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Te Kaporeihana Āwhina Hunga Whara

Evidence-Based Report

Childhood Adversity and Psychotic Disorders

Reviewer	**Mark Ayson**
Literature search	**Amanda Bowens**
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Important Note:

- The purpose of this brief report is to summarise the evidence for an association between childhood adversity and development of psychosis, including schizophrenia. It has been systematically developed according to a predefined methodology.
- It is not intended to replace clinical judgement, or be used as a clinical protocol.
- A reasonable attempt has been made to find and review papers relevant to the focus of this report; however it does not claim to be exhaustive.
- The document has been prepared by the staff of the Research Unit, ACC. The content does not necessarily represent the official view of ACC or represent ACC policy.
- This report is based upon information supplied up to April 2014

1. Executive Summary

- the cause of schizophrenia is most likely multifactorial with a complex interaction between genes and environmental factors
- childhood adversity includes sexual, physical and emotional abuse, parental death, bullying and neglect
- a history of childhood adversity, including forms of abuse, are more than likely to be more frequent in people with psychotic disorders
- there is good evidence that childhood adversity is a likely risk factor for the development of psychotic disorders with an odds ratio of between 2 and 3
- there is some evidence that childhood adversity may be on the causal pathway in the development of psychotic disorders

2. Background

ACC Research was asked to conduct an evidence-based review to investigate whether there is a causal relationship between childhood adversity (particularly abuse) and developing a psychotic disorder (in particular schizophrenia) later in life.

This would be used to assist ACC Branch Advisors Psychology, and the Policy and Legal Teams to develop an approach to cover and entitlements for people who experienced childhood abuse and develop a psychotic disorder at an older age.

3. Investigation

A search was conducted in April 2014 in the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and PsychINFO. The references of any review articles were also investigated, as was the Worldwide Web. Only articles published in English were included.

Search terms used included: schizophrenia, schizophreniform, psychosis, childhood adversity, child abuse, sexual / physical / emotional abuse, neglect, bullying.

Inclusion criteria: systematic reviews looking at the relationship between childhood adversity (abuse, neglect, bullying etc) and psychotic disorders

Exclusion criteria: non-English studies, animal or laboratory study, narrative review, letter or editorial; study designs other than systematic review

This resulted in identifying 38 articles of which 6 systematic reviews were used in this report.

Evidence tables were created for each systematic review and they can be found in Appendix 1. A table of the excluded studies can be found in Appendix 2.

Any relevant papers were assessed for their methodological quality using the following SIGN* criteria:

Levels of evidence (LOE)	
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

* Scottish Intercollegiate Guidelines Network http://www.sign.ac.uk/

1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort or studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

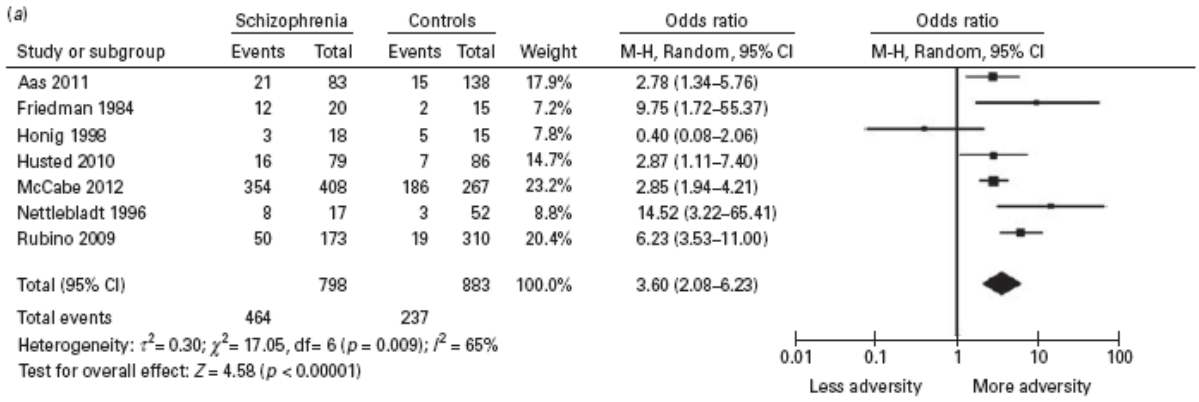
4. Findings

Systematic reviews

Six systematic reviews are included in this report: Matheson (2013)[1], Bonoldi (2013)[2], Varese (2012)[3], van Dam (2012)[4], Chen (2010)[5], and Bendall (2008)[6].

The most recent systematic review by Matheson (2013)[1] looked at published and unpublished studies that reported on rates of childhood adversity in people with a diagnosis of schizophrenia. Childhood adversity included sexual or physical abuse and neglect. The authors included 25 studies, 18 cross-sectional and 7 case-control. The comparator groups were mixed: seven studies used non-psychiatric controls; eight, people with affective psychosis; seven, anxiety disorders; seven depressive disorders; four, dissociative disorders and post-traumatic stress disorder; three, other psychoses; and three, personality disorders.

The odds of people with schizophrenia having experienced childhood adversity were significantly greater than in people with no psychiatric diagnosis (OR[†]=3.60; 95%CI[‡]: 2.08 to 6.23). This pooled estimate was based on seven studies, the data was imprecise and exhibited moderate statistical heterogeneity (I^2=65%)[§]. A planned sensitivity analysis found that removing the obvious outlier (Honig 1998 – see forest plot below) increased the odds ratio to 4.15 and reduced I^2 to 51%. The study used voice-hearing non-patient (psychiatrically healthy) controls which are not ideal. Two other studies used unconventional non-psychiatric control groups; one used unaffected relatives (Husted 2010); the other diabetic patients, their partners and partners of the patients with schizophrenia (Nettlebladt 19996). Removing all three studies did not change the overall results and heterogeneity was reduced (N=4 studies, n=1414 participants, OR=3.92, 95%CI: 2.37 to 6.50, p<0.001, I^2=55%, p=0.08).



Planned subgroup analysis found no differences in results due to adversity type or adversity measure[**]. The lack of any significant change in the odds ratio supports the idea that the findings from the meta-analysis are robust. The authors' rightly concluded that these results indicated a moderate to high quality evidence of increased adversity in people with schizophrenia compared to people without any psychiatric diagnosis. In addition, the

[†] odds ratio

[‡] 95% confidence interval

[§] a measure of heterogeneity i.e. variation in treatment effects above that expected by chance; see Appendix 3 for more details about heterogeneity and the I^2 statistic

[**] reported narratively

evidence is consistent (without the outlier), uses large sample, but has considerable imprecision (indicated by the wide confidence interval).

Moreover, this systematic review was of good methodological quality (1++) which had no language restriction in its inclusion criteria and sought out unpublished research as well as published. Publication bias was also assessed using a funnel plot and found no obvious bias.

Six other meta-analyses were conducted, all using comparator groups who all had a particular psychiatric diagnosis: affective psychosis, anxiety disorders, depressive disorders, dissociative/PTSD[††], other psychosis, and personality disorders. Moderate quality evidence supported a medium effect of increased risk of childhood adversity in people withy schizophrenia compared to anxiety disorders and a large effect of increased risk of adversity in people with dissociative disorders or PTSD. No differences were reported in moderate to high quality evidence comparing people with schizophrenia and an affective psychosis, or in moderate to low quality evidence comparing people with schizophrenia with those with depression, other psychoses, and personality disorders (see evidence table in Appendix 1 for more details). These findings highlight a lack of specificity of childhood adversity as a possible risk factor for schizophrenia.

