Post-Traumatic Stress Disorder (PTSD) in People with Psychosis: Acceptability of PTSD Interventions and the Prevalence and Risk Factors of Psychosis-Related PTSD

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Thesis Portfolio Abstract

Background: This portfolio contains two systematic reviews and several meta-analyses in the clinical field of psychosis and trauma. The aim of the first review was to synthesise findings relating to the acceptability of post-traumatic stress disorder (PTSD) treatments in people with psychosis. The aim of the second review was to synthesise and meta-analyse the prevalence figures and risk factors for psychosis-related PTSD (PR-PTSD).

Methods: The reviews were conducted using narrative and meta-analytic techniques. Search processes followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results and Conclusion: Detailed statistics are presented for each review. The first review found that PTSD treatments are generally acceptable in people with psychosis. Non-participation rates were low, feedback about the tolerability of treatments was generally good and dropout rates were comparable to other PTSD treatment studies. The second review largely agrees with earlier studies' conclusion that the evidence base for PR-PTSD as it stands makes it difficult to draw conclusions about prevalence rates. Hopefully, as awareness is raised into the issue of PR-PTSD firmer assessment processes will emerge, leading to more robust meta-analytic findings and research syntheses in the future.

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Chapter 1.

Systematic review prepared for submission to: Clinical Psychology Review

Acceptability of Treatments for Post-Traumatic Stress Disorder in People With Psychosis: Systematic Review and Meta-Analyses

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Abstract

Research suggests that clinicians are reluctant to offer treatments for post-traumatic stress disorder (PTSD) to people with psychosis due to fears that they will not be able to tolerate them and they may be harmful through exacerbating symptoms or increasing levels of risk. PTSD treatments have been found to be effective in psychotic populations; however, given that they are somewhat controversial, this review aimed to assess their acceptability. Studies' findings relating to treatment credibility and satisfaction, attendance and adverse events were synthesised. Meta-analyses were carried out on non-participation and dropout data. Non-participation rates were low and had minimal heterogeneity. Dropout rates were significantly higher in studies from the USA than from The Netherlands, but it is likely that this was confounded by use of a stabilisation phase. Studies that did not use a stabilisation phase had higher retention of participants, perhaps because they experienced gains more quickly due to attending active treatment, which may have made them more motivated to continue. Participants generally found the treatments to be acceptable and reported satisfaction. Adverse effects are discussed in relation to this population. Finally, further clinical implications and study limitations are discussed.

Introduction

Between 50% and 90% of people with psychosis have experienced at least one trauma in their lives (Read, van Os, Morrison & Ross, 2005). Accordingly, the prevalence of post-traumatic stress disorder (PTSD) in people with psychotic disorders is relatively high, ranging from 12% to 29% (Achim et al., 2011). This is a clinically important issue as comorbid PTSD in psychosis has been associated with more severe PTSD symptoms, poorer quality of life and increased use of mental health services (Fan et al., 2008). Mueser, Rosenberg, Goodman and Trumbetta (2002) argue that PTSD can exacerbate psychosis directly, via hyperarousal, reliving and avoidance, and indirectly through outcomes associated with PTSD, such as substance misuse, retraumatization and difficulties socially.

There are many established treatments for PTSD, for example in a meta-analysis, Bisson and Andrew (2009) found trauma-focused cognitive behavioural therapies such as prolonged exposure and cognitive processing therapy to be effective. They also found eye movement desensitization and reprocessing therapy (EMDR) and stress management training to be effective. Despite this range of treatments, they are not routinely being offered in clinical practice for people with psychosis (Walters, Hogg & Gillmore, 2016). This may be because people with psychosis are often excluded in PTSD treatment research, thus limiting the evidence base for this population. Even research promoting broader inclusion of service users in PTSD research makes a special case for psychosis (Bradley, Greene, Russ, Dutra, & Westen, 2005). De Bont, van Minnen and de Jongh (2013) found no adverse effects when offering PTSD treatments to people with psychosis and argue that this should be encouraging for clinicians who believe these treatments to be harmful (Frueh, Cusack, Grubaugh, Sauvageot & Wells, 2006).

It could be argued that given these concerns, understanding the acceptability of psychological interventions for post-traumatic stress disorder (PTSD) in people with

psychosis is as important as investigating their effectiveness. A systematic review by Swan, Keen, Reynolds and Onwumere (2017) briefly discusses dropout rates and adverse effects during PTSD treatments with this population; however, this is not the focus of their review, and these data are not meta-analysed. This review builds upon Swan et al.'s (2017) work in this area, by considering 'acceptability' of these treatments more comprehensively, as in Sekhon, Cartwright and Francis' (2017) research. As such, the following questions will be answered in this review, when possible using meta-analyses alongside a narrative approach:

1) What is the estimated non-participation rate?

2) What are the reasons for non-participation?

3) What is the estimated level of attendance at intervention sessions?

4) What is the estimated dropout rate?

5) What are the reasons and risk factors for dropout?

6) What is the perceived acceptability of interventions?

7) How satisfied are participants with the interventions?

8) What adverse effects are caused by interventions?

Method

This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman & The PRISMA Group, 2009). The protocol for this review was published on PROSPERO: the international prospective register of systematic reviews (National Institute for Health Research & University of York, 2016).

Study selection

Studies were identified by systematic searches of the following databases: PsycInfo, Embase, Cinahl, Medline, the National Center for PTSD research's Published International Literature on Traumatic Stress (PILOTS), Cochrane Library and OpenGrey. Filters were applied to publication date and language in line with the inclusion criteria. Specific journals were searched separately: Schizophrenia Research, Schizophrenia Bulletin, Psychological Medicine and the Journal of Traumatic Stress.

The following search terms were entered: ptsd or 'post traumatic stress' or 'posttraumatic stress' or 'post-traumatic stress' or trauma* AND psychosis or psychotic or schizo* or 'severe mental' or 'serious mental' AND Treatment* or intervention* or therap* or psychotherap* or counselling or program* or rct or trial or pilot or feasibility.

The reference sections of relevant review articles, book chapters and research papers were searched by hand. Unpublished data were sought by making a request from key authors (for example, authors of studies meeting inclusion criteria) and through ordering full texts of relevant dissertations and theses.

Inclusion criteria

The inclusion criteria were as follows:

- Peer reviewed journal articles, dissertations and theses produced between 1980 and 2017 and available in English;

- Controlled or uncontrolled treatment studies exploring psychological interventions exclusively targeting PTSD and involving exposure to trauma related thoughts/memories/stimuli;
- Participants meet PTSD threshold on a validated measure or interview for PTSD;
- Participants meet criteria for psychosis on a validated measure or interview, or participants have an existing diagnosis of psychosis, or at least 50% of a mixed sample with severe mental illness have psychosis, or data were available for the subgroup of participants with psychosis.

The term psychosis in this review refers to non-organic psychotic symptoms or psychotic disorders, including mood disorders with psychotic features. Disorders which may or may not include psychotic symptoms, such as bipolar disorder are excluded unless the presence of psychotic symptoms is mentioned. Articles reporting on the same dataset were included if they contained additional data related to the review questions. Case studies and qualitative studies were excluded.

Screening

Titles and abstracts were screened by the primary researcher and irrelevant studies were excluded. A collaborator cross-checked excluded titles. Full texts of relevant studies were retrieved and inclusion criteria applied independently by the primary researcher and collaborator. Further information was sought from authors when necessary. Disagreements were discussed and a second collaborator was consulted when necessary.

Data extraction

Data were extracted independently by the researcher and collaborator using a data extraction form and coding instructions (Appendix C). Disagreements were discussed and a second collaborator was consulted if required. Data were extracted in relation to methodology, population, setting, clinical characteristics, the psychological intervention

delivered, non-participation, attendance, dropout, perceived acceptability and satisfaction with the intervention, and adverse effects. This review focuses on these issues in relation to participants in the active treatment groups only.

This review differentiates 'non-participation' from 'dropout'. It defines 'non-participation' as failing to attend any intervention sessions once assessed as eligible to receive the intervention, in line with Popay et al.'s (2006) definition. In controlled studies this refers only to those participants randomized to the treatment arm(s). As such, participants are considered non-participators if they withdrew after being offered treatment for their PTSD. Non-participation rates are calculated by dividing the number of non-participators by the total number of participants eligible for treatment (in uncontrolled studies) or randomized to treatment (in controlled studies). The concept of non-participation aims to capture participants actively opting out and therefore does not include those who were excluded by the researcher or were uncontactable. The number of participants who declined to take part in the study at any stage *prior* to eligibility assessments (in uncontrolled studies) or randomization (in controlled studies) will also be extracted and this will be referred to as 'declining' as opposed to 'non-participating' in order to differentiate between the two.

'Dropouts,' for the purpose of this review refers to participants who attended at least one intervention session but failed to complete a sufficient 'dose' of sessions. It does not include those who completed a sufficient dose but were lost to follow up assessments.

Non-participation reasons are any reasons given by participants for deciding not to take part in any intervention sessions once deemed eligible. These reasons are extracted separately from dropout reasons, which are reasons given by participants for dropping out of the study after completing at least one intervention session.

Treatment acceptability and satisfaction refers broadly to any evaluative data or statements from participants about the treatment. The term 'adverse effects' refers broadly

to any negative outcome during treatment, including exacerbation of psychological symptoms, deterioration in functioning and any adverse events such as self-harm or drug use, including 'serious adverse events' such as deaths or incidents that require high-intensity treatment (Klatte, Strauss, Flückinger & Rosendahland, 2018). All mentions of adverse effects and, crucially, whether they were treatment-induced will be extracted from the studies. As such, if studies found no adverse effects this will also be reported in this review, as this is considered just as relevant in understanding the acceptability of these treatments.

Study quality

Overall study quality was assessed using the Clinical Trials Assessment Measure on a scale of 0-100 (Wykes, Steel, Everitt, & Terrier, 2008).

Data analysis

Data were analysed using narrative and meta-analytic approaches. In order to calculate estimated non-participation and dropout rates, proportion meta-analyses were carried out using the statistical software Comprehensive Meta-Analysis Version 2 (Borenstein, Hedges, Higgins, & Rothstein, 2005). A random effects model was used, as is preferable in social science research (Cooper, Hedges & Valentine, 2009). The inverse variance method was used in order to apply different weighting to studies based on sample size. Cochran's *Q* was used as an indicator of heterogeneity and the I^2 statistic to indicate how much of the variance observed between the results was due to random error.

Subgroup analysis

Subgroup analyses were carried out to determine whether intervention, population and methodological variables significantly affected non-participation and dropout rates. This was dependent on enough studies reporting the outcome of interest.

Publication bias

Publication bias was explored via funnel plots when there were sufficient studies.

Results

Included studies

Seventeen eligible studies were identified, based on 11 independent datasets (see Figure 1). Interrater agreement for study inclusion was 96.5% (Cohen's Kappa 0.73, reflecting 'substantial agreement'). Steel et al.'s study (2017) was included despite their inclusion of participants with PTSD *symptoms*, because the majority had a diagnosis.

Study characteristics are displayed in Table 1. In total, the studies included 333 participants offered a PTSD intervention. Of these, 98.8% had a diagnosis of a psychotic disorder. The remaining participants took part in Sacks, Schwartz and Mueser's study (2017) and had a diagnosis of bipolar disorder.

PTSD treatments

In this review, treatments referred to as 'CBT' use cognitive restructuring as the active treatment component. With the exception of Trappler and Newville (2007), the studies offering CBT used Mueser et al. (2007)'s protocols for group CBT or individualised CBT (Mueser, Rosenberg, Jankowski, Hamblen & Descamps, 2004), developed specifically for PTSD in people with serious mental illness (SMI). Trappler and Newville's (2007) program includes elements of behavioural and schema modification but emphasises safety and emotional regulation. In this sense, it could be viewed as an enhanced and extended version of a traditional pre-exposure 'stabilisation phase.' Notably, three studies (de Bont et al., 2013; van den Berg & van der Gaag 2012; van den Berg et al., 2015) purposefully omitted a 'stabilisation phase.' The remaining studies did not make reference to 'stabilisation' but initially offered relaxation skills and safety planning which typically serve this purpose. With the exception of three studies (de Bont et al., 2013; van den Berg & van der Gaag, 2012; van den Berg et al., 2015) treatments were adapted for people with psychosis or SMI, although in Grubaugh, Veronee, Ellis, Brown and Knapp (2017) the adaptation was simply offering additional sessions.

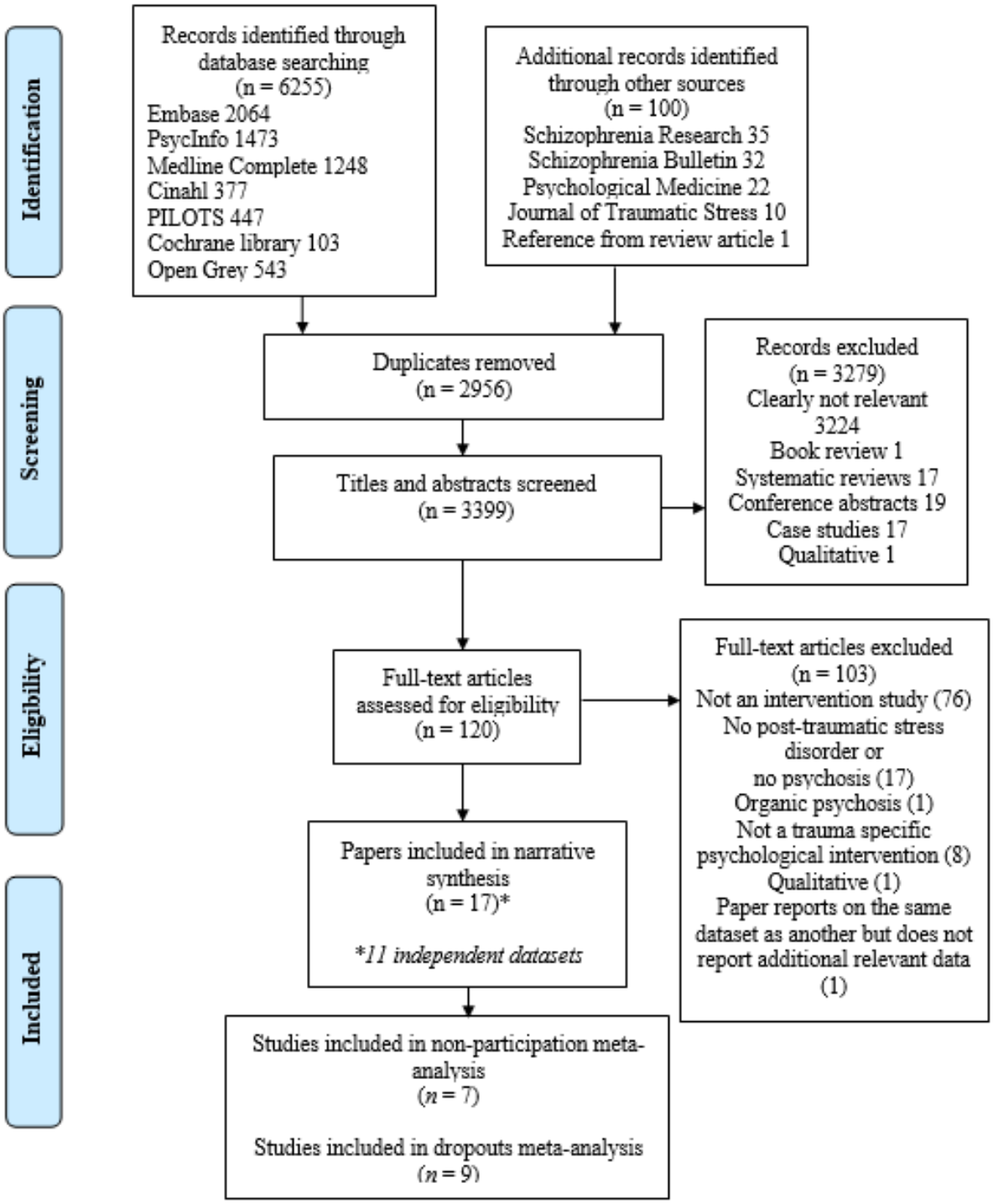

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

Table 1

Study characteristics

Study no.	First author	Year	Country	Study design	Treatment	N in treatment arm(s)	% Non-participation	Max. sessions offered	No. sessions for 'completion'	Dropout (%)
1	de Bont	2013	Netherlands	Feasibility	PE / EMDR	10	16.7	12	-	20.0
2	Frueh	2009	USA	Pilot	Group / 1:1 PE	20	23.1	22	16	35.0
3	Gottlieb[a]	2011	USA	RCT	CBT	8	5.0	16	6	42.9
4	Grubaugh[b]	2017	USA	Open trial	PE	14	14.3	15	4	28.6
5	Jansen	2017	Netherlands	Case series	ACT	3	-	12	-	-
6	Sacks	2017	USA	Pilot	Group CBT	14	-	21	11	28.6
7	Steel	2017	UK	RCT	CBT	30	10.0	16	6	3.7
8	Trappler	2007	USA	Controlled	Group CBT	24	-	12	-	-
9	van den Berg	2012	Netherlands	Pilot	EMDR	27	10.0	6	-	18.5
10	van den Berg[c]	2015	Netherlands	RCT	PE / EMDR	108	18.0	8	8	15.2
11	Yanos[d]	2016	USA	RCT	CBT	75	-	16	6	36.0

Note. [a] relates to the dataset Mueser et al., 2008, [b] relates to the dataset Grubaugh et al., 2016, [c] three secondary analysis studies were based on this dataset: van den Berg et al., 2016a, van den Berg et al., 2016b and van Minnen et al., 2016, [d] relates to the dataset Mueser et al., 2015.

