Depressive symptoms during first episode psychosis and functional outcome: A systematic review and meta-analysis

Jessica McGinty\textsuperscript{a}, Rachel Upthegrove\textsuperscript{a,b,c,}

\textsuperscript{a} University of Birmingham, College of Medical and Dental Sciences, Birmingham, United Kingdom
\textsuperscript{b} University of Birmingham, Institute for Mental Health, Birmingham, United Kingdom
\textsuperscript{c} Early Intervention Service, Birmingham Women's and Childrens NHS Trust, Birmingham, United Kingdom

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A B S T R A C T

Objectives: First episode psychosis (FEP) is associated with functional decline. Existing evidence was synthesised to explore the influence of depressive symptoms during FEP on future social, occupational and global functioning.

Methods: Medline, Embase, PsychINFO, Cochrane Library, Open Grey, NICE Evidence and Web of Science were searched from inception to May 2018; Longitudinal studies of FEP patients were included. Study quality was assessed using the Downs and Black instrument. Two meta-analyses were performed using random effect models. The first meta-analysis correlates depressive symptoms during FEP with follow-up Global Assessment of Functioning (GAF) scores. The second meta-analysis shows the odds of long-term functional remission if depressive symptoms are present during FEP.

Results: 4751 unique abstracts were found. 36 articles were included. The first meta-analysis included 7 studies (932 participants) and showed depressive symptoms during FEP were negatively correlated with follow-up GAF scores (\(r = 0.16, 95\% \text{ CI}: 0.24 \text{ to } 0.09, p < 0.001\)). The second meta-analysis of 9 studies (2265 participants) showed weak evidence of an association between the presence of depressive symptoms in FEP and reduction in functional remission (OR = 0.87, 95\% CI: 0.68 to 1.13, \(p = 0.294\)).

Conclusion: Depressive symptoms during FEP are associated with poorer long-term global functioning and may be associated with a reduced chance of achieving functional remission. Clinical trials are needed to identify efficacious management of depressive symptoms in early psychosis.

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1. Introduction

First episode psychosis (FEP) describes the initial phases of psychotic illness and is frequently defined by first treatment contact (Breitborde et al., 2009). Diagnoses include schizophrenia-spectrum disorders, mood disorders and other psychotic disorders such as delusional disorder. FEP tends to be associated with functional decline, including social withdrawal, vocational or academic deterioration and increased dependence on others (Chudleigh et al., 2011; Grant et al., 2001). Whilst a recent systematic meta-analysis found the long-term symptomatic remission rate of FEP to be 58\% (Lally et al., 2017), long-term functional remission after FEP has been quoted at 73.5\% (Chang et al., 2018a, 2018b; Jaracz et al., 2015; Petersen et al., 2008; Ventura et al., 2011) with poor social and occupational functioning persisting despite symptomatic improvement (Chang et al., 2012). Modifiable clinical targets associated with long-term functioning must be identified to improve functional outcomes, especially those present in FEP as it is during these early stages of psychosis that trajectories for long-term outcomes are set (Harrison et al., 2001; Wiersma et al., 1998).

Depressive symptoms during FEP may be an important factor to consider as their prevalence is high during FEP (Häfner et al., 2005). Older theories suggest mood symptoms may be a good prognostic factor as patients resemble a more bipolar type illness on a psychosis-continuum (Craddock et al., 2005), especially as social functioning has been shown to be better in bipolar disorder with psychotic features compared to schizoaffective disorder and poorest in schizophrenia, suggesting the greater the prevalence of affective symptoms the better the outcome (Martin et al., 2015). However, depression is a leading cause of disability world-wide (WHO, 2017) and has been found to be associated with poor occupational, global and interpersonal functioning in chronic schizophrenia (Conley et al., 2007; Foussias et al., 2011).

Previous systematic reviews have investigated the association of many factors with long-term functional outcomes after FEP (Lally et al., 2017; Menezes et al., 2006; Santesteban-Echarri et al., 2017), however more studies have been published since the most re-
cent review completed its searches in March 2016 (Santesteban-Echarri et al., 2017). Furthermore, only two reviews have specifically identified depression during FEP as a potential predictor of functioning, but neither examined its influence with statistical analysis (Menezes et al., 2006; Santesteban-Echarri et al., 2017). To our knowledge, there has been no previous systematic meta-analysis completed investigating the relationship between depressive symptoms during FEP and long-term functional outcome.

1.1. Aims of the study

The aim of this review was to systematically synthesise all existing literature which examine the influence of depressive symptoms during first episode psychosis on any long-term social, occupational and global functional outcome. Our secondary aims were to statistically combine data which analyse the influence of depressive symptoms during FEP on long-term global functioning, and functional remission, through two separate meta-analyses.

