Children's responses to trauma: a study of cortisol and PTSD and a meta-analysis on the prevalence of panic disorder

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Abstract

A significant number of young people experience trauma exposure and a substantial minority of those develop post-traumatic stress disorder (PTSD). Both trauma exposure and PTSD are related to wide-ranging impacts. Two areas receiving significant attention are the extent to which trauma relates to physiological changes and wider psychopathology. There is increasing evidence linking early life trauma to the development of panic disorder. The wide heterogeneity in prevalence estimates for panic disorder following trauma exposure in youth requires further research to understand its prevalence. The HPA-axis plays an important role in our neurobiological response to stress with research often focussing on cortisol secretion. Research suggests that PTSD in youth is associated with elevated cortisol, however there is broad heterogeneity in findings.

This portfolio presents a systematic review and meta-analysis investigating the prevalence of panic disorder in trauma-exposed youth. Following this, an empirical paper presents analysis of pre-existing data to investigate differences in salivary cortisol in children and adolescents exposed to recent single incident trauma.

The meta-analysis identified a pooled prevalence rate of 7.1% (95% CI 2.7, 13.5) among thirteen studies involving 14,170 participants, exceeding general population estimates. Results of the empirical study found no significant differences in cortisol levels across different sample times or in total cortisol output across the morning and the day, but noted blunting of the Cortisol Awakening Response in the non-PTSD trauma exposed group relative to controls.

Findings of the meta-analysis suggested higher prevalence of panic disorder in trauma-exposed youth compared to general populations. This suggests that clinicians should routinely consider panic when assessing trauma exposed youth. Findings of the empirical

study do not support the hypothesis that PTSD is characterised by elevated cortisol at around three months post trauma, reflecting the heterogeneity in existing literature. Future longitudinal research is required, closely adhering to guidelines for assessing and reporting cortisol data.

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Chapter One: Introduction to the thesis portfolio^1

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^1 Footnote: This thesis portfolio draws from materials written for the Thesis Proposal which was submitted as a summative assessment in preparation for the development of the thesis and as part of fulfilment of the Doctorate in Clinical Psychology. This material has been used throughout the portfolio.

Traumatic events are situations involving actual or perceived threats of death, serious injury, or sexual violence (American Psychiatric Association, 2013). The prevalence of trauma exposure is remarkably high, with more than 70% of people experiencing a traumatic event at least once in their lifetime and 30% facing four or more such events (Benjet et al., 2016). This prevalence extends into childhood where a significant percentage of children and adolescents experience traumatic events, ranging from 15% to 82.5%, with the variation in estimates reflecting differences in approaches used and the various kinds of trauma considered (Lewis et al., 2019).

A significant number of children exposed to traumatic incidents develop post-traumatic stress disorder (PTSD). Studies have suggested a lifetime prevalence of 7.8% among UK samples, and an overall lifetime prevalence of 15.9% of children and adolescents experiencing trauma developing PTSD (Alisic et al., 2014; Lewis et al., 2019). PTSD manifests through four main groups of symptoms related to the traumatic experience, including distressing intrusions such as thoughts and memories, cognitive and behavioural avoidance of reminders, hyperarousal and reactivity and negative alterations to cognition and mood (American Psychiatric Association, 2013). The likelihood of developing PTSD after experiencing trauma shows considerable variation based on factors such as the nature of the trauma and the gender of the individual, with a multitude of further risk factors identified in previous meta-analyses (Alisic et al., 2014; Smith et al., 2019).

Both trauma exposure and PTSD are related to impacts in social, emotional, and educational outcomes, and have been increasingly linked to adverse health outcomes such as gastrointestinal disorders and cardiovascular disease (Copeland et al., 2007; Hiller at al., 2016; Kessler et al., 1995; Sowder et al., 2018). The impacts of trauma can be particularly detrimental when experienced in childhood with disruptions in the development of cognitive, emotional, and social domains leading to an array of negative longer-term outcomes with

substantial impacts relating to the individual and the broader public health burden (Magruder et al., 2017). Two areas that have received significant attention in previous literature are *the extent to which trauma relates to wider psychopathology* and the high levels of comorbidity between PTSD and other psychiatric conditions and the *extent to which trauma can lead physiological changes* in the body and how these changes relate to broader psychopathology and physical health (D'Andrea et al., 2011; Krantz et al., 2022).

Trauma exposure is strongly associated with wider psychopathology beyond PTSD and represents one of the most consistently identified risk factors for the development of psychiatric conditions (McLaughlin et al., 2012). Previous research has highlighted that trauma-exposed children are around twice as likely to develop wider psychopathology than non-exposed counterparts, with major depressive disorder, generalized anxiety disorder, panic disorder, and substance abuse among the most commonly identified (Lewis et al., 2019; McLaughlin et al., 2020). A number of studies have begun to explore the prevalence of these conditions following trauma exposure such as Vibhakar et al., (2019) who identified a prevalence of 24.2% of children experiencing trauma meeting criteria for depression. Despite the growing body of research exploring psychopathology following trauma exposure in children, further elaboration is required, and many conditions remain without reliable estimates of prevalence. For panic disorder there remains extensive heterogeneity in estimates of panic disorder in trauma-exposed youth, ranging from 8% after exposure to the World Trade Centre attack (Goodwin et al., 2021) to 32.2% after exposure to the 2013 Ya'an (China) earthquake (Tang et al., 2020).

There is increasing evidence which links the experience of traumatic events in early life to the development of panic disorder. A number of studies have identified that individuals presenting with panic disorder in adulthood are more likely to report childhood trauma (Asselmann et al., 2016; Zhang et al., 2021). Further, the relationship between panic disorder

and PTSD is marked by significant comorbidity and often overlapping clinical presentations, with panic symptoms commonly experienced by those with PTSD and evidence suggesting that perievent experience of panic attacks can be predictive of later development of PTSD (Feldner et al., 2009; Adams & Boscarino, 2011). The research delineating the relationship between panic, trauma exposure and PTSD remains limited. However, a number of theoretical perspectives have been put forwards highlighting the importance of conditioned trauma related fear responses, cognitive models relating catastrophic misinterpretations in appraisals of the somatic sensations experienced during the traumatic event and its sequelae and the relationship between anxiety and anxiety sensitivity which may be a common factor in the development of both panic disorder and PTSD (Hinton et al., 2008; Joscelyne et al., 2012; Lissek et al., 2005; Stephenson et al., 2009).

The wide heterogeneity in estimates for the prevalence of panic disorder in trauma-exposed youth suggests that additional moderating factors may need to be explored to understand the relationship between panic disorder and trauma in youth and its prevalence. To the best of the authors knowledge, a systematic review on the prevalence of panic disorder in trauma exposed youth and youth with PTSD has not previously been conducted. Understanding the relationship between trauma exposure and panic disorder in youth is important given the high prevalence of trauma exposure, the early onset of panic disorder in development, the negative outcomes associated with panic disorder and its implications for treatment approaches (Carrion et al., 2002; Jensen-Doss & Weisz, 2008; Goodwin et al., 2021).

Aside from explorations into the associations of trauma exposure with wider psychopathology, much of the prior research on the consequences of trauma exposure has also focussed on the physiological changes associated with trauma exposure and PTSD. The research investigating these psychophysiological changes is wide-ranging and relates to

investigations of areas such as the sympathetic and parasympathetic nervous system, the immune system, and changes within the hypothalamic-pituitary-adrenal (HPA) axis (Kirsch et al., 2011). Understanding changes in these systems is of important clinical significance as whilst adaptive changes in these systems may promote short term adaptation to a stressor, these changes persisting beyond the original stressor can result in allostatic load and have wide ranging detrimental impacts which are linked to chronic disease progression and a wide range of negative physical and mental health outcomes (Danese & McEwen, 2012). These changes are argued to be particularly relevant in children, where development is still underway and changes can become embedded (Danese & McEwen, 2012; Tarullo & Gunnar, 2006).

One area which has received particular attention is trauma-exposure related changes in the HPA axis. The HPA-axis plays an important role in our neurobiological response to stress, and functions to mobilize and distribute resources throughout the body which are required for daily activity and for responding to threats which require anticipatory and reactive responses (Herman et al., 2016; Weems & Carrion, 2009). Lots of the research exploring HPA-axis changes has focused on cortisol secretion, which is released by the adrenal glands following a cascade of processes beginning with the hypothalamus when triggered by a stressor (Guilliams & Edwards, 2010). Under normal conditions cortisol can be readily assayed in blood, urine, and saliva, which makes it a convenient index of HPA functioning (Weems & Carrion, 2009).

Initial studies suggested the presence of lower cortisol levels in adults with PTSD, with many subsequent studies supporting this (Mason et al., 1986; Yehuda et al., 1990; Morris et al., 2012; Pan et al., 2020; Schumacher et al., 2019). However, the findings have varied, ranging from no significant differences to mixed or contradictory results (Klaassens et al., 2012; Meewisse et al., 2007; Miller et al., 2007). Research on cortisol in children with

PTSD is sparse in comparison but shows a different response, with findings generally demonstrating the presence of higher cortisol levels (Carrion et al., 2002, De Bellis & Zisk, 2014; Delahanty et al., 2000; Delahanty et al., 2005; Zantvoord et al., 2019: Zimmerman et al., 2020). However, there remains inconsistency in these findings, and a growing number of other studies have shown no significant difference or demonstrated lower cortisol (Pervanidou et al., 2020).

Numerous explanations have been put forth as to the wider heterogeneity of findings across the literature with relevance for understanding cortisol in childhood PTSD. These include: differential inclusion of PTSD groups, trauma-exposed control groups and non-trauma-exposed control groups; different cortisol measurement approaches and approaches to analysis employed; differential inclusion of factors influencing cortisol such as age, gender, wake time, depression, time since trauma exposure, and different trauma types examined (Hulett et al., 2019; Pervanidou 2008; Schumacher et al., 2019; Steudte-Schmiedgen et al., 2016).

Given previous heterogeneity observed and longer-term negative impacts of changes to the HPA-axis, providing greater specificity in the context of heterogeneity in identifying the relationship between salivary cortisol, PTSD and trauma exposure in children and adolescents is of great importance. A more in-depth understanding of cortisol and trauma exposure also has important clinical implications for PTSD treatment approaches which could be instrumental in further elucidating treatment mechanisms, predictors of success and the improvement of assessment and psychotherapeutic approaches (Schumacher et al., 2019).

This thesis portfolio aimed to further investigate these two different areas of consequences of trauma exposure. Chapter two presents a systematic review and metanalysis of the prevalence of panic disorder in trauma-exposed children and adolescents. Chapter three

is an empirical research study using a pre-established data set which was generated as part of the Acute Stress Programme for Children and Teenagers (ASPECTS) study to investigate differences in salivary cortisol in children and adolescents exposed to recent single incident trauma. The ASPECTS study explored PTSD mechanisms in youth recently exposed to trauma, comparing those with and without PTSD and without trauma exposure and explored the efficacy and treatment mechanisms of cognitive behavioural therapy (CBT). The study included a screening phase, a prospective longitudinal study, a case-control study, and a randomized controlled trial (RCT). All groups underwent a comprehensive experimental battery, encompassing a parental interview, self-report questionnaires, a narrative task, psychophysiological assessments, and a series of neuropsychological tests. Part of this battery included the use of a salivary cortisol assessment, which had not previously been interpreted elsewhere and which forms the basis of the present empirical study. Chapter four provides an integrated summary of both the meta-analysis and empirical study findings, offering a comprehensive appraisal of the strengths and weaknesses of the thesis portfolio. Theoretical and clinical implications are discussed as well as avenues for further investigation.

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Chapter Two: Systematic Review and Meta-Analysis

Prepared for submission to Journal of Clinical Child & Adolescent Psychology

Author Guidelines available in Appendix A.

A systematic review and meta-analysis on the prevalence of panic disorder in trauma-exposed children and adolescents.

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Abstract

Objective: Panic disorder significantly impacts the well-being of young people. While community sample prevalence rates are around 1%, emerging research suggests a link between panic disorder and trauma exposure. However, there remains wide heterogeneity in estimates. This meta-analysis aimed to provide an estimate of panic disorder prevalence in trauma exposed youth.

Methods: Thirteen studies involving 14,170 participants were used to determine the pooled prevalence of panic disorder in trauma-exposed youth. Moderator and subgroup analyses were conducted to assess the impact of factors such as trauma type, assessment method, age, and country income status. Additional analyses explored the prevalence of panic disorder in children and adolescents with PTSD (k=7, n= 618), and the prevalence of PTSD in children and adolescents with panic disorder (k=4, n= 445).

Results: The pooled prevalence of panic disorder in trauma-exposed youth was 7.1% (95% CI 2.7, 13.5), exceeding general population estimates. However, there was a large degree of heterogeneity. Approximately 20.7% (95% CI 5.6, 41.9) of children and adolescents with PTSD also experienced panic disorder, and 79.8% (95% CI 48.46, 98.25) of those with panic disorder met criteria for PTSD. Results should be interpreted with caution due to high levels of heterogeneity across analyses and the small number of studies available, particularly for the moderator analyses conducted and additional meta-analyses.

Conclusions: The findings indicate higher prevalence of panic disorder in trauma-exposed youth compared to general populations. The high prevalence observed suggests that clinicians should routinely consider panic in their diagnostic assessments of trauma exposed youth.

Key words: panic disorder, trauma exposure, post-traumatic stress disorder, prevalence, child, adolescent.

Introduction

Panic disorder is an anxiety disorder characterised by recurrent, unexpected panic attacks accompanied by persistent concern and behaviour changes relating to these attacks. These attacks are discrete episodes of intense fear which feature both physical symptoms of autonomic arousal and cognitive symptoms such as catastrophic thoughts relating to the attacks (American Psychiatric Association [APA], 2013). The suggested lifetime prevalence of panic disorder in the general population is between 3.4-4.7% (Guo et al., 2016; Kessler et al., 2006). Onset of panic disorder often occurs in childhood and adolescence with a prevalence of below 1%, which increases towards 2-3% in older adolescence, with peak onset between 15 and 19 years of age (Beesdo, Knappe, & Pine, 2009; Essau et al., 2000; Merikangas et al., 2010; Vizard et al., 2018). Prevalence is substantially elevated in clinical settings where observed incidence of adolescent panic disorder rises to 2-15% (Diler et al., 2004; Masi et al., 2000).

Panic disorder across the lifespan is linked to significant reductions in quality of life, poorer occupational and health outcomes, increased health costs and increased risk of comorbid mental disorders (Goodwin et al., 2021; Kessler et al. 2006). In childhood and adolescence panic disorder is associated with psychosocial and academic difficulties, increased mental health comorbidity and increased risk of suicidal ideation and attempts (Beesdo et al., 2009; Boden et al., 2007; Diler et al., 2004). Earlier age of onset is also associated with greater severity and poorer outcomes later in life (Ramsawh et al., 2011). Prompt and effective treatment of panic disorder can mitigate the risk of these consequences and the development of further anxiety and mood disorders (Goodwin & Olfson, 2001).

There is a growing body of evidence which links the experience of traumatic events in early life to the development of panic disorder. Traumatic events are those which involve real

or perceived threats of death, significant harm, or sexual violence (APA, 2013). The prevalence of experiencing a traumatic event at least once in a lifetime is remarkably high, typically exceeding 70%, with 30% of individuals encountering four or more such events (Benjet et al., 2016). This notable lifetime prevalence extends into childhood and adolescence, with rates ranging widely from 15% to 82.5% with heterogeneity largely relating to the methodological approaches employed (Lewis et al., 2019). Multiple studies have highlighted that individuals presenting with panic disorder report higher instances of childhood trauma exposure (e.g. Asselmann et al., 2016; Bandelow et al., 2002; Leskin and Sheikh, 2002). Similarly, a 21-year longitudinal study found exposure to sexual and physical abuse to be associated with increased risk of developing panic disorder (Goodwin, Fergusson & Horwood, 2005). A recent meta-analysis by Zhang and colleagues (2021) suggested that individuals who have experienced Adverse Childhood Experiences (ACE's) which can include abuse, neglect, and household dysfunction are 2.2 times more likely to develop panic disorder in adulthood compared to those not exposed.

The relationship between panic disorder and PTSD is marked by significant comorbidity and often overlapping clinical presentations. A significant proportion of children encountering traumatic events will go on to develop PTSD, with around 7.8% of UK youth affected over their lifetime and approximately 15.9% of those exposed to trauma developing PTSD (Alisic et al. 2014; Lewis et al., 2019). PTSD encompasses four symptom groups linked to the experience of trauma, including intrusive thoughts, avoidance behaviours, heightened arousal, and mood and cognitive changes (APA, 2013). Panic symptoms have consistently been demonstrated to be common in adults with PTSD with prevalence estimates of 35% of people with PTSD experiencing panic attacks and a prevalence of panic disorder of 18.6% in men and 17.5% in women with lifetime PTSD history (Cougle et al., 2010; Feldner et al., 2009). Studies also suggest that perievent experience of panic attacks can be predictive

of later development of PTSD (Adams & Boscarino, 2011). A study by Berenz and colleagues (2019) examining trauma exposed adults suggests a bidirectional pathway of risk between panic disorder and PTSD in trauma-exposed adults, indicating that the presence of either condition significantly raises the risk of developing the other.

