Exploring the association between traumatic brain injury and psychotic-like experiences in children

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Thesis Declaration Form

I confirm that the work presented in this thesis is my own. Where information has
been derived from other sources, I confirm that this has been indicated in the thesis.

Signature:

Name: King-Chi Yau

Date: 25th April 2023

Overview

This thesis studies the relationships between exposure to paediatric traumatic brain injury (TBI) and psychosis outcomes, and is presented in three parts.

Part 1 is a systematic review and meta-analysis of the association between paediatric TBI and subsequent psychotic disorders/symptoms. We identified 10 relevant studies, of which eight were included in the meta-analysis. Based on a pooled sample size of 479,686, the pooled odds ratio (*OR*) for the association between paediatric TBI and psychosis outcomes was found to be marginally significant. Part 1 reports cautious meta-analytic evidence for a positive association between paediatric TBI and future psychosis.

Part 2 utilised the Adolescent Brain Cognitive Development (ABCD) large cohort data from children aged 9 to 10 years old at baseline (*n* = 11,875), with longitudinal and prospective 3-year follow-up to investigate the extent to which TBI at baseline predicted psychotic-like experiences (PLEs) in children, using multi-level logistic regression analyses. It was found that the presence of paediatric TBI at baseline was a significant predictor of the occurrence of PLEs at 36 months, with the relationship remaining robust after controlling for potential confounders. However, no significant association was found between the presence of TBI and the presence of PLEs at baseline. Additionally, no significant relationships were observed between the number of TBIs and the presence of PLEs at both baseline and 36 months, whilst the severity of TBI was only found to be significantly associated with the presence of PLEs at baseline, but not at 36 months. In conclusion, part 2 provides evidence indicating (i) a delayed occurrence of PLEs following TBI among children aged 9 to 10 years old; (ii) weak associations between TBI and PLEs; however, (iii) a persistence of post-TBI PLEs and (iv) a dose–response relationship could not be observed.

Part 3 is a critical appraisal which presents considerations in relation to three broad topics, including (i) transparency, accessibility, and reproducibility of the conducted research;

(ii) reasons for and likely impact of a lack of expert by experience (EbE) involvement in the research design, conduct, analysis, and interpretation; and (iii) an exploration of the relationships between paediatric TBI and mental health outcomes in children.

Impact Statement

This thesis explores the association between paediatric traumatic brain injury (TBI) and psychotic disorders or symptoms. Psychosis is one of the most disabling psychiatric disorders. Paediatric TBI has been cited as a developmental risk factor for psychosis; however, this association has never been assessed meta-analytically. Part 1 is a systematic review and meta-analysis of the association between paediatric TBI and subsequent psychotic disorders or symptoms, with findings providing cautious meta-analytic evidence for a positive association between paediatric TBI and future psychosis. The meta-analysis is available online as a computational notebook with an open dataset to enhance openness and reproducibility. This is in line with open science practices, facilitating other researchers to update the current pooled estimates as new evidence emerges. Additionally, given the concordance between the findings reported here and the developmental models of psychosis, this suggests that investigating the occurrence of paediatric TBI over a lifetime may be a useful addition when taking a history of patients with psychosis, and that public health measures preventing paediatric TBI may have longer-term benefits for lifetime mental health.

Investigating the role of paediatric TBI as a potential risk factor for psychotic-like experiences (PLEs) in children is crucial, given the current key developmental models of psychosis, indicating that risk factors disrupting typical neurodevelopment can sustain normally transient PLEs, thereby increasing the likelihood of transitioning to a later psychotic disorder. Part 2 adds to the empirical evidence base on TBI and PLEs in children by analysing a large cohort dataset, reporting a delayed occurrence of PLEs following TBI among children and weak associations between TBI and PLEs; however, a persistence of

post-TBI PLEs and a dose–response relationship could not be observed. Findings from part 2 suggest that paediatric TBI might either indirectly contribute to the development of PLEs or be unrelated to the occurrence of PLEs. More research is required to ascertain the relationships, especially by addressing the potential bias arising from measures and study design, and most importantly, overcoming the challenge of reverse causality. Future findings will be of paramount importance in determining the potential development of psychological interventions as preventive measures for children exposed to TBI, addressing their mental health needs.

In addition to the current thesis, our research findings have been disseminated as a preprint on an open-access public platform (Yau et al., 2023). The results will also be published on other academic and non-academic outlets, in alignment with open science practices.

References

Yau, K. -C., Revill, G., Blackman, G., Shaikh, M., & Bell, V. (2023). *Paediatric traumatic brain injury as a risk factor for psychosis and psychotic symptoms: A systematic review and meta-analysis.* medRxiv. https://doi.org/10.1101/2023.02.17.23286118

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Part 1: Literature Review

Paediatric traumatic brain injury as a risk

factor for psychosis and psychotic symptoms:

A systematic review and meta-analysis

Abstract

Background: Psychosis is one of the most disabling psychiatric disorders. Paediatric traumatic brain injury (TBI) has been cited as a developmental risk factor for psychosis; however, this association has never been assessed meta-analytically.

Aims and Methods: A systematic review and meta-analysis of the association between paediatric TBI and subsequent psychotic disorders/symptoms was performed. The study was pre-registered (CRD42022360772), adopting random-effects model to estimate meta-analytic odds ratio (*OR*) and 95% confidence interval (CI) using the Sidik–Jonkman method. Subgroup (study location, study design, outcome type, assessment type, and adult verses adolescent onset) and meta-regression (quality of evidence) analyses were also performed. The robustness of findings was assessed through sensitivity analyses. The meta-analysis is available online as a computational notebook with an open dataset.

Results: We identified 10 relevant studies, of which eight were included in the meta-analysis. Based on a pooled sample size of 479,686, it was found that the pooled *OR* for the association between paediatric TBI and psychosis outcomes was 1.88 (95% CI [1.07, 3.30]). There were no subgroup effects and no outliers identified. The association remained robust after removal of studies with low quality of evidence; however, the *OR* reduced to 1.45 (95% CI [1.02, 2.07]). A leave-one-out sensitivity analysis showed the pooled association changed from marginally significant to marginally non-significant after removal of any one of three studies.

Conclusions: We report cautious meta-analytic evidence for a positive association between paediatric TBI and future psychosis. New evidence will be key in determining long-term reliability of this finding.

Introduction

There is consistent evidence indicating that traumatic brain injury (TBI) is associated with an increased risk of adverse neuropsychiatric outcomes in adults, including depression, anxiety, posttraumatic stress symptoms, cognitive impairment, personality change, and neurodegenerative disorders (Carroll et al., 2014; Cnossen et al., 2017; Fleminger, 2008; Perry et al., 2016; Rogers & Read, 2007; Schwartz et al., 2019; van Reekum et al., 2000). One association that has proved more controversial, however, has been the link between TBI and psychosis. Although there are clearly cases of post-TBI psychosis (Fujii & Ahmed, 2002), the extent to which TBI is a reliable population risk factor for psychosis has been debated. In a narrative review of the evidence, David and Prince (2005) concluded that it was unlikely brain injury reliably causes psychosis given the published data available at the time. In a subsequent narrative review, Batty et al. (2013) estimated that psychosis following TBI appears to be three times more prevalent than psychotic disorders in the general population. Looking specifically at the association between TBI and schizophrenia in case-control studies, Molloy et al.'s (2011) meta-analysis reported a significant association and, through the inclusion of family studies, suggested this effect was larger in those with a genetic predisposition to psychosis.

Notably, however, the studies considered in these reviews largely examined the impact of adult TBI on later psychosis. Although clearly important, studies that focus solely on adult TBI may miss longer-term associations between TBI that occurs before the age of 18 and an increased risk of psychotic disorders or symptoms later in life. The association between paediatric TBI and psychosis is plausible given what is known about risk factors for psychosis in childhood and adolescence. Key developmental models of psychosis, including the psychosis-proneness–persistence–impairment model (Linscott & van Os, 2013; van Os et al., 2009) and the developmental risk factor model (Howes & Murray, 2014; Murray et al.,

2017), are based on evidence that adverse experiences that impair typical neurodevelopment can maintain normally transient sub-threshold symptoms of psychosis during adolescence, and increase the risk of later transition to psychotic disorders (Rubio et al., 2012; Trotta et al., 2015). It has been suggested that paediatric TBI could be one such neurodevelopmental risk factor (AbdelMalik et al., 2003), but this has never been subjected to systematic review and meta-analysis. Although Molloy et al. (2011) included a subgroup analysis on paediatric TBI cases in their meta-analysis, only three studies were available at the time, indicating a clear need for a more systematic analysis of this issue as new studies have emerged.

Consequently, we conducted a pre-registered systematic review and meta-analysis (see Appendix S1: Pre-registration of the review; CRD42022360772; Yau et al., 2022) to determine the association between paediatric TBI and later psychotic disorders or symptoms. To the best of our knowledge, this is the first meta-analysis to examine paediatric TBI as a potential risk factor for psychotic disorders or symptoms.

Methods

The present systematic review and meta-analysis was undertaken and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

Eligibility Criteria

Participants

We included studies that recruited participants of any age or gender with a diagnosis of paediatric traumatic brain injury.

Exposures

Paediatric traumatic brain injury (TBI) was defined as an onset of TBI before adulthood (i.e., < 18 years old). Paediatric TBI could be determined by the age of the study population (e.g., children or adolescents with TBIs) or the time of onset of TBI (e.g., adults

with a history of paediatric TBI). We included participants with a diagnosis of paediatric TBI based on validated screening tools, structured clinical interviews, medical records reviews, or clinical diagnosis. TBIs with severity ranging from mild (including concussion) to severe were included. For exclusion, we did not select studies where the occurrence of paediatric TBI could not be determined, and when psychotic disorders or symptoms were not measured. In addition, we did not include studies where exposure to TBI could not be differentiated from other non-TBI conditions within a single group.

Comparators

Studies with and without comparison groups were included, with no exclusion criteria applied.

Outcomes

The main outcome of interest was presence of a psychotic disorder or psychotic symptoms based on validated screening tools, psychometric measures, structured clinical interviews, medical records reviews, or clinical diagnosis. Psychotic disorders included schizophrenia and related disorders, whilst psychotic symptoms included psychotic-like experiences, psychosis-risk syndromes, and psychotic symptoms reaching threshold of clinical relevance. We only included studies where the onset of the psychotic disorders/symptoms occurred after the TBI. We excluded studies reporting only broad neuropsychiatric outcomes (such as behavioural difficulties) without any specific assessment of psychosis.

Types of Studies Included

We included all peer-reviewed primary studies published in English with no date restrictions. The following types of design were included: randomised or non-randomised controlled trials, retrospective or prospective cohort studies, and case-control studies (including nested case-control and family studies). We excluded meta-analyses, systematic

reviews, literature reviews, case reports, case series, qualitative studies, opinion pieces, editorials, comments, newsletters, book chapters, and congress papers.

Information Sources and Search Strategy

The databases of PsycINFO (Ovid; from 1806 onwards) and MEDLINE (Ovid; from 1946 onwards) were searched based on the strategy outlined in Table 1 (see Appendix S2: Full search strategy), with the search carried out independently by two reviewers (KCY, GR). Studies were screened according to the above criteria. Prior to the final analysis, searches were re-run on 1st December 2022 to identify any further studies that could be included in the review.

Table 1. Search strategy

Main term	Search term with operator (PsycINFO)	Search term with operator (MEDLINE)
Traumatic brain injury	(brain injuries/ OR traumatic brain injury/ OR brain concussion/) OR (TBI OR traumatic brain injur* OR brain injur* OR head injur* OR cerebral trauma OR craniocerebral injur* OR concussion* OR skull fracture*).ab,id,ti	(brain injuries/ OR brain injuries, traumatic/ OR brain concussion/) OR (TBI OR traumatic brain injur* OR brain injur* OR head injur* OR cerebral trauma OR craniocerebral injur* OR concussion* OR skull fracture*).ab,kw,ti
Psychotic disorders or symptoms	(psychosis/ OR schizophrenia/) OR (psychosis OR psychotic OR psychotic disorder* OR psychotic exp* OR psychotic?like exp* OR schizophreni* OR delusional disorder* OR delusion* OR hallucinat* OR psychiatric illness* OR psychiatric disorder*).ab,id,ti	(psychotic disorders/ OR schizophrenia/) OR (psychosis OR psychotic OR psychotic disorder* OR psychotic exp* OR psychotic?like exp* OR schizophreni* OR delusional disorder* OR delusion* OR hallucinat* OR psychiatric illness* OR psychiatric disorder*).ab,kw,ti
Child	(childhood birth 12 yrs OR preschool age 2 5 yrs OR school age 6 12 yrs OR adolescence 13 17 yrs).ag OR (infan* OR baby* OR babies OR toddler* OR preschool* OR child* OR pediat* OR paediat* OR prepubescen* OR prepuberty* OR puberty OR pubescen* OR teen* OR young* OR youth* OR minors* OR underag* OR juvenile* OR preadolesc* OR adolesc*).ab,id,ti	(infant/ OR child, preschool/ OR child/ OR adolescent/) OR (infan* OR baby* OR babies OR toddler* OR preschool* OR child* OR pediat* OR paediat* OR prepubescen* OR prepuberty* OR puberty OR pubescen* OR teen* OR young* OR youth* OR minors* OR underag* OR juvenile* OR preadolesc* OR adolesc*).ab,kw,ti

Note. ab = abstract; ag = age group; id = key concepts; kw = keyword heading; ti = title

Study Selection Process

Following removal of duplicates, two reviewers (KCY, GR) independently screened the titles and abstracts of all the records retrieved. A third reviewer (VB) was consulted when a consensus could not be reached. Two reviewers (KCY, GR) independently screened the full-text reports based on the above eligibility criteria (Cohen's κ = .89), and processes of discussion between the two reviewers and consultation with the third reviewer (VB), in the case of disagreement, were held.

Data Extraction Process

A data extraction excel sheet was developed by one of the reviewers (KCY). Two reviewers (KCY, GR) independently extracted study characteristics and outcomes from all the included studies, and data were compared (Cohen's κ = .72). A third reviewer (VB) was consulted when a consensus could not be reached.

Data Items

Outcomes

The main outcome was presence of a psychotic disorder or psychotic symptoms including schizophrenia, psychosis, hallucinations, delusions, psychosis-risk syndromes, and psychotic-like experiences. Diagnoses of schizophrenia, psychosis, hallucinations, and delusions based on the *International Statistical Classification of Diseases and Related Health Problems* (ICD), the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), or Feighner et al. (1972) criteria were used. We also extracted sub-threshold symptoms of psychosis including psychosis-risk syndromes (McGlashan et al., 2010) and psychotic-like experiences (PLEs; Lee et al., 2016). For methods of outcome measurement, validated screening tools and psychometric measures (including Prodromal Psychosis Questionnaire – Brief Child Version [PQ-BC] by Karcher et al. (2018)), structured clinical interviews, medical records reviews, and clinical diagnosis were included. Regarding the onset of a

psychotic disorder or symptoms, any time points were eligible (i.e., childhood, adolescence, or adulthood) provided the onset was after paediatric TBI.

Regarding the major outcome data, we primarily extracted the number of participants experiencing psychotic disorders or symptoms after paediatric TBI. When studies used several methods for reporting the relevant data, we followed a priori defined rules of decision to select corresponding data. (i) When both the raw number of participants experiencing psychotic disorders or symptoms and the calculated statistics (e.g., incidence rate ratios [*IRRs*]; odds ratio [*ORs*]) were available, we extracted the raw number. (ii) When descriptive statistics of interval measures of psychotic disorders or symptoms and the calculated statistics (e.g., p values or effect sizes) were available, we extracted the descriptive statistics. (iii) When both non-imputed and imputed data were reported, we chose the imputed. (iv) Lastly, we extracted the set of raw number based on primary analysis of the original study.

Where the required data had not been published (three studies: Lopez et al., 2022; Orlovska et al., 2014; Timonen et al., 2002), authors were contacted for the required information (e.g., asking for total number of participants in the exposure group of paediatric TBI). Two authors responded but only one (Lopez et al., 2022) could provide the required raw data. The remaining two studies were only included in narrative synthesis but not meta-analysis.

Exposures

We included all TBIs with severity ranging from mild (including concussion) to severe. For methods of measurement, validated screening tools (including the Ohio State University TBI Identification Method [OSU TBI-ID]; Corrigan & Bogner, 2007), structured clinical interviews, medical records reviews, and clinical diagnosis were included. Regarding the major exposure data, we primarily extracted the number of participants experiencing TBI.

Study Characteristics

For the characteristics of included studies, apart from the above exposure and outcome data items, we also extracted the (i) year and location of the study, (ii) study design, and (iii) participant characteristics (in the exposure and control groups, if any).

Quality Assessment

Two reviewers (KCY & GR) independently assessed the quality of included studies using Kmet et al.'s (2004) quality assessment scale (Cohen's κ = .84). This consisted of a 14-item checklist on a 3-point scale (0 = criteria not met; 1 = partially met; 2 = fully met) generating a summary score (total sum / total possible sum) ranging from 0 to 100, to categorise the low (≤ 54), moderate (55–74), and high (≥ 75) quality of evidence. The areas of assessment included evaluation of appropriateness of research objectives, study design, sampling methods, recruitment of participants, adoption of measures, sample size, statistical analyses, estimate of variance, control for confounders, results reported, and conclusions drawn. All disagreements were resolved by consensus.

Synthesis Methods

We estimated the meta-analytic odds ratio (*OR*) with 95% confidence interval (CI) of psychotic disorders or symptoms associated with preceding paediatric TBI among the included studies using the R package "meta" (Balduzzi et al., 2019). We computed the I^2 statistic to measure heterogeneity among included studies, and the levels of low, moderate, and high heterogeneity were assigned to I^2 values of 25%, 50%, and 75% respectively (Higgins et al., 2003). We expected a moderate-to-high I^2 value due to methodological heterogeneity, and subsequently we opted to use a random-effects model to estimate pooled estimates, using the statistical method of Sidik–Jonkman estimator (Sidik & Jonkman, 2005). We used a funnel plot to test for evidence of publication bias and Egger's test was planned to provide a statistical test of funnel plot asymmetry (Ioannidis & Trikalinos, 2007). Subgroup

analyses based on (i) study location, (ii) study design (i.e., case-control study versus cohort study), (iii) type of outcome being measured (i.e., psychotic disorders versus symptoms/sub-threshold symptoms of psychosis), (iv) type of outcome measurement (i.e., clinical diagnosis versus validated/structured method), and (v) time of onset of the outcomes (i.e., childhood/adolescence versus adulthood) were conducted. We followed the suggested guidelines reporting any detections of statistically significant subgroup differences (Richardson et al., 2019). Afterwards, we conducted a leave-one-out sensitivity analysis to assess the presence of any overly-influential studies in estimating the pooled effect. We also completed a meta-regression to estimate whether study quality was related to study outcome. If the meta-regression was statistically significant, a sensitivity analysis was performed to assess whether the pooled association remained robust after removing studies of low quality.

All analyses were conducted with R (version 4.2.1; R Core Team, 2020) and were conducted on a Linux x86_64 platform. All R code and data for the analyses are available online in the following archive: https://github.com/vaughanbell/pTBI_psychosis_meta-analysis

For any studies that did not yield meta-analysed results, we planned to conduct a narrative synthesis to assess how the additional studies might affect the interpretation of the overall findings, using ESRC guidelines (Popay et al., 2006).

Results

Study Selection

A total of 850 records resulted from searching the PsycINFO ($n = 365$) and MEDLINE ($n = 485$) databases. After removing duplicates by Ovid's automatic deduplication feature, 688 records remained. Seventy records were eligible for full-text screening, of these 60 were excluded. A total of 10 studies were included in this review. See Figure 1 for PRISMA 2020 flow diagram.