2. Materials and methods

This systematic review has been written in accordance with the PRISMA (Moher et al., 2009) and MOOSE guidelines (Stroup et al., 2000). A protocol can be found online (PROSPERO 2017: CRD42017055881).

2.1. Search strategy

The search strategy has been previously described (McGinty et al., 2018). MEDLINE, EMBASE, PsycINFO, Cochrane Library, Open Grey, NICE Evidence and Web of Science (limited to psychology) were searched from inception to 25 Jan 2017 and updated 8 May 2018. The search strategy combined terms describing FEP with AND to terms describing longitudinal study design. For example, MEDLINE was searched with [(initial or first or recent onset or early) adj3 (psychosis or psychotic or schizo*)] AND [longitudinal or follow-up or prospective or retrospective or cohort or case-control]. Search terms were adjusted between database for differences in subject headings and proximity operators. No date, follow-up time or language restrictions applied. Non-English studies were excluded from synthesis as translation was not possible due to time and resource constraints. A list of potentially useful non-English studies can be found in the Appendix (6 studies). Hand searching reference lists and citation searches using Web of Science were completed on all eligible studies. Additionally, authors were contacted and asked of any ongoing or recently published studies.

2.2. Study selection

Articles were assessed against the following eligibility criteria: a) longitudinal study design (prospective or retrospective); b) all participants experiencing FEP at baseline; c) mean age of participants between 13 and 45 years; d) a credible measure of depressive symptoms during FEP at baseline; e) any measure of social, occupational or global functioning (e.g. GAF, SOFAS etc.), or functional remission or recovery (any definition as justified by authors) measured at a specified follow-up time; and e) statistics that associated baseline depressive symptoms with follow-up functional outcome. Randomised controlled trials (RCTs) were excluded as they do not focus on the specific influence of depressive symptoms. Conference proceedings were excluded as they do not sufficiently report to allow adequate quality assessment. Studies exclusively including patients with first episode substance-related or affective psychosis (i.e. major depressive disorder or bipolar disorder with psychotic symptoms) were excluded, however studies which included these diagnoses with non-affective psychoses (i.e. schizophrenia spectrum and other psychotic disorders) were included. Studies reporting an overall recovery or remission outcome with a clinical and functional component were included. Those reporting quality of life, social network and social cognition as outcomes were excluded.

One author screened titles and abstracts before thoroughly assessing the full text of potentially eligible studies. Another author checked the final included study list. Any disagreements between authors were discussed with reference to the full text. Where eligibility was unclear, authors were contacted.

2.3. Data extraction and quality assessment

One author, non-blind, extracted data from studies into an Excel spreadsheet and discussed with the second author. Data was extracted on study identifying details; population characteristics; recruitment methods and period; measures of depressive symptoms; measures of social, occupational or global functional outcome reported; and calculated statistics with p-values. Where data was missing, authors were contacted. Where two studies reported the same sample, the study with the longer follow-up period was chosen for calculations. Where follow-up was the same, the study with the larger sample size was chosen. A template data extraction table was piloted on the first five studies.

Quality of studies was assessed using the Downs and Black Instrument (Downs and Black, 1998). This is a 27-item check list tool which allows homogenous quality assessment across studies of different design. It has been shown to be one of the few tools credible enough for use in systematic reviews of observational studies (Deeks et al., 2003). 5 items of the tool were not used as they specifically relate to RCTs. Attribution bias was assumed high if attribution rate was > 20% and the characteristics of those lost to follow-up were not described. Study recruitment using consecutive or all admissions were deemed low risk of selection bias (item 11). Studies giving little or no information on non-response rate were deemed unclear risk of non-response bias (item 12). Quality assessment was performed non-blind by one author.

2.4. Statistical analysis

Two meta-analytic calculations were performed. Pearson’s r was calculated from studies correlating baseline depressive symptoms with Global Assessment of Functioning (GAF) scores at follow-up. Studies reporting GAF total and GAF (f) were combined but are also reported as separate sub groups. One study reporting Global Assessment Scale (GAS) (Salokangas, 1999) was included. For one study (Sonmez et al., 2013), Cohen’s d was calculated using pooled published means (SD), and then converted to r using methods described by Borenstein et al. (2009). Sensitivity analysis included the exclusion of these two papers.

In a second meta-analysis, odds ratios (OR) were calculated from studies reporting functional remission at follow-up with depressive symptoms at baseline compared to no depressive symptoms at baseline. Definitions of functional remission (including definitions of functional recovery or good outcome ) had to have fulfilment of multiple criteria as per individual author’s definitions, for instance joint fulfilment of an occupational, social relationship, and independent living achievements. Studies using definitions that included clinical and functional components were combined with those exclusively reporting functional remission but are also reported as separate subgroups. InOR were used. Where count data was given, OR were calculated using methods described by Altman (1991). Coefficients of logistic regressions ( ) were exponentiated to obtain OR. Inverse of OR were taken where studies reported results in the opposite direction. Where continuous data was given, Cohen’s d was calculated and converted to lnOR using methods outlined by Chinn (2000).

