Psychological Medicine

cambridge.org/psm

A systematic review on mediators between adversity and psychosis: potential targets for treatment

Luis Alameda[1,2,3,4], Victoria Rodriguez[1], Ewan Carr[5], Monica Aas[1,6], Giulia Trotta[1], Paolo Marino[1], Natasha Vorontsova[7], Andrés Herane-Vives[8,9], Romayne Gadelrab[8], Edoardo Spinazzola[1,10], Marta Di Forti[1,11], Craig Morgan[12] and Robin M Murray[1]

[1]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [2]Service of General Psychiatry, Treatment and Early Intervention in Psychosis Program, Lausanne University Hospital (CHUV), CH-1008 Lausanne, Switzerland; [3]Department of Psychiatry, Hospital Universitario Virgen del Rocío, Universidad de Sevilla, Spain; [4]Instituto de Investigacion Sanitaria de Sevilla, IBiS, Spain; [5]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [6]Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway; [7]Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [8]Department of Psychological Medicine, Centre for Affective Disorders, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [9]Departamento de Clínicas, Facultad de Medicina, Universidad Católica del Norte, Coquimbo, Chile; [10]Psychiatry Residency Training Program, Faculty of Medicine and Psychology, Sapienza University of Rome, Italy; [11]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK and [12]ESRC Centre for Society and Mental Health, King's College London, UK

Abstract

Various psychological and biological pathways have been proposed as mediators between childhood adversity (CA) and psychosis. A systematic review of the evidence in this domain is needed. Our aim is to systematically review the evidence on psychological and biological mediators between CA and psychosis across the psychosis spectrum. This review followed PRISMA guidelines. Articles published between 1979 and July 2019 were identified through a literature search in OVID (PsychINFO, Medline and Embase) and Cochrane Libraries. The evidence by each analysis and each study is presented by group of mediator categories found. The percentage of total effect mediated was calculated. Forty-eight studies were included, 21 in clinical samples and 27 in the general population (GP) with a total of 82 352 subjects from GP and 3189 from clinical studies. The quality of studies was judged as 'fair'. Our results showed (i) solid evidence of mediation between CA and psychosis by negative cognitive schemas about the self, the world and others (NS); by dissociation and other post-traumatic stress disorder symptoms; and through an affective pathway in GP but not in subjects with disorder; (iii) lack of studies exploring biological mediators. We found evidence suggesting that various overlapping and not competing pathways involving post-traumatic and mood symptoms, as well as negative cognitions contribute partially to the link between CA and psychosis. Experiences of CA, along with relevant mediators should be routinely assessed in patients with psychosis. Evidence testing efficacy of interventions targeting such mediators through cognitive behavioural approaches and/or pharmacological means is needed in future.

Review Article

Cite this article: Alameda L *et al* (2020). A systematic review on mediators between adversity and psychosis: potential targets for treatment. *Psychological Medicine* **50**, 1966–1976. https://doi.org/10.1017/S0033291720002421

Received: 24 February 2020
Revised: 12 June 2020
Accepted: 22 June 2020
First published online: 3 August 2020

Key words:
Adversity; mechanisms; mediation; psychosis

Author for correspondence:
Luis Alameda,
E-mail: laluisalameda@gmail.com

Introduction

Evidence has accumulated over the past 15 years showing that exposure to childhood adversity (CA) – in the form of abuse, neglect and bullying – is associated with increased risk of psychosis across the spectrum, from low-level experiences to disorder (Varese et al., 2012*b*). This has led to substantial research trying to understand possible underlying psychological and biological mechanisms, thus a systematic review in the topic is needed.

In terms of biological mechanisms, evidence covers dysfunction in pathways such as the stress response system (Ruby et al., 2014), dopaminergic neurotransmission (Howes, McCutcheon, Owen, & Murray, 2017), inflammation and redox dysregulation (Steullet et al., 2016), and changes in stress-related brain structures such as the amygdala or the hippocampus (Van Winkel, Van Nierop, Myin-Germeys, & Van Os, 2013). For example, it has been suggested that excessive exposure to stress might lead to an overactivation of the hypothalamic–pituitary–adrenal axis. This could be toxic for hippocampal functioning (Aas et al.,

CAMBRIDGE UNIVERSITY PRESS

2014; Teicher, Anderson, & Polcari, 2012), which might in turn contribute to the emergence of psychosis. Furthermore, acute social stress has also been found to increase striatal dopamine release in individuals with a psychotic disorder, and in individuals with CA (Howes et al., 2017). In addition, inflammatory dysfunctions as well as redox dysregulation conditions (Alameda et al., 2018; Steullet et al., 2016) have been found among individuals exposed to CA and among patients with psychosis.

Several psychological models have also been proposed to explain the relationship between CA and psychosis. These models look at the same epiphenomena from different angles and can be complementary, thus they should not be considered necessarily as competing explanations. One theory postulates that CA may lead to psychosis through a pathway of heightened emotional distress, characterised by hypersensitivity to daily-life stressors, leading to anxiety and depression (Bebbington, 2015; Myin-Germeys & van Os, 2007) and it is often called 'affective pathway to psychosis'. Another model proposes that severe forms of CA might lead to cognitive biases, such as negative schema about the self and the world, and others (NS) which, in addition to a heightened tendency to attribute experiences to external causes, might give rise to paranoia, ideas of reference (Garety, Bebbington, Fowler, Freeman, & Kuipers, 2007; Morrison, Frame, & Larkin, 2003). Another putative pathway emphasises the mediating role of post-traumatic stress disorder (PTSD)-related symptoms, such as dissociation and intrusive memories (Hardy, 2017). It is suggested that flash-backs could be interpreted as being externally generated, leading to hallucinatory experiences and hampering reality testing (Allen, Coyne, & Console, 1997; Morrison et al., 2003). Other possible mediators have been proposed such as dysfunctional attachment (Gumley, Taylor, Schwannauer, & MacBeth, 2014; Read & Gumley, 2010).

Despite the fact that several narrative reviews on the topic exist (Bebbington, 2015; Bentall et al., 2014; Freeman & Garety, 2014; Gibson, Alloy, & Ellman, 2016; Misiak et al., 2017; Morgan & Gayer-Anderson, 2016; Read, Fosse, Moskowitz, & Perry, 2014; Van Winkel et al., 2013), to date only a single systematic review has been conducted (Williams, Bucci, Berry, & Varese, 2018). Williams et al. (2018) examined psychological mediators between CA and psychosis including papers up to September 2017, which consisted of a total of 37 studies. They found evidence for a mediation by cognitive bias, by symptoms of PTSD, and by affective processes. However, this review is limited by the fact that (i) they did not analyse and discuss the evidence of all the mediation pathways tested within each study and limited to the summary of the main conclusions provided by each author; (ii) no information on the percentage of total effect mediated was systematically extracted and summarised; (iii) did not include biological mediators. The present study overcomes these limitations and includes additional papers published up to July 2019, providing an additional period of 22 months of research in the field.

Our aim is to systematically review the evidence on psychological and biological mediators between CA and psychosis across the spectrum from low-level experiences in general populations (GP) to disorder. Based on the concept of psychosis as a continuum (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), covering all the spectrum may allow a better understanding of the mediational processes operating at different stages. Results will be grouped based on existing proposed theoretical mechanisms and discussed in terms of potential treatment interventions.

Methods

Search strategy

A systematic review of the literature was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009) guidelines and was registered in PROSPERO (Moher, Booth, & Stewart, 2014) in July 2018 (registration number: CRD42018100846). The main search was conducted on MEDLINE, EMBASE and PsycINFO, through Ovid provider, and in Cochrane Libraries in June 2018 and it was updated in July 2019. We searched Medical Subjects Headings (MeSH) and keywords related to: (1) CA, (2) mediation and (3) psychosis, using the Boolean operator 'AND' (full list of search terms as well as details on the screening procedure are provided in online Supplementary Material.

Inclusion and exclusion criteria

Included studies were those that (1) examined psychological or biological mediators of the relationship between CA and (i) psychosis onset (these include case-control studies), (ii) severity of positive symptoms in patients with a psychotic disorder, in subjects at risk for psychosis [as described by the Yung et al. (2005)] or (iii) severity of attenuated psychotic symptoms (these include also studies measuring psychosis proneness and psychotic-like experiences) in the GP; (2) for clinical studies only (not for GP), psychotic disorder was defined according to Diagnostic and Statistical Manual of Mental Disorders [DSM-III, DSM-III-R, DSM-IV, DSM IV-TR (American Psychiatric Association, 1994)], or International Classification of Diseases, Ninth or Ten Revision (ICD-9, ICD-10) (World Health Organization, 1992); and (3) were performed in humans; (4) included CA occurring before age 18 and involving exposure to sexual, physical and emotional abuse, physical and emotional neglect or bullying (or equivalent experiences); (5) assessed both mediators and outcomes using validated methods and scales; (6) employed a robust method for testing mediation in the analyses and fulfilling the Baron and Kenny criteria (Hayes, 2009); used pathways analyses or structural equation models; (7) had been published as original research.