Figure 1. PRISMA 2020 flow diagram for literature search

Identification of studies via databases and registers

Identification

Records identified from:
PsycINFO database
($n = 365$)
MEDLINE database
($n = 485$)
Registers
($n = 0$)

Records removed *before screening*:
Duplicate records removed
($n = 162$)
Records marked as ineligible by
automation tools ($n = 0$)
Records removed for other
reasons ($n = 0$)

Screening

Records screened
($n = 688$)

Records excluded
($n = 618$)

Reports sought for retrieval
($n = 70$)

Reports not retrieved
($n = 0$)

Reports assessed for eligibility
($n = 70$)

Reports excluded ($n = 60$):
   26: neither psychotic disorders
      nor psychotic symptoms
   20: TBI not specified in
      childhood
   8: review papers
   2: case reports or case series
   1: TBI or neurological disorders
   1: early brain trauma not TBI
   1: same dataset as Orlovska et
      al. (2014)
   1: congress paper

Included

Studies included in review
($n = 10$)
Reports of included studies
($n = 10$)

Study Characteristics

Among the 10 included studies, five adopted case-control designs (AbdelMalik et al., 2003; Deighton et al., 2016; Harrison et al., 2006; Helgeland & Torgersen, 2005; Wilcox & Nasrallah, 1987) and five adopted cohort designs (Ledoux et al., 2022; Lopez et al., 2022; Massagli et al., 2004; Orlovska et al., 2014; Timonen et al., 2002). Four studies were carried out in the United States (Deighton et al., 2016; Lopez et al., 2022; Massagli et al., 2004; Wilcox & Nasrallah, 1987), whilst the remaining six studies were undertaken in other places including Canada (AbdelMalik et al., 2003; Ledoux et al., 2022), Denmark (Orlovska et al., 2014), Finland (Timonen et al., 2002), Norway (Helgeland & Torgersen, 2005), and Sweden (Harrison et al., 2006). Five studies measured schizophrenia as an outcome (AbdelMalik et al., 2003; Harrison et al., 2006; Helgeland & Torgersen, 2005; Timonen et al., 2002; Wilcox & Nasrallah, 1987), four studies measured psychosis (Harrison et al., 2006; Ledoux et al., 2022; Massagli et al., 2004; Orlovska et al., 2014), and two studies investigated sub-threshold symptoms of psychosis (Deighton et al., 2016; Lopez et al., 2022). For the method of outcome measurement, six studies adopted clinical diagnosis (Harrison et al., 2006; Ledoux et al., 2022; Massagli et al., 2004; Orlovska et al., 2014; Timonen et al., 2002; Wilcox & Nasrallah, 1987), whilst the remaining four studies adopted validated psychometric measures or structured clinical interviews (AbdelMalik et al., 2003; Deighton et al., 2016; Helgeland & Torgersen, 2005; Lopez et al., 2022). Finally, in terms of the window of interest regarding the onset of a psychotic disorder or psychotic symptoms, six studies reported psychotic disorders or symptoms in adulthood (AbdelMalik et al., 2003; Deighton et al., 2016; Harrison et al., 2006; Orlovska et al., 2014; Timonen et al., 2002; Wilcox & Nasrallah, 1987), whilst the remaining four studies reported childhood and adolescence (Helgeland & Torgersen, 2005; Ledoux et al., 2022; Lopez et al., 2022; Massagli et al., 2004). Detailed characteristics of all the included primary studies are shown in Table 2. A summary of included study

characteristics is presented in Table 3. Details of the quality assessment ratings are reported in Table 4, with seven studies rated as demonstrating high quality of evidence, one moderate, and two low.

Table 2. Characteristics of primary studies from MEDLINE & PsycINFO included in the systematic review

Study, year (location)	Study design	Participant	Exposure	Outcome	Finding	Sig. assoc.
AbdelMalik 2003 (Canada)	Case-control – family	169 individuals (67 with narrowly defined schizophrenia; 102 siblings without schizophrenia) from 23 Canadian families with schizophrenia	Modified Structured Clinical Interview for DSM-III-R (SCID-I), supplemented by collateral information from medical records and family. Occurrence & severity of childhood head injuries (≤ 10 years old) rated by three investigators independently	SCID-I by a psychiatrist to diagnose narrowly defined schizophrenia (i.e., schizophrenia or chronic schizoaffective disorder)	Participants in the schizophrenia group ($n = 16$ [23.9%]) had higher likelihood than the unaffected siblings group ($n = 12$ [11.8%]) to have a history of head injury in childhood ($OR = 2.35$, 95% CI [1.03, 5.36], $p = 0.04$)	+
Deighton 2016 (United States)	Case-control	1,025 help-seekers (747 clinical high risk [CHR] of psychosis; 278 healthy controls [HC]) recruited from the 8-site North American Prodrome Longitudinal Study (NAPLS 2)	Traumatic Brain Injury (TBI) Interview, assessing previous history of TBI, including the age at first TBI, age at most recent TBI, count of the number of TBIs, and severity of TBI. Only mild TBI was included	Structured Interview for Psychosis-risk Syndromes (SIPS) to assess the Criteria of Psychosis-risk Syndromes (COPS). If the Presence of Psychotic Symptoms Criteria (POPS) was met, further clinical assessment to determine diagnosis of psychosis	Participants in the CHR group experienced a mild TBI ($n = 232$ [31.0%]) more often than the HC ($n = 55$ [19.8%]; $\chi^2 = 12.77$, $p < 0.001$) CHR participants who experienced a mild TBI and later made the transition to psychosis were significantly younger at the age at first ($M = 7.8$, $SD = 3.0$) and most recent TBI ($M = 10.1$, $SD = 5.5$), than those who did not develop psychosis (M of age at first TBI = 10.6, $SD = 5.6$, U = 1732.00, $p = 0.02$; M of age at most recent TBI = 12.4, $SD = 6.0$, U = 1818.50, $p = 0.04$)	+
Harrison 2006 (Sweden)	Nested case-control	Swedish individuals born between 1973 and 1980 (748 cases of schizophrenia and 14,960 matched controls; 1,526 non-affective psychosis and 30,520 matched controls) from a cohort of 731,305 members obtained from several linked Swedish registers	Swedish Inpatient Discharge Register to identify hospital admission for concussion with/without any face/head/skull injuries, as well as all skull/intracranial injuries (ICD-10 codes: S02.0, S02.1, S02.7–S02.9, S06.0, S06.1–S06.9, S09.7). Only severe head injury was included	Swedish Inpatient Discharge Register to identify cases of schizophrenia (ICD-10 code: F20) and non-affective psychosis (ICD-10 codes: F21-29)	Participants in the non-affective psychosis group ($n = 131$ [8.6%]) were more likely than the matched control group ($n = 1,918$ [6.3%]) to have a history of severe head injury ($aOR = 1.37$, 95% CI [1.14, 1.66], $p = 0.001$), but no association was found when comparing the schizophrenia group ($n = 54$ [7.2%]) and matched controls ($n = 986$ [6.6%]) for the likelihood of previous severe head injury ($aOR = 1.10$, 95% CI [0.82 1.47], $p = 0.51$)	–

			Timing of the head injury was collected to determine childhood exposure (< 10 years old)		No evidence of the effects of childhood exposure to head injury (< 10 years old) on non-affective psychosis (*aOR* = 0.94, 95% CI [0.68, 1.29], *p* = 0.70) or schizophrenia (*aOR* = 0.81, 95% CI [0.50, 1.31], *p* = 0.38) was found	
Helgeland 2005 (Norway)	Case-control	145 patients (13 cases of schizophrenia; 132 controls without schizophrenia) admitted to the adolescent unit at The National Centre for Child and Adolescent Psychiatry (NCCAP) in Norway from 1963 to 1978	Hospital records of concussion and head traumas. Further blind review of the detailed medical records by the first author	Hospital records of psychiatric diagnoses. The detailed records were anonymised in advance by second author, and reviewed by first author with blinding based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), to ascertain diagnosis of schizophrenia (early onset was defined as < 18 years old)	Participants with an early onset of schizophrenia (< 18 years old; *n* = 3 [33.3%]) were significantly more likely than the control group without schizophrenia (*n* = 12 [9.1%]) to have a history of head traumas (*p* < 0.05). No evidence was found in the case of concussion (*p* = ns)	+/–
Ledoux 2022 (Canada)	Retrospective cohort	448,803 children and youth aged 5 to 18 years old (152,321 with exposure to concussion; 296,482 controls with orthopaedic injury) presented to an emergency department, primary health care, or mental health practitioner from 2010 to 2020 in Canada	Canadian national healthcare databases capturing data on visits to emergency department (ICD-10-CA codes: S06.0) and primary health care (Ontario Health Insurance Plan [OHIP] diagnosis code: 850) to ascertain concussion	National healthcare databases capturing data on psychiatric hospitalisation (ICD-10-CA codes: F20, F22, F23, F24, F25, F28, F29; OHIP codes: 295, 297, 298; and Ontario Mental Health Reporting System [OMHRS] codes: Q1E_RETIRED_2016 Q1B) to establish schizophrenia	The exposed group had a higher risk of subsequently developing mental health conditions (including other non-schizophrenia diagnoses) when compared with the non-exposed control group (*aHR* = 1.39, 95% CI [1.37, 1.40], *p* < 0.001) Data on the development of schizophrenia in the exposed (*n* = 1,058 [0.7%]) and non-exposed control group (*n* = 1,705 [0.6%]) were reported in the supplemental materials	NR
Lopez 2022 (United States)	Prospective cohort	11,876 children aged 9–10 (128 with exposure to mild TBI; 322 possible mild TBI; 11,415 controls without TBIs) from 21 research sites at the United States from the Adolescent Brain Cognitive	The Ohio State University TBI Identification Method (OSU TBI-ID) – Short Modified, with questions directed at parents or guardians, to assess the number of possible mild and mild TBIs	Prodromal Questionnaire – Brief Child Version (PQ-BC), a self-report instrument for children and adolescents, to measure the number of distressing psychotic-like experiences (PLEs) in the past	The exposed-group children with mild TBI had a non-significant 22% increased risk of experiencing distressing PLEs (*aIRR* = 1.22, 95% CI [0.94, 1.57], *p* = 0.1395) when compared with the non-exposed control group, using imputed data	–

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		Development (ABCD) Study, with year-1 and year-2 follow-up		month weighted by level of distress		
Massagli 2004 (United States)	Prospective cohort	1,960 children (≤ 14 years old; 490 sustained a mild TBI; 1,470 matched controls) attending emergency department, hospital, or outpatient clinic in the Washington State in 1993, with a 3-year follow-up	Washington State's counties' healthcare database capturing data on visits to emergency department, hospitals, or outpatient clinics, to indicate mild TBI including skull fractures (ICD-9-CM codes: 800.0–801.9, 803.0–804.9) and intracranial injury such as concussion (ICD-9-CM codes: 850.0–854.1). Mild TBI was indicated by less than 1-hour or no loss of consciousness and no traumatic intracranial lesions	Washington State's counties' healthcare database capturing data on psychiatric diagnosis, prescription for psychiatric medication, or using psychiatric services, to indicate psychotic disorders including organic psychotic disorders (ICD-9-CM codes: 290.0–.9, 293.0–294.9); schizophrenia, hallucinations, paranoia (ICD-9-CM codes: 295, 297.0–299.9, 780.1), and prescription for antipsychotics	The TBI-exposed group children had higher cumulative incidence estimates for any psychiatric illnesses (including psychotic disorders and conditions other than psychotic disorders) in the 3 years ($n = 146$ [30%]) when compared with the non-exposed controls ($n = 293$ [20%]; $p = .0001$) The development of psychotic disorder in the TBI-exposed group ($n = 7$ [1.43%]) and non-exposed control group ($n = 7$ [0.48%]) were reported in Table 3 of the original study	NR
Orlovska 2014 (Denmark)	Prospective cohort	1,438,339 individuals born in Denmark between 1977 and 2000 (113,906 with hospital contacts for head injury; 1,324,433 without) included in the Danish nationwide population-based registers, followed for 34 years from 1977 to 2010	Danish National Hospital Register capturing data on visits to emergency department, inpatient and outpatient services, to identify mild head injury (ICD-10 code: S06.0), skull fracture (ICD-10 codes: S02.0, S02.1, S02.7, S02.9), and severe head injury (ICD-10 codes: S06.1–S06.9)	Danish Psychiatric Central Register capturing data on visits to emergency department, inpatient and outpatient psychiatric services, to identify schizophrenia spectrum disorder (ICD-10 codes: F20–F29)	When compared with those without hospital contact for head injury ($n = 9,303$), the group exposed to head injury between ages 0 and 5 years ($n = 226$) significantly predicted subsequent development of schizophrenia spectrum disorders ($aIRR = 1.35$, 95% CI [1.18, 1.54]). Significant effects of head injury started from 6–10 years ($n = 242$; $aIRR = 1.33$, 95% CI [1.16, 1.50]) and 11–15 years ($n = 334$; $aIRR = 1.86$, 95% CI [1.66, 2.07]) were observed	+
Timonen 2002 (Finland)	Prospective cohort	10,934 individuals (256 with preceding TBI up to age 15 years old; 10,678 without) from the database of the 1966 Birth Cohort Study of Northern Finland, followed through the pre-natal stages prospectively up to the age of 31 years old	Finnish Hospital Discharge Registers capturing data on treatment episodes in hospitals and inpatient wards of health centres nation-wide, to identify TBI (ICD-9 codes: 800–801, 803, 804 except for facial traumas, 850–854, 950–951) up to 15 years	Finnish Hospital Discharge Registers capturing data on treatment episodes in hospitals and inpatient wards of health centres nation-wide, to identify psychiatric disorders (ICD-9 codes for schizophrenia not specified). Case notes of the	The exposure to TBI during childhood and adolescence significantly increased the likelihood of developing mental disorders ($aOR = 2.1$, 95% CI [1.2, 3.6]) in the male cohort Although not originally reported by Timonen et al., Molloy et al. (2011) contacted the	–

			old. Case notes of the cohort members with TBI up to 15 years old were screened further by the authors	cohort members with psychiatric disorders were checked against the criteria from DSM-III-R by the authors	original authors and reported the following risk estimate for schizophrenia following paediatric TBI (OR = 1.1, 95% CI [0.41, 2.96]) for this study	
Wilcox 1986 (United States)	Case-control	659 hospitalised patients (200 with schizophrenia; 122 bipolar disorder; 203 depressive disorder; and 134 surgical controls) admitted to a large university hospital from 1934 to 1944	Hospital records of head traumas. Further blind rating of head injury by the authors without knowledge of psychiatric diagnosis whilst reviewing the medical records Exposure to childhood head trauma was defined as the onset before 10 years old	Diagnosis of schizophrenia based on diagnostic criteria by Feighner et al. (1972)	The group of patients with schizophrenia had significantly more cases of childhood head trauma (n = 22 [11%]) when compared with the surgical control group (n = 1 [0.7%]; p = 0.0001) and depression group (n = 3 [1.5%]; p = 0.0001), but not the bipolar group (n = 6 [4.9%]; p = 0.06).	+/–

Note. *aHR* = adjusted hazard ratio; *aIRR* = adjusted incidence rate ratio; *aOR* = adjusted odds ratio; DSM = Diagnostic and Statistical Manual of Mental Disorders; ICD = International Statistical Classification of Diseases and Related Health Problems; NR = not reported; sig. assoc. = significant association; TBI = traumatic brain injury; (+) = significant association; (–) = non-significant association; (+/–) = mixed findings

Table 3. Comparison data for probability of psychotic disorders or psychotic symptoms following pTBI

Study, year	Exposure n/N[a]	Control n/N[b]	Location	Design	Outcome	Outcome measure	Time of onset (outcome)
AbdelMalik, 2003[c]	16/28	51/141	Canada	Case-control – family	Schizophrenia	SCID-I	Adulthood
Deighton, 2016[d]	232/287	515/738	United States	Case-control	Sub-threshold symptoms of psychosis	SIPS	Adulthood
Harrison, 2006[e]	18/455	730/15,253	Sweden	Nested case-control	Schizophrenia	Clinical diagnosis	Adulthood
Helgeland, 2005[f]	4/26	5/115	Norway	Case-control	Schizophrenia	SCID-I	Childhood/adolescence
Ledoux, 2022[g]	1,058/152,321	1,705/296,482	Canada	Retrospective cohort	Psychosis	Clinical diagnosis	Childhood/adolescence
Lopez, 2022[h]	45/128	3,279/11,419	United States	Prospective cohort	Sub-threshold symptoms of psychosis	PQ-BC	Childhood/adolescence
Massagli, 2004[i]	7/489	7/1,470	United States	Prospective cohort	Psychosis	Clinical diagnosis	Childhood/adolescence
Orlovska, 2014[j]	802/NR	9,805/NR	Denmark	Prospective cohort	Psychosis	Clinical diagnosis	Adulthood
Timonen, 2002	NR/256	NR/10,678	Finland	Prospective cohort	Schizophrenia	Clinical diagnosis	Adulthood
Wilcox, 1986[k]	22/23	178/311	United States	Case-control	Schizophrenia	Clinical diagnosis	Adulthood

Note. NR = not reported; PQ-BC = Prodromal Questionnaire – Brief Child Version; pTBI = paediatric traumatic brain injury; SCID-I = Structured Clinical Interview for DSM Axis I Disorders; SIPS = Structured Interview for Psychosis-risk Syndromes

[a]Exposure n/N = (number of participants in pTBI exposure group having psychotic disorders or symptoms)/(number of participants in pTBI exposure group)

[b]Control n/N = (number of participants in non-pTBI control group having psychotic disorders or symptoms)/(number of participants in non-pTBI control group)

[c]TBI in childhood (≤ 10 years old) was chosen over throughout adolescence (≤ 17 years old) due to primary analysis of the original study

[d]Comparison between clinical high risk (CHR) of psychosis and healthy controls (HC) was chosen due to primary analysis of the original study

^eSchizophrenia was chosen over non-affective psychosis due to more precise measurement of psychotic disorder

^fBoth concussion and head traumas were chosen and aggregated

^gRaw data on number of participants in relation to psychosis reported in the supplemental materials were used

^hData provided by the original author

ⁱ3-year follow-up was chosen due to primary analysis of the original study

^jHospital contacts for head injury from 0–15 years old were chosen

^kSurgical control was chosen due to primary analysis of the original study

Table 4. Quality assessment ratings for included studies

Study, year	Checklist for quality assessment[a]											Overall quality of evidence (summary score)
	Q1: Objective described	Q2: Appropriate design	Q3: Appropriate sampling	Q4: Participant described	Q8: Well-defined measure	Q9: Appropriate sample size	Q10: Appropriate analysis	Q11: Estimate of variance	Q12: Confounder controlled	Q13: Result in detail	Q14: Conclusion supported	
AbdelMalik, 2003	++	++	++	++	++	+	++	++	+	++	++	High (90.9)
Deighton, 2016	++	++	++	++	++	+	++	+	+	++	++	High (86.4)
Harrison, 2006	++	++	++	++	+	++	++	++	++	++	+	High (90.9)
Helgeland, 2005	++	+	+	++	+	–	+	–	+	+	+	Low (50)
Ledoux, 2022	++	++	++	++	+	++	++	++	++	++	++	High (95.5)
Lopez, 2022	++	++	++	++	+	++	++	++	+	++	++	High (90.9)
Massagli, 2004	++	++	++	++	+	+	++	++	+	++	++	High (86.4)
Orlovska, 2014	++	++	++	+	+	++	++	++	++	++	++	High (90.9)
Timonen, 2002	++	++	+	+	+	++	+	++	++	+	+	Moderate (72.7)
Wilcox, 1986	+	+	+	–	+	–	+	–	+	+	+	Low (36.4)

Note. (++) = yes; (+) = partially yes; (–) = no; NA = not applicable

[a]Q5–7 not applicable due to observational nature of included studies

Synthesis of Results

Overall Pooled Analysis

Among the 10 included studies, raw data from two were either not published or not provided by the original authors after contacts and were therefore excluded from the meta-analysis. Based on eight studies, with a pooled sample size of 479,686 (153,757 in the paediatric TBI group; 325,929 in the control group), there was an overall significant positive association between paediatric TBI and psychotic disorders/symptoms (pooled odds ratio [*OR*] = 1.88, 95% CI [1.07, 3.30]) with moderate between-study heterogeneity (I^2 = 69%, τ^2 = 0.49, $p < 0.01$). Figure 2 shows the comparison data and forest plot of the corresponding analysis.