Study quality

Quality assessment scores are presented in Table 2. Interrater agreement was 87.0% (Cohen's Kappa 0.64, reflecting 'substantial agreement.') As in Wykes et al. (2008), a cut-off score of 65 on the CTAM has been used. Studies scoring 65 or greater are referred to as 'high quality' and those with less than 65 'low quality.' Areas of strength for this set of studies were treatment process and analysis. Treatment processes include use of protocols and therapist adherence to these. Items relating to analysis include use of 'intention to treat' analysis and appropriate handling of missing data.

Table 2

Quality assessment scores using the Clinical Trials Assessment Measure (CTAM

First author (date)	Sampling (max. 10)	Randomisation (max. 16)	Assessment process (max. 32)	Control group (max. 16)	Analysis (max. 15)	Treatment (max. 11)	Total score	Study quality
van den Berg (2015)	7	16	26	16	15	11	91	High
Steel (2017)	7	16	26	6	15	11	81	High
Gottlieb (2011)	2	16	29	6	15	11	79	High
Yanos (2016)	7	13	26	10	5	11	72	High
de Bont (2013)	2	10	6	10	11	6	45	Low
Grubaugh (2017)	7	0	6	0	15	11	39	Low
Frueh (2009)	2	0	6	0	15	11	34	Low
Sacks (2017)	2	0	6	0	15	6	29	Low
van den Berg (2012)	2	0	6	0	15	6	29	Low
Trappler (2007)	0	0	6	10	5	0	21	Low
Jansen (2017)	2	0	6	0	5	6	19	Low

Non-participation rates

Seven studies reported non-participation data. In three studies (van den Berg et al., 2015; de Bont et al., 2013 & Frueh et al., 2009) it was unclear if participants had withdrawn pre or post-eligibility assessments; however, it was assumed they were eligible, as they were listed separately from those participants excluded due to ineligibility.

A proportion meta-analysis using logits (see Figure 2) produced a pooled estimate of 12.1% for non-participation (95% CI 8.3%, 17.2%), with minimal heterogeneity (Q = 4.77, df = 6, p = 0.574, I^2 = 0.00). The two studies with the highest scores for quality had the lowest non-participation rates; however, meta-regressions were not possible due to the small number of studies.

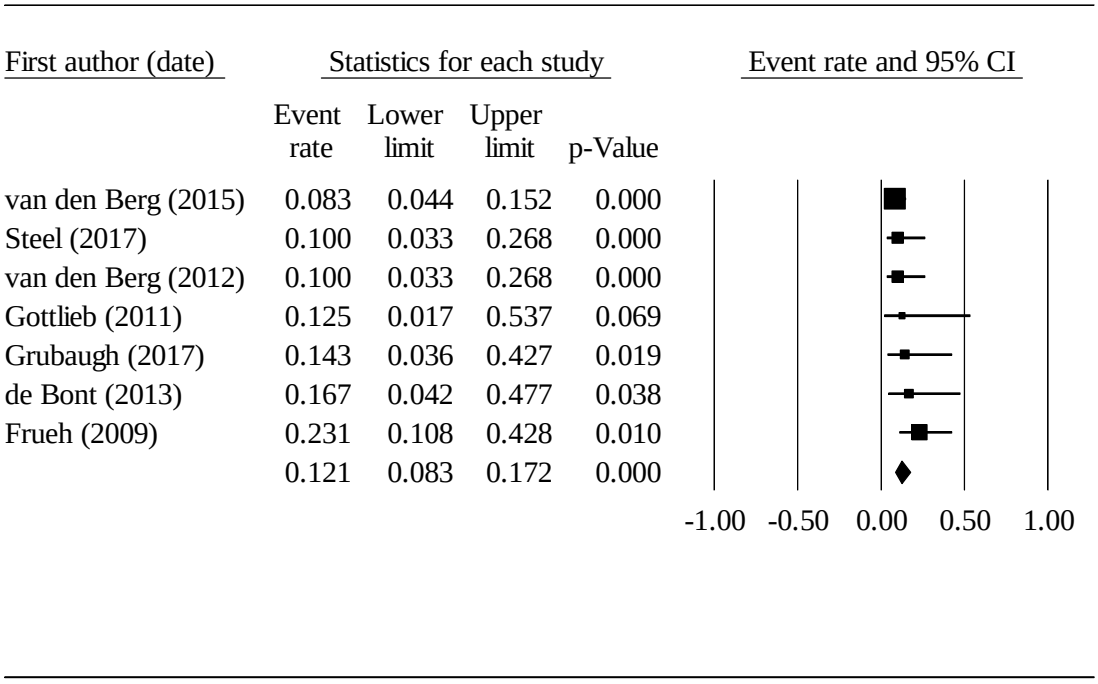

Figure 2. Forest plot of non-participation meta-analysis.

Three studies reported the number of participants declining to be involved in the study pre-randomization. Van den Berg et al. (2015) and Steel et al. (2017) reported the number of participants who declined to take part in the study during the assessment phase, pre-randomization: 5.1% and 8.1% respectively of the total number of participants assessed. De Bont et al. (2013) reported the number of participants who declined when they were initially referred, pre-assessment, as 31.3%. No other studies reported the number of participants declining to be involved either pre-assessment (in uncontrolled studies) or pre-randomization (in controlled studies).

Non-participation reasons

Only two studies reported non-participation reasons. In de Bont et al (2013), two participants withdrew due to experiencing paranoia triggered by the video camera used to record sessions. In van den Berg and van der Gaag (2012), one participant withdrew due to ill health and the other withdrew due to increased stress caused by talking about his trauma. No further information was given. No studies reported data for differences between participators and non-participators.

Attendance rates

Attendance at treatment sessions cannot easily be summarised due to the inconsistencies in reporting. Three studies did not report on attendance. The remaining studies reported average attendance for either the intention to treat sample, treatment completers only, or treatment completers and non-completers combined. Alternatively, studies did not specify which participants had been included in the calculation.

Dropout rates

Figure 3 displays the forest plot for a proportion meta-analysis of dropout rates. The pooled estimate was 24.6%, (95% CI 16.9%, 34.4%) with significant heterogeneity (Q = 17.22, df = 8, p = <0.05, I^2 = 53.54). Steel et al. (2017) was identified as an outlier.

When this study was removed, the overall estimate increased marginally to 26.4% (95% CI 19.0%, 35.5%) but heterogeneity remained significant (Q = 12.50, df = 7, p = 0.085, I^2 = 43.99).

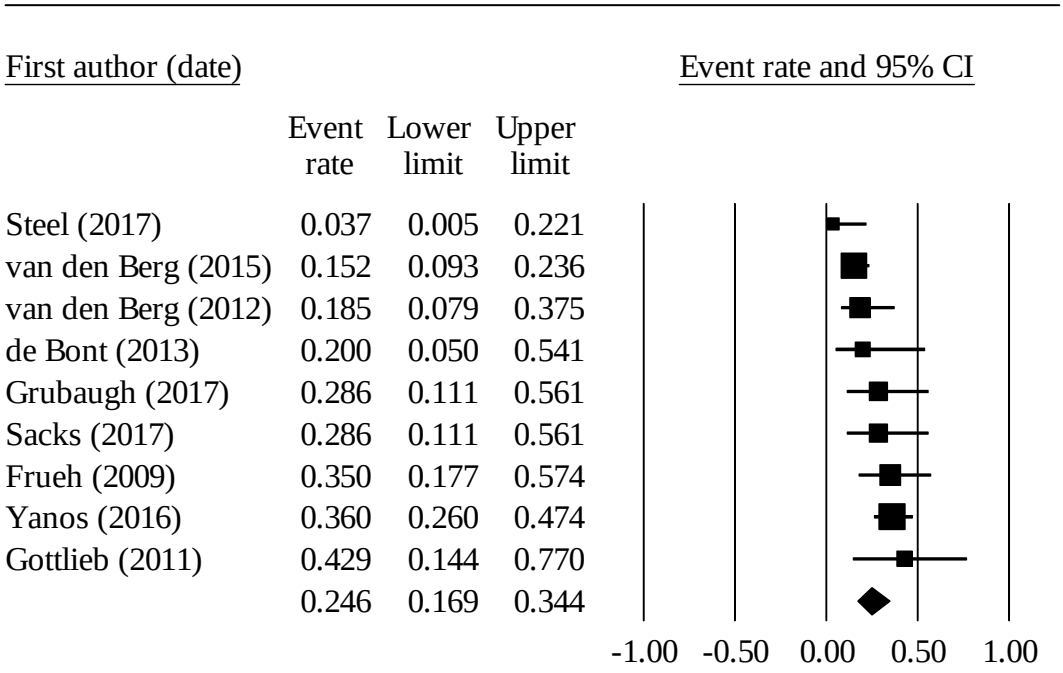

Figure 3. Forest plot for dropout meta-analysis.

Moderator analyses results are displayed in Table 3. Further variables could not be analysed as they had multiple subgroups with a very small number of studies in each. Notably, country and stabilisation were found to be significantly associated with dropout and resulted in considerable reductions in heterogeneity. High quality studies had reduced heterogeneity as a group, but quality as a variable overall was not significant.

Table 3

Moderator Analysis Results

Moderator	*k*	Dropout rate (%)	95% CI	I^2 (%)	Between groups test (Q)
Overall	9	24.6	16.9, 34.4	53.5	-
Study quality	-	-	-	-	1.78
High	4	30.6	19.5, 44.6	4.7	-
Low	5	20.0	12.2, 31.0	50.3	-
Country					16.21***
The Netherlands	3	16.2	10.9, 23.4	0.0	-
USA	5	34.7	27.0, 43.3	0.0	-
UK	1	3.70	-	-	-
Intervention	-	-	-	-	0.80
CBT	4	29.4	17.4, 45.2	57.1	-
Non-CBT	5	21.8	13.6, 32.9	16.4	-
Stabilisation phase	-	-	-	-	7.94**
Yes	6	32.8	25.5, 41.1	30.1	-
No	3	16.2	10.9, 23.4	0.0	-

Note. **p=<0.01, ***p = <0.001

Dropout reasons and risk factors

Three studies reported dropout reasons. In de Bont et al (2013), one participant's hallucinations forbade her from talking about her trauma. In van den Berg and van der Gaag (2012), reasons were: moving abroad, improvement in symptoms, no improvement in symptoms and not believing the treatment would be effective. One of the non-completers in Grubaugh et al. (2017) felt that the distress experienced when talking about the trauma had not improved. Notably, in Grubaugh et al. (2017) most of the non-completers did not attend any exposure sessions.

Frueh et al. (2009), Grubaugh et al. (2017) and van den Berg et al. (2015) found no differences in demographics between non-completers and completers. Sacks, Schwartz and

Mueser (2017) found that non-completers were younger. Frueh et al. (2009) found that dropout was associated with being male and receiving an outpatient service as opposed to an intensive day-hospital program; however, these two variables (gender and service) were highly correlated.

Clinical characteristics were not associated with dropout in Sacks et al. (2017). Frueh et al. (2009) found that non-completers had higher scores for anger than completers, but no differences in other clinical outcomes, treatment credibility rated pre-treatment, or treatment satisfaction scores. Yanos, Vayshenker, Pleskach and Mueser (2016) found that participants' severity of impairment in insight was associated with dropout. Grubaugh et al. (2017) found that pre-treatment PTSD severity was associated with dropout, but index trauma was not. Referring to van den Berg et al.'s (2015) dataset, van Minnen et al. (2016) found that the dissociative subtype of PTSD was associated with dropout and van den Berg et al. (2016b) found no significant differences between dropouts and treatment completers in baseline variables (severity of PTSD symptoms, paranoia, auditory verbal hallucinations, negative symptoms, suicide risk, recent adversities such as self-harm or drug use, working memory or dose of antipsychotic medication). Finally, based on the same dataset, van den Berg et al. (2016a) found that exacerbation of PTSD, paranoid and depressive symptoms was not associated with dropout, although 2 of the 15 non-completers experienced a significant exacerbation in PTSD symptoms.

Treatment acceptability and satisfaction

De Bont et al. (2013) reported that their treatment was acceptable as most participants could comply with it. Jansen and Morris (2017) asked open questions on how helpful the treatment was and how it could be improved. They reported 'acceptability and satisfaction' of the treatment but no details of participants' responses. Sacks et al. (2017)

found participants to be ‘very satisfied’ with treatment, with an average score of 6.8 out of 7 on a novel questionnaire.

Frueh et al. (2009) used the Charleston Psychiatric Outpatient Satisfaction Scale (Pellegrin, Stuart, Maree, Frueh, & Ballenger, 2001) and reported that scores improved; however, only 5 of the 15 questions related to the treatment. They also used the treatment expectancy scales (Borkovec & Nau, 1972) and found that participants considered the treatment logical, were confident in its effectiveness in treating their current concerns and other fears, and would recommend it. Grubaugh et al. (2017) used the same measure with similar results, although participants were less confident of the treatment’s effectiveness, but more likely to recommend it. All items scored reasonably highly in both studies (between 6.83 and 8.47 out of 10). Grubaugh et al. (2017) also reported how difficult, confusing, and distressing participants found the treatment to be and how satisfying and worthwhile treatment had been. They reported low to moderate scores in the former category and moderate to high scores in the latter.

In qualitative interviews, Grubaugh et al.’s (2017) participants reported that the treatment seemed credible and logical. Unfortunately, one participant’s experience was that although they found the treatment logical, they ‘failed’ because they ‘couldn’t handle it.’ The interviews also revealed that participants were initially very concerned about managing their distress during exposure, but for most people this reduced over the course of the treatment.

Adverse effects

Five studies of the 11 included in this review did not report whether they monitored for adverse effects. No serious adverse events caused by the treatments were observed in any of the studies. In the original paper for this study, van den Berg et al. (2015) state that

three serious adverse events occurred in the treatment conditions, but they were not deemed to be induced by the study and no other information was given.

Frueh et al. (2009) reported hospitalisations during the treatment but did not consider these to be treatment-induced adverse events. They also reported no significant deterioration in psychological symptoms or functioning, due to the treatment or otherwise. Qualitative interviews in Grubaugh et al. (2017) indicated that neither PTSD or SMI symptoms were exacerbated by the treatment. Jansen and Morris (2017) asked participants open questions about whether the treatment had been unhelpful, harmful or distressing. They reported that there were no treatment-induced adverse effects; however, no information was given regarding participants' responses. De Bont et al. (2013) also reported no adverse effects, which they defined as exacerbation of any psychological symptoms, deterioration in functioning, hospital admissions or other crisis interventions, change in medication, suicide attempts or self-harm.

In terms of adverse effects caused by the treatments, van den Berg and van der Gaag (2012) found that their treatment exacerbated PTSD symptoms in some participants; however, in each case a single session on coping skills was sufficient to manage this. One participant sought support from his case manager due to increased arousal and this was managed by reminding him that EMDR causes temporary side effects. A relapse in drug use also occurred because a participant became able to leave the house alone due to treatment.

Using reliable change indexes, van den Berg et al. (2016a) explored the rates of treatment-related symptom exacerbation during van den Berg et al. (2015)'s treatment. Pre to post-therapy exacerbation rates were 3.3% for PTSD interview scores, 3.3% for paranoid ideation, 9.9% for depressive symptoms and 0% for self-reported PTSD symptoms. They also assessed paranoid ideation, auditory verbal hallucinations,

dissociative feelings and suicidal ideation prior to treatment and after the first two sessions and found no exacerbation. By follow up, 11% of the participants in the treatment group began to hear voices, compared to 12% in the waiting list group. They report that overall, the treatment group experienced fewer adverse events (suicide attempts, aggressive incidents, alcohol and drug abuse and crisis interventions) than the control group and were less likely to experience revictimisation, but more likely to self-harm. The authors discuss the positive role the intervention may have played in the reduced number of adverse events in the treatment group as compared to the control group, but not the potential negative role the intervention could have played in causing the adverse events that *did* occur in the treatment group.

Discussion

Non-participation

Despite the ambiguity in reporting, the studies showed minimal heterogeneity suggesting a robust overall summary estimate of 12.1% for non-participation. Unfortunately, this cannot be compared to a non-psychotic PTSD population as there are no reviews on this to the author's knowledge.

As the non-participation decisions were post-randomization to treatment condition(s) (in controlled studies), non-participators were aware that they would receive a PTSD intervention if they continued to be involved in the study. As such, it could be interpreted that the participants withdrew because they did not find the treatment to be acceptable from the information they had been given. If this is generalisable to clinical practice, the *perceived* acceptability of these treatments (prior to receiving them) needs to be improved in this population, as otherwise approximately one in eight people with psychosis will refuse a potentially acceptable and effective treatment that they have been considered appropriate for.

Pre-randomization non-participation rates are arguably less reflective of finding the treatment acceptable. Instead, it could be that the chance of being randomized to the control group may have lessened participants' motivation to continue with the study. However, it would still be helpful for these data to be reported, with greater clarity as to the stage participants had reached in the recruitment process when they withdrew, to see when rates are highest and as a starting point for exploring the reasons.

Dropout

Dropout rates are comparable to other PTSD treatment studies (Hembree et al., 2003, Bisson & Andrew, 2009), suggesting that when using dropout as a marker of

acceptability, these treatments are equally acceptable in psychotic as non-psychotic populations.

Country is likely to be a confounder of the relationship between stabilisation and dropout, as Netherlands studies did not use stabilisation and USA studies did. Two studies (Frueh et al., 2009; Gottlieb, Mueser, Rosenberg, Xie, & Wolfe, 2011) found that most participants dropped out during skills training phase, which may suggest that engagement could be increased by omitting the stabilisation phase, so that participants are able to experience symptom improvement earlier on in the therapy. This is supported by a review by de Jongh et al., (2016), which raises doubt as to the necessity of a stabilisation phase given that the original research favouring its use was, in their opinion, methodologically flawed.