Exclusion criteria were: (1) including more than 20% of participants aged 65 years or over, in accord with others (Van Os et al., 2009); (2) being performed in homogeneous samples of specific populations (such as pregnant women or samples from forensic settings); (3) including non-psychological mediators (e.g. being exposed to later life hassles or level of education); (4) not being published in the English language.

Quality assessment and data extraction methodology

Quality assessment was carried out using the Newcastle–Ottawa Scale (Stang, 2010) for cohort studies by two independent reviewers (LA and PM). Details on the instrument items and quality assessment procedures can be found in online Supplementary Material.

The agreed quality grades of each study are presented in online Supplementary Table S1a–S1c. To summarise the evidence, we constructed Tables 1–3 and online Supplementary Table S2. We enumerated the number of studies and analyses indicating whether there was evidence for mediation or lack of mediation in clinical samples and in GP studies.

These results were extracted from the text or tables of each paper. We included all mediation analyses (i.e. distinct pathways

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

Table 1. Summary of evidence for mediators between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population

	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
Category (*N* total analyses/studies[a])	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Dissociation (43/12)	6(4)	20(6)	23%	12(6)	5(1)	70%	42%
Dysfunctional attachment (18/5)	1(1)	3(2)	25%	7(3)	7(2)	50%	44%
Affective pathway (32/15[b,c])	–	3(1)	0%	21(9)	8(5)	72%	66%
Loneliness (7/4)	1(1)	–	100%	4(3)	2(1)	66%	83%
Cognitive biases (53/21[c])	8(6)	13(5)	38%	20(8)	12(7)	62.5%	53%
Others PTSD symptoms (7/4)	5(3)	1(1)	83%	1(1)	–	100%	86%
Others[d] (10/6)	1(1)	1(1)	50%	7(3)	1(1)	87.5%	80%

[a]We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.
[b]Isvoranu et al. was only included in the articles count within but not in the analyses count.
[c]Ashford et al. was only included in the articles count but not in the analyses count.
[d]Others included anomalous self-experiences; mania; time-perspective capabilities and compulsions as mediators.

tested) from each paper, meaning the total number of analyses was greater than the number of papers. In Tables 1–3 and online Supplementary Table S2, as well as in the text we provided the 'percentage of analyses showing evidence of mediation', across all categories of mediators (see online Supplementary Material for more details). We also collected information on the percentage of total effect that was mediated, which is equivalent to the amount of mediation in each pathway tested. Figure 1 represents the percentage of the total effect mediated by each analysis for which information was available across the most meaningful categories described in the Results section. The type of adversity and outcome are also shown to have a visual representation of the pathway. As an indicative measure, the median value of all the analyses per category is also highlighted in the figure and presented in the text.

Further details on data extraction procedures can be found in online Supplementary Material and in Fig. 1 footnote. In online Supplementary Tables S1a–S1c, we also provide details on the significance of the indirect and direct effects as well as the proportion of total effect mediated in each study.

Results

We identified 48 studies that met our inclusion criteria from the 2310 studies found in the initial searches (2018 and 2019 combined) (online Supplementary Fig. S1).

Twenty-one studies were conducted in clinical samples [four in First Episode of Psychosis (FEP) or early psychosis patients (Evans, Reid, Preston, Palmier-Claus, & Sellwood, 2015; Morgan et al., 2014; Peach, Alvarez-Jimenez, Cropper, Sun, & Bendall, 2019; Sun et al., 2018), three in Ultra High Risk (UHR) patients (Appiah-Kusi et al., 2017; McDonnell, Stahl, Day, McGuire, & Valmaggia, 2018; Thompson et al., 2016), 14 in non-FEP patients (Cancel et al., 2015; Chatziioannidis et al., 2019; Choi et al., 2015; Hardy et al., 2016; Isvoranu et al., 2017; Perona-Garcelán et al., 2012; Quidé, O'Reilly, Watkeys, Carr, & Green, 2018; Schalinski et al., 2019; Steenkamp, Weijers, Gerrmann, Eurelings-Bontekoe, & Selten, 2019; Styła, Stolarski, & Szymanowska, 2019; Van Dam, Korver-Nieberg, Velthorst, Meijer, & de Haan, 2014; Varese, Barkus, & Bentall, 2012a; Weijers et al., 2018; Wickham & Bentall, 2016) 27 in GP (Ashford, Ashcroft, & Maguire, 2012; Bortolon & Raffard, 2018; Bortolon, Seillé, & Raffard, 2017; Boyda & McFeeters, 2015; Boyda, McFeeters, Dhingra, & Rhoden, 2018; Cole, Newman-Taylor, & Kennedy, 2016; Fisher, Appiah-Kusi, & Grant, 2012, 2013; Gawęda, Göritz, & Moritz, 2019; Gibson, Reeves, Cooper, Olino, & Ellman, 2019; Goodall, Rush, Grünwald, Darling, & Tiliopoulos, 2015; Jaya, Ascone, & Lincoln, 2017; Lincoln, Marin, & Jaya, 2017; Marwaha & Bebbington, 2015; Marwaha, Broome, Bebbington, Kuipers, & Freeman, 2014; McCarthy-Jones, 2018; Mętel et al., 2020; Murphy, Murphy, & Shevlin, 2015; Perona-Garcelán et al., 2014; Pinto-Gouveia, Matos, Castilho, & Xavier, 2014; Rössler, Ajdacic-Gross, Rodgers, Haker, & Müller, 2016; Sheinbaum, Kwapil, & Barrantes-Vidal, 2014; Shevlin, McElroy, & Murphy, 2015; Sitko, Bentall, Shevlin, O'Sullivan, & Sellwood, 2014; van Nierop et al., 2014; Wolke, Lereya, Fisher, Lewis, & Zammit, 2014; Yamasaki et al., 2016)]. Our review included 82 352 subjects from the GP and 3189 subjects from clinical studies. Participant ages ranged from 18.5 to 44.6 years old in clinical samples (30.4 on average) and between 9.8 and 51.7 in the GP (34.3 on average). In clinical samples, 35% of the participants were women, compared with 37% of the volunteers.

This total number of analyses excludes two studies with an extremely high number of analyses [one used a network-based approach exploring multiple connections between adversity and symptoms (Isvoranu et al., 2017), the other included up to 28 (Ashford et al., 2012)]. These studies would have distorted the numerical summaries and therefore are described narratively but are not considered in the summary tables. Overall, 170 analyses were included in this review (ranging between 1 and 12 analysis per paper).

The quality check agreement between the two raters was 81.8%. Overall, the quality was graded as 'fair' (between 4 and 7) for all studies except one, where quality was judged as 'good' (Fisher et al., 2013). Studies of biological mediators tended to be graded with lower scores failing to provide estimates of the

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

Table 2. Summary of evidence for mediators within the affective pathway category between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population

	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
Category (*N* total analyses/studies[a])	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Affective pathway (32/15)[b,c]	–	3(1)	0%	21(9)	8(5)	72%	66%
Anxiety (7/4)	–	1(1)	0%	4(2)	2(2)	66%	57%
Depression (9/6)	–	1(1)	0%	4(2)	4(3)	50%	44%
Emotional dysregulation (8/4)	–	1(1)	0%	5(2)	2(2)	71%	62.5%
Stress sensitivity/perception (5/2)	–	–	–	5(3)	–	100%	100%
Composite (2/1)	–	–	–	2(2)	–	100%	100%

[a]We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.
[b]Isvoranu et al. was only included in the articles count within but not in the analyses count.
[c]Ashford et al. was only included in the articles count but not in the analyses count.

Table 3. Summary of evidence for mediators within the cognitive biases category between adversity and psychosis in clinical samples (subjects at risk for psychosis and with psychotic disorder) and in general population

	Clinical samples Number of analyses (number of studies)			General population Number of analyses (number of studies)			Total
Category (*N* total analyses/studies)	Evidence of mediation	Null mediation	% analyses supporting mediation	Evidence of mediation	Null mediation	% analyses supporting mediation	% analyses supporting mediation
Cognitive biases (53/21)[a]	8(6)	13(5)	38%	20(8)	12(7)	62.5%	53%
Negative schemas (16/7)	5(3)	2(1)	71%	5(4)	4(1)	55.5%	62.5%
ELC (5/3)	–	–	–	4(2)	1(1)	80%	80%

[a]We considered one analysis as 'supportive of mediation' when a significant mediation (partial, total or 'suggested') was found, and negative when null mediation was found.

indirect effects, relying on small samples, and/or cross-sectional data (Cancel et al., 2015; Quidé et al., 2018). Overall, only 4/47 studies (Fisher et al., 2013; Lincoln et al., 2017; Thompson et al., 2016; Wolke et al., 2014) used a prospective design. Eight (Ashford et al., 2012; Bortolon et al., 2017; Boyda et al., 2018; Boyda & McFeeters, 2015; Cancel et al., 2015; Isvoranu et al., 2017; Jaya et al., 2017; Marwaha et al., 2014) of the 47 studies reported a mediating effect but failed to provide estimates of the indirect and direct effects and thus were classified as 'suggested mediation', as described above and in online Supplementary. Table 1 summarises the evidence for each analysis by mediator category. Given the high number of analyses and the heterogeneity found for the affective pathway, cognitive schema pathway and dissociation, three detailed tables were constructed for these groups (see Tables 2 and 3 and online Supplementary Table S2, respectively) presenting the evidence for each subcategory.

