Psychological Medicine

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Are adult stressful life events associated with psychotic relapse? A systematic review of 23 studies

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Review Article

Cite this article: Martland N, Martland R, Cullen AE, Bhattacharyya S (2020). Are adult stressful life events associated with psychotic relapse? A systematic review of 23 studies. *Psychological Medicine* **50**, 2302–2316. https://doi.org/10.1017/S0033291720003554

Received: 3 June 2020
Revised: 5 September 2020
Accepted: 9 September 2020
First published online: 15 October 2020

Key words:
Adult; bipolar disorder; life event; psychosis; relapse; review

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Abstract

Relapse rates among individuals with psychotic disorders are high. In addition to the financial burden placed on clinical services, relapse is associated with worse long-term prognosis and poorer quality of life. Robust evidence indicates that stressful life events commonly precede the onset of the first psychotic episode; however, the extent to which they are associated with relapse remains unclear. The aim of this systematic review is to summarize available research investigating the association between recent stressful life events and psychotic relapse or relapse of bipolar disorder if the diagnosis included psychotic symptoms. PsycINFO, Medline and EMBASE were searched for cross-sectional, retrospective and prospective studies published between 01/01/1970 and 08/01/2020 that investigated the association between adult stressful life events and relapse of psychosis. Study quality was assessed using the Effective Public Health Practice Project guidelines. Twenty-three studies met eligibility criteria (prospective studies: 14; retrospective studies: 6; cross-sectional: 3) providing data on 2046 participants in total (sample size range: 14–240 participants). Relapse was defined as a return of psychotic symptoms ($n = 20$), a return of symptoms requiring hospitalization ($n = 2$) and a return of symptoms or hospitalization ($n = 1$). Adult stressful life events were defined as life events occurring after the onset of psychosis. Stressful life events included but were not limited to adult trauma, bereavement, financial problems and conflict. Eighteen studies found a significant positive association between adult stressful life events and psychotic relapse and five studies found a non-significant association. We conclude that adult stressful life events, occurring after psychosis onset, appear to be associated with psychotic relapse.

Introduction

Rates of relapse are high among individuals with psychotic disorders. It is estimated that only 28% of people who suffer from a first episode of psychosis (FEP) will never re-experience another episode in their lifetime (Alvarez-Jimenez et al., 2012). Relapse is associated with an increased financial burden: it has been estimated that direct healthcare costs (encompassing both inpatient and outpatient care) are four times greater for those who relapse compared to those who do not over a 6-month period (Almond, Knapp, Francois, Toumi, & Brugha, 2004), with one study estimating these costs to be even higher (Ascher-Svanum et al., 2010). Coupled with this financial strain, relapse is associated with poorer quality of life (Bobes, Garcia-Portilla, Bascaran, Saiz, & Bousoño, 2007), poorer social and occupational functioning (Mattsson, Topor, Cullberg, & Forsell, 2008), more severe clinical symptoms (Wiersma, Nienhuis, Slooff, & Giel, 1998) and emotional burden placed on patients and their families (Brady & McCain, 2005). Hence, gaining a better understanding of factors that influence relapse in psychosis is of critical importance to clinical services, patients and their families.

The association between life events and psychosis onset is well-established. A previous systematic review and meta-analysis of 26 studies reported that individuals experiencing life events are three times more likely to develop psychosis (Beards et al., 2013). In contrast, there has been no attempt to examine the role of recent stressful life events in psychotic relapse by means of a robust systematic review. This area of research is of clinical importance because we cannot assume that factors associated with illness onset are necessarily associated with subsequent relapse. For example, whilst meta-analyses show that childhood trauma confers increased risk for psychosis (Varese et al., 2012), a systematic review found only two of seven studies reported a positive association between childhood trauma and risk of relapse of a pre-existing psychotic disorder during adulthood (Petros et al., 2016).

Whilst early studies examining life events and psychotic relapse provide evidence to suggest that stressful life events occurring after the onset of psychosis confer poorer prognosis (Castine, Meadorwoodruff, & Dalack, 1998) and greater risk of relapse (Birley & Brown,

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1970), evidence remains equivocal, with some studies showing that life events are not significantly associated with psychotic relapse (Dols et al., 2018; McPherson, Herbison, & Romans, 1993). A robust review is needed to determine the consistency of findings across studies as such efforts may ultimately inform treatment approaches. We therefore sought to address this gap in current understanding by summarizing available research investigating the influence of stressful life events experienced after the onset of psychotic disorders (or bipolar disorder if the diagnosis included psychotic symptoms rather than solely affective symptoms) on relapse. We aimed to investigate whether a consistent pattern of evidence exists that suggests that life events occurring after the onset of psychotic disorders have an adverse impact on psychotic relapse, and we aimed to conduct a robust appraisal of the extant literature by assessing study quality and risk of bias.

Methods

Adult stressful life events were defined as events occurring after the onset of psychosis, but before the occurrence of a relapse of psychosis, that were subjectively defined as 'stressful'. This included, but was not limited to: family problems, relationship difficulties, job worries, money problems and personal injury (Holmes & Rahe, 1967). The Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines for a systematic review of observational studies were followed in preparing this report (Stroup, 2000). The study protocol was registered on PROSPERO (CRD42018100396).

Search strategy

A systematic search strategy was employed following the methods recommended by the Cochrane Handbook (Higgins & Green, 2008). Relevant studies were identified by searching PsycINFO, Medline and EMBASE from inception to 08/01/2020. Titles and abstracts were searched for the presence of search terms. Multiple search terms were used to describe relapse, the study population and adult stressful life events. The search terms used were as follows: (*outcome or hospital* or relapse or readmission*) *and* (*bipolar or psychot* or psychos* or schizophren* or schizoaff**) *and* (*life event* or adult trauma* or social advers* or adult advers**). These search terms for adult stressful life events were used after using 'stress' as a search term yielded too many irrelevant results. Reference lists of included articles were also hand searched.

Inclusion and exclusion criteria

Two researchers (NM and RM) independently assessed articles based on inclusion and exclusion criteria, with a senior researcher (AEC) consulted when disagreements arose. Studies were considered eligible for inclusion if they satisfied the following inclusion criteria: (1) study participants had a pre-existing psychotic disorder (i.e. psychosis, schizophrenia, schizoaffective or bipolar disorder if the latter included psychotic symptoms rather than solely affective symptoms); (2) adult stressful life events occurred after psychosis onset and prior to psychotic relapse; and (3) relapse was defined as either readmission to hospital, a return of psychotic symptoms or both. All study designs were eligible for inclusion. There were no restrictions regarding participant stage of illness; studies examining relapses after the first psychotic episode and studies examining remission following previous relapse episodes were included.

Studies were excluded if: (1) the stressful life event occurred either during childhood or before the onset of psychosis; (2) it could not be established when the stressful life event occurred or studies reporting stressful events in one's lifetime rather than specifically after psychosis onset; (3) the study did not carry out a quantitative analysis or explicitly measure the relationship between life events and relapse; or (4) the study was published before 1970 [the first studies explicitly looking at life events and psychotic relapse commenced with the notable Birley and Brown paper in 1970 (Birley & Brown, 1970)]. Conference abstracts and non-English language articles were excluded.