The theory that dropout rates may be associated with severity of PTSD is supported by the findings of Grubaugh et al. (2017) of higher pre-treatment PTSD in non-completers. Also, there was a high dropout rate in Yanos et al.'s (2016) study, which was the only one to exclusively recruit participants with severe PTSD. Van den Berg et al. (2016a) found that exacerbation of PTSD, paranoid and depressive symptoms was not associated with dropout; however, this was based on data from only 37.5% of the dropout group and is therefore not representative of their experiences.

Broadly, the idea that severity of symptoms may predict dropout may be supported by the significant associations of anger, impaired insight and dissociative insight with dropout. It will be important to explore these hypotheses further in psychotic populations, particularly given de Bont et al. (2013)'s finding that dropout was caused by the interaction of psychotic and trauma symptoms (hallucinations forbade discussion of the trauma). Research results are mixed as to the impact of severity of PTSD symptoms on dropout in

CBT for PTSD in non-psychotic populations. Whilst Garcia, Kelley, Rentz & Lee (2011)'s findings support this, Belleau et al.'s (2017) do not.

Acceptability and satisfaction

The findings regarding acceptability and satisfaction should be interpreted with caution as the data are very limited. Also, the range of assessments used, both qualitative and quantitative made reviewing the findings difficult. In the future, validated quality measures that are appropriate to this population should be used, such as the Verona Service Satisfaction Scale (Ruggeri et al., 2000).

Questionnaire findings generally reflected satisfaction with the treatments; however, these results were often from treatment completers, therefore this outcome is somewhat expected. It will be important for future research to capture satisfaction scores and qualitative information from non-completers.

Participants generally perceived the treatment to be credible and logical, although one participant withdrew from receiving EMDR as he did not. In Tarrier, Liverside and Gregg (2006)'s research, EMDR was deemed one of the least preferred treatments for PTSD.

Adverse effects

Research suggests that therapists are reluctant to offer PTSD treatments to people with psychosis due to fear of exacerbating their symptoms (van Minnen, Harned, Zoellner & Mills, 2012). This review suggests that for most participants, this does not occur, but when it does it does not usually prevent treatment completion or effectiveness.

Van den Berg et al. (2016a) reported that a proportion of participants with no auditory hallucinations pre-treatment experienced them post-treatment; however, this was at a lower rate than in the 'treatment as usual' group and may have occurred regardless of the intervention given the fluctuating nature of psychotic illnesses.

Adverse effects are not always reported in psychological treatment studies and use inconsistent definitions adapted from drug trials (Klatte et al., 2018). The issue of whether adverse effects are caused by treatment is complex, particularly in psychotic populations given the higher level of risk behaviours. Many of the studies reporting on adverse effects relied on participants' reports of whether they were precipitated by the treatment. This could bias responses, particularly if participants were motivated to continue with the treatment. Further research should explore whether adverse events such as hospitalisations, drug or alcohol abuse or revictimisation occur more frequently for people with psychosis after the onset of PTSD treatments, perhaps using staggered baseline periods before the introduction of treatments. This research would need to be large scale to ensure analysis was not underpowered, given it would involve naturalistic observation over time of relatively infrequent events. Other adverse effects, such as the exacerbation of clinical symptoms could also be recorded within this design.

Clinical recommendations

This review should increase clinicians' confidence to offer evidence-based PTSD treatments to people with psychosis. The generalizability of the findings may be affected as not all participants in this review had a diagnosis of a psychotic disorder; however, the vast majority did, so the impact of this is likely to be negligible.

Naturally, clinical judgement will determine the most appropriate timing and circumstances for these treatments, especially given the (albeit tentative) finding from this review that severity of symptoms may be associated with dropout. Engagement models which are common in specialist psychosis teams should be recreated in other settings when possible, to ensure that people with psychosis and severe PTSD are supported in accessing trauma therapy. It may also be important in treating PTSD in psychosis to determine the interaction between the two conditions and to create an integrated formulation as this may

increase the acceptability or effectiveness of the PTSD intervention. For example, a preliminary study using imaginal reprocessing to target both PTSD and psychotic symptoms gained positive feedback, had no dropout and there was no reliable worsening in any symptoms (Keen, Hunter & Peters, 2017).

This review found that not including a stabilisation phase in PTSD treatments for psychosis may be associated with improved engagement; however, this should be interpreted with caution due to the very small number of studies. A randomised control trial is underway which is comparing stabilisation with no stabilisation in PTSD treatment (van Vliet, Huntjens, van Dijk, & de Jongh, 2018), so the results of this will further our understanding of this issue.

Research recommendations

Barriers to emotional engagement in the sessions could be explored, based on O'Driscoll, Mason, Brady, Smith and Steel's (2016) finding that attendance at sessions does not always means people are engaging emotionally, which is required for treatment success. Session by session acceptability measures could be used to identify which elements or stages of treatment people struggle with. The Treatment Expectancy Scales could be asked in relation to different elements of the treatment and open questions could elicit more information as to how the treatment was perceived. Clearer and more consistent reporting of non-participation and dropout could be utilised, for example following the guidelines in Schottenbauer, Glass, Arnkoff, Tendick and Gray's (2008) research.

Reviews and empirical studies into the impact of PTSD treatments on psychotic symptoms should be carried out, so that the relative frequencies of exacerbation and improvement can be understood. Finally, it was beyond the scope of this review to include purely qualitative studies; however, further qualitative data would have enriched the findings about the acceptability of treatments. In future, a meta-synthesis of qualitative

studies and case studies would help to develop our understanding of the benefits and harms experienced by people with psychosis undertaking treatment for PTSD.

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Chapter 2.

Bridging Chapter

The previous chapter reviewed the acceptability of psychological interventions for post-traumatic stress disorder (PTSD) in people with comorbid psychotic disorders. These interventions are particularly important given the high comorbidity in these two disorders (Dallel, Cancel & Fakra, 2018) and worse prognosis if the two occur together (Fan et al., 2008). The participants included in the review met diagnostic criteria for PTSD and a psychotic disorder; however, the order in which these developed, and any overlap or interaction between the two disorders were not reported. As mentioned briefly in the previous chapter, these issues could have implications for the acceptability and effectiveness of PTSD interventions in people with psychosis and therefore they warrant further understanding.

Some of the potential pathways between PTSD and psychosis will be outlined here in order to highlight the complexity and uncertainty in this clinical field. Considering these mechanisms will expand on the diagnostic labels used in the previous chapter and provide a context for the content of the next chapter. Firstly, models proposing that trauma and PTSD contribute to psychosis will be reviewed. Secondly, some of the ways in which PTSD may develop after psychosis will be considered. Thirdly, the concept of psychosis-related PTSD (PR-PTSD) will be introduced, followed by an exploration of the issues arising in defining and measuring this phenomenon.

Schizophrenia spectrum disorders have traditionally been thought of as biologically based (Chua and Murray, 1996) but this research has been criticised for lacking methodological vigour (Bentall, 2013). This, in addition to the high prevalence of traumatic experiences observed in people with schizophrenia (Read & Ross, 2003) has led to a reconsideration of the importance of environmental influences, particularly childhood trauma (see Varese et al., 2012 for a review). Findings of a ‘dose response’ (Shevlin, Houston, Dorahy & Adamson, 2007) in which the risk of psychosis increases with the

amount of trauma experienced may also indicate that trauma contributes to the development of psychosis. The associations found between specific traumas and psychotic symptoms, such as between childhood sexual abuse and hallucinations, and between emotional abuse and delusions (Sitko, Bentall, Shevlin, O'Sullivan & Sellwood, 2014) are also thought to support this theory.

One pathway to comorbid PTSD and psychosis is therefore that both disorders develop in response to trauma. The mechanisms for this remain unknown, but have gained increasing attention in the literature. For example, Read, Perry, Moskowitz and Connolly (2001) concluded through reviewing the data, that all the structural and chemical abnormalities found to be related to a genetic predisposition for schizophrenia had also been observed in traumatised children. This led to the traumagenic neurodevelopmental account of psychosis (Read et al., 2001) which states that if trauma is severe enough and occurs early enough in life, it can contribute to the development of psychosis through its impact on stress sensitivity, via the hypothalamic-pituitary-adrenal (HPA) axis and its subsequent impact on dopamine. PTSD has also been found to be associated with this dysfunction (Collip et al., 2013). Stress sensitivity is thought to result in either dissociation, or hypervigilance which are both maladaptive, but were initially adaptive coping strategies when the trauma could not be processed, or to protect against further abuse (Perry, Pollard, Blakley, Baker & Vigilante, 1995). These strategies may increase the risk for what we view as psychotic experiences. For example, Read et al., (2001) suggested that dissociation may be linked with negative symptoms, and hypervigilance with positive symptoms. These ideas extend the traditional stress-diathesis model (Walker & DiForio, 1997) that stress, including traumatic stress, simply serves to activate underlying neurobiological disturbances related to the stress sensitivity linked to schizophrenia.

Similarly, although from a cognitive perspective, Morrison, Frame & Larkin (2003) proposed that PTSD and psychosis are on a spectrum of responses to trauma and that both involve intrusions, but interpretation is the differentiating factor. It is the fact that people interpret intrusions as coming from an external source that leads us to classify the resulting symptoms as psychotic, because unlike other interpretations, these are considered culturally unacceptable (Morrison 2001). These attributions are thought to be influenced by beliefs about the self and others (Thomas, Farhall & Shawyer, 2015) which are themselves likely to be more negative and threat-based if the person has experienced trauma (Ehlers & Steil, 1995). Davidson and Strauss (1992) note that in trauma and in psychosis, cognitive appraisals of the self, the world and others have been shattered. It has been suggested that the variation in interpretation of trauma-related intrusions may be due to the extent to which the trauma-related memory was contextualised initially (Steel, Fowler & Holmes, 2005). This draws upon Brewin (2001) and Ehlers and Clark's (2002) cognitive models of PTSD and Hemsley's (1994) information processing account of schizophrenia. Morrison et al. (2003) hypothesised that the more severe this contextualisation dysfunction, the more likely intrusions are and the more likely they are to be appraised as external. This could account for comorbid diagnoses of PTSD and psychosis following trauma; some intrusions could be viewed as trauma-related by the individual, and conceptualised by clinicians as flashbacks, whereas others could be viewed as coming from an external source and conceptualised as voice-hearing. It could also account for the finding that the more severe the PTSD, the more likely psychotic symptoms are to occur in conjunction with it, perhaps as a subtype of PTSD (Lindley, Carlson & Sheikh, 2000). This concept is limited in generalisability as much of the associated research focused exclusively on combat veterans, therefore a consensus on its existence has not yet been reached (Braakman, Kortmann & van den Brink, 2009).

The ideas summarised so far have focused on those with psychosis originating from trauma. Further research is required into the assumption that intrusions are qualitatively identical to anomalous experiences, and that risk of psychosis is on a continuum with a psychotic disorder, as many of the studies mentioned have used samples at risk of psychosis. Nonetheless, the potential route between trauma and psychosis is important as it offers a less stigmatising view of psychosis, and it may open up the potential for formulating and then treating the two sets of symptoms in an integrated way, potentially leading to faster recovery. It also helps to explain the overlap in symptoms in PTSD and psychosis, such as between negative psychotic symptoms and emotional numbing and avoidance in PTSD, and between hallucinations and trauma flashbacks. Further research is also needed on the differences between psychosis developing after a trauma history and in the absence of one. However, it is important to note that even if they did not experience trauma, it is likely that they experienced stressful events precipitating the psychosis which may have been perceived as traumatic despite not objectively being viewed as such (Fowler, 1997).

An alternative potential pathway to a comorbid diagnosis of PTSD and psychosis is that psychosis predates the PTSD and they are discrete conditions. Sekar et al. (2016) propose that psychosis can have a strong genetic component or organic basis and Stevens, Spencer and Turkington (2017) argue that this type is distinct from a trauma-based psychotic presentation. This group are purportedly more emotionally avoidant and socially isolated which can lead to negative symptoms such as communication difficulties, poor cognitive functioning and poor motivation. Regardless of earlier trauma, those with existing psychosis may be more prone to experiencing trauma due to poorer coping strategies, income and overall quality of life (Norholm & Bech, 2007). For example, severe mental illness has been found to increase likelihood of violent victimization (Latalova,

Kamaradova & Prasko, 2014). Rates of substance use are also thought to be higher in people with psychotic disorders (Gregg, Barrowclough & Haddock, 2007) and Mueser, Rosenberg, Goodman & Trumbetta (2002) hypothesise that this may increase risk of trauma via exposure to unsafe situations, disinhibition or impaired judgement, although this is speculative and further research is required. Further to this, people with psychosis may be more likely to experience PTSD as a result of trauma due to their increased stress-sensitivity (Walker & DiForio, 1997).

The final pathway that will be considered is that the experiences of psychosis and its treatment can be sufficiently traumatic that they cause PTSD, referred to as PR-PTSD (psychosis-related PTSD). Critical to this concept is that psychosis can be defined as an index event for PTSD, yet this is a controversial issue. This will be discussed further in the next chapter, which reviews the prevalence and risk factors for PR-PTSD. Naturally the authors of the studies reviewed assume that psychosis *can* cause trauma as their starting point for their research.

There are many important issues relating to the assessment of PR-PTSD. Psychotic and treatment experiences are likely to have persisted for a long time, so this makes it difficult for people to select the most distressing experience, as they would be asked to do in mainstream PTSD research (Green, 1996). The ongoing nature of the experiences may mean they would be better categorised as 'complex trauma' (than a single trauma) which may have a different symptom profile to PTSD (Cloitre et al., 2009). If the psychotic experiences are ongoing at the point of assessing PR-PTSD then it could reflect acute stress disorder (American Psychiatric Association, 2013) and not PTSD. Ongoing psychosis may also make it difficult to differentiate an intrusive *memory* of a hallucination or delusional belief from those occurring in present time. For example, a reminder of a delusion might trigger reliving the delusion, or it could be interpreted in a delusional way.

Intrusive memories reflecting PTSD must not be confused with more contextualised autobiographical memories which have been found in psychosis as well as other disorders (Brewin, Gregory, Lipton & Burgess, 2010). Finally, it may be difficult for people to determine whether their distress and dysfunction is caused by current symptoms of psychosis as opposed to past memories of it.

The previous chapter involved participants with PTSD due to any traumatic event, but as these events were not always reported it is possible that a subset of the participants had PR-PTSD. Likewise, people could have had PR-PTSD alongside PTSD due to another traumatic event, developing either before or after the onset of the psychosis. Unlike the first chapter which focused on treating any PTSD comorbid to psychosis, the next chapter will only include studies in which the PTSD has been caused by the psychosis. As it is a new area of research, it will review the prevalence and risk factors of this proposed subtype of PTSD rather than its treatment as few treatment studies have been carried out.

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Chapter 3.

Meta-analysis prepared for submission to Early Intervention in Psychiatry

A Meta-Analytic Review of the Prevalence and Risk Factors of Psychosis-related PTSD

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Abstract

Background: People with psychosis are more likely to have experienced trauma; however, there is a growing body of evidence indicating that psychosis itself can cause post-traumatic stress disorder. The aim of this meta-analytic review was to determine the prevalence and risk factors of psychosis-related post-traumatic stress disorder (PR-PTSD).

Method: Studies were identified in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A random effects proportion meta-analysis was used to pool prevalence rates and the effect size Pearson's *r* was extracted for meta-analysing for risk factors.

Results: The review included 22 studies reporting on prevalence and/or risk factors for PR-PTSD for studies published between 1980 and 2017. The pooled prevalence estimate for PR-PTSD was 35.0% (95% CI 28.7%, 41.7%), with significant heterogeneity. Moderator analyses were conducted to explore this heterogeneity and whilst no factors were found to be significant, analyses of the following subgroups appeared to explain some of the heterogeneity: format of assessment, continent, non-affective psychosis and specificity of index trauma. The following risk factors had a moderate effects size: number of previous traumas, number of negative hospital experiences, anxiety, overall psychosis and depression, with the last two explored in more detail.

Discussion: Findings are discussed in relation to the existing evidence base. Recommendations are made for clinical practice and further research. The strengths and limitations of this review are considered.

Introduction

High rates of trauma and post-traumatic stress disorder (PTSD) have been found in people with psychotic disorders (Resnick, Bond & Mueser, 2003; Read & Ross, 2003); however, PTSD is often under-diagnosed in this population (Lommen & Restifo, 2009). This is particularly concerning given that this comorbidity is associated with a worse prognosis (Fan et al., 2008). It is therefore important that clinicians recognise symptoms of PTSD alongside psychosis so that appropriate treatments can be offered.

There are many potential routes to comorbid PTSD and psychosis and interactions between the two. Consistently, trauma has been found to be an important contributor to the development of psychosis (Morgan & Gayer-Anderson, 2015) but conversely, people with psychosis may also be more susceptible to future trauma and PTSD (Stevens, Spencer & Turkington, 2017). A further pathway, that will be the focus of this review, is that the psychotic experience and its treatment could be sufficiently traumatic as to cause PTSD. This was first discussed by Shaner and Eth in 1989 and represents a growing area for both empirical studies and systematic reviews. Berry, Ford, Jellicoe-Jones, and Haddock (2013) first coined the term psychosis-related PTSD (PR-PTSD) which will be used throughout this review. This is defined as 'PTSD induced as a result of experiencing psychotic symptoms and/or distressing experiences related to the treatment of psychosis.'