Figure 2. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms

Study	Events	pTBI Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight
AbdelMalik 2003	16	28	51	141		2.35	[1.03; 5.36]	12.4%
Deighton 2016	232	287	515	738		1.83	[1.31; 2.55]	15.9%
Harrison 2006	18	455	730	15253		0.82	[0.51; 1.32]	15.0%
Helgeland 2005	4	26	5	115		4.00	[0.99; 16.09]	8.3%
Ledoux 2022	1058	152321	1705	296482		1.21	[1.12; 1.31]	16.8%
Lopez 2022	45	128	3279	11419		1.35	[0.93; 1.94]	15.7%
Massagli 2004	7	489	7	1470		3.04	[1.06; 8.70]	10.6%
Wilcox 1986	22	23	178	311		16.44	[2.19; 123.49]	5.3%
Random effects model		**153757**		**325929**		**1.88**	**[1.07; 3.30]**	**100.0%**
Prediction interval							**[0.30; 11.99]**	

Heterogeneity: I^2 = 69%, τ^2 = 0.4904, $p < 0.01$

Subgroup Analyses

Subgroup analyses based on study location (*p* = 0.36), design (*p* = 0.36), type of psychotic disorder/symptom (i.e., narrowly defined schizophrenia versus broadly defined psychosis/sub-threshold symptoms of psychosis; *p* = 0.37), measurement type (*p* = 0.83), time of onset (that psychotic disorders/symptoms emerged; *p* = 0.67) were all non-significant, suggesting that these variables did not modify the effect of paediatric TBI on the probability

of psychotic disorders/symptoms. Forest plots of all the above subgroup analyses are reported as Figure 3–7 below.

Figure 3. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – study-location subgroup analysis

Figure 4. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – study-design subgroup analysis

Figure 5. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – type-of-outcome subgroup analysis

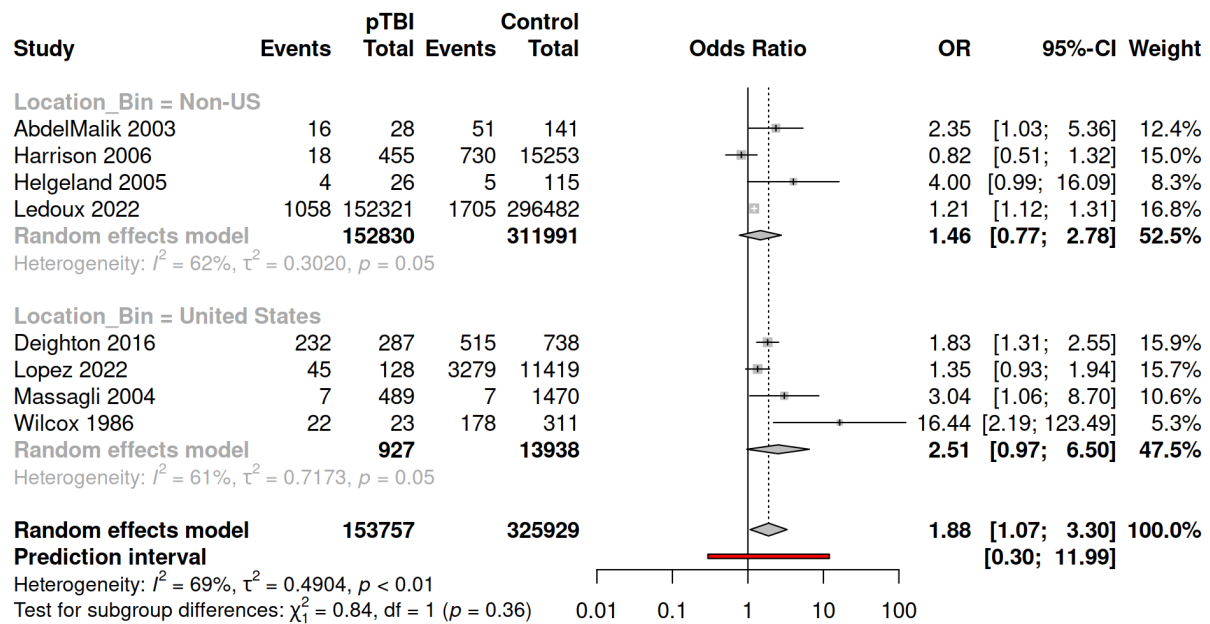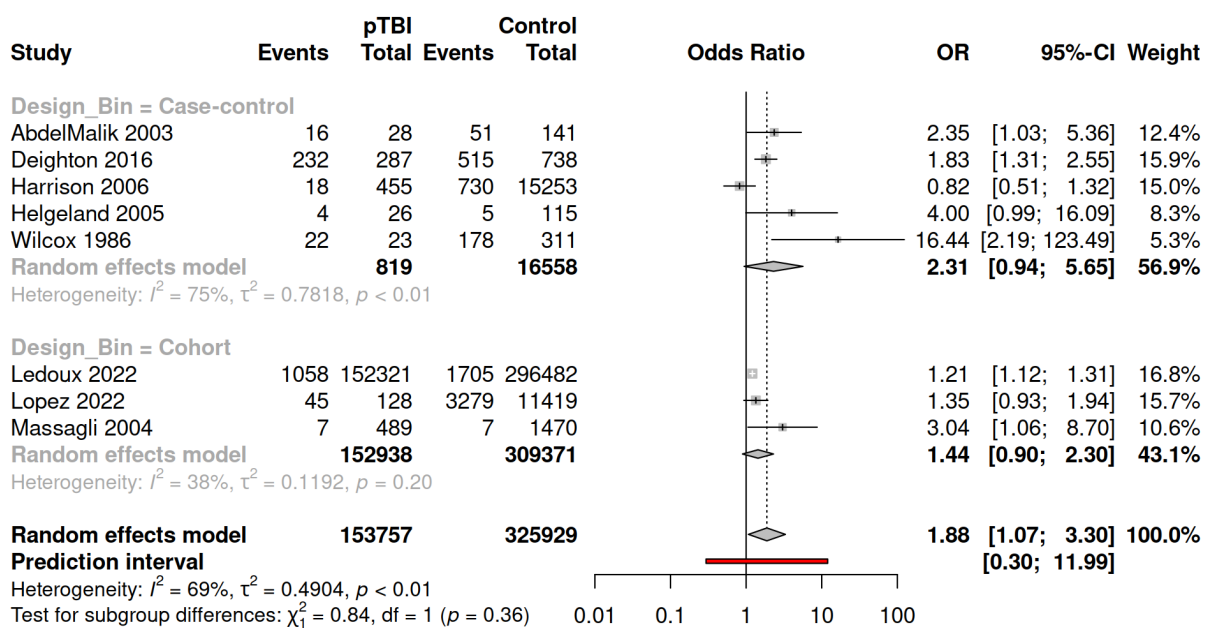| Study	Events	pTBI Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight
Outcome_Bin = Schizophrenia								
AbdelMalik 2003	16	28	51	141		2.35	[1.03; 5.36]	12.4%
Harrison 2006	18	455	730	15253		0.82	[0.51; 1.32]	15.0%
Helgeland 2005	4	26	5	115		4.00	[0.99; 16.09]	8.3%
Wilcox 1986	22	23	178	311		16.44	[2.19; 123.49]	5.3%
Random effects model		**532**		**15820**		**2.63**	**[0.82; 8.48]**	**41.0%**
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 1.0627$, $p < 0.01$								
Outcome_Bin = Psychosis/sub-threshold symptoms of psychosis								
Deighton 2016	232	287	515	738		1.83	[1.31; 2.55]	15.9%
Ledoux 2022	1058	152321	1705	296482		1.21	[1.12; 1.31]	16.8%
Lopez 2022	45	128	3279	11419		1.35	[0.93; 1.94]	15.7%
Massagli 2004	7	489	7	1470		3.04	[1.06; 8.70]	10.6%
Random effects model		**153225**		**310109**		**1.51**	**[1.07; 2.11]**	**59.0%**
Heterogeneity: $I^2 = 65\%$, $\tau^2 = 0.0790$, $p = 0.04$								
Random effects model		**153757**		**325929**		**1.88**	**[1.07; 3.30]**	**100.0%**
Prediction interval							**[0.30; 11.99]**	
Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.4904$, $p < 0.01$								
Test for subgroup differences: $\chi^2_1 = 0.81$, df = 1 ($p = 0.37$)								

Figure 6. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – type-of-outcome-measurement subgroup analysis

Study	Events	pTBI Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight
OutcomeMeasure_Bin = Validated/structured method								
AbdelMalik 2003	16	28	51	141		2.35	[1.03; 5.36]	12.4%
Deighton 2016	232	287	515	738		1.83	[1.31; 2.55]	15.9%
Helgeland 2005	4	26	5	115		4.00	[0.99; 16.09]	8.3%
Lopez 2022	45	128	3279	11419		1.35	[0.93; 1.94]	15.7%
Random effects model		**469**		**12413**		**1.81**	**[1.20; 2.72]**	**52.3%**
Heterogeneity: $I^2 = 21\%$, $\tau^2 = 0.0844$, $p = 0.28$								
OutcomeMeasure_Bin = Clinical diagnosis								
Harrison 2006	18	455	730	15253		0.82	[0.51; 1.32]	15.0%
Ledoux 2022	1058	152321	1705	296482		1.21	[1.12; 1.31]	16.8%
Massagli 2004	7	489	7	1470		3.04	[1.06; 8.70]	10.6%
Wilcox 1986	22	23	178	311		16.44	[2.19; 123.49]	5.3%
Random effects model		**153288**		**313516**		**2.07**	**[0.63; 6.77]**	**47.7%**
Heterogeneity: $I^2 = 75\%$, $\tau^2 = 1.2086$, $p < 0.01$								
Random effects model		**153757**		**325929**		**1.88**	**[1.07; 3.30]**	**100.0%**
Prediction interval							**[0.30; 11.99]**	
Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.4904$, $p < 0.01$								
Test for subgroup differences: $\chi^2_1 = 0.04$, df = 1 ($p = 0.83$)								

Figure 7. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – onset-time-of-outcome subgroup analysis
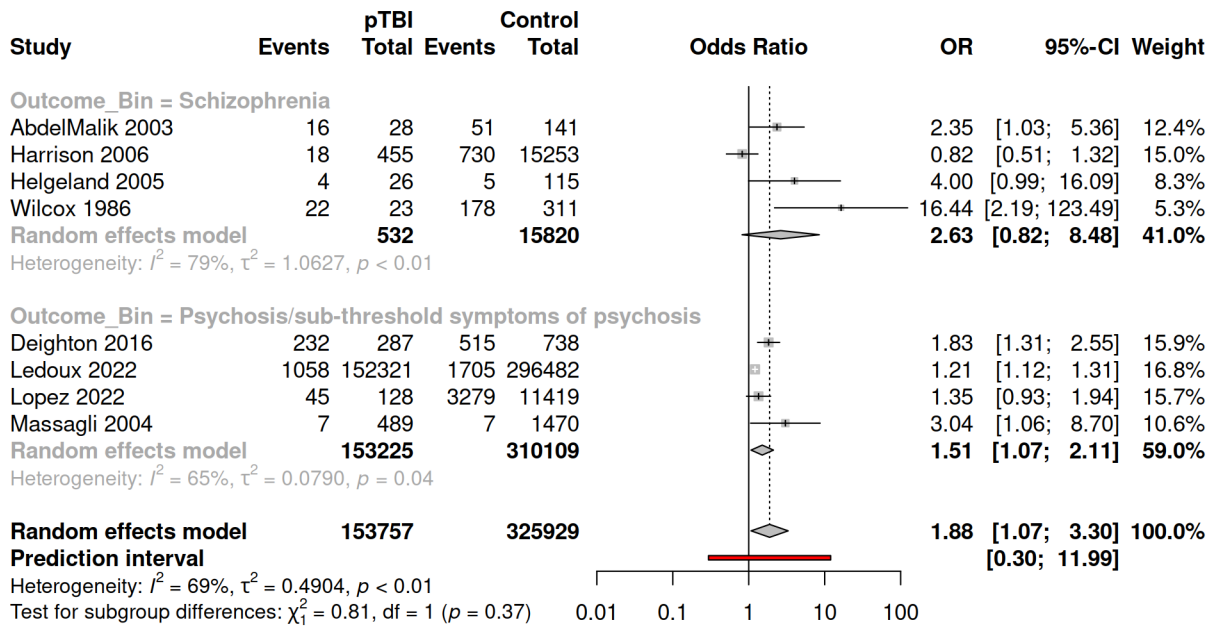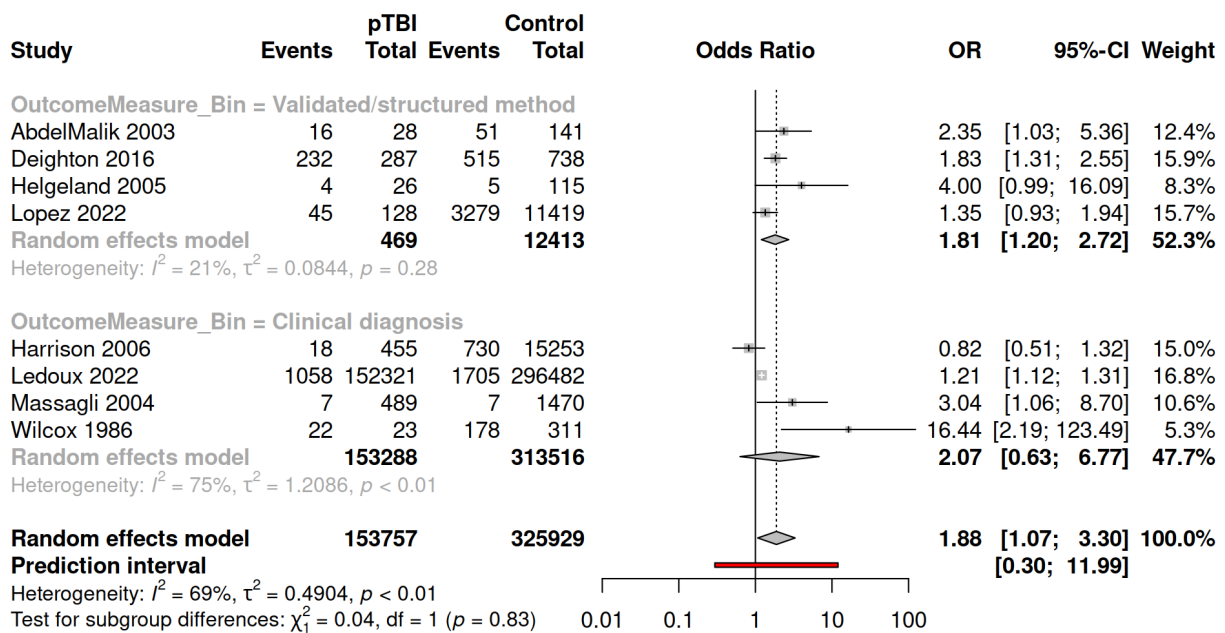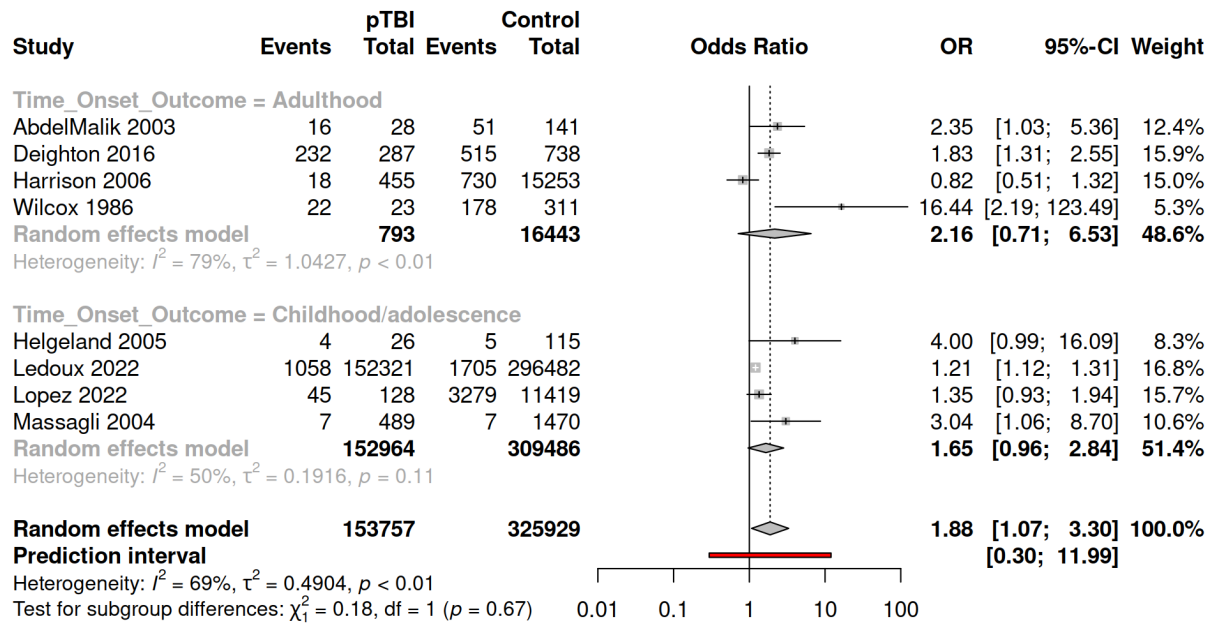
Study	Events	pTBI Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight
Time_Onset_Outcome = Adulthood								
AbdelMalik 2003	16	28	51	141		2.35	[1.03; 5.36]	12.4%
Deighton 2016	232	287	515	738		1.83	[1.31; 2.55]	15.9%
Harrison 2006	18	455	730	15253		0.82	[0.51; 1.32]	15.0%
Wilcox 1986	22	23	178	311		16.44	[2.19; 123.49]	5.3%
Random effects model		793		16443		2.16	[0.71; 6.53]	48.6%
Heterogeneity: $I^2 = 79\%$, $\tau^2 = 1.0427$, $p < 0.01$								
Time_Onset_Outcome = Childhood/adolescence								
Helgeland 2005	4	26	5	115		4.00	[0.99; 16.09]	8.3%
Ledoux 2022	1058	152321	1705	296482		1.21	[1.12; 1.31]	16.8%
Lopez 2022	45	128	3279	11419		1.35	[0.93; 1.94]	15.7%
Massagli 2004	7	489	7	1470		3.04	[1.06; 8.70]	10.6%
Random effects model		152964		309486		1.65	[0.96; 2.84]	51.4%
Heterogeneity: $I^2 = 50\%$, $\tau^2 = 0.1916$, $p = 0.11$								
Random effects model		**153757**		**325929**		**1.88**	**[1.07; 3.30]**	**100.0%**
Prediction interval							**[0.30; 11.99]**	
Heterogeneity: $I^2 = 69\%$, $\tau^2 = 0.4904$, $p < 0.01$								
Test for subgroup differences: $\chi_1^2 = 0.18$, df = 1 ($p = 0.67$)								

Robustness and Sensitivity Analyses

For the assessment of publication bias, visual inspection of the funnel plot (see Figure 8) appeared to exhibit asymmetry. Egger's test was completed ($p = 0.052$) although was likely under-powered given 10 studies are considered the minimum for a reliable assessment of publication bias (Ioannidis & Trikalinos, 2007).
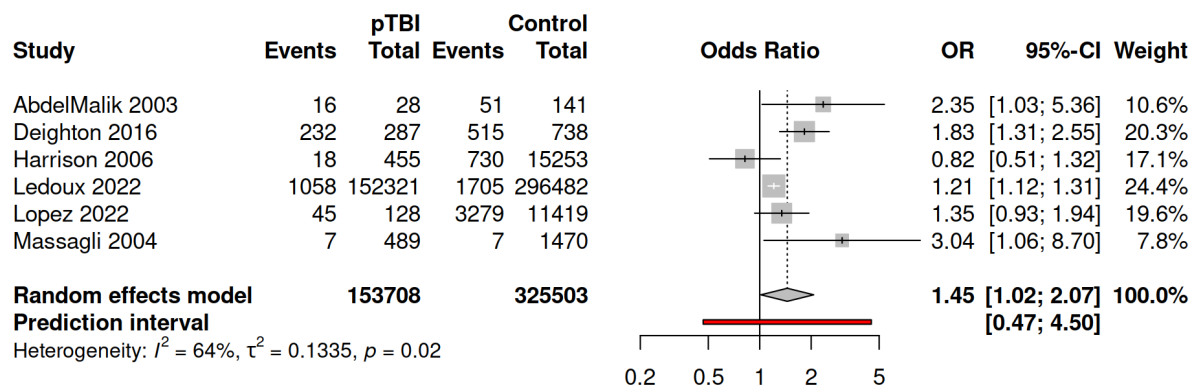
Figure 8. Funnel plot of standard error by odds ratio in meta-analysis
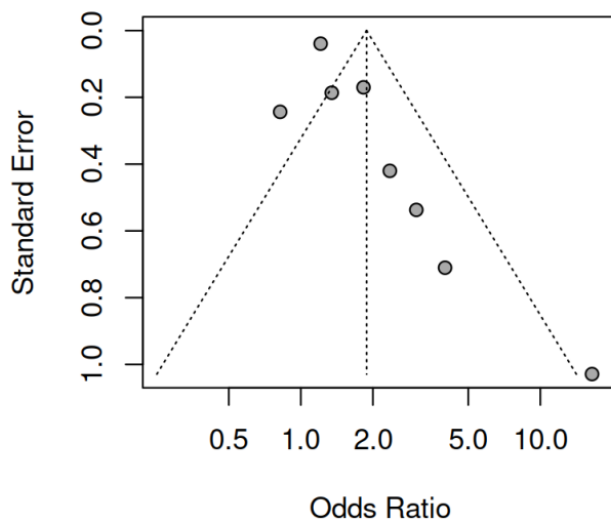
No studies were identified as outliers and no studies were identified as excessively influential using Viechtbauer and Cheung's (2010) outlier and influential diagnostics. A leave-one-out sensitivity analysis revealed only minor changes to the estimated *OR* and heterogeneity estimates. However, the removal of any one of three studies altered the estimate to the non-significant range, namely AbdelMalik et al. (2003): revised estimate *OR* = 1.87, 95% CI [0.97, 3.59]; Helgeland and Torgersen (2005): revised estimate *OR* = 1.77, 95% CI [0.96, 3.27]; or Massagli et al. (2004): revised estimate *OR* = 1.81, 95% CI [0.96, 3.43].