Figure 1 summarises the percentage of total effect mediated for 58 analyses included in 25 papers across the most relevant category of mediators found in our review (only categories being explored in at least three papers are shown in Fig. 1, the percentage of total effect mediated of the remaining analyses is shown in online Supplementary Tables S1a–S1c).

The most relevant categories of mediators found in our review were: dissociation, dysfunctional attachment, affective pathway to psychosis, loneliness, cognitive biases, other PTSD symptoms, other psychological mediators and biological mediators.

Dissociation

Despite only 42% of analyses showing evidence of mediation, 10/12 studies (Bortolon et al., 2017; Bortolon & Raffard, 2018; Cole et al., 2016; Gibson et al., 2019; Perona-Garcelán et al., 2012, 2014; Schalinski et al., 2019; Sun et al., 2018; Varese et al., 2012*a*; Yamasaki et al., 2016) were supportive of mediation, against 2/12 that were not (Evans et al., 2015; Thompson et al., 2011). The percentage of total effect mediated was consistently high across analyses within this category, with a median of around 50% of total effect explained (Fig. 1). As illustrated in Fig. 1, most of the studies showing evidence of mediating effects used hallucinations as an outcome and explored trauma as a composite score (Bortolon et al., 2017; Cole et al., 2016; Gibson et al., 2019; Perona-Garcelán et al., 2012, 2014; Varese et al., 2012*a*; Yamasaki et al., 2016), while only two (Cole et al., 2016; Sun et al., 2018) studies found positive effects with delusions as an

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

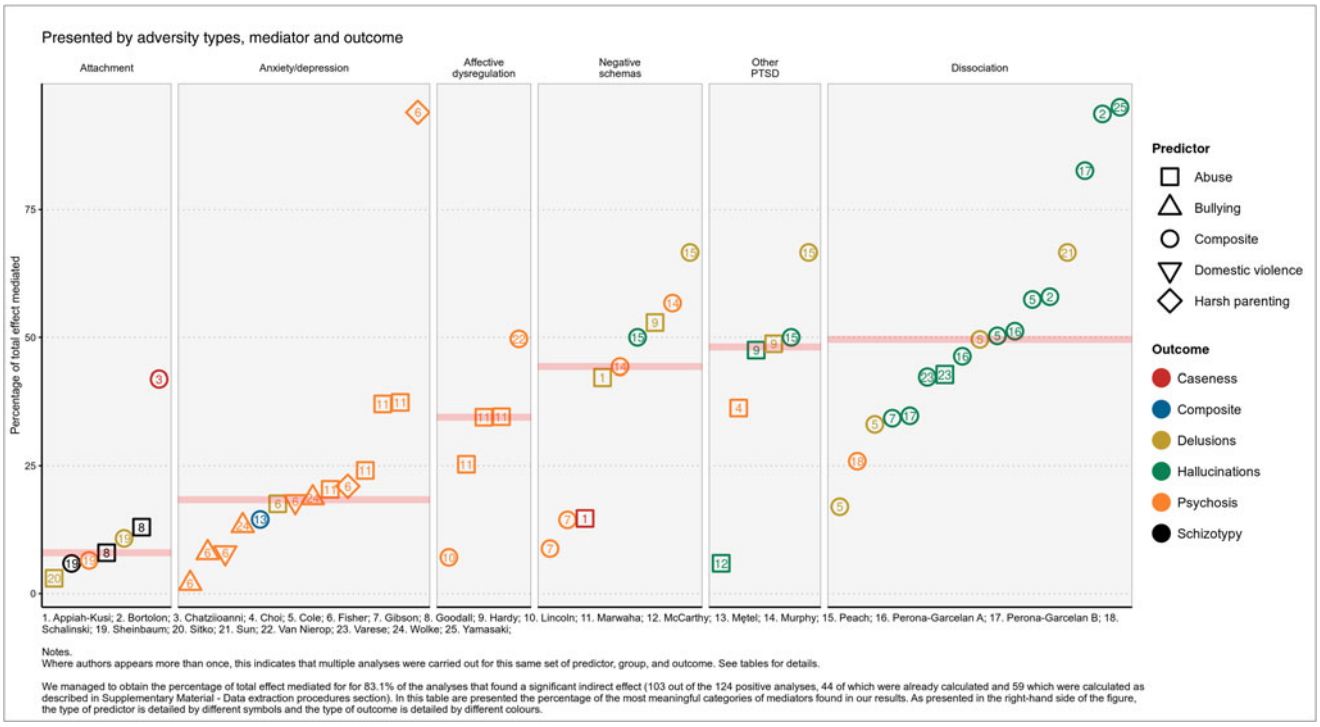


Fig. 1. Percentage of total effect mediated by each mediator. Presented by adversity types, mediator and outcome.

outcome . As shown in online Supplementary Table S2, it was not possible to draw conclusions about which dissociative symptoms were more likely to mediate the adversity–psychosis association.

Dysfunctional attachment

Despite overall 44% of analyses showing evidence of mediation, 3/5 (Chatziioannidis et al., 2019; Sheinbaum et al., 2014; Sitko et al., 2014) papers showed mixed findings, 1/5 (Van Dam et al., 2014) showed no evidence of mediation and just 1/5 (Goodall et al., 2015) showed consistent evidence of mediation across all its analyses. As seen in Fig. 1, the percentages of total effect mediated showed a small median value of around 12%.

Affective pathway

Only one paper explored this pathway in clinical samples (Thompson et al., 2016) showing no evidence of mediation. The remaining 14 (Ashford et al., 2012; Fisher et al., 2012, 2013; Gibson et al., 2019; Isvoranu et al., 2017; Lincoln et al., 2017; Marwaha et al., 2014; Marwaha & Bebbington, 2015; McCarthy-Jones, 2018; Mętel et al., 2020; Rössler et al., 2016; van Nierop et al., 2014; Wolke et al., 2014; Yamasaki et al., 2016) papers (including 29 analyses) were conducted in GP samples, with 66% of analyses supporting mediation. In total, 12/14 (Ashford et al., 2012; Fisher et al., 2012, 2013; Gibson et al., 2019; Isvoranu et al., 2017; Lincoln et al., 2017; Marwaha et al., 2014; Marwaha & Bebbington, 2015; Mętel et al., 2020; Rössler et al., 2016; van Nierop et al., 2014; Wolke et al., 2014) of the GP studies found evidence of mediation and three of them were prospectively graded high in quality assessment (Fisher et al., 2013; Lincoln et al., 2017; Wolke et al., 2014) (online Supplementary Table S1b).

We divided the affective pathway into these subcategories: anxiety, depression, affective dysregulation and stress sensitivity (Table 2), results per subcategories showed an overall high proportion of analyses supporting mediation (Table 2). As seen in Fig. 1, the median percentages of total effect mediated for anxiety and depression were at around 20% while that of affective dysregulation was at around 35%.

Feeling of loneliness

In total, 83% of analyses showed evidence of mediation. Only one study (Steenkamp et al., 2019) was conducted in clinical samples and showed evidence for mediation. In GP, two studies showed evidence of mediation (Boyda & McFeeters, 2015; Jaya et al., 2017) and another showed mixed findings (Shevlin et al., 2015). The low number of analyses did not allow us to draw consistent conclusions in terms of specific pathways between adversity–psychosis (see online Supplementary Tables S1a, S1b for details).

Cognitive biases

In total, 53% of analyses overall showed evidence of mediation in this category. In terms of papers, 17/22 were supportive of mediation (Appiah-Kusi et al., 2017; Ashford et al., 2012; Bortolon et al., 2017; Boyda et al., 2018; Evans et al., 2015; Fisher et al., 2013; Gawęda et al., 2019; Gibson et al., 2019; Hardy et al., 2016; Jaya et al., 2017; McDonnell et al., 2018; Mętel et al., 2020; Murphy et al., 2015; Peach et al., 2019; Pinto-Gouveia et al., 2014; van Nierop et al., 2014; Wickham & Bentall, 2016), 5/20 were not (Fisher et al., 2012; Morgan et al., 2014; Perona-Garcelán et al., 2014; Weijers et al., 2018; Yamasaki et al., 2016). Results were more likely to show evidence of mediation when conducted in the GP, compared with clinical samples

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

(62.5% *v.* 38% of analyses were supportive of mediation, respectively, Table 1).