Quality assessment

Studies were assessed for quality using assessment criteria set by the Effective Public Health Practice Project (EPHPP, 2003), modified to include items of relevance to the present review (Petros et al., 2016). We included an additional category pertaining to the quality of the statistical analysis. Each study was assessed on seven main areas: selection bias, quality of measurement of life events, quality of measurement of psychosis, quality of measurement of relapse, adjustment for confounding variables, data collection methods and statistical analysis. The maximum score that could be awarded was 18. Quality scores were independently generated by two researchers (NM and RM).

Data extraction process and data analysis

From each study, we extracted: study type, participant information, diagnosis, life event measurement, relapse measurement, statistical test used and main findings (statistical results and narrative synthesis). We then examined whether the pattern of results varied across study design, patient diagnosis, relapse measurement, life event measurement and analysis approach (adjustment for confounders) to investigate the extent to which these factors influenced the pattern of results. We also noted whether studies made a distinction between independent life events (events occurring out of a person's control) and dependent life events (events attributable to a person's behaviour or illness) and whether the type of life event had any impact on the occurrence of relapse.

An estimation of the pooled effect size was not carried out due to the heterogeneity in study design, measurement of life events and relapse, and analytic procedures employed. For instance, some studies defined relapse in categorical terms (relapse *v.* no relapse) whilst others used a continuous variable (number of relapse events). Moreover, the method of analysis varied between studies (regressions, *t* tests, χ^2 and correlations were carried out) and there were differences in adjustment for potential confounders.

Results

Study characteristics

The initial search identified 3039 articles published between 1970 and January 2020. After removing duplicates, 1958 articles were assessed for eligibility, of which 47 were read in full. Twenty-three articles satisfied study eligibility criteria (see Fig. 1). A list of articles excluded after full-text review and reasons is provided in Appendix 1.

https://doi.org/10.1017/S0033291720003554 Published online by Cambridge University Press

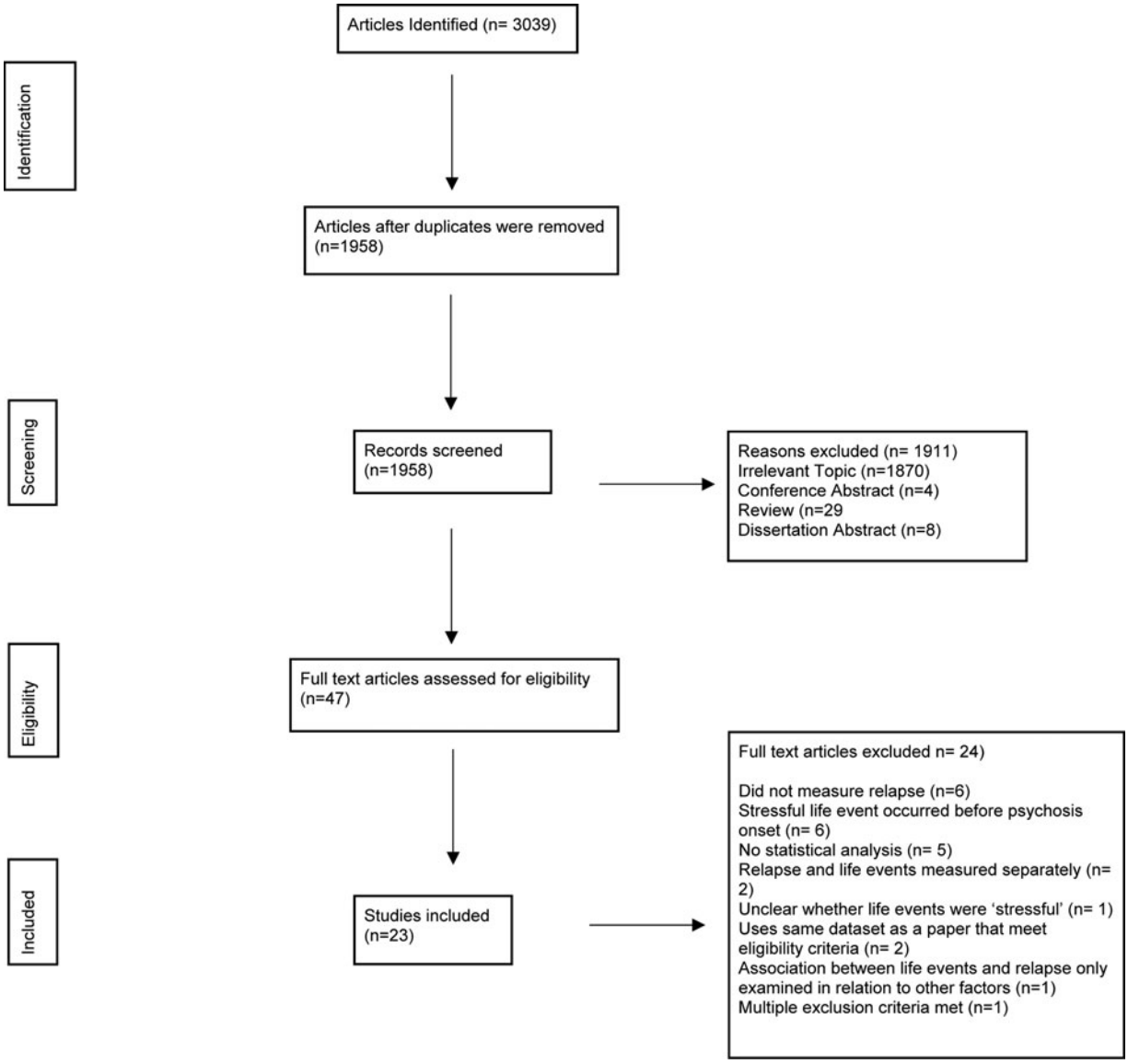

Fig. 1. Flow diagram.

Data from the included studies are summarized in Table 1. Of the 23 eligible studies, all studies except one used interviews to obtain information about exposure to past life events, the remaining study compared the occurrence of relapse between patients who were affected by a hurricane (the adult stressful life event exposure) to those not affected by a hurricane (Aronson & Shukla, 1987). Fourteen studies recruited subjects who had a clinical diagnosis of schizophrenia, schizoaffective disorder or schizophreniform disorder, and nine studies included individuals with bipolar I or bipolar II disorder.

The 23 studies included 2046 participants in total, 1539 (75%) of whom had psychosis or were in remission, 507 participants were healthy controls. Of the 1539 participants with a psychotic disorder, 672 (44%) were diagnosed with schizophrenia or schizoaffective psychosis and 867 (56%) were diagnosed with either bipolar I disorder or bipolar II disorder. Of studies reporting age and gender, the mean age was 46 years and 51% were male.

