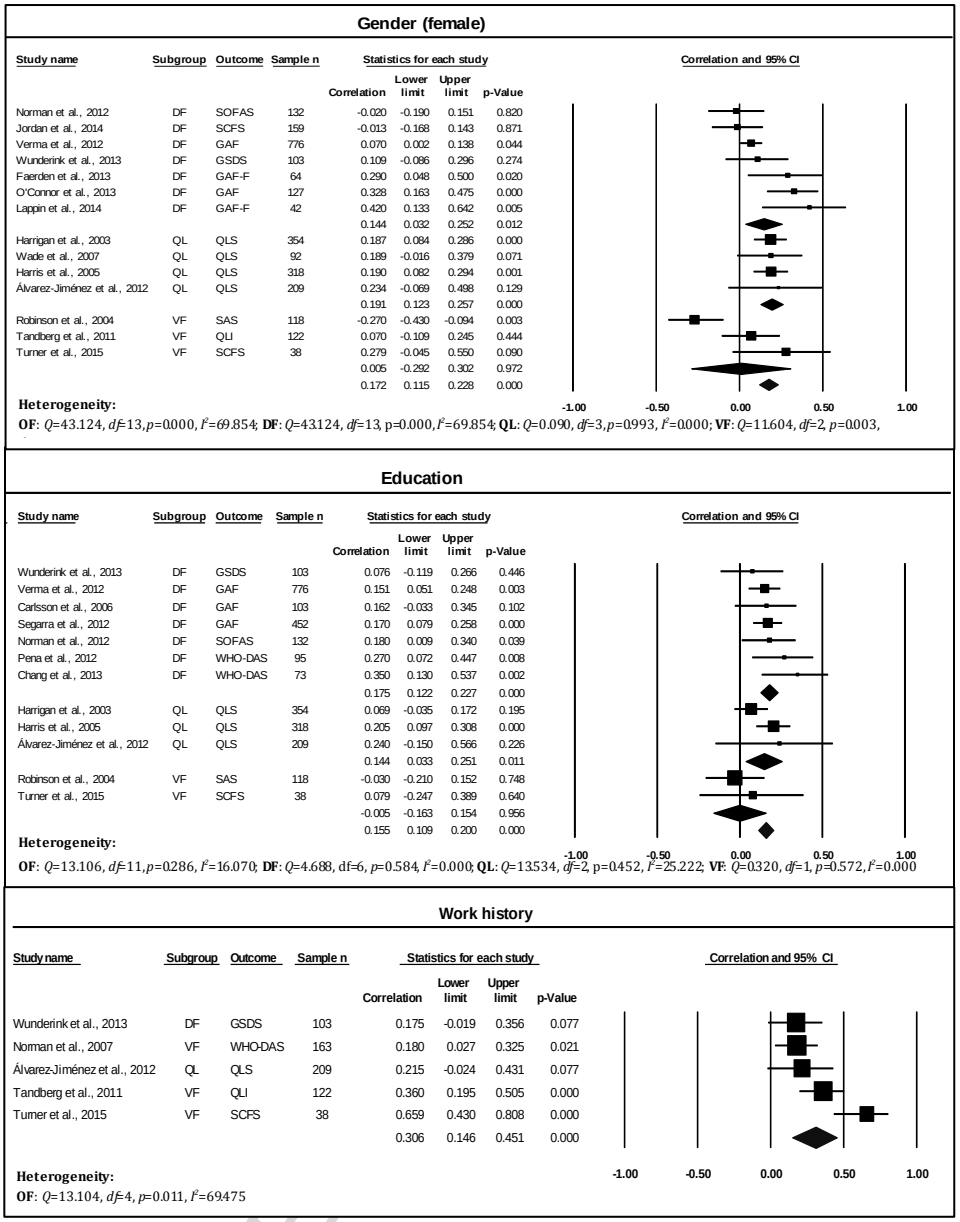
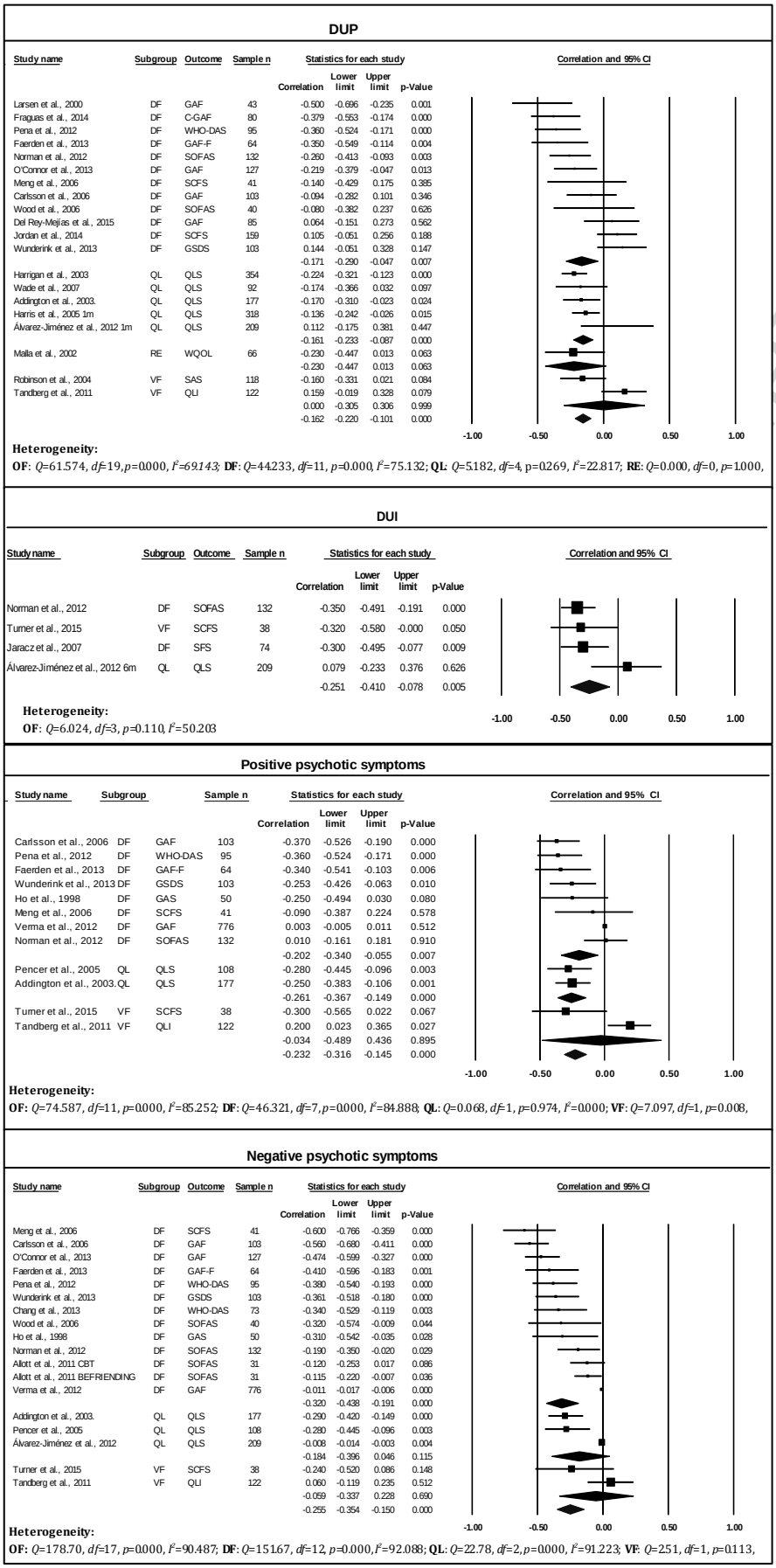
Figure 1. Summary correlations for sociodemographic variables.



