Evidence-Based Report

Childhood Adversity and Psychotic Disorders

<table>
<thead>
<tr>
<th>Reviewer</th>
<th>Mark Ayson</th>
</tr>
</thead>
<tbody>
<tr>
<td>Literature search</td>
<td>Amanda Bowens</td>
</tr>
<tr>
<td>Date Report Completed</td>
<td>5 June 2014</td>
</tr>
</tbody>
</table>

**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:

<table>
<thead>
<tr>
<th>Levels of evidence (LOE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
</tr>
<tr>
<td>1+</td>
</tr>
</tbody>
</table>

* Scottish Intercollegiate Guidelines Network [http://www.sign.ac.uk/](http://www.sign.ac.uk/)
<table>
<thead>
<tr>
<th>Level</th>
<th>Type of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>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</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>
4. Findings

Systematic reviews

Six systematic reviews are included in this report: Matheson (2013), Bonoldi (2013), Varese (2012), van Dam (2012), Chen (2010), and Bendall (2008).

The most recent systematic review by Matheson (2013) 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 (I²=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 I² 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 1999). 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, I²=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

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Schizophrenia</th>
<th>Controls</th>
<th>Weight</th>
<th>M-H, Random, 95% CI</th>
<th>M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>Ax 2011</td>
<td>21</td>
<td>83</td>
<td>15</td>
<td>138</td>
<td>17.9</td>
</tr>
<tr>
<td>Fraldman 1984</td>
<td>12</td>
<td>20</td>
<td>2</td>
<td>16</td>
<td>7.2%</td>
</tr>
<tr>
<td>Honig 1998</td>
<td>3</td>
<td>18</td>
<td>5</td>
<td>15</td>
<td>7.9%</td>
</tr>
<tr>
<td>Husted 2010</td>
<td>15</td>
<td>79</td>
<td>1</td>
<td>86</td>
<td>14.7%</td>
</tr>
<tr>
<td>McCal 2012</td>
<td>354</td>
<td>408</td>
<td>186</td>
<td>267</td>
<td>23.2%</td>
</tr>
<tr>
<td>Nettlebladt 1996</td>
<td>9</td>
<td>17</td>
<td>3</td>
<td>62</td>
<td>10.8%</td>
</tr>
<tr>
<td>Ricci 2009</td>
<td>50</td>
<td>173</td>
<td>19</td>
<td>216</td>
<td>26.4%</td>
</tr>
<tr>
<td>Total (65% CI)</td>
<td>799</td>
<td>982</td>
<td>100%</td>
<td>26.9</td>
<td>(2.08-6.23)</td>
</tr>
<tr>
<td>Total events</td>
<td>464</td>
<td>237</td>
<td></td>
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</tr>
</tbody>
</table>

Heterogeneity: I²=65%

Test for overall effect: Z=4.58 (p<0.00001)

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1 odds ratio
2 95% confidence interval
3 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 I² statistic
4 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 with 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 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) 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) 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) 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).

This result contrasts with the findings from Matheson (2013), van Dam (2012), and Varese (2012) 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) 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).

DynaMed™

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

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*** 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)\textsuperscript{8}

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

- Family history of schizophrenia
  - Monozygotic twin \( RR = 50–70 \)
  - Both parents affected \( RR = 40–60 \)
  - Dizygotic twin or 1st degree relative \( RR = 9–18 \)
  - 2nd degree relative (e.g., grandparent) \( RR = 3–6 \)
  - 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\textsuperscript{1}
- good quality evidence from one systematic review that childhood adversity and trauma substantially increases the risk of psychosis (OR=2.8)\textsuperscript{3}
- good quality evidence from one systematic review that childhood sexual abuse non-significantly increases the risk of psychosis (OR=1.4)\textsuperscript{5}
- fair quality evidence from one systematic review that bullying is associated with psychotic disorders (OR=2.3)\textsuperscript{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\textsuperscript{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\textsuperscript{15}. 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 on this report but several authors mention evidence for this\textsuperscript{3,10,11}. The association is also plausible (within the limits of present understanding) and there is some coherence with other clinical research\textsuperscript{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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
</table>