Main findings

Results from included studies are summarized in Table 1. Eighteen studies ($n = 1513$) reported a significant association between stressful life events and subsequent relapse of psychosis (Aronson & Shukla, 1987; Birley & Brown, 1970; Castine et al., 1998; Chabungbam, Avasthi, & Sharan, 2007; Christensen et al., 2003; Das, Kulhara, & Verma, 1997; Ellicott, Hammen, Gitlin, Brown, & Jamison, 1990; Hirsch et al., 1996; Hui et al., 2016; Hultman, Wieselgren, & Öhman, 1997; Hunt, Bruce-Jones, & Silverstone, 1992; Leff, Kuipers, Berkowitz, Vaughn, & Sturgeon, 1983; Nuechterlein et al., 1992; Pallanti, Quercioli, & Pazzagli, 1997; Sam, Nisha, & Varghese, 2019; Simhandl, Radua, König, & Amann, 2015; Subramanian, Sarkar, Kattimani, Philip Rajkumar, & Penchilaiya, 2017; Ventura, Nuechterlein, Lukoff, & Hardesty, 1989), whereas five studies ($n = 531$) found a non-significant association between stressful life events and subsequent relapse of psychosis (Al Khani, Bebbington, Watson, & House, 1986; Dols

https://doi.org/10.1017/S0033291720003554 Published online by Cambridge University Press

Table 1. Characteristics of studies included in the systematic review and main study findings

Authors (date) location	Design	Participants	Relapse measurement	Life events measurement	Statistical test used	Main findings
Sam et al. (2019). India.	Cross-sectional retrospective design	Bipolar affective disorder patients meeting ICD-10 criteria ($N = 128$): mean age: 40.19 (s.d =. 8.7) years; % male (57%)	ICD-10 criteria for illness relapse and admission	PSLES	Mann–Whitney *U* test	SLEs, predominantly family conflicts and finance-related problems, reported by 70% of relapsed BAD patients. The mean duration between SLEs and relapse = 19.7 ± 4.8 days
Dols et al. (2018), The Netherlands	Prospective cohort study	Bipolar I and II disorder patients meeting Neuropsychiatric Interview Plus criteria ($N = 101$): mean age: 68.9 (s.d. = 7.8) years; % male (46.5%)	Dutch version of QBP-NL	Adapted questions about 16 negative and 8 positive life events from the QBP-NL	Linear regression and logistic regression	SLEs, predominantly somatic illness, bereavements and financial problems, reported by 68.8% of patients. However, life events were not significantly associated with episode recurrence
Subramanian et al. (2017), India	Cross-sectional retrospective design	Bipolar I disorder patients meeting DSM-IV criteria ($N = 149$): mean age: 37.7 (s.d. = 9.7) years; % male (47.7%)	National Institute of Mental Health-Life Chart Methodology Clinician Retrospective Chart	PSLES	Correlational analysis and Somer's *d*	SLEs, predominantly family conflict, noted in 298 episodes (37.7% of all episodes). The Somer's *d* metric for the number of episodes as a dependent variable and presence of a life stressor as an independent variable was −0.299 ($p < 0.001$). The results for those having more than 6 episodes was still significant (Somer's $d = -0.260$, $p < 0.001$)
Hui et al. (2016). Hong Kong	Randomized controlled trial	Schizophrenia or non-affective psychosis patients meeting DSM-IV criteria ($N = 102$): mean age: 23.7 (s.d. = 4.8) years; % male (45%)	PANSS criteria for illness	12-item List of Threatening Experiences questionnaire	Logistic regression	SLEs were a significant predictor of relapse at 1 year ($p = 0.014$). Relapse was associated with more SLEs 1 month before relapse (OR 2.11, 95% CI 1.20–3.72, $p = 0.01$)
Simhandl et al. (2015), Austria	Prospective cohort study	Bipolar I and II disorder patients meeting ICD-10 criteria ($N = 222$): mean age: 32.4 (s.d. = 12.0) years; % male (30.2%)	Deterioration or change of the affective state needing an explicit pharmacological intervention and/or re-hospitalization	Standardized interview. Did not use a life events scale	Cox regression analysis	SLEs were reported by 49.5% of patients after the index episode, before relapse. The risk of a depressive relapse in bipolar I patients was associated with the number of SLEs after the index episode (Hazard ratio = 1.64, $z = 3.08$, $p = 0.002$). The risk of a manic relapse was not associated with the number of SLEs after the index episode

(*Continued*)

Table 1. (*Continued.*)

Authors (date) location	Design	Participants	Relapse measurement	Life events measurement	Statistical test used	Main findings
Chabungbam et al. (2007), India	Retrospective case-control design	Schizophrenia patients in relapse or remission according to ICD-10 criteria (relapsed $N = 20$; in remission $N = 20$); mean age of relapsed: 33.8 years (S.D. =10.2); mean age of remitted group: 33.85 years (S.D. = 11.02; % male (70% or relapsed; 60% of remitted patients)	ICD-10 criteria for illness relapse	PSLES	Unpaired Student's *t* test and Fisher's exact test	Significantly higher stress scores in relapse group than the remitted patient group on PSLES ($p < 0.05$). Relapsed group total score 73.00 (S.D= 56.39), remitted group total score 29.65 (S.D = 33.33), *t* (df = 38), $p = 2.95$*
Draman et al. (2005), Malaysia	Retrospective case-control design	Schizophrenia patients meeting DSM-IV criteria ($N = 120$); healthy controls ($N = 120$); % male (78% of schizophrenia patients; 75% of controls)	DSM-IV criteria for illness relapse	Standardized questionnaire on life events	Multiple logistic regression	No significant association ($p > 0.05$) between life events and repeated admissions
Christensen et al. (2003), Denmark	Prospective cohort study	Bipolar affective disorder patients meeting ICD-10 criteria ($N = 56$); mean age 53 (range: 30–76) years; % male (34%)	Hamilton Depression Rating Scale, the Newcastle Depression Rating Scale and the Bech–Rafaelsen Mania Rating Scale	The Interview for Recent Life Events	Spearman's rank correlation	Women experienced a significantly higher number of SLEs than men (21% of relapses proceeded by a SLE compared to 8% in men). The distribution of SLEs in relation to affective phase showed no significant difference in men, whereas there was a significant piling of life events preceding female depressive episodes ($p < 0.01$)
Castine et al. (1998), USA	Cross-sectional retrospective design	Schizophreniform disorder, schizophrenia or schizoaffective disorder-depressed subtype meeting DSM-III criteria ($N = 32$); mean age: 43.3 (S.D. = 10.2) years, % male (100%)	DSM-III-R, BPRS and SANS criteria for relapse	PLES	Spearman rank correlation	SLEs were negatively correlated with number of episodes ($p < 0.05$). The number of life events and years of illness were negatively correlated (Spearman's rank correlation $Z = -1.98$; $p < 0.05$)
Hultman et al. (1997), Sweden	Prospective cohort study	Schizophrenia patients meeting DSM-III criteria ($N = 42$); mean age: 32.3 (S.D. = 8.3) years, % male (79%)	Exacerbation or return of schizophrenia symptoms that required inpatient care or an expansion or initiation of out-patient care	LEDS	*t* tests for independent samples were performed. Spearman rank correlation was used for ordinal data and Wilcoxon rank-sum test as the non-parametric measure	There was a significant increase in SLE frequency 3 weeks before relapse compared to baseline frequency, $t(11,3) = 2.25$, $p < 0.05$ for the relapsing patients compared to non-relapsing patients
Pallanti et al. (1997), Italy	Prospective cohort study	Schizophrenia patients meeting DSM-III-R criteria ($N = 41$); mean age: 23.7 (S.D. = 3.6) years % male (76%)	DSM III criteria for illness relapse	PLES	McNemar's test	The magnitude of SLEs, particularly independent ones, increased in the 13 weeks before relapse, increasing especially during the 4 weeks before the psychotic episodes. Life event score was