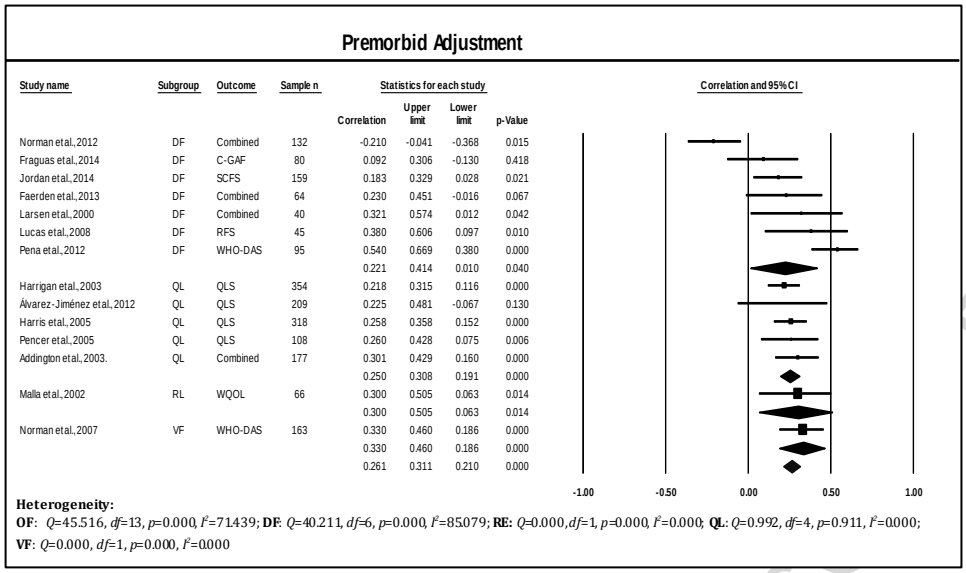
Note 1: OF: Overall functioning; DF: Domain of functioning; QL: Quality of life; VF: Vocational functioning; CI: Confidence interval.
Note 2: GAF: Global Assessment of Functioning Scale; GAF-F: Global Assessment of Functioning Scale split version; GSDS: Groningen Social Disabilities Schedule; SAS: Social Adjustment Scale; SCFS: Strauss-Carpenter Functioning Scale; SOFAS: Social and Occupational Functioning Assessment Scale; QLI: Quality of Life Inventory; QLS: Quality of Life Scale; WHO-DAS: World Health Organization Psychiatric Disability Assessment Schedule.

