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Loneliness in psychosis: a meta-analytical review.

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Abstract

Loneliness may be related to psychotic symptoms but a comprehensive synthesis of the literature in this area is lacking. The aim of the current study is to determine the magnitude and reliability of the loneliness-psychosis relationship in people diagnosed with schizophrenia or related disorders, taking into account study quality, and whether it is moderated by method of assessment. A search of electronic databases was conducted (PsychINFO, MEDLINE, EMBASE and Web of Science). A random effects meta-analysis was used to compute a pooled estimate of the correlation between loneliness and psychotic symptoms. Study and outcome quality were assessed using adapted versions of the Agency for Healthcare Research and Quality (AHRQ) tool and GRADE approach, respectively. Thirteen studies were included, providing data from 15,647 participants. A moderate association between psychosis and loneliness was observed (k=13, N=15,647, r=0.32, 95% CI 0.20, 0.44; I^2 97.56%; moderate quality evidence). Whether loneliness was assessed by a single-item or a more comprehensive measure had no moderating effect on the estimate. Results indicate that there is a significant positive relationship between loneliness and psychosis. Further studies are needed to determine the causal status of this relationship, but this robust finding should be considered in clinical practice and treatment provision for those with psychotic disorders.

Keywords: psychotic disorders, schizophrenia, social isolation, loneliness measures, review.

INTRODUCTION

People with psychotic disorders frequently feel lonely and many expect to be lonely in the future [1]. Stain et al. [2] report that as many as 80% of adults with a diagnosis of psychosis in Australia endorsed feeling lonely in the past 12 months. People with psychosis often struggle to develop and preserve functioning relationships, have limited social networks and restricted access to social support outside of what is provided by mental health services [3, 4].

Although feelings of loneliness and social isolation are generally thought to reflect the negative impact of psychotic experiences [5], more recently it has been reported that loneliness may also play a causal role in the development of psychotic experiences [6]. A self-perpetuating cycle of exclusion may develop, whereby the disorder limits connections and support, which then leads to a removal of important buffers, thereby increasing risk of relapse and causing an escalation of psychotic episodes, further social disengagement, and so forth [7].

The majority of studies examining social support in psychosis have concentrated on quantitative features of the social network such as size and reciprocity instead of more functional aspects such as loneliness or satisfaction with relationships [7]. This is of particular relevance, as objective features of social support are related but distinct from these more subjective aspects of social relationships. Loneliness is an unpleasant and distressing experience resulting from a perceived deficiency in the quantity or quality of one's social relationships [8]. While social isolation can be measured objectively, loneliness is a subjective emotional state of the individual, which may be present in individuals with large social networks, and absent in isolated individuals with minimal social contact [9].

Loneliness has been associated with depression and suicide ideation[10], lower life satisfaction[11], elevated blood pressure levels [12], increased stress hormone levels[13] and compromised immune system [14]. Loneliness has also been related to an increased tendency to

experience subclinical and clinical hallucinations [15,16] and to nonclinical paranoid thinking [17, 18].

There are several possible mechanisms linking loneliness to psychotic symptoms such as hallucinations. For example, loneliness may directly increase anxiety and depression [10] which in turn may exacerbate symptoms of psychosis [19]. Loneliness may also perpetuate negative beliefs about oneself and other people, which may in turn increase the frequency of paranoid thoughts. Another pathway may involve 'anthropomorphism', whereby social isolation and feelings of loneliness might lead to increased human agency detection in one's immediate environment, therefore increasing likelihood of hearing voices or perceiving human agency in non-human stimuli [20]. This relationship may also work in the other direction, whereby psychotic symptoms lead one to experience feelings of exclusion and stigma, which in turn increases likelihood of feeling lonely. Some authors report case-studies where hallucinating patients actually perceived their imaginary companions as helpful in managing their sense of loneliness [21]. Similar findings have been reported with otherwise healthy children who have imaginary companions.

Although there has been much focus on the co-occurrence of loneliness and psychosis, their relationship is still unclear. While there is a consensus that loneliness is a prominent feature in psychosis, some researchers report correlations near zero between psychotic symptoms and loneliness [22]. Additionally, while some authors report a high prevalence of loneliness in people with psychosis [15], this conclusion is often derived from a single-item measure of loneliness, rather than a valid and reliable instrument, which might lead to confusion and limited replicability of studies. There also appears to be no gold standard in regards to how single-item measures are conceptualised and interpreted, with various authors asking for feelings of loneliness across the past week, past 2 weeks or past 12 months, or taking a measure of the number of 'lonely days in a week'. Some researchers divide Likert scale

measures of loneliness into a dichotomous measure, while others keep it as a continuous variable.

Improving our understanding of the relationship between psychosis and loneliness has important theoretical and practical implications. In order to design effective interventions for loneliness, and potentially enable services to best organise their resources to support the wellbeing of individuals with psychosis, a deeper understanding of the nature of loneliness and its impact on mental functioning in this population is needed. An important first step is to provide a definitive estimate of the magnitude of the relationship, taking into account study quality. Whether the results depend on the way loneliness is measured is also important to consider, both for interpreting the available evidence and for planning future research. Therefore, the primary aim of the current study is to provide a systematic review and meta-analysis of the association between loneliness and psychotic symptoms in people with psychosis.

METHOD

Search Strategy

The electronic databases (PsycINFO, MEDLINE, EMBASE and Web of Science) were searched up to February 2016 using the following terms: (psychos* or schiz* or halluc* or paran* or delus* or psychotic) AND (lonel*) AND/OR (at risk or ultra high risk or clinical high risk or UHR or CHR or prodrom* or psychosis risk or psychosis transition or psychosis onset). Screening was undertaken independently by two authors (B.M., E.V.) First, titles and abstracts were screened, followed by the full text of remaining articles. Hand searches of references in eligible articles and key review articles were also undertaken. Conference abstracts and theses identified through the searches were also followed-up. All corresponding authors of selected papers were contacted (where possible) regarding any unpublished work they were involved in that could be suitable for the purpose of the current review.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they (1) measured psychotic symptoms and loneliness in people experiencing psychosis, (2) measured loneliness symptoms in people diagnosed with psychosis and provided a suitable control group. Cross-sectional baseline data were extracted from longitudinal studies where possible. If not possible an average of reported values was calculated. Authors were contacted in every case where usable but unpublished data were thought to exist.

For the purposes of this review we defined loneliness as dissatisfaction with the desired and actual number or quality of social relationships [23]. We did not examine social isolation or size of social network unless it clearly reflected our measure of loneliness. While social isolation can be an objectively quantifiable variable, loneliness is a subjective emotional state of the

individual, which may be present in non-isolated individuals with large social networks, and absent in isolated individuals with minimal social networks, and thus involves necessarily subjective measurement.