Univariate data was used where possible due to the heterogeneity in confounders controlled for amongst studies. If unavailable, data
from regression models were used and excluded as part of sensitivity analyses. Random effects models were used as inherent heterogeneity was anticipated. Heterogeneity was assessed by calculating $I^2$. Analyses were two-tailed, with a significance of 0.05. Publication bias was examined by Egger’s (Egger et al., 1997) and Begg’s (Begg and Mazumdar, 1994) test. Funnel plots for each meta-analysis are also presented. Where publication bias was found to be significant, the Duval and Tweedie trim and fill method was used to calculate estimates using inputted missing values (Duval and Tweedie, 2000). Meta-regression was performed to determine the influence of length of follow-up and severity of depressive symptoms during FEP on r for the GAF outcome. Mean depressive symptom scores were standardized by dividing by the standard deviation. Meta-analytic calculations were performed using Comprehensive Meta-Analysis Version 3 and Review Manager Version 5.3.

3. Results

4751 unique abstracts were found and screened. 633 full texts were assessed for eligibility and 597 were excluded (see Fig. 1). Thirty-six studies, reporting on 30 unique samples of 5631 followed-up participants, fulfilled the eligibility criteria and were included in qualitative review. The mean age at baseline was 27.6 (8.1) and 60.8% were male. The median length of follow-up time was 2.6 years (IQR 1.5 years). Thirteen samples were recruited from early intervention services, 8 from inpatients, four from outpatients and four from both inpatients and outpatients. For one study, the recruitment setting was not reported. 14 samples included patients with FEP that included affective-psychoses and three samples included patients with substance-related psychosis. The main outcomes reported were functional remission (14 studies), Global Assessment of Functioning (GAF) (8 studies) and vocational outcome (6 studies). Other outcome measures included Specific Levels of Functioning Scale (SOFAS), Strauss and Carpenter Scale and Disability Assessment Schedule (DAS). Studies were published from 1987 to 2018. A summary of included studies is presented in Table 1.