A meta-regression analysis indicated that the quality of evidence summary score predicted the association between paediatric TBI and psychotic disorders/symptoms, albeit weakly (random-effects estimate = -0.036, 95% CI [-0.06, -0.01], *p* = 0.012). Consequently, we completed a sensitivity analysis removing studies with evidence rated as low quality and recalculating the pooled estimate. The revised pooled estimate (see Figure 9) remained significant with narrower confidence intervals suggesting a more accurate estimate (*OR* = 1.45, 95% CI [1.02, 2.07]) and slightly reduced heterogeneity (I^2 = 64%, τ^2 = 0.13, *p* = 0.02).

Figure 9. Comparison data and forest plot of odds ratio meta-analysis for psychotic disorders or symptoms – sensitivity analysis by the removal of studies with low quality of evidence

Study	Events	pTBI Total	Control Events	Total	Odds Ratio	OR	95%-CI	Weight
AbdelMalik 2003	16	28	51	141		2.35	[1.03; 5.36]	10.6%
Deighton 2016	232	287	515	738		1.83	[1.31; 2.55]	20.3%
Harrison 2006	18	455	730	15253		0.82	[0.51; 1.32]	17.1%
Ledoux 2022	1058	152321	1705	296482		1.21	[1.12; 1.31]	24.4%
Lopez 2022	45	128	3279	11419		1.35	[0.93; 1.94]	19.6%
Massagli 2004	7	489	7	1470		3.04	[1.06; 8.70]	7.8%
Random effects model		**153708**		**325503**		**1.45**	**[1.02; 2.07]**	**100.0%**
Prediction interval							**[0.47; 4.50]**	

Heterogeneity: I^2 = 64%, τ^2 = 0.1335, *p* = 0.02

0.2　0.5　1　2　5

Narrative Synthesis Including Additional Studies

Two cohort studies were not included in the meta-analysis due to insufficient data, namely Orlovska et al. (2014) and Timonen et al. (2002). Orlovska et al. reported that, compared with individuals without hospital contact for head injury, those exposed to head injury between ages 0 and 5 years had higher rates of schizophrenia spectrum disorders (adjusted incident rate ratio [*aIRR*] = 1.35, 95% CI [1.18, 1.54]). In addition, differing effects of head injury at 6–10 years (*aIRR* = 1.33, 95% CI [1.16, 1.50]) and 11–15 years (*aIRR* = 1.86, 95% CI [1.66, 2.07]) were observed. In Timonen et al., although the original analysis focussed on the association between preceding paediatric TBI and the broad mental health outcomes, Molloy et al. (2011) contacted the original authors and reported a non-significant association between paediatric TBI and the subsequent development of schizophrenia (odds ratio [*OR*] = 1.1, 95% CI [0.41, 2.96]), whilst the wide confidence intervals indicate that the estimate would carry less weight in estimating an overall effect.

Discussion

We conducted a systematic review and meta-analysis to estimate the association between paediatric TBI and psychosis, including both frank psychotic disorders and psychotic symptoms. Based on a pooled sample size of 479,686, it was found that paediatric TBI was associated with an increased probability of psychotic disorders or symptoms, with moderate between-study heterogeneity. Regarding the robustness of findings, the estimated association passed robustness tests for study quality, outliers, and excessively influential studies, although the removal of any one of three studies would have reduced confidence in a reliable association in a leave-one-out sensitivity analysis. This reflects the fact that the lower bound of the confidence interval for the pooled estimate was only marginally above one and therefore confidence in the reliability of this estimate must be taken cautiously. Two studies which were identified in the systematic review could not be included in the meta-analysis,

and these studies reporting conflicting results. However, given the characteristics of these additional studies, we consider that including them would have moderately increased our confidence in an association between paediatric TBI and psychosis. Consequently, we conclude that this analysis provides additional evidence for an association between paediatric TBI and psychosis. However, concerns remain about the long-run reliability of this estimate and new studies will be crucial in deciding this issue.

In relating the above findings to the field, our results raise the feasibility of potential causal associations between paediatric TBI and psychosis. Developmental models of psychosis suggest that paediatric TBI could be a plausible risk factor for psychosis, given that the full spectrum of paediatric TBI (from mild paediatric TBI to severe brain injury) has established effects on neurodevelopment (Emery et al., 2016; Goh et al., 2021), and events that have an adverse impact on neurodevelopment are known risk factors for psychosis (Howes & Murray, 2014; Murray et al., 2017). Our meta-analytic results seem to suggest the role of paediatric TBI as a risk factor for psychosis. However, reverse causality or shared risk factor pathways are also possible. Brain injuries have been hypothesised to be more common in young people who have a higher risk for psychosis, as they may already show subtle premorbid difficulties such as motor coordination leading to a higher risk for accidental injuries (AbdelMalik et al., 2003; David & Prince, 2005). Furthermore, psychotic symptoms, including in people without frank psychosis, are associated with higher rates of early-life bullying (Catone et al., 2015; Valmaggia et al., 2015), suggesting a possible reverse or reciprocal association between psychotic spectrum phenomena and acquired brain injury through victimisation violence. A well-designed prospective cohort study would be needed to reliably identify relationships between paediatric TBI, psychotic symptoms, and any potential confounders and/or mediators.

Nevertheless, given the concordance between the findings reported here and the developmental models of psychosis (Howes & Murray, 2014; Murray et al., 2017), this suggests that investigating the occurrence of paediatric TBI over a lifetime may be a useful addition when taking a history of patients with psychosis, and that public health measures preventing paediatric TBI may have longer-term benefits for lifetime mental health.

A strength of this study is the use of systematic procedures to comprehensively search for eligible studies. We also included sensitivity analyses to ensure robustness of the findings. In addition, we pre-registered the review to reduce the risk of bias. Moreover, the meta-analysis is available online as a computational notebook with an open dataset, to enhance openness and reproducibility.

However, we note several limitations of this study. The first is that the included studies are heterogeneous in terms of their research design (case control versus cohort), outcome (symptoms versus disorder), outcome measure (clinical diagnosis versus validated measure), and life-stage of measured psychosis outcome (adulthood versus childhood/adolescence). Our subgroup analyses found no evidence for difference of association between subgroups but largely because, in contrast to the overall pooled estimate, the estimate of effect within any one subgroup was non-significant. We note the potential for low statistical power to make identifying associations within subgroups difficult, given that subgroups typically included 3–4 studies. However, the heterogeneity of studies reflects the fact that many were not primarily designed to assess the association between paediatric TBI and psychosis spectrum phenomena, and more focussed and better design studies are clearly needed. Inspection of the funnel plot indicated a potential for publication bias which could have reduced the accuracy or the direction of the estimate. We also note that we solely included studies published in English, and listed in primarily English language databases, potentially missing some useful evidence.

Based on the above discussions, it is recommended that future research should focus on specifically assessing the association between paediatric TBI and psychosis spectrum phenomena. In addition, to rule out the possible reverse association, a well-designed prospective cohort study would be needed to reliably identify relationships between paediatric TBI, psychotic symptoms, and any potential confounders and/or mediators. Additionally, future studies specifying the type of TBI (e.g., due to accidents or other sources) and location of injury, would enhance our understanding of the presence/absence of an aetiological relationship between paediatric TBI and psychosis. Lastly, future reviews should consider including non-English language databases.

Conclusions

In conclusion, our systematic review and meta-analysis reports evidence for a positive association between paediatric TBI and subsequent psychotic disorders or symptoms, but with caveats regarding our confidence in the long-term reliability of this association as new evidence emerges.

References

AbdelMalik, P., Husted, J., Chow, E. W. C., & Bassett, A. S. (2003). Childhood head injury and expression of schizophrenia in multiply affected families. *Archives of General Psychiatry*, *60*(3), 231–236. https://doi.org/10.1001/archpsyc.60.3.231

Balduzzi, S., Rücker, G., & Schwarzer, G. (2019). How to perform a meta-analysis with R: A practical tutorial. *Evidence Based Mental Health*, *22*(4), 153–160. https://doi:10.1136/ebmental-2019-300117

Batty, R. A., Rossell, S. L., Francis, A. J. P., & Ponsford, J. (2013). Psychosis following traumatic brain injury. *Brain Impairment*, *14*(1), 21–41. https://doi.org/10.1017/BrImp.2013.10

Carroll, L. J., Cassidy, J. D., Cancelliere, C., Côté, P., Hincapié, C. A., Kristman, V. L., Holm, L. W., Borg, J., Nygren-de Boussard, C., & Hartvigsen, J. (2014). Systematic review of the prognosis after mild traumatic brain injury in adults: Cognitive, psychiatric, and mortality outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation*, *95*(3), S152–S173. https://doi.org/10.1016/j.apmr.2013.08.300

Catone, G., Marwaha, S., Kuipers, E., Lennox, B., Freeman, D., Bebbington, P., & Broome, M. (2015). Bullying victimisation and risk of psychotic phenomena: Analyses of British national survey data. *The Lancet Psychiatry*, *2*(7), 618–624. https://doi.org/10.1016/S2215-0366%2815%2900055-3

Cnossen, M. C., Scholten, A. C., Lingsma, H. F., Synnot, A., Haagsma, J., Steyerberg, E. W., & Polinder, S. (2017). Predictors of major depression and posttraumatic stress disorder following traumatic brain injury: A systematic review and meta-analysis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(3), 206–224. https://doi.org/10.1176/appi.neuropsych.16090165

Corrigan, J. D., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University TBI Identification Method. *The Journal of Head Trauma Rehabilitation*, *22*(6), 318–329. https://doi.org/10.1097/01.HTR.0000300227.67748.77

David, A. S., & Prince, M. (2005). Psychosis following head injury: A critical review. *Journal of Neurology, Neurosurgery & Psychiatry*, *76*(suppl 1), i53–i60. https://doi.org/10.1136/jnnp.2004.060475

Deighton, S., Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T. H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W., Bearden, C. E., Mathalon, D., & Addington, J. (2016). Traumatic brain injury in individuals at clinical high risk for psychosis. *Schizophrenia Research*, *174*(1–3), 77–81. https://doi.org/10.1016/j.schres.2016.04.041

Emery, C. A., Barlow, K. M., Brooks, B. L., Max, J. E., Villavicencio-Requis, A., Gnanakumar, V., Robertson, H. L., Schneider, K., & Yeates, K. O. (2016). A systematic review of psychiatric, psychological, and behavioural outcomes following mild traumatic brain injury in children and adolescents. *The Canadian Journal of Psychiatry*, *61*(5), 259–269. https://doi.org/10.1177/0706743716643741

Feighner, J. P., Robins, E., Guze, S. B., Woodruff Jr., R. A., Winokur, G., & Munoz, R. (1972). Diagnostic criteria for use in psychiatric research. *Archives of General Psychiatry*, *26*(1), 57–63. https://doi.org/10.1001/archpsyc.1972.01750190059011

Fleminger, S. (2008). Long-term psychiatric disorders after traumatic brain injury. *European Journal of Anaesthesiology*, *25*, 123. https://doi.org/10.1017/S0265021507003250

Fujii, D., & Ahmed, I. (2002). Characteristics of psychotic disorder due to traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(2), 130–140. https://doi.org/10.1176/jnp.14.2.130

Goh, M. S. L., Looi, D. S. H., Goh, J. L., Sultana, R., Goh, S. S. M., Lee, J. H., & Chong, S. -
L. (2021). The impact of traumatic brain injury on neurocognitive outcomes in
children: A systematic review and meta-analysis. *Journal of Neurology, Neurosurgery
& Psychiatry*, *92*, 847–853. https://doi.org/10.1136/jnnp-2020-325066

Harrison, G., Whitley, E., Rasmussen, F., Lewis, G., Dalman, C., & Gunnell, D. (2006). Risk
of schizophrenia and other non-affective psychosis among individuals exposed to
head injury: Case control study. *Schizophrenia Research*, *88*(1–3), 119–126.
https://doi.org/10.1016/j.schres.2006.07.001

Helgeland, M. I., & Torgersen, S. (2005). Stability and prediction of schizophrenia from
adolescence to adulthood. *European Child & Adolescent Psychiatry*, *14*, 83–94.
https://doi.org/10.1007/s00787-005-0436-0

Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring
inconsistency in meta-analyses. *BMJ (Clinical research ed.)*, *327*(7414), 557–560.
https://doi.org/10.1136/bmj.327.7414.557

Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-
cognitive model. *The Lancet*, *383*(9929), 1677–1687. https://doi.org/10.1016/S0140-
6736%2813%2962036-X

Ioannidis, J. P. A., & Trikalinos, T. A. (2007). The appropriateness of asymmetry tests for
publication bias in meta-analyses: A large survey. *Canadian Medical Association
Journal*, *176*(8), 1091–1096. https://doi.org/10.1503/cmaj.060410

Karcher, N. R., Barch, D. M., Avenevoli, S., Savill, M., Huber, R. S., Simon, T. J., Leckliter,
I. N., Sher, K. J., & Loewy, R. L. (2018). Assessment of the Prodromal
Questionnaire-Brief Child Version for measurement of self-reported psychoticlike
experiences in childhood. *JAMA Psychiatry*, *75*(8), 853–861.
https://doi.org/10.1001/jamapsychiatry.2018.1334

Kmet, L. M., Cook, L. S., & Lee, R. C. (2004). *Standard quality assessment criteria for evaluating primary research papers from a variety of fields*. Edmonton, AB: Health Technology Assessment Initiative. https://doi.org/10.7939/R37M04F16

Ledoux, A. -A., Webster, R. J., Clarke, A. E., Fell, D. B., Knight, B. D., Gardner, W., Cloutier, P., Gray, C., Tuna, M., & Zemek, R. (2022). Risk of mental health problems in children and youths following concussion. *JAMA Network Open*, *5*(3), e221235. https://doi.org/10.1001/jamanetworkopen.2022.1235

Lee, K. -W., Chan, K. -W., Chang, W. -C., Lee, E. H. -M., Hui, C. L. -M., & Chen, E. Y. -H. (2016). A systematic review on definitions and assessments of psychotic-like experiences. *Early Intervention in Psychiatry*, *10*(1), 3–16. https://doi.org/10.1111/eip.12228

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: On the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149. https://doi.org/10.1017/S0033291712001626

Lopez, D. A., Christensen, Z. P., Foxe, J. J., Ziemer, L. R., Nicklas, P. R., & Freedman, E. G. (2022). Association between mild traumatic brain injury, brain structure, and mental health outcomes in the Adolescent Brain Cognitive Development Study. *NeuroImage*, *263*, 119626. https://doi.org/10.1016/j.neuroimage.2022.119626

Massagli, T. L., Fann, J. R., Burington, B. E., Jaffe, K. M., Katon, W. J., & Thompson, R. S. (2004). Psychiatric illness after mild traumatic brain injury in children. *Archives of Physical Medicine and Rehabilitation*, *85*(9), 1428–1434. https://doi.org/10.1016/j.apmr.2003.12.036

McGlashan, T., Walsh, B., & Woods, S. (2010). *The psychosis-risk syndrome: Handbook for diagnosis and follow-up*. Oxford University Press.

Molloy, C., Conroy, R. M., Cotter, D. R., & Cannon, M. (2011). Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies. *Schizophrenia bulletin*, *37*(6), 1104–1110. https://doi.org/10.1093/schbul/sbr091

Murray, R. M., Bhavsar, V., Tripoli, G., & Howes, O. (2017). 30 years on: How the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophrenia Bulletin*, *43*(6), 1190–1196. https://doi.org/10.1093/schbul/sbx121

Orlovska, S., Pedersen, M. S., Benros, M. E., Mortensen, P. B., Agerbo, E., & Nordentoft, M. (2014). Head injury as risk factor for psychiatric disorders: A nationwide register-based follow-up study of 113,906 persons with head injury. *The American Journal of Psychiatry*, *171*(4), 463–469. https://dx.doi.org/10.1176/appi.ajp.2013.13020190

Page, M. J., McKenzie, J., Bossuyt, P., Boutron, I., Hoffmann, T., Mulrow, C., Shamseer, L., Tetzlaff, J., Akl, E., Brennan, S., Chou, R., Glanville, J., Grimshaw, J., Hróbjartsson, A., Lalu, M., Li, T., Loder, E., Mayo-Wilson, E., McDonald, S., … Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, *372*(n71), https://doi.org/10.1136/bmj.n71

Perry, D. C., Sturm, V. E., Peterson, M. J., Pieper, C. F., Bullock, T., Boeve, B. F., Miller, B. L., Guskiewicz, K. M., Berger, M. S., Kramer, J. H., & Welsh-Bohmer, K. A. (2016). Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. *Journal of Neurosurgery*, *124*(2), 511–526. https://doi.org/10.3171/2015.2.JNS14503

Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., Roen, K., & Duffy, S. (2006). *Guidance on the conduct of narrative synthesis in systematic reviews. A product from the ESRC methods programme*. UK: Lancaster University.

R Core Team (2020). *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria.