We defined psychotic disorders as severe mental disorders that cause abnormal thinking and perceptions and included studies that involved people diagnosed with schizophrenia, schizoaffective disorder, schizotypal personality disorder, bipolar disorder with psychotic features, depressive psychosis, delusional disorders and other non-organic psychosis. These included both long-term, established psychosis and first-episode psychosis.

Design

A range of study designs was suitable for inclusion, such as case-control studies, where the cases may be defined either by the presence or absence of psychosis, cross-sectional correlational studies and prospective designs where the relationship between psychosis and loneliness was examined over time. We did not include qualitative studies.

Additional criteria

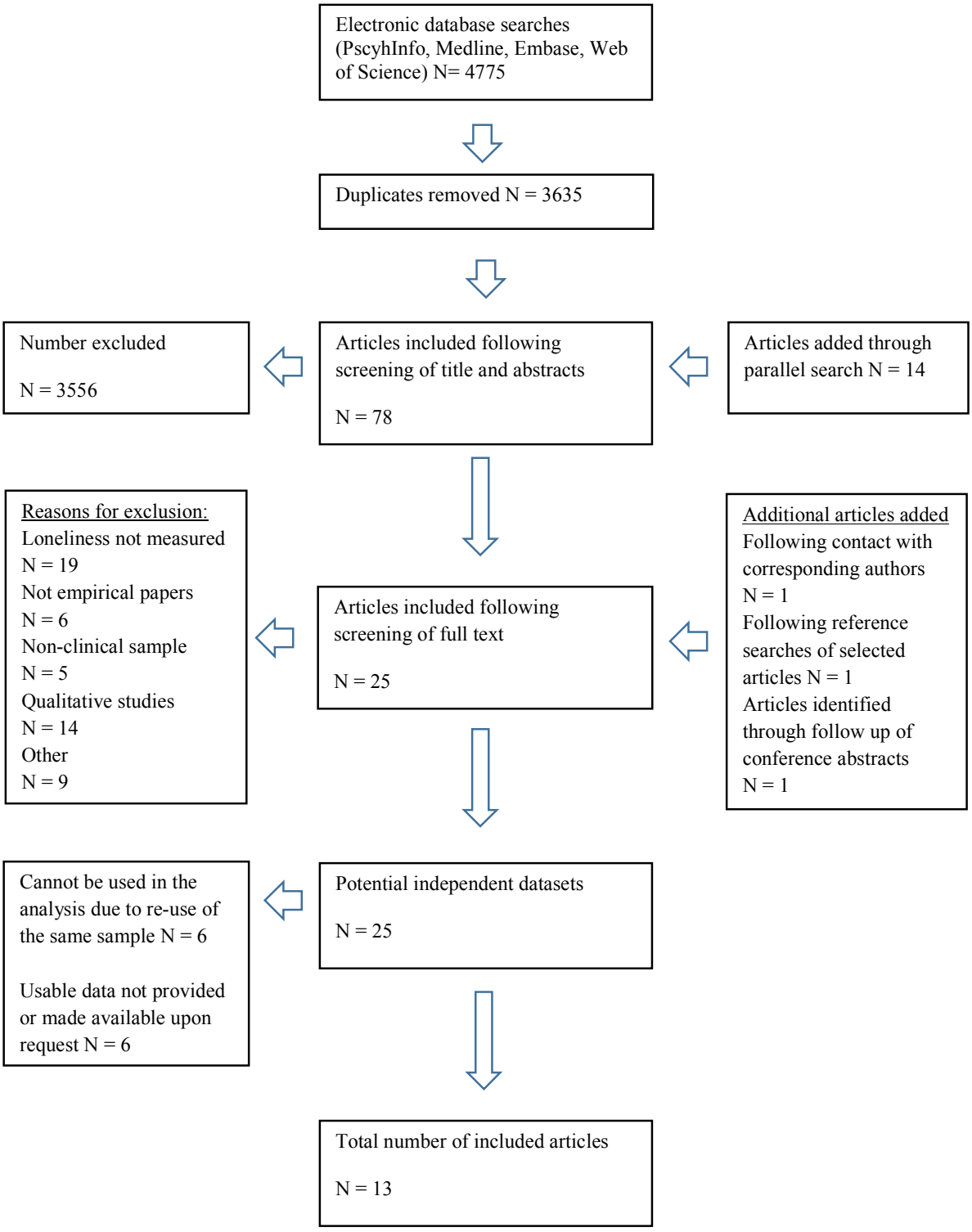
Only English language articles were included. We did not include studies that did not provide sufficient information for our analysis. For example, studies were excluded if they reported only mean loneliness scores for a group of people with psychosis, but with no control group provided and where no dichotomous distinction was made (lonely vs not lonely). We also did not include papers where a control group was used, but it was not representative of general population (e.g. self-reported lonely people from the general population).

Data extraction

Extraction of study details was undertaken by one author (BM) using a pre-specified data collection form. In case of any uncertainty articles were discussed further with other authors

(PH, SR). In two cases additional information regarding unpublished studies was obtained from authors (Switaj, personal communication; Ludwig, personal communication). In another case further information regarding a relevant study was obtained from authors [24], while in six cases further information was needed but contact could not be established with the corresponding author [6, 25-29]. All relevant statistics were estimated from available datasets, with missing cases excluded. In longitudinal studies where correlation between psychotic symptoms and loneliness were reported across different time points, an average correlation was calculated. Similarly, for studies where correlations were reported for separate subscales of psychotic experiences, an average raw correlation was calculated. Where effect size transformation was required, guidelines in Borenstain et al. [30] were followed.

Figure 1. Prisma Chart



Methodological quality

The methodological quality of studies was assessed using an adapted version of the Agency for Healthcare Research and Quality (AHRQ) tool [31]. The assessment of all included studies was done by the lead author (BM). In order to ascertain that the quality assessment was accurate, a proportion of papers (6) was also independently assessed for quality by another author (EV) with an inter-rater reliability of 80%, and any disagreements resolved by a third author (PH). The devised quality criteria checklist followed closely from Taylor et al. [32]. Studies were rated on a number of methodological parameters as either fulfilling the criteria in full, partially or not fulfilling it. A copy of this adapted measure is provided in supplementary material.

The overall quality of the final outcome was assessed using an adapted version of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach GRADE Working [33]. The general GRADE rating includes review of quality of data, publication bias, inconsistency and imprecision and produces the final grade of either high, moderate, low or very low quality. General data quality was assessed by using the AHRQ reports for studies contributing to that specific outcome. Publication bias was assessed using funnel plot, Egger's regression test and the Rank correlation test. Inconsistency was assessed via assessment of heterogeneity and overall direction and magnitude of effect, and imprecision was assessed via assessment of effect size, confidence intervals and overall number of participants contributing to the analyses. The specific criteria that were used for making AHRQ and GRADE ratings are detailed in supplementary material.

