

## Evidence-Based Report

# Childhood Sexual Abuse and Trauma-Related Responses

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### Important Note:

- The purpose of this brief report is to summarise the evidence for an association between childhood sexual abuse and the development of trauma-related responses, including post-traumatic stress disorder and adjustment disorder.
- 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.
- This report is based upon information supplied up to November 2015.

## 1. Executive Summary

- Childhood sexual abuse can have significant short- and long-term effects, including the subsequent development of trauma-related responses. Trauma-related responses include adjustment and post-traumatic stress disorders.
- The purpose of this report is to provide an evidence-based guide on the association between childhood sexual abuse and trauma-related responses as a teenager/adult. These findings will be used to assist in the decision making process regarding cover and entitlements of those who have experienced childhood sexual abuse and later developed a trauma-related response.
- A literature search was conducted in November 2015 using Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Cochrane Database of Systematic Reviews, PsycINFO, and the Worldwide Web. Further literature was also located through reading the reference list of review articles.
- Findings from the one systematic review, one meta-analysis, two cohort studies, and one review identified in this report showed that:
  - There is fair quality evidence that childhood sexual abuse is a likely risk factor for the development of trauma-related responses, namely post-traumatic stress symptoms, with an odds ratio of between 2 and 2.5.
  - Evidence from cohort studies in New Zealand and Australia suggest that exposure to childhood sexual abuse increases the risk of developing subsequent post-traumatic stress disorder.
  - There is some evidence that experience of childhood sexual abuse is associated with a higher odds ratio of developing post-traumatic stress than childhood child abuse/neglect, community violence, and complex trauma.
  - There is some evidence that increasing severity of childhood sexual abuse (i.e., childhood sexual abuse involving attempted or completed penetration) is associated with an increasing number of post-traumatic stress disorder symptoms.
  - There is evidence that childhood sexual abuse is associated with post-traumatic stress disorder or symptomatology among pregnant and postpartum women; however, some findings are mixed.
  - Limitations of the current research examining the association between childhood sexual abuse and trauma-related responses include no identified studies investigating adjustment disorder, methodological limitations of studies included in reviews, childhood sexual abuse and outcomes being assessed

using a variety of different methods, abuse being reported retrospectively, and the range of confounding variables present across studies.

- There is some evidence for higher prevalence of post-traumatic stress disorder among females than males; however, factors attributing to these sex differences remain unclear.
- There is a lack of research examining the mechanisms underlying the relationship between childhood sexual abuse and the subsequent development of trauma-related responses. Further research in this area is required.
- Given the limited research in this area, identified limitations of the current literature, and that there are likely to be many causes of and risk factors for trauma-related responses, it is difficult to conclude whether childhood sexual abuse is a direct and sufficient cause of trauma-related responses. However, there is some evidence that childhood sexual abuse is likely to be a risk factor for developing post-traumatic stress disorder later in life.

## 2. Introduction

Although trauma-related responses encompass both post-traumatic stress and adjustment disorders, majority of research in relation to these difficulties has focused on post-traumatic stress disorder. Global lifetime prevalence estimates for post-traumatic stress disorder are approximately 7% (Kessler et al. 2005). Prevalence for post-traumatic stress disorder is typically highest among those aged between 30 and 44 years, with a decrease in prevalence seen in older age groups (Kessler et al. 2005). Trauma related responses can have a significant impact on an individual's quality of life including their vitality, subjective wellbeing, and mental and physical health (Olatunji, Cisler, & Tolin, 2007).

The estimated prevalence of childhood sexual abuse for females is between 8 to 31%, and between 3 to 17% for males; the wide estimate ranges reflecting the heterogeneity of studies (Barth, Bermetz, Heim, Trelle, & Tonia, 2013). Despite the methodological challenges inherent in conducting international systematic reviews and meta-analyses, most studies have consistently shown that worldwide more than 1 out of 5 women, and 1 out of 10 men experience childhood sexual abuse (Pereda, Guilera, Forns, & Gómez-Benito, 2009). However, underreporting of childhood sexual abuse is a well-documented phenomena and likely impacts these prevalence rates (Leclerc & Wortley, 2015).

For victims of childhood sexual abuse, the effects can be devastating both in the short- and long-term. Frequently reported short-term effects include fear, anxiety, depression, aggression, anger and hostility, and sexually inappropriate behaviour. Long-term effects

include ongoing depression and anxiety, poor self-esteem, difficulty in trusting others, self harm and suicide, a tendency toward revictimisation, feelings of isolation and stigma, substance abuse, and a host of other mental health problems (Browne & Finkelhor, 1986; Fergusson, McLeod, & Horwood, 2013; Paolucci, Genuis, & Violato, 2001). One such group of mental health disorders which has been linked to childhood sexual abuse is trauma-related responses, which is the focus of this report.

### 3. Background

ACC Research subcontracted Associate Professor Ian Lambie to conduct an evidence-based review to investigate the association between childhood sexual abuse and the subsequent development of trauma-related responses as a teenager/adult.

This evidence-based report will be used to provide ACC clinical advisors, claims management staff and service providers with an evidence-based guide on the relationship between childhood sexual abuse and the development of trauma-related responses. In addition, this report will be used to assist in the development of an approach to deciding cover and entitlements for people who have experienced childhood sexual abuse and develop a trauma-related response at an older age.

### 4. Investigation

A search was conducted in November 2015 in the following databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Cochrane Database of Systematic Reviews, and PsychINFO. Further literature was also located through searching the Worldwide Web and reading the reference list of review articles. Only articles in English and published between 2000 and 2015 were included.

Search terms used included: Post-traumatic stress, adjustment disorder, childhood sexual abuse, child sexual abuse, sexual abuse.

Original Inclusion criteria: Systematic reviews and meta-analyses looking at the relationship between childhood sexual abuse and trauma-related responses.

Original Exclusion criteria: Non-English studies, animal or laboratory studies, narrative reviews, letters or editorials; study designs other than systematic review or meta-analysis.

This resulted in identifying 160 articles, of which one systematic review and one meta-analysis were used in this report.

Revised criteria: Due to limited findings, inclusion criteria were revised to include narrative reviews from 2015 and cohort studies with a comparison group published since Chen et al.'s (2010) meta-analysis<sup>‡</sup>. This resulted in the identification of one narrative review and two cohort studies examining the association between childhood sexual abuse and trauma-related responses.

Evidence tables were created for the systematic review and meta-analysis, and these can be found in Appendix 1. A table of the excluded studies can be found in Appendix 2. Evidence tables were also created for the two cohort studies identified following the revised inclusion criteria, and can be found in Appendix 3. A description of the excluded studies based on the revised inclusion criteria can be found in Appendix 4.

**Note:** Limited research was located examining the relationship between childhood sexual abuse and the subsequent development of trauma-related responses, including post-traumatic stress disorder (PTSD). A likely explanation for this is that in DSM-5, PTSD was reclassified as a Trauma and Stressor-Related Disorder as opposed to an anxiety disorder as outlined in the DSM-IV. Therefore, PTSD has largely been investigated in studies examining anxiety disorders. A separate evidence-based report has been completed outlining the evidence for the association between childhood sexual abuse and anxiety disorders.

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<sup>‡</sup> Included in Maniglio's (2013) systematic review of reviews

Any relevant papers were assessed for their methodological quality using the following SIGN<sup>1</sup> criteria:

<b>Levels of evidence (LOE)</b>	
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
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

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<sup>1</sup> Scottish Intercollegiate Guidelines Network <http://www.sign.ac.uk/>

## 5. Findings

### Systematic Reviews

One systematic review is included in this report: Maniglio (2013)<sup>1</sup>.

The systematic review by Maniglio (2013)<sup>1</sup> examined published reviews investigating the role of child sexual abuse in the aetiology of anxiety disorders<sup>ϕ</sup>. This fair quality (1+) systematic review included four reviews: Neumann et al. (1996; 15 meta-analyses investigating the relationship between child sexual abuse and a variety of psychological, behavioural and sexual problems), Rind et al. (1998; 18 meta-analyses examining the relationship between child sexual abuse and a variety of psychological, behavioural and sexual problems), Paolucci et al. (2001; 6 meta-analyses examining the relationship between child sexual abuse and a variety of psychological, behavioural and sexual problems), and Chen et al. (2010; 8 meta-analyses examining the association between prior history of sexual abuse and a variety of psychiatric symptoms or disorders). Paolucci et al. (2001) and Chen et al. (2010) reviewed a range of samples (i.e., young and adult, male and female, clinical and nonclinical samples), while Neumann et al. (1996) and Rind et al. (1998) focused on adult female (both clinical and nonclinical) samples and college (both male and female) samples, respectively.