Richardson, M., Garner, P., & Donegan, S. (2019). Interpretation of subgroup analyses in systematic reviews: A tutorial. *Clinical Epidemiology and Global Health*, *7*(2), 192–198. https://doi.org/10.1016/j.cegh.2018.05.005

Rogers, J. M., & Read, C. A. (2007). Psychiatric comorbidity following traumatic brain injury. *Brain Injury*, *21*(13–14), 1321–1333. https://doi.org/10.1080/02699050701765700

Rubio, J. M., Sanjuan, J., Florez-Salamanca, L., & Cuesta, M. J. (2012). Examining the course of hallucinatory experiences in children and adolescents: A systematic review. *Schizophrenia Research*, *138*(2–3), 248–254. https://doi.org/10.1016/j.schres.2012.03.012

Schwartz, J. A., Jodis, C. A., Breen, K. M., & Parker, B. N. (2019). Brain injury and adverse outcomes: A contemporary review of the evidence. *Current Opinion in Psychology, Genetics*, *27*, 67–71. https://doi.org/10.1016/j.copsyc.2018.09.006

Sidik, K., & Jonkman, J. N. (2005). Simple heterogeneity variance estimation for meta-analysis. *Applied Statistics*, *54*(2), 367–384. https://doi.org/10.1111/j.1467-9876.2005.00489.x

Timonen, M., Miettunen, J., Hakko, H., Zitting, P., Veijola, J., von Wendt, L., & Räsänen, P. (2002). The association of preceding traumatic brain injury with mental disorders, alcoholism and criminality: The Northern Finland 1966 Birth Cohort Study.

Psychiatry Research, *113*(3), 217–226. https://doi.org/10.1016/S0165-1781%2802%2900269-X

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the persistence of psychotic symptoms: A systematic review and meta-analysis. *Psychological Medicine*, *45*(12), 2481–2498. https://doi.org/10.1017/S0033291715000574

Valmaggia, L. R., Day, F. L., Kroll, J., Laing, J., Byrne, M., Fusar-Poli, P., & McGuire, P. (2015). Bullying victimisation and paranoid ideation in people at ultra high risk for psychosis. *Schizophrenia Research*, *168*(1–2), 68–73. https://doi.org/10.1016/j.schres.2015.08.029

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A systematic review and meta-analysis of the psychosis continuum: Evidence for a psychosis proneness–persistence–impairment model of psychotic disorder. *Psychological Medicine*, *39*(2), 179–195. https://doi.org/10.1017/S0033291708003814

van Reekum, R., Cohen, T., & Wong, J. (2000). Can traumatic brain injury cause psychiatric disorders? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(3), 316–327. https://doi.org/10.1176/jnp.12.3.316

Viechtbauer, W., & Cheung, M. W. -L. (2010). Outlier and influence diagnostics for meta-analysis. *Research Synthesis Methods*, *1*(2), 112–125. https://doi.org/10.1002/jrsm.11

Wilcox, J. A., & Nasrallah, H. A. (1987). Childhood head trauma and psychosis. *Psychiatry Research*, *21*(4), 303–306. https://doi.org/10.1016/0165-1781%2887%2990013-8

Yau, K. -C., Revill, G., & Bell, V. (2022) A systematic review of paediatric traumatic brain injury as a risk factor for psychotic experiences. *PROSPERO, CRD42022360772*. https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360772

Part 2: Empirical Paper

Exploring the association between traumatic

brain injury and psychotic-like experiences in

children

Abstract

Background: Investigating the role of paediatric traumatic brain injury (TBI) as a potential risk factor for psychotic-like experiences (PLEs) in children is crucial, given the current key developmental models of psychosis, indicating that risk factors disrupting typical neurodevelopment can sustain normally transient PLEs, thereby increasing the likelihood of transitioning to a later psychotic disorder.

Aims: The current study aimed to investigate the extent to which TBI predicted PLEs in children.

Methods: The present study utilised the Adolescent Brain Cognitive Development (ABCD) large cohort data from children aged 9 to 10 years old at baseline ($n = 11,875$), with longitudinal and prospective follow-up (release 4.0; timepoints adopted = baseline & 3-year follow-up) to investigate whether the presence of paediatric TBI, the severity of paediatric TBI, or the number of paediatric TBIs at baseline predicted the presence of PLEs at baseline or 36 months, using multi-level logistic regression analyses.

Results: It was found that the presence of paediatric TBI at baseline was a significant predictor of the occurrence of PLEs at 36 months, with the relationship remaining robust after controlling for potential confounders ($OR = 2.15$, 95% CI [1.26, 3.65], $p = 0.005$). However, no significant association was found between the presence of TBI and the presence of PLEs at baseline ($OR = 1.35$, 95% CI [0.92, 1.99], $p = 0.124$). Additionally, among all other adjusted regression models, no significant relationships were observed between the number of TBIs and the presence of PLEs at both baseline ($OR = 1.28$, 95% CI [0.96, 1.71], $p = 0.097$) and 36 months ($OR = 1.42$, 95% CI [1.00, 2.03], $p = 0.051$), whilst the severity of TBI was only found to be significantly associated with the presence of PLEs at baseline ($OR = 1.18$, 95% CI [1.01, 1.38], $p = 0.040$), but not at 36 months ($OR = 1.13$, 95% CI [0.92, 1.37], $p = 0.244$).

Conclusions: The present study provides evidence indicating (i) a delayed occurrence of PLEs following TBI among children aged 9 to 10 years old; (ii) weak associations between TBI and PLEs; however, (iii) a persistence of post-TBI PLEs and (iv) a dose–response relationship could not be observed. Future research should address the potential bias arisen from measures and study design, and most importantly, overcome the challenge of reverse causality.

Introduction

There is compelling evidence demonstrating that traumatic brain injury (TBI) is associated with increased likelihood of subsequent adverse neuropsychiatric outcomes, including depression, anxiety, posttraumatic stress symptoms, cognitive impairment, personality change, and neurodegenerative conditions (Carroll et al., 2014; Cnossen et al., 2017; Fleminger, 2008; Hesdorffer et al., 2009; Perry et al., 2016; Rogers & Read, 2007; Schwartz et al., 2019; van Reekum et al., 2000).

Traumatic Brain Injury and Psychosis

Notably, psychosis is one of the most debilitating psychiatric disorders (American Psychiatric Association, 2013). Efforts have been made to suggest that TBI might contribute to the development of psychosis by damaging the frontal and temporal areas and through compromised dopamine regulation (Fujii & Ahmed, 2002b, 2014). Emerging data have shown that a post-TBI reduction in hippocampal volume predicts an increase in psychotic symptoms over time, indicating potential roles of hippocampal atrophy (i.e., degeneration of hippocampi in the temporal areas) in the delayed onset of post-TBI psychotic symptoms (Bray et al., 2021). Furthermore, another neuroimaging study found that adults in a perinatal brain injury group exhibited a significant decrease in hippocampal volume and changes in dopamine synthesis capacity compared with healthy controls, suggesting a potential mechanism underlying brain injuries and the subsequent development of adult mental illnesses, such as psychosis (Froudist-Walsh et al., 2017). In population-based studies, to date, one meta-analysis has been conducted, revealing a 65% increase in the risk of developing a psychotic disorder following TBI (Molloy et al., 2011).

Traumatic Brain Injury, Psychosis, and Psychotic-Like Experiences in Children

Compared with research in adults, the relationships between childhood TBI and psychotic disorders/symptoms are less extensively studied, and the findings remain

conflicting and controversial. Some empirical studies have reported an increased risk of developing adverse emotional, behavioural, and psychiatric outcomes following TBI exposure in childhood (Arif et al., 2021; Ledoux et al., 2022; Lopez et al., 2022; Massagli et al., 2004; Timonen et al., 2002). However, the association between childhood TBI and the development of psychotic disorders remains unclear.

On one hand, a large-scale nested case-control study found no evidence of increased risk for psychosis following TBI exposure in children before the age of 10 (Harrison et al., 2006), which is consistent with a meta-analytic study reporting a non-significant pooled odds ratio for the risk of psychotic disorder following childhood TBI (Molloy et al., 2011). This meta-analysis, however, relied on a subgroup analysis of only three primary studies focussing on children (AbdelMalik et al., 2003; Massagli et al., 2004; Timonen et al., 2002).

On the other hand, several case-control and cohort studies not included in Molloy et al.'s (2011) meta-analysis reported increased likelihood of a history of paediatric TBI among participants with psychotic disorders or psychotic-like experiences, compared with control groups (Deighton et al., 2016; Orlovska et al., 2014; Wilcox & Nasrallah, 1986). Psychotic-like experiences (PLEs) refer to subclinical levels of psychotic symptoms (e.g., mild delusional thoughts, perceptual disturbances; Karcher et al., 2018; Linscott & van Os, 2013). Research has shown that PLEs in adolescence are associated with higher likelihood of developing clinical psychosis (Dominguez et al., 2011). Additionally, a meta-analysis of epidemiological studies found evidence for continuity between earlier PLEs and later psychotic disorders (Linscott & van Os, 2013).

Despite these findings, the results of various case-control, cohort, and meta-analytic studies on paediatric TBI and PLEs/clinical psychosis remain conflicting (Deighton et al., 2016; Harrison et al., 2006; Molloy et al., 2011; Orlovska et al., 2014; Wilcox & Nasrallah, 1986). If an exposure-outcome relationship exists, the strength of the association is likely to

be small. Kim et al. (2007) recommended adopting a large-scale multicentre design to investigate post-TBI psychosis outcomes. Furthermore, Schwartz et al.'s (2019) narrative review of existing literature on post-TBI neuropsychiatric outcomes identified threats to internal validity, including potential confounding variables such as socioeconomic status and parental maltreatment. As a result, an analysis of a large cohort dataset with control for confounding variables is needed to better understand the relationships between paediatric TBI and psychotic symptoms. Despite the potential relationship between paediatric TBI and PLEs, subclinical psychotic symptoms might exhibit considerable overlaps with common post-TBI sequelae such as cognitive impairment, anxiety, and personality changes (Fleminger, 2008; Schwartz et al., 2019). Consequently, readers should interpret the occurrence of PLEs in the typical trajectory of TBI with caution.

Persistence of Psychotic-Like Experiences in Children

Investigating the role of paediatric TBI as a potential risk factor for PLEs in children is crucial, given the current key developmental models of psychosis. Both the psychosis-proneness–persistence–impairment model (Linscott & van Os, 2013; van Os et al., 2009) and the developmental risk factor model (Howes & Murray, 2014; Murray et al., 2017) suggest a psychosis continuum or spectrum, with compelling evidence indicating that risk factors disrupting typical neurodevelopment (e.g., dysregulated striatal dopamine) can sustain normally transient PLEs, thereby increasing the likelihood of transitioning to a later psychotic disorder. Evidence has also shown that PLEs commonly occur and subsequently remit during childhood and adolescence (Rubio et al., 2012). Meanwhile, exposure to adverse childhood events has been found to be associated with the persistence of PLEs and clinically relevant symptoms of psychosis (Trotta et al., 2015). Although paediatric TBI has been proposed as a neurodevelopmental risk factor (AbdelMalik et al., 2003), it remains unclear whether exposure to head injury actually contributes to the persistence of PLEs during childhood and

adolescence, subsequently increasing the risk of developing a later psychotic disorder.

Therefore, a longitudinal dataset with multiple timepoints is necessary to detect the potential

persistence of PLEs (i.e., occurrence at both baseline and follow-up) in children and to better

understand the impact of paediatric TBI on the development and persistence of PLEs.

Dose–Response Relationship

David and Prince (2005), in a narrative review of evidence, concluded that it was

unlikely that brain injury reliably led to psychosis outcomes based on the data available at the

time. Another narrative review by Batty et al. (2013) also urged caution regarding the

certainty of establishing a causal relationship between TBI and psychosis based on the

available evidence. Therefore, the presence of a dose–response relationship (i.e., changes in

severity or number of TBI events resulting in changes in outcomes) is considered necessary

to enhance confidence in potentially making a causal inference.

A systematic review reported that the relationship between TBI and psychiatric

outcomes among children and adolescents was moderated by factors, including the

occurrence of multiple TBIs over a lifetime (Emery et al., 2016). Another empirical study

found a trend towards more severe symptoms associated with the number of prior head

injuries experienced by adolescent patients, although a statistically significant relationship

could not be established (Mooney et al., 2022). Similarly, some other reviews and a meta-

analysis generally could not find sufficient evidence supporting the presence of a dose–

response relationship (or biological gradient) between the variables of TBI severity and

subsequent psychotic disorders (Molloy et al., 2011; Rogers & Read, 2007; van Reekum et

al., 2000). If TBI truly leads to later psychotic symptoms, it is essential to study the dose–

response relationship. Consequently, the selection of exposure variables, such as TBI severity

and number of TBIs (instead of just the occurrence of TBI), is warranted in the dataset.

Temporal Sequence

The temporal sequence between paediatric TBI and psychotic disorders/symptoms is also complex. Whilst a systematic review reported children's recovery of psychosocial functioning within a short period after head injury (Keightley et al., 2014), other data demonstrated a delayed occurrence of psychotic disorders or symptoms following TBI (Bray et al., 2021; Fujii & Ahmed, 2001, 2002a; Sachdev et al., 2001). Fujii and Ahmed's (2014) review paper suggested a delayed onset with a mean latency of around 36 months after sustaining head injury. Given this complexity, a longitudinal dataset with multiple timepoints is necessary to detect potential delayed onset of PLEs (i.e., absent at baseline but present at follow-up) and better understand the temporal relationships between paediatric TBI and psychotic symptoms.

Selection of the Dataset

To conclusively determine whether TBI is a risk factor for PLEs in children, it is necessary to overcome the existing challenges of: (i) detecting a potentially small magnitude of association (thus requiring large cohort data); (ii) minimising potential threats to internal validity due to confounders (hence controlling for a list of confounding variables); (iii) detecting the persistence of PLEs across time (requiring multiple timepoints); (iv) recognising a delayed onset of PLEs (necessitating multiple timepoints); and (v) detecting a dose–response relationship between the severity/number of TBI events and paediatric PLEs (requiring variables of TBI severity and number of TBIs). Consequently, we selected a large cohort dataset (Adolescent Brain Cognitive Development [ABCD]) with longitudinal and prospective follow-up, examining the primary variables of TBI occurrence, TBI severity, number of TBIs, and the occurrence of PLEs across multiple timepoints, whilst controlling for potential confounders based on the literature. Although Lopez et al. (2022) also utilised the ABCD dataset to investigate the relationship between paediatric TBI and PLEs, their

study included data only up to the 2-year follow-up and limited the exposure variable to mild TBI. This approach may have overlooked measurements at 36 months (i.e., the mean latency of psychosis outcomes after sustaining a head injury as indicated by the literature) and the full range of TBI severity. Both of these potential limitations will be addressed in the current study.

Aims of the Study

The present study utilised the Adolescent Brain Cognitive Development (ABCD) large cohort data with longitudinal and prospective follow-up (release 4.0) to investigate the extent to which TBI at baseline predicted PLEs in children. Specifically, we examined the following six research questions:

RQ1. Is the presence of traumatic brain injury (TBI) in children associated with the presence of their psychotic-like experiences (PLEs) within the same baseline timepoint?

RQ2. Is the severity of TBI in children associated with the presence of their PLEs at baseline?

RQ3. Is the number of TBIs in children associated with the presence of their PLEs at baseline?

RQ4. Does the presence of TBI in children predict the occurrence of their PLEs at 36 months?

RQ5. Does the severity of TBI in children predict the occurrence of their PLEs at 36 months?

RQ6. Does the number of TBIs in children predict the occurrence of their PLEs at 36 months?

Methods

Sample and Design

The Adolescent Brain Cognitive Development (ABCD) longitudinal cohort dataset comprises over 11,800 children aged 9–10 years old from 21 research sites in the United States, spanning regions that are demographically diverse (National Institute of Mental Health, 2022). Participants were included to aim for general representativeness of the national population by matching sociodemographic characteristics, such as age, gender, ethnicity, socioeconomic status, and urbanicity, in the country (Garavan et al., 2018). Children and adolescents were primarily recruited through the school systems, with parental consent for participation. The biological and behavioural development of individuals is tracked longitudinally for 10 years, starting in 2019, with data released yearly. The full protocol and sampling method have been reported in Garavan et al. (2018). The design of the current research was a longitudinal, prospective, and observational study of the cohort data.

The present analysis used the ABCD release 4.0 dataset, which includes baseline and 3-year follow-up data for 11,875 and 6,251 individuals, respectively. At the time of writing, the ABCD release 4.0 dataset contains only partial data from the 3-year follow-up, whilst data from the full cohort will be released later (National Institute of Mental Health Data Archive, 2021). However, it is important to clarify that the seemingly missing data at the 3-year follow-up are not due to attrition, and thus it is unlikely that the sample is biased with regard to missing data points.

Specific variables, including child's traumatic brain injury (TBI; exposure variable), child's psychotic-like experiences (PLEs; outcome variable), and a list of potential confounders consisting of child's gender, ethnicity, IQ, adverse life events, parenting practices, and household income, were extracted from the total dataset for analyses.

Ethics

The use of anonymised data for secondary data analysis has been ethically approved by the Institutional Review Board (IRB) at the University of California, San Diego (UCSD). Additionally, informed consent has been obtained from participants in the ABCD study. Moreover, data were accessed through the Data Safe Haven (DSH) of the University College London (UCL) – a secure platform for analysing sensitive data, and relevant training on information governance has been attended by the investigators.

Measures

Exposure Variable: Traumatic Brain Injury

Child's TBI was assessed using The Ohio State University Traumatic Brain Injury Screen – Short Modified (OTBI-SM), which is a parent-reported structured interview designed for detecting exposure to TBI (Corrigan & Bonger, 2007). The parent is asked if the child has had any experience of head injuries (yes/no) over a lifetime (e.g., hospitalised following an injury to head or neck; head or neck being hit; nearby when an explosion occurs; etc.). Additionally, the presence of loss of memory and the duration of loss of consciousness are inquired. Based on these responses, summary indices of the severity of TBI and number of TBIs can then be computed (see below). This measurement tool was reported to be reliable and valid in several settings (Bogner & Corrigan, 2009; Bogner et al., 2017; Corrigan & Bonger, 2007).

The following dimensions of the measure were used in the current study, including (i) the dichotomous score of the occurrence of TBI (0 = absence of TBI; 1 = presence of TBI [covering severity from mild to severe TBI]); (ii) the continuous score of the severity of the worst TBI (1 = absence of TBI [i.e., no TBIs or TBI without loss of consciousness or memory loss]; 2 = possible mild TBI [i.e., TBI without loss of consciousness but with memory loss]; 3 = mild TBI [i.e., TBI with loss of consciousness less than 30 minutes]; 4 =

moderate TBI [i.e., TBI with loss of consciousness more than 30 minutes but less than 24 hours]; and 5 = severe TBI [i.e., TBI with loss of consciousness more than 24 hours]); and (iii) the continuous score of the count of the total number of TBIs experienced in a lifetime.

Outcome Variable: Psychotic-Like Experiences

Child's PLEs were assessed by the Prodromal Psychosis Questionnaire – Brief Child Version (PQ-BC), which is a self-reported 21-item measure assessing the presence of PLEs in children (Loewy et al., 2011). The child is asked if they have had any experience of positive symptoms, covering mild delusional thoughts and disturbances of the visual or auditory perceptions, in the past month (yes/no), such as hearing strange sounds; possessing unusual powers. Then, a total score of the sum of the endorsed items is calculated (range 0–21). The questionnaire has been validated using data from the ABCD study, showing good reliability and construct validity (Karcher et al., 2018).

The dichotomous outcome of the occurrence of PLEs was used in the present study, with the total score transformed into the categories of absence (0 = no PLEs) and presence (1 = at least one PLE) of the experiences, at baseline and 3-year follow-up.

Potential Confounders

The present study included child's gender, child's ethnicity, child's IQ, child's adverse life events, parenting practices, and household income as potential confounding variables, which were reported in the literature to relate independently to the exposure and outcome variables of interest.

Child's Gender. Child's gender (female/male) was reported in the demographic survey of the ABCD study. In the literature, there is evidence of significant gender differences in the incidence rates of TBI (e.g., boys are more likely than girls to sustain a TBI) and the response to TBI among children (Arambula et al., 2019). Additionally, gender was found to be a pre-injury risk factor significantly associated with TBI in another study

(McKinlay et al., 2010). Regarding PLEs and gender, there is evidence indicating the effects of gender on PLEs in the community, demonstrating that females are more likely than males to be associated with PLEs (Schultze-Lutter et al., 2020).