Registration of Protocol and Subsequent Changes

The review protocol was registered and published in the public domain (PROSPERO Registration CRD42016015371) before searches, data extraction and analysis were conducted. Subsequent changes included narrowing the research question from psychosis continuum to people with established psychosis and addition of a second person to conduct the search in parallel. In addition, a decision was made to run the meta-analysis on correlational data rather than odds ratios. This decision was made once papers were screened in full and it became apparent that majority of the included studies reported correlations; it therefore seemed more appropriate to convert effect sizes to the one most commonly reported in our specific pool of studies, therefore reducing reliance on potentially untested assumptions. Due to insufficient data, it was decided to drop a comparison between people diagnosed with psychosis and those with other non-psychotic mental health problems or at risk of developing psychosis. Finally, we performed an additional moderator analysis to examine whether the results were affected by stage of illness of study participants.

Data synthesis and analysis

For each of the studies, a correlation coefficient (r) of the relationship between psychosis and loneliness was computed. Data conversion was conducted in accordance with guidelines in Borenstein et al. [30] Converting effect sizes into one metric allows continuous and binary data from a range of different measures reported in a range of different study designs to be combined, thus increasing the efficiency and power of the analysis. These correlation coefficients were then transformed into Fisher's z and entered into a random-effects meta-analysis. Meta-analysis was conducted with a use of R version 3.2.3, package: Metafor [34].

RESULTS

Study characteristics

As shown in Figure 1, there were 13 eligible studies, reported data related to 15,647 participants. Study characteristics are presented in Table 1. Two studies were conducted on people with first onset psychosis and one related to people with late onset psychosis, while the remaining ten assessed people with established psychosis. Nearly all of the studies employed a cross-sectional design. Studies originated from a variety of countries including the USA, Great Britain, Australia, Germany, Israel and Poland. A list of excluded studies, with reasons for exclusion, is provided in the supplementary material.

Study quality

The assessment of study methodological quality is outlined in Table 2. The most prevalent methodological weaknesses related to justification of sample size, reporting of how missing data was handled and ascertaining an appropriately matched control group. Studies varied in how the psychotic symptoms were reported, with some studies reporting presence of diagnosis of psychosis only, while others reported scores on validated measures of psychotic symptoms such as BPRS or SANS/SAPS. This, however, is partially related to the fact that not all of the studies were designed to answer the specific question of the current meta-analysis. Four studies measured loneliness with a single-item measure. Only one study reported a power calculation (Sündermann et al.) [35]. Most studies provided adequate information regarding sample characteristics and used valid and reliable measures to rate loneliness and psychotic symptoms.

Outcome quality

Based on the GRADE criteria we downgraded the overall outcome by 1 point due to the high heterogeneity as indicated by the I^2 statistic and estimated the quality of the final outcome as moderate (please see supplementary material for more detail).

Table 1. Characteristics of included studies

Authors, year, Country	Groups included in review / Design	N participants	Age, mean (SD)	Proportion male (%)	Recruitment source	Ethnicity	Psychotic symptoms measure	Loneliness measure
Angell et al., 2002, USA	adults with schizophrenia schizoaffective disorder schizotypal personality disorder total *longitudinal design*	61 21 2 87	20-24 n=44 25-29 n=26 30-32 n=17 mean age not reported	62/87 (71%)	Evaluation of the Program of Assertive Community Treatment (PACT)	Caucasian (95%) African-American (4%) Latino (1%)	18-item version of the Brief Psychiatric Rating Scale	1-item scale: Loneliness defined as the number of days (range = 0-7) in which the subject reported feeling lonely and in need of companionship during the week preceding the interview
Badcock et al., 2015, Australia (also: Stain et al 2012)	Schizophrenia Schizoaffective disorder Bipolar disorder with psychotic features Depressive psychosis Delusional disorders and other non-organic psychosis Total Authors referred to a similar survey conducted on general population in New Zealand as a control group / *cross-sectional*	835 287 314 80 87 1603	Not lonely 37.5 (11.4) Lonely 38.3 (10.9)	979/1603 (61%)	The second Australian National Survey of Psychosis	Not reported	No measure/ Diagnostic Interview for Psychosis Diagnosis	1-item scale: "In the last 12 months have you felt lonely?" 4-point scale: (1) I have plenty of friends and have not been lonely; 2) Although I have friends I have been lonely occasionally; 3) I have some friends but have been lonely for company; 4) I have felt socially isolated and lonely.
Gayer-Anderson et al., 2014, England conference abstract	first-presentation psychosis cases unaffected population-based controls	227 199	Not reported	Not reported	the Childhood Adversity and Psychosis (CAPsy) Study	Not reported	Not reported	Not reported
Giblin et al., 2004 UK	people with a diagnosis of late-onset psychosis (LOP) late-onset depression (DEP) healthy older volunteers (HEV;) *cross-sectional design*	14 13 18	77.7 (6.6) 76.1 (6.4) 73.4 (7.8)	2/14 5/13 3/18	Patients: recruited via mental health teams controls: recruited from local community sources.	Not reported	No measure/ diagnosis instead	'Lonely dissatisfaction' item on Philadelphia Geriatric Center Morale Scale (higher score – higher morale)

Authors, year, Country	Groups included in review / Design	N participants	Age, mean (SD)	Proportion male (%)	Recruitment source	Ethnicity	Psychotic symptoms measure	Loneliness measure
Lindner at al., 2014 Germany	schizophrenia patients	36	30.8 (7.9)	22/36	psychiatric in-patients	Not reported	SANS and SAPS	multidimensional loneliness questionnaire (Multidimensionaler Einsamkeitsfragebogen; MEF
	healthy controls *cross-sectional design.*	40	29.5 (8.3)	27/40	controls: not reported			
Ludwig et al., 2013 USA Conference abstract –unpublished study	Persons with schizophrenia	34	34.1 (9.0)	23:11	recruited from a pool of potential participants within the Brain Behavior Laboratory at the University of Pennsylvania	Not reported	SAPS, SANS	Revised UCLA
	Controls *cross-sectional design.*	33	32.5 (11.2)	22:11				
Meltzer et al., 2013. England (also; Shevlin et al., 2015, Boyda et al., 2015 and McManus et al., 2009)	'probable psychosis' of schizophrenia or affective disorder *cross-sectional design.*	23	Not reported	Not reported	adult psychiatric morbidity survey 2007	Not reported	no measure / diagnosis based on SCAN (Schedule for Clinical Assessment in Neuropsychiatry	1-item ''I feel lonely and isolated from other people" (over the past 2 weeks) Likert scale ranging from ''1–Not at all'' to ''4–Very much''.
Roe et al., 2011 Israel	People diagnosed with schizophrenia or schizoaffective disorder *cross-sectional design*	159	43.2 (10.7)	66.7% men	psychiatric rehabilitation residential centers	Not reported	Modified BPRS-E	Social and emotional loneliness scale—short version (S-SELAS)
Stein et al., 2013 USA	young adults diagnosed with schizophrenia or bipolar disorder	30	23.7 (2.75)	18 men, 12 women	Participants were part of a longitudinal research project that examined life course changes for individuals and families coping with serious mental illness.	Proportions in both samples were the same: Caucasian (80%) African American (20%).	no measure/ diagnosis	UCLA Loneliness Scale.
	parents of these young adults *cross-sectional design*	30	50.3 (7.4)	28 mothers, 2 fathers				
Sundermann et al., 2014, England	individuals with a first episode in psychosis *cross-sectional design*	38	23/38 (60.5%)	32.3 (9.6)	NHS outpatient services within a South London NHS Foundation Trust	Caucasian 20 (52.6 %) African American 13 (34.2 %) Other 5 (13.3 %)	SAPS, SANS	1-item measure 'how many days have you felt lonely and in need of companionship in the past week?'