Three reviews found a significant association between child sexual abuse and post-traumatic stress symptoms (Neumann et al. 1996 ( $d^c = .52$ ; 95% CI<sup>±</sup>: .44 to .59); Paolucci et al. 2001 ( $d = .40$ ; 95% CI: .37 to .43); Chen et al. 2010 (OR<sup>†</sup> = 2.34; 95% CI: 1.59 to 3.43))<sup>\*</sup>. Significant associations were also found between child sexual abuse and generic anxiety symptoms (Neumann et al. 1996 ( $d = .40$ ; 95% CI: .34 to .47); Rind et al. 1998 ( $r^{\ddagger} = .13$ ; 95% CI: .10 to .15;  $\chi^2_{\varphi} = 4.62$ ); Chen et al. 2010 (OR = 3.09; 95% CI: 2.43 to 3.94))<sup>\*\*</sup>, obsessive-compulsive

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<sup>ϕ</sup> In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association; (DSM-5), PTSD was reclassified from being an Anxiety Disorder to a Trauma and Stressor-Related Disorder. Therefore, PTSD has largely been investigated in studies examining anxiety disorders. A separate evidence-based report has been completed outlining the evidence for the association between childhood sexual abuse and anxiety disorders.

<sup>c</sup> Cohen's d; measure of effect size

<sup>±</sup> 95% confidence interval

<sup>†</sup> odds ratio

<sup>\*</sup> converted effect size to OR for post-traumatic stress symptoms: Neumann et al. (1996): 2.57; Paolucci et al. (2001): 2.07

<sup>‡</sup> correlation coefficient; measure of effect size

<sup>ϕ</sup> Chi-squared test

<sup>\*\*</sup> converted effect size to OR for generic anxiety symptoms: Neumann et al. (1996): 2.07; Rind et al. (1998): 1.60

symptoms (Neumann et al. 1996 ( $d = .34$ ; 95% CI: .22 to .46); Rind et al. 1998 ( $r = .10$ ; 95% CI: .06 to .15;  $\chi^2 = 5.01$ ))<sup>\*\*\*</sup>, and phobic symptoms (Rind et al. 1998 ( $r = .12$ ; 95% CI: .07 to .17;  $\chi^2 = 8.08$ ))<sup>\*\*\*\*</sup>.

Moderator variables<sup>φ</sup> included definition of abuse, abuse involving contact, relationship to the perpetrator (greater risk of anxiety problems in college survivors of intrafamilial abuse, and in college female victims of abuse – both wanted and unwanted sex), and sample source (samples from non-clinical populations yielded smaller effect sizes than clinical samples). In addition, some evidence suggested larger effect sizes among college samples whose results were published. Gender, socioeconomic status, age of subjects at time of assessment, penetration, force, frequency, duration of abuse, age when abused, level of contact and consent, publication date, sampling strategy, method of assessment of abuse, type of statistics, sample size, as well as type of institution were not statistically significant moderators.

The authors concluded that there is evidence that child sexual abuse is a significant, although general and nonspecific, risk factor for anxiety disorders, especially post-traumatic stress disorder (regardless of gender of the victim and severity of abuse). However, the authors note that causal inferences cannot be made because of the presence of both confounding variables and methodological limitations in the studies included in each review. Nonetheless, child sexual abuse should be considered one of the several risk factors for anxiety disorders, including post-traumatic stress disorder, and included in multifactorial etiological models for anxiety disorders.

## Meta-analyses

One meta-analysis was included in this report: Martinez et al. (2014)<sup>2</sup>.

The meta-analysis by Martinez et al. (2014)<sup>2</sup> was of fair quality (1+) and looked at determinants of differential responses to trauma exposure. The authors included 74 studies with samples of youth exposed to traumatic events and who completed the Trauma Symptom Checklist for Children (TSCC).

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<sup>\*\*\*</sup> converted effect size to OR for obsessive compulsive symptoms: Neumann et al. (1996): 1.85; Rind et al. (1998): 1.43

<sup>\*\*\*\*</sup> converted effect size to OR for phobic symptoms: Rind et al. (1998): 1.55

<sup>φ</sup> variables that account for significant heterogeneity in effect size estimates; variable that affects the strength of relationship



The authors found that sexual abuse was associated with higher post-traumatic stress than child abuse/neglect ( $t^4(19) = 3.19, p = .005$ ), community violence ( $t(24) = 5.47, p < .001$ ), and complex trauma<sup>λ</sup> ( $t(20) = 3.66, p = .002$ ). Among sexual abuse samples, female representation was associated with higher post-traumatic stress ( $\beta^\emptyset = .62, Q^*(1, 17) = 10.88, p = .001$ ), as well as anger and dissociation, but not anxiety or depression. Among sexual abuse samples, older age was associated with higher post-traumatic stress  $\beta = .60, Q(1, 15) = 8.30, p = .004$ ), as well as anxiety, depression and dissociation.

Limitations of the meta-analysis were only including published studies which may have resulted in a bias in the study sample; and the decision to focus only on the Trauma Symptom Checklist for Children disregarding other measures of symptomology (e.g., structured interviews or other symptom checklists).

## Cohort Studies

Two cohort studies are discussed in this report: Fergusson et al. (2013)<sup>3</sup> and Cutajar et al. (2010)<sup>4</sup>.

The cohort study by Fergusson et al. (2013)<sup>3</sup> reported on findings from a 30-year longitudinal study conducted in New Zealand. The authors aimed to examine the linkages between childhood sexual abuse and a wide range of developmental outcomes over a protracted time period to age 30.

Data from over 900 members of the New Zealand birth cohort Christchurch Health and Development Study (CHDS) were examined. The CHDS is a longitudinal study of 1,265 children (630 females) born in the Christchurch urban region over a 4-month period during 1977. This cohort has been studied at birth, 4 months, 1 year, annually to age 16, then at ages 18, 21, 25, and 30 using a combination of interviews with parents and participants, standardized testing, teacher report, and official record data. At age 30, 987 (80%; 509 females) of the surviving cohort members were assessed.

Childhood sexual abuse prior to age 16 was assessed at ages 18 and 21 years, and severity of childhood sexual abuse was classified on a 4-point scale: no childhood sexual abuse, non-

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<sup>4</sup> t-test

<sup>λ</sup> Complex PTSD (cPTSD) differs from ordinary PTSD in three psychobiological areas, namely emotional processing, self-organization, and relational security (Ford & Courtois, 2014). cPTSD is not a recognised disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association)

<sup>∅</sup> standardised regression coefficient

<sup>\*</sup> Q statistic; used to assess the magnitude of variability in the weighted mean t-scores

contact childhood sexual abuse, contact childhood sexual abuse not involving attempted penetration, and childhood sexual abuse involving attempted or completed penetration. At ages 21, 25 and 30 years, mental health, psychological wellbeing, sexual risk-taking behaviours, physical health and socioeconomic outcomes were assessed.

Extent of childhood sexual abuse was associated with an increased number of post-traumatic stress disorder symptoms when unadjusted and adjusted for 10 covariates spanning sociodemographic, family functioning, and child factors disorder symptoms ( $B = 0.294$ ,  $SE = 0.045$ ,  $p < .001$  and  $B = 0.120$ ,  $SE = 0.051$ ,  $p = .017$ , respectively;  $d^{\ddagger} = .23$ ). Increasing exposure to childhood sexual abuse (i.e., childhood sexual abuse involving attempted or completed penetration) was associated with an increase in the number of post-traumatic stress disorder symptoms ( $p < .001$ ). Childhood sexual abuse was also associated with a range of additional outcomes, such as psychological wellbeing, sexual risk-taking and physical health, and severity of childhood sexual abuse was linked with severity of various adult outcomes.

This cohort study was of adequate methodological quality (2+). Limitations of the study include findings being based on a specific birth cohort studied in a historical context; the use of self-report interview data; and that the number of cohort members who had sought treatment for the effects of childhood sexual abuse was unknown.

The second cohort study by Cutajar et al. (2010)<sup>4</sup> looked at psychopathology in a large cohort of sexually abused children up to 43 years. Forensic medical records of 2,759 sexually abused children assessed between 1964 and 1995 were linked with a public psychiatric database between 12 and 43 years later. Cases were compared to control subjects matched on gender and age groupings drawn from the general population through a random sample of the electoral database. This research was the only study discussed in this report to use non-retrospective reports and the public record for both sexual abuse and subsequent use of the public mental health system.