Child's Ethnicity. Ethnicity (white/black/Hispanic/Asian/other) was reported in the demographic questionnaire of the ABCD dataset. The current study recoded this variable into white/non-white for regression analyses. In the literature, a higher rate of sustaining TBI was demonstrated among ethnically minoritised populations (Brenner et al., 2020). Similarly, there is consistent evidence of higher incidence rates of PLEs among minoritised ethnic groups across several countries (Morgan et al., 2010).

Child's IQ. Child's IQ was assessed using the matrix reasoning subscale score of WISC-V, with higher values representing higher IQ (range 1–19). In previous studies, reduced cognitive function was found to be associated with an increased risk of TBI later in life (Nordström & Nordström, 2011; Nordström et al., 2013). Additionally, there is evidence suggesting more pre-morbid cognitive deficits and impairment in the general population who experience PLEs (Sheffield et al., 2018).

Child's Adverse Life Events. Adverse life events were indexed by 17 items searching for the occurrence of a list of traumatic events, such as serious car accidents, significant accidents requiring intensive medical treatment, community violence, sexual abuse, physical abuse, child maltreatment, etc., that happened in a child's lifetime (yes/no), as reported by parents in the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS; Townsend et al., 2020). The current study recoded the events into a dichotomous variable (0 = absence of adverse life events; 1 = presence of adverse life events) for regression analyses. In the literature, there is evidence that adverse life events are a pre-injury risk factor associated with TBI (McKinlay et al., 2010). In

addition, an increased risk of psychosis, including PLEs following childhood adversity, was found in a meta-analysis (Varese et al., 2012).

Parenting. Parenting practices were assessed using the acceptance subscale of the Children's Report of Parental Behavioural Inventory (CRPBI; Schaefer, 1965), with items related to aspects such as effective communication and display of affection. Higher values indicated higher levels of acceptance communicated in parenting (range 5–15). In the literature, a punitive parenting style was found to be a pre-injury risk factor predicting TBI (McKinlay et al., 2010). Additionally, a population-based study reported a mediating effect of parental supervision and parental support on PLEs in adolescents (McMahon et al., 2021).

Household Income. Household income was assessed in the parent demographic survey of the ABCD study. The present study recoded this variable into three levels of annual household income in USD (less than 50K/between 50K and 100K/more than 100K). Regarding TBI and household income, a population-based case-control study of 8,291 paediatric patients provided evidence that children with a socioeconomically deprived background demonstrated an increased risk of TBI (Liao et al., 2012). Another large-scale epidemiological study by Yates et al. (2006) identified the role of socioeconomic factors contributing to the variation in attending an emergency department for head injury. Concerning PLEs outcome, a large cohort study found that socioeconomic factors such as financial distress and food security made significant contributions to more PLEs in Black adolescents (Oh et al., 2022).

Analysis

All analyses in the present study were carried out using R (version 4.1.2), and the analysis code adopted can be found here: (public link to be added after the upcoming release of the latest ABCD dataset). First, comparisons of demographic characteristics between the exposure and control groups were made using chi-square tests of independence (for

categorical data including child's gender, child's ethnicity, presence of child's adverse life events, and levels of household income) and independent sample *t* tests (for continuous data including child's IQ and levels of acceptance in parenting practices). Subsequently, a series of logistic regression analyses were employed to examine the six research questions (RQ1– RQ6). Each regression model was first tested by computing the exposure (i.e., child's TBI) and outcome (i.e., child's PLEs) variables, then the same model was run again by adjusting for potential confounders listed above (i.e., child's gender, child's ethnicity, child's IQ, child's adverse life events, levels of acceptance in parenting practices, and household income) to test whether any associations found remained significant.

Additionally, due to potential risks of non-independence of observations (e.g., geographically clustered participants being more similar than those from different study sites) and selection bias (e.g., the process of obtaining parental consent might selectively influence final features of the sample), Heeringa and Berglund (2020) recommended using multi-level regression modelling with clustering specifications for study sites and family units. Consequently, for the current study, multi-level regression analyses, with specifications to include random effects for study sites and family units, were conducted to examine RQ1– RQ6 as follows.

RQ1. Is the presence of traumatic brain injury (TBI) in children associated with the presence of their PLEs within the same baseline timepoint?

A multi-level logistic regression was conducted to test cross-sectionally if the presence of TBI in children (dichotomous data) was associated with the likelihood of the presence of their PLEs at baseline (dichotomous data).

RQ2. Is the severity of TBI in children associated with the presence of their PLEs at baseline?

A multi-level logistic regression was performed to test cross-sectionally if a higher level of severity of TBI in children (continuous data) was associated with increased likelihood of the presence of their PLEs at baseline (dichotomous data).

RQ3. Is the number of TBIs in children associated with the presence of their PLEs at baseline?

A multi-level logistic regression was used to test cross-sectionally if a greater number of TBIs occurred in children (continuous data) was associated with increased likelihood of the presence of their PLEs at baseline (dichotomous data).

RQ4. Does the presence of TBI in children predict the occurrence of their PLEs at 36 months?

A multi-level logistic regression was conducted to test longitudinally if the presence of TBI in children at baseline (dichotomous data) predicted the occurrence of their PLEs at the 3-year follow-up (dichotomous data).

RQ5. Does the severity of TBI in children predict the occurrence of their PLEs at 36 months?

A multi-level logistic regression was performed to test longitudinally if a higher level of severity of TBI in children at baseline (continuous data) predicted the occurrence of their PLEs at the 3-year follow-up (dichotomous data).

RQ6. Does the number of TBIs in children predict the occurrence of their PLEs at 36 months?

A multi-level logistic regression was used to test longitudinally if a greater number of TBIs in children at baseline (continuous data) predicted the occurrence of their PLEs at the 3-year follow-up (dichotomous data).

Statistical Power and Sensitivity

No additional data were collected for the existing dataset of the Adolescent Brain

Cognitive Development (ABCD) study, which consisted of data from 11,875 participants.

Given the sample size, we carried out a sensitivity analysis using G*Power (3.1) to determine

the minimum effect size detectable. Taking an alpha value of 0.05 and a required power of

0.9, we found that a logistic regression could detect effect sizes of odds ratios (*ORs*) greater

than or equal to 1.16. Chen et al. (2010) proposed classification criteria where *ORs* greater

than 1.68 are considered in the small range, indicating that the power of the current study

would be sufficient to detect effects of very small magnitudes or above.

Results

Descriptive Statistics

Descriptive statistics for the demographic and key study variables are displayed in

Table 5. Almost all of the demographic characteristics remained consistent between child

participants with and those without exposure to traumatic brain injury (TBI; i.e., TBI

exposure group versus non-TBI control group). Results of the independent sample *t* tests

showed that there were no significant differences between the TBI and non-TBI groups in (i)

scaled IQ (a mean score of 9.6 in the TBI group versus a mean score of 9.9 in the non-TBI

group), $t(134) = 0.877$, $p = 0.382$; and (ii) levels of acceptance in parenting practices (a mean

score of 14.1 in the TBI group versus a mean score of 13.9 in the non-TBI group), $t(137.75)$

$= -1.55$, $p = 0.123$. Results of the chi-square tests of independence showed that there were no

significant differences between the exposure and control groups in the proportions of (iii)

gender (40.7% female in the TBI group versus 47.9% female in the non-TBI group), χ^2 (1, *N*

$= 11,875) = 2.75$, $p = 0.097$; (iv) ethnicity (42.2% non-white participants in the TBI group

versus 48.0% non-white participants in the non-TBI group), χ^2 (1, $N = 11,873) = 1.79$, $p =$

0.180; and (v) levels of household income (23.7% below 50K USD in the TBI group versus

27.2% below 50K USD in the non-TBI group), χ^2 (2, N = 10,857) = 2.53, p = 0.283. The only

significant difference between the two groups was the proportion of (vi) the presence of

adverse life events (52.6% with adverse life events in the TBI group versus 34.8% with

adverse life events in the non-TBI group), χ^2 (1, N = 11,589) = 18.73, p < 0.001. However,

this should be expected since the presence of paediatric TBI naturally falls under some of the

adverse life events experienced, such as significant accidents requiring intensive medical

treatment.

Table 5. Descriptive statistics

Demographic variable	Absence of TBI (*n* = 11,736)	Presence of TBI (*n* = 135)	Total (*n* = 11,875)
Age – *M* (*SD*)	9.92 (0.62)	9.92 (0.67)	9.92 (0.63)
Gender			
Female – *n* (%)	5,623 (47.9%)	55 (40.7%)	5,680 (47.8%)
Male – *n* (%)	6,113 (52.1%)	80 (59.3%)	6,195 (52.2%)
Ethnicity			
White – *n* (%)	6,100 (52.0%)	78 (57.8%)	6,179 (52.0%)
Black – *n* (%)	1,772 (15.1%)	10 (7.4%)	1,784 (15.0%)
Hispanic – *n* (%)	2,380 (20.3%)	30 (22.2%)	2,411 (20.3%)
Asian – *n* (%)	252 (2.1%)	0 (0%)	252 (2.1%)
Other – *n* (%)	1,230 (10.5%)	17 (12.6%)	1,247 (10.5%)
Scaled IQ – *M* (*SD*)	9.9 (3.0)	9.6 (3.0)	9.9 (3.0)
Adverse life events			
Absence – *n* (%)	7,374 (62.8%)	61 (45.2%)	7,437 (62.6%)
Presence – *n* (%)	4,080 (34.8%)	71 (52.6%)	4,152 (35.0%)
Parenting – *M* (*SD*)	13.9 (1.5)	14.1 (1.4)	13.9 (1.5)
Household income in USD			
< 50K – *n* (%)	3,191 (27.2%)	32 (23.7%)	3,223 (27.1%)
≥ 50K & < 100K – *n* (%)	3,038 (25.9%)	33 (24.4%)	3,071 (25.9%)
≥ 100K – *n* (%)	4,500 (38.3%)	62 (45.9%)	4,563 (38.4%)
Key study variable	**Absence of TBI (*n* = 11,736)**	**Presence of TBI (*n* = 135)**	**Total (*n* = 11,875)**
OTBI-SM at T0			
Severity – *M* (*SD*)	1.0 (0.2)	3.1 (0.3)	1.1 (0.3)
No. of TBIs – *M* (*SD*)	0 (0)	1.4 (0.6)	0.1 (0.3)
PLEs at T0			
Absence – *n* (%)	4,450 (38.7%)	44 (32.6%)	4,584 (38.6%)
Presence – *n* (%)	7,184 (61.2%)	91 (67.4%)	7,279 (61.3%)
PLEs at T3			
Absence – *n* (%)	3,954 (33.7%)	33 (24.4%)	3,987 (33.6%)
Presence – *n* (%)	2,214 (18.9%)	35 (25.9%)	2,249 (18.9%)

Note. OTBI-SM = The Ohio State University Traumatic Brain Injury Screen – Short Modified; PLEs = psychotic-like experiences; PQ-BC = Prodromal Questionnaire – Brief Child Version; TBIs = traumatic brain injuries; T0 = baseline; T3 = 3-year follow-up

Results of Regression Analyses in Relation to the Research Questions

RQ1. Is the presence of traumatic brain injury (TBI) in children associated with the presence of their psychotic-like experiences (PLEs) within the same baseline timepoint?

The presence of TBI in children was not associated with the presence of their PLEs at baseline in the unadjusted model ($OR = 1.35$, 95% CI [0.92, 1.99], $p = 0.124$); therefore, the adjusted analysis was not performed.

RQ2. Is the severity of TBI in children associated with the presence of their PLEs at baseline?

A higher severity of TBI in children was significantly associated with increased likelihood of the presence of their PLEs at baseline ($OR = 1.18$, 95% CI [1.02, 1.37], $p = 0.028$). After adjusting for potential confounders including child's gender, child's ethnicity, child's IQ, child's adverse life events, levels of acceptance in parenting practices, and household income, the association remained significant ($OR = 1.18$, 95% CI [1.01, 1.38], $p = 0.040$). The results of the multi-level logistic regression analyses in relation to this research question are presented in Table 6.

RQ3. Is the number of TBIs in children associated with the presence of their PLEs at baseline?

An increased number of TBIs in children was associated with higher odds of the presence of their PLEs at baseline in the unadjusted model ($OR = 1.34$, 95% CI [1.01, 1.76], $p = 0.039$), but the relationship was not significant after controlling for the confounding variables including child's gender, child's ethnicity, child's IQ, child's adverse life events, levels of acceptance in parenting practices, and household income ($OR = 1.28$, 95% CI [0.96, 1.71], $p = 0.097$). The results of the logistic regression analyses relating to this research question can be found in Table 7.

RQ4. Does the presence of TBI in children predict the occurrence of their PLEs at 36 months?

The presence of TBI in children at baseline was found to predict the occurrence of their PLEs 3 years later (OR = 1.95, 95% CI [1.17, 3.24], p = 0.010), and the association became even stronger after adjusting for potential confounders including child's gender, child's ethnicity, child's IQ, child's adverse life events, levels of acceptance in parenting practices, and household income (OR = 2.15, 95% CI [1.26, 3.65], p = 0.005), with the odds of having later PLEs raised by 115% for the presence of TBI at baseline. The results of the logistic regression analyses associated with this research question are reported in Table 8.

Table 6. Multi-level logistic regression analyses of the association between severity of TBI and PLEs at baseline

Model (outcome)	Parameter	*OR*	95% CI	*p* value	AIC
Model 2a (PQ-BC cut-off at T0)	OTBI-SM severity at T0	1.18	1.02, 1.37	0.028	15283
Model 2b (PQ-BC cut-off at T0)	OTBI-SM severity at T0	1.18	1.01, 1.38	0.040	13059
	Gender [Male]	1.13	1.03, 1.23	0.007	
	Ethnicity [Non-white]	1.30	1.17, 1.44	<0.001	
	IQ	0.96	0.95, 0.98	<0.001	
	Adverse life events [Presence]	1.16	1.06, 1.28	0.001	
	Parenting	0.84	0.82, 0.87	<0.001	
	Household income [≥50K & <100K]	0.82	0.73, 0.93	0.002	
	Household income [≥100K]	0.59	0.52, 0.67	<0.001	

Note. AIC = Akaike information criterion; CI = confidence interval; OTBI-SM = The Ohio State University Traumatic Brain Injury Screen – Short Modified; PQ-BC = Prodromal Questionnaire – Brief Child Version; T0 = baseline

Table 7. Multi-level logistic regression analyses of the association between number of TBIs and PLEs at baseline

Model (outcome)	Parameter	*OR*	95% CI	*p* value	AIC
Model 3a (PQ-BC cut-off at T0)	OTBI-SM number of TBIs at T0	1.34	1.01, 1.76	0.039	3293
Model 3b (PQ-BC cut-off at T0)	OTBI-SM number of TBIs at T0	1.28	0.96, 1.71	0.097	2869
	Gender [Male]	1.07	0.88, 1.28	0.505	
	Ethnicity [Non-white]	1.35	1.09, 1.68	0.007	
	IQ	0.96	0.93, 0.99	0.027	
	Adverse life events [Presence]	1.20	1.00, 1.45	0.051	
	Parenting	0.80	0.75, 0.86	<0.001	
	Household income [≥50K & <100K]	0.83	0.64, 1.09	0.177	
	Household income [≥100K]	0.58	0.45, 0.76	<0.001	

Note. AIC = Akaike information criterion; CI = confidence interval; OTBI-SM = The Ohio State University Traumatic Brain Injury Screen – Short Modified; PQ-BC = Prodromal Questionnaire – Brief Child Version; TBIs = traumatic brain injuries; T0 = baseline

Table 8. Multi-level logistic regression analyses of whether presence of TBI predicts PLEs at 3-year follow-up

Model (outcome)	Parameter	*OR*	95% CI	*p* value	AIC
Model 4a (PQ-BC cut-off at T3)	OTBI-SM cut-off at T0	1.95	1.17, 3.24	0.010	8038
Model 4b (PQ-BC cut-off at T3)	OTBI-SM cut-off at T0	2.15	1.26, 3.65	0.005	6957
	Gender [Male]	0.90	0.80, 1.01	0.066	
	Ethnicity [Non-white]	1.41	1.23, 1.62	<0.001	
	IQ	0.98	0.96, 1.00	0.076	
	Adverse life events [Presence]	1.11	0.98, 1.25	0.100	
	Parenting	0.89	0.86, 0.93	<0.001	
	Household income [≥50K & <100K]	0.79	0.67, 0.94	0.006	
	Household income [≥100K]	0.62	0.53, 0.74	<0.001	

Note. AIC = Akaike information criterion; CI = confidence interval; OTBI-SM = The Ohio State University Traumatic Brain Injury Screen – Short Modified; PQ-BC = Prodromal Questionnaire – Brief Child Version; T0 = baseline; T3 = 3-year follow-up

RQ5. Does the severity of TBI in children predict the occurrence of their PLEs at 36 months?

The severity of TBI in children at baseline was not a significant predictor of the occurrence of their PLEs at the later 3-year timepoint ($OR = 1.13$, 95% CI [0.92, 1.37], $p = 0.244$); therefore, potential confounders were not added in a subsequent analysis.

RQ6. Does the number of TBIs in children predict the occurrence of their PLEs at 36 months?

Similarly, the number of TBIs in children at baseline was not found to predict the occurrence of their PLEs at 36 months ($OR = 1.42$, 95% CI [1.00, 2.03], $p = 0.051$), and hence no adjusted analysis was carried out.

Discussion

Overall, the present study aimed to investigate the association between TBI and PLEs among children aged 9–10 years old. Specifically, it was found that the presence of paediatric TBI at baseline was a significant predictor of the occurrence of PLEs at 36 months, with the relationship remaining robust after controlling for potential confounders including child's gender, child's ethnicity, child's IQ, child's adverse life events (e.g., child maltreatment and abuse), levels of acceptance in parenting practices, and household income (RQ4). However, no significant association was found between the presence of TBI and the presence of PLEs at baseline (RQ1). Additionally, among all other adjusted regression models, no significant relationships were observed between the number of TBIs and the presence of PLEs at both baseline (RQ3) and 36 months (RQ6), whilst the severity of TBI was only found to be significantly associated with the presence of PLEs at baseline (RQ2), but not at 36 months (RQ5). Based on these statistical analyses, the results from RQ1 and RQ4 (i) seem to indicate a delayed occurrence of PLEs following paediatric TBI, similar to findings from previous studies on psychotic disorders/symptoms as outcomes (Bray et al., 2021; Fujii & Ahmed,

2001, 2002a; Sachdev et al., 2001); but (ii) do not suggest the persistence of post-TBI PLEs in children over time. Moreover, the results regarding the remaining research questions (i.e., RQ3, RQ5, and RQ6, with the exception of RQ2) generally (iii) do not support a dose–response relationship between severity/number of TBI(s) and PLEs among children, which is consistent with a similar finding of a lack of dose–response relationship from a meta-analysis (Molloy et al., 2011). Furthermore, according to the classification criteria (i.e., odds ratio [OR] = 1.68 [small]; 3.47 [medium]; 6.71 [large]) proposed by Chen et al. (2010), the only significant relationships observed in the present study (i.e., RQ2 and RQ4) had the adjusted ORs of 1.18 (i.e., a very small magnitude) and 2.15 (i.e., a small magnitude) respectively, indicating the observation of (iv) weak relationships between the exposure and outcome variables.

Possible Explanations of the Observations

To explain the observations of a delayed occurrence of PLEs following TBI, an absence of persistence of PLEs, an absence of a dose–response relationship, and weak associations between TBI and PLEs in children, we adopt the conceptual framework proposed by Fujii and Ahmed (2002b, 2014), which suggests the following potential relationships between TBI and PLEs: (i) TBI might directly cause the occurrence of PLEs; (ii) TBI might indirectly contribute to the development of PLEs; or (iii) TBI might not be related to the occurrence of PLEs.

Does TBI in Children Directly Cause the Occurrence of Their PLEs?