Authors, year, Country	Groups included in review / Design	N participants	Age, mean (SD)	Proportion male (%)	Recruitment source	Ethnicity	Psychotic symptoms measure	Loneliness measure
Switaj et al., 2014, Poland (also: Switaj et al., 2015, and Wciorka et al, 2015)	Patients with psychotic disorders *cross-sectional design*	110	38.4 (11.4)	43/110 (39.1%)	Mental health care facilities in Warsaw	Not reported	BPRS	A short version of the De Jong Gierveld Loneliness Scale (DJGLS)
Switaj et al, 2016, Poland (in press)	patients with psychotic disorders (ICD-10 categories: F20-F29) control group	207 207	Not reported	Not reported	Not reported	Not reported	18-item BPRS.	11-item De Jong Gierveld Loneliness Scale
Tietjen, 1993, USA	No clinical diagnosis Diagnosed with affective disorder Diagnosed with schizophrenia (DCM III)	87 92 93	Range: 24-59, mean/sd not reported	24/87 (30.8%) 29/92 (36.3%) 45/93 (57.7%)	Patients receiving treatment at psychiatric hospital Controls: students of general studies	Non clinical Black: 10.4% White 89.6% Affect. Disor. Black:13% White: 87% Schizophrenia Black:16.2% White: 83.8%	SCL-90-R Symptom checklist 90 revised	ESLI, Emotional & Social Loneliness Inventory

Table 2. Assessment of study quality

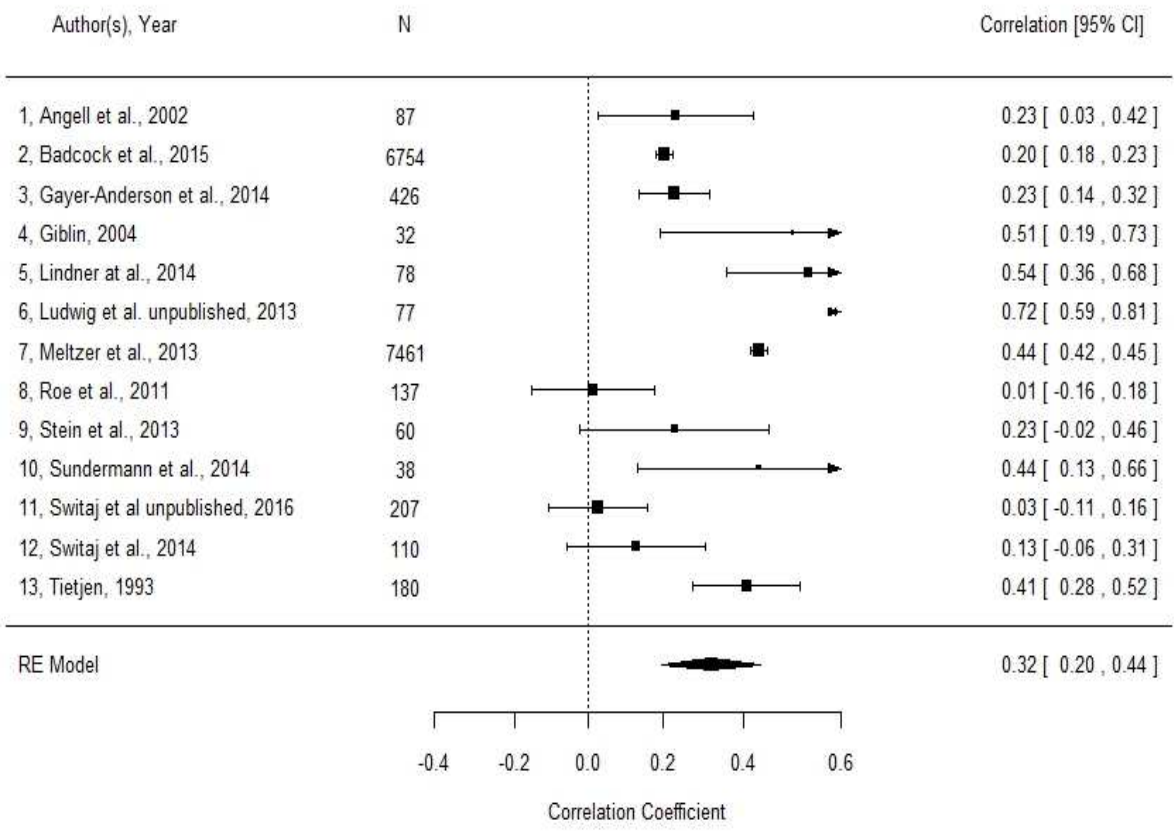
Study Ref	Unbiased Selection of the cohort	Selection Minimises Baseline Differences in Prognostic Factors?	Sample Size Calculated?	Adequate Description of the Cohort?	Validated Method for Ascertaining Psychotic Symptoms	Validated Method for Ascertaining Loneliness	Adequate handling of missing data
Angell et al., 2002	partial	yes	no/not reported	yes	yes	no	yes
Badcock et al., 2015	Yes	partial	n/a	yes	yes	no	yes
Gayer-Anderson et al., 2014 (conference abstract)	not reported	not reported	no/not reported	not reported	not reported	not reported	not reported
Giblin et al., 2004	partial	partial	no/not reported	partial	yes	yes	not reported
Lindner at al., 2014	unclear	not reported	no/not reported	partial	yes	yes	not reported
Ludwig et al., 2013 unpublished	partial	yes	no/not reported	partial	yes	yes	not reported
Meltzer et al., 2013	Yes	yes	n/a	yes	partial	no	no
Roe et al., 2011	partial	n/a (no control group)	no/not reported	yes	yes	yes	yes
Sundermann et al., 2014	partial	n/a (no control group)	yes	yes	yes	no	yes
Stein et al., 2013	partial	no	no/not reported	yes	partial	yes	not reported
Switaj et al., 2014	partial	n/a (no control group)	no/not reported	partial	yes	yes	not reported
Switaj et al, 2016 – in press	not reported	yes	no/not reported	Not reported	yes	yes	not reported
Tietjen, 1993	partial	no	no/not reported	yes	yes	yes	not reported

Association between loneliness and psychotic symptoms

There was moderate quality evidence suggesting a significant moderate association between psychosis and loneliness (Fisher's z estimate = 0.33, SE = 0.07, z-value = 4.81, $p < .001$, 95% CI: 0.1981, 0.4704). These values were converted back to correlation coefficient which produced the estimate of r = 0.32 (95% CI: 0.20, 0.44) which is considered a medium effect size, according to Cohen's criteria [36].