						significantly different from preceding 1-month period (paired *t* test; $t = 3.21$, df = 40, $p < 0.01$)
Das et al. (1997), India	Retrospective case-control design	Schizophrenia patients meeting DSM-III-R criteria ($N = 60$) (30 relapsed and 30 stable)	DSM-III-R criteria for illness relapse	PSLES	For comparison of means Student's *t* test was performed. For non-parametric parameters, χ^2 was performed. Stepwise multiple regression was also performed	Significantly more SLEs in relapsed compared to stable group (23 *v.* 16) ($\chi^2 = 3.95$; df = 1, $p < 0.05$). Comparison of occurrence of undesirable life events showed that significantly more relapsers had undesirable life events than the stable group (18 relapsed *v.* 9 stable patients) ($\chi^2 = 4.31$, df = 1, $p < 0.05$)
Hirsch et al. (1996), UK	Prospective design including a 9-month randomized controlled trial	Schizophrenia patients meeting DSM-III-R criteria ($N = 71$); mean age: 45.2; % male (41%)	DSM- III R criteria for illness relapse.	LEDS	Proportional hazards regression model	SLEs made a significant cumulative contribution over time ($p < 0.05$) to the risk of relapse
McPherson et al. (1993), New Zealand	Prospective cohort study	Bipolar affective disorder patients meeting SADS-L criteria ($N = 58$); mean age: 37 years (range 18–64 years), % male (58%)	SADS-L criteria for illness relapse	Interview for Recent Life Events	Cox's proportional hazard model	The mean number of SLEs in the 3-month period prior relapse was 0.62 for patients and 0.64 for controls, $t = 0.15$, this was not significant. There was a non-significant pattern of more SLEs in the third months before relapse than in the control months, 0.3 for patients, 0.22 for controls, $t = 1.14$
Nuechterlein et al. (1992), USA	Prospective cohort study	Schizophrenia patients meeting RDC criteria ($N = 30$).[†1]	RDC criteria for illness relapse	PERI-LE	*t* test and McNemar's test	McNemar test showed significantly more independent SLEs in the month before relapse (mean = 0.73; S.D. = 1.00) compared with an analogous month for the same patients who did not relapse (mean = 0.07, S.D. = 0.24; $f = 2.32$; df = 10; $p < 0.025$; one-tailed, paired test)
Hunt et al. (1992), England	Prospective cohort study	Bipolar affective disorder patients meeting SADS criteria ($N = 62$); mean age: 43 (age range from 26 to 69) years, % male (25.8%)	SADS and RDC criteria for illness relapse	Interview for Recent Life Events	Mann–Whitney *U* test to look at events in 3 months prior to relapse. McNemar's test to look at events in 1-month period prior to relapse	Significantly more SLEs in 3 months prior to relapse in relapsed than non-relapsed (mean number of events = 0.85 *v.* 0.51), ($p < 0.001$). The number of SLEs also significantly higher in 1 month prior to relapse in relapse group *v.* non-relapsed ($p = 0.02$). 20 relapsing patients ($n = 52$) reported an event compared to 23 non-relapsed ($n = 144$) $\chi^2 = 10$, $p < 0.001$)

(*Continued*)

Table 1. (*Continued.*)

Authors (date) location	Design	Participants	Relapse measurement	Life events measurement	Statistical test used	Main findings
Ellicott et al. (1990), USA	Prospective cohort study	Bipolar I and II patients meeting DSM III criteria ($N = 61$); mean age: 39.6 (s.d. ± 10.2) years, % male (45.9%)	DSM III criteria for illness relapse	Life stress assessment	Cox's proportional hazards model	Stress was defined on a scale of 1 (lowest level of stress) to 4 (highest level of stress). Patients with highest levels of stress had a risk 4.53 times higher than the patients without stress. Relative hazard for relapse at various levels of stress was 1.08 for stress level 2, coefficient: 0.07, s.e.: 0.60. t (df = 25)b: 0.12. Relative hazard for stress level 3 was 0.91, coefficient: −0.10, s.e.:0.63, t (df = 25)b: −0.15. Finally, for stress level 4 the relative hazard was 4.53, coefficient: 1.51, s.e.: 044, t(df = 25)b: 3.41
Malla et al. (1990), Canada	Prospective cohort study	Schizophrenia patients meeting DSM-III-R criteria ($N = 22$); mean age: 26.6 years for male patients and 40.2 years for females, % males (57%)	Re-emergence of positive symptoms for at least one week and a Global Assessment Score dropping below 50	PERI	t test using a two-tailed t test statistic	Over the 1-year period the relapsed subjects ($n = 7$) experienced more SLEs compared to the non-relapsed group (7.3 *v.* 5.8). This failed to reach significance (t-value 2.06, df = 9.4, 2-tail prob. <0.06). More independent events in the relapsed group in the 3-month period prior to relapse compared to the other 3-month periods during the 1 year of follow-up (1.9 *v.* 1.1), but this difference failed to reach significance ($p < 0.06$)
Ventura et al. (1989), USA	Prospective cohort study	Schizophrenia patients meeting DSM-III criteria ($N = 30$); mean age: 23.2 (s.d. = 3.5); % male (73%)	DSM-III criteria for illness relapse	PER-LE	t test	Significantly more SLEs in 1 month prior to relapse (M = 1.05, s.d. = 1.38) compared to non-relapse period ($M = 0.15$, s.d. = 0.48), $t(10) = 2.74$, $p <$ 0.025, one-tailed, paired test
Aronson and Shuukla, (1987), USA	Retrospective case–control design	Bipolar patients meeting DSM-III criteria ($N = 30$)20 of whom were controls and 10 who relapsedp); mean age of relapsed: 37.5 (s.d. = 14.2) years, mean age of controls: 44 (s.d. = 14.8) years; % males (80% of relapsed and 80% of non-relapsed)	DSM III criteria for illness relapse	Hurricane Gloria	Students t test and the McNemar test for continuous variables and χ^2 tests for dichotomous data	This was a significant increase in the number of acutely relapsing patients, following Hurricane Gloria, from four to 14, confirmed by the McNemar test of symmetry ($x = 10\,000$, df = 1, $p = 0.0016$)
Al Khani et al. (1986), Saudi Arabia	Retrospective case–control design	Schizophrenia patients meeting PSE criteria ($N = 48$ schizophrenia patients and 62 controls); mean age	PSE criteria for relapse	WHO Life Events Schedule	t test	Female patients had on average 2.36 SLEs compared to 1.04 in controls. Significant at $p = 0.014$,