In order to explore specific domains within the category, we divided this category into: negative schemas about self, others and the world (NS) and external locus of control (ELC) as they were the most represented subdomains. Briefly, the evidence for the former showed that 62.5% of analyses were supportive of mediation with a proportion of total effect mediated of around 47% of median value (Fig. 1). No studies in clinical samples explored the ELC and 2/3 studies in general GP showed evidence of mediation (Fisher et al., 2013; Gibson et al., 2019). Other biases such as maladaptive schemas (Bortolon et al., 2017; Boyda et al., 2018), low self-esteem (Fisher et al., 2013), aberrant salience (Gawęda et al., 2019) were insufficient in numbers of studies to draw conclusions. No specific pathways could be highlighted between some types of adversities and outcomes.

Other PTSD symptoms, time perspective, mania, compulsions and psychological resilience

Other PTSD symptoms not described in the other categories included post-traumatic intrusions, avoidance and numbing, or a general measure of post-traumatic symptoms. Overall, the results suggested evidence of mediation (Choi et al., 2015; Hardy et al., 2016; McCarthy-Jones, 2018; Peach et al., 2019). The percentage of total effect mediated was also high, with a median value just below 50% (see Fig. 1). Other mediators including five studies that did not fit into the aforementioned categories are presented in online Supplementary Table S1a, S1b and include time perspective (Styła et al., 2019), mania (Thompson et al., 2016), compulsions (McCarthy-Jones, 2018), a measure of psychological resilience (Mętel et al., 2020) and self-disturbances (Gawęda et al., 2019). Particularly, strong mediating effects were found through anomalous self-experiences (Gawęda et al., 2019).

Biological mediators

Surprisingly, only two studies examining biological mechanism as potential mediators between CA and psychosis were included (online Supplementary Table S1c). One found no evidence for a mediation of the inferior frontal gyrus activation between CA and positive symptoms (Quidé et al., 2018); another showed that the grey matter density in the dorsolateral prefrontal cortex was mediating the link between emotional neglect and disorganised symptoms in patients (Cancel et al., 2015).

Discussion

From this systematic review of 47 papers, we found evidence of partial mediation between adversity and psychosis through various overlapping and not competing psychological mechanisms. The link between adversity and psychosis was particularly driven by NS, by dissociation and other PTSD symptoms. For GP samples there was good evidence for mediation through an affective pathway (affective dysregulation, anxiety and depression), but there were insufficient studies looking at this in individuals at risk for psychosis and in patients suffering from the disorder to allow conclusions to be drawn about its mediating role in clinical settings. We found no evidence supporting the mediating role of dysfunctional attachment styles in the GP; there were too few studies addressing this mediator in clinical samples to permit conclusions. Other mediators showing interesting findings included loneliness, stress sensitivity, anomalous self-disturbances and ELC, but generalisation of findings is limited due to the low number of studies. Contrary to our expectations, only two papers (Cancel et al., 2015; Quidé et al., 2018) fulfilled our inclusion criteria examining biological mediators. There is evidence that potential biological mediators are associated with adversity and with psychosis, but very few considering mediation effects directly, using psychosis as an outcome in the pathway. So, the speculation on biological mediators is currently mostly conjecture showing an urgent need for more research in this field.

Strengths and limitations

The findings of this review should be interpreted in the context of various strengths and limitations. A major strength is the large scale of this review including 47 studies, 82 352 subjects from the GP and 3189 from clinical studies. This has allowed us to cover multiple mediator groups with a sufficient number of participants and show new pathways that did not appear in William et al., systematic review (Williams et al., 2018), such as the role of loneliness. Second, we have not limited our analysis to the description of the main finding of each study and to report whether the mediation was present or absent, but we have also examined the amount of mediation of each pathway by providing the percentage of total effect mediated (when this was possible). We believe this is an important point given that just limiting to the significance of the p value of the indirect effects is highly dependent on the sample size and thus totally limited. Calculating the proportion of the effect that is mediated provides a more accurate understanding of the mediational processes. Moreover, we believe that our concrete clinical implications (see below) may be useful and could contribute to a better knowledge of trauma-informed care in services treating individuals with psychosis.

Some limitations must be mentioned. First, only four studies used a prospective design to estimate the indirect effects, while in the remaining studies, it cannot be excluded that the mediator resulted as a consequence of psychosis. Second, CA was measured retrospectively in all studies except two (Fisher et al., 2013; Wolke et al., 2014) which were conducted in GP. In patients, this can constitute a risk of bias given the difficulties of patients to recall their experiences and to disclose these openly in assessment by research assistants. Third, the percentage of total effect could not be obtained nor calculated in 17% of the analyses that were supportive of mediation (authors did not provide details on the indirect, direct and total effects), thus our Fig. 1 is not totally representative of the total number of analyses included in this review. In addition, some mediators (i.e. attachment styles, anxiety and depression) were found to be highly explored in the GP but very little in clinical samples, which is an important limitation of current literature in the field and which limits the extent to which we can extrapolate our conclusions to clinical intervention in clinical settings. Furthermore, papers in this review considered that null mediation occurred when the indirect or mediating effects did not reach a significant p value of <0.05. Considering the p value to test the null hypothesis is limited by the fact that is highly dependent on the sample size. Thus, it is likely that in our review, studies conducted in small samples are underestimating potential mediating effects, and this should be taken into consideration when interpreting our conclusions. The age range of studies in the GP was quite wide (9.8–51.7 years), and thus the population included in these studies is quite heterogeneous as

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

different confounding factors may operate at different ages; this should be considered as a limitation when interpreting our results. Furthermore, only three papers took into account different mediating effects based on the timing of adversity (McDonnell et al., 2018; Schalinski et al., 2019; Wolke et al., 2014) which is an important limitation of current research as different mediating mechanisms may operate differently based on the developmental period (McGrath et al., 2017). Lastly, there was a time lag between the systematic literature search, in July 2019, and the submission date in February 2020, which means newer studies were not included in the current work.

Evidence for mediational pathways between childhood adversity and psychosis

Here we will discuss each pathway separately, but as it will be further developed in the clinical implications (Fig. 2) and the conclusions, we believe that the mediating mechanism between CA and psychosis is complex, possibly involving an interplay between these different complementary, con-competing pathways.

Pathway 1: dissociation and PTSD symptoms

Mediation through this pathway was more common when hallucinations were used as an outcome. These two categories, intimately related, showed the highest percentages of total effect mediated (Fig. 1).

The role of post-traumatic dissociation in psychosis was already the focus of research at the end of the eighteenth century, when Janet, among others, defined hysterical psychosis as characterised by its dissociative and stress-related nature (Moskowitz, Schäfer, & Dorahy, 2009). Current international classifications do not include dissociation among the diagnostic criteria for any form of psychosis. However, contemporary authors such as Ross (2006) and Moskowitz et al. (2009) suggest the existence of a dissociative type of psychosis that could potentially be responsive to psychotherapy focused on trauma.

Accordingly, our findings showing mediation by PTSD symptoms in clinical samples (Choi et al., 2015; Hardy et al., 2016; Peach et al., 2019) are consistent with reports suggesting that similar mechanisms could be involved in psychotic experiences and symptoms of PTSD. For instance, it has been suggested that some hallucinations represent a dissociated type of post-traumatic intrusion, which may not be recognised as such by people with psychosis (Allen et al., 1997; Moskowitz et al., 2009). Our results therefore support the possibility of applying specific psychological interventions, such as cognitive behavioural therapy (CBT), for patients with psychosis, dissociation and PTSD symptoms and with a history of clear-cut traumatic episode. In this regard, two recent systematic reviews exploring the safety and efficacy of trauma-focused therapies in individuals with comorbid PTSD symptoms and psychosis have shown that trauma-focused CBT is safe (Sin & Spain, 2017), can reduce PTSD symptoms (Swan, Keen, Reynolds, & Onwumere, 2017) and can lead to small improvements in positive symptoms after treatment (Brand, McEnery, Rossell, Bendall, & Thomas, 2018).

Pathway 2: cognitive biases

Cognitive schemas about the self, the world and others were the most consistent mediator between CA and psychosis in both clinical samples and GP. Moreover, this category contributed highly to the total effect between CA and psychosis, with a median percentage mediated of around 46% across all analyses (Fig. 1).