**Schizophrenia Bulletin 34(3): 568-79.**

**Australia**

**Included studies:**


**Freq of psychosis in groups**

### Studies (N=26) of frequency of childhood trauma in groups with a psychotic disorder

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>CT</th>
<th>CSA</th>
<th>CPA</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beck 1987</td>
<td>26</td>
<td>46%</td>
<td></td>
<td></td>
<td>Inpatient women with chronic psychosis</td>
</tr>
<tr>
<td>Goff 1991</td>
<td>61</td>
<td>44%</td>
<td></td>
<td></td>
<td>Outpatients with chronic psychosis</td>
</tr>
<tr>
<td>Greenfield 1994</td>
<td>38</td>
<td>53%</td>
<td>29%</td>
<td>45%</td>
<td>Inpatients with first episode psychosis</td>
</tr>
<tr>
<td>Ross 1994</td>
<td>83</td>
<td>45%</td>
<td>25%</td>
<td>31%</td>
<td>Inpatients with schizophrenia</td>
</tr>
<tr>
<td>Trojan 1994</td>
<td>96</td>
<td>26%</td>
<td></td>
<td></td>
<td>Inpatients with schizophrenia or &quot;manic-depressive psychosis&quot;</td>
</tr>
<tr>
<td>Darves-Bornoz 1995</td>
<td>64</td>
<td>36%</td>
<td></td>
<td></td>
<td>Inpatient men with schizophrenia</td>
</tr>
<tr>
<td>Heads 1997</td>
<td>102</td>
<td>20%</td>
<td>36%</td>
<td></td>
<td>Inpatients with severe schizophrenia with a history of violence</td>
</tr>
<tr>
<td>Lysaker 2001</td>
<td>54</td>
<td>35%</td>
<td></td>
<td></td>
<td>Outpatients with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Neria 2002</td>
<td>426</td>
<td>32%</td>
<td></td>
<td></td>
<td>First-episode psychosis</td>
</tr>
<tr>
<td>Scheller-Gilkey 2002</td>
<td>40</td>
<td>53%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Shaw 2002</td>
<td>45</td>
<td>13%</td>
<td></td>
<td></td>
<td>Inpatients with acute psychosis</td>
</tr>
<tr>
<td>Gearon 2003</td>
<td>54</td>
<td>61%</td>
<td>48%</td>
<td></td>
<td>Outpatient women with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Offen 2003</td>
<td>26</td>
<td>35%</td>
<td></td>
<td></td>
<td>Outpatients with psychiatric disorders with hallucinations</td>
</tr>
<tr>
<td>Resnick 2003</td>
<td>47</td>
<td>36%</td>
<td></td>
<td></td>
<td>Outpatients with schizophrenia</td>
</tr>
<tr>
<td>Compton 2004</td>
<td>18</td>
<td>50%</td>
<td>61%</td>
<td></td>
<td>Inpatients with first episode psychosis</td>
</tr>
<tr>
<td>Lysaker 2004</td>
<td>37</td>
<td>38%</td>
<td></td>
<td></td>
<td>Outpatient men with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Braehler 2005</td>
<td>14</td>
<td>50%</td>
<td></td>
<td></td>
<td>Outpatients with schizophrenia</td>
</tr>
<tr>
<td>Hardy 2005</td>
<td>75</td>
<td>18%</td>
<td></td>
<td></td>
<td>Inpatients and outpatients with non-affective psychosis</td>
</tr>
<tr>
<td>Hlastala 2005</td>
<td>75</td>
<td>62%</td>
<td></td>
<td></td>
<td>Inpatients and outpatients with early onset psychosis</td>
</tr>
<tr>
<td>Kilcommons 2005</td>
<td>32</td>
<td>13%</td>
<td>10%</td>
<td></td>
<td>Outpatients with schizophrenia spectrum disorder</td>
</tr>
<tr>
<td>Lysaker 2005</td>
<td>65</td>
<td>28%</td>
<td></td>
<td></td>
<td>Outpatient men with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Lysaker 2004</td>
<td>30</td>
<td>40%</td>
<td></td>
<td></td>
<td>Outpatient men with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Neria 2005</td>
<td>109</td>
<td>28%</td>
<td></td>
<td></td>
<td>Inpatients with first episode bipolar disorder with psychosis</td>
</tr>
<tr>
<td>Schenkel 2005</td>
<td>40</td>
<td>45%</td>
<td></td>
<td></td>
<td>Inpatients with schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Kim 2006</td>
<td>100</td>
<td>37%</td>
<td>34%</td>
<td></td>
<td>Inpatient women with schizophrenia</td>
</tr>
<tr>
<td>Schafer 2006</td>
<td>30</td>
<td>73%</td>
<td>37%</td>
<td></td>
<td>Inpatient women with psychosis</td>
</tr>
</tbody>
</table>