Although there remains a paucity of research delineating the relationship between panic disorder and PTSD comorbidity, particularly in childhood, several studies have begun to put forward possible explanatory linking mechanisms. Theoretical models highlight the importance of conditioned fear responses to aversive experiences which are common across anxiety disorders (Lissek et al., 2005). In keeping with these ideas, the Panic Attack-PTSD Model put forth by Hinton and colleagues (2008) suggests that physiological arousal present during perievent panic attacks may lead to conditioned trauma related fear responses which can trigger subsequent panic attacks through the activation of trauma memory networks. Cognitive models of panic disorder and PTSD share similar cognitive mechanisms that emphasise the role of catastrophic interpretations which exacerbate fear responses in relation to either somatic sensations in panic disorder or in appraisals of the traumatic event and its sequelae in PTSD (Ehlers & Clark, 2000). A further area of interest is anxiety sensitivity (AS) which relates to the fear of anxiety related sensations (Reiss, 1991). The association between AS and panic disorder is widely established and there is a growing evidence base which suggests that trauma exposure increases AS and that it may be a common factor in the development of both panic disorder and PTSD (Stephenson et al., 2009). A recent review by Chiu and colleagues (2023) suggested a significant relationship between anxiety sensitivity and PTSD among children and adolescents exposed to trauma.

It is suggested that although individuals with PTSD fear somatic sensations during panic, their attacks may differentiate from those without PTSD in that they are marked by fear of trauma memories (Joscelyne et al., 2012). Jocelyne and colleagues (2012) identified

that individuals with panic disorder and PTSD reported similar somatic symptoms during panic attacks as those with panic disorder but experienced more intense fear of trauma memories, including traumatic intrusions and fears of re-experiencing harm, compared to those with panic disorder who predominantly feared aversive somatic outcomes. This suggests that panic attacks in PTSD may be more closely linked to trauma-related memories than somatic sensations which could have important implications for treatment approaches which may benefit from focusing on trauma memory processing rather than interoceptive exposure alone.

Despite the growing body of research there remains extensive heterogeneity in estimates of panic disorder in trauma-exposed youth in larger scale studies (e.g. including over 5000 trauma-exposed youth); these can range from 8% after exposure to the World Trade Centre attack (Goodwin et al., 2021) to 32.2% after exposure to the 2013 Ya'an (China) earthquake (Tang et al., 2020). The wide heterogeneity suggests that additional moderating factors may need to be explored to understand the relationship between panic disorder and trauma in youth and its prevalence. To the best of the authors' knowledge, a systematic review on the prevalence of panic disorder in trauma exposed youth and youth with PTSD has not previously been conducted. Understanding of the relationship between trauma exposure and panic disorder in youth is particularly important due to the high prevalence of trauma exposure, the early onset of panic disorder and the distinct psychological and physiological responses to trauma expressed throughout development (Carrion et al., 2002). A more thorough estimate of the prevalence of panic disorder in trauma exposed children and adolescents is required to shape future clinical practices in the identification and treatment of trauma-exposed youth with panic disorder.

The present systematic review and meta-analysis sought to answer the following research questions:

RQ1). What is the prevalence of panic disorder in children and adolescents after exposure to trauma?

RQ2). What is the prevalence of panic disorder in children and adolescents who meet criteria for PTSD diagnosis?

RQ3). What is the prevalence of PTSD in trauma-exposed children and adolescents who meet criteria for panic disorder diagnosis?

Possible moderators which could influence the prevalence rates of panic disorder were also explored for the primary research question RQ1: self-report questionnaire vs diagnostic interview, individual vs collective trauma, trauma type (interpersonal violence IPV), and high income (HIC) vs low or middle-income country (LMIC).

Method

The protocol for the study was pre-registered on the Prospective Register of Systematic Reviews (PROSPERO; CRD42023432495).

Systematic searches were conducted using four electronic literature databases covering medical and psychological fields (APA PsycINFO, PTSDpubs, PubMed and Web of Science). The searches used variations of the following search terms across both study title and abstract, adapted to the syntax requirements of each database: ("Panic" OR "agoraphobi*" OR "anxiety Disorder*") AND (child* OR teen* OR youth* OR youngster* OR "young person" OR adolesc* OR boy OR girl OR pupil) AND ("trauma" OR "post-traumatic stress disorder" OR PTSD OR hurricane* OR flood* OR tsunami* OR earthquake* OR disaster* OR accident OR collision OR abuse OR violence OR assault OR maltreatment OR war OR conflict).

Searches were restricted to those published between 1980 (when PTSD was first classified as a disorder in the DSM-III) and July 2023.

Inclusion and exclusion criteria

Studies were included if:

1) A diagnosis of panic disorder and PTSD was be made according to DSM or ICD criteria and was made using diagnostic interview or a validated questionnaire measure providing a cut-off score for clinical caseness based on DSM or ICD criteria.

2) Trauma exposure was defined by the A1 Criteria for PTSD in either DSM-IV or DSM-5, or additional information for the trauma-exposed group was available to validate trauma exposure such as living in an area affected by a disaster, war or terrorist attack or a survey of trauma exposure was conducted.

3) Participants in the study were between the ages of 5 and 18 years old at the time of initial assessment or the mean age of the participants was between 5 and 18 years.

4) The studies provided adequate information to derive prevalence of panic disorder or panic disorder in children and adolescents exposed to trauma; or compared rates of panic disorder between trauma exposed groups and a suitable non-trauma exposed comparison group; or provided continuous measures of panic disorder and PTSD severity.

5) Participants did not represent a clinic-referred sample and were not selected based on seeking/receiving treatment due to risk of including high prevalence rate samples.

6) Studies included longitudinal cohort and cross-sectional studies of trauma-exposed children and adolescents and did not include qualitative studies, single case studies, systematic reviews, meta-analyses.

7) Studies not reporting the relevant statistics or data to calculate effect sizes were not included.

8) Studies in which prevalence was measured before one-month post-trauma (due to DSM PTSD diagnosis criteria) and studies only reporting lifetime prevalence were excluded.

Study collection and data extraction

The author screened the titles and abstracts of all studies from the initial searches according to eligibility criteria and those included were taken to a second stage of full text review, where there was uncertainty, the studies were included for review of the full text. The author assessed all articles at the full text review stage according to inclusion and exclusion criteria, the first reason encountered for inclusion or exclusion was recorded. An independent researcher (LG) also assessed the full list of full text articles and deemed all studies recorded as meeting criteria for inclusion.

The author completed data extraction of the included studies and a sample of 50% was checked for errors by LG. A data extraction spreadsheet was used to record the following extracted information: study details (author, title, year of publication, journal); study design (longitudinal cohort and cross-sectional studies); sample characteristics (age range, mean age, age standard deviation); country and country income status; trauma type (broad description of trauma e.g. hurricane or earthquake, whether trauma was collective or individual, whether trauma involved interpersonal violence); time since trauma; single vs multiple trauma; information relating to diagnostic approach used (measure used, measure type as either interview or self-report and diagnostic criteria used as DSM or ICD); and outcome data (number identified with panic disorder, number in trauma exposed sample, number with PTSD, number with comorbid panic disorder and PTSD, number with panic disorder in non-trauma exposed control groups, total number in control group, mean severity scores and

standard deviations for trauma exposed and non-trauma exposed controls and correlations of panic severity with trauma exposure).

Quality assessment

Consistent with established guidelines, an evaluation the risk of bias was performed for each study included, considering the variations in methodological quality (Higgins & Altman, 2008). A tool was developed (Appendix B) for the purposes of this review which was based on the risk of bias tool developed by Hoy and colleagues (2012) for prevalence studies and incorporated guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data established by Munn et al. (2014). The tool consisted of seven criteria. Four criteria related to external validity and scored studies on the sampling methods and representativeness of the sample, likelihood of non-response bias, description of study subjects and setting and specification of the index trauma and time since trauma. A further three criteria related to internal validity and scored studies on objectivity, validity and reliability of measurement criteria used, reliability of measurement approach and whether confounding factors were accounted for. The seven questions were scored with binary outcomes with a maximum score of seven, with higher scores indicating lower risk of bias. These scores were further categorised as low risk of bias (6-7), moderate risk of bias (3-5) and high risk of bias (0-2). Risk of bias was assessed in all included studies by the author and by LG.

Statistical Analysis

Statistical analysis was conducted using the metafor package (Viechtbauer, 2010) in R (v4.2.1: R Core Team, 2021). Random effects models were used to compute weighted estimates of panic disorder prevalence in children and adolescents exposed to trauma, and of those with PTSD. As heterogeneity was expected to be high due to diversity of index traumas

and study design the arcsine transformation was used to account for heterogeneity which may impact study weightings (e.g. 95% confidence intervals going below zero) when estimating prevalence (Barendregt et al., 2013). Heterogeneity among studies was evaluated using the Cochran's Q test, I^2 statistic and prediction intervals. Using the I^2 statistic, a value over 50% represents moderate heterogeneity, while a value of 75% or higher signifies a high degree of heterogeneity (Higgins & Thompson, 2002). The Cochran's Q test indicates whether heterogeneity was significant within the studies (Cochran, 1954). The prediction interval is an estimate of the range within which future observations are expected to fall 95% of the time.

Moderator analyses were also conducted using random effects models to establish factors related to prevalence in RQ1. Moderator analyses were decided *a-priori* and included self-report questionnaire vs diagnostic interview, individual vs collective trauma, age (younger child <13, older child >13), trauma type (interpersonal violence IPV), and high income (HIC) vs low or middle-income country (LMIC) and study quality which was defined as high or moderate quality vs low quality studies. Moderator analyses were restricted to RQ1 as the number of available studies pertinent to RQ2 and RQ3 was comparatively fewer, limiting the statistical power to detect significant moderator effects and increasing the risk of overfitting the model if included. Consequently, for these more exploratory research questions a cautious approach was adopted, and focus was directed on direct estimates rather than possible moderators. Analyses were only conducted when at least four independent trials were available for comparison for main analyses and four per group were available for the moderator analyses (Morina et al., 2021). This meant moderator analyses could not be conducted in RQ1 for self-report questionnaire vs diagnostic interview and high/moderate quality vs low quality studies.

Results

A Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart (Fig. 1) is provided as a summary of the search and selection process.

Search outcomes

Fig. 1 shows the PRISMA flow chart. The search identified 8345 references. Following removal of 3338 duplicates there remained 5007 studies which were screened on title and abstract. Full text screening was carried out for the 371 papers which were screened as relevant. Full text screening was checked by LG with 100% inter-rater reliability.

Only one study reported data on the correlation between panic disorder severity and trauma exposure and only two studies reported data on panic disorder in non-trauma exposed controls. As such, previously planned meta-analyses relating to the extent to which panic disorder severity, trauma exposure and PTSD severity were related and the difference in the odds of developing panic disorder between children and adolescents based on trauma exposure could not be undertaken. Two further studies were dropped from analysis as they used a prior data set already used in one of the studies selected for inclusion. 16 studies met final inclusion criteria for this review.

Figure 1 PRISMA flow chart

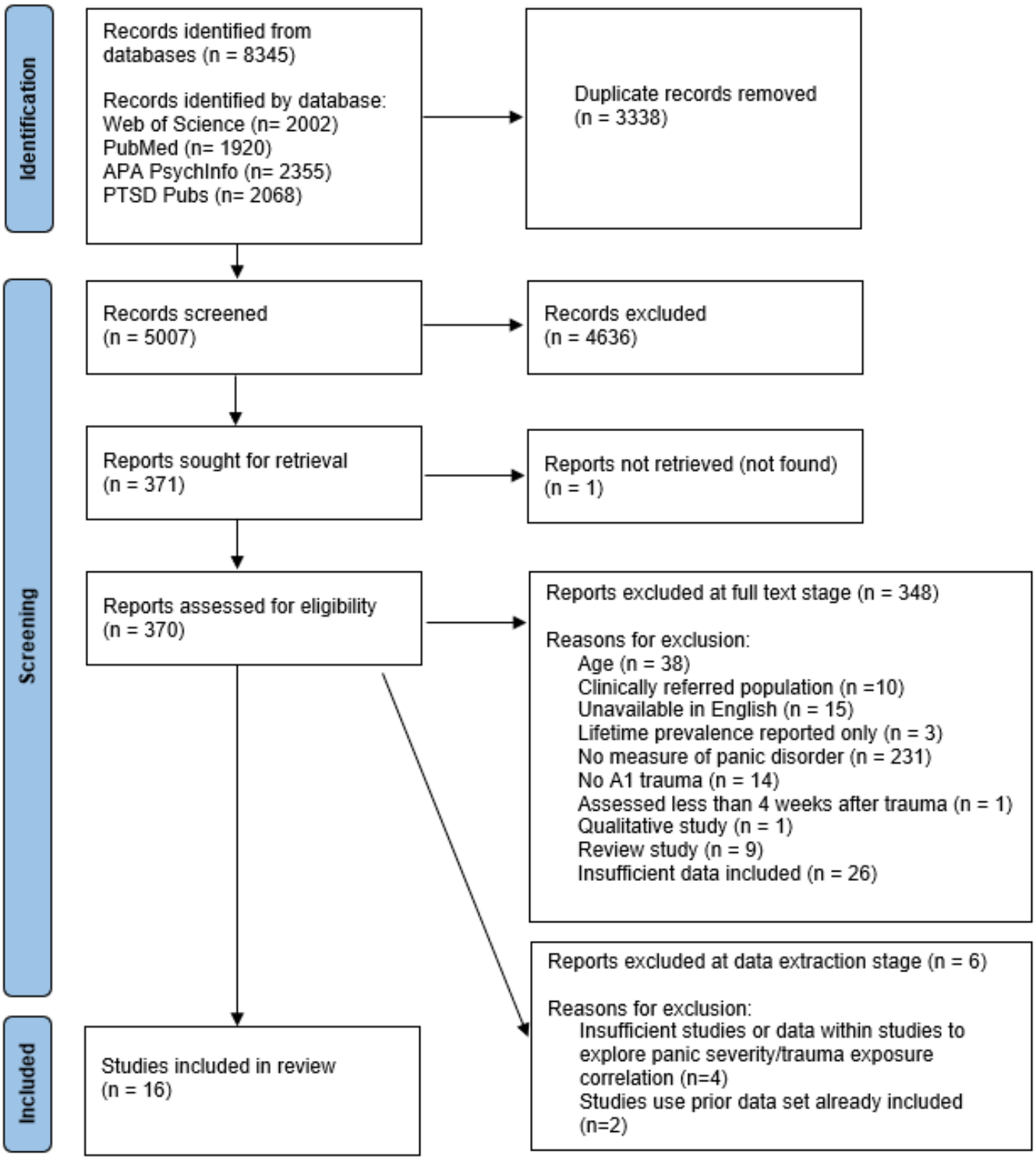


Table 1 Study Characteristics

Study	N*	Age Range (mean, SD)	Country	Country Status	Trauma Type	IPV	Collective/ Individual	Trauma Event Type	Interview/ Self-report	Panic Measure	DSM/ ICD	Risk of Bias
Boer et al., 2009	779	9-14 (11.6, 1.1)	Netherlands	HI	Technological disaster	No	Collective	Single	Self-report	SCARED	DSM	6 (Low Risk)
Ceri et al., 2018	117	7-17 (12.7, 2.1)	Turkey	UMI	War	Yes	Collective	NR	Interview	K-SADS	DSM	3 (Mod risk)
Coulon et al., 2022	39	16-18 (16.9**)	France	HI	Terrorist Attack	Yes	Collective	Single	Interview	MINI KID	DSM	6 (Low Risk)
Essau et al., 2000	17	8-17 (14.3, 1.7)	Germany	HI	NR	NR	NR	NR	Interview	CAPI	DSM	5 (Mod risk)
Geng et al., 2019	1573	12-16 (15, 1.26)	China	UMI	Earthquake	No	Collective	Single	Self-report	SCARED	DSM	6 (Low Risk)
Hoven et al., 2005	5490	9-21 (13.6, 2.6)	USA	HI	Terrorist Attack	Yes	Collective	Single	Interview	DISC-IV	DSM	6 (Low Risk)
Linning & Kearney, 2004	55	8-17 (12.7, 2.58)	USA	HI	Maltreatment	Yes	Individual	NR	Interview	ADIS-C	DSM	5 (Mod risk)
Luis & Mittenberg, 2002	96	6-15	USA	HI	TBI	NR	Individual	Single	Interview	DISC-IV	DSM	5 (Mod risk)
Math et al., 2008	37	≤18	India	LMI	Tsunami	No	Collective	Single	Interview	Psych Interview	ICD	6 (Low Risk)
Max et al., 2011	141	5-14	Canada	HI	Traumatic Brain Injury	Mixed (1/177)	Individual	Single	Interview	K-SADS	DSM	7 (Low Risk)
Meiser-Stedman et al., 2007	57	10-16 (13.8, 1.9)	UK	HI	Mixed (ED)	Mixed (50/90)	Individual	Single	Interview	ADIS-C/P	DSM	7 (Low Risk)
Mirza et al., 1998	33	8-16 (13.6, 2.44)	UK	HI	Road Traffic Accident	No	Individual	Single	Interview	K-SADS	DSM	7 (Low Risk)
Okello et al., 2007	153	11-19	Uganda	LI	War	Yes	Collective	NR	Interview	MINI KID	DSM	6 (Low Risk)
Scheeringa & Zeanah, 2008	70	3-7 (5.1)	USA	HI	Hurricane	No	Collective	Single	Interview	PAPA	DSM	7 (Low Risk)
Tang et al., 2017	191	8-18 (13.7, 2.3)	China	UMI	Earthquake	No	Collective	Multi	Interview	K-SADS	DSM	7 (Low Risk)
Tang et al., 2020	5563	9-18	China	UMI	Earthquake	No	Collective	Multi	Self-report	SCAS	DSM	7 (Low Risk)

Notes: N* = N of trauma exposed children and adolescents assessed for panic disorder; NR = Not reported; HI = High Income; UMI = Upper Middle Income; LMI = Lower Middle Income; LI = Low Income; TBI = Traumatic Brain Injury; IPV = Interpersonal violence; ED = Emergency department; SCARED = Screen for Child Anxiety Related Disorders; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; MINI-KID = The Mini-International Neuropsychiatric Interview for Children and Adolescents; CAPI = computerized Munich version of the Composite International Diagnostic Interview; DISC-IV = the Diagnostic Interview Schedule for Children Version IV; PAPA = Preschool age psychiatric assessment; Mod = Moderate risk of bias. **Indicates median reported as opposed to mean.