The authors found that exposure to sexual abuse significantly increased the risk of subsequent post-traumatic stress disorder ( $OR = 5.56$ , 95% CI: 3.44 to 8.99,  $p < 0.001$ ), as well as psychotic disorders, affective disorders, anxiety disorders, alcohol abuse, drug abuse and a number of personality disorders, and had three times the mental health burden of the general community.

Females were significantly more likely than males to be diagnosed with post-traumatic stress disorder ( $ORs = 7.25$  and  $2.19$ , respectively), an affective disorder, and borderline personality

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<sup>‡</sup> Cohen's  $d$  is the estimated standardized comparison of no exposure to CSA versus any exposure to CSA

disorder. Males were significantly more likely to be diagnosed with other disorders and antisocial personality disorder.

This cohort study was of adequate methodological quality (2+). Limitations of the study included the extent of available information collected on cases and controls for purposes other than intended for the study (i.e., information on potentially confounding covariates such as family history of mental illness and social background factors could not be taken into account and controlled for). The authors also noted that caution should be taken when interpreting results on sexual abuse variables as not all cases had information collected and recorded by forensic medical examiners on sexual abuse variables.

## Reviews

One review is included in this report: Wosu et al. (2015)<sup>5</sup>.

The review by Wosu et al. (2015)<sup>5</sup> looked at childhood sexual abuse and post-traumatic stress disorder among pregnant and postpartum women. The authors included five quantitative cross-sectional studies in the review: Cohen et al. (2004), Morland et al. (2007), Seng et al. (2008), Lev-Wiesel et al. (2009), and Lang et al. (2010). All studies were cross-sectional and reported specific results relevant to antepartum or postpartum periods.

Findings from all five studies supported a higher prevalence of post-traumatic stress disorder diagnosis or symptomatology among women with a history of childhood sexual abuse; however, only findings from two studies were statistically significant (Lev-Wiesel & Daphna-Tekoah, 2010; Seng et al. 2008). Lev-Wiesel et al. (2009) observed higher overall post-traumatic stress disorder scores in women with childhood sexual abuse history compared to women with non-childhood sexual abuse trauma history or no trauma history at 4 to 7 months of pregnancy (mean± SD: 1.47 (0.51) vs. 1.33 (0.41) vs. 1.22 (0.29),  $p < 0.001$ ), at 2 months postpartum (mean± SD: 1.43 (0.49) vs. 1.26 (0.38) vs. 1.19 (0.35),  $p < 0.001$ ), and at 6 months postpartum (mean± SD: 1.36 (1.43) vs. 1.20 (0.33) vs. 1.14 (0.27),  $p < 0.001$ ). Seng et al. (2008) found the prevalence of post-traumatic stress disorder during pregnancy was 4.1% in women with no history of physical or sexual abuse, 11.4% in women with adult physical or sexual abuse history, 16.0% in women with childhood physical or sexual abuse history, and 39.0% in women exposed to both childhood and adult physical or sexual abuse ( $p < 0.001$ ). In the same study, the authors reported that pregnant women with post-traumatic stress disorder had over 5-fold odds of having a history of childhood completed rape compared to their counterparts without post-traumatic stress disorder (OR = 5.3; 95% CI: 3.2 to 8.7).

This review was of adequate methodological quality (2+). Limitations of the review include inadequate control of confounding factors; small sample sizes; a lack of information on

maternal pre-pregnancy post-traumatic stress disorder status resulting in an inability to distinguish between prevalent versus incident post-traumatic stress disorder; results may not be generalizable to all pregnant women as participants were recruited at obstetric centres; retrospective self-report assessment of childhood sexual abuse; and the use of different scales to evaluate post-traumatic stress disorder prevalence across studies. In addition, the authors noted that the three studies which found non-significant associations between childhood sexual abuse and post-traumatic stress disorder may have had limited statistical power to detect moderate associations.

## 6. Additional Information

### **Other Risk Factors of Trauma-Related Responses**

Although not the focus of this report, other causes and/or risk factors for the development of trauma-related responses will give context to the evidence about childhood sexual abuse. One source was used (with no formal methodological appraisal): *DynaMed*<sup>TM\*\*\*</sup>. Due to no information available regarding adjustment disorder, the following is an outline of identified risk factors for post-traumatic stress disorder.

### **DynaMed<sup>TM</sup>**

#### **Likely risk factors:**

- exposure to life-threatening trauma
- physical injury from traumatic event
- surviving a disaster (man-made or natural)
- history of directed trauma such as sexual or physical assault:
  - sexual violence exposure increased rates of post-traumatic stress disorder and major depressive disorder and decreased social functioning in combatants
    - based on cross-sectional survey of 1,666 adults ≥ 18 years old who were former combatants in Liberia
- poor psychosocial support, especially following trauma
- history of mental health problems
- exposure to combat or war-related violence:

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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

- combat exposure and deployment to Iraq or Afghanistan associated with post-traumatic stress disorder in armed forces in United Kingdom
  - based on cohort study of > 93,000 members of United Kingdom armed forces
- history of being a child soldier
  - based on cohort study
- refugee resettlement:
  - refugee and conflict-related risk factors associated with increased risk for post-traumatic stress disorder
    - based on systematic review of observational studies
    - systematic review of 161 studies reporting on 181 surveys in 81,866 refugees and other conflict-affected persons
  - refugees resettled in western countries may be 10 times more likely to have post-traumatic stress disorder than general population in western countries
    - based on systematic review of 20 studies with 6,743 adult refugees from 7 countries and 5 studies with 260 child refugees from 3 countries
  - war-related internal displacement (seeking refuge in secure areas of own country) associated with increased risk of post-traumatic stress disorder
    - based on cross-sectional study of 1,517 Jaffna District households in Sri Lanka
- prior post-traumatic stress disorder
  - based on prospective cohort study
- psychological response to national trauma, higher levels of post-traumatic stress symptoms associated with:
  - female gender (OR = 1.64)
  - marital separation (OR = 2.55)
  - pre-September 11 physician-diagnosed depression or anxiety disorder (OR = 1.84)
  - severity of exposure to attacks (OR = 1.31)
  - early disengagement from coping efforts (OR = 1.68)
    - based on survey of 3,496 persons in United States 9-23 days after September 11 terrorist attack
- high rates of long-term post-traumatic stress disorder persist after major trauma in adolescents
  - based on cohort study of 401 patients aged 12-19 years exposed to trauma, followed for 2 years
- exposure to country level conflict associated with post-traumatic stress disorder
  - based on retrospective population-based cohort study of 1,236,600 Libya residents exposed to high level of political terror and traumatic events during 2011 conflict

### **Possible risk factors:**

- lower score on mental and physical evaluations
  - based on cohort study of 5,410 military personnel with mean 3-year follow-up
  - based on co-twin study with 2,386 male Vietnam-era twin veterans
- severe animal-induced injury in children associated with post-traumatic stress disorder at 3 months
  - based on prospective cohort study of 358 children admitted to emergency room for animal-induced injury and tested for post-traumatic stress disorder at 3 months
- traffic accidents in children
  - based on prospective cohort study
- higher heart rate at emergency department
  - based on prospective cohort study of 190 children aged 8-17 years hospitalized for traffic-related injury and followed for 6 months
- mild traumatic brain injury
  - based on cohort study, United States soldiers
- many factors associated with post-traumatic stress disorder following childbirth
  - risk factors for post-traumatic stress disorder following childbirth include:
    - infant complications
    - low support during labour and delivery
    - psychological difficulties in pregnancy
    - previous traumatic experiences
    - obstetrical emergencies
      - based on systematic review of 27 observational studies and 4 reviews
- long-term post-traumatic stress disorder symptoms may occur after secondary peritonitis
  - based on retrospective cohort of 100 patients treated for secondary peritonitis
- childhood cancer associated with increased risk of post-traumatic stress disorder in adulthood
  - based on cohort study

### **Sex Differences**

Sex differences in the development of trauma and post-traumatic stress disorder have been investigated by numerous studies. Understanding of these sex differences can provide further insight to the association between childhood sexual abuse and trauma-related responses, such as post-traumatic stress disorder. Two sources were used (with no formal methodological

appraisal): a meta-analysis by Tolin and Foa (2006) and a review article by Walker et al. (2004).