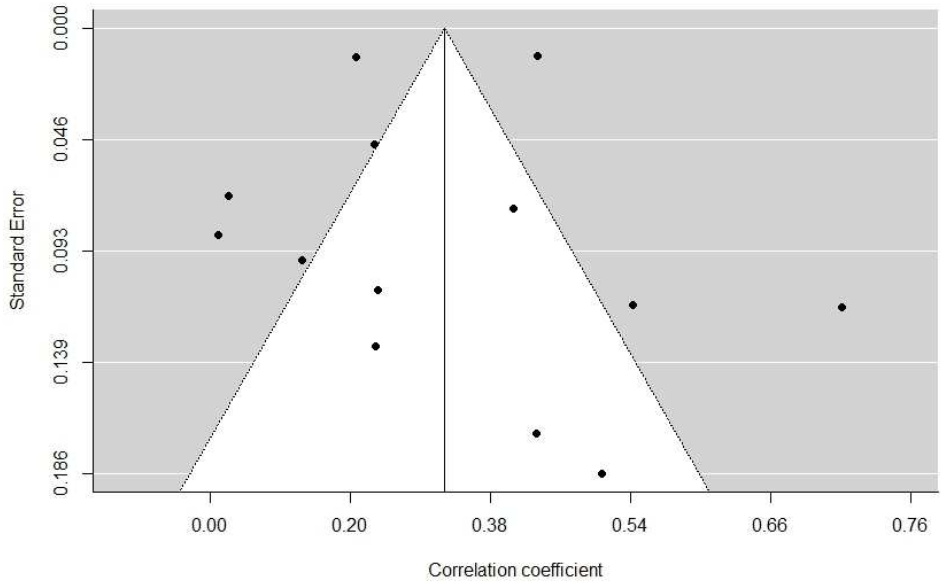
The I^2 statistic was 97.56% indicating that the majority of variation in the estimated effect sizes reflected actual differences in the population mean (95% CI: 94.42, 99.20, Q(12) = 316.43, $p < .001$). A Bajaut plot suggested that one study (Ludwig et al., unpublished) was influential in its contribution to the overall heterogeneity and the overall result. However, because exclusion of this study did not lead to a reduction in the proportion of true heterogeneity (I^2 = 95.93, 95% CI: 89.62, 98.83) nor did it significantly change the overall effect size (r = 0.28, 95% CI: 0.17, 0.38), consequently it was decided to keep the study in the meta-analysis.

Figure 2. Forest plot



Although a funnel plot of effect size against standard error (Figure 3) appeared to be asymmetric, neither Egger's regression test ($p = 0.29$) nor the Rank correlation test ($p = 0.13$) was statistically significant. Overall, there was no clear evidence of publication bias according to these tests.