Figure 2. Summary correlations for clinical variables.



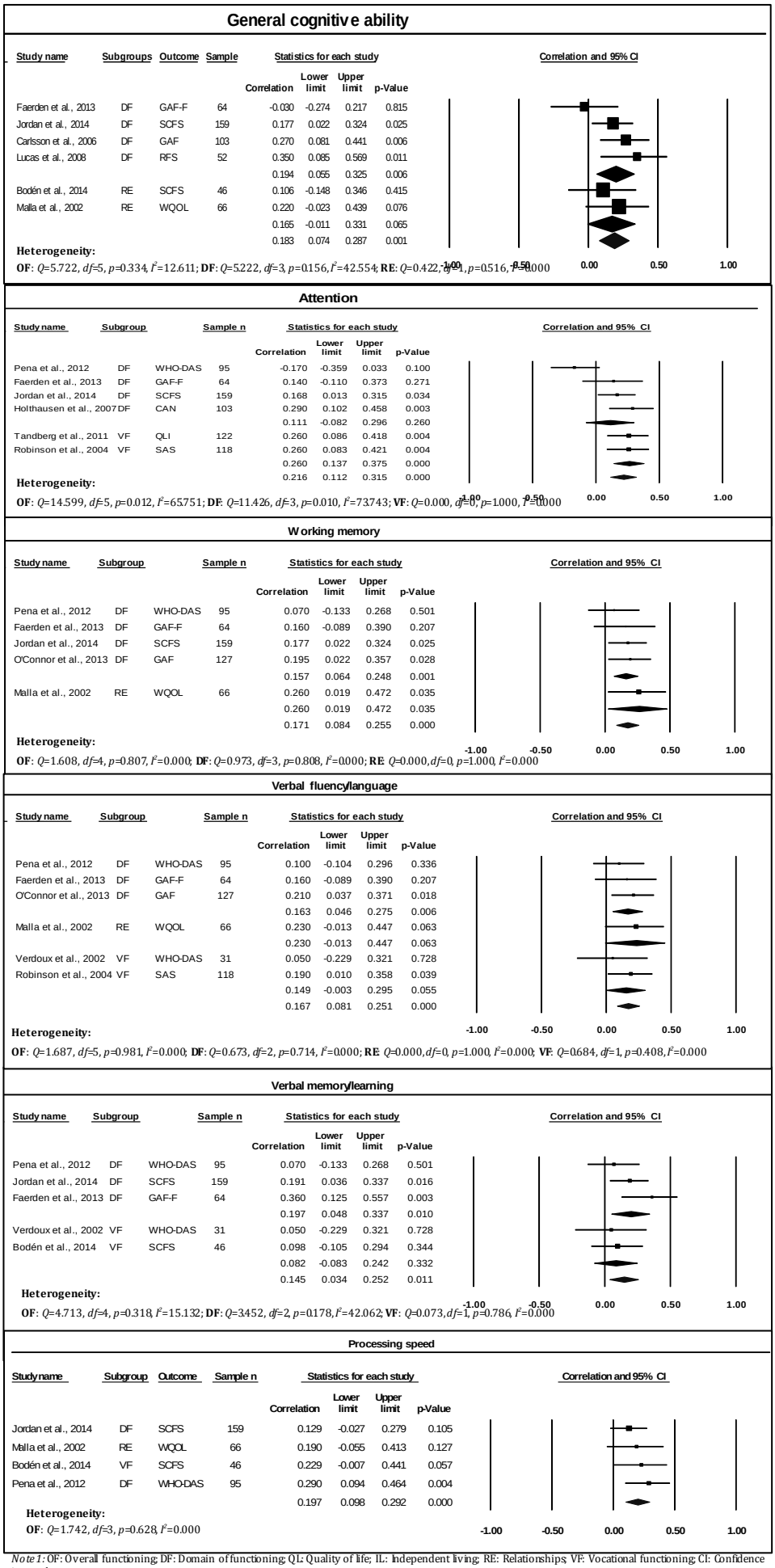
Note 1: OF: Overall functioning; DF: Domain of functioning; QL: Quality of life; RE: Relationships; VF: Vocational functioning; CI: Confidence interval.
Note 2: C-GAF: Children's Global Assessment of Functioning; GAF: Global Assessment of Functioning Scale; GAF-F: Global Assessment of functioning (split version); GAS: Global Assessment Scale; GSDS: Groningen Social Disabilities Schedule; QLI: Quality of Life Inventory; QLS: Quality of Life Scale; SAS: Social Adjustment Scale; SCFS: Strauss-Carpenter Functioning Scale; SFS: Social Functioning Scale; SOFAS: Social and Occupational Functioning Assessment Scale; WHO-DAS: World Health Organization Psychiatric Disability Assessment Schedule; WQOL: Wisconsin Quality of Life Questionnaire.