		of controls: 26.8 years; mean age of schizophrenia patients: 28.5 years, for controls and 28.5years for schizophrenia patients; % males (54.2% of schizophrenic patients, 61.3% of controls)				1 df. However, SLEs were associated with onset rather than relapse, no significant association found for relapse
Leff et al. (1983), UK	Randomized controlled trial	Schizophrenia patients meeting PSE criteria ($N = 14$) (6 of whom relapsed and 8 of whom did not relapse); mean age: 34 years for 8 well patients and 29 years for relapsed patients; % male (50%)	PSE criteria for illness relapse	Brown and Birley's Life Events Manual	Parametric measures	No significant difference in SLEs between relapsed and non-relapsed in 3-week period. However, the exclusion of events with a short-term threat rating of 4, representing a trivial threat or none at all, resulted in the emergence of a significant difference in the proportions of well and relapsed patients experiencing a life event in the 3 weeks before interview or relapse ($p = 0.049$)
Birley and Brown (1970), UK	Retrospective case–control	Psychosis patients meeting psychiatric classification for relapse by Wing et al. (1974) ($N = 50$), healthy controls ($N = 325$); age of schizophrenia population ranged from 15 to 71 years; % males (48% of schizophrenia patients)	Readmission to hospital	Retrospective interview whereby they had to recall recent life events from the past 4 months	*t* test	SLEs occurred with increasing frequency in the period leading up to the onset or exacerbation of psychotic symptoms in schizophrenia ($p < 0.01$). These results held true for all events, including independent events, not secondary to illness

[†]The notes appear after the main text.

[1]As these data are part of a wider trial we do not have the specific demographics for these 30 patients but rather the 106 schizophrenic patients taking part in overall trial, mean age: 23.3 years; % male (82%).

SLE, stressful life events; PSLES, Presumptive Stressful Life Events Scale; QBP-NL, Questionnaire for Bipolar Disorder; PANSS, Positive and Negative Syndrome Scale; PLES, Paykel Life Events Schedule; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; LEDS, Life Event and Difficulty Schedule; SADS, Schedule for Affective Disorders and Schizophrenia, lifetime version (SADS-L); PERI-LE, Psychiatric Epidemiology Research Interview for Life Events; PSE, Present State Examination; S.D., standard deviation; S.E., standard error.

et al., 2018; Draman et al., 2005; Malla, Cortese, Shaw, & Ginsberg, 1990; McPherson et al., 1993).

Measurement of life events

Of the 22 studies that employed checklists to assess life event exposure, the most commonly employed was the Paykel's Interview for Recent Life Events (Paykel, 1997) which was included in six studies. Five studies used the Presumptive Stressful Life Events Scale or adapted versions of the scale [PSLES: (Singh, Kaur, & Kaur, 1984)], three studies used the Psychiatric Epidemiology Research Interview [PERI: life-event schedule (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978)], two studies used the Life Event and Difficulty Schedule [LEDS: (Brown, 1989)], one study used the World Health Organization Life Events Scale (WHO, 1973), while the remaining six studies used standardized interviews and questionnaires, list of threatening experiences questionnaires, life stress assessments and life event manuals (Birley & Brown, 1970; Draman et al., 2005; Ellicott et al., 1990; Hui et al., 2016; Leff et al., 1983; Simhandl et al., 2015).

Of the different life events scales used, the number of different life events assessed across these measures ranged from a single event (hurricane) (Aronson & Shukla, 1987) to 102 different events (Dohrenwend et al., 1978). Items commonly assessed across multiple measures included, but were not limited to, death of a loved one, financial difficulties, marital problems, somatic illness and illness within the family. Further, the measurement of certain life events varied between studies. For example, the criteria relating to the life event 'bereavement' varied between studies. In some instances the category 'bereavement' included solely bereavement of a first-degree relative (Hunt et al., 1992) whereas in other instances the category 'bereavement' included the death of any close family member (Subramanian et al., 2017). The latter question is broader so perhaps more participants could identify.

Thirteen studies explicitly made a distinction between the dependent and independent life events, with 10 of these studies finding a significant association between independent life events and psychotic relapse (Aronson & Shukla, 1987; Birley & Brown, 1970; Christensen et al., 2003; Hirsch et al., 1996; Hultman et al., 1997; Hunt et al., 1992; Leff et al., 1983; Nuechterlein et al., 1992; Pallanti et al., 1997; Ventura et al., 1989), indicating that the observed association is not restricted to life events occurring in the context of illness.

Relapse and psychosis measurements

Relapse measurement varied across studies. One study defined relapse as readmission or a return of symptoms (Simhandl et al., 2015); three studies defined relapse as a return of symptoms requiring hospitalization (Birley & Brown, 1970; Hultman et al., 1997; Sam et al., 2019); and the remaining 20 studies defined relapse as a return of symptoms. Various scales were used to measure a return of psychotic symptoms including: the DSM III criteria (Kendell, 1980); the DSM IV criteria (Kutchins & Kirk, 1995); the Schedule for Affective Disorders and Schizophrenia (Endicott & Spitzer, 1978); the Global Assessment Scores (Kutchins & Kirk, 1995); the Presumptive Stressful Events Scale (Singh, Kaur, & Kaur, 1984); ICD-10 criteria (WHO, 2011); the National Institute of Mental Health-Life Chart Methodology Clinician Retrospective Chart (Roy-Byrne, Post, Uhde, Porcu, & Davis, 1985); the Neuropsychiatric Interview Plus (MINI) (Dols et al., 2018); the Brief Psychiatric Rating Scale (Overall & Gorham, 1962); the Scale for the Assessment of Negative Symptoms (Andreasen, 1989), Hamilton Depression Rating Scale (Hamilton, 1980), the Newcastle Depression Rating Scale (Carney, Roth, & Garside, 1965), the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998); and the Bech–Rafaelsen Mania Rating Scale (Bech, Bolwig, Kramp, & Rafaelsen, 1979).

Of the 19 studies defining relapse as a return of psychotic symptoms, 14 studies (74%) found a significant association between stressful life events and relapse (Aronson & Shukla, 1987; Castine et al., 1998; Chabungbam et al., 2007; Christensen et al., 2003; Das et al., 1997; Ellicott et al., 1990; Hirsch et al., 1996; Hui et al., 2016; Hunt et al., 1992; Leff et al., 1983; Nuechterlein et al., 1992; Pallanti et al., 1997; Subramanian et al., 2017; Ventura et al., 1989), whereas five studies did not find a signficant association (Al Khani, Bebbington, Watson, & House, 1986; Dols et al. 2018; Draman at al., 2005; Malla, Cortese, Shaw, & Ginsberg, 1990; McPherson et al., 1993). The one study defining relapse as readmission or a return of symptoms found a positive association between stressful life events and relapse (Simhandl et al., 2015). The three studies defining relapse as a return of symptoms requiring hospitalization all found a significant association between stressful life events and relapse (Birley & Brown, 1970; Hultman et al., 1997; Sam et al., 2019). Whilst this tentatively suggests that non-significant associations were only found in studies that defined relapse on the basis of symptoms only (as opposed to hospitalization), the smaller number of studies in the latter group prevents us from drawing this conclusion.