First of all, data from the present study does not seem to support a direct causal relationship between the exposure to TBI and subsequent PLEs in a cohort of 9- to 10-year-old children. Hill (2015) proposed nine criteria (also widely known as Bradford Hill's criteria for causation), including strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy, to infer potential causal relationships

between exposure and outcome variables from observational data within epidemiological studies. Although the current research was not designed to address every single criterion mentioned, our findings of weak associations between paediatric TBI and PLEs (e.g., RQ2 and RQ4; as related to the criterion of strength) and a lack of a dose–response relationship (e.g., number of TBIs occurred in children as addressed in RQ3 and RQ6; severity of TBI in children as addressed in RQ5; as related to the criterion of biological gradient) seem to indicate high likelihood of failing to fulfil all nine Bradford Hill's criteria for causal inference.

Does TBI in Children Indirectly Contribute to the Development of Their PLEs?

The indirect contribution of TBI to the development of psychosis appears to be one of the plausible explanations for our findings. Fujii and Ahmed (2002b, 2014) have proposed the conceptualisation of psychosis as a neuro–behavioural disorder, meaning that damage to parts of the psychosis-associated neurocircuit in the brain, to a degree exceeding the onset threshold for psychosis, would produce similar syndromes (e.g., PLEs such as mild hallucinations and delusions), regardless of the origins of the damage (e.g., seizure disorder, substance abuse, etc.). It has been suggested that TBI increases the level of biological (e.g., damage to the frontal or temporal structures; damage to the regulation of neurotransmitters such as dopamine and glutamate) and psychological (e.g., reduced problem-solving ability) vulnerability to stress (Fujii & Ahmed, 2002b, 2014). Indeed, there is evidence supporting the association between loss of the right hippocampal volume and an increase in PLEs after TBI over time, suggesting that TBI might be a neurodegenerative condition (Bray et al., 2021).

When individuals experience further stressful events after exposure to TBI, the onset threshold for PLEs could then be surpassed; and it has been argued that these multiple processes of physiological and psychological interactions might explain a delayed occurrence of psychosis after exposure to TBI (Fujii & Ahmed, 2002b, 2014). Referring back to the main

findings of our study, the above vulnerability and neurodegenerative models seem to be able, to a certain extent, to explain why a significant relationship between TBI and PLEs could not be observed at baseline (i.e., findings from RQ1), since the exposure to TBI might only make the children more vulnerable physiologically and psychologically, without exceeding the onset threshold for PLEs. However, throughout the temporal passage of a prolonged period of time (e.g., a duration of 3 years in the current longitudinal study), exposures to further stressful events in childhood might finally surpass the threshold for onset of PLEs (i.e., findings from RQ4). It should be noted that Lopez et al. (2022) also utilised the ABCD dataset, but only with data from the baseline to the 2-year follow-up. Their team did not find a significant relationship between mild paediatric TBI and PLEs. This could suggest that the most optimal timeframe to detect post-TBI PLEs may be at 3 years, especially when considering the findings of the current study (e.g., results from RQ4). Furthermore, the absence of a dose-response relationship could potentially be explained by the characteristics of the injury and the specific regions of the brain that were affected. This potentially plausible interpretation might also explain why only weak associations between TBI and PLEs in children were observed in our study (e.g., results from RQ2 and RQ4), since there might be several other variables and pathways contributing to the final occurrence of PLEs throughout time, after sustaining a paediatric TBI. However, clinicians are advised to be mindful whilst offering this plausible explanation (i.e., the indirect contribution of TBI to PLEs) to patients, considering the potential risks of psychological burdening.

Is TBI in Children Unrelated to the Occurrence of Their PLEs?

Another explanation for the observations made in the present study could simply be artifacts, meaning that the inferences made from the collected data result from errors (e.g., imperfect construct validity, dichotomisation of measures, measurement error), rather than the underlying reality (Schmidt, 2010). In other words, it is possible that TBI is indeed

unrelated to the occurrence of PLEs in children at all (i.e., rejecting the above explanation of indirect contribution of paediatric TBI to PLEs), whilst the significant but weak relationships observed (i.e., findings in relation to RQ2 and RQ4) are simply due to the distorting effects of artifacts (Schmidt, 2010). For example, whilst we adopted a validated tool: The Prodromal Psychosis Questionnaire – Brief Child Version (PQ-BC) in the measurement of PLEs (Karcher et al., 2018), we cannot exclude the possibility of child participants erroneously endorsing the items of PLEs, which might lead to the presence of false positives (Karcher et al., 2020). Extra caution should be exercised when interpreting the positive association found between paediatric TBI at baseline and the occurrence of PLEs at 36 months (i.e., findings from RQ4). This caution is especially warranted given the prevalence of PLEs during childhood, which is estimated to range from 13% to as high as 68% (Karcher et al., 2018). Regarding our exposure group, it could be argued that the endorsement of the PLEs items in the PQ-BC may be further inflated due to potential cognitive impairments (e.g., diminished insight and self-awareness) caused by TBI. As a result, our confidence in the relationship between TBI and PLEs could potentially be compromised by the false discovery rate of the PQ-BC measure, especially in the context of paediatric TBI. Furthermore, one should be mindful of potential overlaps between PLEs and other common post-TBI sequelae. This again underscores the importance of the validity and precision of measurement. In addition, dichotomisation of measures (e.g., the employment of dichotomous outcome of the occurrence of PLEs in the present study) can create loss of information and increased variability in findings (Schmidt, 2010).

Additionally, the practice of statistically controlling for mediators (i.e., a third variable explaining the relationship between the exposure and outcome) and colliders (i.e., a third variable causally influenced by the exposure and outcome) can harmfully induce spurious associations (Rohrer, 2018). On one hand, concerning potential mediators, the

present study has deliberately avoided controlling for the variable of child's epilepsy, since there is evidence of head injury potentially causing epilepsy (Fleminger, 2008), which has been found to be associated with an increased risk of developing psychosis (Qin et al., 2005). Indeed, epilepsy and psychosis might share the same genetic or environmental causes (Qin et al., 2005), possibly suggesting a mediating role of epilepsy in the relationship between TBI and PLEs. On the other hand, when considering potential colliders in the present research, although we have controlled for potential confounders including child's gender, child's ethnicity, child's IQ, child's adverse life events, levels of acceptance in parenting practices, and household income based on the existing literature, we cannot entirely rule out the possibility of some of the confounders being a collider at the same time (e.g., the variable of child's adverse life events). Lastly, the measurement error in the confounding variables included in the present study has not been fully addressed (e.g., by taking the reliability values of the measures into account whilst performing statistical analyses), which might again increase the rate of false positives (Rohrer, 2018).

Strengths and Limitations

On one hand, the current study has several strengths, including a large sample of child participants, producing sufficient power to detect effects of very small sizes or above. Additionally, the matching of the sociodemographic characteristics of the sample from the ABCD study with the national population allows a higher confidence in generalising the findings. Another strength is the longitudinal design, which allows the measurement of PLEs over time (i.e., at baseline and after 36 months). Furthermore, the adoption of multi-level regression analyses with the specification of including random effects for study sites and family units addresses the potential risks of non-independence of observations (e.g., participants' similarities arising from the same study site or family unit) and selection bias (e.g., process of seeking parental consent influencing sample characteristics). Lastly, a range

of variables across the individual (e.g., child's gender), parental (e.g., levels of acceptance in parenting practices), and environmental (e.g., household income) domains has been considered and included to account for the effects of confounders on the variable of interest, i.e., PLEs in children.

On the other hand, apart from the artifacts mentioned above (i.e., imperfect construct validity, dichotomisation of measures, lack of identification of potential colliders, and measurement error), this study also has the limitation of its observational nature, which limits the causal inference we can develop. It is well-known that making causal inference based on observational data is challenging, requiring at least consideration of all the potential confounding variables (or "back-door paths") in order to estimate the real causal effect, if applicable (Rohrer, 2018). However, we cannot rule out that some other confounders were left out (i.e., not entirely blocking all the "back-door paths"), based on our ongoing understanding of the relationships between the variables of child's TBI and child's PLEs in the field. In addition, we included data for TBI and confounders only at baseline, but not at the 3-year follow-up. This limits the robustness of our approach in accounting for potential confounders. Moreover, our choice of measures is limited by the original design of the ABCD study. For example, child's TBI was reported by parents retrospectively using The Ohio State University Traumatic Brain Injury Screen – Short Modified (OTBI-SM), without further verification by additional sources such as hospital records, potentially inducing recall bias. Additionally, the cause of injury (e.g., assault, road traffic accident, sports concussion) was not considered in this study. However, these causes can have varying influences on a child's psychological wellbeing, highlighting potential moderating effects on the relationship of interest. Nonetheless, even if we have considered all the "back-door paths" and chosen the most appropriate measures, there is still the limitation and challenge of determining the direction of the relationship between TBI and PLEs (i.e., ruling out reverse causality). For

example, a possibility of reverse causality has been proposed, hypothesising that brain injuries could be more common in children who have a higher risk for psychosis, as they may already show subtle premorbid difficulties such as motor coordination leading to a higher risk for accidental injuries (AbdelMalik et al., 2003; David & Prince, 2005; Deighton et al., 2016). Since the ABCD longitudinal study is still ongoing, future research employing the corresponding dataset should consider the timing of occurrence of the first TBI; timing of occurrence of the first PLE; location and type of injury; and information about other non-TBI-related accidents experienced (i.e., to rule out the above-mentioned reverse causality of psychosis increasing proneness to accidents), in a prospective manner.

Conclusions

In conclusion, the present study provides evidence indicating (i) a delayed occurrence of PLEs following TBI among children aged 9 to 10 years old; (ii) weak associations between TBI and PLEs; however, (iii) a persistence of post-TBI PLEs and (iv) a dose–response relationship could not be observed. Future research should address the potential bias arisen from measures (e.g., imperfect construct validity, dichotomisation, measurement error, recall bias) and study design (e.g., failure to include all potential confounders; failure to exclude all potential colliders), and most importantly, overcome the challenge of reverse causality.

References

AbdelMalik, P., Husted, J., Chow, E. W. C., & Bassett, A. S. (2003). Childhood head injury and expression of schizophrenia in multiply affected families. *Archives of General Psychiatry*, *60*(3), 231–236. https://dx.doi.org/10.1001/archpsyc.60.3.231

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). https://doi.org/10.1176/appi.books.9780890425596

Arambula, S., Reinl, E., El Demerdash, N., McCarthy, M., & Robertson, C. (2019). Sex differences in pediatric traumatic brain injury. *Experimental Neurology*, *317*, 168–179. https://doi.org/10.1016/j.expneurol.2019.02.016

Arif, H., Troyer, E. A., Paulsen, J. S., Vaida, F., Wilde, E. A., Bigler, E. D., Hesselink, J. R., Yang, T. T., Tymofiyeva, O., Wade, O., & Max, J. E. (2021). Long-term psychiatric outcomes in adults with history of pediatric traumatic brain injury. *Journal of Neurotrauma*, *38*(11), 1515–1525. https://doi.org/10.1089/neu.2020.7238

Batty, R. A., Rossell, S. L., Francis, A. J. P., & Ponsford, J. (2013). Psychosis following traumatic brain injury. *Brain Impairment*, *14*(1), 21–41. https://doi.org/10.1017/BrImp.2013.10

Bogner, J., & Corrigan, J. D. (2009). Reliability and predictive validity of the Ohio State University TBI Identification Method with prisoners. *The Journal of Head Trauma Rehabilitation*, *24*(4), 279–291. https://doi.org/10.1097/HTR.0b013e3181a66356

Bogner, J. A., Whiteneck, G. G., MacDonald, J., Juengst, S. B., Brown, A. W., Philippus, A. M., Marwitz, J. H., Lengenfelder, J., Mellick, D., Arenth, P., & Corrigan, J. D. (2017). Test-retest reliability of traumatic brain injury outcome measures: A traumatic brain injury model systems study. *The Journal of Head Trauma Rehabilitation*, *32*(5), E1–E16. https://doi.org/10.1097/HTR.0000000000000291

Bray, M. J. C., Sharma, B., Cottrelle, J., Peters, M. E., Bayley, M., & Green, R. E. A. (2021). Hippocampal atrophy is associated with psychotic symptom severity following traumatic brain injury. *Brain Communications*, *3*(2), 1–15. https://doi.org/10.1093/braincomms/fcab026

Brenner, E. K., Grossner, E. C., Johnson, B. N., Bernier, R. A., Soto, J., & Hillary, F. G. (2020). Race and ethnicity considerations in traumatic brain injury research: Incidence, reporting, and outcome. *Brain Injury*, *34*(6), 799–808. https://doi.org/10.1080/02699052.2020.1741033

Carroll, L. J., Cassidy, J. D., Cancelliere, C., Côté, P., Hincapié, C. A., Kristman, V. L., Holm, L. W., Borg, J., Nygren-de Boussard, C., & Hartvigsen, J. (2014). Systematic review of the prognosis after mild traumatic brain injury in adults: Cognitive, psychiatric, and mortality outcomes: Results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation*, *95*(3), S152–S173. https://doi.org/10.1016/j.apmr.2013.08.300

Chen, H., Cohen, P., & Chen, S. (2010). How big is a big odds ratio? Interpreting the magnitudes of odds ratios in epidemiological studies. *Communications in Statistics—Simulation and Computation*®, *39*(4), 860–864. https://doi.org/10.1080/03610911003650383

Cnossen, M. C., Scholten, A. C., Lingsma, H. F., Synnot, A., Haagsma, J., Steyerberg, P., & Polinder, S. (2017). Predictors of major depression and posttraumatic stress disorder following traumatic brain injury: A systematic review and meta-analysis. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *29*(3), 206–224. https://doi.org/10.1176/appi.neuropsych.16090165

Corrigan, J., & Bogner, J. (2007). Initial reliability and validity of the Ohio State University

 TBI Identification Method. *The Journal of Head Trauma Rehabilitation*, *22*(6), 318–

 329. https://doi.org/10.1097/01.HTR.0000300227.67748.77

David, A. S., & Prince, M. (2005). Psychosis following head injury: A critical review.

 Journal of Neurology, Neurosurgery & Psychiatry, *76*(suppl 1), i53–i60.

 https://doi.org/10.1136/jnnp.2004.060475

Deighton, S., Buchy, L., Cadenhead, K. S., Cannon, T. D., Cornblatt, B. A., McGlashan, T.

 H., Perkins, D. O., Seidman, L. J., Tsuang, M. T., Walker, E. F., Woods, S. W.,

 Bearden, C. E., Mathalon, D., & Addington, J. (2016). Traumatic brain injury in

 individuals at clinical high risk for psychosis. *Schizophrenia Research*, *174*(1–3), 77–

 81. https://dx.doi.org/10.1016/j.schres.2016.04.041

Dominguez, M. D. G., Wichers, M., Lieb, R., Wittchen, H. -U., & van Os, J. (2011).

 Evidence that onset of clinical psychosis is an outcome of progressively more

 persistent subclinical psychotic experiences: An 8-year cohort study. *Schizophrenia

 Bulletin*, *37*(1), 84–93. https://doi.org/10.1093/schbul/sbp022

Emery, C., Barlow, K., Brooks, B., Max, J., Villavicencio-Requis, A., Gnanakumar, V., . . .

 Yeates, K. (2016). A systematic review of psychiatric, psychological, and behavioural

 outcomes following mild traumatic brain injury in children and adolescents. *Canadian

 Journal of Psychiatry*, *61*(5), 259–269. https://doi.org/10.1177/0706743716643741

Fleminger, S. (2008). Long-term psychiatric disorders after traumatic brain injury. *European

 Journal of Anaesthesiology*, *25*(S42), 123–130.

 https://doi.org/10.1017/S0265021507003250

Froudist-Walsh, S., Bloomfield, M. A. P., Veronese, M., Kroll, J., Karolis, V., Jauhar, S.,

 Bonoldi, I., McGuire, P., Kapur, S., Murray, R., Nosarti, C., & Howes, O. (2017). The

effect of perinatal brain injury on dopaminergic function and hippocampal volume in adult life. *eLife*, *6*, e29088. https://doi.org/10.7554/eLife.29088

Fujii, D., & Ahmed, I. (2001). Risk factors in psychosis secondary to traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *13*(1), 61–69. https://doi.org/10.1176/jnp.13.1.61

Fujii, D., & Ahmed, I. (2002a). Characteristics of psychotic disorder due to traumatic brain injury: An analysis of case studies in the literature. *The Journal of Neuropsychiatry and Clinical Neurosciences*, *14*(2), 130–140. https://doi.org/10.1176/jnp.14.2.130

Fujii, D., & Ahmed, I. (2002b). Psychotic disorder following traumatic brain injury: A conceptual framework. *Cognitive Neuropsychiatry*, *7*(1), 41–62. https://doi.org/10.1080/135468000143000131

Fujii, D. E., & Ahmed, I. (2014). Psychotic disorder caused by traumatic brain injury. *The Psychiatric Clinics of North America*, *37*(1), 113–124. https://doi.org/10.1016/j.psc.2013.11.006

Garavan, H., Bartsch, H., Conway, K., Decastro, A., Goldstein, R., Heeringa, S., Jernigan, T., Potter, A., Thompson, W., & Zahs, D. (2018). Recruiting the ABCD sample: Design considerations and procedures. *Developmental Cognitive Neuroscience*, *32*, 16–22. https://doi.org/10.1016/j.dcn.2018.04.004

Harrison, G., Whitley, E., Rasmussen, F., Lewis, G., Dalman, C., & Gunnell, D. (2006). Risk of schizophrenia and other non-affective psychosis among individuals exposed to head injury: Case control study. *Schizophrenia Research*, *88*(1–3), 119–126. https://dx.doi.org/10.1016/j.schres.2006.07.001

Heeringa, S., & Berglund, P. (2020). *A guide for population-based analysis of the adolescent brain cognitive development (ABCD) study baseline data*. bioRxiv. https://doi.org/10.1101/2020.02.10.942011

Hesdorffer, D. C., Rauch, S. L., & Tamminga, C. A. (2009). Long-term psychiatric outcomes following traumatic brain injury: A review of the literature. *The Journal of Head Trauma Rehabilitation*, *24*(6), 452–459. https://doi.org/10.1097/HTR.0b013e3181c133fd

Hill, A. B. (2015). The environment and disease: Association or causation? (Reprinted from JRSM, vol 58, 1965). *Journal of the Royal Society of Medicine*, *108*(1), 32–37. https://doi.org/10.1177/0141076814562718

Howes, O. D., & Murray, R. M. (2014). Schizophrenia: An integrated sociodevelopmental-cognitive model. *The Lancet*, *383*(9929), 1677–1687. https://doi.org/10.1016/S0140-6736%2813%2962036-X

Karcher, N. R., Barch, D. M., Avenevoli, S., Savill, M., Huber, R. S., Simon, T. J., Leckliter, I. N., Sher, K. J., & Loewy, R. L. (2018). Assessment of the Prodromal Questionnaire-Brief Child Version for measurement of self-reported psychoticlike experiences in childhood. *JAMA Psychiatry*, *75*(8), 853–861. https://doi.org/10.1001/jamapsychiatry.2018.1334

Karcher, N. R., Loewy, R. L., Savill, M., Avenevoli, S., Huber, R. S., Simon, T. J., Leckliter, I. N., Sher, K. J., & Barch, D. M. (2020). Replication of associations With psychotic-like experiences in middle childhood from the Adolescent Brain Cognitive Development (ABCD) Study. *Schizophrenia Bulletin Open*, *1*(1), sgaa009–sgaa009. https://doi.org/10.1093/schizbullopen/sgaa009

Keightley, M. L., Côté, P., Rumney, P., Hung, R., Carroll, L. J., Cancelliere, C., & Cassidy, J. D. (2014). Psychosocial consequences of mild traumatic brain injury in children: Results of a systematic review by the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation*, *95*(3 Suppl 2), S192–S200. https://doi.org/10.1016/j.apmr.2013.12.018

Kim, E., Lauterbach, E. C., Reeve, A., Arciniegas, D. B., Coburn, K. L., Mendez, M. F.,

    Rummans, T. A., Coffey, E. C., & ANPA Committee on Research (2007).