### **Tolin and Foa (2006)**

This meta-analysis examined sex differences in trauma and post-traumatic stress disorder. The authors included 290 studies, all of which represented independent samples.

The authors found that the odds of meeting criteria for post-traumatic stress disorder was almost twice as high among female participants as among male participants (OR = 1.98), regardless of the type of study, population, type of assessment, or other methodological variables. Across studies, female participants were more likely to report experiencing sexual assault and child sexual abuse. However, when further investigated, there was no overall sex difference in post-traumatic stress disorder for child sexual abuse.

The authors concluded that the higher prevalence of post-traumatic stress disorder among females cannot be attributed to a higher risk of child sexual abuse. It is possible that sex differences in post-traumatic stress disorder are due to factors not captured in most studies (e.g., aspects of the traumatic event, pre-existing cognitive and affective reactions to traumatic events, and tendency toward different expressions of distress for males versus females).

### **Walker et al. (2004)**

This review article examined the gender differences in the prevalence of childhood sexual abuse and the development of paediatric post-traumatic stress disorder. The authors included 16 studies, 5 of which looked at post-traumatic stress disorder rates among sexually abused girls and boys.

The authors concluded that despite the heavy bias towards female representation in studies, the literature supports increased rates of childhood sexual abuse and heightened vulnerability to post-traumatic stress disorder in females, and that female gender appears to be an independent risk factor for the development of paediatric post-traumatic stress disorder following childhood sexual abuse. They also report that after childhood sexual abuse, gender appears to affect the development of either externalising or internalising behaviours and impacts on the biological abnormalities seen in paediatric post-traumatic stress disorder.

However, the authors noted that inconsistency remains in the literature with respect to the role of gender in the risk of childhood sexual abuse and subsequent post-traumatic stress disorder. In addition, with regard to psychopathology following childhood sexual abuse, independent of gender, multiple trauma-related factors including frequency, nature, relationship to

perpetrator, unexpected nature, and social network all increase risk for post-traumatic stress disorder.

### **Mediators of the Association between Childhood Sexual Abuse and Trauma-Related Responses - Theories**

Trauma-related responses encompass both adjustment disorder and post-traumatic stress disorder. However, there has been a lack of research conducted on the relationship between childhood sexual abuse and the development of adjustment disorders later in life, including theories explaining such association. Similarly, there is limited information available regarding proposed mechanisms underlying the relationship between childhood sexual abuse and the development of post-traumatic stress disorder. This is likely due to previous research largely examining and conceptualising post-traumatic stress as an anxiety disorder<sup>φ</sup>. Please refer to the evidence-based report regarding anxiety disorders for an outline of proposed theories concerning mediators of the link between childhood sexual abuse and the subsequent development of anxiety disorders in later life.

Further research is needed to investigate the mechanisms underlying the association between childhood sexual abuse and trauma-related responses.

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<sup>φ</sup> In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (American Psychiatric Association; (DSM-5), PTSD was reclassified as a Trauma and Stressor-Related Disorder as opposed to an anxiety disorder as outlined in the DSM-IV. Therefore, PTSD has largely been investigated in studies examining anxiety disorders.



## 7. Conclusions

The one systematic review, one meta-analysis, two cohort studies, and one review in this report found:

- Fair quality evidence (i.e., the review was of fair methodological quality (1+/1-)) from one systematic review of an association between childhood sexual abuse and post-traumatic stress symptoms (OR range = 2.07 to 2.57)<sup>1</sup>
- Fair quality evidence from one meta-analysis that sexual abuse is associated with higher post-traumatic stress than child abuse/neglect, community violence, and complex trauma<sup>2</sup>
- Adequate evidence (i.e., the study/review was of adequate methodological quality (2+)) from one cohort study conducted in New Zealand that childhood sexual abuse is associated with an increase in the number of post-traumatic stress symptoms<sup>3</sup>
- Adequate evidence from one cohort study conducted in Australia that exposure to childhood sexual abuse significantly increases the risk of subsequent post-traumatic stress disorder<sup>4</sup>
- Adequate evidence from one review that childhood sexual abuse is associated with post-traumatic stress disorder or symptomatology among pregnant and postpartum women; however, some findings are mixed<sup>5</sup>

This report also found some evidence suggesting higher prevalence of post-traumatic stress disorder among females than males; however, factors attributing to these sex differences remain unclear.

Using Bradford Hill's guide to causation (Appendix 6), the strength of association between childhood sexual abuse and the development of a trauma-related response, namely post-traumatic stress disorder, is in the order of 2 to 2.5 increased odds, and appears to be relatively consistent. Temporality (i.e., abuse occurs before the development of a trauma-related response) cannot be certain due to the largely retrospective design of studies.

The biological gradient (i.e., greater exposure leads to greater incidence of the effect) was investigated by two authors<sup>1,3</sup>. The systematic review identified in this report found that aspects of the abuse experience (penetration, force, frequency, duration of abuse, age of victim when abused, level of contact and consent) were not a statistically significant moderator variables<sup>1</sup>; however, the absence of a dose-response relationship does not rule out causality. One cohort study found increasing severity of childhood sexual abuse (i.e., childhood sexual

abuse involving attempted or completed penetration) was associated with an increasing number of post-traumatic stress disorder symptoms<sup>3</sup>.

In relation to plausibility, there is a lack of research examining the mechanisms underlying the relationship between childhood sexual abuse and the subsequent development of trauma-related responses. Further research in this area is required.

<sup>2</sup>Limitations of the current research examining the association between childhood sexual abuse and trauma-related responses include no identified studies specifically investigating adjustment disorder, methodological limitations of studies included in reviews, and childhood sexual abuse and outcomes being assessed using a variety of different methods. Additional limitations include abuse being reported retrospectively and the range of confounding variables present across studies.

Given the limited research in this area, identified limitations of the current literature, and that there are likely to be many causes of and risk factors for trauma-related responses, it is difficult to conclude whether childhood sexual abuse is a direct and sufficient cause of these disorders. However, there is some evidence that childhood sexual abuse is likely to be a risk factor for developing post-traumatic stress disorder later in life.

## 8. Limitations

As only English language articles were included, the presence of publication bias in this report is a possibility. In addition, only focussing on systematic reviews, meta-analyses, reviews and cohort studies with comparison groups may have missed more recent research. The dearth of systematic reviews and meta-analyses mean research findings need to be replicated in order to more fully investigate and understand the aetiology of trauma-related responses with regard to childhood sexual abuse.

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<sup>2</sup> Limited research was located examining the relationship between childhood sexual abuse and the subsequent development of trauma-related responses, including post-traumatic stress disorder (PTSD). A likely explanation for this is that in DSM-5, PTSD was reclassified as a Trauma and Stressor-Related Disorder as opposed to an anxiety disorder as outlined in the DSM-IV. Therefore, PTSD has largely been investigated in studies examining anxiety disorders. A separate evidence-based report has been completed outlining the evidence for the association between childhood sexual abuse and anxiety disorders.

## 9. Appendix 1: Evidence Table for Original Inclusion Criteria

Reference and study design	Studies	Results				
<p>Maniglio (2013)</p> <p>“Child sexual abuse in the aetiology of anxiety disorders: A systematic review of reviews.”</p> <p><u>Trauma, Violence &amp; Abuse</u> 14(2): 96-112.</p> <p>Italy</p> <p><u>Included studies:</u> Chen et al. 2010, Neumann et al. 1996, Paolucci et al. 2001, Rind et al. 1998</p>	<p><u>Number of studies:</u> 4</p> <p><u>Total number of participants in the studies:</u> 3,214,482</p> <p><u>Inclusion criteria:</u> studies need to have appeared in peer-reviewed journals; be published in full; be critical reviews of the literature; review studies sampling human subjects; investigate medical, neurobiological, psychological, behavioural, sexual, or other health problems following CSA; have primary and sufficient data derived from longitudinal, cross-sectional, case-control or cohort studies; reviews must address the significance, strength, and/or nature of the relationship between CSA and later anxiety symptoms or disorders and/or the potential effects of third</p>	Source	Subjects	Outcome variables	Significant outcomes (effect sizes or odds ratios [95%CI]; homogeneity)	Significant moderators (between-group homogeneity)
		Chen et al. (2010)	Male and female young and adult patients and non-patients (37 studies, 3,162,318 subjects)	Post-traumatic stress, anxiety, depression, eating disorders, sleep disorders, suicide attempts, schizophrenia, somatoform disorders	Post-traumatic stress (OR= 2.34 [1.59, 3.43]), Anxiety (OR =3.09 [2.43-3.94]), depression (OR =2.66 [2.14, 3.30]), eating (OR =2.72 [2.04, 3.63]), sleep (OR =16.17 [2.06-126.76]), suicide (OR=4.14 [2.98, 5.76])	Post-traumatic stress: history of rape (females abused in adulthood, OR=2.57 [1.13, 5.87])
Neumann et al., 1996	Female adult patients & nonpatients (38 studies, 11,162 subjects)	Post-traumatic stress, anxiety, obsessions or compulsions, anger, depression, revictimization, self-mutilation, sex problems, substance abuse, suicide, self-concept, interpersonal problems, dissociation, somatization, general	Post-traumatic stress (d =.52 [.44, .59]), anxiety (d =.40 [.34,.47]), obsessions/ compulsions (d= .34 [.22, .46]), depression (d= .41 [.36, .46]), anger (d =.39 [.25, .51]), revictimization (d= .67 [.50, .84]), self-mutilation (d= .42 [.19, .64]), sex problems (d =.36 [.30, .42]), substance abuse (d= .41 [.31, .51]), suicide (d = .34 [.24, .44]), self-concept (d = .32 [.32, .47]), interpersonal problems (d =.39 [.22, .46]), dissociation (d= .39	Overall impairment: sample source (Q <sub>B</sub> =9.40, p < .01)		