Diagnosis

Clinical diagnosis varied between studies. Fourteen studies included participants with a diagnosis of schizophrenia, psychosis or schizoaffective psychosis, of these, 11 studies (79%) found a significant association between stressful life events and relapse (Birley & Brown, 1970; Castine et al., 1998; Chabungbam et al., 2007; Das et al., 1997; Dols et al., 2018; Hirsch et al., 1996; Hui et al., 2016; Hultman et al., 1997; Leff et al., 1983; Nuechterlein et al., 1992; Pallanti et al., 1997; Ventura et al., 1989). Eleven studies included participants with bipolar I or bipolar II disorder, of these, nine found a significant association between stressful life events and relapse (Aronson & Shukla, 1987; Christensen et al., 2003; Ellicott et al., 1990; Hunt et al., 1992; Sam et al., 2019; Simhandl et al., 2015; Subramanian et al., 2017). It does not therefore appear that diagnosis had any impact on whether the association between life events and relapse was significant.

Study design

Fourteen studies used a prospective design, of which 11 (79%) found a significant association between life events and relapse (Christensen et al., 2003; Dols et al., 2018; Ellicott et al., 1990; Hirsch et al., 1996; Hui et al., 2016; Hultman et al., 1997; Hunt et al., 1992; Leff et al., 1983; Malla et al., 1990; McPherson et al., 1993; Nuechterlein et al., 1992; Pallanti et al., 1997; Simhandl et al., 2015; Ventura et al., 1989). The follow-up period for these studies ranged from 9 months to 6 years (mean 2.5 years). Three studies used a cross-sectional design, all of these studies (100%) found a significant association between life events and relapse (Castine et al., 1998; Sam et al., 2019; Subramanian et al., 2017). The remaining six studies used a retrospective design, four of these studies (67%) found a

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significant association between life events and relapse (Al Khani et al., 1986; Aronson & Shukla, 1987; Birley & Brown, 1970; Chabungbam et al., 2007; Das et al., 1997; Draman et al., 2005). Overall, it appears that there is no relationship between study design and whether an association between life events and relapse was found.

Time frame for stressful life events and relapse

Of those studies reporting a positive association between adult stressful life events and psychotic relapse, nine studies (39%) reported that life events occurring in the month before relapse had a significant association with relapse (Aronson & Shukla, 1987; Castine et al., 1998; Hui et al., 2016; Hultman et al., 1997; Hunt et al., 1992; Leff et al., 1983; Nuechterlein et al., 1992; Sam et al., 2019; Ventura et al., 1989). One study (4%) reported that life events occurring in the 3 months prior to relapse had a significant association with relapse (Christensen et al., 2003). The remaining 13 studies (57%) neitherstated when most life events occurred nor assessed life events in relation to time frames over the course of illness or around outcome events of interest. Hence, it is difficult to draw conclusions regarding windows of vulnerability to relapse following exposure to life events or whether time frame may indeed moderate the association between life events and relapse.

Confounders

It is certainly worth noting that all five of the studies which did not find a significant association between life events and relapse did not adjust for confounders. This may show that perhaps other factors are more important in causing relapse and only when these are adjusted for can we see the true association between life events and psychotic relapse (Al Khani et al., 1986; Dols et al., 2018; Draman et al., 2005; Malla et al., 1990; McPherson et al., 1993).

Quality score

Quality scores are presented in Table 2. The mean quality score across all studies was 11.74 (range: 5–18), indicating modest quality. Eighty-three per cent of studies used a standardized life events checklist delivered via semi-structured interview and 87% of studies measured relapse using objective tools. In general, high scores were awarded for the measurement of psychosis and the measurement of relapse. In contrast, few studies were awarded points for adjustment for confounding variable(s) or conducting in-depth statistical analyses. Only five studies adjusted for basic demographics and/or potential risk factors, such as drug and alcohol use, social support and medication adherence (Al Khani, Bebbington, Watson, & House, 1986; Chabungbam et al., 2007; Hirsch et al., 1996; Hui et al., 2016; Simhandl et al., 2015).

There did not appear to be an effect of study quality score on the occurrence of relapse. The mean quality score for studies finding a non-significant association between life events and relapse scores (mean quality score: 10.6, range: 9–13) was broadly similar to the mean quality score for studies reporting a significant association between life events and relapse (mean quality score: 11.8, range: 5–18) and there was substantial overlap in the ranges of these scores.

A median split based on quality ratings found that 67% of studies below the median quality score found a significant association between life events and relapse whereas 86% of studies above the median quality score found a significant association between life events and relapse [non-significant difference, χ^2=(1)1.168, $p = 0.280$].

Discussion

Findings and interpretation

The aim of this systematic review was to qualitatively summarize currently available evidence regarding the relationship between adult stressful life events and relapse of psychosis in those with an established psychotic disorder. We found that 18 of the 23 included studies provided evidence of an association between adult stressful life events (occurring after illness onset) and subsequent relapse. Moreover, there were no discernible differences between studies that found a significant association between life events and relapse and those that did not in terms of relapse measurement, diagnosis, study design, quality score or whether the life event was an independent or dependent life event. However, as the majority of studies did not examine the time frame between adult stressful life events and psychotic relapse, we cannot draw conclusions regarding the proximity of life events to relapse occurrence and recommend that future studies investigate whether life events more frequently occur close to relapse.

The included studies measured multiple types of adult stressful life events including family conflict, bereavement, work conflict, education, financial issues, social problems, marital conflict, marriage, moving house, illness and injury, and natural disasters. Of the studies reporting a significant association between stressful life events and relapse, family conflict (Christensen et al., 2003; Sam et al., 2019; Subramanian et al., 2017), financial loss (Sam et al., 2019), unemployment (Hultman et al., 1997; Sam et al., 2019), somatic illness (Christensen et al., 2003; Hunt et al., 1992) and illness within the family (Hultman et al., 1997; Hunt et al., 1992; Sam et al., 2019) were rated as the most common stressful life events occurring prior to relapse. It is important for both patients and their care teams to be mindful of these common stressful life events so that help can be given to mitigate their effects soon after they occur. We cannot, however, say that these most commonly reported events are necessarily the most important, particularly as many studies used structured checklists which only capture specific events (i.e. there may be other events experienced by patients that were not measured but were nonetheless important for relapse). Future work could investigate whether certain life events are more important in causing psychotic relapse than others. It may be that this varies considerably across patients such that one event is particularly salient to some patients but not others.

Of the included studies, 61% used a prospective cohort (longitudinal) design, the mean quality score was 11.74 out of a possible 18, and only 22% of studies adjusted for confounders. An important conclusion drawn from the present review is the need for studies employing better methodological approaches, particularly longitudinal designs, as well as consideration of potential confounders that may provide more robust evidence and therefore meaningfully inform practice and policy.

Despite the modest quality of included studies, our findings suggest that adult stressful life events, occurring after illness onset, may have a triggering role in increasing the risk of psychotic relapse. However, it is important to note that all studies included in this review were observational and are therefore unable to assess whether the association is causal in nature.