There are some limitations to these meta-analyses: reliance on retrospective measures of childhood adversity may introduce recall bias; causation and specificity for schizophrenia have not been established; the authors' were unable to investigate dose dependence (a requirement for causation according to Hill Bradford's causation criteria – see Appendix 4).

The second systematic review by Bonoldi (2013)[2] investigated the prevalence of childhood abuse in people with a psychotic disorder. This well conducted (1++) review included 23 retrospective studies (2017 subjects) and calculated a pooled prevalence of self-reported childhood sexual abuse (CSA) of 26% from 20 studies with a high degree of heterogeneity (I^2=83%). The pooled prevalence of self-reported childhood physical abuse (CPA) was 39% from 15 studies. Again there was a high level of statistical heterogeneity of 93%. Finally, the pooled prevalence of self-reported childhood emotional abuse (CEA) was 34% from 8 studies. There was a moderate degree of heterogeneity at 54% (see the forest plots in the evidence table for more details).

The authors' also investigated potential moderating factors that could explain the moderate to high heterogeneity including age, gender, substance abuse, publication year, and clinical setting. Any variations between the primary studies' results included in the meta-analyses could be a result of between-study differences in these factors.

For CSA, age, gender, publication year, and substance abuse were significant moderators explaining about 60% of the observed between-studies heterogeneity. There was no effect for clinical setting. For CPA, publication year, age, clinical setting, and substance abuse explained about 60% of the statistical heterogeneity with age accounting for 40% alone. Gender did not have any effect on heterogeneity. Lastly for CEA, gender, and publication year account for 23% of the heterogeneity observed. Age, clinical setting and substance abuse were not tested due to insufficient data.

The authors discuss these moderating factors and separate substance abuse and gender as "true moderators" from age, publication year, and clinical setting which they call "sampling phenomena". In other words, gender and substance abuse are probably confounding factors i.e. both associated with the outcome, psychotic disorders, whereas the other factors are related to the way the studies were conducted.

[††] post-traumatic stress disorder

Taking these factors into account, the pooled prevalence of childhood abuse is still higher in people with psychotic disorders compared to the general population.

Limitations of this systematic review include: the inability to determine causation as the studies included are not prospective in nature; recall bias is possible because the studies are retrospective; and that there is high statistical heterogeneity. The first limitation cannot be mitigated; recall bias may not be too much of a problem; and the high heterogeneity has been investigated and found reasons i.e. the pooled effect measure is moderated by age, gender, substance abuse, among other factors. This suggests that the results of the study are relatively robust and can be believed.

The third systematic review by Varese (2012)[3] was of good methodological quality (1++) and investigated the association between childhood adversity (sexual abuse, physical abuse, emotional/psychological abuse, neglect, parental death, and bullying) and psychotic disorders by searching the scientific literature for cross-sectional, case-control, and cohort studies. They located 40 studies and in their meta-analysis (N=36 studies) found a significantly increased odds of psychosis of 2.78 in people who had experienced some sort of childhood adversity.

The authors conducted sensitivity analysis by study design and found similar statistically significant pooled odds ratios: 2.72 for the case-control studies; 2.99 for the cross-sectional studies; and, 2.75 for the cohort studies. There was moderate to high heterogeneity for all these results but exploration by sensitivity and subgroup analysis supported the view that the pooled estimates were probably robust.

Assuming a causal relationship between childhood adversity and psychotic disorders, the estimated population attributable risk[‡‡] was 33% (95%CI: 16% to 47%). All these findings suggest that childhood adversity is associated with an increased risk of psychosis.

The forth fair quality (1+) systematic review by van Dam (2012)[4] investigated the association (if any) between childhood bullying and psychotic disorders. They included 14 studies with a total number of subjects of 49,231 and divided these studies into those which sampled from 'non-clinical' populations (participants were recruited from general populations) and those sampled from 'clinical' populations (samples included people who had had at least one contact with mental health services).

Ten studies were included in the 'non-clinical' group and eight had found a significant relationship between being bullied and psychotic symptoms; the other two found a non-significant result after adjustment for other negative life events.

The four 'clinical' studies found no significant association between bullying and psychosis after adjustment for confounding variables.

A meta-analysis of seven population-based studies with similar study designs using unadjusted effect sizes calculated a pooled odds ratio of 2.7 (95%CI: 2.0 to 3.6). When the six studies with adjusted effect sizes were used in the meta-analysis an odds ratio of 2.3 (95%CI: 1.5 to 3.4) was arrived at. Statistical heterogeneity was low for both estimates.

This systematic review supports the role of bullying in the development of psychotic symptoms later in life, particular in population-based samples of study participants.

[‡‡] the proportion of all psychotic disorders in the population which is associated with childhood adversity (NB: this is assuming causality)

Chen (2010)[5] investigated sexual abuse and a lifetime diagnosis of psychiatric disorders by looking at any longitudinal observational studies (case-control and cohort) in the clinical literature. The authors included 37 studies with 3,162,318 participants.

They found that sexual abuse was significantly associated with anxiety disorders, depression, eating disorders, PTSD, sleep disorders and suicide attempts but not schizophrenia or somatoform disorders. No studies were located for obsessive-compulsive disorders or bipolar disorder. The meta-analysis for schizophrenia was based on only two studies (Pettigrew 1997 and Spataro 2004) of which the results for men and women were entered separately for Spataro (2004)[7].

This result contrasts with the findings from Matheson (2013)[1], van Dam (2012)[4], and Varese (2012)[3] and might be explained by the more restrictive inclusion criteria and the effect size from Pettigrew (1997) being an outlier with a wide confidence interval.

The final systematic review is by Bendall (2008)[6] is much wider in its inclusion criteria with 46 studies included that included studies measuring the frequency of childhood trauma[§§] in groups with a psychotic disorder, others which measured the frequency of trauma in groups with a psychotic disorder compared to a comparison group, and also others that measured the frequency of any psychotic disorder in groups who had experienced childhood trauma compared to another comparison group. The results were reported narratively and are summarised in the evidence table in Appendix 1.

From the prevalence studies (N=26), rates of childhood trauma in people with various psychotic disorders ranged from 28% to 73% for childhood trauma; 18% to 61% for childhood sexual abuse; and 10% to 61% for childhood physical abuse.

From the 12 studies in people with psychotic disorders that compared rates of childhood trauma to a control group, seven compared the prevalence of childhood trauma in groups with psychotic disorders with groups with other psychiatric diagnoses, three studies had both a psychiatric and non-clinical control group, and two studies employed a non-clinical control group alone. Of those that employed a control group with an other psychiatric diagnosis, there was no consistent pattern to the prevalence of childhood trauma. These studies are difficult to interpret because using a 'clinical' control group does not adequately answer the question of an association between trauma and psychosis; for an association to be established, childhood trauma must be reported at a greater frequency in people with a psychotic disorder than in a non-clinical control group.