This evidence supports previous cognitive models of the development of positive symptoms (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001; Morrison et al., 2003) which suggest that exposure to severe trauma might contribute to the development of cognitive bias such as NS. Further exposure to stressors or to subtle perceptual abnormalities that are common in the GP (Van Os et al., 2009), and even more common in genetically predisposed individuals, will lead to anomalous conscious self-experiences which will trigger the search for an explanation. The biased schemas, in combination with anomalous self-experience, disrupt the appraisal process leading to a misinterpretation of reality, and subsequently delusional ideas (Garety et al., 2001; Howes & Murray, 2014; Morrison et al., 2003). Other factors are important in this process, such as the ELC (Thompson et al., 2011), which has shown evidence for mediation, especially in GP (Fisher et al., 2013; Gibson et al., 2019). It would be interesting for future research to explore if other cognitive biases such as jumping to conclusions and meta-cognitive deficits can moderate or mediate the connections between CA and psychosis in combination with NS and ELC.

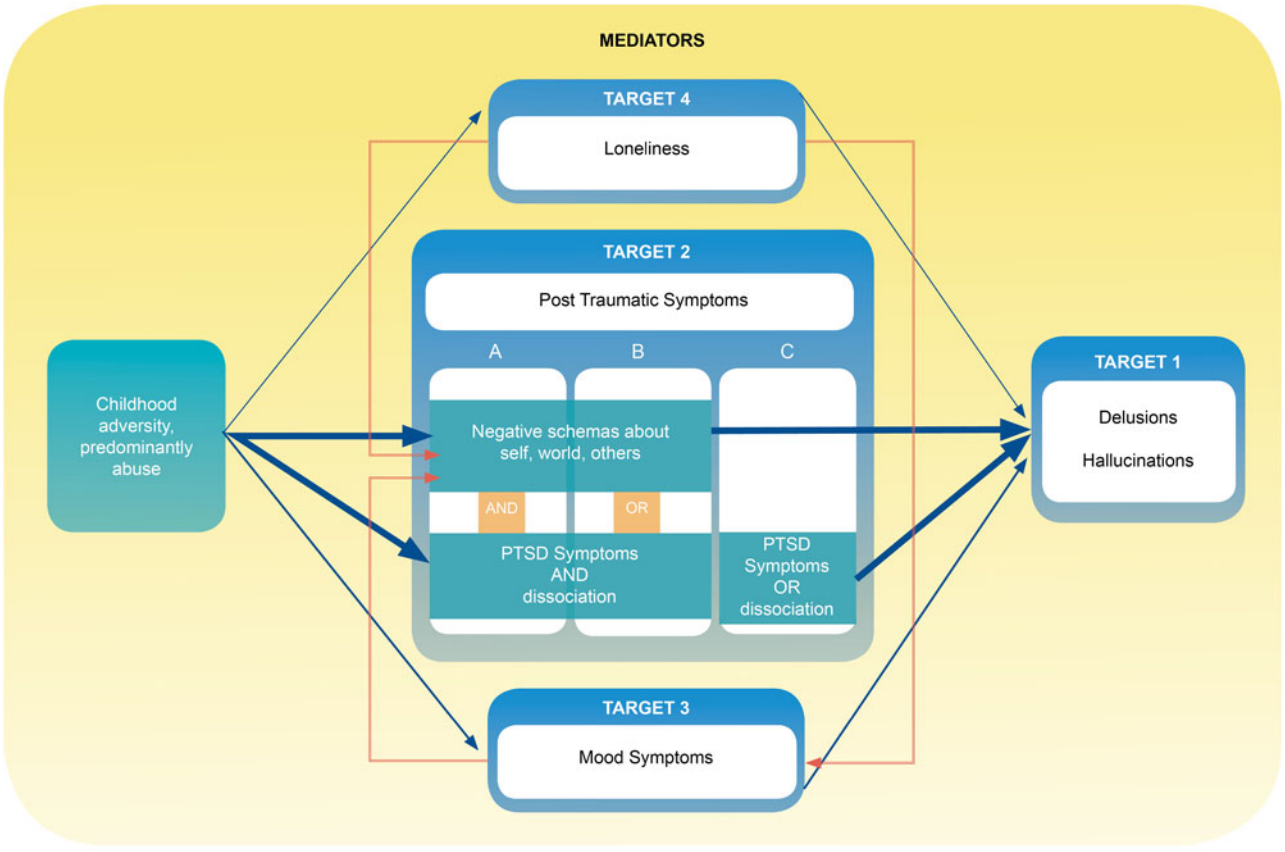
Pathway 3: affective pathway

We found consistent evidence suggesting that anxiety, depression and affective dysregulation might partially mediate the link between CA and low-level psychotic experiences in the GP. The affective component could be a mediational partner along with other mechanisms such as cognitive bias or PTSD-related symptoms. For example, Fisher et al. (2013) report on a large prospective study, where 100% of the total effect was mediated only when anxiety and depression were added to the model in combination with cognitive bias and low self-esteem. Unfortunately, our interpretation is restricted to GP (and thus to attenuated positive symptoms) due to the lack of studies performed in clinical settings. Nevertheless, these results support previous claims that the association between CA and psychosis might be mediated by non-psychotic symptoms [otherwise the so-called 'ancillary symptoms of psychosis' (Bebbington, 2015) such as anxiety and depression and affective dysregulation]. These symptoms might be determinants of paranoid thinking; for example, anxiety might lead to anticipation of threat, and low mood might drive negatively biased interpretations of ongoing experience and impact self-esteem and negative schemas about the self, which in turn are precursors of psychotic symptoms, as illustrated in Fig. 2.

Pathway 4: feeling of loneliness

Although only explored in four studies (Boyda & McFeeters, 2015; Jaya et al., 2017; Shevlin et al., 2015; Steenkamp et al., 2019), we found good evidence suggesting that a feeling of loneliness might mediate the CA–psychosis relationship. We could hypothesise that social withdrawal and loneliness may increase an individual's sensitivity to potential stressors in daily life restrict access to balanced information from the environment, maintaining biased cognitive biases. This could, in turn, predispose an individual to lower mood and anxiety, which would constitute a favourable ground for the emergence of psychotic symptoms. Thus, the feeling of loneliness and isolation must be taken very seriously as it might operate as a potential condition allowing other mediators to operate.

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press



This figure displays the potential targets for treatment that could be addressed in individuals with psychosis who have been exposed to adversity. The choice of the pathways is based on evidence of mediation found in our review, but the implications remain hypothetical and should be tested empirically with randomized controled trials.
Beyond the traditional treatment of psychotic symptoms **(Target 1)** different clinical presentations with various targets for treatment can occur: **Target 2** represent targets from the post traumatic spectrum such as Negative Schemas about the Self, Others and the World (NS) and PTSD related symptoms, including Dissociation. These can be combined in different forms as displayed in **Target 2A, 2B** and **2C. Target 3** represents mood-related symptoms and **Target 4** represent the presence of feeling of loneliness. The treatment options could be adapted depending on which targets are present or predominant in the clinical picture. For **Target 2 A:** CBT-trauma focused therapy (for PTSD symptoms and NS) + sensory grounding techniques (for dissociation) + SSRI/ antagonists α1 if required (for PTSD symptoms).
The implementation of these interventions would be adapted according to the presence/absence of the aforementioned targets (**Target 2 B** and **C**). **Target 3**: CBT techniques such as behavioural activation and graded exposure, relaxation techniques and mindfulness + SSRI if needed for anxiety and depressive symptoms. **Target 4**: Promoting social inclusion and community membership through therapy/activity groups and vocational support. Improving existing interpersonal relationships using family therapy approaches.
The thickness of the arrows shows the robustness of the evidence according to our results. The square arrows represent a hypothetical connexion not addressed in our review.

Fig. 2. Potential targets for treatment based on the evidence of mediational pathways between adversity and psychosis.

Pathway 5: biological measures

Despite the high emphasis put on the search for biomarkers during the last 20 years of psychiatric research, we could identify just two eligible papers exploring biological mechanisms using psychosis as an outcome (Cancel et al., 2015; Quidé et al., 2018). This highlights the limited evidence in this field and the need for future studies testing mediation in longitudinal samples.

Clinical implications for clinical settings

Our results provide evidence to support some potential treatment implications for traumatised individuals with psychosis, in addition to the treatment of positive symptoms, which often remain high in this vulnerable group (Ajnakina et al., 2016; Alameda et al., 2016). Figure 2 displays a model with the different potential treatment targets derived from the pathways mentioned above. Beyond the traditional treatment of psychotic symptoms (Target 1 in Fig. 2), we propose targeting the relevant mediators found in our review, hypothesizing that an improvement in such targets would then have an indirect beneficial effect on positive symptoms.