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Table 2. Study quality rating

	Agreement to participate (Max 3)	Sample size (Max 2)	Life event measurement quality (Max 2)	Psychosis measurement quality (Max 2)	Adjustment for potential confounders (Max 2)	Relapse measurement quality (Max 2)	Data collection valid (Max 2)	Data collection reliable (Max 2)	Statistical analysis (Max 2)	Total score (Max 18)
Sam et al. (2019)	0	2	2	2	0	2	2	2	1	13
Dols et al. (2018)	2	2	1	2	0	0	2	2	1	12
Subramanian et al. (2017)	2	2	2	2	0	2	2	2	2	16
Hui et al. (2016)	2	2	2	2	2	2	2	2	2	18
Simhandl et al. (2015)	2	2	1	2	2	2	2	1	2	16
Chabungbam et al. (2007)	0	0	2	2	1	2	2	2	1	12
Draman et al. (2005)	0	2	1	1	0	2	1	1	0	8
Christensen et al. (2003)	0	1	2	0	0	2	2	2	1	10
Castine et al. (1998)	1	0	2	2	0	2	2	2	1	12
Hultman et al. (1997)	2	0	2	2	0	2	2	2	2	14
Das et al. (1997)	0	1	2	0	0	2	2	2	1	10
Pallanti et al. (1997)	0	1	2	2	0	2	2	2	1	12
Hirsch et al. (1996)	0	1	2	2	1	2	2	2	2	15
McPherson et al. (1993)	0	1	2	2	0	2	2	2	2	13
Nuechterlein et al. (1992)	0	0	2	2	0	0	0	0	1	5
Hunt et al. (1992)	2	1	2	2	0	2	0	0	1	10
Ellicott et al. (1990)	0	1	2	2	0	2	2	2	1	12
Malla et al. (1990)	0	0	2	2	0	2	2	2	1	11
Ventura et al. (1989)	2	0	2	2	0	2	2	2	1	13
Aronson et al. (1987)	0	0	0	2	1	2	0	0	1	6
Al Khani et al. (1986)	0	0	2	1	0	0	2	2	2	9
Leff et al. (1983)	0	0	2	2	0	2	2	2	1	11
Birley & Brown (1970)	0	1	2	2	0	2	2	2	1	12

Nevertheless, the studies reviewed (particularly prospective studies measuring life events prior to relapse onset) indicate a temporal relationship between exposure to stressful life events and subsequent relapse amongst psychosis subjects.

It has long been assumed that stressful life events are relevant to the course of psychosis, and stress has been considered as a precipitating factor in aetiological theories of schizophrenia (Howes & Murray, 2014); moreover, plausible mechanisms have been proposed to explain this relationship. For example, stressful life events may increase the risk of psychotic relapse via activation of the hypothalamic–pituitary–adrenal (HPA) axis. The neural diathesis stress model proposed by Walker and Diforio (1997) and updated by Pruessner, Cullen, Aas, and Walker (2017) proposes that stress exposure may trigger or exacerbate psychotic symptoms by augmenting dopamine activity, particularly in the subcortical region of the limbic circuitry. The updated model also suggests that the HPA axis interacts with the immune-inflammatory system (Pruessner et al., 2017). In support of the model, patients with psychosis and those at increased risk for the disorder (due to a family history of illness or clinical features) have been found to show HPA axis abnormalities, including elevated basal and diurnal cortisol, a blunted cortisol awakening response and pituitary volume abnormalities (Berger et al., 2016; Borges, Gayer-Anderson, & Mondelli, 2013; Chaumette et al., 2016; Cullen et al., 2014; Day et al., 2014; Girshkin, Matheson, Shepherd, & Green, 2014; Nordholm et al., 2013; Saunders, Mondelli, & Cullen, 2019). However, a recent meta-analysis of 134 effect sizes from 18 studies (Cullen et al., 2020) found that, in psychosis spectrum groups and healthy controls, psychosocial stressors were only weakly (and not significantly) correlated with cortisol measures. Whilst these findings imply that the HPA abnormalities characterising psychosis spectrum groups are not driven by psychosocial stressors, the authors identified a range of methodological issues that may have obscured the ability to detect significant associations. Thus, further research, accounting for these methodological issues, is needed to determine whether the relationship between life events and relapse might be mediated by the HPA axis.

Implications

The findings from this review suggest that adult stressful life events are associated with psychosis relapse and may increase the risk of psychosis relapse. Future research could investigate novel treatments that mitigate the harm from stressful life events and thus prevent psychosis relapse. For example, newly-developed methods for allowing patients to monitor life events by the use of smartphone apps could be beneficial in targeting relapse. Smartphone apps are emerging as a method to monitor psychosis symptoms as relapse predictors (Eisner et al., 2019). A future target of these smartphone apps could be the addition of life event monitoring. It may also be wise to educate patients, carers and healthcare professionals about the role of stressful life events and to offer practical and emotional support to patients who have experienced stressful life events.

Limitations

Several limitations of the present systematic review are worth noting. Firstly, in our systematic search, a variety of terms to describe life events were used, however, we excluded the word 'stress' as this yielded too many irrelevant results. Relevant articles may subsequently have been excluded. However, reference lists of all relevant studies were hand searched to ensure all pertinent articles were included and to overcome this limitation.

Secondly, there was methodological heterogeneity between the studies which made it difficult to compare and integrate results from studies that were included in this review. Studies used different criteria to measure psychotic relapse and recent life experiences, differed in study design, and recruited participants with different diagnoses (schizophrenia and psychotic disorders, and bipolar disorder). This may have made it difficult to separate the potential confounding effect of illness diagnosis on outcome (Mallett, Hagen-Zanker, Slater, & Duvendack, 2012). As stated previously, these differences meant the data could not be combined with a quantitative synthesis.

Thirdly, many studies in the present review did not account for potential confounding variables, future work should ensure confounders are accounted for. Fourthly, many studies used retrospective measures which may make them susceptible to recall bias. This can limit validity, if there is a long gap between the event and recall (Howard, 2011). However, this may not have been an issue as only recent adult stressful life events were analysed.

Lastly, we should note that while the included studies may suggest that life events likely have a causal role in subsequent relapse, evidence summarized here is based on observational rather than experimental data and also predominantly from cross-sectional rather than longitudinal studies. Hence, we cannot demonstrate a causal relationship, so an alternative suggestion is that life events and relapse simply co-occur at the same time. However, as the included studies examined life events occurring prior to the psychotic relapse, and longitudinal studies have demonstrated that life events increase the risk of illness onset (Beards et al., 2013), this lends support to the notion that life events may have a causal role in psychotic relapse.

Conclusion

In conclusion, there may be a link between recent adult stressful life events and relapse of psychosis. These findings may have clinical implications via informing the development of ways to mitigate the harm from stressful life events and thereby reduce the risk of psychotic relapse.

Financial support. AEC was supported by a Sir Henry Wellcome Postdoctoral Fellowship (107395/Z/15/Z) and a NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (28336). SB has been supported by an NIHR Clinician Scientist Award (NIHR CS-11-001), and the NIHR Efficacy and Mechanism Evaluation grant (16/126/53). The authors acknowledge infrastructure support from the NIHR Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Conflict of interest. The authors declare no conflict of interest.