![Fig. 1. Study selection process.](image-url)
<table>
<thead>
<tr>
<th>Location</th>
<th>Study type</th>
<th>Setting</th>
<th>Population/diagnoses</th>
<th>Recruitment dates</th>
<th>N recruited</th>
<th>N at follow-up</th>
<th>Follow-up period</th>
<th>Functional outcome measure</th>
<th>Depressive symptom measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copenhagen, Aarhus County; Denmark</td>
<td>Sub study of a trial</td>
<td>Inpatient and outpatient OPUS cohort; schizophrenia-spectrum; 18-45 years</td>
<td>Jan 1998 - Dec 2000</td>
<td>468</td>
<td>255</td>
<td>5 years</td>
<td>Recovered defined as stable remission of negative and psychotic symptoms during the last 2 years (based on LFS); not hospitalised or lived in supported housing facility during the last 2 years; and GAF (&gt;60 and had job/studying Working defined as having a job, self-employed or studying Fulfill ICD-10 criteria for depression</td>
<td>CESD-R</td>
<td>40/255 recovered 76/255 working</td>
<td>OR = 1.05 (95% CI: 0.49 - 2.24)</td>
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<td>496</td>
<td>304</td>
<td>10 years</td>
<td>Full recovery defined as stable remission of negative and positive symptoms; no psychiatric admissions to hospital or living in supported accommodation for the past 2 years; currently engaged in work or study; and have a GAF/PSP score of over 60 Fulfill ICD-10 criteria for depression</td>
<td>43/304 achieved full recovery</td>
<td>OR = 1.08 (95% CI: 0.84 - 1.38)</td>
<td>0.571</td>
</tr>
<tr>
<td>Melbourne; Australia</td>
<td>Sub study of a trial</td>
<td>Early intervention service EPPIC cohort; schizophrenia-spectrum; 15-24 years</td>
<td>Oct 2005 - Apr 2006</td>
<td>41</td>
<td>35</td>
<td>6 mo.</td>
<td>Vocational recovery defined as securing a place in competitive employment or attending a course of education at any point during the 6-month follow-up period</td>
<td>CESD-R</td>
<td>23/35 achieved vocational recovery</td>
<td>NA</td>
</tr>
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<td>Ontario; Canada</td>
<td>Prospective cohort</td>
<td>Early intervention service Heads up! cohort; schizophrenia spectrum; 18-55 years</td>
<td>NA</td>
<td>145</td>
<td>144</td>
<td>Avg. 10 mo.</td>
<td>GAF, SOFAS, PANSS</td>
<td>PANSS depressive symptoms: depression defined as obtaining 3-7 points on subscale P</td>
<td>NA</td>
<td>r = 0.293 (95% CI: 0.523 to 0.061) (n = 70)</td>
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<tr>
<td>Sweden</td>
<td>Prospective cohort</td>
<td>Multicentre, outpatient Swedish Parachute Project cohort; Schizophrenia spectrum, affective psychoses, other psychotic disorder; 18-45 years</td>
<td>Jan 1996 - Dec 1997</td>
<td>120</td>
<td>115</td>
<td>1 year</td>
<td>3 years GAF (dichotomised as ≤ 60 low GAF score; &gt;60 - high GAF score)</td>
<td>BPRS depressive symptoms: depression defined as obtaining ≥ 3 points on subscale</td>
<td>81/115 achieved high GAF score 68/106 achieved high GAF score</td>
<td>t(1) = 5.135 (OR = 0.39) t(1) = 21.812 (OR = 0.13)</td>
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<td>Hong Kong; China</td>
<td>Prospective cohort</td>
<td>Inpatient and outpatient</td>
<td>Schizophrenia spectrum; 18–55 years</td>
<td>NA</td>
<td>138</td>
<td>93</td>
<td>3 years</td>
<td>Vocational outcome defined by dichotomisation of length of full-time employment over 3 years, MARDG = 0.14 (95% CI: 0.55 to 0.26), t = 0.70, p = 0.482</td>
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<td>Schizophrenia spectrum; 18–55 years</td>
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<td>114</td>
<td>1 year</td>
<td>Depression as PANSS depression, r = 0.175, p = 0.062</td>
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<tr>
<td>Hong Kong; China</td>
<td>Sub-study of trial</td>
<td>Early intervention service</td>
<td>EASY program cohort; schizophrenia spectrum, affective psychoses, other psychotic disorders; 15–25 years</td>
<td>Nov 2010 – Aug 2011</td>
<td>160</td>
<td>156</td>
<td>1 year</td>
<td>Functional remission defined by SOFAS score &gt;60, RFS independent living and immediate social network subscale scores &gt;5, RFS work productivity and extended social network subscale scores &gt;4, and engaged in competitive employment (full- or part-time work or full-time study) at 6 and 12-months, CDSS = 31/156, OR = 0.69, p = 0.002</td>
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<tr>
<td>Hong Kong; China</td>
<td>Sub-study of trial</td>
<td>Early intervention service</td>
<td>EASY program cohort; schizophrenia spectrum, other psychotic disorders; 15–25 years</td>
<td>Jul 2001 – Aug 2003</td>
<td>617</td>
<td>478</td>
<td>3 years</td>
<td>Health trajectory as measured by SOFAS scores, 4 distinct trajectories: early improved, gradually improved, improved-deteriorated, and persistently poor, CGI-BP = 2.1 (SD 1.2), t = 1.9, p = 0.14</td>
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<td>Location</td>
<td>Study type</td>
<td>Setting</td>
<td>Population/diagnoses</td>
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<tr>
<td>Melbourne; Australia</td>
<td>Retrospective cohort</td>
<td>Early intervention service</td>
<td>EPPIC cohort; schizophrenia spectrum, affective psychoses, other psychotic disorders, substance-related psychoses; 15–29 years</td>
<td>Jan 1998 – Dec 2000</td>
<td>661</td>
<td>566</td>
<td>Avg. 14.6 mo.</td>
<td>Functional recovery defined as occupational/vocational status as measured by the MVSI (paid/unpaid full- or part-time employment or volunteer, being a school/university student, or head of household with employed partner); and independent living according to MLCI (head of household, living alone, with partner, or with peers, and living with family with minimal supervision)</td>
<td>CGI-BP depression score</td>
<td>246/556 achieved functional recovery</td>
</tr>
<tr>
<td>Melbourne; Australia</td>
<td>Retrospective cohort</td>
<td>Early intervention service</td>
<td>Never exposed to adequate antipsychotic; Schizophrenia-spectrum, affective psychoses, substance-related psychoses, other psychotic disorders; 15–29 years</td>
<td>Jan 1998 – Dec 2000</td>
<td>108</td>
<td>100</td>
<td>Avg. 15.0 mo.</td>
<td>Functional recovery defined as having a regular activity based on MVSI; and independent living according to the MLCI</td>
<td>CGI-BP depression score</td>
<td>33/100 achieved functional recovery</td>
</tr>
<tr>
<td>Maryland; USA</td>
<td>Prospective cohort</td>
<td>Inpatients and day hospital program</td>
<td>Schizophrenia spectrum, affective psychoses, other psychotic disorders; 18–45 years</td>
<td>Aug 2003 – Oct 2006</td>
<td>94</td>
<td>71</td>
<td>Avg. 6.1 mo.</td>
<td>Occupational status dichotomized into employed and unemployed. Employed defined as levels 1–5 of MVI (full-time gainful employment, homemaker or student, part-time gainful employment, retired, full or part-time volunteer) and unemployed defined as levels 6–7 of MVI (on medical leave or unemployed).</td>
<td>CDSS 56/71 achieved occupational status; CDSS: 5.6 (SD 5.7)</td>
<td>15/71 did not achieve occupational status; CDSS: 9.2 (SD 7.6)</td>
</tr>
<tr>
<td>Oslo; Norway</td>
<td>Prospective cohort</td>
<td>Psychiatric treatment units</td>
<td>Schizophrenia spectrum, affective psychoses, other psychotic disorders; 18–65 years</td>
<td>Jul 2004 – Jun 2006</td>
<td>71</td>
<td>64</td>
<td>1 year</td>
<td>GAF (f)</td>
<td>CDSS</td>
<td>NA</td>
</tr>
<tr>
<td>London; England</td>
<td>Prospective cohort</td>
<td>Inpatients</td>
<td>Northwick Park Study cohort; first episode schizophrenia only</td>
<td>Aug 1979 – Dec 1981</td>
<td>51</td>
<td>44</td>
<td>5 years</td>
<td>Occupational level classified in terms of the Office of Population Censuses and Surveys Classification of Occupations (1980). Good outcome: occupation better or the same as at first admission. Poor outcome: unemployed or a poorer level of occupation</td>
<td>CATEGO: simple depression syndrome</td>
<td>NA</td>
</tr>
<tr>
<td>Study Type</td>
<td>Setting</td>
<td>Location</td>
<td>Population/diagnoses</td>
<td>Treatment</td>
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</table>
| Early and non-early intervention | Hospital | Spain | Schizophrenia-spectrum; brief psychotic disorder, other psychotic disorders; other psychotic spectrum, affective spectrum, other spectrum; 752 on entry, 132/174 did not meet neuroleptic dose criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); and adequate understanding as symptom remission in accordance with PROOF criteria (<4 for 6 months); 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</tr>
</thead>
<tbody>
<tr>
<td>Depression spectrum</td>
<td>0.24</td>
<td>0.16</td>
<td>0.07</td>
<td>0.09</td>
<td>0.00</td>
</tr>
<tr>
<td>Schizophrenia only</td>
<td>0.37</td>
<td>0.35</td>
<td>0.28</td>
<td>0.26</td>
<td>0.16</td>
</tr>
</tbody>
</table>