Whilst significant distress has been reported due to psychosis and its treatment (Bendall, Alvarez-Jimenez, Hulbert, McGorry & Jackson, 2012), psychosis does not technically meet the A criterion for an index trauma in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5; American Psychiatric Association, 2013) which requires direct or indirect exposure to actual or threatened death, serious injury or sexual violence. However, it is argued that PTSD develops based on appraisal of threat, regardless of objective risk (Kilpatrick, Saunders & Amick-McMullan, 1989) and levels of

perceived threat experienced by people with psychosis can be extremely high (Underwood, Kumari & Peters, 2016).

Similarly to PTSD, PR-PTSD is often not recognised in clinical practice, which can lead to an increase in its severity (Hamner, Frueh, Ulmer & Arana, 1999). It is also thought to be associated with increased severity of psychotic symptoms, worse social functioning, drug and alcohol use and increased use and subsequent cost of mental health services (Mueser et al., 2002a). It is therefore important that awareness of PR-PTSD is raised.

Many people suffering from an acute psychotic episode will continue to be supported by mental health services in the aftermath, thus providing opportunities for assessment and intervention of PR-PTSD. It is therefore important that clinicians are aware of the rates of PR-PTSD that could be expected and understand which factors may contribute to its development. A systematic review of PR-PTSD (Berry et al., 2013) from 1980 to 2011 found prevalence rates of 11% to 67% for PR-PTSD. Given this large range, this review aims to meta-analyse prevalence rates in order to update Berry et al.'s (2013) review and explore reasons for the large range of prevalence estimates found. In a recent systematic review, Fornells-Ambrojo, Gracie, Brewin and Hardy, (2016) found many differences in the assessment of PR-PTSD, but not did conduct meta-analyses and moderator analyses to explore the impact of these variables on prevalence. Rodrigues and Anderson (2017) reviewed PR-PTSD in first-episode psychosis only and found a pooled prevalence estimate of 30% (95% CI 21%, 40%).

This review aims to synthesise and meta-analyse the prevalence figures and risk factors for PR-PTSD (without the restriction to first-episode psychosis). 'Risk factor' is used broadly to represent characteristics or experiences found to be associated with having or developing PR-PTSD.

Aims of the review

1) What is the estimated prevalence of PR-PTSD?

1a) What population and methodological variables moderate the estimated prevalence?

2) What are the predictive strengths of risk factors of PR-PTSD?

Method

The protocol for this review can be accessed on PROSPERO: the international prospective register of systematic reviews (National Institute for Health Research & University of York, 2016). This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009).

Study selection

This study sought to identify journal articles, dissertations or theses published in English from 1980 to October 2017. This was because in 1980 PTSD was first included in the DSM-III (American Psychiatric Association, 1980). The search terms used were:

1) Psychosis OR psychotic OR postpsychotic OR post-psychotic OR 'post psychotic' OR psychosis-related OR 'psychosis related' OR schizo* OR 'severe mental illness' OR 'serious mental illness' OR 'serious mental health'

AND

2) 'Posttraumatic stress' OR 'post-traumatic stress' OR 'post traumatic stress' OR PTSD OR trauma*

Studies were identified through the following databases: PsycInfo, Embase, Cinahl, Medline, PubMed and the National Center for PTSD research's Published International Literature on Traumatic Stress (PILOTS). The following journals were searched individually: Schizophrenia Research, Schizophrenia Bulletin, Psychological Medicine and the Journal of Traumatic Stress. Additionally, the author checked the reference sections of relevant review articles, book chapters and research papers. In order to identify 'grey literature' relating to PR-PTSD, full texts of relevant dissertations and theses were requested and authors of key papers were contacted for unpublished data.

Inclusion criteria

For review question 1, it was essential that studies included: (1) participants who have experienced at least one acute psychotic episode, (2) a validated self-report measure or interview for PTSD, rated based on the participants' acute psychotic episode and/or its treatment, (3) prevalence of suspected PR-PTSD or sufficient data to calculate this. For review question 2, it was necessary that studies reported at least one factor associated with PR-PTSD, either explored through a correlation or comparison of the frequency or severity of the factor in PR-PTSD and no PR-PTSD groups. Qualitative studies and case studies were excluded. Studies were also excluded if the prevalence of PR-PTSD or effect size of a factor associated with PR-PTSD could not be established once the author had been contacted. If several papers referred to the same dataset, the paper judged as most relevant was selected, followed by the largest study if all papers were relevant.

For the purposes of this review, an 'acute psychotic episode' was defined as a 'period of time in which severe symptoms of psychosis, including at least one positive symptom, required inpatient care or intensive outpatient care.'

Screening

Initially, irrelevant studies were eliminated by the primary author based on their titles and abstracts. Full texts were retrieved for the remaining studies and reviewed against the inclusion criteria by the primary author. All studies were reviewed independently by a collaborator and disagreements were resolved by a second collaborator. Authors were consulted for further information if it was unclear if a study met the inclusion criteria.

Data extraction

The primary author extracted data for all included studies and a collaborator independently extracted the data for 50% of these, selected at random. A second collaborator was used as a mediator for any disagreements. Detailed data extraction was

carried out using a data extraction spreadsheet capturing the following areas: methodology, population, setting, clinical characteristics, study quality, reporting of prevalence of PR-PTSD and analysis of factors associated with PR-PTSD (see Appendix C).

The effect size Pearson's *r* was chosen as the common metric for the risk factor meta-analyses due to ease of interpretation (Cooper, Hedges & Valentine, 2009). For non-correlation studies, effect sizes were converted to *r* using Rosenthal's guidance (1991). To do this, effect sizes were calculated from the descriptive data provided.

When studies reported results at more than one timepoint the timepoint closest to the average time that measures were completed in the other studies was used. Outcomes from measures definitely completed within a month of the psychotic episode were excluded from analysis as PTSD cannot reliably be diagnosed at this time. When studies used a continuous measure and a categorical measure of the same risk factor, the effect size from the continuous measure was extracted due to its greater sensitivity. When studies reported prevalence or risk factors of both psychosis-related PTSD and hospital-related PTSD the two were merged using the guidance in Corey, Dunlap and Burke (1998). Subscales of measures were also merged to create a total score for the measure if necessary. Where beta coefficients were reported in the absence of any other data to calculate effect size, they were converted to *r* using Peterson and Brown's (2005) technique. When necessary, Spearman's *r* was used as a substitute for Pearson's *r* (Hauke & Kossowski, 2011). When studies reported no association, but insufficient data were provided to calculate an effect size for the risk factor, $r = 0$ was used (Rosenthal, 1995).

Study quality and risk of bias

In order to determine study quality novel scoring criteria were created, based on the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data (Munn, Moola, Lisy, Riitano & Tufanaru, 2015) and the JBI Critical Appraisal

Checklist for Analytical Cross Sectional Studies (Moola et al., 2017). Duplications between the two checklists were removed and remaining items were adapted for the purpose of this meta-analysis to form a 10-point scoring system (higher scores reflecting higher quality studies with less risk of biased data). For the purpose of the analysis, studies with a score of 6 or greater were deemed 'high' quality and anything less than this 'low quality.'

In order to explore potential publication bias in the meta-analyses, funnel plots were explored when at least 10 studies were included (Higgins & Green, 2011) and the significance of this bias was tested using Egger's test (Egger, Davey-Smith & Minder, 1997).

Prevalence of PR-PTSD

A proportion meta-analysis with logit transformations was carried out to estimate the prevalence of PR-PTSD (Barendregt, Doi, Lee, Norman & Vos, 2013). For the risk factor meta-analyses, values of *r* were converted to Fisher's *z* for the analysis and converted back to *r* for interpretation of the result. Meta-analyses were carried out on risk factors that were reported in three or more studies, as in Witt, van Dorn and Fazel, (2013).

Random effects meta-analyses (Hedges & Olkin, 1985) were carried out using the statistical software Comprehensive Meta-Analysis, with studies weighted using the inverse variance method. Heterogeneity was assessed using Q and I^2 statistics.

Subgroup analyses

The following subgroup analyses were planned, subject to study numbers: demographics, basic study characteristics such as location and design and methodological variables such as assessment measured used.

Results

Included studies

The search process produced 22 eligible studies for inclusion in the prevalence meta-analysis and/or in the risk factors meta-analyses (see Figure 1). Interrater agreement for inclusion/exclusion of studies was 95.2% (Cohen's Kappa 0.63) reflecting 'substantial agreement.'

See Table 1 for the characteristics of the included studies. Interrater agreement of extracted data items was 87.3% which reflects 'fair agreement' (Cohen's Kappa 0.29). Two studies were theses (Pietruch & Jobson, 2012; Stubbins, 2004) and the rest were peer-reviewed journal articles. Participants were civilian adolescents and adults, presenting to non-forensic inpatient services or community outpatient services. In the eight studies that assessed for previous trauma the average prevalence of previous trauma was 67.8%.

Study quality

Quality assessment and grading are displayed in Table 2. Four of the studies were deemed high quality. Interrater agreement for classification as high/low quality was 90.9%, reflecting 'substantial agreement' (Cohen's Kappa 0.74). Most of the studies lacked power, had low response rates and had used convenience samples.

Studies were inconsistent in their reporting of the timing of PTSD assessments post-psychosis (the range of means was 1.1 months to 4 years, with 14 not reporting this time). Studies were also unclear whether participants were assessed as inpatients or outpatients, whether the psychotic episodes had required hospitalisation and on whether a specific experience was the index trauma or the whole psychotic episode.

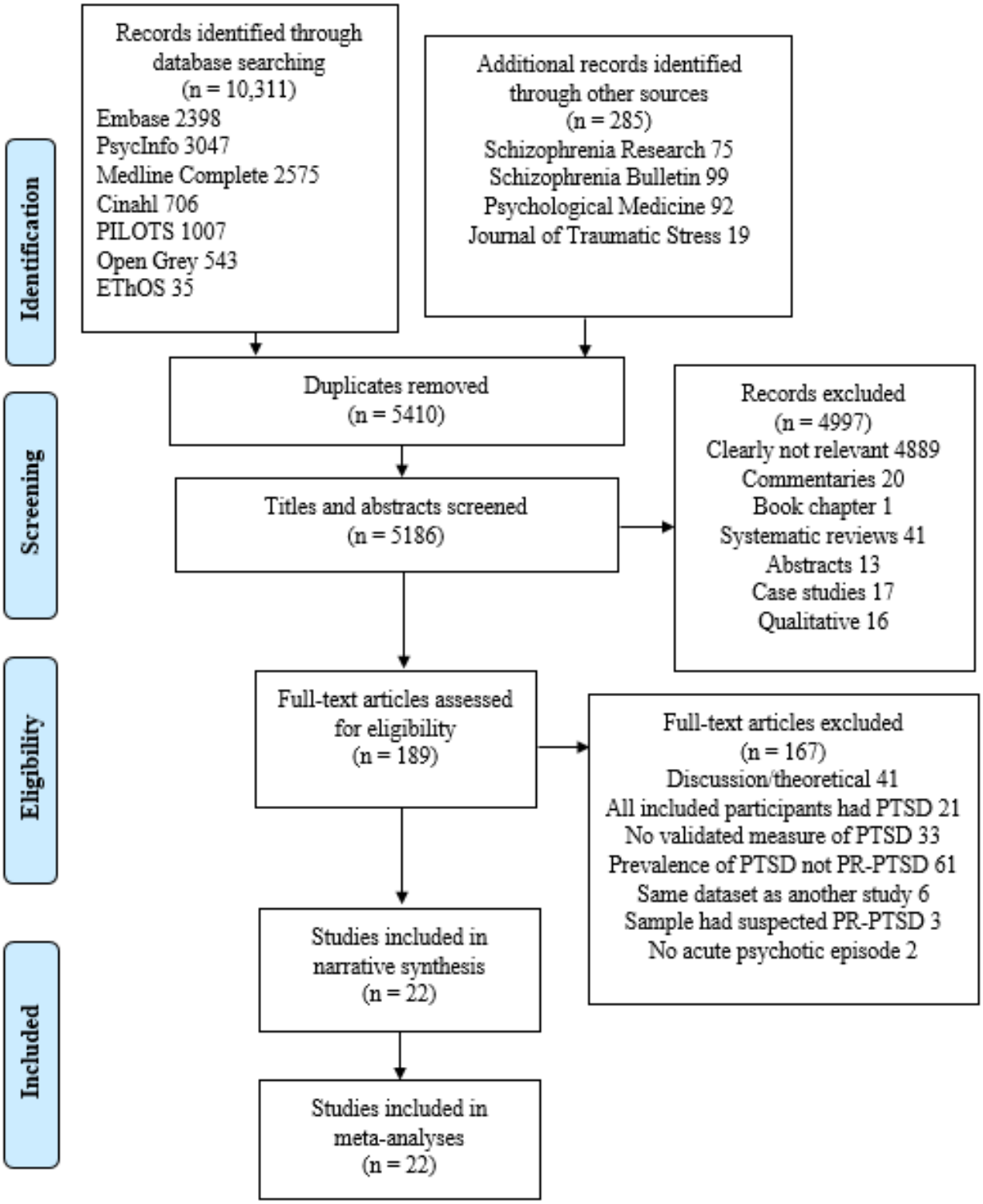

Figure 1. Preferred Reporting Items for Systematic Reviews (PRISMA) diagram.

Table 1

Study Characteristics

Study no.	First author	Date	Country	N	Study design	Data extracted (prevalence, risk factors, or both)	Mean age of sample	Female (%)	PR-PTSD measure	PR-PTSD prevalence (%)	High/low quality
1	Abdelghaffar	2016	Tunisia	52	Cross sectional	Both	27.6	48	CAPS	22.7	Low
2	Beattie	2009	UK	47	Cross sectional	Risk factors	37.5	25	IES-R	47.2	Low
3	Bendall	2012	Australia	36	Cross sectional	Both	21.4	39	IES-R	-	Low
4	Bernard	2006	UK	25	Cross sectional	Prevalence	25.0	41	IES-R	42.3	Low
5	Berry	2015	UK	50	Cross sectional	Both	37.7	20	IES-R	38.2	Low
6	Brunet	2012	UK	50	Prospective	Both	22.4	34	PSS-I	23.3	High
7	Centofanti	2005	Australia	20	Cross sectional	Both	33.4	35	CAPS	31.4	Low
8	Chisholm	2006	UK	36	Cross sectional	Both	34.1	42	IES	10.9	Low
9	Harrison	2004	UK	38	Cross sectional	Risk factors	36.5	21	IES-R	61.1	Low
10	Jackson	2009	UK	66	RCT	Prevalence	23.3	26	IES	52.4	Low
11	Jackson	2004	UK	35	Cross sectional	Both	25.8	26	PTSD Scale	51.4	Low
12	Kennedy	2002	USA	30	Cross sectional	Both	35.2	23	Penn Inventory	56.5	Low
13	Lu	2011	USA	50	Cross sectional	Both	36.8	46	PDS	30.0	Low
14	McGorry	1991	Australia	36	Prospective	Both	25.0	28	PTSD Scale	30.8	Low
15	Meyer	1999	Finland	46	Cross sectional	Both	40.8	61	CAPS	25.0	High
16	Mueser	2010	USA	38	Cross sectional	Both	22.5	32	PDS	-	Low
17	Pietruch	2010	UK	34	Cross sectional	Prevalence	25.7	35	IES-R	68.0	Low
18	Priebe	1998	Germany	105	Cross sectional	Both	38.6	45	DSM-III	34.5	High
19	Shaw	2002	Australia	42	Cross sectional	Both	29.8	38	CAPS-1	65.8	High
20	Sin	2010	Singapore	61	Cross sectional	Both	25.8	51	CAPS	19.7	Low
21	Stubbins	2014	UK	51	Cross sectional	Both	26.9	37	IES-R	52.0	Low
22	Turner	2013	UK	50	Cross sectional	Both	24.5	?	IES-R interview	14.0	Low

Note. CAPS (Clinician Administered PTSD Scale), IES (Impact of Events Scale), IES-R (Impact of Events Scale - Revised), PDS (Posttraumatic Diagnostic Schedule), PSS-I (PTSD Symptom Scale – Interview)

Table 2

Assessment scores on the Clinical Treatments Assessment Measure (CTAM)

	Sampling				Validity of assessments			Analysis				
Study no.	Sampling frame appropriate	Minimal sampling bias	Adequate response rate	Sample well described	Valid diagnosis PTSD	Valid risk factor measures	Assessors trained	Sufficient coverage of sample	Analysis appropriate	Powered to determine prevalence	Powered to determine risk factors	Confounding variables considered
1	x	x	-	x	✓	✓	-	-	✓	x	x	x
2	x	-	x	✓	x	✓	-	-	✓	x	x	✓
3	x	x	✓	✓	x	✓	-	-	✓	x	x	✓
4	x	x	x	x	x	✓	-	-	✓	x	x	x
5	x	-	✓	✓	x	✓	-	-	✓	x	x	✓
6	x	x	✓	✓	✓	✓	-	✓	✓	x	x	✓
7	x	x	x	✓	✓	✓	-	-	✓	x	x	x
8	x	x	✓	✓	x	✓	-	-	✓	x	x	✓
9	x	x	-	✓	x	✓	-	-	✓	x	x	✓
10	x	x	x	✓	x	✓	✓	-	✓	x	x	x
11	x	x	✓	✓	x	✓	-	-	✓	x	x	x
12	x	x	-	x	x	✓	-	-	✓	x	x	✓
13	x	x	-	✓	✓	✓	-	-	✓	x	x	x
14	x	x	✓	✓	x	✓	-	✓	✓	x	x	x
15	x	x	✓	✓	✓	✓	-	✓	✓	x	x	✓
16	x	x	-	✓	✓	✓	-	-	✓	x	x	x
17	x	x	x	x	x	✓	-	-	✓	x	x	x
18	x	x	✓	x	✓	✓	-	-	✓	✓	✓	x
19	x	✓	✓	✓	✓	✓	-	-	✓	x	x	✓
20	x	x	-	✓	✓	✓	✓	-	✓	x	x	✓
21	x	x	x	✓	x	✓	-	-	✓	x	x	✓
22	x	x	-	✓	x	✓	-	-	✓	x	x	✓

Lu et al., (2011), Abdelghaffar, Ouali, Jomli, Zgueb, and Nacef, (2016) and Mueser, Lu, Rosenberg and Wolfe, (2010) were the only studies to assess the trauma index event against criteria A1 and A2 in the Diagnostic and Statistical Manual of Mental Disorders 4th edition: DSM-IV (American Psychiatric Association, 2000). All other studies either excluded the need for these criteria to be met and thus did not assess for them or did not report anything regarding these criteria.