A common clinical picture corresponds to a situation where a traumatised patient with psychosis suffers from NS and PTSD symptoms, including dissociation. If these are present (Target 2A in Fig. 2), a trauma-focused therapy, such as trauma-focused CBT could be appropriate, integrating treatment of negative schemas and traumatic intrusions, in addition to dissociative symptoms. Briefly, this could include grounding techniques, imaginal exposure, memory updating and cognitive restructuring, alongside more general CBT elements such as the use of behavioural experiments to gather new information about current safety (Hardy, 2017). In some cases, dissociative symptoms may be very disruptive and prevent access to the other targets; in this case, they can be prioritised and targeted using sensory grounding techniques to help the individual reliably regain contact with present external stimuli (Keen, Hunter, & Peters, 2017; Steel et al., 2017).

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

In addition to psychological interventions, some patients with highly distressing PTSD symptoms might respond to adjunctive pharmacological treatments such as selective serotonin reuptake inhibitors or other antidepressants blocking α1 adrenoceptors commonly used in patients with PTSD (Steckler & Risbrough, 2012). This integrated approach could be adapted depending on which mediators are present or predominant, as described in Fig. 2.

Anxiety and depressive symptoms could be, in isolation or in combination with other mediators (such as cognitive bias and post-traumatic symptoms), another target for treatment (Target 3, Fig. 2) that could indirectly ameliorate positive symptoms as suggested in previous reviews (Bebbington, 2015). The use of antidepressants and CBT techniques such as behavioural activation and graded exposure (Waller et al., 2013), as well as relaxation techniques and mindfulness, could then be useful, targeting low mood and anxiety, respectively (Waller et al., 2013).

Lastly, it is important to highlight the possible role of loneliness as another mediator that could be targeted for treatment. Promoting social inclusion and community membership through group interventions and vocational support could be beneficial, as well as improving existing interpersonal relationships using family therapy approaches. Also, as previously mentioned, loneliness might co-occur with other mediators.

Our review indicates that routine assessment of trauma history should be necessary in clinical settings treating individuals with psychosis. Furthermore, given the possible importance of mediators, it is also important to carry out a careful assessment of the cognitive biases, PTSD, dissociative symptoms, anxiety, mood and feelings of loneliness.

Conclusions

Our review suggests that the association between adversity and psychosis is mediated by various overlapping non-competing mechanisms. Cognitive schemas about the self and the world and post-traumatic symptoms (particularly dissociation) seem to play an important role in the association, while other factors such as mood and feeling of loneliness seem to contribute partially to this link and interact mutually in contributing to the effect. Our findings support the routine assessment of experiences of CA in clinical settings, alongside with all the potential mediators. More evidence testing the efficacy of interventions targeting such mediators through cognitive behavioural approaches using trauma-focused therapy and/or pharmacological means is needed in future.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291720002421.

Acknowledgements. We thank our funding bodies (Swiss National Science Foundation, the National Institute for Health Research, NARSAD, ESRC Centre for Society and Mental Health) for their support.

Financial support. This work was supported by the Swiss National Science Foundation (Grant P2LAP3_171804 to L.A.). This paper represents independent research part funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, South-Eastern Norway Health Authority (#2017060) and the NARSAD Young Investigator Award to Monica Aas (#22388). This paper represents an independent research part supported by the ESRC Centre for Society and Mental Health at King's College London (ESRC Reference: ES/S012567/1). The views expressed are those of the author(s) and not necessarily those of the ESRC, the NIHR, the NHS, the Department of Health and Social Care or King's College London.

Conflict of interest. None.

References

Aas, M., Haukvik, U. K., Djurovic, S., Tesli, M., Athanasiu, L., Bjella, T., … Melle, I. (2014). Interplay between childhood trauma and BDNF val66met variants on blood BDNF mRNA levels and on hippocampus subfields volumes in schizophrenia spectrum and bipolar disorders. *Journal of Psychiatric Research*, *59*, 14–21.

Ajnakina, O., Trotta, A., Oakley-Hannibal, E., Di Forti, M., Stilo, S. A., Kolliakou, A., … Fisher, H. L. (2016). Impact of childhood adversities on specific symptom dimensions in first-episode psychosis. *Psychological Medicine*, *46*, 317–326.

Alameda, L., Fournier, M., Khadimallah, I., Griffa, A., Cleusix, M., Jenni, R., … Do, K. Q. (2018). Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. *National Academy of Sciences Proceedings of the National Academy of Sciences of the USA*, *115*, 12495–12500.

Alameda, L., Golay, P., Baumann, P. S., Ferrari, C., Do, K. Q., & Conus, P. (2016). Age at the time of exposure to trauma modulates the psychopathological profile in patients with early psychosis. *The Journal of Clinical Psychiatry*, *77*, e612–e618.

Allen, J. G., Coyne, L., & Console, D. A. (1997). Dissociative detachment relates to psychotic symptoms and personality decompensation. *Comprehensive Psychiatry*, *38*, 327–334.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders: DSM-IV* (4th ed.). Washington, DC: American Psychiatric Association.

Appiah-Kusi, E., Fisher, H. L., Petros, N., Wilson, R., Mondelli, V., Garety, P. A., … Bhattacharyya, S. (2017). Do cognitive schema mediate the association between childhood trauma and being at ultra-high risk for psychosis? *Journal of Psychiatric Research*, *88*, 89–96.

Ashford, C. D., Ashcroft, K., & Maguire, N. (2012). Emotions, traits and negative beliefs as possible mediators in the relationship between childhood experiences of being bullied and paranoid thinking in a Non-clinical sample. *Journal of Experimental Psychopathology*, *3*, 624–638.

Bebbington, P. (2015). Unravelling psychosis: Psychosocial epidemiology, mechanism, and meaning. *Editorial Department of the Shanghai Archives of Psychiatry Shanghai Archives of Psychiatry*, *27*, 70–81.

Bentall, R. P., De Sousa, P., Varese, F., Wickham, S., Sitko, K., Haarmans, M., & Read, J. (2014). From adversity to psychosis: Pathways and mechanisms from specific adversities to specific symptoms. *Social Psychiatry and Psychiatric Epidemiology*, *49*, 1011–1022.

Bortolon, C., & Raffard, S. (2018). Dissociation mediates the relationship between childhood trauma and experiences of seeing visions in a French sample. *Journal of Nervous and Mental Disease*, *206*, 850–858.

Bortolon, C., Seillé, J., & Raffard, S. (2017). Exploration of trauma, dissociation, maladaptive schemas and auditory hallucinations in a French sample. *Taylor & Francis Cognitive Neuropsychiatry*, *22*, 468–485.

Boyda, D., & McFeeters, D. (2015). Childhood maltreatment and social functioning in adults with sub-clinical psychosis. *Psychiatry Research*, *226*, 376–382.

Boyda, D., McFeeters, D., Dhingra, K., & Rhoden, L. (2018). Childhood maltreatment and psychotic experiences: Exploring the specificity of early maladaptive schemas. *Journal of Clinical Psychology*, *74*, 2287–2301.

Brand, R. M., McEnery, C., Rossell, S., Bendall, S., & Thomas, N. (2018). Do trauma-focussed psychological interventions have an effect on psychotic symptoms? A systematic review and meta-analysis. *Schizophrenia Research*, *195*, 13–22.

Cancel, A., Comte, M., Truillet, R., Boukezzi, S., Rousseau, P. F., Zendjidjian, X. Y., … Fakra, E. (2015). Childhood neglect predicts disorganization in schizophrenia through grey matter decrease in dorsolateral prefrontal cortex. *Acta Psychiatrica Scandinavica*, *132*, 244–256.

Chatziioannidis, S., Andreou, C., Agorastos, A., Kaprinis, S., Malliaris, Y., Garyfallos, G., & Bozikas, V. P. (2019). The role of attachment anxiety in the relationship between childhood trauma and schizophrenia-spectrum psychosis. *Psychiatry Research*, *276*, 223–231.