Of the five studies with a non-clinical comparison group, all of them reported a greater frequency of childhood trauma in people with psychosis but only two studies reported that the difference was statistically significant and one reported a non-significant difference. In addition, only two (of the 5 studies) used either a matched or general population comparison group. Again, this makes it very difficult to come to any definitive conclusions as we cannot be certain that the comparison groups are similar to the psychotic groups in all ways except for the psychotic disorder.

The final group of 8 studies measured the frequency of psychosis in groups with childhood trauma compared to a control group. Four of these used a clinical sample for comparison and showed mixed results with 2 studies finding greater prevalence of psychosis in the childhood trauma group (one was statistically significant) and 2 finding less prevalence in the trauma group. The remaining 4 used non-clinical comparison groups; three found a non-significant greater prevalence in the trauma group and the other found a significantly greater prevalence.

[§§] child physical abuse (CPA), child sexual abuse (CSA), child emotional abuse, and childhood neglect

The authors' conclude that this systematic review presents evidence suggestive of an association between childhood trauma and psychotic disorders, however, due to lack of any or adequate control groups and any methodological assessment of study quality at best this review is hypothesis-generating.

5. Additional Information

Although not the focus of this report, other causes and/or risk factors for the development of schizophrenia will give context to the evidence about childhood adversity. Two sources were used (with no formal methodological appraisal): *DynaMed*™[***] and a narrative review by Tandon (2008)[8].

DynaMed™[9]

Causes and risk factors for schizophrenia:

- The cause is likely multifactorial, with multi-gene interaction and environmental influences in susceptible person.

Likely risk factors include:

- genetic or familial disposition
    - heritability about 80% based on twin studies
    - environmental effects may be moderated by genes (gene–environment interaction)
    - epigenetic factors susceptible to environmental influence might also affect twin heritability estimates
    - family members of patients with schizophrenia and bipolar disorder may have increased risk for both disorders
    - specific single nucleotide polymorphisms associated with increased risk of psychiatric illness
    - some genetic conditions associated with increased risk for schizophrenia
    - maternal schizophrenia associated with increased risk of development of schizophrenia spectrum disorders and cannabis-induced psychosis in offspring
- urban birth or residence
- personal or family history of migration
- cannabis (marijuana) use
- substance abuse associated with earlier onset of schizophrenia
- lower-than-expected IQ at age 17 years associated with increased risk for schizophrenia

Possible risk factors:

- prenatal exposures and obstetric complications
    - pre- or perinatal hypoxia
    - maternal infection / stress / malnutrition
    - premature birth
    - low birth weight

[***] a clinical reference resource tool created by physicians for physicians and other health care professionals with conclusions based on the best available clinical evidence which has been consistently and systematically identified, evaluated and selected

Tandon (2008)[8]

Estimates of average relative risk (RR) for schizophrenia due to various genetic and environmental risk factors from a narrative review by Tandon (2008)[8]

• Family history of schizophrenia	RR = 2–70
o Monozygotic twin	RR = 50–70
o Both parents affected	RR = 40–60
o Dizygotic twin or 1st degree relative	RR = 9–18
o 2nd degree relative (e.g., grandparent)	RR = 3–6
o 3rd degree relative (e.g., 1st. cousin)	RR = 2–3
• Any specific single gene variant	RR = 1.1–1.5
• Urbanicity	RR = 2–3
• Migration	RR = 2–3
• 1st or 2nd trimester maternal infection or malnutrition	RR = 2–3
• Winter birth	RR = 1.1
• Obstetric and perinatal complications	RR = 2–3
• Cannabis or stimulant use	RR = 2–3
• Paternal age <35 years	RR = 1.5–3
• Male gender	RR = 1.4

6. Conclusions

The six systematic reviews included in this report found:

- moderate to high quality of evidence from one systematic review that people with schizophrenia have significantly greater odds (OR=3.6) of having experienced childhood adversity compared to non-psychiatric controls [1]
- good quality evidence from one systematic review that childhood adversity and trauma substantially increases the risk of psychosis (OR=2.8)[3]
- good quality evidence from one systematic review that childhood sexual abuse non-significantly increases the risk of psychosis (OR=1.4)[5]
- fair quality evidence from one systematic review that bullying is associated with psychotic disorders (OR=2.3)[4]
- fair to good quality evidence from two systematic reviews that the prevalence of childhood trauma or abuse is higher in people with psychotic disorders than the general population[2 6]

Using Bradford Hill's guide to causation (Appendix 4), the strength of association between childhood adversity or abuse and having a diagnosis of a psychotic disorder is in the order of 2 to 3 increased odds and the association appears to be relatively consistent but not specific to schizophrenia or psychotic disorders[1 5]. Temporality i.e. that the abuse occurs before the development of the psychotic disorder, is not always certain due to the study design used in many studies but there are some prospective studies that demonstrate this. The biological gradient or dose-response i.e. more exposure results in greater risk of developing a psychotic disorder has not been directly investigated ion this report but several authors mention evidence for this[3 10 11]. The association is also plausible (within the limits of present understanding) and there is some coherence with other clinical research[12].

Saying this, the causes of schizophrenia are probably many and involve a complex interaction between genes and the environment, so one cannot conclude that childhood adversity or abuse is a direct and sufficient cause of this disorder. However, there is some

good quality evidence that childhood adversity, including forms of abuse, are a likely risk factor for developing schizophrenia with an odds ratio of between 2 and 3.

7. Limitations

As only English language articles were included, the presence of publication bias in this report is a possibility. In additional, only focussing on systematic reviews may have missed some more recent research, although this is mitigated by discussing some of the recent literature.