Prevalence of PR-PTSD

Twenty studies reported prevalence of PR-PTSD, yielding a sample of 892 participants. A forest plot of the meta-analysis of prevalence is presented (Figure 2). No clear outliers were observed. Overall prevalence was estimated at 35.0% (95% CI 28.7%, 41.7%, $p = 0.00$) and the Q test was significant ($X^2 = 72.72$, $df = 19$, $p = 0.00$, $I^2 = 73.87$). This summary finding is reported as it may be of interest to the reader; however, it should not be considered a reliable estimate of PR-PTSD prevalence due to the 'considerable' heterogeneity (Deeks, Higgins & Altman, 2011) between studies.

Sensitivity analysis

Study quality (high/low) was not a significant moderator of prevalence. A meta-regression of total quality score criteria was also non-significant.

Priebe, Bröker and Gunkel, (1998) was the only study to assess PR-PTSD caused by treatment only (instead of treatment combined with psychotic symptoms). Removing this study had little impact, suggesting it was not unduly affecting the overall result.

The decision was made to include all studies with a validated measure of PTSD in this review; however, three studies (Chisholm, Freeman, & Cooke, 2006; Jackson, Knott, Skeate, & Birchwood, 2004; Meyer, Taiminen, Vuori, Äijälä, & Helenius, 1999) used unconventional cut-off scores for their respective measures. When these studies were removed from the analysis, the impact on overall prevalence and heterogeneity was

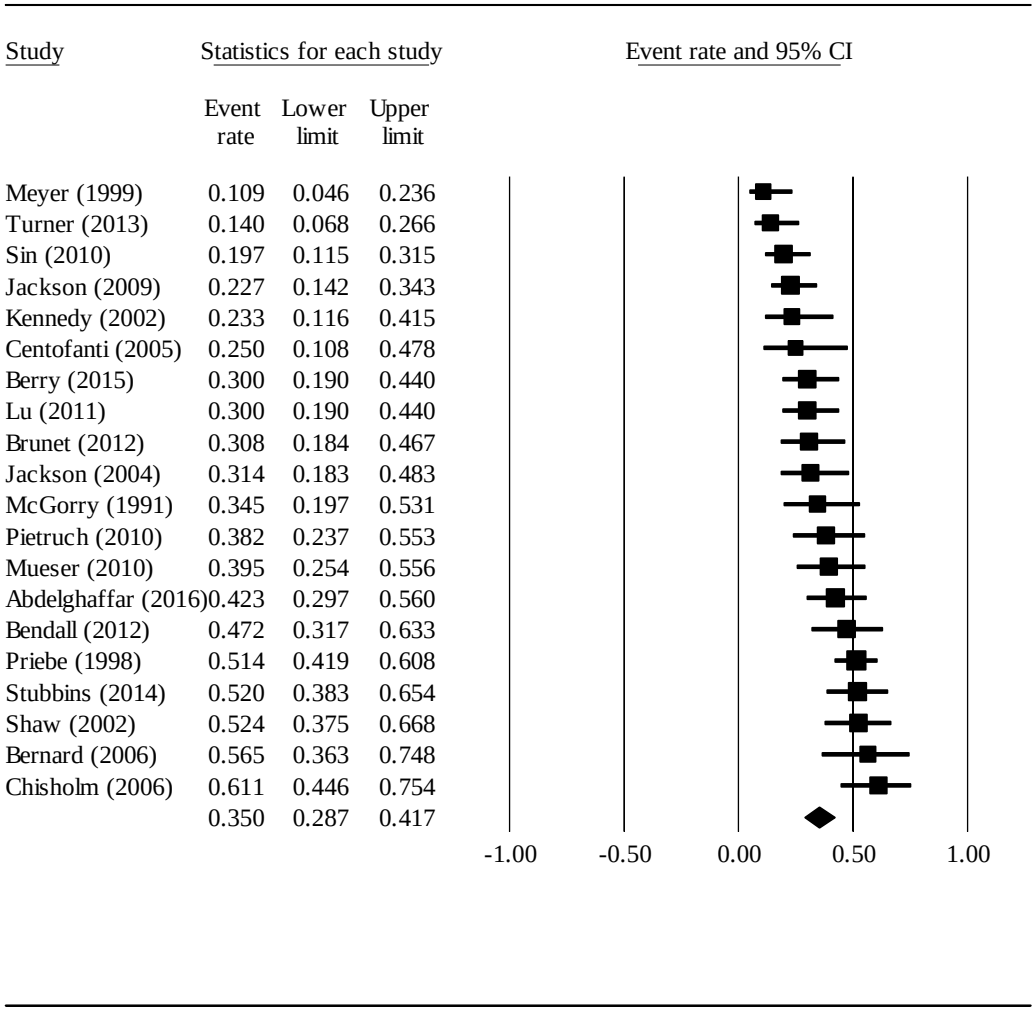

Figure 2. Forest plot showing the results of the meta-analysis of PR-PTSD prevalence.

negligible. This was perhaps because this group of studies included both the lowest and highest rates of prevalence. However, 'leave one out' analyses also had little impact on the overall outcome.

It was decided that two studies (Brunet, Birchwood, Upthegrove, Michail & Ross, 2012 & Kennedy et al., 2002) should be included despite slight ambiguity in the papers as to whether they used psychosis as the index event when assessing traumatic symptoms. Exclusion of these studies from the analysis caused a slight increase in overall prevalence and increased unexplained heterogeneity (I^2) to 75.5%.

Moderator analysis

It was not possible to explore all the moderator variables defined *a priori* due to insufficient data reported. For example, studies did not use (or report on) subsamples of ages or gender. Summary statistics (e.g., percentage female/male or mean age) were not used as study-level characteristics for moderator analysis due to the loss of data involved in summarising in this way. It was also not possible to examine the time elapsed since the psychotic episode or ethnicity due to inconsistent reporting of these variables.

Table 3 displays the moderator variables examined. None of these variables were found to be significant; however, this should be interpreted with caution as the analyses were underpowered. The impact of subgroupings on prevalence estimates and heterogeneity can be also be seen in Table 3. It should be noted that the level of specificity of index trauma was not always clearly reported, which affects the reliability of this analysis.

Table 3

Moderators of prevalence

Moderator	*k*	Prevalence (%)	95% CI	I^2 (%)	Between groups test (*Q*)
All studies	20	35.0	0.29, 0.42	73.9	
Location					0.004
Europe	11	35.1	26.7, 44.6	81.5	
Non-Europe	9	35.8	30.8, 41.1	56.2	
Affective psychosis					0.548
Included	10	37.1	27.8, 47.5	84.4	
Excluded	9	32.0	23.0, 42.6	57.6	
Psychotic episode					0.671
First	7	37.5	26.6, 49.8	74.8	
Worst	8	31.5	22.2, 42.5	70.8	
Most recent	5	36.9	23.8, 52.3	70.8	
Psychotic episode					0.584
Specific experience	6	32.0	21.8, 44.2	66.6	
Whole episode	13	36.9	28.9, 45.7	76.2	
Type of measure					1.368
Interview	10	31.0	22.9, 40.6	80.0	
Self-report	10	39.0	29.7, 49.3	66.6	

Notably, heterogeneity reduced when studies using self-report measures to determine PR-PTSD were analysed separately and when studies excluding affective psychosis were analysed separately.

Publication bias

Egger's test (Egger et al., 1997) for asymmetry of the funnel plot (see Figure 3) was significant ($p = 0.02$); however, the pooled prevalence estimate was not affected by the trim and fill method (Duval & Tweedie, 2000).

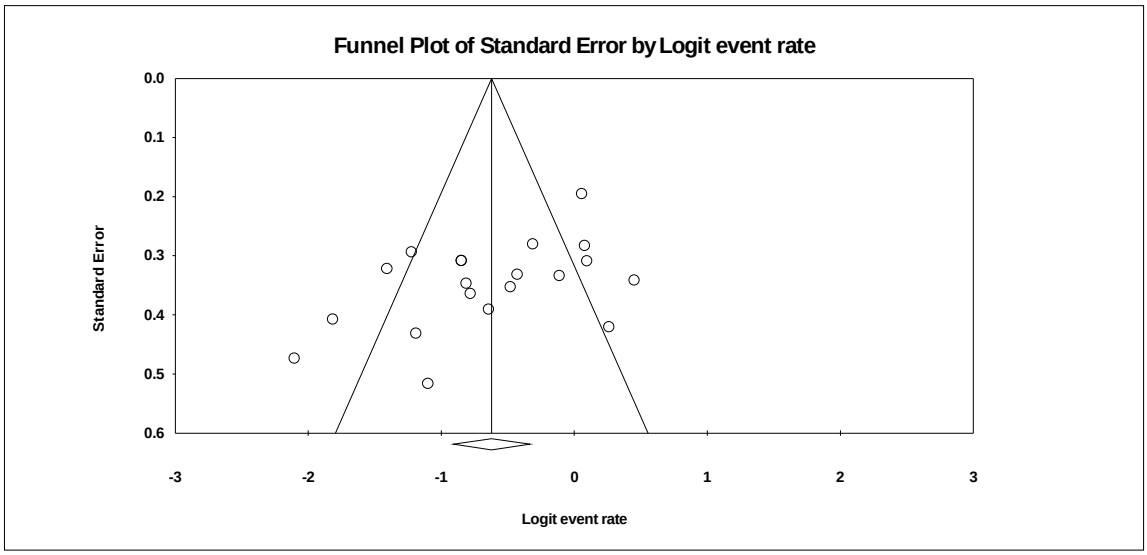

Figure 3. Publication bias for PR-PTSD prevalence data.

Risk factors of PR-PTSD

Risk factors reported in three or more studies were analysed using separate meta-analyses (see Table 4). These findings should be interpreted with caution if the meta-analyses included a small number of studies, particularly if the studies in these analyses had small sample sizes.

Eight of the studies assessed participants for previous trauma, but due to differences in the aspects of this that were assessed, the only risk factor meta-analysis performed was on number of previous traumas. The remaining findings related to previous trauma (that could not be meta-analysed) had mixed results ranging from non-significant effects for sexual abuse (Mueser et al., 2010) to a large effect size for the presence of childhood trauma (Bendall et al., 2012).

Table 4

Meta-analyses of risk factors of PR-PTSD

Risk factors	*k*	*r*	95% CI		Heterogeneity	
			Lower	Upper	X^2	I^2
Demographics						
Level of education	3	-0.02	-0.16	0.12	0.21	0.00
Unemployed status	3	0.03	-0.34	0.40	15.31*	86.94
Gender (female)	5	0.04	-0.07	0.16	3.09	0.00
Age	4	-0.05	-0.17	0.08	1.56	0.00
Clinical characteristics						
Alcohol abuse severity (past 30 days)	3	0.00	-0.19	0.20	2.54	21.23
No. of previous admissions	5	0.02	-0.11	0.15	1.70	0.00
'Sealing over' recovery style	3	-0.06	-0.25	0.12	1.81	0.00
Negative symptoms severity	3	0.08	-0.17	0.32	4.66	57.10
Involuntary psychiatric admission	6	0.08	-0.05	0.20	4.88	0.00
Time since psychotic episode	3	-0.08	-0.41	0.26	4.81	58.38
Drug abuse severity (past 30 days)	3	0.09	-0.08	0.25	0.67	0.00
Duration of untreated psychosis (DUP)	4	-0.12	-0.27	0.04	3.28	8.49
Positive symptoms severity	3	0.17	-0.03	0.37	3.12	35.98
Psychosis severity (all symptoms)	10	0.22*	0.06	0.37	29.60**	69.56
No. of previous traumas	4	0.32*	0.11	0.49	4.97	39.57
No. of negative hospital experiences	3	0.32*	0.14	0.49	1.86	0.00
Anxiety severity	5	0.44*	0.13	0.64	20.98*	80.93
Depression severity	10	0.46**	0.28	0.61	40.71**	77.89

Note. *p = <0.01, **p = <0.001

Number of previous traumas, number of negative hospital experiences, overall psychosis severity, anxiety and depression were found to have moderate effect sizes using Cohen's (1988) criteria. The latter three were found to have high heterogeneity. Moderator

analyses were carried out for depression and overall psychosis severity as there were sufficient studies (k = 10; Deeks et al., 2011).

Depression

Studies used self-report measures to assess depression; however, it was not possible to explore the impact of measure on effect size due to the wide range of measures used. A meta-regression based on study quality was non-significant (Q = 1.98, p = 0.159). I^2 reduced from 77.9% to 75.0%.

Studies using correlations were compared to those in which r had been calculated based on Cohen's d from a comparison of means. Figure 4 shows that this had a significant impact on the outcome. This was also significant (p = <0.05), although unexplained heterogeneity remained high (I^2 = 62.6%).

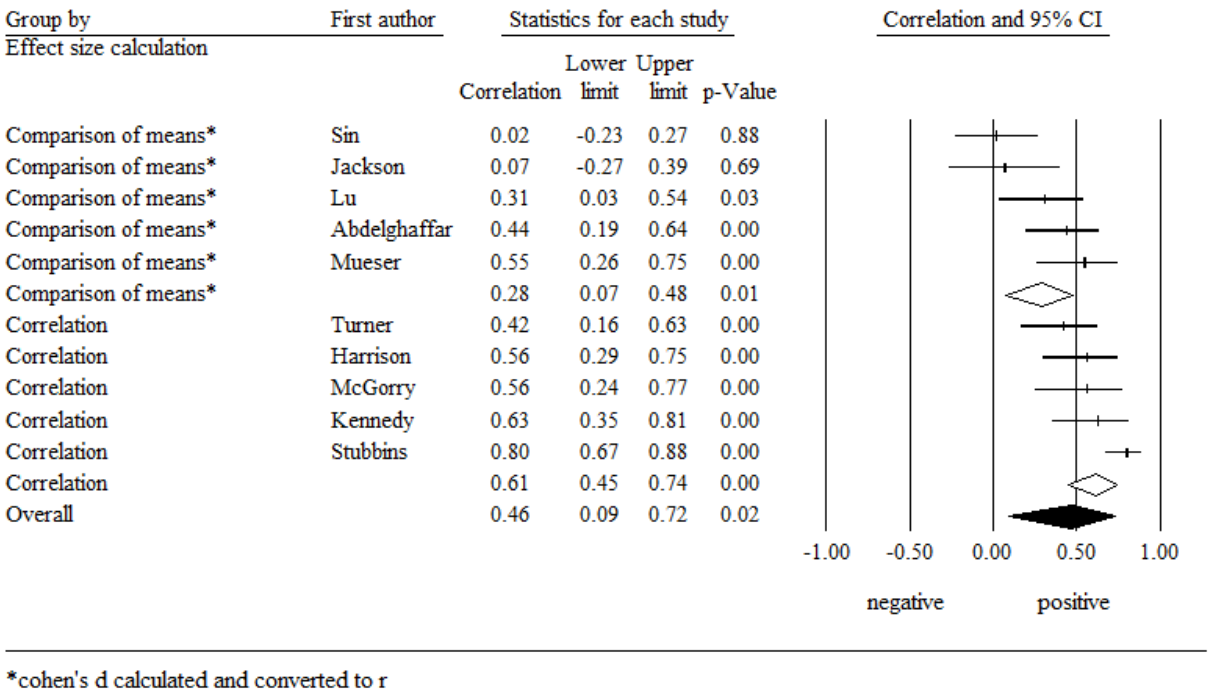

Figure 4. Moderator analysis of the associations between depression and PR-PTSD.

Psychosis severity

Study quality was not found to moderate the strength of psychotic symptom severity as a risk factor. The measure used and the effect size calculation were also non-significant as moderators. Heterogeneity reduced marginally when only analysing the subgroup of three studies in which the Brief Psychiatric Rating Scale (Overall & Gorham,1962) was used, but not when a subgroup of those using the PANSS (Positive and Negative Syndrome Scale for Schizophrenia; Kay, Fiszbein & Opler, 1987) was used, or any other measure.

Discussion

Prevalence of PR-PTSD

This review found that approximately a third of people experiencing psychosis have PR-PTSD. Rodrigues and Anderson (2017) found a similar result (30%; 95% CI 21%, 40%) when recruiting participants with first-episode psychosis; however, this study included 11 of the 22 studies included in this review, therefore we would expect these estimates to be similar.

Moderator analyses suggest that affective psychosis is associated with higher prevalence of PR-PTSD than non-affective psychosis. This is supported by findings that PTSD rates are higher in people with schizoaffective disorder than schizophrenia and higher still in depression and bipolar disorder (Mueser et al., 2004). It may be the case that an intense emotional reaction to trauma is negated by the negative symptoms of schizophrenia-spectrum conditions (Seow et al., 2016).