	<p>variables on such relationship.</p> <p><u>Exclusion criteria:</u> Must not be dissertation papers, editorials, letters, conference proceedings, books and book chapters</p> <p><u>Databases used:</u> AMED, Cochrane Reviews, EBSCO, ERIC, MEDLINE, PsycINFO, ScienceDirect (Jan 1996 – December 2008 and January 2009 – December 2010) + reference lists search</p> <p><u>Description of the methodological assessment of studies:</u> Methodological Quality Checklist</p> <p><u>Fixed or variable effects:</u> not applicable</p> <p><u>Heterogeneity</u><sup>§</sup>: Chen et al. (2010) used I<sup>2</sup>; Neumann et al. (1996) used Hedges' between-group heterogeneity statistic (Q<sub>BET</sub>); Rind et al. (1998) used normal deviate z (equivalent to Q<sub>BET</sub>).</p>	<p>Paolucci et al., 2001</p> <p>Male &amp; female young &amp; adult patients &amp; nonpatients (37 studies, 88 samples, 25,367 subjects)</p> <p>Rind et al., 1998</p> <p>Male &amp; female adult nonpatients (59 studies, 51 samples, 15,635 subjects)</p>	<p>symptoms, overall psychopathology</p> <p>Post-traumatic stress, depression, suicide or self-injury, early sex or prostitution, sex perpetration, intelligence or learning</p> <p>Anxiety, obsessions or compulsions, phobia, alcohol, depression, dissociation, eating disorders, hostility, interpersonal sensitivity, locus of control, paranoia, psychosis, self-esteem, sex problems, social impairment, somatization, suicide, general</p>	<p>[.32, .47]), somatization (d = .34 [.24, .45]), general symptoms (d = .46 [.40, .52]), overall psychopathology (d = .37 [.33, .41]; Q = 62.36, p &lt; .01)</p> <p>Post-traumatic stress (d = .40 [.37, .43]), depression (d = .44 [.41, .47]), suicide/ self-injury (d = .44 [.40, .48]), early sex/ prostitution (d = .29 [.25-.32]), sex perpetration (d = .16 [.11, .21]), intelligence/ learning (d = .19 [.12, .26])</p> <p>Anxiety (r = .13 [.10, .15]; <math>\chi^2 = 4.62</math>), obsessions / compulsions (r = .10 [.06, .15]; <math>\chi^2 = 5.01</math>), phobia (r = .12 [.07, .17]; <math>\chi^2 = 8.08</math>), alcohol (r = .07 [.02, .12]; <math>\chi^2 = 2.97</math>), depression (r = .12 [.10, .14]; <math>\chi^2 = 25.71</math>), dissociation (r = .09 [.04, .15]; <math>\chi^2 = 1.86</math>), eating disorders (r = .06 [.02, .10]; <math>\chi^2 = 9.92</math>), hostility (r = .11 [.06, .16]; <math>\chi^2 = 11.22</math>, p &lt; .05), interpersonal sensitivity (r = .10 [.06, .15]; <math>\chi^2 = 11.78</math>), paranoia (r = .11 [.07, .16]; <math>\chi^2 = 10.34</math>),</p>	<p>Overall impairment: published study (r = .25, p = .08), incest (r = .09 [.01- .17]; <math>\chi^2 = 15.20</math>), consent gender interaction (z = 2.51, p &gt; .02; females, r = .11 [.09-.13]; <math>\chi^2 = 14.50</math>)</p>
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<sup>§</sup> 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<sup>2</sup> statistic

	<p>Paolucci et al. (2001) did not use statistics to quantify heterogeneity of effect sizes.</p>	<p>symptoms, overall psychopathology</p> <p>psychosis (r = .11 [.06, .15]; <math>\chi^2 = 10.13</math>), self-esteem (r = .04 [.01, .07]; <math>\chi^2 = 51.31</math>, p &lt; .05), sex problems (r = .09 [.07, .11]; <math>\chi^2 = 39.49</math>, p &lt; .05), social impairment (r = .07 [.04, .10]; <math>\chi^2 = 20.37</math>), somatization (r = .09 [.06, .12]; <math>\chi^2 = 15.20</math>), suicide (r = .09 [.06, .12]; <math>\chi^2 = 10.94</math>), general symptoms (r = .12 [.08, .15]; <math>\chi^2 = 18.77</math>), overall psychopathology (r = .09 [.08, .11]; <math>\chi^2 = 49.19</math>, p &gt; .50)</p> <p><b>Significant confounders</b>  <u>Rind et al., 1998:</u>  Overall impairment: nonsexual abuse or neglect (r = .19 [.13, .25]; <math>\chi^2 = 2.36</math>), family adaptability (r = .13 [.06, .19]; <math>\chi^2 = 20.38</math>), family conflict or pathology (r = .14 [.12, .17]; <math>\chi^2 = 0.74</math>), family structure (r = .09 [.06, .12]; <math>\chi^2 = 6.54</math>), family support or bonding (r = .13 [.09, .16]; <math>\chi^2 = 36.46</math>), family traditionalism (r = .16 [.09, .22]; <math>\chi^2 = 8.26</math>).  Anxiety: overall family (r = .34 [-.28, .40]; <math>\chi^2 = 19.80</math>).  Obsessions / compulsions: overall family (r = .27 [-.20, .34]; <math>\chi^2 = 4.02</math>).  Phobia: overall family (r = .18 [-.08, .28]; <math>\chi^2 =</math> value not provided).</p>
<p><b>Conclusions</b></p> <p><u>Author's conclusions:</u> Across methodologies, samples and measures, survivors of CSA are significantly at risk for anxiety problems, such as post-traumatic stress symptomology, generic anxiety, obsessive/compulsions, and phobia. However, causal inferences cannot be made, because of the presence of both confounding variables and methodological limitations in the studies included in each review.  CSA should be considered a general, non-specific risk factor for anxiety symptoms or disorders.</p> <p><u>Reviewer's conclusions:</u> This systematic review presents evidence suggestive of an association between CSA and anxiety disorders, including PTSD, but is not definitive due to the limitations of the studies and confounding variables.</p>		

**Study type: Systematic review**

**Quality: 1+**

**Comments:** Adequately conducted systematic review with no meta-analysis. Multiple databases searched. Methodological assessment adequate. Heterogeneity considered. Subgroup analyses conducted by Chen et al. (2010) were discussed.