8. Appendix 1: Evidence Tables

Reference and study design	Studies	Results
Bendall (2008). "Childhood trauma [CT] and psychotic disorders: a systematic, critical review of the evidence." Schizophrenia Bulletin **34**(3): 568-79. Australia Included studies: *Frequency of CT in groups with psychosis:* Beck 1987, Goff 1991, Greenfield 1994, Ross 1994, Trojan 1994, Darves-Bornoz 1995, Heads 1997, Lysaker 2001, Neria 2002, Scheller-Gilkey 2002, Shaw 2002, Gearon 2003, Offen 2003, Resnick 2003, Compton 2004, Lysaker 2004, Braehler 2005, Hardy 2005, Hlastala 2005, Kilcommons 2005, Lysaker 2005, Lysaker 2004, Neria 2005, Schenkel 2005, Kim 2006, Schafer 2006 *Freq CT in groups with or without psychosis:* Emslie 1983, Haley 1988, Ross 1989, Fink 1990, Nurcombe 1996, Wexler 1997, Frieman 2002, Wurr 1996, Honig 1998, Convoy 1995, Friedman 1984, Nettelbladt 1996 *Freq of psychosis in groups*	Number of studies: N=46 Total number of patients in the studies: n= Inclusion criteria: Studies investigating childhood trauma (CT) and psychotic disorder in any group of individuals; Psychotic disorder = schizophrenia, schizoaffective disorder, schizophreniform disorder, psychosis not otherwise specified, first episode psychosis, delusional disorder, depression with psychotic features, and bipolar disorder with psychotic features; CT = child physical abuse (CPA), child sexual abuse (CSA), child emotional abuse, and childhood neglect. Exclusion criteria: adult and CT were not reported separately; studies of CT in people with serious mental illness, only some of whom had a diagnosis of psychosis; studies where a continuous rather than a discrete measure of CT was utilized; and studies where CT was not measured in all participants; 'overlapping' studies Databases used: PsychINFO, Medline, EMBASE to Nov 2006 + reference lists search	**Studies (N=26) of frequency of childhood trauma in groups with a psychotic disorder** ***Reference*** ***n*** ***CT*** ***CSA*** ***CPA*** ***Population*** Beck 1987 26 46% Inpatient women with chronic psychosis Goff 1991 61 44% Outpatients with chronic psychosis Greenfield 1994 38 53% 29% 45% Inpatients with first episode psychosis Ross 1994 83 45% 25% 31% Inpatients with schizophrenia Trojan 1994 96 26% Inpatients with schizophrenia or ‘‘manic-depressive psychosis’’ Darves-Bornoz 1995 64 36% Inpatient women with schizophrenia Heads 1997 102 20% 36% Inpatients with severe schizophrenia with a history of violence Lysaker 2001 54 35% Outpatients with schizophrenia or schizoaffective disorder Neria 2002 426 32% First-episode psychosis Scheller-Gilkey 2002 40 53% Outpatients with schizophrenia or schizoaffective disorder Shaw 2002 45 13% Inpatients with acute psychosis Gearon 2003 54 61% 48% Outpatient women with schizophrenia or schizoaffective disorder Offen 2003 26 35% Outpatients with psychotic disorders with hallucinations Resnick 2003 47 36% Outpatients with schizophrenia Compton 2004 18 50% 61% Inpatients with first episode psychosis Lysaker 2004 37 38% Outpatient men with schizophrenia or schizoaffective disorder Braehler 2005 14 50% Outpatients with schizophrenia Hardy 2005 75 18% Inpatients and outpatients with non-affective psychosis Hlastala 2005 75 62% Inpatients and outpatients with early onset psychosis Kilcommons 2005 32 13% 10% Outpatients with schizophrenia spectrum disorder Lysaker 2005 65 28% Outpatient men with schizophrenia or schizoaffective disorder Lysaker 2004 30 40% Outpatient men with schizophrenia or schizoaffective disorder Neria 2005 109 28% Inpatients with first episode bipolar disorder with psychosis Schenkel 2005 40 45% Inpatients with schizophrenia or schizoaffective disorder Kim 2006 100 37% 34% Inpatient women with schizophrenia Schafer 2006 30 73% 37% Inpatient women with psychosis **Studies (N=12) of frequency of childhood trauma in groups with a psychotic disorder compared to clinical and/or non-clinical control group(s)** ***Reference*** ***% Childhood trauma*** ***Population vs. control group (number)*** ***Trauma type*** *'Psychosis' group Comparison group* Emslie 1983 10% 50% Inpatient girls with severe psychosis (10) vs. inpatient girls with severe non-psychotic disorders (16) CSA Haley 1988 67% 11%* Adolescents with depression with psychotic features (15) vs.

with or without CT: Brown 1991, Pribor 1992, Cohen 1996, Briere 1997, Famularo 1992, Stein 1988, Janssen 2004	Description of the methodological assessment of studies: not reported Fixed or variable effects: not applicable Heterogeneity: not discussed				adolescents with depression without psychotic features (18)	CSA
		Ross 1989	10%	80%*	Schizophrenia (20) vs. Multiple personality disorder (20)	CSA
			25%	75%*	Schizophrenia (20) vs. Multiple personality disorder (20)	CPA
			10%	10%	Schizophrenia (20) vs. Panic disorder (20)	CSA
			25%	5%	Schizophrenia (20) vs. Panic disorder (20)	CPA
			10%	20%	Schizophrenia (20) vs. Eating disorder (20)	CSA
			25%	25%	Schizophrenia (20) vs. Eating disorder (20)	CPA
		Fink 1990	9%	64%*	Schizophrenia (11) vs. Borderline personality disorder (11)	CSA
			18%	64%*	Schizophrenia (11) vs. Borderline personality disorder (11)	CPA
			9%	94%*	Schizophrenia (11) vs. Multiple personality disorder (16)	CSA
			18%	75%*	Schizophrenia (11) vs. Multiple personality disorder (16)	CPA
		Nurcombe 1996	55%	77%	Schizophrenia, schizophreniform disorder, or dissociative hallucinosis (22) vs. Post- traumatic stress disorder (13)	CSA
			41%	23%	Schizophrenia, schizophreniform disorder, or dissociative hallucinosis (22) vs. post-traumatic stress disorder (13)	CPA
		Wexler 1997	19%	36%	Schizophrenia (217) vs. Depression (212)	CT
		Frieman 2002	32%	19% NS	Schizophrenia (22) vs. Anxiety (160)	CSA
			32%	43% NS	Schizophrenia (22) vs. Anxiety (160)	CPA
			32%	39% NS	Schizophrenia (22) vs. Depression (19)	CSA
			32%	40% NS	Schizophrenia (22) vs. Depression (19)	CPA
		Wurr 1996	38%	49%	Schizophrenia and related psychoses (34) vs. non-psychotic inpatients (86)	CSA
			38%	10%	Schizophrenia and related psychoses (34) vs. non-clinical controls (2019)	CSA
		Honig 1998	83%	86%	Schizophrenia (18) vs. Dissociative disorder (15)	CT
			17%	57%*	Schizophrenia (18) vs. Dissociative disorder (15)	CSA
			61%	67%	Schizophrenia (18) vs. Dissociative disorder (15)	CPA
			83%	73%	Schizophrenia (18) vs. Hallucinatory non-patients [sic] (15)	CT
			17%	47%	Schizophrenia (18) vs. Hallucinatory non-patients [sic] (15)	CSA
			61%	47%	Schizophrenia (18) vs. Hallucinatory non-patients [sic] (15)	CPA
		Convoy 1995	16%	20% NS	Psychosis (100) vs. ‘‘Neuroses’’ (100)	CSA
			16%	15% NS	Psychosis (100) vs. "Alcoholism’’ (100)	CSA
			16%	11% NS	Psychosis (100) vs. Non-psychiatric controls (100)	CSA
		Friedman 1984	60%	13%*	Schizophrenia (20) vs. Non-psychiatric controls (15)	CSA
		Nettelbladt 1996	47%	6%*	Schizoaffective disorder (17) vs. Combined non-psychotic groups (54)	CSA

Studies (N=8) of frequency of a psychotic disorder in groups with childhood trauma compared to clinical and/or non-clinical control group(s)

Reference	***% with psychosis***		***Population vs. control group (number)***	***Psychosis type***
	CT group	*Comparison group*		
Brown 1991	2%	12%	CSA/CPA (166) vs. No CSA/CPA (853)	Schizophrenia, delusional disorder
Pribor 1992	4%	0%*	CSA by family member (52) vs. No CSA/CPA (23)	Schizophrenia/form

		Cohen 1996	6%	14%	CSA/CPA (70) vs. No CSA/CPA (35)	Psychosis
		Briere 1997	53%	25%	CSA (49) vs. No CSA (44)	Psychosis
			49%	33%	CPA (39) vs. No CPA (54)	Psychosis
		Famularo 1992	9%	0% NS	Documented maltreatment (61) vs. no maltreatment (35)	Psychosis
		Stein 1988	3%	0.3% NS	CSA (82) vs. No CSA or adult sexual abuse (2601)	Schizophrenia spectrum
		Janssen 2004	0.9%	0.1%*	CA (412) vs. No CA (3595)	Psychosis
		Spataro 2004	0.8%	0.7% NS	Children on Victorian State sexual abuse register (1612) vs. not on register (3139745)	Schizophrenic disorders