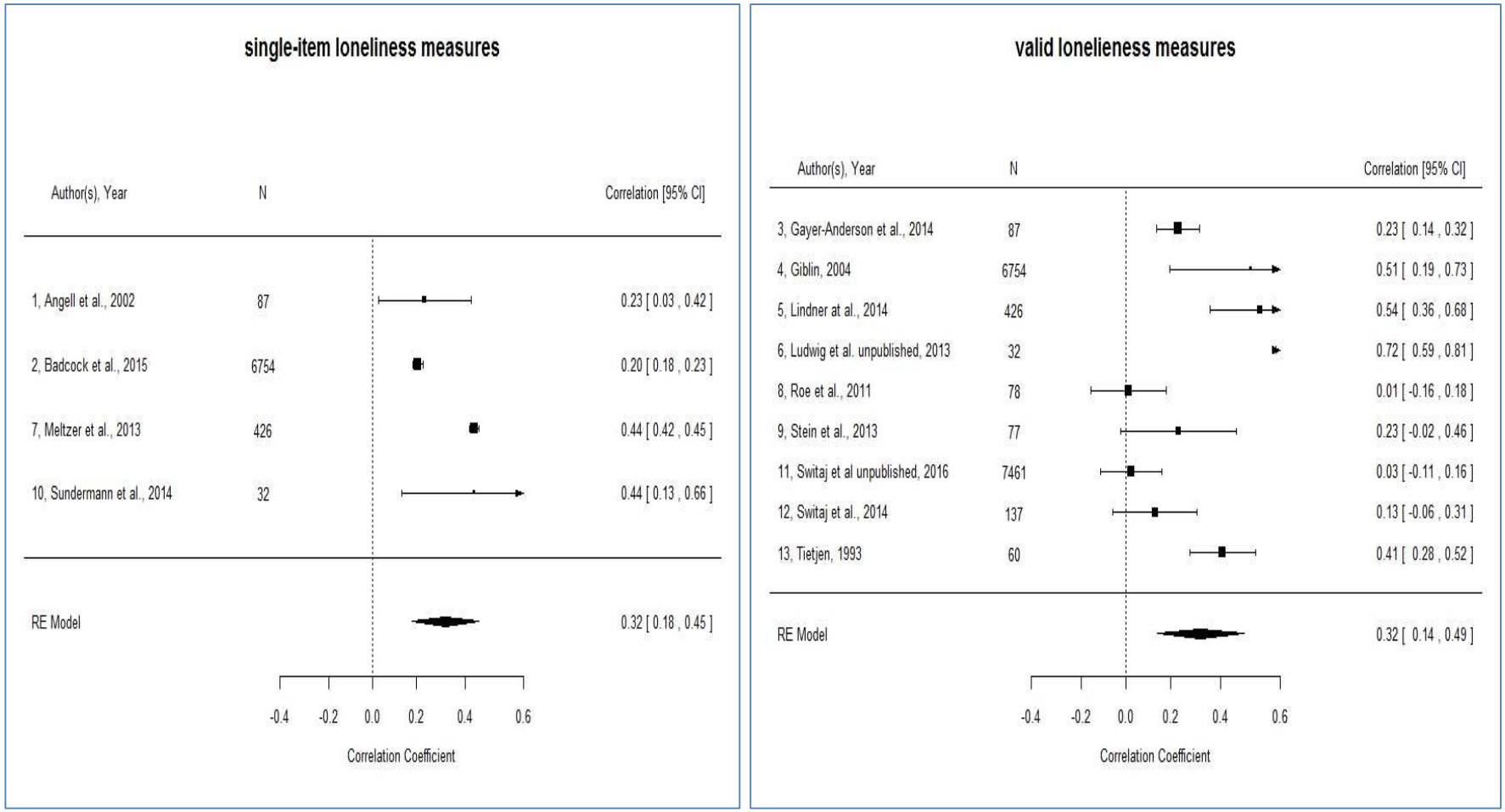
Figure 3. Funnel plot



Moderator Analyses

Whilst blinding of researcher to participant status (e.g. psychosis or control) had been pre-specified as a potential moderator of interest, none of the studies reported using blinding, therefore this analysis was not possible. Results of the moderator analysis for single-item vs comprehensive self-report measure of loneliness was not significant ($Q(1) = 0.001$, $p = 0.97$). As Figure 4 illustrates, there was no evidence that studies that employed very brief measures of loneliness produced different estimates to studies using more comprehensive assessments. We also examined whether the results were affected by stage of illness (first onset/late onset [k=3] versus established psychosis [k=10]), and found no significant differences ($Q(1) = 0.01$, $p = 0.92$).

Figure 4. Sensitivity analysis



DISCUSSION

The current analysis confirms that there is a significant relationship between loneliness and psychotic symptoms in people with psychosis. This finding is in line with growing evidence that loneliness is a common feature in psychosis [15, 37] and should be considered in further conceptualisations of psychotic disorders and treatment planning.

Could loneliness cause psychotic symptoms?

While the evidence from the current analysis supports the concept of psychosis and loneliness being significantly inter-related, the nature of this relationship is still unclear. Gayer-Anderson and Morgan [7] postulated the self-preserving cycle of psychosis and loneliness, and suggested that loneliness playing a maintaining role in psychotic experiences; however, it is also possible that loneliness might serve a crucial role in psychosis onset [6]. The concept of a psychosis phenotype can be expressed at levels below its clinical manifestation, commonly referred to as psychosis proneness, psychotic experiences, schizotypy or at-risk mental states[38,39]. It therefore seems likely that loneliness might be inter-related to psychotic symptoms at earlier, subclinical stages of psychotic presentation. A cognitive model of psychosis proposed by Garety et al. [40] suggests that one of the pathways to the development of psychosis might be via poor self-concept and self-esteem [41, 42] which might impact on maladaptive cognitions of self and others. Self-esteem is poor in many people with psychosis[43] while hallucinations and delusions that have negative content are associated with negative self-concepts [44]. It would be reasonable to assume that feelings of loneliness can strengthen negative self-concepts and impact negatively on self-esteem. Garety et al. [40] suggest that psychotic beliefs are likely to be more rigidly held if they are consistent with firmly-held distorted beliefs about the self (e.g. that one is different), others (e.g. that others are hostile) and the world (e.g. the world is dangerous). In other words, this cognitive model

would fit well with the hypothesis that loneliness could increase psychotic symptoms. While some authors propose that loneliness mediates the development of psychotic symptoms[6,45], others suggest that loneliness might be secondary to psychotic experiences. Riggio and Kwong[18], for example, reported that deficits in social skills and paranoid thinking independently predicted greater loneliness and fewer social supports in otherwise healthy individuals. Further studies aimed at investigating the occurrence and role of loneliness across psychotic continuum would be helpful in determining whether it precedes the onset of psychosis or occurs as a result of the condition. In particular, studies of experimental design with loneliness as the manipulated variable would be helpful in establishing whether there is a casual relationship.

Single-item loneliness measures

The findings of the moderator and sensitivity analyses regarding the type of loneliness measures used supports the idea that a single item loneliness measure produces results in line with those acquired using valid and reliable instruments. It seems important, however, to highlight that the way the single-item measures are used is usually influenced by the type of study conducted. They seem particularly prevalent in surveys, where participants respond to a large number of questions and the analysis of findings might be exploratory, rather than set out to test a primary hypothesis. There is a risk in interpreting results obtained in this fashion, as no reliability is guaranteed, while the large number of responders is likely to produce significant effects. One example of how unreliable single-item measures might be is provided in Angell and Test[46], where in their longitudinal design researchers took measure of loneliness across different time points (using a single-item measure). The correlation in endorsement of state loneliness between two time points (at 18 months after study entry, and then at 24 months) was r = .14, whereas the correlation on a valid measure of thought

disturbance at these time points was r = .45. Although this may reflect inherent instability in state loneliness rather than poor reliability, it is important that results from single-item measures are considered with care.

Implications for clinical practice

Some authors suggest a link between loneliness and recovery from psychosis. Jackson et al. [47] compared the effectiveness of Active Cognitive Therapy and Befriending in reduction of psychosis symptoms and functional improvement in people with first episode of psychosis. They reported equal effectiveness of the two treatments, which is suggestive of a significant role of befriending in psychosis recovery. This finding is congruent with findings of Roe et al.[24] who reported that patient's subjective recovery from psychosis was significantly associated with a decrease in loneliness. It therefore appears that increased loneliness may play a role in the maintenance of psychosis, but also that a decrease in loneliness may be related to subsequent recovery. However, the results of the Adult Psychiatric Morbidity Survey in England [15] suggest that traditional approaches to reducing loneliness, such as increased social support and participation, had only a limited effect on subjective loneliness. This raises the possibility that these strategies, which are often applied in order to reduce loneliness in people with psychotic disorders, might not be very effective. Badcock et al. [37] reported that loneliness amongst people with psychotic disorders was particularly associated with thought disturbance and reduced sense of pleasure. Thus, increasing possibilities for social interaction might not always be effective; if one does not derive pleasure from social contact or has negative cognitions related to social participation, then a positive outcome of the intervention is unlikely. In addition, having a confidante has been associated with lower levels of loneliness [48] which would be suggestive of the importance of the quality of interaction rather than the quantity. It thus seems essential that in clinical practice particular

attention is given to loneliness and the maintaining role it might have in psychotic experiences. It is important to consider that patients with psychosis are often longing for social contact but lacking resources to build them and maintain. Consequently, treatment options might involve changing maladaptive cognitions [49], while at the same time providing high quality social contact. Indeed, this may be one reason why the therapeutic relationship has been found to be such a crucial factor in ensuring effective and safe psychological therapy for psychosis [50].

Strengths and limitations

We decided, a priori, to adopt a deliberately inclusive approach for this meta-analysis. Although this is recommended [51] and although it ensures we made the best use of the limited studies available, the cost is inevitably considerable heterogeneity between studies in terms of population (including stage of illness), methodological design and quality. It may be argued that limiting the analysis to studies that look at one particular type of psychotic disorder, or at one particular population (e.g. late onset only, first episode only) may have increased the homogeneity of the results – thus giving us confidence that any residual heterogeneity was not attributable to these factors. However, an inclusive approach to meta-analysis is arguably more transparent and informative. Unlike a more restrictive meta-analysis, this approach minimises the number of a priori assumptions we have to make about moderating factors, and instead allows us to produce empirical data on the effect of excluding such subgroups. Indeed, we found no evidence that stage of illness acted to moderate the overall effect, which suggests the observed relationship between psychosis and loneliness is a robust one.