**Notes:**
- Depression spectrum includes psychotic disorders and affective disorders.
- Schizophrenia only includes people with a diagnosis of schizophrenia only.
- The data is from various studies and cohorts, including:
  - 1984: Study by Mattsson et al., 2007.
  - 1999: Study by Minor et al., 2007.
  - 2001: Study by Rammou et al., 2015.
  - 2004: Study by Mattsson et al., 2008.
  - 2008: Study by Minor et al., 2008.
<table>
<thead>
<tr>
<th>Location</th>
<th>Study type</th>
<th>Setting</th>
<th>Population/diagnoses</th>
<th>Recruitment dates</th>
<th>N recruited</th>
<th>N at follow-up</th>
<th>Follow-up period</th>
<th>Functional outcome measure</th>
<th>Depressive symptoms measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumbai, India</td>
<td>Prospective cohort</td>
<td>Inpatients</td>
<td>Schizophrenia; 18-45 years</td>
<td>1993-2007 (study period)</td>
<td>201</td>
<td>101</td>
<td>10 years</td>
<td>Good outcome defined as</td>
<td>HDRS 61/101 achieved good outcome: HDRS 12.5 (SD 5.3)</td>
<td>[SMD = \frac{1.6}{\text{SD 5.2}} (95% CI: 0.5 to 3.7)] 0.14</td>
</tr>
<tr>
<td>Oslo, Norway</td>
<td>Prospective cohort</td>
<td>Psychiatric treatment centres</td>
<td>TOP cohort; non-affective psychoses: schizophrenia spectrum, other psychotic disorders; 18-65 years</td>
<td>March 2004-February 2010</td>
<td>198</td>
<td>127</td>
<td>1 year</td>
<td>GAF (f)</td>
<td>Mean GAF in those with: Persistent dep: 42.42 (SD 11.22); dep follow-up: 43.82 (13.35); dep baseline: 57.48 (15.58); No dep: 56.60 (SD 16.07)</td>
<td>Significance between persistent dep and no dep. Significance between persistent dep and baseline dep.</td>
</tr>
<tr>
<td>Rogaland County, Oslo, Norway, Denmark</td>
<td>Prospective cohort</td>
<td>Inpatients and outpatients</td>
<td>Schizophrenia spectrum; affective psychoses, other psychotic disorders; 18-65 years</td>
<td>NA</td>
<td>299</td>
<td>186</td>
<td>10 years</td>
<td>GAF (f)</td>
<td>Mean GAF in those with persistent dep: 52 (95% CI: 48-58); no dep: 48 (95% CI: 46-50.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Madras, Southern India</td>
<td>Prospective cohort</td>
<td>Outpatients</td>
<td>Schizophrenia, as per modified Feigner's criteria</td>
<td>1981-1982</td>
<td>50</td>
<td>40</td>
<td>10 years</td>
<td>Good occupational outcome defined as no change or improvement in work performance and level of earned income</td>
<td>PSE simple depression syndrome 21 achieved good occupational outcome (of which 15 had PSE depression) 19 did not achieve good occupational outcome (of which 13 had PSE depression)</td>
<td>OR = 1.15 0.83</td>
</tr>
<tr>
<td>The Hague, The Netherlands</td>
<td>Prospective cohort</td>
<td>Outpatients</td>
<td>Non-affective psychoses: schizophrenia spectrum; other psychotic disorders;</td>
<td>December 2009-December 2011</td>
<td>153</td>
<td>153</td>
<td>1 year</td>
<td>PSP work and study problem domain: 2.37 (SD 1.09)</td>
<td>OR = 0.272 (a &lt;0.05)</td>
<td></td>
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| NS | N of case |你看 |＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜＜&n
3.1. GAF outcome meta-analysis