*=p<0.05 i.e. statistically significant; NS=not statistically significant @ 0.05; n= numbers of subjects in study

CT=childhood trauma; CSA=child sexual abuse; CPA=child physical abuse

Conclusion

Authors' conclusions: The lack of adequate control groups has severely limited the conclusions that can be drawn from the reviewed studies, with only 6 studies able to adequately address the association between CT and psychosis. Of these, 3 found an association between CT and psychosis (Wurr 1996; Nettlebladt 1996; Janssen 2004), 2 found potentially real differences that failed to reach significance (Famularo 1992; Stein 1988), and the last had systematic methodological biases (Spataro 2004) that could explain the lack of association.
The methodological differences between these studies preclude quantification of any association by meta-analysis.
Nonetheless, these studies present preliminary evidence of an association between CT and psychosis, but one that must be seen in light of the following methodological problems.
Reviewer's conclusion: This systematic review presents evidence suggestive of an association between childhood trauma and psychotic disorders but is not definitive and, at best, is hypothesis-generating..

Study type: Systematic review

Quality: 1+

Comments: Wide ranging systematic review with appropriately no meta-analysis; Adequate search of multiple guidelines; No formal methodological assessment but good narrative of methodological limitations; Only 6 studies able to estimate any association;

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions

Bonoldi (2013). "Prevalence of self-reported childhood abuse in psychosis: A meta-analysis of retrospective studies." Psychiatry Research **210**(1): 8-15. UK/Italy Included studies: Craine 1988, Goff 1991, Palmer 1992, Greenfield 1994, Honig 1998, Scheller-Gilkey 2002, Resnick 2003, Gearon 2003, Hardy 2005, Kilcommons 2005, Schafer 2006, Lysaker 2007, Rosenberg 2007, Ucok 2007, Beattie 2009, Dorahy 2009, Mason 2009, Fisher 2009, Rubino 2009, Conus 2010, Kingdon 2010, Vogel 2011, Alvarez 2011	Number of studies: N=23 Total number of patients in the studies: n=2017 Inclusion criteria: original retrospective study in a peer-reviewed journal; had involved inpatient, outpatient or mixed sample of patients with DSM or ICD psychosis in a retrospective design; and had measured childhood sexual / physical / emotional abuse (CSA, CPA or CEA) with psychometric instruments; the abuse had to occur before the person was 18 yrs of age Exclusion criteria: psychometric instruments not clearly defined; chart reviews; studies just asking whether a person had been abused Databases used: Pubmed, EMBASE (to July 2011) plus reference list search Description of the methodological assessment of studies: MOOSE approach Fixed or variable effects: random effects Heterogeneity: I2 statistic Patient characteristics: Mean age = 36.6 yrs (SD 6.07) 45.6% women	Childhood abuse (sexual, physical or emotional)	Event rate (prevalence) Moderating factors	Prevalence of self-reported CSA in people with psychosis (N=20 studies) **26.3% (95%CI: 21.2 to 32.1%)** I^2=83% Prevalence of self-reported CPA in people with psychosis (N=15 studies) **38.8% (95%CI: 36.2 to 41.4%)** I^2=93% Prevalence of self-reported CEA in people with psychosis (N=8 studies) **34.0% (95%CI: 29.7 to 38.5%)** I^2=54% CSA: age, gender, publication year, and substance abuse were significant moderators explaining about 60% of the observed between-studies heterogeneity; there was no effect for clinical setting i.e. out- or in-patient CPA: Publication year, age, clinical setting, and substance abuse explained about 60% of the statistical heterogeneity with age accounting for 40% alone; gender did not have any effect on heterogeneity CEA: Gender, and publication year account for 23% of the heterogeneity observed; age, clinical setting and substance abuse were not tested due to insufficient data	Authors' conclusion: "In psychotic patients, the proportion of self-reported childhood abuse, as investigated retrospectively, is consistently high and moderated by different methodological and sociodemographic factors." Reviewer's conclusion: Well conducted systematic review with meta-analysis finding pooled estimates of CSA in people with psychosis at about 26%, CPA at 40%, and CEA at 34%. Limitations include the high degree of heterogeneity across studies, explained by moderating factors in CSA and CPA; the use of retrospective studies may introduce recall bias; this review does not test any causal hypothesis.

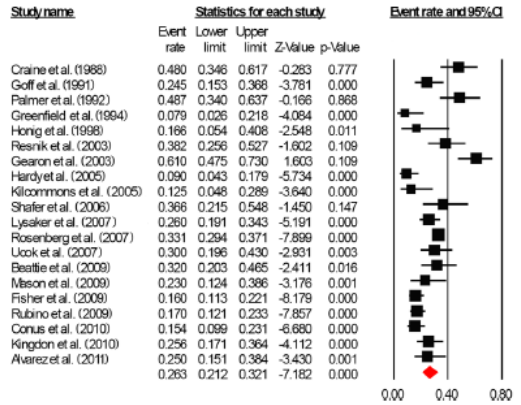


Fig. 2. Prevalence of self-reported CSA in psychosis, random effect models applied.

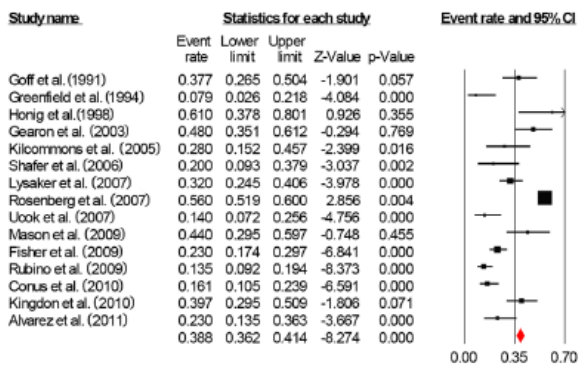


Fig. 3. Meta-analysis of self- reported CPA in psychosis, random effect models applied.

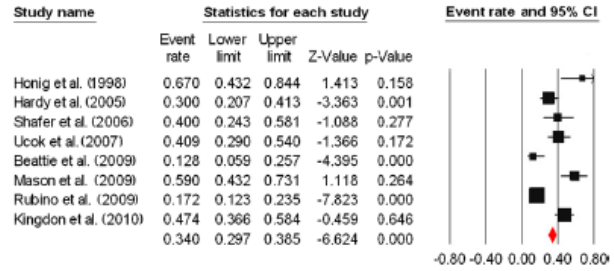


Fig. 4. Meta-analysis of self-reported CEA in psychosis, random effect models applied.

Study type: Systematic review with meta-analysis

Quality: 1++

Comments: Well conducted SR with meta-analysis. Systematic search of two databases. No language restriction reported. Publication bias assessed by funnel plot and statistical tests – no obvious pub bias present. Methodological assessment adequate. Sensitivity analysis undertaken by study quality. Heterogeneity considered. Subgroup analysis undertaken. Meta-analysis appears appropriate.