Prevalence was higher in first-episode psychosis as opposed to most recent or worst episodes. This may be because of the negative impact the first-episode has on people's views of themselves, the world and others (Dunkley, Bates & Findlay, 2015). Two further aspects of assessment may have resulted in an overestimation of the overall prevalence of PR-PTSD in this review. Firstly, the majority of studies did not rate PR-PTSD based on a specific experience. Secondly, most studies assessed for it while psychosis was ongoing, therefore potentially not allowing the recovery period of 1 month post-trauma before a diagnosis of PTSD can be made (American Psychiatric Association, 2013).

There were insufficient studies to explore the effects of moderator variables when the impact of PR-PTSD measure was partialled out. This would have been useful as the tentative analyses conducted in this review indicate that a degree of heterogeneity can be explained by the specific measure used to assess PR-PTSD. For example, those studies that

assessed PR-PTSD using self-report measures may have overestimated its prevalence because these tools do not discriminate between symptoms caused by comorbid disorders as accurately as interviews such as the clinician-administered PTSD scale (CAPS; Blake et al., 1995) do.

Risk factors of PR-PTSD

Severity of depression and anxiety were found to be associated with severity of PR-PTSD in this review; however, this finding does not imply causation and cannot explain the temporal order of these symptoms. Ginzburg, Ein-Dor & Solomon (2010) found PTSD to be a predictor of depression and not the other way around. The finding could also be due to psychosis causing high rates of both PR-PTSD and post-psychotic depression (Iqbal, Birchwood, Hemsley, Jackson & Morris, 2004) or they could both be due to a mediating factor. Notably, Sin et al., (2010) accounted for confounding variables and found no significant association between PR-PTSD and depression or anxiety.

The finding that number of previous traumas was associated with PR-PTSD is interesting given the 'dose effect' (Shevlin, Houston, Dorahy & Adamson, 2007) of cumulative trauma on likelihood of psychosis. It may be that the risk of PR-PTSD after considerable previous trauma is mediated by the severity of the psychotic symptoms, as this was also found to have a moderate association with PR-PTSD.

Strengths and limitations of this review

This was an ambitious review in its scope and inclusion criteria. Search terms were sufficiently broad to avoid missing relevant papers, evidenced by the large number of studies retrieved initially. Protocols were followed and the levels of interrater reliability suggest the design is replicable. The findings must be viewed in the context of the methodological limitations of the study; however, they provide a useful snapshot of early hypotheses regarding PR-PTSD.

Recommendations for future clinical practice

Clinicians should monitor for PR-PTSD, particularly in cases with comorbid depression and anxiety, or with a significant trauma history, including distressing hospitalisations. Rates of PR-PTSD could perhaps be reduced by improving experiences of treatment for psychosis. Interestingly, Meyer et al.'s (1999) study, which found a relatively low prevalence of PR-PTSD, included participants who were being treated using an actively non-coercive model. However, there are many other variables potentially impacting prevalence rates, so this hypothesis would need to be explored further.

Recommendations for future research

For many people, the experience of psychosis is highly distressing (Lu, Mueser, Rosenberg, Yanos & Mahmoud, 2017); however, its status as an index event for PTSD is unclear. In line with Brewin, Lanius, Novac, Schnyder & Galea's (2009) recommendations, many studies in this review have emphasised core PTSD phenomena over trauma criteria and so this issue has not been discussed. This could be viewed as a passive approach, which is unlikely to lead to developments in defining PR-PTSD consistently. Fornells-Ambrojo et al., (2016) differentiate between PTSD caused by psychosis when criterion A in the DSM-5 (American Psychiatric Association, 2013) is met, referred to as 'PR-PTSD,' and PTSD caused by psychosis when this criterion is not met, referred to as 'distorted reality PTSD.' They describe the latter occurring when people are unable to appraise threat rationally due to their psychotic symptoms. These definitions may be a helpful way forward.

The measure used to assess PR-PTSD explained some heterogeneity in prevalence. Ideally assessments would be consistent; perhaps the clinician-administered PTSD scale for schizophrenia (CAPS-S; Gearon, Thomas-Lohrman & Bellack, 2001) should be viewed

as the ‘gold standard’ due to its attempts to differentiate between PTSD symptoms and psychotic symptoms.

When reporting assessments of PR-PTSD, the level of specificity of the index event should be explicitly stated, for example, whether participants’ symptoms were rated based on a particular hallucination or experience of restraint in hospital, or on their psychotic experience or admission in its entirety. For PTSD to be diagnosed as it would be in mainstream PTSD research, a specific event should be used as the index event.

Research should continue to explore which elements of psychosis and treatment participants find most distressing in order to further our understanding of the mechanisms involved in the development of PR-PTSD. It is particularly important that prospective longitudinal studies are carried out into risk factors as opposed to correlational cross-sectional studies. Qualitative research informed by a meta-synthesis would also be helpful in informing our understanding of potential risk factors for PR-PTSD, especially related to experiences of treatment. For example, Dunkley et al.’s (2015) qualitative study found that first-episode psychosis disrupted people’s views of the self, others and the world. They also argue that a PTSD diagnosis is too narrow to capture the extent of the distress caused by psychosis and its treatment. Finally, further randomised controlled trials into treatments for PR-PTSD should also be conducted in order that evidence-based interventions can be offered in clinical services.

Conclusion

Many complex potential interactions have been proposed between trauma, PTSD and psychosis and this remains an uncertain and developing clinical area. For example, trauma may cause psychosis and PTSD as discrete conditions (Okkels, Trabjerg, Arendt & Pedersen, 2017), PTSD and psychosis may be on a continuum of responses to trauma (Morrison, Frame & Larkin, 2003) or PTSD may develop after psychosis because of

increased risk to trauma due to the psychosis (Mueser, Rosenberg, Goodman & Trumbetta, 2002). Finally, psychosis itself may cause PTSD, as has been discussed in this review. The latter pathway was the main focus for the authors in this review, which meant that only eight studies considered the role of previous trauma and only two studies assessed for PTSD concurrent with the PR-PTSD. These are important issues given the high rates of trauma in people with psychosis (Read & Ross, 2003), which were also reflected in this study; of those assessed, 67.8% on average had experienced a previous trauma. Given the well-established links between childhood trauma and psychosis (Varese et al., 2012) and to a lesser extent adult abuse and psychosis, (Pinheiro, Peixoto, Gomes, Campos & Mota, 2015) it certainly seems important that future PR-PTSD research considers the prevalence and role of pre-existing trauma and PTSD and the potentially retraumatizing impact of psychosis.

This is a relatively new area for research and it is unclear how PR-PTSD fits with the conceptualisation of PTSD in the DSM-5 (American Psychiatric Society, 2003). Perhaps inevitably given its novelty, there are many issues in its assessment, and inconsistencies in how it is defined. There is considerable heterogeneity in these areas in the studies reviewed, which precludes a robust conclusion regarding prevalence. Of particular note is the use of self-report measures in many of the studies, which is likely to lead to an overestimation in the rate of PR-PTSD as these tools do not distinguish between PTSD or other disorders as accurately as interviews do. This is particularly problematic given the high comorbidity in both PTSD and psychosis, (Strakowski, Keck & McElroy, 1995; Bleich, Koslowsky, Dolev & Lerer, 1997) including overlap between psychotic and PTSD symptoms.

Recommendations are that PR-PTSD should be assessed using a validated tool such as the CAPS-S (Gearon et al., 2004) on the basis of a specific traumatic event, at least a

month after it occurred and a differentiation should be made between objectively and subjectively traumatic psychotic or treatment experiences.

Overall, the research reviewed raises helpful questions for developing our thinking around PR-PTSD and perhaps most importantly ensures that attention is drawn to the potentially traumatic nature of psychosis and its treatment. As discussed, PR-PTSD needs further investigation in order to determine the potential mechanisms involved and whether it has diagnostic validity. Regardless of the outcome, this will initiate discussion as to how we assess, treat and where possible prevent potential harm and distress that has been reported as a result of psychosis and its treatment (Lu et al., 2017).

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Chapter 4.

Critical Evaluation & Additional Information

Critical Evaluation & Additional Information

This portfolio contains two systematic reviews and meta-analyses in the clinical field of psychosis and trauma, referred to in this chapter as 'reviews' for simplicity. Firstly, this chapter includes reflections on the overall process of conducting these reviews, with reference to the rationale behind important decisions. Secondly, their overall strengths and limitations as reviews are considered. Thirdly, the clinical and research implications of the findings of these reviews will be discussed.

Reflections on review processes

A proposal for the second review in this portfolio was approved by the University of East Anglia (Appendix D). The recommended changes were incorporated into the final design or considered carefully in research supervision if they were not. Dr Bonnie Teague confirmed that ethical approval was not required from the University of East Anglia Faculty of Medical and Health Sciences Ethics Committee for these reviews (Appendix E). Had the review identified restricted or confidential data, the issue of ethical approval would have been addressed accordingly with guidance from the university. This was not necessary, as the only unpublished data retrieved were from theses, which were openly available and had been approved by Ethics Committees at their respective universities.

The reviews' protocols were submitted to PROSPERO (National Institute for Health Research & University of York, 2016) which ensures transparency in the process, as the specifics in the original protocol must be adhered to regardless of how ideas for further research questions and analyses may develop as the review progresses. However, the earliest stage of these reviews naturally involved the iterative process of identifying broad aims and then conducting preliminary searches to gauge the evidence base, which further informs the aims. Given the relatively low number of studies identified initially, the

topics seemed appropriate choices for review; finding the balance between a novel area or angle and sufficient studies.

When identifying aims for these reviews my placement was in an 'early intervention in psychosis service' and I heard that EMDR seemed an unwise choice for people with psychosis given its unusual methods, which it was thought could be interpreted as magical and enhance delusions. No reviews were found on the acceptability of PTSD treatments in people with psychosis; however, the research findings that therapists were reluctant to offer these treatments (Gairns, Alvarez-Jimenez, Hulbert, McCorry & Bendall, 2015) seemed to suggest it was very important to understand this. The aims of my second review were based on the finding that no single review had encompassed the literature on the prevalence and risk factors for PR-PTSD in psychotic populations. Again, the complexity of differentiating between trauma symptoms and psychotic symptoms that was apparent on my placement led me to read about this issue, and subsequently to learn that psychosis itself could have been traumatising. A review of the measures used to determine PR-PTSD found high heterogeneity (Fornells-Ambrojo, Gracie, Brewin & Hardy, 2016); however, it seemed important that this area should be thoroughly reviewed and meta-analysed so that readers could consider the findings and make their own judgements as to how useful the findings may be in furthering their understanding.

Rationale for decisions

The meta-analyses in this portfolio were either proportional using logits (Barendregt, Doi, Lee, Norman & Vos, 2013) or used correlations transformed to Fisher's *z* for the analysis. Many methods are available for meta-analysis; however, these seemed appropriate due to their use in previous risk factor analyses (Trickey, Siddaway, Meiser-Stedman, Serpell, & Field, 2012; Alisic et al., 2014) and as they were default settings on Comprehensive Meta-Analysis. Logits have been found to be less successful in stabilising

the variance (Barendregt et al., 2013); however, this particularly affects proportions close to zero or one so in practice the difference between the two methods was negligible. Using an effect size of zero for non-significant associations was conservative and may have underestimated the effect size, but this is thought to be preferable to excluding these data (Rosenthal, 1995).

In the first review in this portfolio, the quality of studies was assessed using the Clinical Treatments Assessment Measure (CTAM; Appendix F). This was chosen due to its applicability to the studies in the review, based on preliminary searches during the design of the protocol. It was quickly apparent that pilots had been conducted alongside a few randomised controlled trials on this subject, which meant that standard quality tools such as the Cochrane Collaboration's tool (Higgins & Green, 2011) which assesses against a gold standard of randomised controlled trials would have been inappropriate. The CTAM has been used in psychotic populations and whilst it includes items relating to randomisation and control groups these form part of a broader measure of study strengths. A cut-off score of 65 (used in Wykes, Steel, Everitt & Tarrier, 2008) was used for this review which was helpful for creating the distinction of 'high quality' and 'low quality' as a moderator variable. This approach has been argued to be preferable to using a continuous score for a quality measure, as it gives an overall flavour of study quality, whereas continuous scores can be misleading as they have often not received points due to a lack of reporting as opposed to a true lack of quality in the design. As long as this does not happen too often, it would not affect the assignment of 'high' or 'low' quality, and indeed if it did it could be argued to reflect genuine low quality as the more omissions made the less likely it may be that this is due to chance in what they decided to report.

In the second review, a novel assessment tool was created, based on the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data

(Munn, Moola, Lisy, Riitano & Tufanaru, 2015) and the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies (Moola et al., 2017). See Appendices G and H for copies of these tools. It seemed appropriate to combine these two tools due to the range of types of study in the review.

Strengths & limitations of these reviews

These reviews were clinically relevant and cover issues that clinicians will face in every day practice when providing psychological assessments and treatments. However, the reviews may have benefited from being more restricted in the scope of what they intended to cover, in order to allow expansion of a few key ideas. Failure to report findings would have introduced bias that should be avoided; however, this meant that many ideas had to be covered relatively briefly.

Collaborators were two research assistants and interrater agreement was high, particularly regarding the inclusion and exclusion criteria. This supports the potential replicability of this review in the future, perhaps when enough new studies have been published to warrant this.

Implications for research and clinical practice

The first review found that PTSD treatments are generally acceptable in people with psychosis. Intuitively, the non-participation rates seem low with psychosis (less than 2 in every 10 people); however, it was difficult to view this in the context of other treatments due to the specific and detailed way it was accessed in this review. The finding that dropout may be prevented though failing to use a stabilisation phase may be somewhat controversial, given the rationale for stabilisation seems very logical. When writing this review, I wondered whether or not any acceptability findings would be acted upon, given the current climate in health services and limited resources. Whilst offering service users choice about which PTSD treatment they preferred would be an ideal situation, I wondered

if this would be possible in practice given that clinicians in different localities may be trained in different specialist therapies. Finally, I wondered if changing the way these treatments are talked about may improve participants' perceptions of them and perhaps lead to improved engagement. It would be difficult to assess this impact and would perhaps be experienced more as a 'cultural shift' in services.

The second review largely agrees with Fornells-Ambrojo et al.'s (2016) conclusion that the evidence base for PR-PTSD as it stands makes it difficult to draw conclusions about prevalence. Hopefully, as awareness is raised into the issue of PR-PTSD firmer assessment processes will emerge, leading to more robust meta-analytic findings and research syntheses in the future.

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Appendix A – Clinical Psychology Review Submission Guidelines

Submission

Our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Peer review

This journal operates a single blind review process. All contributions will be initially assessed by the editor for suitability for the journal. Papers deemed suitable are then typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

Use of word processing software
It is important that the file be saved in the native format of the word processor used. The text should be in single-column format. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article. In particular, do not use the word processor's options to justify text or to hyphenate words. However, do use bold face, italics, subscripts, superscripts etc. When preparing tables, if you are using a table grid, use only one grid for each individual table and not a grid for each row. If no grid is used, use tabs, not spaces, to align columns. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier). Note that source files of figures, tables and text graphics will be required whether or not you embed your figures in the text. See also the section on Electronic artwork.
To avoid unnecessary errors you are strongly advised to use the 'spell-check' and 'grammar-check' functions of your word processor.

Article structure

Manuscripts should be prepared according to the guidelines set forth in the Publication Manual of the American Psychological Association (6th ed., 2009). Of note, section headings should not be numbered.

Manuscripts should ordinarily not exceed 50 pages, **including** references and tabular material. Exceptions may be made with prior approval of the Editor in Chief. Manuscript length can often be managed through the judicious use of appendices. In general the References section should be limited to citations actually discussed in the text. References to articles solely included in meta-analyses should be included in an appendix, which will appear in the on line

version of the paper but not in the print copy. Similarly, extensive Tables describing study characteristics, containing material published elsewhere, or presenting formulas and other technical material should also be included in an appendix. Authors can direct readers to the appendices in appropriate places in the text.

It is authors' responsibility to ensure their reviews are comprehensive and as up to date as possible (at least through the prior calendar year) so the data are still current at the time of publication. Authors are referred to the PRISMA Guidelines (http://www.prisma-statement.org/statement.htm) for guidance in conducting reviews and preparing manuscripts. Adherence to the Guidelines is not required, but is recommended to enhance quality of submissions and impact of published papers on the field.

Appendices
If there is more than one appendix, they should be identified as A, B, etc. Formulae and equations in appendices should be given separate numbering: Eq. (A.1), Eq. (A.2), etc.; in a subsequent appendix, Eq. (B.1) and so on. Similarly for tables and figures: Table A.1; Fig. A.1, etc.

Essential title page information

Title. Concise and informative. Titles are often used in information-retrieval systems. Avoid abbreviations and formulae where possible. **Note: The title page should be the first page of the manuscript document indicating the author's names and affiliations and the corresponding author's complete contact information.**

Author names and affiliations. Where the family name may be ambiguous (e.g., a double name), please indicate this clearly. Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address. Provide the full postal address of each affiliation, including the country name, and, if available, the e-mail address of each author within the cover letter.

Corresponding author. Clearly indicate who is willing to handle correspondence at all stages of refereeing and publication, also post-publication. **Ensure that telephone and fax numbers (with country and area code) are provided in addition to the e-mail address and the complete postal address.**

Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a "Present address"' (or "Permanent address") may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

A concise and factual abstract is required (not exceeding 200 words). This should be typed on a separate page following the title page. The abstract should state briefly the purpose of the research, the principal results and major conclusions. An abstract is often presented separate from the article, so it must be able to stand alone. References should therefore be avoided, but if essential, they must be cited in full, without reference to the reference list.