### Studies (N=12) of frequency of childhood trauma in groups with a psychotic disorder compared to clinical and/or non-clinical control group(s)

<table>
<thead>
<tr>
<th>Reference</th>
<th>% Childhood trauma</th>
<th>Population vs. control group (number)</th>
<th>Trauma type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emslie 1983</td>
<td>10%</td>
<td>50%</td>
<td>Inpatient girls with severe psychosis (10) vs. inpatient girls with severe non-psychotic disorders (16)</td>
</tr>
<tr>
<td>Haley 1988</td>
<td>67%</td>
<td>11%*</td>
<td>Adolescents with depression with psychotic features (15) vs.</td>
</tr>
</tbody>
</table>

---

**Databases used:** Psychiatry, Medline, EMBASE to Nov 2006 + reference lists search
### Description of the methodological assessment of studies: not reported

**Ross 1989**
- Gender: not applicable
- Heterogeneity: not discussed
- Study design: not applicable
- Study quality: not applicable

<table>
<thead>
<tr>
<th>Reference</th>
<th>% with psychosis</th>
<th>Population vs. control group (number)</th>
<th>Psychosis type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown 1991</td>
<td>2%</td>
<td>CSA/CPA (166) vs. No CSA/CPA (853)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Frieman 2002</td>
<td>32%</td>
<td>Schizophrenia (22) vs. Anxiety (160)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Fink 1990</td>
<td>9%</td>
<td>Schizophrenia (11) vs. Borderline personality disorder (11)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Wexler 1997</td>
<td>19%</td>
<td>Schizophrenia (217) vs. Depression (212)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Frieman 2002</td>
<td>32%</td>
<td>Schizophrenia (22) vs. Anxiety (160)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Nurcombe 1996</td>
<td>55%</td>
<td>Schizophrenia, schizophreniform disorder, or dissociative hallucinosis (22) vs. Post-traumatic stress disorder (13)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Honig 1998</td>
<td>83%</td>
<td>Schizophrenia (18) vs. Dissociative disorder (15)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Conroy 1995</td>
<td>16%</td>
<td>Psychosis (100) vs. &quot;Neuroses&quot; (100)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Friedman 1984</td>
<td>60%</td>
<td>Schizophrenia (20) vs. Non-psychiatric controls (15)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
<tr>
<td>Nettelbladt 1996</td>
<td>47%</td>
<td>Schizoffective disorder (17) vs. Combined non-psychotic groups (54)</td>
<td>Schizophrenia, delusional disorder</td>
</tr>
</tbody>
</table>

**Fixed or variable effects: not applicable**

**Heterogeneity: not discussed**

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

<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Studies</th>
<th>Exposure</th>
<th>Outcome measure</th>
<th>Results/effect size</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohen 1996</td>
<td>6% 14%</td>
<td>CSA/CPA (70) vs. No CSA/CPA (35)</td>
<td></td>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td>Briere 1997</td>
<td>53% 25%</td>
<td>CSA (49) vs. No CSA (44)</td>
<td></td>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td></td>
<td>49% 33%</td>
<td>CPA (39) vs. No CPA (54)</td>
<td></td>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td>Famularo 1992</td>
<td>9% 0% NS</td>
<td>Documented maltreatment (61) vs. no maltreatment (35)</td>
<td></td>
<td></td>
<td>Psychosis</td>
</tr>
<tr>
<td>Stein 1988</td>
<td>3% 0.3% NS</td>
<td>CSA (82) vs. No CSA or adult sexual abuse (2601)</td>
<td>Schizophrenia spectrum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen 2004</td>
<td>0.9% 0.1%*</td>
<td>CA (412) vs. No CA (3595)</td>
<td>Psychiatry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spataro 2004</td>
<td>0.8% 0.7% NS</td>
<td>Children on Victorian State sexual abuse register (1612) vs. not on register (3139745)</td>
<td>Schizophrenic disorders</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* = 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
<table>
<thead>
<tr>
<th>Number of studies: N=23</th>
<th>Childhood abuse (sexual, physical or emotional)</th>
<th>Event rate (prevalence)</th>
<th>Moderating factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients in the studies: n=2017</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: psychometric instruments not clearly defined; chart reviews; studies just asking whether a person had been abused</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Databases used: Pubmed, EMBASE (to July 2011) plus reference list search</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Description of the methodological assessment of studies: MOOSE approach</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fixed or variable effects: random effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: I2 statistic</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patient characteristics: Mean age = 36.6 yrs (SD 6.07) 45.6% women</td>
<td></td>
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</tr>
</tbody>
</table>