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Chen (2010). "Sexual abuse and lifetime diagnosis of psychiatric disorders: systematic review and meta-analysis." Mayo Clinic Proceedings **85**(7): 618-29. USA Included studies: *Case-control studies*: Brown 1997, Cachelin 2005, Cheasty 1998, De Bellis 1994, Deep 1999, Figueroa 1997, Garnefski 1992, Pettigrew 1997, Price 2002, Roelofs 2002, Spitzer 2008, Steiger 2000, Striegel-Moore 2002, Stuart 1990, Tanskanen 2004, Welch 1996, Wise 2001 *Cohort studies*: Aglan 2008, Brezo 2008, Brown 1999, Buist 2001, Chowdhary 2008, Dinwiddie 2000, Ernst 1993, Fergusson 2000, Fergusson 2002, Fergusson 2008, Fiorentine 1999, Frank 1987, Gutner 2006, Harvey 1994, Kolko 2003, Pearce 2008, Plunkett 2001, Rimsza 1988, Spataro 2004, Widom 1999	Number of studies: N=37 (17 case-control, 20 cohort) Total number of patients in the studies: n=3,162,318 Inclusion criteria: cohort and case-control studies comparing individuals with a history of sexual abuse to another control group; outcomes included anxiety disorders, bipolar disorder, depression, eating disorders, obsessive-compulsive disorder, PTSD, schizophrenia, sleep disorders, somatoform disorders, and suicide attempts. Exclusion criteria: none reported Databases used: PsychINFO, Medline, EMBASE, CINAHL, Current Contents, ACP Journal Club, CCTR, CDSR & DARE (Jan 1980 to Dec 2008) Description of the methodological assessment of studies: Newcastle-Ottawa assessment scale Fixed or variable effects:	Sexual abuse‡‡‡	Odds ratio (OR) of lifetime diagnosis of a psychiatric disorder	Anxiety disorder (N=8 studies) OR=3.09 (95% CI: 2.43 to 3.94) I^2=40% Depression (N=16 studies) OR=2.66 (2.14 to 3.30) I^2=57% Eating disorders (N=11 studies) OR=2.72 (2.04 to 3.63) I^2=20% Post-traumatic stress disorder (N=3) OR=2.34 (1.59 to 3.43) I^2=0% Sleep disorders (N=1) OR=16.17 (2.06 to 126.76) I^2 not applicable Suicide attempts (N=19) OR=4.14 (2.98 to 5.76) I^2=60% Schizophrenia (N=3) OR=1.36 (0.81 to 2.03) I^2=0% Somatoform disorders (N=3) OR=1.90 (0.81 to 4.47) I^2=4% No studies located for bipolar or obsessive-compulsive disorders	Authors' conclusion: A history of sexual abuse is associated with an increased risk of a lifetime diagnosis of multiple psychiatric disorders. There was no statistically significant association between sexual abuse and a diagnosis of schizophrenia or somatoform disorders. Reviewer's conclusion: Well conducted systematic review that found no statistically significant association between sexual abuse and a lifetime diagnosis of schizophrenia. This is based on a meta-analysis of only 2 studies.

‡‡‡ see full text paper for definition

	random effects Heterogeneity: I^2 statistic				

Study type: Systematic review with meta-analysis

Quality: 1++

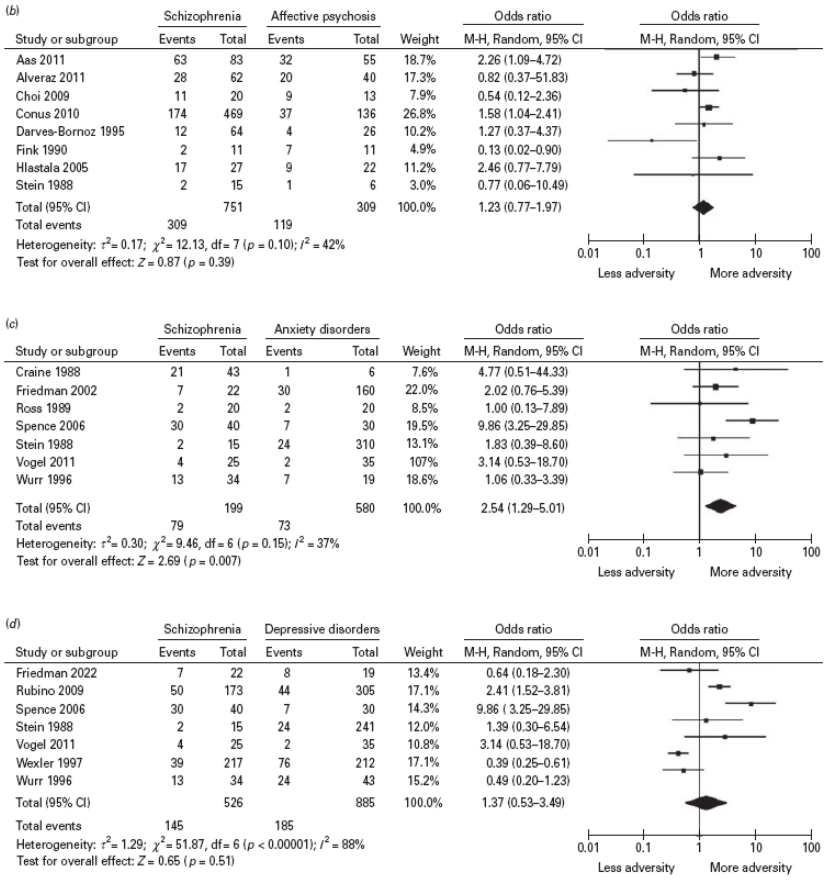
Comments: Well conducted SR with meta-analysis. Comprehensive search of multiple databases. No language restriction. Unpublished research included. Publication bias assessed by funnel plot and statistical tests – no obvious pub bias present. Methodological assessment good. Sensitivity analysis undertaken. Heterogeneity considered. Subgroup analysis undertaken. Meta-analysis appears appropriate.