Seven studies, with 932 participants, were included for the GAF outcome meta-analysis. Two studies reporting GAF were excluded as they were duplicate samples. The median length of follow-up time was 12 months (IQR: 12–42 months). Depressive symptoms during FEP were measured by the Calgary Depression Scale for Schizophrenia (CDSS) (two studies); depression subscale from the Positive and Negative Syndrome Scale (PANSS) (2 studies); Brief Psychiatric Rating Scale (BPRS) (1 study); the Montgomery-Asberg Depression Rating Scale (MADRS) (1 study) and the Centre of Epidemiologic Studies Depression Scale-Revised (CESD-R) (1 study). 3 studies used GAF total, 3 used GAF (0) and the final used GAS.

The correlation coefficient calculated shows that depressive symptoms during FEP are negatively correlated with follow-up GAF scores with statistical significance ($r = 0.16$, $95\%$ CI: 0.24 to 0.09, $p < 0.001$) (Fig. 2). No significant heterogeneity ($I^2 = 23.3$, $p = 0.26$) nor publication bias (Egger's test $p = 0.62$, Begg's test $p = 0.37$) was found (Fig. 3). Estimates of $r$ did not differ in direction nor significance during sensitivity and sub-group analyses (Table 2).

Meta-regression included 6 studies with 776 participants. One study was excluded as severity of depressive symptoms during FEP was not reported (Salokangas, 1999). In meta-regression, $r$ was not related to length of follow-up time or severity of depressive symptoms during FEP ($p = 0.1274$).

3.2. Functional remission meta-analysis

Nine studies, with 2265 participants, were included in the functional remission meta-analysis. Three studies were excluded as they were duplicate data and 2 reported inadequate reporting of information for imputation. The median length of follow-up time was 3 years (IQR: 1.25–10 years). Two studies measured depressive symptoms during FEP with CDSS, two used the Hamilton Depression Rating Scale (HDRS), two used depression subscales of the Clinical Global Impression scales, one used a depression subscale of the PANSS and the final study used depression diagnostic criteria.

The OR calculated show the odds of functional remission are reduced if depressive symptoms are present during FEP; however this was not statistically significant in a random effects model (OR = 0.87, $95\%$ CI: 0.68 to 1.13, $p = 0.294$) (Fig. 4). Significant heterogeneity was present ($I^2 = 65.6$, $p = 0.003$). Publication bias was significant with Begg's test ($p = 0.02$), but not Egger's test ($p = 0.11$). Duval and Tweedie trim and fill method found 2 missing values and with these estimated OR as 1.00, $95\%$ CI: 0.75 to 1.32 (Fig. 5). OR were reduced in sensitivity analysis but not statistically significant (Table 2).

No significant heterogeneity was found using only studies with clinical and functional definitions of remission ($I^2 = 26.9$, $p = 0.250$), however this was present using studies with functional remission definition alone ($I^2 = 78.3$, $p = 0.001$). In sub-group analysis, there was no significant difference in OR estimates using studies with functional with clinical remission criteria and those using only functional remission criteria ($p = 0.401$).