Prevalence of self-reported CSA in people with psychosis (N=20 studies)

- **26.3% (95%CI: 21.2 to 32.1%)**
  - I²=83%

Prevalence of self-reported CPA in people with psychosis (N=15 studies)

- **38.8% (95%CI: 36.2 to 41.4%)**
  - I²=93%

Prevalence of self-reported CEA in people with psychosis (N=8 studies)

- **34.0% (95%CI: 29.7 to 38.5%)**
  - I²=54%

**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.**
Study type: Systematic review with meta-analysis

Quality: 1++

<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Studies</th>
<th>Exposure</th>
<th>Outcome measure</th>
<th>Results/effect size</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen (2010).</td>
<td></td>
<td>Sexual abuse‡‡‡</td>
<td>Odds ratio (OR) of lifetime diagnosis of a psychiatric disorder</td>
<td>Anxiety disorder (N=8 studies) OR=3.09 (95% CI: 2.43 to 3.94) I²=40%</td>
<td>Authors' conclusion: A history of sexual abuse is associated with an increased risk of a lifetime diagnosis of multiple psychiatric disorders.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Depression (N=16 studies) OR=2.66 (2.14 to 3.30) I²=57%</td>
<td>There was no statistically significant association between sexual abuse and a diagnosis of schizophrenia or somatoform disorders.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Eating disorders (N=11 studies) OR=2.72 (2.04 to 3.63) I²=20%</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>Post-traumatic stress disorder (N=3) OR=2.34 (1.59 to 3.43) I²=0%</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Sleep disorders (N=1) OR=16.17 (2.06 to 126.76) I² not applicable</td>
<td></td>
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<td></td>
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<td></td>
<td>Suicide attempts (N=19) OR=4.14 (2.98 to 5.76) I²=60%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Schizophrenia (N=3) OR=1.36 (0.81 to 2.03) I²=0%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Somatoform disorders (N=3) OR=1.90 (0.81 to 4.47) I²=4%</td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>No studies located for bipolar or obsessive-compulsive disorders</td>
<td></td>
</tr>
</tbody>
</table>

‡‡‡ see full text paper for definition
random effects
Heterogeneity: $i^2$ statistic

<table>
<thead>
<tr>
<th>Study type: Systematic review with meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality: 1++</td>
</tr>
<tr>
<td>Reference and study design</td>
</tr>
<tr>
<td>---------------------------</td>
</tr>
<tr>
<td>Matheson (2013).</td>
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</tbody>
</table>

$^{§§§}$ Strengthening the Reporting of Observational Studies in Epidemiology

**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.
<table>
<thead>
<tr>
<th>Quality assessed by GRADE**** approach</th>
<th>Fixed or variable effects: random effects</th>
<th>Heterogeneity: $I^2$ statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Data imprecise
- Considerable heterogeneity i.e. $I^2$=88%

**Schizophrenia vs. dissociative disorders and PTSD:**
N=4

<table>
<thead>
<tr>
<th>OR=0.03 (95%CI: 0.01 to 0.15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data imprecise but consistent</td>
</tr>
<tr>
<td>Moderate heterogeneity i.e. $I^2$=51%</td>
</tr>
</tbody>
</table>

**Schizophrenia vs. other psychosis:**
N=3

<table>
<thead>
<tr>
<th>OR=0.69 (95%CI: 0.28 to 1.68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data imprecise but consistent</td>
</tr>
<tr>
<td>Low heterogeneity i.e. $I^2$=2%</td>
</tr>
</tbody>
</table>

**Schizophrenia vs personality disorders:**
N=3

<table>
<thead>
<tr>
<th>OR=0.65 (95%CI: 0.09 to 4.77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data imprecise but consistent</td>
</tr>
<tr>
<td>Substantial heterogeneity i.e. $I^2$=80%</td>
</tr>
</tbody>
</table>

**Forest plots for meta-analyses**

---

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

**Accident Compensation Corporation**
Study type: Systematic review with meta-analysis

Quality: 1++

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:

<table>
<thead>
<tr>
<th>Number of studies: N=14</th>
<th>Childhood bullying Non-clinical populations†††† (N=10)</th>
<th>Childhood bullying Clinical populations‡‡‡‡ (N=8)</th>
<th>Authors' conclusion:</th>
</tr>
</thead>
</table>
| Total number of patients in the studies: n=49231 | | | "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."