Choi, J. Y., Choi, Y. M., Kim, B., Lee, D. W., Gim, M. S., & Park, S. H. (2015). The effects of childhood abuse on self-reported psychotic symptoms in

severe mental illness: Mediating effects of posttraumatic stress symptoms. *Psychiatry Research*, *229*, 389–393.
Cole, C. L., Newman-Taylor, K., & Kennedy, F. (2016). Dissociation mediates the relationship between childhood maltreatment and subclinical psychosis. *Journal of Trauma and Dissociation*, *17*, 577–592.
Evans, G. J., Reid, G., Preston, P., Palmier-Claus, J., & Sellwood, W. (2015). Trauma and psychosis: The mediating role of self-concept clarity and dissociation. *Psychiatry Research*, *228*, 626–632.
Fisher, H. L., Appiah-Kusi, E., & Grant, C. (2012). Anxiety and negative self-schemas mediate the association between childhood maltreatment and paranoia. *Psychiatry Research*, *196*, 323–324.
Fisher, H. L., Schreier, A., Zammit, S., Maughan, B., Munafò, M. R., Lewis, G., & Wolke, D. (2013). Pathways between childhood victimization and psychosis-like symptoms in the ALSPAC birth cohort. *Schizophrenia Bulletin*, *39*, 1045–1055.
Freeman, D., & Garety, P. (2014). Advances in understanding and treating persecutory delusions: A review. *Social Psychiatry and Psychiatric Epidemiology*, *49*, 1179–1189.
Garety, P. A., Bebbington, P., Fowler, D., Freeman, D., & Kuipers, E. (2007). Implications for neurobiological research of cognitive models of psychosis: A theoretical paper. *Psychological Medicine*, *37*, 1377–1391.
Garety, P. A., Kuipers, E., Fowler, D., Freeman, D., & Bebbington, P. E. (2001). A cognitive model of the positive symptoms of psychosis. *Psychological Medicine*, *31*, 189–195.
Gawęda, Ł, Göritz, A. S., & Moritz, S. (2019). Mediating role of aberrant salience and self-disturbances for the relationship between childhood trauma and psychotic-like experiences in the general population. *Schizophrenia Research*, *206*, 149–156.
Gibson, L. E., Alloy, L. B., & Ellman, L. M. (2016). Trauma and the psychosis spectrum: A review of symptom specificity and explanatory mechanisms. *Clinical Psychology Review*, *49*, 92–105.
Gibson, L. E., Reeves, L. E., Cooper, S., Olino, T. M., & Ellman, L. M. (2019). Traumatic life event exposure and psychotic-like experiences: A multiple mediation model of cognitive-based mechanisms. *Schizophrenia Research*, *205*, 15–22.
Goodall, K., Rush, R., Grünwald, L., Darling, S., & Tiliopoulos, N. (2015). Attachment as a partial mediator of the relationship between emotional abuse and schizotypy. *Psychiatry Research*, *230*, 531–536.
Gumley, A. I., Taylor, H. E. F., Schwannauer, M., & MacBeth, A. (2014). A systematic review of attachment and psychosis: Measurement, construct validity and outcomes. *Acta Psychiatrica Scandinavica*, *129*, 257–274.
Hardy, A. (2017). Pathways from trauma to psychotic experiences: A theoretically informed model of posttraumatic stress in psychosis. *Frontiers Research Foundation Frontiers in Psychology*, *8*, 697.
Hardy, A., Emsley, R., Freeman, D., Bebbington, P., Garety, P. A., Kuipers, E. E., … Fowler, D. (2016). Psychological mechanisms mediating effects between trauma and psychotic symptoms: The role of affect regulation, intrusive trauma memory, beliefs, and depression. *Schizophrenia Bulletin*, *42*, S34–S43.
Hayes, A. F. (2009). Beyond Baron and Kenny: Statistical mediation analysis in the new millennium. *Communication Monographs*, *76*, 408–420.
Howes, O. D., McCutcheon, R., Owen, M. J., & Murray, R. M. (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *USA Biological Psychiatry*, *81*, 9–20.
Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. *The Lancet*, *383*, 1677–1687.
Isvoranu, A. M., Van Borkulo, C. D., Lou, B. L., Wigman, J. T. W., Vinkers, C. H., Borsboom, D., … Myin-Germeys, I. (2017). A network approach to psychosis: Pathways between childhood trauma and psychotic symptoms. *Schizophrenia Bulletin*, *43*, 187–196.
Jaya, E. S., Ascone, L., & Lincoln, T. M. (2017). Social adversity and psychosis: The mediating role of cognitive vulnerability. *Schizophrenia Bulletin*, *43*, 557–565.
Keen, N., Hunter, E. C. M., & Peters, E. (2017). Integrated trauma-focused cognitive-behavioural therapy for post-traumatic stress and psychotic symptoms: A case-series study using imaginal reprocessing strategies. *Frontiers in Psychiatry*, *8*, 92.
Lincoln, T. M., Marin, N., & Jaya, E. S. (2017). Childhood trauma and psychotic experiences in a general population sample: A prospective study on the mediating role of emotion regulation. *Masson SAS European Psychiatry*, *42*, 111–119.
Marwaha, S., & Bebbington, P. (2015). Mood as a mediator of the link between child sexual abuse and psychosis. *Social Psychiatry and Psychiatric Epidemiology*, *50*, 661–663.
Marwaha, S., Broome, M. R., Bebbington, P. E., Kuipers, E., & Freeman, D. (2014). Mood instability and psychosis: Analyses of British national survey data. *Schizophrenia Bulletin*, *40*, 269–277.
McCarthy-Jones, S. (2018). Post-traumatic symptomatology and compulsions as potential mediators of the relation between child sexual abuse and auditory verbal hallucinations. *Behavioural and Cognitive Psychotherapy*, *46*, 318–331.
McDonnell, J., Stahl, D., Day, F., McGuire, P., & Valmaggia, L. R. (2018). Interpersonal sensitivity in those at clinical high risk for psychosis mediates the association between childhood bullying victimisation and paranoid ideation: A virtual reality study. *Schizophrenia Research*, *192*, 89–95.
McGrath, J. J., Saha, S., Lim, C. C. W., Aguilar-Gaxiola, S., Alonso, J., Andrade, L. H., … Wojtyniak, B. (2017). Trauma and psychotic experiences: Transnational data from the World Mental Health survey. *British Journal of Psychiatry*, *211*, 373–380.
Mętel, D., Arciszewska, A., Daren, A., Pionke, R., Cechnicki, A., Frydecka, D., & Gawęda, Ł (2020). Mediating role of cognitive biases, resilience and depressive symptoms in the relationship between childhood trauma and psychotic-like experiences in young adults. *Early Intervention in Psychiatry*, *14*, 87–96.
Misiak, B., Krefft, M., Bielawski, T., Moustafa, A. A., Sąsiadek, M. M., & Frydecka, D. (2017). Toward a unified theory of childhood trauma and psychosis: A comprehensive review of epidemiological, clinical, neuropsychological and biological findings. *Neuroscience and Biobehavioral Reviews*, *75*, 393–406.
Moher, D., Booth, A., & Stewart, L. (2014). How to reduce unnecessary duplication: Use PROSPERO. *BJOG: An International Journal of Obstetrics and Gynaecology*, *121*, 784–786.
Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *American College of Physicians Annals of Internal Medicine*, *151*, 264–269.
Morgan, C., & Gayer-Anderson, C. (2016). Childhood adversities and psychosis: Evidence, challenges, implications. *World Psychiatry*, *15*, 93–102.
Morgan, C., Reininghaus, U., Fearon, P., Hutchinson, G., Morgan, K., Dazzan, P., … Craig, T. (2014). Modelling the interplay between childhood and adult adversity in pathways to psychosis: Initial evidence from the AESOP study. *Psychological Medicine*, *44*, 407–419.
Morrison, A. P., Frame, L., & Larkin, W. (2003). Relationships between trauma and psychosis: A review and integration. *British Journal of Clinical Psychology*, *42*, 331–353.
Moskowitz, A., Schäfer, I., & Dorahy, M. J. (2009). *Psychosis, trauma and dissociation: Emerging perspectives on severe psychopathology*. Hoboken, NJ, USA: John Wiley and Sons.
Murphy, S., Murphy, J., & Shevlin, M. (2015). Negative evaluations of self and others, and peer victimization as mediators of the relationship between childhood adversity and psychotic experiences in adolescence: The moderating role of loneliness. *British Journal of Clinical Psychology*, *54*, 326–344.
Myin-Germeys, I., & van Os, J. (2007). Stress-reactivity in psychosis: Evidence for an affective pathway to psychosis. *Clinical Psychology Review*, *27*, 409–424.
Peach, N., Alvarez-Jimenez, M., Cropper, S. J., Sun, P., & Bendall, S. (2019). Testing models of post-traumatic intrusions, trauma-related beliefs, hallucinations, and delusions in a first episode psychosis sample. *British Journal of Clinical Psychology*, *58*, 154–172.
Perona-Garcelán, S., Carrascoso- López, F., García-Montes, J. M., Ductor-Recuerda, M. J., López Jiménez, A. M., Vallina-Fernández, O., … Gómez-Gómez, M. T. (2012). Dissociative experiences as mediators between childhood trauma and auditory hallucinations. *Journal of Traumatic Stress*, *25*, 323–329.
Perona-Garcelán, S., García-Montes, J. M., Rodríguez-Testal, J. F., López-Jiménez, A. M., Ruiz-Veguilla, M., Ductor-Recuerda, M. J., … Pérez-Álvarez, M. (2014). Relationship between childhood trauma,