Studies of various types of psychotic disorders were included in our meta-analysis. This reflects our decision to operate with a broad definition of psychosis, rather than focus on specific symptoms. However, we note that negative symptoms such as withdrawal or loss of

pleasure are significantly different to positive symptoms such as hallucinations and delusions. For example, Badcock and colleagues[37] reported data on twelve specific symptoms, including delusions, hallucinations, thought disorder, passivity etc. and found significant correlations with loneliness only for two of them (thought disorder and loss of pleasure). Although our meta-analysis provides important data on the nature of the psychosis-loneliness relationship, future meta-analyses may benefit from adopting a symptom-specific approach. Their results may present less heterogeneity as a consequence, and the value of such work for understanding the onset and maintenance of specific psychotic symptoms may be high.

It is also important to consider that our quality assessment relates very much to the hypothesis we are testing. Although we criticised the quality of several of the included studies, we did this simply so that we could form a view as to the reliability of the estimate. We fully recognise that many of the studies did not set out to examine the link between psychosis and loneliness, and often only reported loneliness data as a secondary outcome.

Some of the included studies reported adjusted odds ratio only [15] which further complicates the analysis, for various authors adjust for different parameters and this leads to difficulty in interpreting the synthesised results. Nonetheless, there was no evidence that the overall effect was moderated by these individual studies.

Although tests of publication bias were not significant, it is possible that this was due to a limited number of studies included in this analysis [52]. A visual inspection of the funnel plot did suggest that small studies reporting limited or no relationship between psychosis and loneliness may be lacking. Publication bias is of course an endemic problem [53] and, as with clinical trials, pre-registration of empirical research could help to reduce – or at least measure – non publication of non-significant results [53].

Six studies that appeared relevant for the current analysis were not included due to difficulty in obtaining usable data. In addition, we did not include studies that were not published in English. Non-inclusion of studies is of particular concern in systematic reviews of observational studies as there is inevitably a greater threat of publication bias with this sort of research than, for example, treatment effectiveness research [54]. On the other hand, we were not completely unsuccessful in acquiring unpublished data or information; in fact, three authors replied to our queries meaning we were able to include data from 13 studies, instead of 10.

A particular strength of our review and meta-analysis is that we sought to pre-register the hypotheses and methodology in the public domain [55, 56]. As noted elsewhere [55, 57], systematic reviews and meta-analysis are far from immune from risks of selective reporting bias and hypothesising after the results are known. Although we made some changes to our protocol after registering it (largely to reduce scope), pre-registration ensures complete transparency about these, thus allowing readers to judge for themselves whether they are driven by issues relating to feasibility, new information, or bias.

Conclusion

This review and meta-analysis has provided clear evidence that there is a significant relationship, moderate in magnitude, between loneliness and psychotic symptoms in people with psychosis. Although there was high heterogeneity across different studies, the overall relationship was robust. Such a finding is congruent with other evidence, as well as recent theoretical accounts of psychosis [40, 58]. This finding should be considered in clinical practice and treatment provision for those with psychotic disorders. However further studies are needed to test the hypothesis that loneliness may *cause* psychosis. In particular, studies

examining the effect of experimentally manipulating loneliness on psychotic symptoms are essential for understanding the causal status and direction of the relationship we have observed here.

The Authors have declared that there are no conflicts of interest in relation to the subject of this study.

Acknowledgements

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Supplementary Material

List of content

Appendix A - Study Quality Assessment Tool

This is an adapted version of a tool for assessing the methodological quality of observational studies that has been successfully employed in prior research undertaken by the Agency for Healthcare Research and Quality (AHRQ). Each study is assessed on a range of methodological quality criteria that are rated as being met, not met, partially met, or being unclear. This tool has been followed closely from Taylor at al., (2015).

In the current study scale-based or aggregated study quality rating was not performed, based on the guidance of experts in the field of meta-analysis. Quality assessments were presented descriptively to guide the interpretation of findings, rather than used as a means to weight or adjust aggregated effect sizes. The tool we applied is presented below.

General instructions: Grade each criterion as 'Yes', 'No', 'Partially', or 'Can't tell'. Factors to consider when making an assessment are listed under each criterion. Where appropriate (particularly when assigning a 'No', 'Partially', or 'Can't tell' score), please provide a brief rationale for your decision (in parentheses) in the evidence table.

1. Unbiased selection of the cohort?

Factors that help reduce selection bias:

○ Inclusion/exclusion criteria:

○ Recruitment strategy

- Clearly described
- Criteria for inclusion in psychosis/delusions and comparison groups clearly outlined.
- Relatively free from bias (selection bias might be introduced, for example, by recruitment via advertisement).

2. Selection minimizes baseline differences in prognostic factors?

Factors to consider:

○ Was selection of the comparison group appropriate?

○ Is the comparison group matched with the clinical group on key demographics (that is age and gender)?

3. Sample size calculated?

Factors to consider:

○ Did the authors report conducting a power analysis or describe some other basis for determining the adequacy of study group sizes for the primary outcome(s) of interest to us?

○ Where a power calculation is presented, do the final numbers obtained match up to this (for example, within 10% of required numbers)?

4. Adequate description of the cohort?

Consider whether the cohort is well-characterized in terms of baseline:

○ Age

○ Sex

○ Ethnicity

○ Diagnosis/clinical status

5. Validated method for ascertaining psychotic disorder or delusions?

Factors to consider:

○ Was the method used to ascertain exposure clearly described (details should be sufficient to permit replication in new studies)?

○ Was a valid and reliable measure used to ascertain exposure (subjective measures based on self-report tend to have lower reliability and validity than objective measures such as clinical interview)? Likewise, relying on medical notes is likely to introduce bias due to variation in how assessment is undertaken.

6. Validated method for ascertaining 'jumping to conclusions'?

Factors to consider:

○ The beads task or a conceptually equivalent variant should be used

○ Were these measures implemented consistently across all study participants?

○ Were several trials and/or a practice run included in the procedure?

7. Outcome assessment blind to exposure?

Factors to consider:

○ Were the study investigators who assessed outcomes blind to whether participants had a psychotic disorder or delusions (this criterion will not apply in the case of Internet-based or automated designs where a researcher is not present)?

8. Adequate handling of missing data?

Factors to consider:

○ Are the details of missing data clearly reported, including how missing data was handled in the analyses? If not, is there any reason to believe missing data was present (for example, lower N in analysis than initially reported in the participants section).

○ Did missing data from any group exceed 20%?