Study characteristics

Table 1 provides a summary of information for included studies. The studies were published between 1998 and 2020 and examined a total of 14,411 trauma exposed children and adolescents assessed for panic disorder, the number of participants varied from 17 to 5563. Participants ranged from age three to twenty-one. The studies spanned countries including the United States (k= 4), China (k= 3), the United Kingdom (k = 2), Germany (k = 1), India (Andaman and Nicobar Islands) (k = 1), the Netherlands (k = 1), Canada (k = 1), Turkey (k = 1), Uganda (k = 1) and France (k = 1). All studies used recognised diagnostic criteria to assess panic disorder (DSM [k = 15], ICD [k = 1]). Twelve studies used standardised structured or semi-structured interviews to assess panic disorder, three used standardised self-report questionnaires and the remaining study used psychiatric interviews. Different types of traumas were reported: five studies reported interpersonal violence (IPV), seven reported non-IPV, two studies reported mixed trauma types. Ten studies reported collective trauma and five reported individual trauma. Ten studies reported single event trauma and two reported multiple event trauma. Several studies did not provide information to specify trauma type, particularly around single or multiple event trauma where it was difficult to discern whether the participants had been exposed multiple times.

Risk of bias assessment

The 16 included studies were assessed using the risk of bias tool. Twelve studies were rated as low risk (i.e. scoring six or seven out of a total of seven), and four studies were rated as medium risk (three studies scoring five and one study scoring three). Inter-rater reliability was calculated using intraclass correlation coefficient (ICC) analysis, using a two-way mixed-effects model. The ICC indicated a high level of inter-rater reliability across the author and LG (ICC = 0.938, 95% CI 0.831, 0.978).

RQ1: Prevalence of panic disorder in trauma exposed children and adolescents

With 13 studies included with data available for RQ1 and a total number of 14,170 participants, the pooled prevalence of panic disorder within trauma exposed children and adolescents was 7.1% (95% CI 2.7, 13.5). The Q-test for pooled estimates was significant with considerable heterogeneity observed between studies ($Q(df = 12) = 1433.1$, $p < .0001$, $I^2 = 99.1\%$); the prediction interval was 0.0% to 36.9%. For the forest plot see Fig.2.

Figure 2 RQ1 forest plot for prevalence of panic disorder

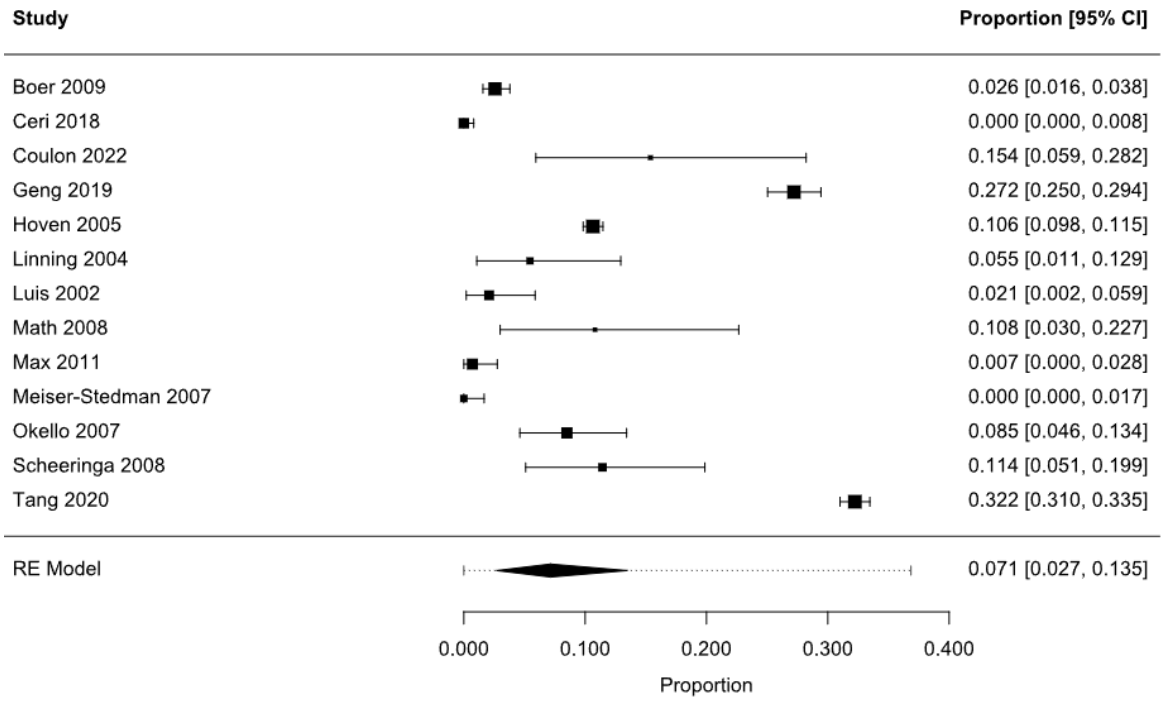


Table 2 Meta-analysis outcomes for RQ1, including sub-group and moderator analyses.

				Heterogeneity			
	K	**N**	**Prevalence (%)**	95% CI	**Q test**	**I^2**	**95% PI**
All studies included	13	14,170	7.1	2.7, 13.5	1433.1	99.1	0.0, 36.9
Sub-group analyses							
Self report vs Interview							
Self-report	3	7,915	18.0	2.7, 42.6	535.9	99.8	0.0, 69.3
Interview	10	6,255	4.5	1.5, 9.1	119.8	92.3	0.0, 22.9
Moderation analysis:			Insufficient studies				
Collective vs Individual							
Collective	9	13,821	11.0	4.5, 19.8	1266.3	99.4	0.0, 43.1
Individual	4	349	1.3	0.1, 3.9	7.1¶	59.5	0.0, 7.1
Moderation analysis:			Significant (Q_M(df = 1) = 4.6, p = 0.03)				
Interpersonal vs non-interpersonal							
Interpersonal	5	5,854	6.15	1.3, 14.2	53.8	93.6	0.0, 28.7
Non-interpersonal	5	8,022	15.3	5.6, 28.8	554.2	99.2	0.0, 50.9
Moderation analysis:			Non-significant (QM(df = 1) = 1.9, p = 0.16)				
High-income country vs low-income country							
High income	8	6,727	4.4	1.4, 9	142.2	94.9	0.0, 20.5
Low income	5	7,443	12.4	2.2, 29.4	233.7	99.4	0.0, 58.8
Moderation analysis:			Non-significant (QM(df = 1) = 2.1, p = 0.15)				
Low risk vs moderate risk of bias							
Low risk of bias	10	13,902	9.5	3.7, 17.6	1293.6	99.3	0.0, 41.4
Moderate risk of bias	3	268	1.5	0.0, 6.4	9.5	79.0	0.0, 12.8
Moderation analysis:			Insufficient studies				
Age							
Younger child <13	4	1021	3.2	0.2, 10	22.8	90.7	0.0, 21.2
Older child ≥13	4	7159	10.2	1.0, 27.4	262.1	99.4	0.0, 53.5
Moderation analysis:			Non-significant QM(df = 1) = 1.1, p = 0.29				
Sensitivity analyses							
Collective vs Individual (Self report studies removed)							
Collective	6	5,906	7.7	2.6, 15	52.18	92.2	0.0, 29.3
Individual	4	349	1.3	0.1, 3.9	7.07¶	59.5	0.0, 7.1
Moderation analysis:			Non-significant QM(df = 1) = 3.8, p = 0.05				

Note: ¶Indicates that Q test was nonsignificant at p<.05. PI = Prediction Interval.

RQ1: Moderator and sensitivity analysis

Moderator analyses were conducted using random effects models to test differences in pooled prevalence estimates based on covariates established *a-priori*. Moderator analysis was also conducted to establish differences in prevalence in relationship to study quality which was defined as high or moderate quality as no low-quality studies were identified. Table 2

provides an outline of all results of the meta-analysis outcomes for RQ1 including moderator analyses.

Moderator analyses for IPV, age and country income status did not significantly moderate the prevalence of panic disorder when all studies with available data were included. For these moderators all Q test results were highly significant and had I^2 values >90% indicating significant heterogeneity across studies. No moderator analysis was conducted for risk of bias due to only three studies scoring as moderate risk.

Panic disorder prevalence appeared higher when assessed using self-report methods (18% [95% CI 2.71, 42.59%, 95% PI 0.0, 69.3%]) when compared to interview methods (4.54% [95% CI 1.5, 9.11, 95% PI 0.0, 22.9]) however only subgroup analyses were conducted due to the presence of only three self-report studies precluding moderator analysis comparison. The prevalence of 18% with self-report methods, had a wide confidence interval and a wider prediction interval suggesting considerable uncertainty and variability in the self-reported prevalence of panic disorder. In contrast, studies using interview methods yielded a lower prevalence estimate of 4.54% but had a narrower confidence and prediction intervals suggesting a more conservative and possibly more accurate estimate of prevalence.

Panic disorder prevalence was significantly higher following exposure to collective trauma (10.95%) when compared to exposure to individual trauma (1.3%). For collective vs. individual trauma, the Q test result was significant for collective trauma but was not significant for individual trauma which suggests the variation is not significantly larger than would be expected by chance. However, given the small number of studies in this subgroup ($k = 4$) this finding should be considered with caution. As self-report methods demonstrated high prevalence in subgroup analysis, a sensitivity analysis was run on the collective vs individual moderator analysis, removing self-report studies. This sensitivity analysis

suggested that when self-report studies were removed, that collective vs individual trauma did not significantly moderate the prevalence of panic disorder although it did approach significance (QM[df = 1] = 3.7785, p = 0.052).

RQ2). What is the prevalence of panic disorder in children and adolescents that meet criteria for PTSD diagnosis?

To determine the estimated prevalence of panic disorder in children and adolescents who met thresholds for PTSD diagnosis a further random-effects meta-analysis was conducted using seven studies (N=618) which reported information relating to this question. The pooled prevalence of panic disorder within children and adolescents with PTSD was 20.7% (95% CI 5.6, 41.9). The prediction interval was notable at between 0% and 79.7%, suggesting a high degree of uncertainty regarding the prevalence rate. The Q-test for pooled estimates was significant with considerable heterogeneity observed between studies (Q(df = 6) = 383.8 p < .0001, I^2 = 96.1%, tau^2 = 0.09 [SE = 0.057]).

Sensitivity analysis was also run on RQ3, removing one study (Coulon et al., 2022) that used self-report questionnaires rather than structured interviews. This sensitivity analysis included six studies (N=321). When removing studies using self-report questionnaires the pooled prevalence of panic disorder within children and adolescents with PTSD was 12.8% (95% CI 3.8, 25.9). The prediction interval was lower but remained notable at between 0% and 48.3%, suggesting a high degree of uncertainty regarding the prevalence rate. The Q-test for pooled estimates was significant with considerable heterogeneity observed between studies Q(df = 5) = 36.4, p < .0001, I^2 = 84.5%, tau^2 = 0.035 [SE = 0.028]).

RQ3). What is the prevalence of PTSD in trauma-exposed children and adolescents that meet criteria for panic disorder diagnosis?

For the final research question determining the estimated prevalence of PTSD in children and adolescents meeting criteria for panic disorder diagnosis a further random-effects meta-analysis was conducted using only four studies (N=445) which reported information relating to this question. The pooled prevalence of PTSD within children and adolescents with panic disorder was 79.8% (95% CI 48.5, 98.3). The prediction interval was notable at between 18.5% and 100% suggesting a high degree of uncertainty regarding the prevalence rate. The Q-test for pooled estimates was significant with considerable heterogeneity observed between studies ($Q(df = 3) = 17.4$, $p = 0.0006$), $I^2 = 78.8\%$, $tau^2 = 0.0841$ [SE = 0.0950]. Sensitivity analysis removing the one study that used self-report questionnaires were not conducted due to leaving only three remaining studies with a total of 17 participants, as such these results should be considered with caution.

Figure 3 RQ2 forest plot for prevalence of panic disorder in those meeting criteria for PTSD diagnosis

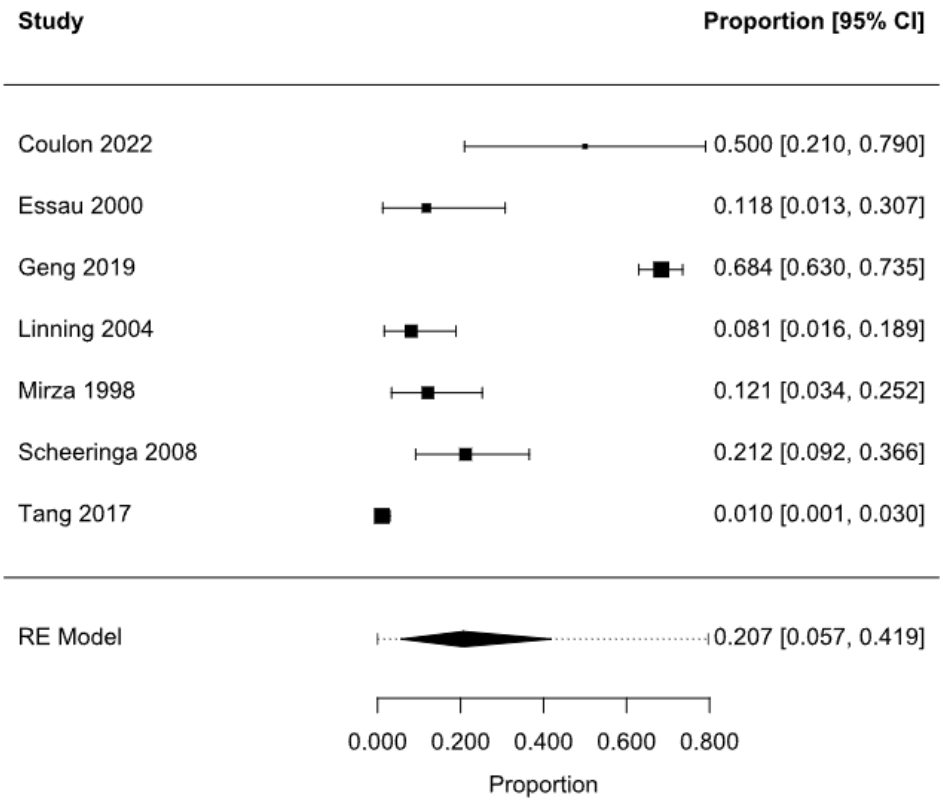
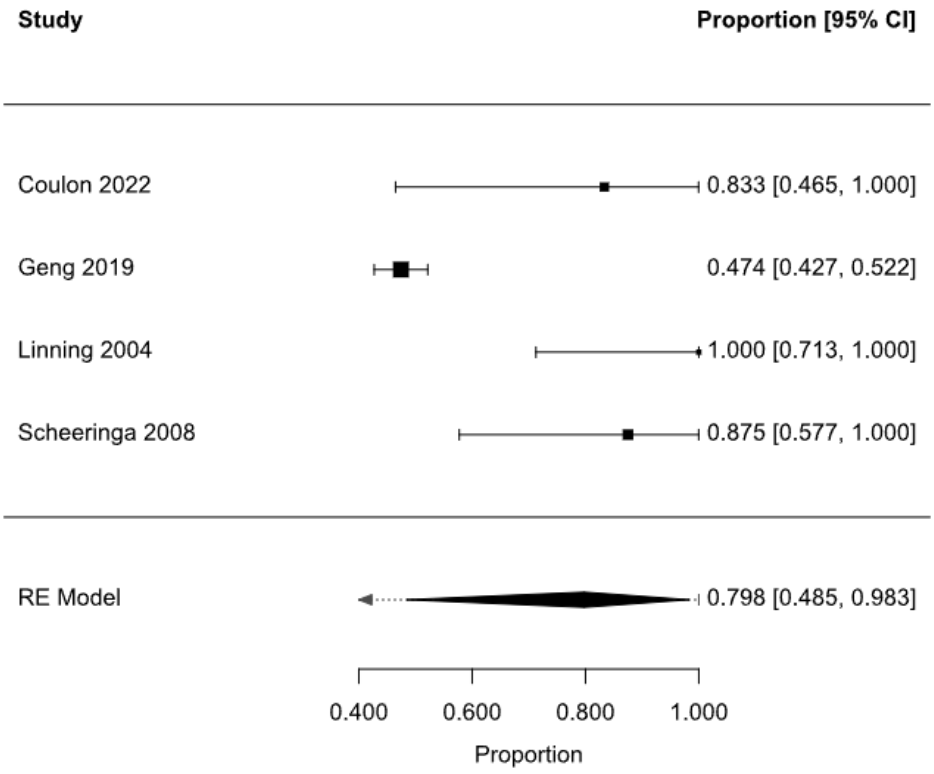


Figure 4 RQ3 forest plot for prevalence of PTSD in those meeting criteria for panic disorder diagnosis