<table>
<thead>
<tr>
<th>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).</th>
<th>Meta-analysis (N=7)</th>
<th>OR=2.7 (95%CI: 2.0 to 3.6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases used: Pubmed, EMBASE, and PsychINFO (to Nov 2011) plus reference search</td>
<td>Unadjusted effect sizes (N=7 studies)</td>
<td>( \hat{\text{I}}^2 = 15 ) §§§§</td>
</tr>
<tr>
<td>Description of the methodological assessment of studies: not reported</td>
<td>Adjusted effect sizes (N=6 studies)</td>
<td>OR=2.3 (1.5 to 3.4)</td>
</tr>
<tr>
<td>Fixed or variable effects: random effects</td>
<td>N=4 studies found no significant association between bullying and psychosis after adjustment for confounders</td>
<td></td>
</tr>
</tbody>
</table>

†††† 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 \( \hat{\text{I}}^2 = (Q – df)/Q \times 100 \) [df=number of studies – 1]
<table>
<thead>
<tr>
<th>Heterogeneity: Cochran Q test</th>
</tr>
</thead>
</table>

**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.
<table>
<thead>
<tr>
<th>Reference and study design</th>
<th>Studies</th>
<th>Exposure</th>
<th>Outcome measure</th>
<th>Results/effect size</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varese (2012).</td>
<td>Number of studies: N=40 (13 cross-sectional, 19 case-control, 8 cohort)</td>
<td>Childhood adversity (i.e. sexual, physical, emotional/psychological abuse, neglect, parental death &amp; bullying)</td>
<td>Odds ratio (OR)</td>
<td>Pooled estimate from 36 studies: OR=2.78 (95%CI: 2.34 to 3.31) I²=72.7%</td>
<td>Authors’ conclusion: “This review finds that childhood adversity and trauma substantially increases the risk of psychosis with an OR of 2.8.”</td>
</tr>
<tr>
<td>Schizophrenia Bulletin 38(4): 661-71.</td>
<td>Meta-analysis: N=36 studies (8 cross-sectional, 18 case-control, 10 prospective studies)</td>
<td></td>
<td></td>
<td>Case-control studies (N=17) OR=2.72 (1.90 to 3.88) I²=76.9%</td>
<td></td>
</tr>
<tr>
<td>UK / Netherlands / NZ</td>
<td>Total number of patients in the studies: n=81,253</td>
<td></td>
<td></td>
<td>Cross-sectional studies OR=2.99 (2.13 to 4.20) I²=73.0%</td>
<td></td>
</tr>
<tr>
<td>Included studies</td>
<td>Inclusion criteria: Any published or unpublished empirical study after 1980 of childhood trauma and psychosis; languages include English, Dutch, French, German, Italian, Portuguese &amp; Spanish; trauma occurred when subjects were &lt;18 yrs</td>
<td></td>
<td></td>
<td>Cohort studies OR= 2.75 (2.17 to 3.47) I²=67.6%</td>
<td>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.</td>
</tr>
<tr>
<td>Case-control studies</td>
<td>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.</td>
<td></td>
<td></td>
<td>Meta-analyses of specific adverse experiences:</td>
<td></td>
</tr>
<tr>
<td>Prospective cohort studies</td>
<td></td>
<td></td>
<td></td>
<td>Physical abuse (N=13) OR=2.95 (2.25–3.88), I²=74.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bullying (N=6) OR=2.39 (1.83–3.11), I²=73.9</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parental death (N=8) OR=1.70 (0.82–3.53), I²=80.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neglect (N=7) OR=2.90 (1.71–4.92), I²=81.8</td>
<td></td>
</tr>
</tbody>
</table>
### 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)
- $\text{PAR}=33\% \ (95\%\text{CI}: \text{16 to 47}\%)$

### 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:

---

††††† 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

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

<table>
<thead>
<tr>
<th>$I^2$ statistic</th>
<th>Suggested Interpretation from Matheson (2013)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-40%</td>
<td>might not be important</td>
</tr>
<tr>
<td>50-75%</td>
<td>may be important</td>
</tr>
<tr>
<td>&gt; 75%</td>
<td>should be regarded as considerable</td>
</tr>
</tbody>
</table>

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 Causation¹³**

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