○ If missing data was present and substantial, were steps taken to minimize bias (for example, sensitivity analysis or imputation).

Appendix B - GRADE assessment of all outcomes

Method

Quality assessments were conducted independently by two reviewers - one reviewer (BM) assessed all of the studies while the second reviewer (EV) assessed a proportion of studies, with any disagreements resolved through discussion with the third author (PH).

For assessment of outcome quality, we downgraded by 1 point if two of the parameters in our quality assessment had ≥50% studies with at least one 'no' or 'unclear' rating, and 2 points if three parameters had ≥50% studies with ratings of 'no or unclear'.

We downgraded by 1 point for inconsistency if the I^2 statistic was ≥40% in the context of an unclear direction of effect or ≥75% in the context of a clear direction of effect. We downgraded by 2 points if the I^2 statistic was ≥75% in the context of an unclear direction of effect. We downgraded an outcome for imprecision if "a recommendation or clinical course of action would differ if the upper versus the lower boundary of the CI represented the truth" and / or the number of events and sample size meant the optimal information size was not reached.

We downgraded for publication bias when funnel-plot suggested asymmetry which would be confirmed in the Egger's regression test and the Rank correlation test, and this was not better explained by selective reporting bias or some other factor.

Outcome

Based on the following criteria we downgraded the overall outcome by 1 point due to the high heterogeneity as indicated by the I^2 statistic.

Appendix C - A list of excluded studies

The following table presents studies excluded after inspection of the full-text report, or via correspondence with authors. Studies excluded on basis of title or abstract alone are not detailed as these are too numerous.

Study	Reason for exclusion
Andersson G., Denhov A., Bulow P., Topor A., 2015	Qualitative study
Barut, Jennifer K., Dietrich, Mary S Zanoni, Paul A, Ridner, Sheila H., 2015	Qualitative study
Bebbington P, Wilkins S, Sham P, et al. 1996	Loneliness not measured
Beebe L.H., 2010	Qualitative study
Behrendt R.P., 2006	Not empirical
Bengtsson-Tops A, Hansson L., 2001	Loneliness not measured
Birnbaum M.L., 2010	Qualitative study
Brown, C 1996	Not specific to psychosis
Corrigan, P. W., & Phelan, S. M., 2004	Loneliness not measured
Cresswell CM, Kuipers L, Power MJ, 1992	Loneliness not measured
Davidson, L; Stayner, D., 1997	Qualitative study
De Niro, Dorothy Ann Nejedlo, 1993	Qualitative study
De Niro D.A., 1995	Qualitative study
de Pater, Margreet, 2012	Qualitative study
Doman, L. C. H.; Roux, A le., 2010	Not empirical
Druz, VF; Budza, VG; Oleinikova, IN; Medvedev, VA., 1998	Not in English
Druz, VF; Oleinikova, IN., 2000	Not in English
Elisha D., Castle D., Hocking B., 2006	Not specific to psychosis
Erdner A., Nystrom M., Severinsson E., Lutzen K., 2002	Qualitative study
Evert, H; Harvey, C; Trauer, T; Herrman, H., 2003	Loneliness not measured
Freeman, D., Gittins, M., Pugh, K., Antley, A., Slater, M., Dunn, G., 2008	Non-clinical sample
Gerstein, 1987	Psychotic symptoms not measured, control group limited to lonely people
Graham C, Arthur A and Howard R (2002)	Loneliness not measured
Granerud, A.; Severinsson, E., 2006	Qualitative study
Gruzelier J.H., 1996	Loneliness not measured
Hamilton NG, Ponzoha CA, Cutler DL, Weigel RM., 1989	Loneliness not measured
Harvey C.A. Brophy L., 2011	Not empirical
Honkonen, T; Saarinen, S; Salokangas, RKR., 1999	Loneliness not measured
Jablensky A, Mcgrath J, Herrman H, et al. (1999)	Loneliness not measured
Kudo J., Mori H., Gomibuchi T., 2002	Qualitative study
Lamster F.G., Nittel C., Lincoln T., Kircher T. et al., 2015	Non-clinical sample
Lim, M., Gleeson, J., 2014	Not empirical
Linz, Sheila J.; Sturm, Bonnie A., 2013	Not empirical

Lysaker PH, Davis LW (2004)	Loneliness not measured
Macdonald EM, Hayes RL, Baglioni AJ., 2000	Loneliness not measured
Maltsberger JT., Pompili M., Tatarelli R., 2006	Qualitative study
Morgan V.A., Jablensky A.V., Waterreus A., Bush R. et al.,2011	Abstract only, published elsewhere
Morgan, V.A., Waterreus, A., Jablensky, A., Mackinnon, A., et al, 2012	Loneliness not measured
Murphy, S; Murphy, J; Shevlin, M., 2015	Non-clinical sample (uses psychotic-like symptom screen but no diagnoses)
Nilsson B., Naden D., Lindstrom U.A., 2008	Qualitative study
Perese E, Marilee, W., 2005	Loneliness not measured
Riggio, HR., Kwong, WY., 2011	Non-clinical sample
Riggio, HR., Kwong, WY., 2009	Non-clinical sample
Romney, D.M., 1995	Loneliness not measured
Salokangas RK., 1997	Loneliness not measured
Schwartz et al., 2009	No measure of psychotic symptoms, no healthy control group
Sorensen, Leif V Mors, Ole., 1992	Loneliness not measured
Sundermann, O Onwumere, J Bebbington, P Kuipers, E., 2013	Not empirical
Talarowska-Bogusz, Monika; Florkowski, Antoni; Zboralski, Krzysztof; Cieslak, Katarzyna; Galecki, Piotr., 2008	Loneliness not measured
Tharayil D., 2005 – unpublished thesis dissertaton	Qualitative study
Tharayil, 2007	No measure of psychotic symptoms, no control group
Westermann S., Lincoln T.M., 2010	Loneliness not measured
Van Der Werf M.Van Winkel R. Van Os J., 2010	Conference abstract, published elsewhere
Boyda et al., 2015	reuse of the same sample
McManus et al., 2009	reuse of the same sample
Shevlin et al., 2015	reuse of the same sample
Stain et al., 2012	reuse of the same sample
Switaj et al., 2014	reuse of the same sample
Wciorka et al., 2015	reuse of the same sample
Borge et al., 1999	Relevant correlation data not provided / no contact with author
Cohen et al.,1997	Relevant correlation data not provided / no contact with author
Pjescic et al., 2014	Relevant correlation data not provided / no contact with author
Tylova et al., 2013	Abstract only, relevant data not provided / no contact with author
Young et al., 2015	Baseline data not accessible / no answer from the author
Van der Werf et al., 2010	Relevant data not provided on request

Appendix D - PRISMA checklist

Section/topic		Checklist item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	11
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6

Section/topic		Checklist item	Reported on page
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1. p. 9
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, appendix A
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	18