Graphical abstract
Although a graphical abstract is optional, its use is encouraged as it draws more attention to the online article. The graphical abstract should summarize the contents of the article in a concise, pictorial form designed to capture the attention of a wide readership. Graphical abstracts should be submitted as a separate file in the online submission system. Image size: Please provide an image with a minimum of 531 × 1328 pixels (h × w) or proportionally more. The image should be readable at a size of 5 × 13 cm using a regular screen resolution of 96 dpi. Preferred file types: TIFF, EPS, PDF or MS Office files. You can view Example Graphical Abstracts on our information site.
Authors can make use of Elsevier's Illustration Services to ensure the best presentation of their images and in accordance with all technical requirements.

Highlights
Highlights are mandatory for this journal. They consist of a short collection of bullet points that convey the core findings of the article and should be submitted in a separate editable file in the online submission system. Please use 'Highlights' in the file name and include 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point). You can view example Highlights on our information site.

Keywords

Immediately after the abstract, provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations
Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.

Acknowledgements
Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Formatting of funding sources
List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Footnotes
Footnotes should be used sparingly. Number them consecutively throughout the article. Many word processors can build footnotes into the text, and this feature may be used. Otherwise, please indicate the position of footnotes in the text and list the footnotes themselves separately at the end of the article. Do not include footnotes in the Reference list.

Tables

Please submit tables as editable text and not as images. Tables can be placed either next to the relevant text in the article, or on separate page(s) at the end. Number tables consecutively in accordance with their appearance in the text and place any table notes below the table body. Be sparing in the use of tables and ensure that the data presented in them do not duplicate results described elsewhere in the article. Please avoid using vertical rules and shading in table cells.

References

Citations in the text should follow the referencing style used by the American Psychological Association. You are referred to the Publication Manual of the American Psychological Association, Sixth Edition, ISBN 1-4338-0559-6, copies of which may be ordered from http://books.apa.org/books.cfm?id=4200067 or APA Order Dept., P.O.B. 2710, Hyattsville, MD 20784, USA or APA, 3 Henrietta Street, London, WC3E 8LU, UK. Details concerning this referencing style can also be found at http://humanities.byu.edu/linguistics/Henrichsen/APA/APA01.html

Citation in text
Please ensure that every reference cited in the text is also present in the reference list (and vice versa). Any references cited in the abstract must be given in full. Unpublished results and personal communications are not recommended in the reference list, but may be mentioned in the text. If these references are included in the reference list they should follow the standard reference style of the journal and

should include a substitution of the publication date with either 'Unpublished results' or 'Personal communication'. Citation of a reference as 'in press' implies that the item has been accepted for publication.

Web references
As a minimum, the full URL should be given and the date when the reference was last accessed. Any further information, if known (DOI, author names, dates, reference to a source publication, etc.), should also be given. Web references can be listed separately (e.g., after the reference list) under a different heading if desired, or can be included in the reference list.

Data references
This journal encourages you to cite underlying or relevant datasets in your manuscript by citing them in your text and including a data reference in your Reference List. Data references should include the following elements: author name(s), dataset title, data repository, version (where available), year, and global persistent identifier. Add [dataset] immediately before the reference so we can properly identify it as a data reference. The [dataset] identifier will not appear in your published article.

References in a special issue
Please ensure that the words 'this issue' are added to any references in the list (and any citations in the text) to other articles in the same Special Issue.

Reference management software
Most Elsevier journals have their reference template available in many of the most popular reference management software products. These include all products that support Citation Style Language styles, such as Mendeley and Zotero, as well as EndNote. Using the word processor plug-ins from these products, authors only need to select the appropriate journal template when preparing their article, after which citations and bibliographies will be automatically formatted in the journal's style. If no template is yet available for this journal, please follow the format of the sample references and citations as shown in this Guide. If you use reference management software, please ensure that you remove all field codes before submitting the electronic manuscript. More information on how to remove field codes.

Users of Mendeley Desktop can easily install the reference style for this journal by clicking the following link:
http://open.mendeley.com/use-citation-style/clinical-psychology-review
When preparing your manuscript, you will then be able to select this style using the Mendeley plug-ins for Microsoft Word or LibreOffice.

Reference style

References should be arranged first alphabetically and then further sorted chronologically if necessary. More than one reference from the same author(s) in the same year must be identified by the letters "a", "b", "c", etc., placed after the year of publication. **References should be formatted with a hanging indent**

(i.e., the first line of each reference is flush left while the subsequent lines are indented).

Examples: Reference to a journal publication: Van der Geer, J., Hanraads, J. A. J., & Lupton R. A. (2000). The art of writing a scientific article. **Journal of Scientific Communications,** 163, 51-59.

Reference to a book: Strunk, W., Jr., &White, E. B. (1979). **The elements of style.** (3rd ed.). New York: Macmillan, (Chapter 4).

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Appendix B –Early Intervention in Psychiatry Submission Guidelines

Author Guidelines

Sections

1. SUBMISSION

Thank you for your interest in *Early Intervention in Psychiatry*. Authors should kindly note that submission implies that the content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium.

Once the submission materials have been prepared in accordance with the Author Guidelines, manuscripts should be submitted online at http://mc.manuscriptcentral.com/eip

For any queries regarding submission, please contact eip.eo@wiley.com.

We look forward to your submission.

By submitting a manuscript to or reviewing for this publication, your name, email address, and affiliation, and other contact details the publication might require, will be used for the regular operations of the publication, including, when necessary, sharing with the publisher (Wiley) and partners for production and publication. The publication and the publisher recognize the importance of protecting the personal information collected from users in the operation of these services, and have practices in place to ensure that steps are taken to maintain the security, integrity, and privacy of the personal data collected and processed. You can learn more at https://authorservices.wiley.com/statements/data-protection-policy.html

2. AIMS AND SCOPE

Early Intervention in Psychiatry publishes original research articles and reviews dealing with the early recognition, diagnosis and treatment across the full range of mental and substance use disorders, as well as the underlying epidemiological, biological, psychological and social mechanisms that influence the onset and early course of these disorders. The journal provides comprehensive coverage of early intervention for the full range of psychiatric disorders and mental health problems, including schizophrenia and other psychoses, mood and anxiety disorders, substance use disorders, eating disorders and personality disorders. Papers in any of the following fields are considered: diagnostic issues, psychopathology, clinical epidemiology, biological mechanisms, treatments and other forms of intervention, clinical trials, health services and economic research and mental health policy. Special features are also published, including hypotheses, controversies and snapshots of innovative service models.

In contrast with mainstream healthcare, early diagnosis and intervention has come late to the field of psychiatry. *Early Intervention in Psychiatry* creates a common forum for researchers and clinicians with an interest in the early phases of a wide range of disorders to share ideas, experience and data. This journal not only fills a gap, but also creates a new frontier in academic and clinical psychiatry.

3. MANUSCRIPT CATEGORIES AND REQUIREMENTS

Articles reporting original work that embodies scientific excellence in psychiatry and advances in clinical research (maximum word count for text 3000; abstract 250);

Reviews which synthesize important information on a topic of general interest to early intervention in psychiatry. (maximum word count for text 5000; abstract 250);

Brief Reports which present original research that makes a single point, or negative studies of important topics (maximum word count for text 1500; abstract 150);

Early Intervention in the Real World, a special features section which focuses on issues such as service descriptions and delivery, and clinical practice guidelines (maximum word count for text 3000; abstract 250);

Editorials or New Hypotheses. Please contact the editorial office before writing an Editorial or New Hypotheses article for the journal (maximum word count for text 1000);

4. PREPARING THE SUBMISSION

Wiley Author Resources

Manuscript Preparation Tips: Wiley has a range of resources for authors preparing manuscripts for submission available here. In particular, authors may benefit from referring to Wiley's best practice tips on Writing for Search Engine Optimization.

Editing, Translation, and Formatting Support: Wiley Editing Services can greatly improve the chances of a manuscript being accepted. Offering expert help in English language editing, translation, manuscript formatting, and figure preparation, Wiley Editing Services ensures that the manuscript is ready for submission.

Style

Spelling. The journal uses UK spelling and authors should therefore follow the latest edition of the Concise Oxford Dictionary.

Units. All measurements must be given in SI or SI-derived units. Please go to the Bureau International des Poids et Mesures (BIPM) website at http://www.bipm.fr for more information about SI units.

Abbreviations. Abbreviations should be used sparingly – only where they ease the reader's task by reducing repetition of long, technical terms. Initially use the word in full, followed by the abbreviation in parentheses. Thereafter use the abbreviation only.

Trade names. Drugs should be referred to by their generic names. If proprietary drugs have been used in the study, refer to these by their generic name, mentioning the proprietary name, and the name and location of the manufacturer, in parentheses.

Parts of the Manuscript

The text file should be presented in the following order:

i. A short informative title that contains the major key words. The title should not contain abbreviations (see Wiley's best practice SEO tips);
ii. A short running title of less than 40 characters;
iii. The full names of the authors;
iv. The author's institutional affiliations where the work was conducted, with a footnote for the author's present address if different from where the work was conducted;
v. Abstract and keywords;
vi. Main text;
vii. Acknowledgements;
viiii. Conflict of interest statement;
ix. References;
x. Tables (each table complete with title and footnotes);
xi. Figure legends;
xii. Appendices (if relevant).

Figures and supporting information should be supplied as separate files.

Authorship

Please refer to the journal's authorship policy the Editorial Policies and Ethical Considerations section for details on eligibility for author listing.

Abstract and key words

All articles must have a structured abstract that states in 250 words (150 words for Brief Reports) or fewer the purpose, basic procedures, main findings and principal conclusions of the study. Divide the abstract with the headings: Aim, Methods, Results, Conclusions. The abstract should not contain abbreviations or references.

Five key words, for the purposes of indexing, should be supplied below the abstract, in alphabetical order, and should be taken from those recommended by the US National Library of Medicine's Medical Subject Headings (MeSH) browser list at http://www.nlm.nih.gov/mesh/meshhome.html.

Text

Authors should use the following subheadings to divide the sections of their manuscript: Introduction, Methods, Results and Discussion.

Acknowledgments

Contributions from anyone who does not meet the criteria for authorship should be listed, with permission from the contributor, in an Acknowledgments section. Financial and material support should also be mentioned. Thanks to anonymous reviewers are not appropriate.

Conflict of Interest Statement

Authors will be asked to provide a conflict of interest statement during the submission process. For details on what to include in this section, see the section 'Conflict of Interest' in the Editorial Policies and Ethical Considerations section below. Submitting authors should ensure they liaise with all co-authors to confirm agreement with the final statement.

References

References should be prepared according to the Publication Manual of the American Psychological Association (6th edition). This means in text citations should follow the author-date method whereby the author's last name and the year of publication for the source should appear in the text, for example, (Jones, 1998). The complete reference list should appear alphabetically by name at the end of the paper.

A sample of the most common entries in reference lists appears below. Note that for journal articles, issue numbers are not included unless each issue in the volume begins with page one, and a DOI should be provided for all references where available.

Journal article

Beers, S. R. , & De Bellis, M. D. (2002). Neuropsychological function in children with maltreatment-related posttraumatic stress disorder. *The American Journal of Psychiatry, 159,* 483–486. doi:10.1176/appi.ajp.159.3.483

Book

Bradley-Johnson, S. (1994). *Psychoeducational assessment of students who are visually impaired or blind: Infancy through high school* (2nd ed.). Austin, TX: Pro-ed.

Internet Document

Norton, R. (2006, November 4). How to train a cat to operate a light switch [Video file]. Retrieved from http://www.youtube.com/watch?v=Vja83KLQXZs

Tables

Tables should be self-contained and complement, not duplicate, information contained in the text. They should be supplied as editable files, not pasted as images. Legends should be concise but comprehensive – the table, legend, and footnotes must be understandable without reference to the text. All abbreviations must be defined in footnotes. Footnote symbols: †, ‡, §, ¶, should be used (in that order) and *, **, *** should be reserved for P-values. Statistical measures such as SD or SEM should be identified in the headings.

Figure Legends

Legends should be concise but comprehensive – the figure and its legend must be understandable without reference to the text. Include definitions of any symbols used and define/explain all abbreviations and units of measurement.

Figures

Although authors are encouraged to send the highest-quality figures possible, for peer-review purposes, a wide variety of formats, sizes, and resolutions are accepted. Click here for the basic figure requirements for figures submitted with manuscripts for initial peer review, as well as the more detailed post-acceptance figure requirements.

Supporting Information

Supporting information is information that is not essential to the article, but provides greater depth and background. It is hosted online and appears without editing or typesetting. It may include tables, figures, videos, datasets, etc.

Click here for Wiley's FAQs on supporting information.

Note: if data, scripts, or other artefacts used to generate the analyses presented in the paper are available via a publicly available data repository, authors should include a reference to the location of the material within their paper.

5. EDITORIAL POLICIES AND ETHICAL CONSIDERATIONS

Peer Review and Acceptance

Manuscripts are judged on the significance of the contribution to the literature, the quality of analysis and the clarity of presentation. Papers are expected to demonstrate originality and meaningful engagement with the global literature.

Except where otherwise stated, manuscripts are double-blind peer reviewed by anonymous reviewers in addition to the Editor. Final acceptance or rejection rests with the Editor-in-Chief, who reserves the right to refuse any material for publication.

Wiley's policy on the confidentiality of the review process is available here.

Authorship Policy

The journal adheres to the definition of authorship as set out by The International Committee of Medical Journal Editors (ICMJE). The ICMJE recommends that authorship be based on the following 4 criteria:

• Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
• Drafting the work or revising it critically for important intellectual content; AND
• Final approval of the version to be published; AND
• Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors. All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors.

Human Studies and Subjects

For manuscripts reporting medical studies that involve human participants, a statement identifying the ethics committee that approved the study and confirmation that the study conforms to recognized standards is required, for example: Declaration of Helsinki; US Federal Policy for the Protection of Human Subjects; or European Medicines Agency Guidelines for Good Clinical Practice. It should also state clearly in the text that all persons gave their informed consent prior to their inclusion in the study.

Patient anonymity should be preserved. Photographs need to be cropped sufficiently to prevent human subjects being recognized (or an eye bar should be used). Images and information from individual participants will only be published where the authors have obtained the individual's free prior informed consent. Authors do not need to provide a copy of the consent form to the publisher; however, in signing the author license to publish, authors are required to confirm that consent has been obtained. Wiley has a standard patient consent form available for use.

Case Reports. In general, submission of a case report should be accompanied by the written consent of the subject (or parent/guardian) before publication; this is particularly important where photographs are to be used or in cases where the unique nature of the incident reported makes it possible for the patient to be identified. While the Editorial Board recognizes that it might not always be possible or appropriate

to seek such consent, the onus will be on the authors to demonstrate that this exception applies in their case.

Use of Animals in Research

Any experiments involving animals must be demonstrated to be ethically acceptable and where relevant conform to national guidelines for animal usage in research.

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9. EDITORIAL OFFICE CONTACT DETAILS

Professor Patrick McGorry, Editorial Office, *Early Intervention in Psychiatry*
C/O Wiley
155 Cremorne St
Richmond, Victoria, 3121

Appendix C: Data extraction form and instructions

Item descriptor	**Possible Codes**	**Code/Value**
Study ID no	Assign unique ID no	
Full Reference	Text. APA format	
Date of publication	YYYY	
Country of origin	Text	
Report type	1=peer reviewed journal article 2=dissertation/thesis 3=unpublished data 4=other (specify)	
Study design	1=cross-sectional 2= prospective longitudinal 3= other	
PR-PTSD data available in study	1=prevalence only 2=prevalence and risk factors	
Sample size	Numeric	
Source of participants	1=community teams 2=psychiatric wards 3= 1 and 2 4 = early intervention teams 5=other/other combination	
Participants' diagnoses	1=functional non-affective psychotic disorders 2=functional affective or non affective psychotic disorders 3 = psychotic disorders not specified	

PTSD 'caseness' according to:	1=DSM III (or III-R) 2 = DSM IV/IV TR 3 = DSM V 4= ICD 10	
Mean age of sample	Numeric	
Age range of sample	Numeric	
Sample included adults only/Sample included adolescents and adults	1=adults only ≥18yrs 2=adolescents/adults ≥14yrs	
Percentage Male	Numeric	
Percentage Female	Numeric	
Sample hospitalised due to acute psychotic episode/mixed sample of hospitalised and non hospitalised	1= hospitalised 2= mixed sample	
Time of PTSD assessment	1= ≤1 month following APE 2 = >1 to ≤6 months following APE 3 = ≥6 months following APE	
PTSD interview used	1 = name 2= name 3 = other validated interview 4= none used	
PTSD self report measure used	1 = name 2= name 3 = other validated questionnaire 4= none used	
Prevalence of caseness PTSD due psychotic symptoms	Numeric	
Prevalence of caseness PTSD due to treatment of psychosis including hospitalisation	Numeric	
Prevalence of caseness PTSD due to combined report of either psychotic symptoms or treatment	Numeric	

Risk factor (1) measure type	1= validated self report 2= validated interview 3-other	
Risk factor (1) measure name	1= name 2= name 3= Other validated measure	
Effect size for risk factor 1 (r)	Numeric	
Effect size calculation for risk factor 1 (if applicable)	Text/numeric specifying data extracted for calculation	
Degrees of freedom	Numeric	
Risk factor (2) measure type	1= validated self report 2= validated interview 3-other	
Risk factor (2) measure name	1= name 2= name 3= Other validated measure	
Effect size for risk factor 2 (r)	Numeric	
Effect size calculation for risk factor 2 (if applicable)	Text/numeric specifying data extracted for calculation	
Degrees of freedom	Numeric	
Risk factor (3) measure type	1= validated self report 2= validated interview	

	3-other	
Risk factor (3) measure name	1= name 2= name 3= Other validated measure	
Effect size for risk factor 3 (r)	Numeric	
Effect size calculation for risk factor 3 (if applicable) Degrees of freedom	Text/numeric specifying data extracted for calculation Numeric	

Appendix D – Feedback on Thesis Proposal

UNIVERSITY OF EAST ANGLIA ClinPsyD
FEEDBACK SHEET FOR ACADEMIC WORK - Clinical Psychology

TRAINEE: Hannah Cole **Date Submitted: 06 October 2015**

MARKER: Siân Coker **Date Marked: 06 November 2015**

TITLE OF THESIS PROPOSAL: Prevalence and predictors of psychosis-related post-traumatic stress disorder: A meta-analysis.