Reference and study design	Studies	Exposure	Outcome Measure	Results	Conclusions
<p>Martinez et al. (2014).            “Symptom variation on the trauma symptom checklist for children: A within-scale meta-analytic review”.</p> <p><u>Journal of Traumatic Stress</u> <b>27</b>(6): 655-663.</p> <p>United States</p> <p><u>Included Studies:</u> not explicitly stated.</p>	<p><u>Number of studies:</u> 74</p> <p><u>Total number of participants in the studies:</u> 14,867</p> <p><u>Inclusion criteria:</u> Studies that provided raw (US or international) or T scores (US only) for at least one TSCC subscale; Included participants exposed to a traumatic event; Included youth ages 8-16 years; Published in a peer-reviewed journal in English; Had a sample size of 15 or greater.</p> <p><u>Exclusion criteria:</u> Not stated</p> <p><u>Databases used:</u> Social Sciences Citations Index, PsycINFO, PubMed, Published International Literature on Traumatic Stress</p> <p><u>Description of the methodological assessment of studies:</u> not reported</p> <p><u>Fixed or variable effects:</u> random effects</p> <p><u>Heterogeneity:</u> Q statistic and I<sup>2</sup> statistic</p>	<p>Trauma (sexual abuse, child abuse/neglect, community violence, complex trauma)</p>	<p>Trauma Symptom Checklist for Children (TSCC; Briere, 1996): Post-traumatic stress, anxiety, depression, anger, dissociation (t-scores)</p>	<p><b>U.S versus international samples</b></p> <p>International samples of youth reported greater post-traumatic stress (<math>Q(1, 63) = 6.90, p = .009</math>), anxiety (<math>Q(1, 57) = 8.43, p = .004</math>), and depressive symptoms (<math>Q(1, 53) = 6.36, p = .012</math>) than youth in U.S. samples. No differences found for anger or dissociation</p> <p><b>Sexual abuse vs. other trauma types</b></p> <p>Sexual abuse associated with higher symptoms of post-traumatic stress than child abuse/neglect (<math>t(19) = 3.19, p = .005</math>), community violence (<math>t(24) = 5.47, p &lt; .001</math>), and complex trauma (<math>t(20) = 3.66, p = .002</math>).</p> <p>Sexual abuse associated with higher anxiety than child abuse/neglect (<math>t(20) = 3.53, p = .002</math>), community violence (<math>t(25) = 5.76, p &lt; .001</math>), and complex trauma (<math>t(21) = 3.69, p = .001</math>).</p> <p>Sexual abuse associated with higher depressive symptoms than child abuse/neglect (<math>t(23) = 2.95, p = .007</math>), community</p>	<p><u>Author’s conclusions:</u> A substantial percentage of youth exposed to a traumatic event do not develop clinically significant levels of post-traumatic symptomology. Youth who experienced sexual abuse displayed the greatest symptoms of post-traumatic stress, anxiety, depression and dissociation compared to exposure to community violence. Older age was associated with higher anxiety, post-traumatic stress, depression and dissociation in sexual abuse samples.</p> <p><u>Reviewer’s conclusions:</u> This meta-analysis presents evidence suggesting that sexual abuse is associated with higher post-traumatic stress than child abuse/neglect, community violence, and complex trauma. In addition, older age is associated with higher post-traumatic stress.</p>

				<p>violence (<math>t(26) = 4.95, p &lt; .001</math>), or complex trauma (<math>t(23) = 3.63, p = .001</math>).</p> <p>No significant differences across trauma types for dissociative or anger symptoms.</p> <p><b>Gender</b></p> <p>Significant positive relationships between the percentage of females in a sample and post-traumatic stress (<math>\beta = .51, Q(1, 68) = 24.62, p &lt; .001</math>), anxiety (<math>\beta = .50, Q(1, 60) = 22.53, p &lt; .001</math>), depression (<math>\beta = .52, Q(1, 56) = 18.36, p &lt; .001</math>), and dissociation (<math>\beta = .35, Q(1, 59) = 8.48, p = .004</math>). No significant relationship was found between gender and anger symptoms.</p> <p>Among sexual abuse samples, female representation was associated with higher post-traumatic stress (<math>\beta = .62, Q(1, 17) = 10.88, p = .001</math>), anger (<math>\beta = .47, Q(1, 18) = 4.69, p = .030</math>), and dissociation (<math>\beta = .53, Q(1, 18) = 8.03, p = .005</math>), but not anxiety or depression.</p> <p><b>Age</b></p>	
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				<p>Age not significantly associated with any TSCC subscale.</p> <p>Among sexual abuse samples, older age associated with higher post-traumatic stress (<math>\beta = .60</math>, <math>Q(1, 15) = 8.30</math>, <math>p = .004</math>), anxiety (<math>\beta = .57</math>, <math>Q(1, 17) = 8.96</math>, <math>p &lt; .003</math>), depression (<math>\beta = .51</math>, <math>Q(1, 16) = 6.00</math>, <math>p = .014</math>), and dissociation (<math>\beta = .50</math>, <math>Q(1, 16) = 5.78</math>, <math>p = .016</math>).</p> <p>No significant interaction found between age and sexual abuse for anger symptoms.</p> <p><b>Ethnicity</b></p> <p>Higher sample representation of ethnic minorities (<math>\beta = -.40</math>) associated with lower depression (<math>Q(1, 33) = 6.27</math>, <math>p = .012</math>).</p> <p>No significant relationships between ethnic minority representation and other subscales found.</p> <p>No significant interactions found between ethnic minority representation and trauma type for any TSCC subscale.</p>	
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**Study type: Meta-Analysis**

**Quality: 1+**

**Comments:** Adequately conducted meta-analysis. Multiple databases searched. Heterogeneity considered. Subgroup analysis undertaken. No formal methodological assessment.

## 10. Appendix 2: Exclusion Study Table for Original Inclusion Criteria

The 160 studies excluded from this report are presented in the table below. These studies had the term “review”, “systematic review”, and/or “meta-analysis” stated in its title and/or abstract.

An additional 1000+ articles were identified by the literature searches conducted. However, these articles were not included in this report based on the exclusion criteria (i.e., non-English studies, animal or laboratory studies, narrative reviews, letters or editorials; study designs other than systematic review or meta-analysis).

Reference	Reason for Exclusion
Aaron et al. 2013	Focus is not on childhood sexual abuse and Trauma-related response causation
Adelson et al. 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Adler-Nevo & Manassis, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Arias, 2004	Short review
Barker-Collo & Read, 2003	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Bauer et al. 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Becker & Walton-Moss, 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Beere et al. 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Bendall et al. 2008	Focus is not on childhood sexual abuse and Trauma-related response causation
Bennett, 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Beveridge & Cheung, 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Bockers & Knaevelsrud, 2011	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Bradley & Follingstad, 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Brewerton, 2007	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Brisch, 2005	Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Brown, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Caldwell & Redeker, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Calhoun & Wilson, 2000	Book chapter
Carello, 2014	Focus is not on childhood sexual abuse and Trauma-related response causation
Carr, 2004	Review; Focus on intervention

Charmandari et al. 2003	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Chen et al. 2010	Systematic review; Included in Maniglio (2013)
Chorpita & Viesselman, 2005	Focus is not on childhood sexual abuse and Trauma-related response causation
Claes, 2004	Focus is not on childhood sexual abuse and Trauma-related response causation
Cohen, 2003	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Cohen, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Coll, 2002	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Cook et al. 2011	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
Corcoran & Pillai, 2008	Meta-analysis; Focus is not on childhood sexual abuse and Trauma-related response causation
Corcoran, 2004	Critical review; Focus is not on childhood sexual abuse and Trauma-related response causation
Corwin & Keeshin, 2011	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Courtois, 2000	Book Chapter
Crisanti & Frueh, 2011	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Cummings et al. 2012	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Davis & Siegel, 2000	Review; Focus on childhood sexual abuse and development of PTSD among children and adolescents
De Bellis et al. 2011	Critical review; Focus is on underlying biological mechanisms of childhood sexual abuse and Trauma-related response causation
de Jongh, 2001	Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Di Giacomo et al. 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
DiMauro et al. 2014	Historical review; Does not examine literature regarding childhood sexual abuse and Trauma-related response causation
Diseth, 2005	Review; Focus is not on Trauma-related response causation
Ehlert, 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Epstein & Bottoms, 2002	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Farrell et al. 2010	Focus on treatment among clergy abuse survivors
Fegert et al. 2013	Not in English
Finkelstein & Yates, 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Flatten & Reddemann, 2003	Not in English
Foa & Street, 2001	Review
Fogler et al. 2008	Review; Focus on clergy-perpetrated CSA and possible moderating factors on sequelae; Does not discuss published literature on the association between clergy-perpetrated CSA and PTSD.
Ford & Gomez, 2015	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Franco, 2007	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Fry et al. 2012	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation

Gavranidou & Rosner, 2003	Review; Focus on gender differences for traumatic events and PTSD; One meta-analysis and review article published since this time that are included in additional information.
Gillies et al. 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Golding et al. 2002	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Goldzweig et al. 2006	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
Goodman & Yehunda, 2002	Focus is not on childhood sexual abuse and Trauma-related response causation
Grad et al. 2014	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Grubaugh et al. 2011	Review; Does not examine literature regarding childhood sexual abuse and Trauma-related response causation
Hamner & Robert, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Heide & Solomon, 2006	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Hellemann & Santhiveeran, 2011	Focus on prostitution
Hetrick et al. 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Honor, 2010	Review; Does not review published literature on the association between CSA and PTSD.
Hulme, 2011	Review; Focus is on underlying biological mechanisms of childhood sexual abuse and Trauma-related response causation
Isaac & Chand, 2006	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Javidi & Yadollahie, 2012	Review; Focus is not on childhood sexual abuse
Jenny & Roesler, 2003	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Julich, 2005	Focus is not on childhood sexual abuse and Trauma-related response causation
Kamier et al. 2000	Review; Focus on child and adolescent outcomes of CSA
Karlsson & Karlsson, 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Kaysen et al. 2003	Review; Examines the impact of chronic traumatisation and the traumatic context on PTSD
Kearney et al. 2010	Review
Kendall-Tackett et al. 2001	Book chapter of re-printed article from 1993
Kern et al. 2005	Focus is not on childhood sexual abuse and Trauma-related response causation
Kerr-Correa et al. 2000	Not in English
King et al. 2000	Review; Focus on treatment
Kinler, 2014	Focus is not on childhood sexual abuse and Trauma-related response causation
Kluft et al. 2000	Focus is not on childhood sexual abuse and Trauma-related response causation
Klump, 2006	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Koss & Kilpatrick, 2001	Book chapter
Krabbendam, 2008	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Kreidler et al. 2002	Review; Focus is not on childhood sexual abuse and Trauma-related response causation

Kuritarne, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Laney & Loftus, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Lang & Sharma-Patel, 2011	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Lang et al. 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Lazar & Offenkrantz, 2010	Focus is not on childhood sexual abuse and Trauma-related response causation
Leserman, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Lev-Wiesel & Daphna-Tekoah, 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Lin, 2006	Literature review; Dissertation
Longden et al. 2012	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Luengo et al. 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
MacIntosh et al. 2015	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Maine, 2005	Dissertation
Maniglio, 2013	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
Martin et al. 2007	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Martorell & Tsakanikos, 2008	Review; Focuses on life events and traumatic experiences as predictors of psychopathology in people with intellectual disability
Mauritz et al. 2013	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
McCall & Lauridsen-Hoegh, 2014	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
McCarthy-Jones, 2011	Critical review; Focus is not on childhood sexual abuse and Trauma-related response causation
McDonnell et al. 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
McNally & Robinaugh, 2015	Book Chapter; Focus is not on childhood sexual abuse and Trauma-related response causation
McNally, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Meewisse et al. 2007	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
Messman-Moore et al. 2003	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Miffitt, 2014	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Miller, 2000	Focus is not on childhood sexual abuse and Trauma-related response causation
Nakatani, 2000	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Noll, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Okasha, 2007	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Ono et al. 2015	Meta-analytic review; Focus is not on childhood sexual abuse and Trauma-related response causation

Ox, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Painter & Scannapieco, 2013	Review; Focus is not on childhood sexual abuse
Paolucci et al. 2001	Included in Maniglio (2013)
Paul et al. 2006	Review; Focus on treatment
Pereda & Gallardo-Pujol, 2011	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Pine & Cohen, 2002	Review
Post et al. 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Poustka, 2011	Not in English
Raphael et al. 2008	Review; Limited focus on association between childhood sexual abuse and Trauma-related response
Regehr & Gutheil, 2002	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Regehr et al. 2012	Focus is not on childhood sexual abuse and Trauma-related response causation
Regehr et al. 2013	Systematic review; Focus is not on childhood sexual abuse and Trauma-related response causation
Robinson et al. 2009	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Robinson, 2003	Focus is not on childhood sexual abuse and Trauma-related response causation
Roller, 2012	Focus is not on childhood sexual abuse and Trauma-related response causation
Ross & O'Carroll, 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Schafer & Fisher, 2011	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Schmidt et al. 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Scott et al. 2003	Review
Seedat, 2012	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Sequeira & Hollins, 2003	Review; Childhood sexual abuse and psychological reactions among people with learning disabilities
Simons & Herpertz-Dahlmann, 2008	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Stallard, 2006	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Stewart & Israeli, 2002	Book Chapter; Focus is not on childhood sexual abuse and Trauma-related response causation
Sundin & Horowitz, 2003	Meta-analysis; Focus is not on childhood sexual abuse and Trauma-related response causation
Taylor, 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Thabrew et al. 2012	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Tyler, 2002	Review
Vickerman & Margolin, 2009	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Vitriol et al. 2014	Focus is not on childhood sexual abuse and Trauma-related response causation
Vizard, 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Walsh et al. 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation

Walsh et al. 2012	Focus is on revictimiation and trauma-related response causation
Walsh et al. 2012	Review; Focus is not on childhood sexual abuse
Watts-English et al. 2006	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Weber & Reynolds, 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Weijenborg et al. 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Weinstein et al. 2000	Literature review; Focus is not on childhood sexual abuse and Trauma-related response causation
Weiss & Curcio, 2013	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Werner & Werner, 2008	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Widom & Hiller-Sturmhofel, 2001	Focus is not on childhood sexual abuse and Trauma-related response causation
Wilson, 2010	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Wolfsdorf & Zlotnick, 2001	Review; Focus is not on childhood sexual abuse and Trauma-related response causation
Woller, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Wyatt et al. 2004	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Yamawaki, 2005	Review; Focus is not on childhood sexual abuse and Trauma-related response causation; Not in English
Yehuda et al. 2001	Book Chapter
Yiming & Fung, 2003	Focus is not on childhood sexual abuse and Trauma-related response causation
Zollman et al. 2013	Focus is not on childhood sexual abuse and Trauma-related response causation



11. Appendix 3: Evidence Tables for Revised Inclusion Criteria

Reference	Data/Participants	Exposure and Outcome Measure	Data Analysis	Results
<p>Fergusson et al. (2013)</p> <p>“Childhood sexual abuse and adult developmental outcomes: Findings from a 30-year longitudinal study in New Zealand”</p> <p><u>Child Abuse &amp; Neglect</u> 37: 664-674.</p> <p>New Zealand</p>	<p><u>Data:</u> Christchurch Health and Development Study (CHDS) birth cohort</p> <p>The CHDS is a longitudinal study of 1,265 children (630 females) born in the Christchurch (New Zealand) urban region over a 4-month period during 1977. This cohort has been studied at birth, 4 months, 1 year, annually to age 16, then at ages 18, 21, 25, and 30 using a combination of interviews with parents and participants, standardized testing, teacher report, and official record data (Fergusson &amp; Horwood, 2001; Gibb, Fergusson, &amp; Horwood, 2012). At age 30, 987 (80%; 509 females) of the surviving cohort members were assessed.</p> <p>941 respondents assessed at age 30 had completed data on the measurement of CSA and mental health variables</p>	<p><u>Exposure:</u> Childhood sexual abuse (prior to age 16)</p> <p><u>Outcome:</u> range of outcomes using a 1.5-3h structured interview. Mental health problems (DSM-IV criteria for PTSD symptoms) from age 18 to 30 years.</p>	<p>Generalised linear regression</p>	<p><b>CSA and PTSD</b></p> <p>Extent of CSA was associated with an increased number of PTSD symptoms when unadjusted and adjusted for 10 covariates spanning sociodemographic, family functioning and child factors disorder symptoms</p> <p>Unadjusted: B = 0.294, SE = 0.045, p &lt; .001 Adjusted: B = 0.120, SE = 0.051, p = .017 Cohen’s d = .23</p> <p>Increasing exposure to CSA was associated with an increasing number of PTSD symptoms (p&lt;.001).</p>
<p><b>Conclusions</b></p> <p><u>Author’s conclusions:</u> The findings of this study generally confirm and extend previous research which has found that exposure to CSA has adverse consequences for a wide range of adult developmental outcomes. In this study, those reporting exposure to CSA had increased risks of mental health problems in adulthood (ages 18–30) and a greater number of PTSD symptoms.</p> <p><u>Reviewer’s conclusions:</u> This cohort study provides evidence of an association between CSA and PTSD but is not definitive.</p>				