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press

mindfulness, and dissociation in subjects with and without hallucination proneness. *Journal of Trauma and Dissociation*, *15*, 35–51.
Pinto-Gouveia, J., Matos, M., Castilho, P., & Xavier, A. (2014). Differences between depression and paranoia: The role of emotional memories, shame and subordination. *Clinical Psychology and Psychotherapy*, *21*, 49–61.
Quidé, Y., O'Reilly, N., Watkeys, O. J., Carr, V. J., & Green, M. J. (2018). Effects of childhood trauma on left inferior frontal gyrus function during response inhibition across psychotic disorders. *Psychological Medicine*, *48*, 1454–1463.
Read, J., Fosse, R., Moskowitz, A., & Perry, B. (2014). The traumagenic neurodevelopmental model of psychosis revisited. *Neuropsychiatry*, *4*, 65–79.
Read, J., & Gumley, A. (2010). Can attachment theory help explain the relationship between childhood adversity and psychosis?. In S. Benamer (Ed.), *Telling stories? Attachment-based approaches to the treatment of psychosis* (pp. 51–94). Karnac Books. https://psycnet.apa.org/record/2010-21228-004.
Ross, C. A. (2006). Dissociation and psychosis: The need for integration of theory and practice. In J. O. Johannessen, B. V. Martindale & J. Cullberg (Ed.), *Evolving psychosis* (pp. 238–254). Routledge/Taylor & Francis Group. https://psycnet.apa.org/record/2006-05781-014.
Rössler, W., Ajdacic-Gross, V., Rodgers, S., Haker, H., & Müller, M. (2016). Childhood trauma as a risk factor for the onset of subclinical psychotic experiences: Exploring the mediating effect of stress sensitivity in a cross-sectional epidemiological community study. *Schizophrenia Research*, *172*, 46–53.
Ruby, E., Polito, S., McMahon, K., Gorovitz, M., Corcoran, C., & Malaspina, D. (2014). Pathways associating childhood trauma to the neurobiology of schizophrenia. *NIH Public Access Frontiers in Psychological and Behavioral Science*, *3*, 1–17.
Schalinski, I., Breinlinger, S., Hirt, V., Teicher, M. H., Odenwald, M., & Rockstroh, B. (2019). Environmental adversities and psychotic symptoms: The impact of timing of trauma, abuse, and neglect. *Schizophrenia Research*, *205*, 4–9.
Sheinbaum, T., Kwapil, T. R., & Barrantes-Vidal, N. (2014). Fearful attachment mediates the association of childhood trauma with schizotypy and psychotic-like experiences. *Psychiatry Research*, *220*, 691–693.
Shevlin, M., McElroy, E., & Murphy, J. (2015). Loneliness mediates the relationship between childhood trauma and adult psychopathology: Evidence from the adult psychiatric morbidity survey. *Social Psychiatry and Psychiatric Epidemiology*, *50*, 591–601.
Sin, J., & Spain, D. (2017). Psychological interventions for trauma in individuals who have psychosis: A systematic review and meta-analysis. *Routledge Psychosis*, *9*, 67–81.
Sitko, K., Bentall, R. P., Shevlin, M., O'Sullivan, N., & Sellwood, W. (2014). Associations between specific psychotic symptoms and specific childhood adversities are mediated by attachment styles: An analysis of the National Comorbidity Survey. *Psychiatry Research*, *217*, 202–209.
Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, *25*, 603–605.
Steckler, T., & Risbrough, V. (2012). Pharmacological treatment of PTSD – established and new approaches. *Neuropharmacology*, *62*, 617–627.
Steel, C., Hardy, A., Smith, B., Wykes, T., Rose, S., Enright, S., … Mueser, K. T. (2017). Cognitive-behaviour therapy for post-traumatic stress in schizophrenia. A randomized controlled trial. *Psychological Medicine*, *47*, 43–51.
Steenkamp, L., Weijers, J., Gerrmann, J., Eurelings-Bontekoe, E., & Selten, J. P. (2019). The relationship between childhood abuse and severity of psychosis is mediated by loneliness: An experience sampling study. *Schizophrenia Research*, in press.
Steullet, P., Cabungcal, J. H., Monin, A., Dwir, D., O'Donnell, P., Cuenod, M., & Do, K. Q. (2016). Redox dysregulation, neuroinflammation, and NMDA receptor hypofunction: A 'central hub' in schizophrenia pathophysiology? *Schizophrenia Research*, *176*, 41–51.
Styła, R., Stolarski, M., & Szymanowska, A. (2019). Linking childhood adversities with schizophrenia: A mediating role of the balanced time perspective. *Schizophrenia Research*, *209*, 281–283.
Sun, P., Alvarez-Jimenez, M., Simpson, K., Lawrence, K., Peach, N., & Bendall, S. (2018). Does dissociation mediate the relationship between childhood trauma and hallucinations, delusions in first episode psychosis? *Comprehensive Psychiatry*, *84*, 68–74.
Swan, S., Keen, N., Reynolds, N., & Onwumere, J. (2017). Psychological interventions for post-traumatic stress symptoms in psychosis: A systematic review of outcomes. *Frontiers Research Foundation Frontiers in Psychology*, *8*, 341.
Teicher, M. H., Anderson, C. M., & Polcari, A. (2012). Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum. *National Academy of Sciences Proceedings of the National Academy of Sciences of the USA*, *109*, E563–E572.
Thompson, A., Marwaha, S., Nelson, B., Wood, S. J., McGorry, P. D., Yung, A. R., & Lin, A. (2016). Do affective or dissociative symptoms mediate the association between childhood sexual trauma and transition to psychosis in an ultra-high risk cohort? *Psychiatry Research*, *236*, 182–185.
Thompson, A., Sullivan, S., Lewis, G., Zammit, S., Heron, J., Horwood, J., … Harrison, G. (2011). Association between locus of control in childhood and psychotic symptoms in early adolescence: Results from a large birth cohort. *Cognitive Neuropsychiatry*, *16*, 385–402.
Van Dam, D. S., Korver-Nieberg, N., Velthorst, E., Meijer, C. J., & de Haan, L. (2014). Childhood maltreatment, adult attachment and psychotic symptomatology: A study in patients, siblings and controls. *Social Psychiatry and Psychiatric Epidemiology*, *49*, 1759–1767.
van Nierop, M., van Os, J., Gunther, N., van Zelst, C., de Graaf, R., ten Have, M., … Van Winkel, R. (2014). Does social defeat mediate the association between childhood trauma and psychosis? Evidence from the NEMESIS-2 Study. *Acta Psychiatrica Scandinavica*, *129*, 467–476.
Van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychological Medicine*, *39*, 179–195.
Van Winkel, R., Van Nierop, M., Myin-Germeys, I., & Van Os, J. (2013). Childhood trauma as a cause of psychosis: Linking genes, psychology, and biology. *Canadian Psychiatric Association Canadian Journal of Psychiatry*, *58*, 44–51.
Varese, F., Barkus, E., & Bentall, R. P. (2012*a*). Dissociation mediates the relationship between childhood trauma and hallucination-proneness. *Psychological Medicine*, *42*, 1025–1036.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., … Bentall, R. P. (2012*b*). Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin*, *38*, 661–671.
Waller, H., Garety, P. A., Jolley, S., Fornells-Ambrojo, M., Kuipers, E., Onwumere, J., … Craig, T. (2013). Low intensity cognitive behavioural therapy for psychosis: A pilot study. *Journal of Behavior Therapy and Experimental Psychiatry*, *44*, 98–104.
Weijers, J., Fonagy, P., Eurelings-Bontekoe, E., Termorshuizen, F., Viechtbauer, W., & Selten, J. P. (2018). Mentalizing impairment as a mediator between reported childhood abuse and outcome in nonaffective psychotic disorder. *Psychiatry Research*, *259*, 463–469.
Wickham, S., & Bentall, R. (2016). Are specific early-life adversities associated with specific symptoms of psychosis?: A patient study considering just world beliefs as a mediator. *Journal of Nervous and Mental Disease*, *204*, 606–613.
Williams, J., Bucci, S., Berry, K., & Varese, F. (2018). Psychological mediators of the association between childhood adversities and psychosis: A systematic review. *Clinical Psychology Review*, *65*, 175–196.
Wolke, D., Lereya, S. T., Fisher, H. L., Lewis, G., & Zammit, S. (2014). Bullying in elementary school and psychotic experiences at 18 years: A longitudinal, population-based cohort study. *Psychological Medicine*, *44*, 2199–2211.
World Health Organization (1992). *The ICD-10 classification of mental and behavioural disorders: Clinical descriptions and diagnostic guidelines*. Geneva: World Health Organization.
Yamasaki, S., Ando, S., Koike, S., Usami, S., Endo, K., French, P., … Nishida, A. (2016). Dissociation mediates the relationship between peer victimization and hallucinatory experiences among early adolescents. *The Authors Schizophrenia Research: Cognition*, *4*, 18–23.
Yung, A. R., Yung, A. R., Pan Yuen, H., Mcgorry, P. D., Phillips, L. J., Kelly, D., … Buckby, J. (2005). Mapping the onset of psychosis: The comprehensive assessment of at-risk mental states. *Journal of Psychiatry*, *39*, 964–971.

https://doi.org/10.1017/S0033291720002421 Published online by Cambridge University Press