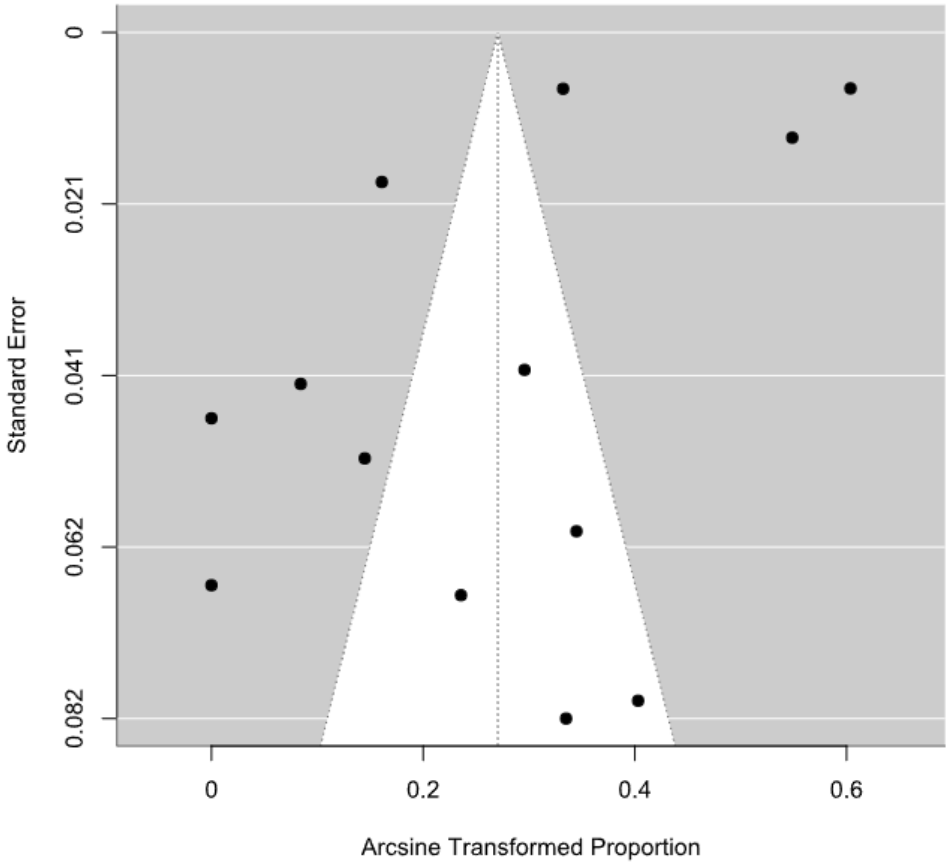


Publication bias

Publication bias was assessed via a visual inspection of a funnel plot, trim and fill analysis, and Egger's regression test for each of the main meta-analyses (Duval & Tweedie, 2000; Egger et al., 1997; Higgins & Altman, 2008). Visual inspection of the funnel plot from RQ1 (Fig.3) suggests some asymmetry with some grouping of studies in the top right and bottom left areas, this suggests that larger or more precise studies tend to report higher effect sizes and that smaller or studies higher in variability tend to report lower effect sizes. However, the Egger test for funnel plot asymmetry suggested no significant publication bias ($t = -1.5550$, $df = 11$, $p = 0.1482$). Similarly, the trim and fill analysis identified zero missing studies on the right side ($SE = 2.2742$).

Publication bias was not assessed for RQ2 and RQ3 due to the number of studies included being less than the recommended number of ten (Higgins et al., 2021).

Figure 5 RQ1 Funnel plot for prevalence of panic disorder in trauma exposed children and adolescents



Discussion

Although there is a growing evidence base that suggests that panic disorder is associated with trauma exposure in children and adolescents, to date there has been no estimate of panic disorder in trauma exposed youth. To the authors knowledge, this is the first meta-analysis to provide an estimate of the prevalence of panic disorder in trauma-exposed children and adolescents. The primary research question RQ1 drew from 13 studies involving 14,170 participants and indicated a pooled prevalence of 7.1%. This figure exceeds prevalence reported in community samples across childhood and adolescence below 1%, increasing to 2-3% in older adolescence, suggesting an impact of trauma exposure on the development of panic disorder in children and adolescents (Essau et al., 2000; Merikangas et al., 2010; Vizard

et al., 2018). The results of the meta-analysis for RQ1 should be interpreted with caution however, due to the high degree of heterogeneity observed across studies in the analyses conducted. Whilst moderator analyses attempted to identify some of the reasons for this heterogeneity, there are likely other unidentified factors moderating the prevalence of panic disorder in trauma exposed youth which have not been accounted for in this review. Despite this heterogeneity, the consistently high prevalence rates across studies point to a robust association between trauma exposure and panic disorder in children and adolescents.

Moderator analyses revealed no evidence for the prevalence rate differing according to country income status and age. Subgroup analysis of IPV and non-IPV trauma type suggested a much higher prevalence within non-IPV trauma, but comparisons remained non-significant. The subgroup analyses of assessment type, self-report and interview demonstrated the highest difference in prevalence observed, suggestive of higher prevalence reported in self-report studies with higher confidence and prediction intervals. Due to limited self-report studies, moderator analyses were not conducted but this difference may highlight the importance of assessment methods in prevalence studies, possibly reflecting differences in reporting bias or sensitivity of the instruments. This finding is echoed in previous prevalence studies of depression, PTSD and anxiety disorders which suggest self-report measures using specified cut-off thresholds for diagnosis may lower thresholds for diagnosis and lead to overestimations of prevalence relative to structured and semi-structured interview approaches (Diamond et al., 2022; Thombs et al., 2018). This may be a particularly important in consideration of panic disorder within the context of trauma-exposure, where significant overlap of symptoms between panic disorder and PTSD may require further probing or clinical decision-making which are not possible using self-report questionnaires (Means-Christensen et al., 2003).

Moderator analysis suggested significant differences between studies examining collective and individual trauma types, with collective trauma associated with a higher prevalence of panic disorder (10.95% [95% CI 4.51, 19.75]) when compared to exposure to individual trauma (1.3% [95% CI 0.08, 3.94], p = .032). However, when sensitivity analyses were applied removing self-report studies from this analysis the differences were not significant (QM[df = 1] = 3.7785, p = 0.052). Given the small number of studies included in this sensitivity analysis this area may warrant further exploration in future research.

The results of the meta-analysis for RQ3 exploring the prevalence of panic disorder in children and adolescents with PTSD indicated a pooled prevalence rate of 20.7% (95% CI: 5.6% to 41.9%). This rate indicates that approximately one in five children and adolescents with PTSD may also experience panic disorder. The broad prediction interval and significant heterogeneity suggest other factors such as study population or methodological approaches may not have been accounted for. Elevated prevalence remained indicated following sensitivity analysis. After the exclusion of self-report-based studies, the pooled prevalence of panic disorder in children and adolescents with PTSD decreased to 12.8% (95% CI: 3.8% to 25.9%). This further indicates the need for careful consideration of the assessment methods used to diagnose panic disorder in prevalence studies, as self-report measures may inflate rates. These results should be interpreted with caution due to the limited number of studies included (k=7) and smaller sample size (n=618).

The results of the final meta-analysis for RQ3 exploring the prevalence of PTSD in children and adolescents with panic disorder indicated a notably high pooled prevalence of PTSD in this group, estimated at 79.75% (95% CI: 48.46% to 98.25%). This finding suggests that a substantial majority of children and adolescents with panic disorder may also meet criteria for PTSD diagnosis. However, these results should be considered with caution due to the relatively low number of studies (k = 4) and participants (n = 445) which were largely

grouped in one study of 428 participants. Furthermore, a significant degree of heterogeneity and a wide prediction interval was also observed suggesting a high degree of variability among studies. The significantly reduced sample size and number of studies could potentially lead to skewed results and limit the scope and generalizability of the findings to a broader population.

Clinical Implications

The high rate of prevalence of panic disorder observed in trauma-exposed youth in this study, likely exceeds that observed in general populations and emphasises the importance of clinicians routinely considering panic disorder alongside PTSD in the assessment and treatment of trauma exposed children and adolescents. These findings share similarity to those observed by Vibhakar et al. (2019) who identified increased prevalence for depression of 24.2% in trauma exposed youth relative to community sample prevalence between 2.6% and 11.3%. These findings are particularly important given the high prevalence of trauma exposure in youth (Lewis et al., 2019). Several studies have highlighted clinicians' difficulties in identifying panic disorder in children and adolescents and in a recent survey of UK Child and Adolescent Mental Health Service (CAMHS) clinicians, less than half were able to accurately identify panic disorder or panic symptoms as the main presenting problem in a vignette (Baker & Waite, 2020). Accurate assessment of panic disorder may be particularly difficult in the context of trauma exposure and PTSD where there is significant symptom overlap. Inaccurate assessment of panic disorder or misdiagnosis may have significant implications for the quality of patient care and could result in poorer treatment outcomes (Jensen-Doss & Weisz, 2008). Given the high prevalence discussed, difficulties in identification, and significant impairments associated with panic disorder which persist into adulthood if left untreated, it is of enormous importance that further work is carried out to aid the identification and treatment of panic disorder in clinical settings.

Limitations

The considerable heterogeneity observed across studies in the meta-analyses conducted raises questions about the generalizability of the findings. This variability could be attributed to differences in study designs, populations, trauma types, and assessment methods. The small number of studies for some research questions, particularly for RQ2 and RQ3 and some of the moderator analyses conducted, limited statistical power and thus the robustness of conclusions that can be drawn.

Most studies included were conducted in high-income countries and studies not written in English were excluded from analysis, this may mean that there is some degree of cultural bias which further limits generalisability of the findings. The diagnostic approach used in the review, relies on DSM or ICD criteria, and could miss certain populations, particularly those with undiagnosed or subclinical symptoms. This may mean individuals who experience significant panic symptoms but do not meet the full criteria for panic disorder or PTSD have been overlooked in the present study. The reliance on self-report measures in some studies might have led to inflated prevalence rates. This is evident in the differences observed in the subgroup analysis in RQ1 and in the sensitivity analysis for RQ2, where excluding self-report questionnaires notably lowered the prevalence rates. Future research should consider these factors when designing studies as it is possible that prevalence studies using self-report questionnaires may inflate prevalence.

Conclusion

This meta-analysis represents a significant step in understanding the prevalence of panic disorder in trauma-exposed children and adolescents. Our primary research question (RQ1) revealed a pooled prevalence of 7.1% among 14,170 participants, a figure higher than general population estimates. This highlights the important impact of trauma exposure on the

development of panic disorder in youth. The moderator analyses showed no significant differences in prevalence rates based on factors like intimate partner violence (IPV) exposure, age, or country income status. However, the assessment method used may have influenced the reported prevalence, with self-report questionnaires yielding much higher rates than interview methods. This points to the importance of assessment techniques in accurately diagnosing panic disorder, especially in the context of overlapping symptoms with PTSD. The exploration of panic disorder in children and adolescents with PTSD in RQ2 and of PTSD in those with panic disorder in RQ3 revealed pooled prevalences of 20.69% and 79.75% respectively, suggesting a substantial overlap between these conditions. However, these findings should be considered exploratory in nature and interpreted cautiously due to the limited number of studies included and the significant heterogeneity observed. These findings highlight the need for heightened awareness and accurate assessment of panic in trauma-exposed youth. The high prevalence rates suggest that clinicians should routinely consider panic in their diagnostic assessments of this population.

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Chapter Three: Empirical Study

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Author Guidelines available in Appendix A.

Salivary Cortisol in Children and Adolescents with and without PTSD Following Single-Incident Trauma.

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Abstract

Objective: Despite prior heterogeneity, there is broad consensus that trauma exposure and PTSD are related to HPA-axis dysfunction in children. There is wide variety in inclusion of different trauma types, duration, time since trauma, non-PTSD controls and measurement approaches applied and little remains known about the impact of single incident trauma. The present study sought to further understandings in the relationship between salivary cortisol, PTSD and trauma exposure in children and adolescents exposed to recent single incident trauma.

Methods: We analysed salivary cortisol from 85 children and adolescents exposed to single incident trauma, with and without PTSD, and a non-exposed control group. Participants collected saliva samples five times daily over two consecutive days. Analysis examined the cortisol awakening response (CAR), sample time, and total cortisol output.

Results: No difference was found in the cortisol levels between groups across sample times or within output of cortisol across the morning and length of the day. Blunting of CAR was observed in the non-PTSD group compared with healthy controls U=257, Z=−2.687, p=.01.

Conclusions: The results of the present study do not support the hypothesis that PTSD is characterised by elevated cortisol in childhood and adolescence at around three months post trauma. These findings reflect the heterogeneity in existing literature. Despite limitations like small sample size, this research adds to existing literature into cortisol's relationship with PTSD and trauma, highlighting the requirement for future research using a longitudinal approach, which closely adheres to consensus guidelines for assessing and reporting of cortisol data.

Key words: Salivary cortisol, trauma exposure, post-traumatic stress disorder, child, adolescent.

Introduction

Traumatic events are situations of actual or potential death, serious injury, or sexual violence (American Psychiatric Association, 2013). Trauma exposure is widespread, with more than 70% of people experiencing it at least once in their lifetime and 30% facing four or more such events (Benjet et al., 2016). A significant portion of children and adolescents, ranging from 15% to 82.5%, are exposed to trauma, with the variation in estimates reflecting methodological differences and the diversity of trauma types included (Lewis et al., 2019).

Many children who experience traumatic events develop post-traumatic stress disorder (PTSD), with studies suggesting a lifetime prevalence of 7.8% among UK youth and about 15.9% of those exposed to trauma showing signs of PTSD (Alisic et al., 2014; Lewis et al., 2019). PTSD manifests through four main groups of symptoms related to the traumatic experience, including distressing intrusions such as thoughts and memories, cognitive and behavioural avoidance of reminders, hyperarousal and reactivity and negative alterations to cognition and mood (American Psychiatric Association, 2013). The likelihood of developing PTSD after experiencing trauma shows considerable variation based on the nature of the trauma and the gender of the individual, with a multitude of further risk factors identified in previous meta-analyses (Alisic et al., 2014; Smith et al., 2019).

Exposure to trauma and the presence of PTSD are both associated with an increased incidence of wider psychopathology with impacts on social, emotional, and educational outcomes, and have been increasingly linked to adverse health outcomes such as gastrointestinal disorders and cardiovascular disease (Copeland et al., 2007; Sowder et al., 2018). These outcomes are proposed to be linked to biological and behavioural pathways, with post-traumatic physiological changes occurring in the endocrine system, central nervous system, autoimmune system, inflammatory system, and cardiovascular system (Krantz et al.,

2021; Sowder et al., 2018). A significant portion of the studies examining the physiological impacts of trauma exposure and PTSD has concentrated on alterations to the hypothalamic-pituitary-adrenal (HPA) axis (Schumacher et al., 2022).

The HPA-axis is a critical component in the in regulating the body's reaction to stress and has been implicated in the development of PTSD (Weems & Carrion, 2009; Zimmerman et al., 2020). Under typical conditions, the HPA-axis functions to mobilize and distribute resources throughout the body, following a marked diurnal rhythm that peaks at waking to maintain homeostasis for daily activities. Upon facing a threat to homeostasis, the HPA-axis is activated, mobilizing resources necessary for both anticipatory and reactive responses (Herman et al., 2016). When triggered by a threat the hypothalamus releases corticotropin releasing factor (CRF) and arginine vasopressin (AVP) which in turn cause the pituitary gland to release adrenocorticotropic hormone (ACHT) and activates the locus coeruleus/norepinephrine (LC/NE) system which is the primary driver of the “fight or flight” response. ACHT released into the blood stream also acts on the adrenal glands which then secrete cortisol, a glucocorticoid hormone; cortisol in turn functions to move cellular processes towards more immediate survival goals (Guilliams & Edwards, 2010). Cortisol production is regulated by a negative feedback mechanism that inhibits CRF and consequently, cortisol production (Weems & Carrion, 2009).

Cortisol as an output of the HPA-axis can be measured in different ways reflecting different underlying processes: within the cortisol awakening response (CAR) reflecting the rise occurring typically within the first 30-45 minutes post waking; within the diurnal pattern of decline throughout the day; and in response to specific stressors (Fries et al., 2009; Pruessner et al., 2003). Under basal conditions cortisol can be readily assayed in blood, urine and saliva (Schumacher et al., 2019). The earliest findings in adults with PTSD suggested the presence of *lower* cortisol levels (Mason et al., 1986; Yehuda et al., 1990). Many studies and

meta-analyses have since replicated these findings (Morris et al., 2012; Pan et al., 2020; Schumacher et al., 2019). However, the results have often been inconsistent, showing no significant differences, mixed outcomes, or contradictory findings (Klaassens et al., 2012; Meewisse et al., 2007; Miller et al., 2007).

Research involving children with PTSD is sparse in comparison but shows a different response, with findings more reliably demonstrating the presence of *higher* baseline and daily cortisol levels (Carrion et al., 2002; De Bellis & Zisk, 2014; Delahanty et al., 2000; Delahanty et al., 2005; Zantvoord et al., 2019: Zimmerman et al., 2020). Higher baseline cortisol has also been demonstrated in children exposed to maltreatment (Cicchetti & Rogosch, 2001). Similarly in a study exploring the impacts of road traffic accidents, higher evening cortisol was observed in children with PTSD at one month, but normalised at six months (Pervanidou et al., 2007).

However there remains inconsistency, and other studies have shown no significant difference in baseline morning and daily cortisol levels based on trauma exposure (Cicchetti et al., 2010; De Bellis et al., 1994). Usta et al., (2016) and Simsek et al., (2015) found no significant difference in cortisol levels of adolescents after single-incident sexual trauma with PTSD compared to controls. In contrast other studies have demonstrated lower cortisol. Blunting of the cortisol awakening response has been demonstrated to be associated with PTSD severity among adolescent girls with recent history of sexual abuse, in youth with high levels of recent trauma with frequent early life exposure and in adolescents and children exposed to maltreatment (Bernard et al., 2010; Bevens et al., 2008; Keeshin et al., 2014). Lower basal cortisol has also been shown in children with PTSD bereaved by the 9/11 attacks and war exposed children with PTSD, relative to those without PTSD (Feldman et al., 2013; Pfefer et al., 2007). Lou and colleagues (2012) showed elevated hair cortisol following an earthquake which, for those developing PTSD dropped significantly over time as compared

to girls without PTSD between months two to four and months five and seven after the traumatic event. Studies involving institutionalized children show more uniform patterns of reduced cortisol with chronic neglect (Koss & Gunnar 2018).