AGREED MARK: 53 **PASS/FAIL**

DETAILED COMMENTS:

GENERAL ORIENTATION (what is the context for the study and why is it interesting/clinically relevant?)

General overview and rationale for the study is presented

BACKGROUND AND INTRODUCTION (provides a review of relevant and contemporary literature, highlights gaps in existing research, provides a coherent theoretical framework for the study)

A descriptive account of relevant literature is provided. More critical appraisal of the research presented is warranted. Careful definition and consistent use of terms such as sub-clinical and sub-threshold. Consider the order that information is presented for the reader in the TP e.g. prevalence rates

RESEARCH QUESTIONS/HYPOTHESES (clear and appropriate questions/hypotheses which follow from the background and which are answerable)

Relevant research questions are posed but further refinement and definition (eg sub-threshold/sub-clinical) as in Introduction section is recommended

DESIGN (clear description of research design which is appropriate for the question)

The elements of the MA are set out

PARTICIPANTS (clearly described inclusion/exclusion criteria, rationale for sample size (e.g. power calculation), clear plan for sampling and recruitment).

MEASURES (clearly described measures/interview topic guide, including rationale for choice and discussion of psychometric properties)

Consider specifying choice of Questionnaire/scales to be used otherwise there will be too much heterogeneity. Specify how will it be possible to reliably define caseness?

PROCEDURE (clearly describes the conduct of the study and what will happen to participants from the point of approach to exit from the study, methodology is appropriate for the research questions and design)

Proposed inclusion and exclusion criteria are outlined
There should to be a flowchart for the planned literature cited. At the start of your literature it would be expected that there are many more studies available for review. A starting point of 27 would appear to an incorrect initial sample and far too low to justify conducting a MA

ETHICAL CONSIDERATIONS (discusses major issues and deals with any potential problems, discusses plans for seeking ethical approval)

ANALYSIS (sets out a clear plan which is compatible with the questions and design)

It would be helpful to provide a more detailed account here, e.g data extraction form, how it will be used and what data are to be used (as opposed to "various"). Provide additional information on how IRR is to be conducted. Demonstrate how ES are to be calculated

STUDY MATERIALS/APPENDICES (provide documentation relevant to the study, including Participant Information Sheets and Consent Forms, copies of measures where relevant, thesis budget and timeline for study completion)

Time line and thesis budget are provided. Budget is subject to review

PRESENTATION (extent of typographical, spelling and grammatical errors, quality of referencing**)**

This needs attention as presentational quality is variable and careful proof reading is required to avoid typos, errors and omissions.

OVERALL STRENGTHS & WEAKNESSES OF THE THESIS PROPOSAL (outline these in detail).

This is a reasonable meta-analysis proposal and it focuses on an interesting clinically relevant area. The introduction is reasonably well written but there are aspects where the presentation could be improved and there is limited critical appraisal of the literature. The elements of a MA are set out with some limitations. There is a lack of specificity evident throughout the TP. There ought to be a flowchart for the planned literature cited for a TP. Twenty seven papers as a stating point for the justification for the ability to conduct a MA and is incorrect and needs to be discussed with the supervisor and revised

Recommended Changes for Discussion with Research Supervisor (re-submission not required)

Revisit and modify 27 papers as starting point for the justification of the MA

Required Changes (if assignment failed).
Any required changes have to be made to the satisfaction of the markers before the script can be passed. A resubmission of an assignment must be accompanied by a cover letter outlining how the marker's points have been addressed.

Appendix E: Correspondence regarding ethics

From: Hannah Cole (MED)
Sent: 17 January 2016 14:52
To: Bonnie Teague (MED)
Subject: Re: Ethics

Hi Bonnie,

That's great. Thank you for checking for me. What are your UEA work days?

BW
Hannah

From: Bonnie Teague (MED)
Sent: 13 January 2016 14:28
To: Hannah Cole (MED)
Subject: RE: Ethics

Hi Hannah,

FMH Ethics have confirmed that if you are using secondary published data already, and no clinical or unpublished data in any context, then you do not need approval. Good luck!

Bonnie

From: Bonnie Teague (MED)
Sent: 11 January 2016 15:42
To: Hannah Cole (MED) <H.Cole@uea.ac.uk>
Subject: RE: Ethics

Hi Hannah,

If you are conducting a meta-analysis only, and this does not include published work (i.e. you are not coupling it with restricted reports/clinical/confidential information from other organisations), then you shouldn't need any approvals as it is secondary anonymised data which is already available and has no material ethics issues to be considered.

Look at 'Flow-chart 1' here for FMH ethics:

https://portal.uea.ac.uk/faculty-school-intranets/fmh-intranet/ethics-committee

Faculty Research Ethics Committee - UEA

portal.uea.ac.uk

Access to content on this page is restricted to UEA Students and Staff - please log in.

I'm just double-checking with FMH ethics in case things have changed though!

Bonnie

From: Hannah Cole (MED)
Sent: 11 January 2016 13:58
To: Bonnie Teague (MED) <B.Teague@uea.ac.uk>
Subject: Ethics

Hi Bonnie,

Hope you are well. Can I just double check that I definitely need FMH ethical approval for my meta-analysis as I've had some conversations with other people doing meta-analyses and it seems unclear what the protocol is.

Thank you

Hannah

Appendix F: Clinical Trials Assessment Measure (CTAM)

The Clinical Trials Assessment Measure (CTAM) (Wykes et al., 2008)

Clinical Trials Assessment Measure (CTAM)

Sample—two questions: maximum score = 10

Q1: is the sample a convenience sample (score 2) or a geographic cohort (score 5), highly selective sample, e.g., volunteers (score 0)

Convenience sample—e.g., clinic attenders, referred patients or Geographic cohort—all patients eligible in a particular area

Q2: is the sample size greater than 27 participants in each treatment group (score 5) or based on described and adequate power calculations (score 5)

Allocation—three questions: maximum score = 16

Q3: is there true random allocation or minimisation allocation to treatment groups (if yes score 10)

Q4: is the process of randomisation described (score 3)

Q5: is the process of randomisation carried out independently from the trial research team (score 3)

Assessment (for the main outcome)—five questions: maximum score = 32

Q6: are the assessments carried out by independent assessors and not therapists (score 10)

Q7: are standardised assessments used to measure symptoms in a standard way (score 6), idiosyncratic assessments of symptoms (score 3)

Q8: are assessments carried out blind (masked) to treatment group allocation (score 10)

Q9: are the methods of rater blinding adequately described (score 3)

Q10: is rater blinding verified (score 3)

Control groups—one question: maximum score = 16

Q11: TAU is a control group (score 6) and/or a control group that controls for non-specific effects or other established or credible treatment (score 10)

Analysis—two questions: maximum score = 15

Q12: the analysis is appropriate to the design and the type of outcome measure (score 5)

Q13: the analysis includes all those participants beginning treatment as randomised (sometimes referred to as an intention to treat analysis) (score 6) and an adequate

investigation and handling of dropouts from assessment if the attrition rate exceeds 15% (score 4)

Active treatment—two questions: maximum score = 11

Q14: was the treatment adequately described (score 3) and was a treatment protocol or manual used (score 3) including adapted

Q15: was adherence to the treatment protocol or treatment quality assessed (score 5)

Where the criterion is not reached for any question score = 0

Total score: maximum score = 100

Appendix G: JBI Appraisal Checklist – Prevalence Studies

JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

Reviewer_____Date_____

Author _____Year_____Record Number_____

		Yes	No	Unclear	Not applicable
1.	Was the sample frame appropriate to address the target population?	☐	☐	☐	☐
2.	Were study participants sampled in an appropriate way?	☐	☐	☐	☐
3.	Was the sample size adequate?	☐	☐	☐	☐
4.	Were the study subjects and the setting described in detail?	☐	☐	☐	☐
5.	Was the data analysis conducted with sufficient coverage of the identified sample?	☐	☐	☐	☐
6.	Were valid methods used for the identification of the condition?	☐	☐	☐	☐
7.	Was the condition measured in a standard, reliable way for all participants?	☐	☐	☐	☐
8.	Was there appropriate statistical analysis?	☐	☐	☐	☐
9.	Was the response rate adequate, and if not, was the low response rate managed appropriately?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

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JBI Critical Appraisal Checklist for Studies Reporting Prevalence Data

How to cite: Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and incidence data. Int J Evid Based Healthc. 2015;13(3):147–153.

Answers: Yes, No, Unclear or Not/Applicable

1. **Was the sample frame appropriate to address the target population?**

   This question relies upon knowledge of the broader characteristics of the population of interest and the geographical area. If the study is of women with breast cancer, knowledge of at least the characteristics, demographics and medical history is needed. The term "target population" should not be taken to infer every individual from everywhere or with similar disease or exposure characteristics. Instead, give consideration to specific population characteristics in the study, including age range, gender, morbidities, medications, and other potentially influential factors. For example, a sample frame may not be appropriate to address the target population if a certain group has been used (such as those working for one organisation, or one profession) and the results then inferred to the target population (i.e. working adults). A sample frame may be appropriate when it includes almost all the members of the target population (i.e. a census, or a complete list of participants or complete registry data).

2. **Were study participants recruited in an appropriate way?**

   Studies may report random sampling from a population, and the methods section should report how sampling was performed. Random probabilistic sampling from a defined subset of the population (sample frame) should be employed in most cases, however, random probabilistic sampling is not needed when everyone in the sampling frame will be included/ analysed. For example, reporting on all the data from a good census is appropriate as a good census will identify everybody. When using cluster sampling, such as a random sample of villages within a region, the methods need to be clearly stated as the precision of the final prevalence estimate incorporates the clustering effect. Convenience samples, such as a street survey or interviewing lots of people at a public gatherings are not considered to provide a representative sample of the base population.

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3. Was the sample size adequate?

The larger the sample, the narrower will be the confidence interval around the prevalence estimate, making the results more precise. An adequate sample size is important to ensure good precision of the final estimate. Ideally we are looking for evidence that the authors conducted a sample size calculation to determine an adequate sample size. This will estimate how many subjects are needed to produce a reliable estimate of the measure(s) of interest. For conditions with a low prevalence, a larger sample size is needed. Also consider sample sizes for subgroup (or characteristics) analyses, and whether these are appropriate. Sometimes, the study will be large enough (as in large national surveys) whereby a sample size calculation is not required. In these cases, sample size can be considered adequate.

When there is no sample size calculation and it is not a large national survey, the reviewers may consider conducting their own sample size analysis using the following formula: (Naing et al. 2006, Daniel 1999)

$$n = \frac{Z^2 P(1-P)}{d^2}$$

Where:

n= sample size

Z = Z statistic for a level of confidence

P = Expected prevalence or proportion (in proportion of one; if 20%, P = 0.2)

d = precision (in proportion of one; if 5%, d=0.05)

Ref:

Naing L, Winn T, Rusli BN. Practical issues in calculating the sample size for prevalence studies Archives of Orofacial Sciences. 2006;1:9-14.

Daniel WW. Biostatistics: A Foundation for Analysis in the Health Sciences.

Edition. 7th ed. New York: John Wiley & Sons. 1999.

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4. **Were the study subjects and setting described in detail?**

   Certain diseases or conditions vary in prevalence across different geographic regions and populations (e.g. Women vs. Men, sociodemographic variables between countries). The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them.

5. **Was data analysis conducted with sufficient coverage of the identified sample?**

   Coverage bias can occur when not all subgroups of the identified sample respond at the same rate. For instance, you may have a very high response rate overall for your study, but the response rate for a certain subgroup (i.e. older adults) may be quite low.

6. **Were valid methods used for the identification of the condition?**

   Here we are looking for measurement or classification bias. Many health problems are not easily diagnosed or defined and some measures may not be capable of including or excluding appropriate levels or stages of the health problem. If the outcomes were assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If the outcomes were assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.

7. **Was the condition measured in a standard, reliable way for all participants?**

   Considerable judgment is required to determine the presence of some health outcomes. Having established the validity of the outcome measurement instrument (see item 6 of this scale), it is important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised? When there was more than one observer or collector, was there comparison of results from across the observers? Was the condition measured in the same way for all participants?

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8. **Was there appropriate statistical analysis?**

   Importantly, the numerator and denominator should be clearly reported, and percentages should be given with confidence intervals. The methods section should be detailed enough for reviewers to identify the analytical technique used and how specific variables were measured. Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.

9. **Was the response rate adequate, and if not, was the low response rate managed appropriately?**

   A large number of dropouts, refusals or "not founds" amongst selected subjects may diminish a study's validity, as can a low response rates for survey studies. The authors should clearly discuss the response rate and any reasons for non-response and compare persons in the study to those not in the study, particularly with regards to their socio-demographic characteristics. If reasons for non-response appear to be unrelated to the outcome measured and the characteristics of non-responders are comparable to those who do respond in the study (addressed in question 5, coverage bias), the researchers may be able to justify a more modest response rate.

Appendix H: JBI Appraisal Checklist – Cross-Sectional Studies

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____Date_____

Author _____Year_____Record Number_____.

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
2. Were the study subjects and the setting described in detail?	☐	☐	☐	☐
3. Was the exposure measured in a valid and reliable way?	☐	☐	☐	☐
4. Were objective, standard criteria used for measurement of the condition?	☐	☐	☐	☐
5. Were confounding factors identified?	☐	☐	☐	☐
6. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
7. Were the outcomes measured in a valid and reliable way?	☐	☐	☐	☐
8. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

_____

_____

_____

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Explanation of analytical cross sectional studies critical appraisal

How to cite: Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P-F. Chapter 7: Systematic reviews of etiology and risk . In: Aromataris E, Munn Z (Editors). *Joanna Briggs Institute Reviewer's Manual.* The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/

Analytical cross sectional studies Critical Appraisal Tool

Answers: Yes, No, Unclear or Not/Applicable

1. **Were the criteria for inclusion in the sample clearly defined?**

   The authors should provide clear inclusion and exclusion criteria that they developed prior to recruitment of the study participants. The inclusion/exclusion criteria should be specified (e.g., risk, stage of disease progression) with sufficient detail and all the necessary information critical to the study.

2. **Were the study subjects and the setting described in detail?**

   The study sample should be described in sufficient detail so that other researchers can determine if it is comparable to the population of interest to them. The authors should provide a clear description of the population from which the study participants were selected or recruited, including demographics, location, and time period.

3. **Was the exposure measured in a valid and reliable way?**

   The study should clearly describe the method of measurement of exposure. Assessing validity requires that a 'gold standard' is available to which the measure can be compared. The validity of exposure measurement usually relates to whether a current measure is appropriate or whether a measure of past exposure is needed.
   Reliability refers to the processes included in an epidemiological study to check repeatability of measurements of the exposures. These usually include intra-observer reliability and inter-observer reliability.

4. **Were objective, standard criteria used for measurement of the condition?**

   It is useful to determine if patients were included in the study based on either a specified diagnosis or definition. This is more likely to decrease the risk of bias. Characteristics are another useful approach to matching groups, and studies that did not use specified diagnostic methods or definitions should provide evidence on matching by key characteristics.

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5. **Were confounding factors identified?**

Confounding has occurred where the estimated intervention exposure effect is biased by the presence of some difference between the comparison groups (apart from the exposure investigated/of interest). Typical confounders include baseline characteristics, prognostic factors, or concomitant exposures (e.g. smoking). A confounder is a difference between the comparison groups and it influences the direction of the study results. A high quality study at the level of cohort design will identify the potential confounders and measure them (where possible). This is difficult for studies where behavioral, attitudinal or lifestyle factors may impact on the results.

6. **Were strategies to deal with confounding factors stated?**

Strategies to deal with effects of confounding factors may be dealt within the study design or in data analysis. By matching or stratifying sampling of participants, effects of confounding factors can be adjusted for. When dealing with adjustment in data analysis, assess the statistics used in the study. Most will be some form of multivariate regression analysis to account for the confounding factors measured.

7. **Were the outcomes measured in a valid and reliable way?**

Read the methods section of the paper. If for e.g. lung cancer is assessed based on existing definitions or diagnostic criteria, then the answer to this question is likely to be yes. If lung cancer is assessed using observer reported, or self-reported scales, the risk of over- or under-reporting is increased, and objectivity is compromised. Importantly, determine if the measurement tools used were validated instruments as this has a significant impact on outcome assessment validity.
Having established the objectivity of the outcome measurement (e.g. lung cancer) instrument, it's important to establish how the measurement was conducted. Were those involved in collecting data trained or educated in the use of the instrument/s? (e.g. radiographers). If there was more than one data collector, were they similar in terms of level of education, clinical or research experience, or level of responsibility in the piece of research being appraised?

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8. Was appropriate statistical analysis used?

As with any consideration of statistical analysis, consideration should be given to whether there was a more appropriate alternate statistical method that could have been used. The methods section should be detailed enough for reviewers to identify which analytical techniques were used (in particular, regression or stratification) and how specific confounders were measured.

For studies utilizing regression analysis, it is useful to identify if the study identified which variables were included and how they related to the outcome. If stratification was the analytical approach used, were the strata of analysis defined by the specified variables? Additionally, it is also important to assess the appropriateness of the analytical strategy in terms of the assumptions associated with the approach as differing methods of analysis are based on differing assumptions about the data and how it will respond.