3.3. Quality assessment

A summary of quality assessment for individual studies can be found in the Appendix. The largest source of potential bias came from incomplete follow-up. Of the 36 included studies, $23$ ($63.9\%$) reported an attrition rate $>20\%$. Around half of these ($12/23$, $52.2\%$) either found significant differences of those lost to follow-up (2 studies) or did not report characteristics of those lost to follow-up (10 studies) and were therefore deemed high risk of attrition bias (33.3\% of all studies). Of the 13 studies (36.1\%) with attrition rate $<20\%$, 9 did not describe baseline characteristics of those lost to follow-up, making attrition bias difficult to assess.

Of the 36 studies, $27$ ($75\%$) recruited a representative sample (defined as all or consecutive admissions). However as 30 studies (83.3\%) did not report response rate, it is difficult to assess if studies included a final representative sample of FEP patients. Furthermore, 25 of 36 studies (69.4\%) did not report if functional outcome was measured blind to depressive symptom status at baseline. 4 of 36 studies (11.1\%) used a retrospective design and may be at risk of record bias.

For the GAF meta-analysis (7 studies), the highest source of potential bias was also from incomplete follow-up, with four of seven studies deemed high risk of attrition bias. Five studies approached a representative sample, however no studies gave detail on response rate, making it unclear if representative FEP samples were included. Only one study reported functional outcome being measured blind to baseline depressive symptom status.

For the functional remission meta-analysis (9 studies), four of nine studies had high risk and three studies low risk attrition bias. All nine studies approached a representative sample, of which two included representative samples. For the remaining seven studies it is unclear if representative samples were included.

4. Discussion

To our knowledge, this is the first systematic meta-analysis to specifically summarise existing literature on the relationship between depressive symptoms during FEP and long-term social, occupational and global functional outcomes. Investigating this longitudinal relationship is especially important in helping to accurately identify modifiable risk factors of poor long-term outcomes during the early stages of psychotic disease. Our findings suggest depressive symptoms during FEP are associated with poorer global long-term functioning, within a median follow-up time of 12 months. These results are strengthened by sensitivity and sub-group analyses where results remained signif-
We found weak evidence for a relationship between depressive symptoms during FEP and functional remission, however this was not statistically significant. This is consistent with a previous systematic review, which found depressive symptoms not to be associated with overall functioning after FEP (Santesteban-Echarri et al., 2017). Additionally, the results of the Duval and Tweedie trim and fill method may suggest that there is no association between depressive symptoms during FEP and functional remission, however our review included additional data and reports a clear result in GAF functional outcome. A lack of evidence for the functional remission outcome may be a result of insufficient current evidence (Altman and Bland, 1995) or may reflect the heterogeneous nature of functional remission criteria used amongst studies. Several other covariates are likely to influence this multifaceted outcome, and the influence of other covariates combined may be stronger than that of depressive symptoms alone, despite the

**Table 2**

Summary of sensitivity analyses and sub-group analyses.

<table>
<thead>
<tr>
<th>GAF outcome</th>
<th>N studies</th>
<th>N participants</th>
<th>r or OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity analysis Exclude study where significant statistical transformation (Sonmez et al., 2013)</td>
<td>6</td>
<td>0.15</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Exclude study using GAS (Salokangas, 1999)</td>
<td>6</td>
<td>0.15</td>
<td>0.07</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Exclude study using regression data (Faerden et al., 2013)</td>
<td>6</td>
<td>0.15</td>
<td>0.08</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Exclude all 3 of above</td>
<td>4</td>
<td>0.12</td>
<td>0.23</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>Subgroup analysis Studies using GAF total</td>
<td>4</td>
<td>0.15</td>
<td>0.23</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Studies using GAF (f)</td>
<td>3</td>
<td>0.18</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Functional remission outcome**

<table>
<thead>
<tr>
<th>N studies</th>
<th>N participants</th>
<th>OR or odds ratio</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity analysis Exclude study using never-treated (Lambert et al., 2008)</td>
<td>8</td>
<td>0.82</td>
<td>0.63</td>
<td>1.34</td>
</tr>
<tr>
<td>Subgroup analysis Studies with definition exclusively functioning</td>
<td>5</td>
<td>0.81</td>
<td>0.51</td>
<td>0.348</td>
</tr>
<tr>
<td>Studies with definition with clinical and functioning component</td>
<td>4</td>
<td>0.88</td>
<td>0.56</td>
<td>0.583</td>
</tr>
</tbody>
</table>

| Heterogeneity Q value: 0.078, 0.780 |

![Funnel plot](image1)

**Fig. 3.** Funnel plot of studies included in GAF scores meta-analysis.

![Forest plot](image2)

**Fig. 4.** Forest plot showing odds of functional remission if depressive symptoms are present during FEP, compared to if no depressive symptoms are present.
strong evidence of a relationship between depressive symptoms during FEP and general functioning demonstrated in the first meta-analysis.