Numerous explanations have been put forth as to the wider heterogeneity of findings across the literature with relevance for understanding cortisol in childhood PTSD. One area of heterogeneity is the differentiation between PTSD groups, trauma-exposed control groups and non-trauma-exposed control groups, with differential inclusion and comparisons of these conditions yielding different results (Meewisse et al., 2007; Schumacher et al., 2019). There is a growing body of evidence suggesting the relevance of trauma exposure as a factor regardless of PTSD diagnosis, advocating for its consideration in future research alongside PTSD groups and non-trauma controls (Steudte-Schmiedgen et al., 2016).

A further source of heterogeneity relates to cortisol measurement approaches employed with differential application of these approaches potentially responsible for some of the differences (Schumacher et al., 2019). Further, due to the diurnal rhythm of cortisol secretion, the measurement parameters and times of day being measured are another source of heterogeneity. Studies often use different combinations of measurement parameters such as the CAR, total daily cortisol output/ area under curve (AUC), slope of cortisol decline throughout the day, or stress response paradigms. Each of these parameters express different aspects of HPA functioning, with suggestions for reporting multiple parameters to establish greater consistency in research (Adam & Kumari, 2009).

Further factors influencing heterogeneity relate to the differential inclusion of factors influencing cortisol such as age, gender, wake time, depression, and time since trauma exposure, which may be particularly important in children who are still developing (Edwards et al., 2001; Kuhlman et al., 2015; Meewisse et al., 2007; Miller et al., 2007; Pervanidou

2008; Tarullo & Gunnar, 2006). Weems and Carrion (2007) suggested a particularly important role of time since trauma with cortisol positively associated with PTSD symptoms among those with recent traumas (within the last year) compared to those with distal traumas. Depression is associated with higher cortisol in children and adolescents compared to controls and is highly prevalent following trauma exposure, with meta-analysis suggesting that 24.2% of children and adolescents exposed to trauma will meet criteria for depression (Pervanidou, 2008; Vibhakar et al., 2019). There is also wide heterogeneity in trauma types and frequencies examined with some studies using events such as parental loss and others looking at wider issues such as neglect or abuse, with different types of trauma exposure associated with distinct impacts on HPA-axis functioning, comparatively little remains known about the impact of single incident trauma (Bevans et al., 2008; Kuhlman et al., 2015; Zimmerman et al., 2020).

The present study sought to add to existing literature, providing greater specificity in the context of heterogeneity in identifying the relationship between salivary cortisol, PTSD and trauma exposure in children and adolescents exposed to recent single incident trauma. The present study focused on children and adolescents aged eight to 17 exposed to single incident trauma within the previous two to eight months, delineating between those with and without PTSD as compared with a non-trauma-exposed healthy control group and incorporating factors such as age, gender, time since trauma, and trauma type. The study explored differences in cortisol levels as a repeated measure between groups and examine composite measures relating to CAR and total cortisol output across the morning and daily timeframes. The study also explored the extent to which differences in cortisol levels between these groups were mediated by other factors such as age, age, gender, wake time, time since trauma and trauma type.

Method

The ASPECTS Study

Data for this study were drawn from the Acute Stress Programme for Children and Teenagers Study (ASPECTS). ASPECTS sought to examine PTSD mechanisms in youth exposed to trauma, comparing those with and without PTSD and without trauma exposure. The study included a screening phase, a prospective longitudinal study, a case-control study, and a randomized controlled trial (RCT).

Participants

This project's data draws from the 105 individuals who participated in the (RCT) and case-control segments of the ASPECTS study. The participants, recruited from the East of England, represented a wide socioeconomic group from both urban and rural settings. The cohort included 29 individuals diagnosed with PTSD; 10 were identified through an initial screening study conducted in emergency departments, 19 were referred from community sources, including mental health services, educational institutions, and general practitioners. Additionally, 40 individuals who experienced trauma but did not develop PTSD were identified through screening in emergency departments. A further 36 participants, with no history of trauma exposure, were recruited via local schools. All participants provided written, informed consent. The study was approved by the UK National Research Ethics Service, Cambridgeshire Research Ethics Committee (10/H0304/11); the RCT element of the project was registered with the ISRCTN Registry (ISRCTN38352118).

The criteria for a traumatic incident were drawn from the DSM-IV (American Psychiatric Association, 1994): directly experiencing or witnessing an invent involving an actual or threatened death, severe injury, or threat to physical integrity of self or others. Inclusion criteria for age was 8-17 years. Participants in the PTSD group required a primary

PTSD diagnosis (using an age-appropriate diagnostic algorithm) determined by the child-reported Children's PTSD Inventory (CPTSD-I; Saigh et al., 2000) as described by Meiser-Stedman et al., (2006). The presence of other co-morbid psychiatric diagnoses was examined using the Anxiety Disorders Interview Schedule (ADIS-C) (Silverman & Eisen, 1992). Inclusion within the trauma-exposed non-PTSD group required a score of less than or equal to seven on Children's Posttraumatic Stress Scale (Foa et al., 2001). The inclusion criteria for the non-trauma-exposed control group were the absence of any current or previous psychiatric diagnoses and trauma exposure. Exclusion criteria were intellectual disability, autism spectrum conditions, assaults where the perpetrator was a caregiver, unconsciousness > 15 minutes following the trauma, non-fluency in English, ongoing threat, organic brain damage, risk of self-harm and symptoms of PTSD stemming from prior trauma. Full details on the screening study recruitment are available in Meiser-Stedman et al., (2019).

Procedure

In the initial phases of the ASPECTS study, participants underwent their first evaluation between two to four weeks after experiencing trauma, followed by a second assessment two months later including PTSD screening. Participants with a primary PTSD were invited into the RCT, those that did not were invited into the case control arm as a trauma-exposed non-PTSD control group. The non-trauma-exposed group were recruited directly into the case control study.

All groups underwent a comprehensive experimental battery, with parental interview, self-report questionnaires, a narrative task, psychophysiological assessments, and neuropsychological tests. Prior to participating in this battery, participants received cortisol collection kits and diaries by mail, which provided the data for the current study.

Participants received comprehensive guidelines on collecting samples, emphasizing the need for adherence to the instructions. They were instructed to gather saliva samples five times daily across two consecutive days. The collection times were immediately upon waking (T1), 30 minutes post-waking (T2), one-hour post-waking (T3), 18:00 (T4) and 20:00 (T5). The accompanying diary advised against actions that could affect cortisol levels and contained questionnaires to identify confounding factors. Recorded collection times were noted in a diary, with samples stored in a freezer before being sent to the lab for analysis. The assays were performed by the NIHR Cambridge Biomedical Research Centre, Core Biochemistry Assay Laboratory. The intra-assay and inter-assay coefficients of variability were 4.6% and 6%, respectively. The analytical sensitivity (lower detection limit) was 0.01 μg/dL.

Measures

The Children's PTSD Inventory (CPTSDI) is a structured interview for ages six to eighteen, evaluating PTSD symptoms, the qualifying event, and current functioning. Utilized for diagnosing PTSD in children, the CPTSDI has strong internal consistency (Cronbach's alpha = .95), inter-rater reliability (ICC = .98), test-retest reliability (kappa = .91), and good convergent validity (r = .70; Saigh et al., 2000; Yasik et al., 2001).

The Child PTSD Symptom Scale (CPSS) is a self-report tool for assessing PTSD severity in line with DSM-IV criteria (APA, 1994). It features a 4-point Likert scale for the 17 DSM-IV PTSD symptoms and their impact across seven life domains. The CPSS demonstrates high internal consistency (r = .89) and acceptable test-retest reliability over 1 to 2 weeks (r = .63 to .85), and strong convergent validity (r = .80; Foa et al., 2001; Nixon et al., 2013).

The Mood and Feelings Questionnaire (MFQ) uses 33 phrases to capture a participant's recent mood and behaviours, rated on a 3-point scale (Costello & Angold, 1988). It shows strong test-retest reliability (r=0.85), and scores above 29 indicate clinically significant depression (Kent et al., 1997).

Statistical Analysis

The statistical approaches used in the present study were pre-registered on AsPredicted (#157628, Appendix D).

Demographic differences between groups were examined by one-way analysis of variance (ANOVA) and chi-square tests for comparisons between the three groups (TE-PTSD, TE-Non-PTSD, Non-TE) for demographic values and values relating to cortisol (Age/wake time/gender/ethnicity/smoking status/contraceptive use/menstrual cycle status [Hulett et al., 2019]) and psychological variables (Trauma type/ time since trauma/CPSS/MFQ).

An aggregate score of the cortisol measures over the two days (mean score) was created (Gunnar et al., 2001). For repeated measures analyses aggregates were made up of means at each sample time, for composite measures the composite calculations were conducted for each day and then averaged. Day 1 and 2 samples were tested to ensure correlation between them. Where there were missing values on either day at each time point, the remaining value was used. Any participants missing data on waketime were excluded from analysis. Values that were more than three standard deviations from the mean were excluded (Gunnar et al., 2001). Participants using corticosteroid medication were excluded from analysis.

The aggregated measures of cortisol and composite measures were assessed for normality using histograms and the Kolmogorov–Smirnov test. Where distributions were

skewed, log transformations were applied. For reasons of physiological meaningfulness, graphical representation of the diurnal curve used absolute cortisol values.

Table 3 Summary of main planned analyses

Name of analysis	Time points used	Description	Analysis approach
AUCgmorning	T1, T2, T3	Composite measure; AUC, CAR, total morning cortisol output	One-way ANOVA
AUCiCAR	T1, T2, T3	Composite measure; AUC, CAR, total increase with respect to T1 cortisol level	Kruskal-Wallis and Man Whitney U
AUCgDaily	T1, T2, T3, T4, T5	Composite measure; AUC, total daily cortisol output	One-way ANOVA
Repeated measures, day	T1, T4, T5	ANOVA, across day	Repeated measures ANOVA
Repeated measures, CAR	T1, T2, T3	ANOVA, across CAR only	Repeated measures ANOVA

Three composite measures of salivary cortisol were calculated using the trapezoidal method for computation of the area under the curve (Pruessner et al., 2003). As cortisol typically increases during the cortisol awakening response (CAR), i.e. during the first hour after awakening (T1, T2, T3), both the area under the curve with respect to ground (AUC_gmorning) as well as with respect to increase (AUC_iCAR) were calculated. AUC_gmorning is a measure of the overall volume of cortisol released across the waking period and the AUC_iCAR is a measure of absolute changes in cortisol levels in the waking period. As a measure of the total salivary cortisol secreted over the day, the area under the curve with respect to ground for the total daily output was calculated using samples from T1, T2, T3, T4 and T5 (AUC_gDaily). All three indices (i.e. AUC_gmorning and AUC_iCAR and AUC_gDaily) are suggested to provide useful and reliable markers of different aspects of HPA-axis activity (Adam & Kumari, 2009; Pruessner et al., 2003).

Once data had been prepared and composite measures calculated, five main analyses were conducted: Group differences in composite measures were conducted using two, one-way ANOVA for the total output across the morning (AUC_gmorning) and total output across the day (AUCgDaily). As AUC_iCAR remained without normal distribution before and following transformation, non-transformed values were analysed using the Kruskal-Wallis H test to identify group differences. Where significant differences were found, post-hoc analyses were conducted using the Mann-Whitney U test with Bonferroni correction to control for Type I error across multiple comparisons. Two repeated measures ANOVAs were conducted. The first explored differences between groups across within group levels of sample times examining the underlying diurnal cycle (cortisol production over the day, samples T1, T4 and T5 excluding the CAR); the second focused exclusively on the CAR (T1, T2, T3), these were analysed separately as they reflect different aspects of HPA functioning (Edwards et al, 2001). Where Mauchly's Test of Sphericity indicated that the assumption of sphericity was violated, degrees of freedom were corrected using Greenhouse-Geisser estimates ($\epsilon < 0.75$), or Huynh-Feldt estimates ($\epsilon \geq 0.75$).

To control for confounding effects, the analyses were repeated with the trauma related covariates which were only collected for the trauma exposed group which included trauma type, depression severity (MFQ) and time since trauma and non-trauma related variables of age, gender, and wake time. Due to the low number of participants using contraceptives, smoking and in menstrual phase of menstrual cycle these were not included as covariates, but further sensitivity analyses were conducted excluding these participants. Further sensitivity analyses were also conducted by establishing a compliance window, calculated as the discrepancy between scheduled and actual sampling time, and excluding samples collected outside of this window. Due to the speed of change of cortisol after waking a compliance

window of 15 minutes was established with a wider window of 60 minutes for the two evening samples (Stalder et al., 2022).

Results

Two participants were excluded due to use of steroid medications. Three participants (one from each group) were excluded due to having cortisol levels three standard deviations from the mean, leaving insufficient data remaining for analysis. A further 15 participants were excluded due to missing data which precluded them from any of the analyses conducted. This left 85 participants (PTSD: n=22, Non-PTSD Trauma Exposed: n=33, Healthy Control: n=30). There was a significant positive correlation across the two days in cortisol at all five sample times (T1 [r=.348, p=.002], T2 [r=.423, p<.001], T3 [r=.345, p=.002], T4 [r=.411, p<.001], T5 [r=.597, p<.001]), supporting the decision to aggregate levels over the two days. Characteristics of the groups are displayed in Table 4. There were no differences between the groups with respect to mean age, proportion female, contraception use, mean wake time, or ethnicity.

Figure 6 Mean Salivary Cortisol (Raw values, standard error bars)

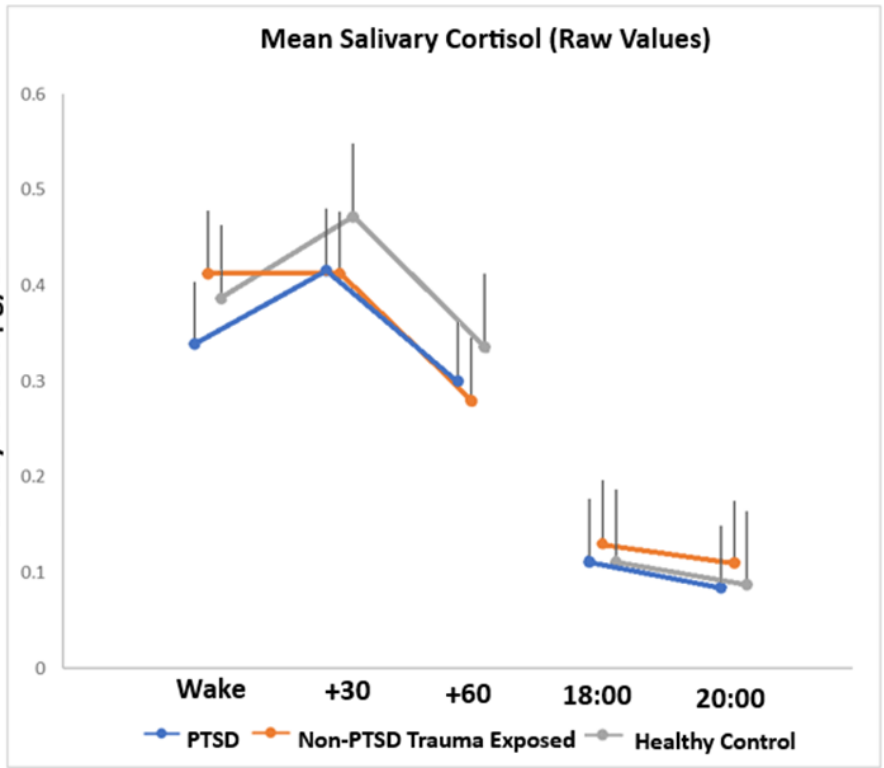

Table 4 Summary of demographic characteristics

	PTSD (n=22)	TE Non-PTSD (n=33)	Healthy Control (n=30)	Total (n=85)	Test
Non-Trauma Related					
Age	13.6 (2.5)	13.1 (3.2)	13.7 (2.5)	13.5 (2.8)	$F(2, 82) = 0.5$, $p = .61$.
Female	15 (68.2%)	18 (54.5%)	21 (70%)	54 (63.5%)	χ^2[df=2]= 1.9, $p = .39$
Contraceptive use	1 (4.5%)	2 (6.1%)	1 (3.3%)	4 (4.7%)	χ^2[df=2] = .26, $p = .88$
Menstrual phase	0 (0%)	0 (0%)	1 (3.3%)	1 (1.2%)	χ^2[df=2] = 1.86, $p = .4$
Smoking status	2 (9.1%)	0 (0%)	0 (0%)	2 (2.4%)	χ^2[df=2] = 5.87, $p = .05$
Wake time	08:47 (89)	08:25 (69)	08:23 (96)	08:30 (84)	$F(1,82) = .62$, $p = .54$
Minority ethnicity	1 (4.5%)	3 (9.1%)	4(13.3%)	8 (9.4%)	χ^2[df=2] = 1.16, $p = .56$
Trauma Related				(n = 55)	
PTSD (CPSS	30.1 (9.3)	2.7 (4.3)	n/a	13.7 (15.1)	($F(1,53) = 220.9$, $p < .001$)
Depression (MFQ)	25.9 (13.2)	4.1 (6.5)	n/a	12.8 (14.4)	($F(1,53) = 66.6$, $p < .001$)
Days since trauma	107.6(39.1)	111.8 (34.3)	n/a	110.2 (36.0)	($F(1,53) = .175$, $p = .678$)
Trauma type					χ^2[df=2]=11.49, p=.01
Assault	6(27.3%)	3 (9.7%)	n/a	9 (17%)	
Accidental	2(9.1%)	13(41.9%)	n/a	15(28.3%)	
RTA	11 (42.3%)	15(57.7%)	n/a	26(49.1%)	
Other	3 (13.6%)	0(0%)	n/a	3(5.7%)	

Data are mean (standard deviation), frequency (percent), mean time (standard deviation in minutes). Two participants were missing data for trauma type. RTA = Road traffic accident, TE = Trauma exposed.