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Matheson (2013). "Childhood adversity in schizophrenia: a systematic meta-analysis." Psychological Medicine 43(2): 225-38. Australia Included studies: **Friedman 1984**; Craine 1988; Stein 1988; Ross 1989; Byrne 1990; Fink 1990; Goff 1991; Darves-Bornoz 1995; **Nettelbladt 1996**; Nurcombe 1996; Wurr 1996; Wexler 1997; **Honig 1998**; Friedman 2002; Hlastala 2005; Spence 2006; Choi 2009; **Rubino 2009;** Conus 2010; **Husted 2010**; Kingdon 2010; **McCabe 2012**; **Aas 2011**; Alvarez 2011; Vogel 2011 NB: bolded studies were those included in schizophrenia vs. non-psychiatric controls meta-analysis	Number of studies: N=25 (18 cross-sectional, 7 case-control) Total number of patients in the studies: n=5, 359 Inclusion criteria: cohort, case-control and cross-sectional studies reporting rates of childhood adversity (age <18 years; including sexual abuse, physical abuse and neglect) in people with a diagnosis of schizophrenia (i.e. schizophrenia, schizo-affective disorder or schizophreniform disorder) and non-psychiatric controls or in people with other psychiatric disorders; no limits on language or publication status Exclusion criteria: none reported Databases used: PsychINFO, Medline, EMBASE (conducted Sept 2011) + reference list search Description of the methodological assessment of studies: study reporting assessed by STROBE[§§§] checklist; pooled evidence	Childhood adversity (i.e. sexual or physical abuse or neglect)	Odds ratio (OR)	Schizophrenia vs. non-psychiatric controls: N=7 **OR=3.60 (95%CI: 2.08 to 6.23)** • Data imprecise but consistent (without the outlier) • Moderate heterogeneity i.e. I^2=65% • No difference in results due to adversity types or measure Schizophrenia vs. affective psychosis: N=8 **OR=1.23 (95%CI: 0.77 to 1.97)** • Data imprecise but consistent • Low/moderate heterogeneity i.e. I^2=42% • No difference in results due to diagnosis, adversity types or measure Schizophrenia vs. anxiety disorders: N=7 **OR=2.54 (95%CI: 1.29 to 5.01)** • Data imprecise but consistent • Low heterogeneity i.e. I^2=37% • Significant difference in results due adversity type i.e. 5 studies of sexual abuse found no differences between groups (OR=1.66; 95%CI: 0.90 to 3.08) but 2 studies with mixed sexual/physical abuse and neglect reporting greater childhood adversity in schizophrenia (OR=6.95; 95%CI: 2.48 to 19.51); other subgroup analyses showed no difference by adversity measure or diagnosis. Schizophrenia vs. depressive disorder: N=7 **OR=1.37 (95%CI: 0.53 to 3.49)**	Authors' conclusion: These findings indicate moderate to high quality evidence of increased childhood adversity in schizophrenia patients compared to non-psychiatric controls. This evidence is consistent (without the outlier), of medium to large effect, uses large samples, but has considerable imprecision. Reviewer's conclusion: Well conducted systematic review with meta-analysis that indicates that people with schizophrenia have greater odds of having experienced childhood adversity compared to non-psychiatric control groups. Of concern is the moderate heterogeneity present however exploration of the heterogeneity by sensitivity and subgroup analysis supported that the pooled estimate is probably robust.

[§§§] Strengthening the Reporting of Observational Studies in Epidemiology

	quality assessed by GRADE[****] approach <u>Fixed or variable effects</u>: random effects <u>Heterogeneity</u>: I^2 statistic			• Data imprecise • Considerable heterogeneity i.e. I^2=88% <u>Schizophrenia vs. dissociative disorders and PTSD:</u> N=4 **OR=0.03 (95%CI: 0.01 to 0.15)** • Data imprecise but consistent • Moderate heterogeneity i.e. I^2=51% <u>Schizophrenia vs. other psychosis:</u> N=3 **OR=0.69 (95%CI: 0.28 to 1.68)** • Data imprecise but consistent • Low heterogeneity i.e. I^2=2% <u>Schizophrenia vs personality disorders:</u> N=3 **OR=0.65 (95%CI: 0.09 to 4.77)** • Data imprecise but consistent • Substantial heterogeneity i.e. I^2=80%	
Forest plots for meta-analyses					

[****] Grading of Recommendations Assessment, Development and Evaluation



Study type: Systematic review with meta-analysis

Quality: 1++

Comments: Well conducted SR with meta-analysis. Multiple databases searched. No language restriction. Unpublished research included. Publication bias assessed by funnel plot– no obvious pub bias present. Methodological assessment adequate. Heterogeneity considered. Planned subgroup and sensitivity analysis undertaken. Meta-analysis appears appropriate.

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions

van Dam (2012). "Childhood bullying and the association with psychosis in non-clinical and clinical samples: a review and meta-analysis." Psychological Medicine **42**(12): 2463-2474. UK/Netherlands Included studies: *Non-clinical-based sample studies*: Morrison 2003, Lataster 2006, Campbell 2007, De Loore 2007, Nishida 2008, Kelleher 2008, Schreier 2009, Arsenault 2011, Mackie 2011, van Nierop 2011, *Clinical-based sample studies*: Bebbington 2004, Sourander 2007/2009, Luukkonen 2010	Number of studies: N=14 Total number of patients in the studies: n=49231 Inclusion criteria: original research papers; published in English; reported information about psychosis outcome (i.e. non-clinical psychotic symptoms or psychotic symptoms or diagnosis of psychosis or the use of antipsychotics); and reported any information about being bullied as the exposure variable. Exclusion criteria: studies were bullying was only analysed as a confounding variable and bullying was not analysed separately but was part of an overall variable (e.g. victimization). Databases used: Pubmed, EMBASE, and PsychINFO (to Nov 2011) plus reference search Description of the methodological assessment of studies: not reported Fixed or variable effects: random effects	Childhood bullying	Non-clinical populations†††† (N=10) Meta-analysis (N=7) Clinical populations‡‡‡‡	N=8 studies found a significant relationship between being bullied and psychotic symptoms in non-clinical samples N=2 studies initially found a significant effect which became non-significant after adjustment for other negative life events Unadjusted effect sizes (N=7 studies) **OR=2.7 (95%CI: 2.0 to 3.6)** I^2=15%§§§§ Adjusted effect sizes (N=6 studies) **OR=2.3 (1.5 to 3.4)** I^2=6% N=4 studies found no significant association between bullying and psychosis after adjustment for confounders	Authors' conclusion: "Although there is some evidence of an association between bullying and psychosis in clinical samples, the research is too sparse to draw any firm conclusions. However, population-based non-clinical studies support the role of bullying in the development of psychotic symptoms later in life. These findings are consistent with findings of an increased risk of psychotic symptoms among those exposed to other types of abuse." Reviewer's conclusion: Appears to be an adequately conducted systematic review with conservative meta-analysis and narrative synthesis. This paper suggests that there is some emerging evidence that there may be an association between bullying and psychosis in clinical populations. However, in non-clinical populations the evidence of an association is stronger.

†††† participants were recruited from general populations

‡‡‡‡ samples included people who had had at least one contact with mental health services

§§§§ calculated from the Cochran Q using $I^2 = (Q - df)/Q \times 100$ [df=number of studies – 1]

	Heterogeneity: Cochran Q test Patient characteristics: Mean age = 36.6 yrs (SD 6.07) 45.6% women				
Study type: Systematic review with meta-analysis **Quality: 1+** **Comments:** Adequately conducted SR with meta-analysis. Systematic search of three databases. Methodological assessment not reported. Publication bias assessed by funnel plot– "difficult to interpret because of the limited number of studies but did not suggest any evidence of publication bias. Meta-analysis appears appropriate. Narrative synthesis as well.					