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Appendix 1. A list of articles excluded after full-text review, with reasons

Study	Reason for Exclusion
Grattan, R. E., & Linscott, R. J. (2019). Components of schizophrenia liability affect the growth of psychological stress sensitivity following major life events. *Schizophrenia Research*, 212, 134–139. https://doi.org/10.1016/j.schres.2019.07.056	1
Cohen, C. I., Palekar, N., Barker, J., & Ramirez, P. M. (2012). The relationship between trauma and clinical outcome variables among older adults with schizophrenia spectrum disorders. *American Journal of Geriatric Psychiatry*, 20(5), 408–415. https://doi.org/10.1097/JGP.0b013e318211817e	1
Gatov, E., Koziel, N., Kurdyak, P., Saunders, N. R., Chiu, M., Lebenbaum, M., … Vigod, S. N. (2019). Epidemiology of Interpersonal Trauma among Women and Men Psychiatric Inpatients: A Population-Based Study. *Canadian Journal of Psychiatry*. https://doi.org/10.1177/0706743719861374	2
Owens, D. C., Johnstone, E. C., Miller, P., Fiona Macmillan, J., & Crow, T. J. (2010). Duration of untreated illness and outcome in schizophrenia: Test of predictions in relation to relapse risk. *British Journal of Psychiatry*, 196(4), 296–301. https://doi.org/10.1192/bjp.bp.109.067694	2
Mansueto, G., & Faravelli, C. (2017). Recent life events and psychosis: The role of childhood adversities. *Psychiatry Research*, 256, 111–117. https://doi.org/10.1016/j.psychres.2017.06.042	2
Villard, E., Védie, C., Lenoir, C., & Faure, M. (2015). Schizophrenic relapses: Correlation between life events and rehospitalization. *Annales Medico-Psychologiques*, 173(5), 443–448. https://doi.org/10.1016/j.amp.2015.04.005	3
Rusaka, M., & Rancans, E. (2014). First-episode acute and transient psychotic disorder in Latvia: A 6-year follow-up study. *Nordic Journal of Psychiatry*, 68(1), 24–29. https://doi.org/10.3109/08039488.2012.761726	2
Liemburg, E. J., Castelein, S., Van Es, F., Scholte-Stalenhoef, A. N., Van De Willige, G., Smid, H., … Bruggeman, R. (2014). The Psychosis Recent Onset GRoningen Survey (PROGR-S): Defining dimensions and improving outcomes in early psychosis. *PLoS ONE*, 9(11). https://doi.org/10.1371/journal.pone.0113521	1
Consoli, A., Brunelle, J., Bodeau, N., Louët, E., Deniau, E., Perisse, D., … Cohen, D. (2014). Diagnostic transition towards schizophrenia in adolescents with severe bipolar disorder type I: An 8-year follow-up study. *Schizophrenia Research*, 159(2–3), 284–291. https://doi.org/10.1016/j.schres.2014.08.010	4
Sariah, A. E., Outwater, A. H., & Malima, K. I. Y. (2014). Risk and protective factors for relapse among Individuals with Schizophrenia: A Qualitative Study in Dar es Salaam, Tanzania. *BMC Psychiatry*, 14(1). https://doi.org/10.1186/s12888-014-0240-9	3
Rusaka, M., & Rancans, E. (2014). A prospective follow-up study of first-episode acute transient psychotic disorder in Latvia. *Annals of General Psychiatry*, 13(1). https://doi.org/10.1186/1744-859X-13-4	2
Fallon, P., & Dursun, S. M. (2011). A naturalistic controlled study of relapsing schizophrenic patients with tardive dyskinesia and supersensitivity psychosis. *Journal of Psychopharmacology*, 25(6), 755–762. https://doi.org/10.1177/0269881109359097	3
Fallon, P. (2009). The role of intrusive and other recent life events on symptomatology in relapses of schizophrenia: A community nursing investigation. *Journal of Psychiatric and Mental Health Nursing*, 16(8), 685–693. https://doi.org/10.1111/j.1365-2850.2009.01451.x	3
Docherty, N. M., St-Hilaire, A., Aakre, J. M., & Seghers, J. P. (2009). Life events and high-trait reactivity together predict psychotic symptom increases in Schizophrenia. *Schizophrenia Bulletin*, 35(3), 638–645. https://doi.org/10.1093/schbul/sbn002	1
Kim, E. Y., Miklowitz, D. J., Biuckians, A., & Mullen, K. (2007). Life stress and the course of early-onset bipolar disorder. *Journal of Affective Disorders*, 99(1–3), 37–44. https://doi.org/10.1016/j.jad.2006.08.022	1
Liu, X. J., & Zhang, Y. L. (2005). Early signs and related factors of schizophrenia relapse during the convalescent period. *Chinese Journal of Clinical Rehabilitation*, 9(32), 88–89.	5
Van Os, J., Fahy, T. A., Bebbington, P., Jones, P., Wilkins, S., Sham, P., … Murray, R. (1994). The Influence of Life Events on the Subsequent Course of Psychotic Illness A Prospective Follow-Up of the Camberwell Collaborative Psychosis Study. *Psychological Medicine*, 24(2), 503–513. https://doi.org/10.1017/S003329170002746X	2
Marneros, A., Rohde, A., & Deister, A. (1993). Factors influencing the long-term outcome of schizoaffective disorders. *Psychopathology*, 26(3–4), 215–224. https://doi.org/10.1159/000284825	1, 2
Ventura, J., Nuechterlein, K. H., Pederson Hardesty, J., & Gitlin, M. (1992). Life events and schizophrenic relapse after withdrawal of medication. *British Journal of Psychiatry*, 161(NOV.), 615–620. https://doi.org/10.1192/bjp.161.5.615	6[a]
Bartkó, G., Mayláth, E., & Herczeg, I. (1987). Comparative study of schizophrenic patients relapsed on and off medication. *Psychiatry Research*, 22(3), 221–227. https://doi.org/10.1016/0165-1781(87)90037-0	7
Edward Lahniers, C., & White, K. (1976). Changes in environmental life events and their relationship to psychiatric hospital admissions. *Journal of Nervous and Mental Disease*, 163(3), 154–158. https://doi.org/10.1097/00005053-197609000-00002	4
Kulhara, P., Avasthi, A., Gupta, N., Das, M. K., Nehra, R., Rao, S. A., & Singh, G. (1998). Life events and social support in married schizophrenics. *Indian Journal of Psychiatry*, 40(4), 376–37682.	1
Hammen, C., & Gitlin, M. (1997). Stress reactivity in bipolar patients and its relation to prior history of disorder. *American Journal of Psychiatry*, 154(6), 856–857. https://doi.org/10.1176/ajp.154.6.856	3
Nuechterlein, K. H., Dawson, M. E., Ventura, J., Gitlin, M., Subotnik, K. L., Snyder, K. S., … Bartzokis, G. (1994). The vulnerability/stress model of schizophrenic relapse: a longitudinal study. *Acta Psychiatrica Scandinavica*, 89, 58–64. https://doi.org/10.1111/j.1600-0447.1994.tb05867.x	6[b]

1. Did not measure relapse.
2. Measured stressful life events before the onset of the psychiatric disorder.
3. Does not provide a statistical analysis.
4. Looked at relapse and life events separately.
5. Life events measured but unclear whether these events were 'stressful'.
6. Uses same dataset as a paper that meet eligibility criteria.
7. Association between life events and relapse only examined in relation to other factors.

[a]This paper provides an evaluation of the following paper that was included in the systematic review (Ventura et al., 1989).
[b]This paper provides an evaluation of the following paper that was included in the systematic review (Nuechterlein et al., 1992).