Repeated Measures ANOVA and ANCOVA T1, T2, T3

A summary of results for the repeated measures ANOVA and ANCOVA for the morning and daily samples is provided in Table 5. Means and standard deviations for raw and log adjusted cortisol aggregated over the two days at T1 to T5 are provided in Table 6 in Appendix E. Significant main effects of time were observed for all repeated measures analyses, consistent with expected effects of the CAR and diurnal decline.

A repeated measures ANOVA analysed morning cortisol levels across three groups, finding no significant differences in cortisol by group or changes over time. Group differences remained non-significant after adjusting for trauma and non-trauma related

Table 5 Summary of repeated measures ANOVA and ANCOVA results

Analysis	Effect	*F*	df	*p*	Partial eta squared ($\eta 2$)
Repeated Measures ANOVA T1,T2,T3	Time	25.06	1.5,122.57	<.001	.23
	Time x group	1.4	3,122.57	.24	.03
	Group	1.4	2,82	.25	.03
Controlling for trauma-related covariates[1]	Group	.02	1,48	.89	.01
Controlling for non-trauma covariates[2]	Group	.94	2,79	.4	.02
Compliance sensitivity[3]	Time	20.74	1.48,106.72	<.001	.22
	Time x group	2.29	2.96,106.72	.08	.06
	Group	.54	2,72	.58	.02
Repeated Measures ANOVA T1,T4,T5	Time	270.93	1.67,137.26	<.001	.77
	Time x group	.23	3.35,137.26	.9	.01
	Group	1.33	2,82	.27	.03
Controlling for trauma-related covariates[1]	Group	1.4	1,40	.24	.03
Controlling for non-trauma covariates[2]	Group	1.31	2,79	.28	.03
Compliance sensitivity[3]:	Time	227.62	1.74,125.07	<.001	.76
	Time x group	0.54	3.47,125.07	.68	.02
	Group	1.06	2,72	.35	.03

[1]Model includes trauma related covariates trauma type, depression severity (MFQ) and time since trauma, comparing between PTSD and trauma exposed non-PTSD groups.
[2]Model includes non-trauma related covariates age, gender, wake-time.
[3]Participants removed with sample times outside of the compliance window (>15 minutes morning samples, >60 minutes evening samples)
Note:η^2 = 0.01 indicates a small effect. η^2 = 0.06 indicates a medium effect. η^2 = 0.14 indicates a large effect.

variables. Only wake time was a significant covariate ($F(1,79) = 11.43$, $p = .001$, $\eta 2 = .13$). Group differences remained non-significant excluding smokers (n=2), contraceptive users (n=4), or those in the menstrual phase of the menstrual cycle. (n=1).

Sensitivity analysis, excluding samples outside the collection compliance window, found no significant differences in cortisol by group or changes over time, remaining non-significant when adjusting for trauma and non-trauma variables and after excluding smokers, contraceptive users, and those in the menstrual phase.

Repeated measures ANOVA and ANCOVA T1, T4, T5

A repeated measures ANOVA examined the differences in cortisol across the day between T1, T4 and T5 across the three groups. The main effect of group and the interaction between sample time and group were not significant. Group differences remained non-significant after adjusting for trauma and non-trauma related variables, none of the covariates were significant. Group differences remained non-significant excluding smokers, contraceptive users, and those in the menstrual phase.

Sensitivity analysis, excluding samples outside intended collection times, found no significant differences in cortisol by group or interactions by time, remaining non-significant when adjusting for trauma and non-trauma variables and after excluding smokers, contraceptive users, and those in the menstrual phase. Among these variables, only the effect of the trauma type (assault) was a significant covariate ($F(1,40) = 4.22$, $p = .046$, $\eta 2 = .1$).

AUCgMorning – One-way ANOVA and ANCOVA

A summary of results for the composite AUC cortisol measures is provided in Table 7. A one-way ANOVA was conducted to explore the differences in AUC_g of the morning values (AUC_gMorning). The between-subjects effects indicated that the differences in AUC_gMorning among the three groups were not statistically significant. Group differences in

AUC_gMorning remained non-significant after adjusting for trauma and non-trauma related variables, none of the covariates were significant. Group differences remained non-significant excluding smokers, contraceptive users, and those in the menstrual phase of the menstrual cycle.

A sensitivity analysis excluding samples outside the collection window were not statistically significant. Group differences AUC_gMorning remained non-significant after adjusting for trauma variables time since trauma and trauma type and non-trauma variables, and after excluding participants who were smoking, using contraceptives or in menstrual phase.

AUC_gDaily – One way ANOVA and ANCOVA

A one-way ANOVA was conducted to examine the differences in the AUC with respect to ground across the diurnal decline (AUC_gDaily). The analysis of between-subjects effects was not statistically significant. Group differences in AUC_gDaily remained non-significant when adjusting for trauma-related and non-trauma variables. Only wake time was a significant covariate (F (1, 74) = 17, $p < .001$, $\eta 2 = .19$). Group differences in AUC_gDaily remained non-significant after excluding smokers, contraceptive users, and those in the menstrual phase, wake time remained a significant covariate ($F(1, 67) = 20.39$, $p < .001$, $\eta 2 = .23$).

A sensitivity analysis was again conducted excluding samples outside the compliance window and was not statistically significant. Group differences in AUC_gDaily remained non-significant after adjusting for trauma-related and non-trauma variables, and after excluding participants who were smoking, using contraceptives or in menstrual phase.

Table 7 Summary of results using composite AUC measures

Analysis	PTSD	TE-non-PTSD	Control	Test
AUC_gMorning				
One way ANOVA	3.2 (.39) (n=21)	3.15 (.33) (n=31)	3.20 (.37) (n=30)	$F(2, 79) = .19$, $p = .83$, $\eta^2 = .01$
Controlling for trauma-related covariates[1]	3.2 (.39) (n=21)	3.15 (.33) (n=31)	n/a	$F(1,45) = 1.0$, $p = .32$, $\eta^2 = .02$
Controlling for non-trauma covariates[2]	3.2 (.39) (n=21)	3.15 (.33) (n=31)	3.20 (.37) (n=30)	$F(2,76) = .299$, $p = .743$, $\eta^2 = .01$
Compliance sensitivity[3]	3.16 (.40) (n=16)	3.15 (.33) (n=31)	3.2 (.38) (n=28)	$F(2,72) = .197$, $p = .822$, $\eta^2 = .01$
AUC_gDaily (n)				
One way ANOVA	4.89 (.52) (n=20)	4.92 (.42) (n=31)	5.00 (.50) (n=29)	$F(2, 77) = .43$, $p = .65$, $\eta 2 = .01$
Controlling for trauma-related covariates[1]	4.89(.52) (n=20)	4.92 (.42) (n=31)	n/a	$F(1, 45) = .56$, $p = .46$, $\eta 2 = .01$
Controlling for non-trauma covariates[2]	4.89 (.52) (n=20)	4.92 (.42) (n=31)	5.00 (.50) (n=29)	$F(2, 74) = .2$, $p = .82$, $\eta 2 = .01$
Compliance sensitivity[3]	5.01 (.48) (n=15)	4.92 (.42) (n=31)	5.06 (.47) (n=27)	$F(2, 70) = .2$, $p = .49$, $\eta 2 = .02$
AUC_iCAR (n)				
Kruskal-Wallis	41.55 (n=21)	34.81 (n=31)	48.38 (n=30)	$H(2)=4.96$, $p=.084$
Compliance sensitivity[3]	42.16 (n=16)	29.65 (n=31)	44.88 (n=28)	$H(2)=7.92$, $p=.019$
Mann-Whitney PTSD & Non-PTSD[3]	29.13 (n=16)	21.35 (n=31)	n/a (n=28)	$U=166$, $Z=-1.84$, $p=.07$
Mann-Whitney PTSD & Healthy control[3]	21.53 (n=16)	n/a	23.05 (n=28)	$U=208.5$, $Z=-1.38$, $p=.71$
Mann-Whitney Non-PTSD & Healthy Control[3]	n/a	24.29 (n=31)	36.32 (n=28)	$U=257$, $Z=-2.687$, $p=.01$

[1]Model includes trauma related covariates trauma type, depression severity (MFQ) and time since trauma, comparing between PTSD and trauma exposed non-PTSD groups.
[2]Model includes non-trauma related covariates age, gender, wake-time.
[3]Participants removed with sample times outside of the compliance window (>15 minutes morning samples, >60 minutes evening samples)
[4]$\eta^2 = 0.01$ indicates a small effect. $\eta^2 = 0.06$ indicates a medium effect. $\eta^2 = 0.14$ indicates a large effect.
Data are n, mean (standard deviation) for parametric tests, mean rank for non-parametric tests.

AUC_iCAR – Kruskal-Wallis and Man-Whitney U tests

The Kruskal-Wallis test was used to explore differences in area under the curve with respect to increase (AUC_iCAR) across groups. Group differences approached significance $H(2)=4.96$, $p=.084$ but were not statistically significant. When sensitivity analyses were applied excluding participants whose sample times deviated from the compliance window, the Kruskal-Wallis test indicated a significant effect of group ($H(2)=7.92$, $p=.019$). As such further exploration was conducted through Mann-Whitney U tests. The comparisons between the PTSD and non-PTSD trauma exposed groups and between PTSD and health controls were not statistically significant. However, a significant difference emerged between the TE-non-PTSD and Control groups, $U=257$, $Z=-2.687$, $p=.01$, suggesting that the cortisol awakening response was significantly flatter in the trauma-exposed non-PTSD group than in healthy controls. This remained significant at the Bonferroni corrected significance level (alpha level .05 divided by three for the number of comparisons) of .0167.

Discussion

The present study aimed to explore the relationship between salivary cortisol, trauma exposure and PTSD in children and adolescents exposed to recent single incident trauma. The findings demonstrated a significant main effect of time, consistent with expected CAR and diurnal decline (Fries et al., 2009). Repeated measures analyses did not suggest differences in cortisol between groups, which remained when including trauma related and non-trauma related covariates associated with cortisol and when conducting sensitivity analysis using a more conservative sampling time compliance window. Trauma type (assault) was a significant covariate for the compliance sensitivity analysis of daily values.

Analysis of the composite measures of AUC_gMorning and AUC_gDaily indicated no significant difference in total cortisol output between groups across the morning and daily

values. Non-parametric analysis of AUC_iCAR approached significance and was significant when controlling for sampling compliance. Post-hoc analysis with Bonferroni corrected alpha level found a significant difference emerged between the TE-non-PTSD and Control groups, suggesting that the cortisol awakening response was significantly flatter in the trauma-exposed non-PTSD group than in healthy controls when controlling for sampling compliance.

Theoretical implications

The results of the present study do not support the hypothesis that PTSD is characterised by elevated cortisol. These results are somewhat inconsistent with previous research which has more typically demonstrated the presence of higher cortisol levels in children with PTSD (Carrion et al., 2002, De Bellis & Zisk, 2014; Delahanty et al., 2000; Delahanty et al., 2005; Zantvoord et al., 2019: Zimmerman et al., 2020). However, these results are not altogether unusual, given the wide heterogeneity in findings and methodology previously observed. For example, these findings are in line with much of the previous research showing no significant difference in baseline morning and daily cortisol levels based on trauma exposure (Cicchetti et al., 2010; De Bellis et al., 1994). They are also consistent with the findings of Usta et al., (2016) and Simsek et al., (2015) who found no significant difference in cortisol levels of adolescents after single-incident sexual trauma with PTSD compared to healthy controls. Further, the findings share similarities to those of Pervanidou et al., (2007) who demonstrated initially elevated evening cortisol which normalised over time towards six months following single incident trauma.

These findings may suggest that HPA-axis dysregulation is not a significant feature of PTSD and trauma exposure, but it is possible the absence of group difference may instead reflect the role of time since trauma, as the average time since exposure in this sample was around three months. Converging results have suggested that cortisol levels follow a two-

staged timeline following trauma exposure in relation to the development of PTSD; in this model, an initial increase in cortisol immediately following trauma might lead to hyper-sensitization of the HPA-axis negative feedback systems, leading to reducing longer term output (Miller et al., 2007; Pervanidou et al., 2007; Steudte-Schmiedgen et al., 2016; Weems & Carrion, 2007). This model suggests that cortisol levels are elevated in the initial stages post trauma, appear normalised in the medium term, and are reduced longer term. Despite heterogeneity it is relatively well established that reduced cortisol is observed in adult survivors of childhood trauma, with this two-staged timeline hypothesised as a potential mechanism for these changes over time but sufficient longitudinal research is currently lacking to validate this hypothesis (Pervanidou, 2008). This is of note when considering the significant result observed in the present study relating to the blunting of CAR in non-PTSD trauma-exposed children with respect to the healthy control group, as it suggests the two trauma exposed groups may exhibit different responses in CAR following similar experiences of trauma exposure when respectively compared to a healthy control group.

To the authors' knowledge, blunted CAR in non-PTSD trauma exposed children relative to healthy controls has not been observed previously. However, assessment of CAR has not been possible in much of prior research due to use of hair or blood analysis and a critique of prior research is that it has often lacked methodological rigor in sampling, collection compliance and analysis of CAR, with significant lag in the development and application of consensus guidelines for rigorous assessment of the CAR (Hulett et al., 2019; Stalder et al., 2022). Further, the use of non-PTSD trauma exposed controls has been inconsistent in early cortisol literature. The present study is contrary to the findings of Keeshin et al., (2014) who observed blunting of CAR to be correlated with PTSD symptoms relative to non-PTSD sexually abused girls and controls, over a similar timeframe with twelve participants in each group. Although Keeshin et al (2014) found an association

between PTSD symptoms and blunted CAR, no significant differences between the abused and control group for the awakening response were observed. Due to the small sample size the results of the present study should be interpreted cautiously. No significant difference was observed comparing the PTSD and non-PTSD groups. Further research including trauma exposed PTSD and non-PTSD samples meeting the rigor of the consensus guidelines for the assessment and analysis of CAR is warranted.

Strengths and Limitations

There are several strengths and limitations of the current study. The sample sizes for the groups were relatively low, particularly when controlling for sampling compliance, making the study more susceptible to bias and Type 1 error. This may be particularly important given the small effect sizes in the analyses of the effects of group on cortisol. As such, these results should be treated as exploratory; effects may exist which this study was not sufficiently powered to identify. The low sample size in part relates to the high level of participants lost (n=17) due to missing data. This is common across cortisol research given the stringent requirements of salivary cortisol collection, but also relates to difficulties in recruitment and screening requirements which is common across child cortisol literature. Whilst a self-report diary and clear instructions were provided the use of an objective method for verification of waking and sample times, or incentives for accurate completion may lead to improved data completeness and accuracy, several technological advances are now available to support this process (Kudielka et al., 2012). Although no effect of gender or age as covariates was shown here, male and females were included together along with prepubertal and pubertal children which may have influenced the results.

A strength of the current study is the steps taken towards providing greater specificity in the context of wider heterogeneity in previous research. This study used a clearly defined

sample of children, experiencing recent single incident trauma, includes a PTSD, non-PTSD and healthy control and includes relevant trauma related and non-trauma related covariates. Due to the wide heterogeneity of inclusion of maltreatment, wider adversity, and multiple or distal traumas and the potential influence of time since trauma in previous studies, it is important for future research to provide greater specificity to aid a more nuanced understanding of the impacts of trauma on the functions of the HPA-axis (Kuhlman et al., 2015; Steudte-Schmiedgen et al., 2016). Given the complex relationship between multiple trauma exposure or prolonged adversity and the HPA-axis, further understanding of cortisol following single incident trauma may provide unique insights into its relationship between cortisol and PTSD. Further, this study used a combination of different measurement parameters such as the CAR, total daily cortisol output/ area under curve (AUC) and repeated measures analysis, which relate to different aspects of HPA-axis function and which have been inconsistently applied in previous research (Adam & Kumari, 2009; Hulett et al., 2019; Schumacher et al., 2019). The present study may have benefited from the additional inclusion of a measure of slope of cortisol decline, although this was not included in the studies preregistration and as such was not applied (Adam & Kumari, 2009).

Clinical implications

Gaining a deeper insight into the relationship between cortisol levels and trauma exposure may hold significant implications for therapeutic strategies in managing PTSD. Cognitive-behavioural therapy methods are widely supported by research as effective treatments for PTSD (NICE, 2018). Additionally, initial studies suggest that psychotherapeutic interventions may contribute to the normalization of HPA-axis activity, and that pre-treatment cortisol may be predictive of outcomes (Fischer et al., 2021; Zantvoord et al., 2019). A more thorough understanding of cortisol with PTSD as it relates to treatment could be important for understanding mechanisms, efficacy and the improvement of

approaches (Schumacher et al., 2019). Further understanding of HPA-axis dysregulation in trauma could also inform pharmacological approaches although research remains preliminary and further research is required (Bertolini et al., 2022).