**Study type:** Cohort

**Quality:** 2+

**Comments:** A well-conducted cohort study (30 year follow-up) with comparison group drawn from the general population.

Reference	Data/Participants	Exposure and Outcome Measure	Data Analysis	Results
<p>Cutajar et al. (2010)</p> <p>“Psychopathology in a large cohort of sexually abused children followed up to 43 years.”</p> <p>Child Abuse &amp; Neglect <b>34</b>: 813-822</p> <p>Australia</p>	<p><u>Data/participants</u>: Forensic medical records of 2,759 sexually abused children assessed between 1964 and 1995 were linked with a public psychiatric database between 12 and 43 years later.</p> <p>Comparison group drawn from a random sample of 4,938 Victorian residents on the electoral role. Control subjects matched on gender and age groupings.</p> <p><u>Average age</u>: Mean age of CSA group at follow-up was 33.82 years</p>	<p><u>Exposure</u>: Childhood sexual abuse (at age 16 years or younger)</p> <p><u>Outcome</u>: Mental health outcomes (from a public psychiatric database; diagnosis generated by treating or responsible psychiatrist using DSM* or ICD<sup>ψ</sup>)</p>	<p>T-tests, Chi-square, odds ratios, logistic regression, Cox regression.</p>	<p><b>CSA and PTSD</b></p> <p>CSA significantly increased the risk of subsequent PTSD OR = 5.56, 95% CI: 3.44 to 8.99, p &lt;0.001</p> <p>Females were significantly more likely to be diagnosed with PTSD than were males (p = .037)</p>
<p><b>Conclusions</b></p> <p><u>Author’s conclusions</u>: Overcoming many of the limitations of previous studies (i.e., retrospective nature), this study confirms that sexual abuse in childhood increases the risk for subsequent psychiatric disorders in both childhood and adulthood.</p> <p><u>Reviewer’s conclusions</u>: This cohort study provides evidence of an association between sexual abuse and subsequent risk of PTSD but is not definitive.</p>				

\* Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)

<sup>ψ</sup> World Health Organisation International Classification of Disease

Reference and study design	Studies	Exposure and Outcome Measure	Results			
			Study	Sample Size and Description	CSA Definition	Summary of Findings
<p>Wosu et al. (2015)</p> <p>“Childhood sexual abuse and posttraumatic stress disorder among pregnant and postpartum women: review of the literature.”</p> <p><u>Archives of Women’s Mental Health</u> <b>18:</b> 61-72</p> <p>United States</p> <p><u>Included Studies:</u> Cohen et al. 2004, Morland et al. 2007, Seng et al. 2008, Lev-Wiesel et al. 2009, Lang et al. 2010.</p>	<p><u>Number of studies:</u> 5</p> <p><u>Total number of participants in the studies:</u> 2,441</p> <p><u>Inclusion criteria:</u> studies had to define CSA as occurring sometime before the age of 18 years; report quantitative associations between CSA and PTSD symptoms or diagnosis; report specific results relevant to antepartum or postpartum periods (studies examining only labour and delivery experience were excluded); study participants had to be ≥18 years of age at the assessment of PTSD status; be full-length papers (conference abstracts, case studies, gray literature, and editorials were excluded); and be in the English language.</p> <p><u>Exclusion criteria:</u> Not stated</p> <p><u>Databases used:</u> PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), PsycINFO, PsycARTICLES</p>	<p><u>Exposure:</u> Childhood sexual abuse (&lt; 18 years)</p> <p><u>Outcome:</u> PTSD (DSM-IV)<sup>ψ</sup></p> <p><sup>ψ</sup> Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association)</p>				<p>Cohen et al. (2004)</p> <p>200 women ≥18 years old who had recently delivered a full term singleton</p> <p>Sexual abuse at &lt;14 years old (phone interviews at 8–10 weeks postpartum)</p> <p>No significant difference in the prevalence of high posttraumatic stress scores within the past week (defined as a response of “yes” to ≥3 items out of 17 on the Davidson Trauma Scale) among those with a history of CSA (39.3 %) and those without CSA history (31.4 %) (p=0.41)</p> <p>Morland et al. (2007)</p> <p>101 women, between ages 18 and 35, seeking prenatal care during the first trimester</p> <p>Sexual abuse by the age of 13 (face-to-face interview using Traumatic Life Events Questionnaire—various types of trauma)</p> <p>No significant difference in the prevalence of CSA history among those with PTSD (37.5 %), those with subclinical PTSD (17.4 %), and those without PTSD (12.9 %), p=0.10</p> <p>Seng et al. (2008)</p> <p>1,259 nulliparous, pregnant women who were ≥18 years old</p> <p>Sexual abuse at &lt;16 years old (phone interviews using the Life Stressor Checklist)</p> <p>Prevalence of PTSD among the women was 4.1 % in women who had never been physical or sexually abused, 11.4 % in women physical or sexually abused as adults, 16.0 % in women exposed to childhood physical or sexual abuse and 39.0 % in</p>

	<p><u>Description of the methodological assessment of studies:</u> not conducted</p> <p><u>Fixed or variable effects:</u> not applicable</p> <p><u>Heterogeneity:</u> not discussed</p>		<p>Lev-Wiesel et al. (2009)</p> <p>837 women (≥ 6 months pregnant)</p> <p>Penetrative and non-penetrative sexual abuse at &lt;14 years old (study interviews using the CSA Scale)</p> <p>Lang et al. (2010)</p> <p>44 pregnant women ≥18 years old (average of 17.3 gestational weeks)</p> <p>Sexual abuse during childhood (self-administered Childhood Trauma Questionnaire)</p>	<p>those exposed to both childhood and adult physical and sexual abuse (p&lt;0.001)</p> <p>Women exposed to CSA had significantly higher overall PTSD scores (during pregnancy, at 2 months postpartum, and at 6 months postpartum) compared to women with non-CSA trauma and women with no experience of a potentially traumatizing event</p> <p>No significant correlation between scores on the PTSD checklist and CSA as measured by the CTQ, either during pregnancy (r= 0.30, p&gt;0.05) or at 1 year postpartum (r=0.11, p&gt;0.05)</p>
<p><b>Conclusions</b></p> <p><u>Author's conclusions:</u> Of the five studies identified for this review, the two largest studies (Seng et al. 2008; Lev-Wiesel and Daphna-Tekoah 2010) observed positive associations of CSA with PTSD in pregnant and postpartum women. The other three studies did not document statistically significant CSA-PTSD associations, although it is likely that the small sample size of these studies resulted in statistically underpowered assessments of the hypothesized associations. Of note, in all three studies, the investigators reported higher rates of PTSD symptoms among women with CSA as compared with controls. Overall, available evidence suggests positive associations of CSA with clinical PTSD or PTSD symptomatology among pregnant and postpartum women.</p> <p><u>Reviewer's conclusions:</u> This review provides evidence of an association between CSA and PTSD among pregnant and postpartum women.</p>				

**Study type:** Review

**Quality:** 2+

**Comments:** A well-conducted review with no meta-analysis. Multiple databases searched.

## 12. Appendix 4: Excluded Studies for Revised Inclusion Criteria

787 articles were identified by literature searches conducted. However, these articles were not included in this report based on the exclusion criteria (i.e., non-English studies, animal or laboratory studies, narrative reviews published prior to 2015, letters or editorials; study designs other than systematic review or meta-analysis, except for cohort studies with comparison groups published since 2010).

In particular:

- Approximately 503 results were excluded because the focus was not on childhood sexual abuse and Trauma-related response causation
- Approximately 187 results were excluded because they were not a cohort study or a review published in 2015
- Approximately 20 results were excluded because they were a book or book chapter
- Approximately 30 results were excluded because they were a dissertation
- Approximately 42 results were excluded because they were not in English
- Approximately 5 results were excluded because they were not a primary study or a review



### 13. Appendix 5: Heterogeneity and the I<sup>2</sup> statistic

Heterogeneity is the variation between the results of a set of studies. It can be clinical, methodological and/or statistical. Clinical heterogeneity can be caused by differences between the studies with respect to participants, interventions, and/or outcome.

Methodological heterogeneity can be caused by differences between studies regarding 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. Statistical heterogeneity is identified graphically and by using a statistical test e.g. the "I<sup>2</sup>" statistic.

The degree of heterogeneity measured by the I<sup>2</sup> statistic assists determination of whether a meta-analysis is appropriate and, if so, what model to use in pooling the results.

<b>I<sup>2</sup> statistic</b>	<b>Suggested interpretation from Matheson (2013)</b>
0-40%	Might not be important
50-75%	May be important
>75%	Should be regarded as considerable

## 14. Appendix 6: Bradford Hill's Criteria of Causation

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.

## 15. References

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