Reference and study design	Studies	Exposure	Outcome measure	Results/effect size	Conclusions
Varese (2012). "Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies." Schizophrenia Bulletin 38(4): 661-71. UK / Netherlands / NZ Included studies: *Case-control studies:* Friedman 1984, Convoy 1995, Furukawa 1998, Agid 1999, Dell' Erba 2003, Giblin 2004, Fennig 2005, Morgan 2007, Weber 2008, Rubino 2009, Cohen 2010, Fisher 2010, Husted 2010, Bartels-Velthuis 2011, Evans 2011 (unpublished doctoral dissertation), Heins 2011, Varese 2011, Daalman 2012 (personal communication), McCabe 2012 *Prospective cohort studies:* Mäkikyrö 1998, Janssen 2004, Spauwen 2006, De Loore 2007, Schreier 2009, Arseneault 2011, Cutajar 2010, Wigman 2011	Number of studies: N=40 (13 cross-sectional, 19 case-control, 8 cohort) Meta-analysis: N=36 studies (8 cross-sectional, 18 case-control, 10 prospective studies) Total number of patients in the studies: n=81,253 Inclusion criteria: Any published or unpublished empirical study***** after 1980 of childhood trauma and psychosis; languages include English, Dutch, French, German, Italian, Portuguese & Spanish; trauma occurred when subjects were <18 yrs Exclusion criteria: Insufficient statistical information in paper to calculate OR; heterogeneous psychiatric populations; organic, drug-induced or secondary psychosis; prodromal population; use of schizotypal personality measures. Databases used: PsychINFO, PubMed, EMBASE, Web of Sciance (1906 to 2011) + reference list search	Childhood adversity (i.e. sexual, physical, emotional/psychological abuse, neglect, parental death & bullying)	Odds ratio (OR)	Pooled estimate from 36 studies: **OR=2.78 (95%CI: 2.34 to 3.31)** I^2=72.7% Case-control studies (N=17‡‡‡‡‡ OR=2.72 (1.90 to 3.88) I^2=76.9% Cross-sectional studies OR=2.99 (2.13 to 4.20) I^2=73.0% Cohort studies OR= 2.75 (2.17 to 3.47) I^2=67.6% Meta-analyses of specific adverse experiences: Sexual abuse (N=20 studies) OR=2.38 (95%CI: 1.98–2.87), I^2=44.9 Physical abuse (N=13) OR=2.95 (2.25–3.88), I^2=74.9 Emotional abuse (N=6) OR=3.40 (2.06–5.62), I^2=78.3 Bullying (N=6) OR=2.39 (1.83–3.11), I^2=73.9 Parental death (N=8) OR=1.70 (0.82–3.53), I^2=80.2 Neglect(N=7) OR=2.90 (1.71–4.92), I^2=81.8	Authors' conclusion: "This review finds that childhood adversity and trauma substantially increases the risk of psychosis with an OR of 2.8." Reviewer's conclusion: This study suggests that childhood adversity was associated with higher odds of developing psychosis. There was significant amount of statistical and clinical heterogeneity which limits the certainty of the conclusion, however exploration of the heterogeneity by sensitivity and subgroup analysis supported that the pooled estimate is probably robust.

***** prospective cohort, large-scale cross-sectional studies, & case-control studies

Cross-sectional studies: Murphy 1988, Ross 1992, Whitfield 2005, Kim 2005, Shevlin 2007, Shevlin 2008, Houston 2008, Kelleher 2008, Nishida 2008, Shevlin 2010, Harley 2010, Bebbington 2011, Van Nierop 2011	Description of the methodological assessment of studies: study reporting assessed by MOOSE†††††† reporting checklist Fixed or variable effects: random effects Heterogeneity: I^2 statistic		Population attributable risk (PAR)	**PAR=33% (95%CI: 16 to 47%)** NB: 4 studies were not included in the meta-analysis (reasons not given) and two studies, one reported as a case-control study and the other as a cross-sectional study were included in the prospective cohort study section in the meta-analysis; whether this influences the results is unclear.	
Study type: Systematic review with meta-analysis **Quality: 1++** **Comments:** Well conducted SR with meta-analysis. Multiple databases searched. No language restriction. Unpublished research included. Publication bias assessed by funnel plot– no obvious pub bias present. Methodological assessment not reported. Heterogeneity considered. Subgroup & sensitivity analysis undertaken –reported narratively. Meta-analysis appears appropriate.					

‡‡‡‡‡ one study was divided into men and women and entered as two studies into the meta-analysis

††††† Meta-analysis of Observational Studies in Epidemiology reporting checklist

9. Appendix 2: Excluded Study Table

Reference	Reason for exclusion
Bartels-Velthuis 2012	in Varese 2012
Bendall 2013	editorial
Cannon 2002	narrative review – levels of analysis in aetiological research
Cantor-Graae 2007	narrative review
Cutajar 2010	in Varese 2010
Forguet 2009	not in English
Gejman 2010	narrative review (genetics aetiology) – doesn't mention adversity
Green 2010	psychotic disorders not included
Heimans 2013	not in English
Insel 2010	narrative review – not about causation
Krabbendam 2008	narrative review
Keshavan 2008	narrative review (pt 3) - doesn't mention adversity
Kopfhammer 2013	not in English
Lakhan 2009	narrative review - doesn't mention adversity
Larkin 2008	narrative review
Lataster 2011	not a systematic review
Meyer-Lindenberg	narrative review - neuroimaging
Morgan 2007	narrative review
Picchioni 2007	narrative review – overview
Read 2012	narrative review / editorial
Read 2005a	narrative review
Read 2005b	narrative review
Read 2009	narrative review
Skehan 2012	narrative review
Spataro 2004	in Bendall 2008 and Chen 2010
van Os 2009	narrative review
van Os 2010	narrative review
van Winkel 2013	narrative review
Whitfield 2005	in Varese 2012

10. Appendix 3: Heterogeneity and the I^2 statistic

Heterogeneity is the variation between the results of a set of studies. It can be clinical, methodological and/or statistical.

Causes of clinical heterogeneity include differences between the studies with respect to participants, interventions, and/or outcome.

Methodological heterogeneity can be caused by differences between the studies with respect to design and/or conduct e.g. blinding, allocation concealment etc.

Statistical Heterogeneity is the excessive variation in the results of studies above that expected by chance; identified graphically and by using a statistical test e.g. the "I^2" statistic.

I^2 statistic	**Suggested Interpretation from Matheson (2013)[1]**
0-40%	might not be important
50-75%	may be important
> 75%	should be regarded as considerable

The degree of heterogeneity measured by the I^2 statistic assists the systematic reviewer in deciding whether a meta-analysis is appropriate and, if so, what model to use in pooling the studies results.

11. Appendix 4: Bradford Hill's Criteria of Causation[13]

A suggested guide to assessing the likelihood of causation

- **Strength of the association**: A small association does not mean that there is not a causal effect, though the larger the association, the more likely that it is causal.
- **Consistency of the association**: Consistent findings observed by different persons in different places with different samples strengthens the likelihood of an effect.
- **Specificity**: Causation is likely if a very specific population at a specific site and disease with no other likely explanation. The more specific an association between a factor and an effect is, the bigger the probability of a causal relationship.
- **Temporality**: The effect has to occur after the cause (and if there is an expected delay between the cause and expected effect, then the effect must occur after that delay).
- **Biological gradient**: Greater exposure should generally lead to greater incidence of the effect. However, in some cases, the mere presence of the factor can trigger the effect. In other cases, an inverse proportion is observed: greater exposure leads to lower incidence.
- **Plausibility:** A plausible mechanism between cause and effect is helpful (but Hill noted that knowledge of the mechanism is limited by current knowledge).
- **Coherence**: Coherence between epidemiological and laboratory findings increases the likelihood of an effect. However, Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations".
- **Experiment**: "Occasionally it is possible to appeal to experimental evidence".
- **Analogy**: The effect of similar factors may be considered.

12. References

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