Conclusion

In conclusion, no difference was found in the cortisol levels between groups across sample times or within total output of cortisol across the morning and length of the day. Blunting of CAR was observed in the non-PTSD group compared with healthy controls. The findings of this exploratory study should be interpreted cautiously due to its small sample size and limited power. This study provides some specificity in the context of wide heterogeneity in previous research in relation to the inclusion of different trauma types and adversity, makes use of PTSD and non-PTSD groups and controls and provides a combination of HPA-axis parameters for analysis. Further research including trauma exposed PTSD and non-PTSD samples exploring similar parameters, in a longitudinal approach, with larger samples is warranted and may benefit from closely adhering to recently established consensus guidelines for assessing and reporting of cortisol data.

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Chapter Four: Thesis Portfolio Discussion and Critical Evaluation

Word count: 4580

Summary of findings

Systematic review and meta-analysis

To the authors knowledge this was the first meta-analysis to provide an estimate of the prevalence of panic disorder in trauma-exposed children and adolescents. The primary research question exploring prevalence of panic disorder following trauma drew from 13 studies involving 14,170 participants and indicated a pooled prevalence of 7.1% (95% CI 2.7, 13.5). This figure exceeds prevalence estimated in community samples which are estimated at below 1%, increasing to 2-3% in older adolescence (Essau et al., 2000; Merikangas et al., 2010; Vizard et al., 2018). As such, these finding suggests a higher prevalence of panic disorder in trauma exposed youth and the consistently high prevalence rates across studies included point to a robust association between trauma exposure and panic disorder in children and adolescents.

These results should be considered with some caution due to the high level of heterogeneity observed across the included studies, and whilst the moderator analyses conducted provided some insight into this heterogeneity there likely remains further factors which are yet to be accounted for. Moderator analyses did not reveal differences in prevalence differing according to country income status and age. Subgroup analysis of IPV and non-IPV trauma type suggested a much higher prevalence within non-IPV trauma, but comparisons remained non-significant. The subgroup analyses of assessment type, self-report and interview demonstrated the highest difference in prevalence observed, suggestive of higher prevalence reported in self-report studies with higher confidence and prediction intervals. Unfortunately, due to limited self-report studies, moderator analyses were not conducted but this difference may highlight the importance of assessment methods in prevalence studies, possibly reflecting differences in reporting bias or sensitivity of the

instruments which may be useful to explore in future research. Moderator analysis suggested significant differences between studies examining collective and individual trauma types, with collective trauma associated with a higher prevalence of panic disorder (10.95% [95% CI 4.51, 19.75]) when compared to exposure to individual trauma (1.3% [95% CI 0.08, 3.94]. However, when sensitivity analyses were applied removing self-report studies from this analysis the differences were no longer significant. Given the small number of studies included in this sensitivity analysis this area may also warrant further exploration in future research.

The results of the meta-analysis exploring the prevalence of panic disorder in children and adolescents with PTSD indicated prevalence of 20.7% (95% CI: 5.6% to 41.9%). Suggesting that approximately one in five children and adolescents with PTSD may also experience panic disorder. This meta-analysis again exhibited a broad prediction interval and significant heterogeneity. Elevated prevalence remained indicated following sensitivity analysis excluding of self-report-based studies, with the pooled prevalence decreasing to 12.8% (95% CI: 3.8% to 25.9%). This estimate showed narrower confidence and prediction intervals which further indicates the need for careful consideration of the assessment methods used to diagnose panic disorder in prevalence studies, as self-report measures may inflate rates. The results of the final meta-analysis exploring the prevalence of PTSD in children and adolescents with panic disorder indicated a notably high pooled prevalence of PTSD in this group, estimated at 79.75% (95% CI: 48.46% to 98.25%). A significant degree of heterogeneity and a wide prediction interval was also observed. The results of both of these additional meta-analyses should be interpreted with caution due to the limited number of studies and lower sample sizes (RQ2 k=7, n=618, RQ3 k=4, n=445) which could potentially lead to skewed results and limit the scope and generalizability of the findings to a broader

population. However, given the high prevalence observed these results suggest further research is warranted to explore the extent of this comorbidity further.

Empirical Study

The empirical study presented explored the relationship between salivary cortisol, trauma exposure and PTSD in children and adolescents exposed to recent single incident trauma. The findings demonstrated a significant main effect of time, consistent with expected CAR and diurnal decline (Fries et al., 2009). Repeated measures analyses did not suggest differences in cortisol between groups, which remained when including trauma related and non-trauma related covariates associated with cortisol and when conducting sensitivity analysis using a more conservative sampling time compliance window. Trauma type (assault) was a significant covariate for daily values which persisted when controlling for sampling compliance. Analysis of the composite measures of AUCgMorning and AUCgDaily indicated no significant difference in total cortisol output between groups across the morning and daily values. Non-parametric analysis of AUCiCAR approached significance and was significant when controlling for sampling compliance. Post-hoc analysis with Bonferroni corrected alpha level suggested found a significant difference emerged between the TE-non-PTSD and Control groups, suggesting that the cortisol awakening response was significantly flatter in the trauma-exposed non-PTSD group than in healthy controls when controlling for sampling compliance.

Strengths and limitations

Systematic review and meta-analysis

There are several strengths and limitations of the meta-analysis presented within this portfolio to consider. The meta-analysis is, to the authors' knowledge, the first to assess the prevalence of panic disorder in trauma exposed children and adolescents, addressing an

important gap in the literature by bringing together findings in the context of high heterogeneity in previous individual studies. The existing literature describing the prevalence of panic disorder in children and adolescents was comprehensively reviewed and consolidated through a rigorous search and screening strategy which included 5007 studies after removing duplicates. The search terms used included "anxiety disorder*" which although generated more studies, reduced chances of missing relevant findings. Further, an evaluation the risk of bias was performed for each study included, considering the variations in methodological quality which is consistent with established guidelines for conducting meta-analyses and which are not always consistently used (Higgins & Altman, 2008).

Despite these strengths there are some important limitations to consider. There was considerable heterogeneity observed between studies in the meta-analysis, which is vital to consider when thinking about the generalizability of the findings. This variability could be attributed to differences in study designs, populations, trauma types, and assessment methods which are incredibly varied within the literature. This is a limitation which occurs regularly within psychological research, and it is suggested that around a quarter of meta-analyses also contain high levels of heterogeneity (Higgins et al., 2003). Most studies included were conducted in high-income countries and studies not written in English were excluded from analysis, this may mean that there is some degree of cultural bias which further limits generalisability of the findings.

An important limitation is the small number of studies and sample sizes for some research questions, particularly for the research questions relating to the prevalence of panic disorder given PTSD and vice versa, and some of the moderator analyses conducted. This limited statistical power and thus the robustness of conclusions that can be drawn and prevented some important moderator analyses which could provide further insight into the heterogeneity observed. The lack of available studies or of studies reporting data relevant to

the research questions also prevented the exploration of other important questions such as the difference in the odds of developing panic disorder between children and adolescents who have been exposed to trauma and those who have not and questions about the extent to which panic disorder severity, trauma exposure and PTSD severity are related. This highlights the need for further research in this area and the more routine reporting of data which may be useful in wider meta-analysis such as prevalence and severity relating to all measures used, even when these might not relate to studies wider research questions.

The reliance on self-report measures in some studies might have led to inflated prevalence rates. This is evident in the differences observed in the subgroup analysis exploring prevalence following trauma exposure and in the sensitivity analysis exploring the prevalence of panic disorder given PTSD, where excluding self-report questionnaires notably lowered the prevalence rates. Future research should consider these factors when designing studies as it is possible that prevalence studies using self-report questionnaires may inflate prevalence. This finding is echoed in previous prevalence studies of depression, PTSD and anxiety disorders which suggest self-report measures using specified cut-off thresholds for diagnosis may lower thresholds for diagnosis and lead to overestimations of prevalence relative to structured and semi-structured interview approaches (Diamond et al., 2022; Thombs et al., 2018). This may be a particularly important in consideration of panic disorder within the context of trauma-exposure, where significant overlap of symptoms between panic disorder and PTSD may require further probing or clinical decision-making which are not possible using self-report questionnaires (Means-Christensen et al., 2003).

Empirical Study

There are several strengths and limitations of the empirical study presented within this portfolio. An important strength of the present study is the steps taken to provide greater

specificity in exploring cortisol between trauma exposed children and adolescents with and without PTSD. This study used a clearly defined sample of children, experiencing recent single incident trauma, includes a PTSD, non-PTSD and healthy control and includes relevant trauma related and non-trauma related covariates. The use of non-PTSD and healthy controls are not always routinely applied in prior research which is identified as one of the causes of heterogeneity in prior findings. Inclusion of these control groups is valuable given the suggestion that trauma exposure may be relevant to cortisol regardless of whether individuals meet criteria for PTSD diagnosis, and as such inclusion is necessary to fully evaluate whether HPA-axis dysregulation differs between these groups (Meewisse et al., 2007; Steudte-Schmiedgen et al., 2016). Another key factor relating to the wide heterogeneity observed previously is the mix of times since trauma and the extent and number of traumas experienced (Bevans et al., 2008; Kuhlman et al., 2015; Weems & Carrion, 2007; Zimmerman et al., 2020). By providing a sample that has experienced recent single incident trauma the present study adds to the specificity of findings which is important for breaking down and understanding the nuanced relationship between trauma exposure and the HPA-axis (Kuhlman et al., 2015; Steudte-Schmiedgen et al., 2016).

A strength of the study is the use of both CAR and diurnal measures of salivary cortisol, which were measured using three samples to measure CAR and were conducted over two days using waking time as the first value rather than a static time. A critique of previous literature has been inconsistent use of diurnal measures, the measurement of cortisol over only one day and the use of universal first sample times as opposed to wake time (Ryan et al. 2016). Further this study used a combination of different measurement parameters such as the CAR, total daily cortisol output/ area under curve (AUC) and repeated measures analysis, which relate to different aspects of HPA-axis function and which have been inconsistently applied in previous research (Adam & Kumari, 2009; Hulett et al., 2019; Schumacher et al.,

2019). This is important for allowing the present findings to be easily integrated into past and future research. This study may have gained from incorporating a measure of cortisol decline over time for completeness; however, this metric was not specified in the study's preregistration and, therefore was not implemented (Adam & Kumari, 2009).

A limitation of the empirical study is the sample sizes for the groups, which were relatively low, particularly when controlling for sampling compliance. This makes the study more susceptible to bias and Type 1 error, particularly given the small effect sizes observed in the analyses of the effects of group on cortisol. As such, these results can only be treated as exploratory; effects may exist which this study was not sufficiently powered to identify. The low sample size in part relates to the high level of participants lost (n=15) due to missing data. High levels of data loss are common across cortisol research given the stringent requirements of salivary cortisol collection. This study did take steps to avoid this data loss as recommended using a self-report diary booklet and clear instructions (Stalder et al., 2016). The use of a more conservative window for compliance as a sensitivity analysis did result in further reductions in sample size but was an important addition as inaccurate sampling times can substantially bias resulting cortisol data and as such should be seen as a strength of the present study (Kudielka et al., 2012). Several technological advances are now available to support accuracy of sampling such as electronic caps on the collection tubes which monitor collection time or wearable devices which more accurately track waking time, it can also be helpful to provide incentives for quick and complete return of samples (Adam & Kumari, 2009; Kudielka et al., 2012). The small sample size also relates to difficulties with recruitment in this sort of study as despite recruiting from a wide area across five counties in England, with several hundred thousand youth within age criteria, and with 29 months to recruit, the recruitment rate remained slow (Meiser-Stedman et al, 2017).

Although no effect of gender or age as covariates was shown here, male and females were included together along with prepubertal and pubertal children which may have influenced the results. The significant difference depression severity observed in the PTSD group, although included as a covariate, may have impacted results as depression is associated with increased cortisol secretion, a larger sample size may have enabled further sensitivity analyses comparing or excluding these participants (Pervanidou, 2008). The sample included was also largely white British and the range of traumas identified were relatively narrow when compared to much of the previous literature, for example none of the sample had been in a large-scale disaster. As such the generalisability of the sample to wider populations of trauma exposed children may be unclear.

Theoretical and clinical implications

Systematic review and meta-analysis

The meta-analysis presented suggests a notably high incidence of panic disorder among youth who have experienced trauma, surpassing rates previously found in the general population. This underscores the need for healthcare providers to consider panic disorder, along with PTSD, when evaluating and treating children and adolescents who have experienced trauma. Given the widespread exposure of youth to traumatic events, these results are especially significant (Lewis et al., 2019). There is evidence pointing to the challenges clinicians face in detecting panic disorder in younger patients. A survey among UK Child and Adolescent Mental Health Service (CAMHS) clinicians revealed that fewer than half could correctly identify panic disorder or symptoms in a case study (Baker & Waite, 2020). The accurate diagnosis of panic disorder is particularly challenging in cases involving trauma and PTSD due to overlapping symptoms. Misdiagnosis or failing to identify panic disorder can adversely affect the quality of care and lead to less effective treatment outcomes

(Jensen-Doss & Weisz, 2008). Considering the high rates of occurrence, difficulties in identification, and the lasting negative impact of untreated panic disorder into adulthood, it is critical to advance efforts in improving the detection and management of panic disorder within clinical settings. This is in keeping with other studies that have observed high comorbidity with other conditions such as depression and generalised anxiety disorder and as such it is vital for clinicians to be aware of and consider the wider impacts of trauma on mental health in youth at assessment to deliver appropriate care (Lewis et al., 2019).

There is some preliminary evidence for the effectiveness of psychological treatment of panic disorder in childhood and adolescence, most of which focussed on Cognitive Behavioural Therapy based approaches (Hoffman & Mattis, 2000; Pincus et al., 2010). However, there remains a need for further research in this area, and at present there remains no recommendations for the assessment or treatment of children and adolescents under the UK National Institute for Health and Care Excellence (NICE). Given the prevalence identified, it is vital that further research into evidence-based treatment approaches for panic disorder in young people more generally is conducted. The findings in the present study relating to the high prevalence of panic disorder in children and adolescents with PTSD and vice versa underscores the significant overlap between these disorders and the need to account for comorbidity in treatment approaches. In adults, childhood trauma is associated with poorer treatment response and higher relapse rates in the treatment of panic disorder (Michelson et al., 1998). Further work is required to understand the relationship between PTSD, trauma exposure and panic disorder and to explore the suitability of existing panic disorder treatments in the context of trauma exposure and PTSD. There have been some developments in adult populations for specific panic disorder treatments in the context of PTSD and treatments which systematically target both panic and PTSD symptoms, however

this research remains relatively sparse and requires testing with children and adolescents (Falsetti & Resnick, 2000; Teng et al., 2008; Teng et al., 2015).

Empirical Study

The findings presented within the empirical study have several key theoretical implications for future research. The findings do not support the hypothesis that PTSD is characterised by elevated cortisol. Whilst these results diverge somewhat from previous literature which has typically suggested higher cortisol levels in youth with PTSD, the results reflect the wider heterogeneity observed previously (Carrion et al., 2002, De Bellis & Zisk, 2014; Delahanty et al., 2000; Delahanty et al., 2005; Zantvoord et al., 2019: Zimmerman et al., 2020). These findings align with some studies focused on single-incident trauma, such as those by Usta et al. (2016) and Simsek et al. (2015), who also reported no significant differences in cortisol levels between adolescents who experienced sexual trauma with PTSD and healthy controls. Similarly, Pervanidou et al. (2007) found that initially elevated cortisol levels normalized in children with PTSD around six months after a single incident trauma, suggesting a temporal dynamic in cortisol responses following trauma exposure. These findings may suggest that HPA-axis dysregulation is not a significant feature of PTSD and trauma exposure following single incident trauma at least in the period observed at around three months after exposure.

Emerging evidence proposes a two-staged model for cortisol response post-trauma exposure within PTSD. Initially, cortisol levels may increase following the trauma, potentially causing hyper-sensitization of the HPA-axis's negative feedback mechanisms. This heightened sensitivity could result in diminished cortisol production over the long term (Miller et al., 2007; Steudte-Schmiedgen et al., 2016; Weems & Carrion, 2007). It is important for future studies to explore this further with longitudinal research which can

measure cortisol responses post trauma from one month to several years later. Although findings have varied, it is relatively well established that adults who experienced trauma in childhood often exhibit lowered cortisol levels with this two-staged model of diminishing cortisol production proposed as a possible explanation for these changes over time. However, longitudinal research necessary to confirm this hypothesis is still required (Pervanidou, 2008). The significant finding of blunted CAR observed in the non-PTSD trauma exposed group is novel but given the limitations of the present study requires further exploration and as such it is important that non-PTSD control groups are included in further research groups (Meewisse et al., 2007; Steudte-Schmiedgen et al., 2016).

The heterogeneity observed in previous research and further suggested by the present study represents an ongoing area of concern for literature regarding cortisol and trauma exposure and for biological mechanisms of trauma and PTSD more widely. Despite the great promise in the biological science of mental disorders in the search for reliable biomarkers or pharmacological treatment approaches for disorders such as PTSD, this promise remains a long way from being realised (Cisler & Herringa, 2021, Engel et al., 2022). Currently, there have been no biomarkers identified that reliably demonstrate clinical applicability for people with PTSD (Morris et al., 2016). The identification of clinically applicable biomarkers is further complicated by the complexity of early life stress which can depend on factors such as individual vulnerability, developmental sensitivity windows, and the type and duration of the trauma experienced (Murphy et al., 2022). As such it is likely that in order to develop useful biomarkers, future research may need to encompass an aggregate of multiple factors (Yehuda et al., 2013). Similarly, although glucocorticoids such as hydrocortisone are currently being explored as pharmaceutical approaches to treatment, aimed at restoring HPA axis function within PTSD, research is in its infancy, requires further elaboration of HPA axis dysfunction following trauma exposure and currently lacks sufficient follow up data to establish evidence

for efficacy (Bertolini et al., 2022). It is important that future research directed towards unpicking changes in the HPA-axis work to address the heterogeneity currently in the field, validating existing findings and further developing consensus guidelines to support the quality of future research. This is particularly important considering cost of high-quality research and the burden placed on families that is inherent with engaging thoroughly with cortisol research and the intensive sampling requirements entailed.