To our knowledge, no widely-accepted functional remission definition for psychosis exists, as compared to symptomatic remission which can be defined by the Remission in Schizophrenia Working Group (RSWG) criteria for instance (Andreasen et al., 2005). Although studies define and justify their individual definitions of function remission, definitions were heterogeneous with many combining different scales to measure similar parameters or using the same scale with different cut off scores. It is arguable that combining studies that estimate different quantities is inappropriate (Higgins and Green, 2011), although previous meta-analyses have taken similar approaches when combining functional recovery outcomes (Lally et al., 2017; Santesteban-Echarri et al., 2017). It may be more meaningful to combine studies where the same functional remission criteria apply to further investigate this relationship.

The inclusion of patients with mild severity of depressive symptoms may also weaken the result for the functional remission outcome. It is perhaps possible that patients with severe depressive symptoms who fulfill criteria for depressive disorder diagnosis during FEP are more likely to have poor outcomes. Additionally, we were not able to explore the influence of persistent and non-persistent depressive symptoms as many studies only use depressive symptom score at presentation in their analysis. Sonmez et al. (2013) have shown that those with persistent depression during the first 12 months after FEP have significantly worse global functioning at 12 months compared to those with non-persistent baseline depression and significantly worse global functioning during the first five years following FEP compared to those who are not depressed in the first 12 months (Sonmez et al., 2016). The influence of a diagnosis of depressive disorder and the persistency of depressive symptoms remain areas of further research.

Whereas the cross-sectional relationship between depressive symptoms and poor global functioning during FEP (Faerden et al., 2013; Humphries et al., 2017) may be explained by the direct consequence of depressive symptoms, such as fatigue, poor cognitive function or deriving little pleasure from activities (Mehta et al., 2014), it is tentative to speculate how depressive symptoms during FEP can be associated with poor global functioning longitudinally. Causal inferences cannot be assumed, although the exclusive inclusion of longitudinal studies increases the plausibility of a cause-effect association. Other factors may confound the relationship, such as premorbid adjustment and level of functioning at baseline which have both been shown to be associated with depressive symptoms during FEP (Faerden et al., 2013; Humphries et al., 2017; Sonmez et al., 2013) and associated with overall functioning after FEP in a recent systematic review (Santesteban-Echarri et al., 2017). Negative symptoms during FEP have also been shown to be significantly related to worse overall functioning (Santesteban-Echarri et al., 2017). Alternatively, depressive symptoms will lead to subsequent risk of further depression after FEP (Sonmez et al., 2013; Sonmez et al., 2016) and may in part, directly explain poorer follow-up. The presence of depression itself may lead to a lack of motivation to engage with interventions known to improve outcome, such as cognitive remediation, vocational interventions and Independent placement and support (IPS) if offered.

A clear strength of this review is the broad search strategy designed to retrieve all longitudinal studies of FEP patients. Additionally, as searches were recently updated, and thorough citation and reference searching were completed, we are confident all relevant articles have been included. Thirdly, using established statistical conversion methods, summary statistics have been able to be combined in meta-analyses for the first time, further adding to the literature. Our findings are also strengthened by consistent results during sensitivity analyses. However, there are limitations. Firstly, as many studies were at high risk of attrition and possible selection bias, the generalisability of results may be limited. Additionally, publication bias may have resulted in underestimates of true effect size. Significant heterogeneity was also present and is perhaps explained by the differing, albeit similar, definitions of functional remission used amongst studies. As univariate data was used for meta-analysis, confounders have not been adjusted for. Future research should aim to use individual participant data to perform persistent adjusted analyses which control for potential confounders such as baseline functioning. Lastly, the exclusion of non-English studies (due to time and resource constraints) may have led to language bias and may have contributed to significant publication bias found for the functional remission meta-analysis.

However, our findings add to the evidence that depressive symptoms are associated with poorer long-term global functioning, and may provide a modifiable clinical target in the early stages of psychotic illness. Currently there are is a lack of specific guidelines on how to manage or prevent depression during FEP, although there is evidence that antidepressants may have a role (Gregory et al., 2017) and our findings suggest that the longer term impact of identification or preven-
tion of depression in FEP may have longer term consequences. Ongoing functional impairment remains a problem in psychotic illness, with the rate of functional remission falling behind that of symptomatic remission. Further trials are needed to identify efficacious management of depressive symptoms during FEP to further improve functional outcomes.

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Contributors

JM and RU devised the conceptual design of the study. JM selected studies, extracted data, assessed study quality and performed statistical analysis. JM and RU wrote the report. Both authors critically reviewed and approved the final manuscript.

Declaration of competing interest

We declare no competing interests.

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