Figure 3. Summary correlations for premorbid variables.



Note 1: OF: Overall functioning; DF: Domain of functioning; RE: Relationships; QL: Quality of life; VF: Vocational functioning; CI: Confidence interval.
Note 2: C-GAF: Children's Global Assessment of Functioning; GAF: Global Assessment of Functioning Scale; SCFS: Strauss-Carpenter Functioning Scale; QLS: Quality of Life Scale; RFS: Role Functioning Scale; WHO-DAS: World Health Organization Psychiatric Disability Assessment Schedule; WQOL: Wisconsin Quality of Life Questionnaire.
Note 3: Combined measures: Combining Premorbid Adjustment Scale (PAS) of childhood (PAS 1), early adolescence (PAS 2), late adolescence (PAS 3), and adulthood (PAS4) for the following outcomes: GAF-F (Faerden et al., 2013), GAF (Larsen et al., 2000) and QLS (Addington et al., 2003). Combining social PAS and educational PAS (Norman et al., 2012).

Figure 4. Summary correlations for cognitive variables.



Note 1: OF: Overall functioning; DF: Domain of functioning; QL: Quality of life; IL: Independent living; RE: Relationships; VF: Vocational functioning; CI: Confidence interval.

Note 2: CAN: Camberwell Assessment of Needs; GAF: Global Assessment of Functioning Scale; GAF-F: Global Assessment of functioning (split version); PSP: The Personal and Social Performance scale; QLI: Quality of Life Inventory; SAS: Social Adjustment Scale; SCFS: Strauss-Carpenter Functioning Scale; RFS: Role Functioning Scale; WHO-DAS: World Health Organization Psychiatric Disability Assessment Schedule; WQOL: Wisconsin Quality of Life Questionnaire.

Highlights

- Systematic review and meta-analysis.
- All predictors of functional recovery in first-episode psychosis patients.
- Shorter duration of untreated psychosis as an important predictor of functioning.
- Cognitive variables as predictors of long-term functioning.
- Importance of early intervention in first-episode psychosis.