The lack of clinically applicable progress with regards to biomarkers and pharmacological approaches is perhaps starker in contrast, given the significant progress made elsewhere. There is an emerging literature which is strongly supportive of the relevance of cognitive models of PTSD which relate to negative appraisals of trauma and its consequences and disturbances in autobiographical memory (Ehlers & Clark, 2000). These models have found support in a number of studies identifying negative appraisals as strong correlates and predictors of PTSD, changes to which are found to at least in part mediate the changes within therapy (Gomez De La Cuesta et al., 2019; Jensen et al., 2018, Smith et al., 2007). Initial research indicates that psychotherapeutic interventions might help normalize HPA-axis activity, with pre-treatment cortisol levels potentially predicting treatment outcomes (Fischer et al., 2021; Zantvoord et al., 2019). Currently, relatively few studies have explored the relationship between cognitive processes in PTSD and psychobiological findings such as those relating to the HPA axis (Olff et al., 2005). A deeper understanding of changes in the HPA axis within PTSD treatment could be important for elucidating mechanisms, enhancing efficacy, and improving therapeutic approaches (Schumacher et al., 2019).

Clinically, the findings from the present study and existing research around changes in the HPA axis relating to PTSD may benefit from integration within a broader biopsychosocial perspective. The biopsychosocial model incorporates the interplay between biological factors (such as genetics, changes in HPA axis, neurological changes) with

psychological factors (such as comorbid mental health disorders, behaviour, personality), and social factors (such as social support, socioeconomic status, culture) (Engel, 1997). Incorporating up to date and accurate information on the bodies stress response systems within a biopsychosocial approach could contribute to formulation and psychoeducational components of treatment for PTSD, which can help people to understand and frame their experiences as normal reactions to trauma (Pheonix, 2007).

Findings more generally on the relationship between the HPA axis and trauma exposure may also have theoretical and clinical relevance for other conditions where both trauma and HPA axis dysregulation have been implicated such as functional neurological disorders and central sensitivity syndromes. Models such as the stress-system model and the diathesis-stress model have recently been applied within functional neurological disorders, aimed at providing a more nuanced understanding of the impact of stress factors such as emotional stress, pain, injury, infection, and psychological trauma on the bodies complex web of interconnected biological stress response systems and how these responses relate to the functional symptoms experienced at the individual level (Keynejad et al., 2019; Kozlowska et al., 2020). This highlights the potential for future research to contribute to the understanding of other trauma and stress related conditions, exploring both the commonalities and differences between PTSD and these other disorders.

Although there remains a lack of clarity with regards to HPA-axis response following trauma across both children and adult samples, the number of studies which have found some effect continue to provide consensus that trauma is under some circumstances related to HPA axis dysfunction (Lehrner et al., 2016; Mehta & Binder, 2012). These alterations remain important to understand further given their significance for health and wellbeing, as changes in HPA-axis function persisting beyond the original stressor can result in allostatic load and have wide ranging detrimental impacts on systems highly integrated with the HPA axis such

as the nervous system and immune system (Danese & McEwen, 2012). Further, these alterations hold particular significance in children within whom the HPA-axis is still developing, potentially leading to enduring changes (Danese & McEwen, 2012; Lehrner et al., 2016; Tarullo & Gunnar, 2006). The prolonged effects of these allostatic modifications in the HPA axis are linked to the development of chronic illnesses and a broad spectrum of adverse physical and mental health conditions, including anxiety, depression, chronic fatigue syndrome, fibromyalgia, rheumatoid arthritis, asthma, obesity, and diabetes (Ehlert, 2013; Fries et al., 2005). Additionally, lower cortisol levels have been suggested as a potential risk factor for the onset of PTSD after further exposure to trauma (Morris et al., 2012). In the shorter term, and of particular concern in childhood PTSD, elevated cortisol levels are implicated in harmful effects on the brain, damaging critical areas like the hippocampus and prefrontal cortex, which play key roles in memory and executive functions (Carrion & Wong, 2012). The severe range and magnitude of these consequences, especially among the young and considering the widespread nature of trauma exposure, underscore the ongoing need to continue to advance our understanding.

Conclusions

In conclusion, this thesis portfolio investigated two different areas of consequences of trauma exposure. The results of the empirical study suggested no significant differences in cortisol levels between groups at various sample times or in total cortisol output throughout the morning and day. A diminished Cortisol Awakening Response (CAR) was noted in the non-PTSD group compared to healthy controls. Due to the small sample size and limited power, these exploratory findings should be approached with caution. The study contributes to the understanding of the variability in previous research, addressing the effects of different trauma types and adversities by comparing PTSD and non-PTSD groups alongside controls, and analysing a range of HPA-axis parameters. Future research should expand on this work

by including larger samples of trauma-exposed individuals with and without PTSD, employing longitudinal designs, and adhering to recent consensus guidelines for cortisol assessment and reporting.

The meta-analysis exploring the prevalence of panic disorder following trauma suggested a pooled prevalence of 7.1% among 14,170 participants, a rate surpassing those previously observed found in the general population. This underscores the significant role trauma plays in the onset of panic disorder in young people. Moderator analysis revealed that prevalence rates did not significantly vary with factors like exposure to intimate partner violence, age, or the economic status of the country. However, the method of assessment seemed to affect prevalence figures, with self-report questionnaires reporting higher rates than interviews, highlighting the critical role of diagnostic methods in identifying panic disorder amidst similar PTSD symptoms. Further exploration into the co-occurrence of panic disorder and PTSD showed high overlap, with 20.7% of children and adolescents with PTSD also experiencing panic disorder, and 79.8% of those with panic disorder having PTSD. These findings, while preliminary due to the small study pool and considerable heterogeneity, underscore the importance of careful screening for panic disorder in trauma-exposed youth by clinicians, emphasizing the need for accurate diagnosis in this demographic and provides a good rationale for further research exploring the relationship between panic disorder, trauma exposure and PTSD.

Taken together these studies add to the growing literature on the consequences of trauma exposure which as has been demonstrated within this thesis portfolio can be wide ranging. These studies emphasize the critical need for comprehensive assessment and intervention strategies that are sensitive to the varied consequences of trauma. Going forwards it is important for research to continue to take a holistic approach to understanding and addressing trauma's aftermath, incorporating both physiological and psychological dimensions.

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Appendices

Appendix A: Author Guidelines for to Journal of Clinical Child and Adolescent Psychology

Instructions for authors

Thank you for choosing to submit your paper to us. These instructions will ensure we have everything required so your paper can move through peer review, production and publication smoothly. Please take the time to read and follow them as closely as possible, as doing so will ensure your paper matches the journal's requirements.

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In addition, a clear developmental rationale is required for the selection of participants at a specific age. The Journal is making diligent efforts to insure that there is an appropriately detailed description of the sample, including a) the population from which the sample was drawn; b) the number of participants; c) age, gender, ethnicity, and SES of participants; d) location of sample, including country and community type (rural/urban), e) sample identification/selection; f) how participants were contacted; g) incentives/rewards; h) parent consent/child assent procedures and rates; i) inclusion and exclusion criteria; j) attrition rate. The Discussion section should include a comment regarding the diversity and generality (or lack thereof) of the sample. The Measures section should include details regarding item content and scoring as well as evidence of reliability and validity in similar populations.

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Appendix B: Risk of Bias Tool

Risk of bias item	Criteria for answers	Outcome
External Validity		
1. Representativeness, Sampling and Recruitment: Do studies detail their sampling methods? Is the sampling frame used representative? Were all necessary participants included/ any groups left out? (Hoy et al., 2012; Munn et al., 2014).	• Yes 1 (LOW RISK): The sampling frame was a true or close representation of the target population. Sampling methods detailed. • No 0 (HIGH RISK): The sampling frame was not a true or close representation of the target population OR sampling methods not detailed.	
2. Likelihood of Non-response Bias: Was the likelihood of non-response bias minimal? (Hoy et al., 2012). Did the authors describe reasons for non-response and compare characteristics of responders and non-responders? (Munn et al., 2014).	• Yes 1 (LOW RISK): The response rate for the study was >/=75%, OR, an analysis was performed that showed no significant difference in relevant demographic characteristics between responders and non-responders • No 0 (HIGH RISK): The response rate was not reported or was <75%, and if any analysis comparing responders and non-responders was done, it showed a significant difference in relevant demographic characteristics between responders and non-responders.	
3. **Detailed Description of Study Subjects and Setting**: Were the study subjects, setting, and relevant characteristics described in sufficient detail to determine comparability to other populations? (Munn et al., 2014).	• Yes 1 (LOW RISK): Study subjects, setting, and relevant characteristics described in sufficient detail to determine comparability to other populations. • No 0 (HIGH RISK): Study subjects, setting, and relevant characteristics not described in sufficient detail to determine comparability to other populations.	
4. Index trauma clearly specified and defined and time since trauma stated as >4 weeks?	• Yes 1 (LOW RISK): Index trauma specified and defined, time since trauma >4 weeks reported. • No 0 (HIGH RISK): Index trauma not specified or defined, time since trauma not specified or <4 weeks.	
Internal validity		
5. **Objective and Standard Measurement Criteria**: Were objective, standard diagnostic criteria used for the measurement of Panic Disorder and PTSD? *(*Munn et al., 2014). Diagnostic interview or self-report questionnaire shown to have validity and reliability? (Hoy et al., 2012; Munn et al., 2014).	• Yes 0 (LOW RISK): Outcomes were assessed based on existing definitions or diagnostic criteria. The measurement tool used was shown to have validity and reliability. • No 1 (HIGH RISK): Outcomes were not assessed based on existing definitions or diagnostic criteria. The measurement tool used was not shown to have validity and reliability.	

6. **Reliability of Measurement**: Were data collectors trained or educated in the use of instruments, and were methods explicit and justifiable? (Munn et al., 2014). Was the same mode of data collection was used for all subjects? (Hoy et al., 2012).	• Yes 1 (LOW RISK): Data collectors were trained or educated in the use of instruments, methods were explicit and justified. The same mode of data collection was used for all subjects. • No 0 (HIGH RISK): Data collectors were not trained or educated in the use of instruments or was not specified, methods were not explicit or justified. The same mode of data collection was NOT used for all subjects.	
7. Accounting for Confounding Factors: Are all important confounding factors, subgroups, and differences identified and accounted for? (Munn et al., 2014).	• Yes 1 (LOW RISK): Important confounding factors, subgroups, and differences identified and accounted for. • No 0 (HIGH RISK): Confounding factors, subgroups, and differences not discussed or accounted for.	
Summary item on the overall risk of study bias • LOW RISK OF BIAS (6-7): Further research is very unlikely to change our confidence in the estimate. • MODERATE RISK OF BIAS (3-5): Further research is likely to have an important impact on our confidence in the estimate and may change the estimate. • HIGH RISK OF BIAS (1-2): Further research is very likely to have an important impact on our confidence in the estimate and is likely to change the estimate.		

Appendix C: References for Studies Included in the Meta-Analysis but not Cited In-Text

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Appendix D: AsPredicted Pre-registration

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Salivary Cortisol in children and adolescents following single incident trauma (#157628)

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1) Have any data been collected for this study already?
It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?
The main question being asked in this study investigates the relationship between trauma exposure, Post-Traumatic Stress Disorder (PTSD), and diurnal salivary cortisol levels in children and adolescents. It is expected that as trauma exposure is recent and single incident that cortisol levels will be higher in trauma exposed individuals and higher still in those with PTSD.

3) Describe the key dependent variable(s) specifying how they will be measured.
The dependent variable in this study is the diurnal salivary cortisol levels in children and adolescents.

4) How many and which conditions will participants be assigned to?
Participants are assigned to three conditions, a non trauma exposed control group, a trauma exposed non-PTSD group and a PTSD group.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.
Demographic differences between groups will be examined by one-way analysis of variance (ANOVA) and chi-square tests for comparisons between the three groups for demographic and psychological variables.
An aggregate score of the cortisol measures from the 2 days (i.e., the mean score across the assessment days) will be created for each of the five time points measured each day so that each participant has one score per timepoint. Day 1 and 2 samples will be tested to ensure significant correlation between them. Where there are missing values on either day one or day two at each time point will the remaining value will be used rather than the average to ensure participants missing single samples will not be excluded from the overall analysis.
The mean cortisol concentration for each time point across the two days will be assessed for normality using histograms and the Kolmogorov–Smirnov test. If distributions are skewed which is likely, log transformations can be applied to correct. For reasons of physiological meaningfulness, graphical representation of the diurnal curve will use absolute cortisol values instead of log transformed cortisol values.
Three composite measures of salivary cortisol will be calculated using the trapezoidal method (Pruessner et al., 2003). The cortisol awakening response with respect to ground (CAR- AUCg) as well as with respect to increase (CAR-AUCi) will be calculated. As a measure of the total salivary cortisol secreted over the rest of the day, the area under the curve with respect to ground for the diurnal decline will also be calculated (AUCg-diurnal).
Group differences in the cortisol awakening response (CAR) between TE-PTSD, TE-Non-PTSD, Non-TE groups will be calculated by one-way repeated measures ANOVA with within-group levels of time as T1 (baseline immediately after awakening), T2 (+30), and T3 (+60). Group differences in the diurnal cycle between TE-PTSD, TE-Non-PTSD, Non-TE groups calculated by one-way repeated measures ANOVA with within-group levels of time T1 (baseline immediately after awakening), T4 (18:00), and T5 (20:00). If repeated-measures ANOVAs reveal significant interactions, one-way ANOVAs at the different sample points will be conducted as post-hoc tests.
Group differences in each of the AUC composite measures for the CAR (CAR- AUCg, CAR-AUCi,), and diurnal cycle (AUCg-diurnal) will be calculated by a one-way ANOVA.
To control for possible confounding effects, the analyses will be repeated with the covariates relevant to cortisol.
As such the Bonferroni adjustment or the Holm-Bonferroni method of correction will be applied to the analyses to adjust the rejection criteria of each of the individual hypotheses.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.
Participants with cortisol values greater than 3 SDs above the mean of the sample will be excluded from analyses as outliers.
Participants missing cortisol values for both day one and two at the same timepoint will be excluded from analysis.
Participants using corticosteroid medication will be excluded from analysis.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.
Data for this project is drawn from the 105 participants who took part in the RCT and case control parts of the ASPECTS study.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)
This project makes use of existing data collected through the Acute Stress Programme for Children and Teenagers Study (ASPECTS). The study aimed to explore the mechanisms of PTSD in trauma-exposed youth with PTSD vs without PTSD vs non-trauma-exposed controls and to investigate the efficacy of

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and component mechanisms of cognitive therapy for PTSD (CT-PTSD) for children and adolescents. The study consisted of a screening study, a prospective longitudinal study, a case control study and randomised controlled trial (RCT). Cortisol data were collected as a variable of interest but never analysed or interpreted.

Appendix E: Means and Standard Deviations – Raw and Log transformed Cortisol

Table 6 Means and Standard Deviations – Raw and Log transformed cortisol

		PTSD	Non-PTSD TE	Healthy Control
Raw Cortisol µg/dL				
		n = 22	n=33	n=30
	T1	0.34 (0.13)	0.41 (0.17)	0.39 (0.21)
	T2	0.42 (0.20)	0.41 (0.14)	0.47 (0.19)
	T3	0.30 (0.18)	0.28 (0.11)	0.34 (0.15)
	T4	0.11 (0.06)	0.13 (0.11)	0.11 (0.05)
	T5	0.08 (0.07)	0.11 (0.13)	0.09 (0.05)
Compliance Sensitivity Raw Cortisol µg/dL		n = 16	n=31	n=28
	T1	0.35 (0.14)	0.42 (0.17)	0.39 (0.22)
	T2	0.47 (0.20)	0.42 (0.14)	0.49 (0.19)
	T3	0.33 (0.18)	0.29 (0.11)	0.35 (0.15)
	T4	0.11 (0.07)	0.13 (0.12)	0.11 (0.05)
	T5	0.09 (0.08)	0.11 (0.13)	0.09 (0.05)
Log Adjusted Cortisol				
		n = 22	n=33	n=30
	T1	-1.23 (0.4)	-0.99 (0.41)	-1.10 (0.50)
	T2	-1.03 (0.51)	-0.99 (0.40)	-0.87 (0.44)
	T3	-1.43 (0.56)	-1.38 (0.39)	-1.22 (0.48)
	T4	-2.40 (0.47)	-2.29 (0.67)	-2.34 (0.51)
	T5	-2.82 (0.49)	-2.60 (0.79)	-2.63 (0.60)
Compliance Sensitivity Log Adjusted Cortisol		n = 16	n=31	n=28
	T1	-1.21 (0.42)	-0.98 (0.42)	-1.11 (0.52)
	T2	-0.91 (0.50)	-0.96 (0.38)	-0.84 (0.44)
	T3	-1.30 (0.49)	-1.35 (0.38)	-1.16 (0.44)
	T4	-2.38 (0.49)	-2.29 (0.70)	-2.29 (0.48)
	T5	-2.84 (0.49)	-2.61 (0.80)	-2.55 (0.54)

Data are n, mean (standard deviation)
Compliance sensitivity excludes samples collected outside of the compliance window (>15 minutes morning sample, >60 minutes evening sample).