    Neuropsychiatric complications of traumatic brain injury: A critical review of the

    literature (A report by the ANPA Committee on Research). *The Journal of*

    Neuropsychiatry and Clinical Neurosciences, *19*(2), 106–127.

    https://doi.org/10.1176/jnp.2007.19.2.106

Ledoux, A. -A., Webster, R. J., Clarke, A. E., Fell, D. B., Knight, B. D., Gardner, W.,

    Cloutier, P., Gray, C., Tuna, M., & Zemek, R. (2022). Risk of mental health problems

    in children and youths following concussion. *JAMA Network Open*, *5*(3), e221235.

    https://dx.doi.org/10.1001/jamanetworkopen.2022.1235

Liao, C., Chang, H., Yeh, C., Chou, Y., Chiu, W., & Chen, T. (2012). Socioeconomic

    deprivation and associated risk factors of traumatic brain injury in children. *The*

    Journal of Trauma and Acute Care Surgery, *73*(5), 1327–1331.

    https://doi.org/10.1097/TA.0b013e31826fc87f

Linscott, R. J., & van Os, J. (2013). An updated and conservative systematic review and

    meta-analysis of epidemiological evidence on psychotic experiences in children and

    adults: On the pathway from proneness to persistence to dimensional expression

    across mental disorders. *Psychological Medicine*, *43*(6), 1133–1149.

    https://doi.org/10.1017/S0033291712001626

Loewy, R. L., Pearson, R., Vinogradov, S., Bearden, C. E., & Cannon, T. D. (2011).

    Psychosis risk screening with the Prodromal Questionnaire – Brief Version (PQ-B).

    Schizophrenia Research, *129*(1), 42–46. https://doi.org/10.1016/j.schres.2011.03.029

Lopez, D. A., Christensen, Z. P., Foxe, J. J., Ziemer, L. R., Nicklas, P. R., & Freedman, E. G.

    (2022). Association between mild traumatic brain injury, brain structure, and mental

health outcomes in the Adolescent Brain Cognitive Development Study. *NeuroImage*, *263*, 119626. https://doi.org/10.1016/j.neuroimage.2022.119626

Massagli, T. L., Fann, J. R., Burington, B. E., Jaffe, K. M., Katon, W. J., & Thompson, R. S. (2004). Psychiatric illness after mild traumatic brain injury in children. *Archives of Physical Medicine and Rehabilitation*, *85*(9), 1428–1434. https://doi.org/10.1016/j.apmr.2003.12.036

McKinlay, A., Kyonka, E. G., Grace, R. C., Horwood, L. J., Fergusson, D. M., & MacFarlane, M. R. (2010). An investigation of the pre-injury risk factors associated with children who experience traumatic brain injury. *Injury Prevention*, *16*(1), 31–35. https://doi.org/10.1136/ip.2009.022483

McMahon, E. M., Corcoran, P., Keeley, H., Clarke, M., Coughlan, H., Wasserman, D., Hoven, C. W., Carli, V., Sarchiapone, M., Healy, C., & Cannon, M. (2021). Risk and protective factors for psychotic experiences in adolescence: A population-based study. *Psychological Medicine*, *51*(7), 1220–1228. https://doi.org/10.1017/S0033291719004136

Molloy, C., Conroy, R. M., Cotter, D. R., & Cannon, M. (2011). Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies. *Schizophrenia Bulletin*, *37*(6), 1104–1110. https://doi.org/10.1093/schbul/sbr091

Mooney, J., Pate, J., Cummins, I., McLeod, M. C., & Gould, S. (2022). Effects of prior concussion on symptom severity and recovery time in acute youth concussion. *Journal of Neurosurgery Pediatrics*, *30*(3), 1–9. https://doi.org/10.3171/2022.5.PEDS2248

Morgan, C., Charalambides, M., Hutchinson, G., & Murray, R. M. (2010). Migration,

    ethnicity, and psychosis: Toward a sociodevelopmental model. *Schizophrenia*

    Bulletin, *36*(4), 655–664. https://doi.org/10.1093/schbul/sbq051

Murray, R. M., Bhavsar, V., Tripoli, G., & Howes, O. (2017). 30 years on: How the

    neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk

    factor model of psychosis. *Schizophrenia Bulletin*, *43*(6), 1190–1196.

    https://doi.org/10.1093/schbul/sbx121

National Institute of Mental Health. (2022). *ABCD study's data* (release 4.0) [Data set].

    ABCD Data Repository. https://nda.nih.gov/abcd/

National Institute of Mental Health Data Archive. (2021). *Release notes: ABCD study data*

    release 4.0 [Data set release notes]. ABCD Data Repository.

    http://dx.doi.org/10.15154/1523041

Nordström, A., Edin, B. B., Lindström, S., & Nordström, P. (2013). Cognitive function and

    other risk factors for mild traumatic brain injury in young men: Nationwide cohort

    study. *BMJ (Online)*, *346*(7899), 2091–f723. https://doi.org/10.1136/bmj.f723

Nordstrom, A., & Nordstrom, P. (2011). Cognitive performance in late adolescence and the

    subsequent risk of subdural hematoma: An observational study of a prospective

    nationwide cohort. *PLoS Medicine*, *8*(12), e1001151–e1001151.

    https://doi.org/10.1371/journal.pmed.1001151

Oh, H., Susser, E., Volpe, V. V., Lui, F., Besecker, M., Zhou, S., & Anglin, D. M. (2022).

    Psychotic experiences among Black college students in the United States: The role of

    socioeconomic factors and discrimination. *Schizophrenia Research*, *248*, 198–205.

    https://doi.org/10.1016/j.schres.2022.09.004

Orlovska, S., Pedersen, M. S., Benros, M. E., Mortensen, P. B., Agerbo, E., & Nordentoft, M.

    (2014). Head injury as risk factor for psychiatric disorders: A nationwide register-

based follow-up study of 113,906 persons with head injury. *The American Journal of Psychiatry*, *171*(4), 463–469. https://dx.doi.org/10.1176/appi.ajp.2013.13020190

Perry, D. C., Sturm, V. E., Peterson, M. J., Pieper, C. F., Bullock, T., Boeve, B. F., Miller, B. L., Guskiewicz, K. M., Berger, M. S., Kramer, J. H., & Welsh-Bohmer, K. A. (2016). Association of traumatic brain injury with subsequent neurological and psychiatric disease: A meta-analysis. *Journal of Neurosurgery*, *124*(2), 511–526. https://doi.org/10.3171/2015.2.JNS14503

Qin, P., Xu, H., Laursen, T. M., Vestergaard, M., & Mortensen, P. B. (2005). Risk for schizophrenia and schizophrenia-like psychosis among patients with epilepsy: Population based cohort study. *BMJ*, *331*(7507), 23. https://doi.org/10.1136/bmj.38488.462037.8F

Rogers, J. M., & Read, C. A. (2007). Psychiatric comorbidity following traumatic brain injury. *Brain Injury*, *21*(13–14), 1321–1333. https://doi.org/10.1080/02699050701765700

Rohrer, J. (2018). Thinking clearly about correlations and causation: Graphical causal models for observational data. *Advances in Methods and Practices in Psychological Science*, *1*(1), 27–42. https://doi.org/10.1177/2515245917745629

Rubio, J. M., Sanjuan, J., Florez-Salamanca, L., & Cuesta, M. J. (2012). Examining the course of hallucinatory experiences in children and adolescents: A systematic review. *Schizophrenia Research*, *138*(2–3), 248–254. https://doi.org/10.1016/j.schres.2012.03.012

Sachdev, P., Smith, J. S., & Cathcart, S. (2001). Schizophrenia-like psychosis following traumatic brain injury: A chart-based descriptive and case–control study. *Psychological Medicine*, *31*(2), 231–239. https://doi.org/10.1017/S0033291701003336

Schaefer, E. (1965). Children's report of parental behavior: An inventory. *Child Development*, *36*(2), 413–424. https://doi.org/10.2307/1126465

Schmidt., F. (2010). Detecting and correcting the lies that data tell. *Perspectives on Psychological Science*, *5*(3), 233–242. https://doi.org/10.1177/1745691610369339

Schultze-Lutter, F., Schimmelmann, B. G., Flückiger, R., & Michel, C. (2020). Effects of age and sex on clinical high-risk for psychosis in the community. *World Journal of Psychiatry*, *10*(5), 101–124. https://doi.org/10.5498/wjp.v10.i5.101

Schwartz, J. A., Jodis, C. A., Breen, K. M., & Parker, B. N. (2019). Brain injury and adverse outcomes: A contemporary review of the evidence. *Current Opinion in Psychology*, *27*, 67–71. https://doi.org/10.1016/j.copsyc.2018.09.006

Sheffield, J., Karcher, N., & Barch, D. (2018). Cognitive deficits in psychotic disorders: A lifespan perspective. *Neuropsychology Review*, *28*(4), 509–533. https://doi.org/10.1007/s11065-018-9388-2

Timonen, M., Miettunen, J., Hakko, H., Zitting, P., Veijola, J., von Wendt, L., & Rasanen, P. (2002). The association of preceding traumatic brain injury with mental disorders, alcoholism and criminality: The Northern Finland 1966 Birth Cohort study. *Psychiatry Research*, *113*(3), 217–226. https://dx.doi.org/10.1016/S0165-1781%2802%2900269-X

Townsend, L., Kobak, K., Kearney, C., Milham, M., Andreotti, C., Escalera, J., Alexander, L., Gill, M. K., Birmaher, B., Sylvester, R., Rice, D., Deep, A., & Kaufman, J. (2020). Development of three web-based computerized versions of the Kiddie Schedule for Affective Disorders and Schizophrenia Child Psychiatric Diagnostic Interview: Preliminary validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, *59*(2), 309–325. https://doi.org/10.1016/j.jaac.2019.05.009

Trotta, A., Murray, R. M., & Fisher, H. L. (2015). The impact of childhood adversity on the

persistence of psychotic symptoms: A systematic review and meta-analysis.

Psychological Medicine, *45*(12), 2481–2498.

https://doi.org/10.1017/S0033291715000574

van Os, J., Linscott, R. J., Myin-Germeys, I., Delespaul, P., & Krabbendam, L. (2009). A

systematic review and meta-analysis of the psychosis continuum: Evidence for a

psychosis proneness–persistence–impairment model of psychotic disorder.

Psychological Medicine, *39*(2), 179–195.

https://doi.org/10.1017/S0033291708003814

van Reekum, R., Cohen, T., & Wong, J. (2000). Can traumatic brain injury cause psychiatric

disorders? *The Journal of Neuropsychiatry and Clinical Neurosciences*, *12*(3), 316–

327. https://doi.org/10.1176/jnp.12.3.316

Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., van

Os, J., & Bentall, R. P. (2012). Childhood adversities increase the risk of psychosis: A

meta-analysis of patient-control, prospective- and cross-sectional cohort studies.

Schizophrenia Bulletin, *38*(4), 661–671. https://doi.org/10.1093/schbul/sbs050

Wilcox, J. A., & Nasrallah, H. A. (1986). Childhood head trauma and psychosis. *Psychiatry

Research*, *21*(4), 303–306. https://doi.org/10.1016/0165-1781%2887%2990013-8

Yates, P., Williams, W., Harris, A., Round, A., & Jenkins, R. (2006). An epidemiological

study of head injuries in a UK population attending an emergency department.

Journal of Neurology, Neurosurgery and Psychiatry, *77*(5), 699–701.

https://doi.org/10.1136/jnnp.2005.081901

Part 3: Critical Appraisal

Overview

This critical appraisal presents considerations in relation to three broad topics. Firstly, I reflect on the foremost strength of the entire thesis, which lies in the transparency, accessibility, and reproducibility of the conducted research. In the second section, I identify the reasons for and likely impact of the primary limitation of the project, namely a lack of expert by experience (EbE) involvement in the research design, conduct, analysis, and interpretation. Lastly, in the concluding section, I explore the relationships between paediatric traumatic brain injury (TBI) and mental health outcomes in children, suggesting potential future research directions that may also serve as the foundation for my planned future PhD research.

Transparency, Accessibility, and Reproducibility of Research

In this research endeavour, I adopted open science practices for the first time, aiming to disseminate scientific knowledge and findings in a transparent and accessible manner. During my undergraduate years, I was often puzzled by the inaccessibility of peer-reviewed journal articles, which typically required either an affiliation with an academic library or an exorbitant payment to the journal. This experience led me to believe that research was confined to the ivory towers and had little relevance to the real world. However, carrying out the current doctoral project based on open science practices has significantly altered my perception of the purposes of undertaking academic research.

Open science is not a single-step process; rather, it involves meticulous and comprehensive planning throughout the research, beginning with the initial stages. For instance, prior to initiating the systematic review and meta-analysis—which encompassed preliminary searches, piloting the study selection process, formal screening of search results based on eligibility criteria, data extraction, quality assessment, and data analysis—I was required to preregister the review protocol with PROSPERO (see Appendix S1: Pre-

registration of the review; CRD42022360772; Yau et al., 2022), the international prospective register of systematic reviews, to minimise the risk of bias during the review. Additionally, I commenced training in the R programming language through Codecademy (see the link here) as guided by my supervisor to ensure that the statistical analyses in both the review and the empirical study could be performed using R, with all the R code subsequently made available online. Together with my supervisor, we developed code for the meta-analysis, subgroup analyses, publication bias assessment, outlier and influential diagnostics, leave-one-out sensitivity analysis, meta-regression, and sensitivity analysis after excluding low-quality evidence. Similarly, we developed code for the multi-level logistic regression analyses in the empirical paper. However, at the time of writing this critical appraisal, we are still waiting for the Adolescent Brain Cognitive Development (ABCD) full cohort data from the 3-year follow-up to be released, so the public link in relation to the analyses cannot be provided yet. Nevertheless, all steps and results from the systematic review and meta-analysis are transparently and thoroughly presented in a computational notebook on a public online platform (see the link here). Furthermore, the datasets utilised for the analyses in the review and the empirical paper are either publicly available (see the link here) or can be openly accessed via a data dictionary from the National Institute of Mental Health Data Archive (NDA; see the link here).

It is well-known that it can take several months or even years for a manuscript to be reviewed, revised, and eventually published in a peer-reviewed journal, creating barriers to the spread of scientific knowledge. As of writing this critical appraisal, my supervisor and I have published a preprint of the systematic review and meta-analysis since February 2023 to expedite the dissemination of scientific findings (see the link here; Yau et al., 2023). This is my first experience sharing a preprint of my work via public platforms, and whilst I have found the process challenging, for example, in addressing comments and questions from

leading experts in the field, it has also been rewarding. The exchange of ideas among academics is based on presenting solid and defensible arguments by "letting the data speak for themselves". Another rewarding aspect is observing the extent to which the work has reached the audience. Thus far, the abstract has garnered over 1,000 views, whilst the full-text PDF has been downloaded more than 100 times. Additionally, the preprint has been shared on Twitter (see the link here) and viewed by the public over 9,000 times. I anticipate that the metrics will be much higher once the peer-reviewed paper is formally published.

Through the exceptional guidance provided by my supervisor and, more importantly, his exemplary demonstration of open science practices—such as consistently advocating for open science in mental health research and adhering to his own proposed recommendations in his work (Bell, 2017)—I have come to appreciate the significance of not merely accumulating academic publications to advance one's career, but truly benefiting the public. In the case of the current thesis, for example, this goal of contributing to the wider public can be achieved by enhancing the existing understanding of the relationships between paediatric TBI and psychosis, whilst ensuring the transparency, accessibility, and reproducibility of rigorous scientific research in the field of clinical psychology.

Reasons for and Likely Impact of a Lack of Expert by Experience Involvement

So far, I have reflected on the foremost strength of my research and will now turn to the other end of the spectrum—one of the major limitations, as demonstrated by the lack of expert by experience (EbE) involvement. I contemplate the reasons behind the absence of initiative to involve EbE, and the immediate "excuses" that come to mind include "no time", "next time maybe", and "I need to prioritise other tasks". I believe these immediate responses reveal how little I have prioritised EbE involvement in designing the present study, which is very concerning to me and necessitates improvements in my research practice. It could be argued that the two primary components of my thesis, i.e., the meta-analysis and the

empirical study, are both secondary analyses in which data have already been collected, thus limiting the possibility of involving EbE in the research process. However, upon reflection, this statement is not entirely accurate, as I could have involved children and young people with TBI and their family members in asking questions such as:

Regarding the Systematic Review and Meta-Analysis

1. What are the EbE's views on paediatric TBI as a risk factor for psychosis as a research topic?

2. What are the EbE's opinions regarding the representation of the evidence base in terms of research locations, primarily Western and high-income countries?

3. What are the EbE's experiences with completing the Structured Clinical Interview for DSM Axis I Disorders (SCID-I), the Structured Interview for Psychosis-risk Syndromes (SIPS), the Prodromal Questionnaire – Brief Child Version (PQ-BC), and the clinical diagnostic interview?

4. What are the EbE's perspectives on communicating the major findings in plain and accessible language?

5. What do the EbE believe to be the most effective way to disseminate findings to reach the largest number of stakeholders, such as service users, patient organisations, and policymakers?

Regarding the Empirical Study

6. What are the EbE's opinions on the six research questions formulated, in relation to exposure to paediatric TBI, TBI severity, number of TBIs experienced, and the psychotic-like experiences (PLEs) outcomes at baseline and 3-year follow-up?

7. What are the EbE's experiences with completing the Ohio State University Traumatic Brain Injury Screen – Short Modified (OTBI-SM)?

8. What are the EbE's views on the selected confounding variables, including child's gender, ethnicity, IQ, adverse life events, parenting practices, and household income? Is there anything missing based on their lived experience?

9. What are the EbE's views on the choice of using odds ratio (*OR*; instead of, for example, risk ratio [*RR*]) as the meta-analytic effect measure?

10. Similar to points 4 and 5 above, what are the EbE's opinions on the best possible ways of communicating and disseminating research findings?

Whilst the list above is not exhaustive, it provides a valuable starting point for involving EbE in academic research. The process of having public involvement in health and social care research has also been reported to be empowering for EbE (Blackburn et al., 2010). Once again, the primary message reflected upon in this section aligns with my previous reflections on the transparency, accessibility, and reproducibility of research, aiming to genuinely benefit the public and the EbE involved.

Paediatric Traumatic Brain Injury and Mental Health Outcomes

In our systematic review and meta-analysis, we cautiously report meta-analytic evidence for a positive association between paediatric TBI and future psychosis. In our empirical study based on a secondary analysis of the Adolescent Brain Cognitive Development (ABCD) longitudinal cohort dataset, we identify a potential delayed occurrence of psychotic-like experiences (PLEs) following TBI among children aged 9 to 10 years old. Overall, the entire thesis focusses on paediatric TBI and psychosis outcomes, which are among the most disabling psychiatric disorders. However, we must not lose sight of the broader mental health outcomes following exposure to paediatric TBI. Although evidence suggests that the psychological consequences of mild TBI in children usually resolve over time (Emery et al., 2016; Keightley et al., 2014), chronic aspects of health/medical, academic/cognitive, emotional/behavioural, and social/family outcomes post-injury have also

been reviewed and emphasised (Babikian et al., 2015). Additionally, there is evidence indicating that TBI severity in children and young people is associated with their quality of life (Di Battista et al., 2012). Several reviews have reported that paediatric TBI is associated with later mental health difficulties such as attention-deficit/hyperactivity disorder (ADHD), conduct disorder, personality change (Max, 2014; Schachar et al., 2015), depression (Laliberté Durish et al., 2018), and substance use in children and adolescents (Adams Nejatbakhsh et al., 2023). Indeed, a recent literature review has shown that approximately 10 to 30% of children with mild TBI experience lingering neuropsychiatric and neuropsychological symptoms three months or more post-injury (Ritchie & Slomine, 2022).

Definition of Mental Health Outcomes in Children with Traumatic Brain Injury

In order to capture the mental health symptoms/difficulties experienced by children and young people without being limited by the criteria of specific psychiatric diagnoses, we define the outcome of interest as a construct of mental health symptoms/difficulties based on the literature in the field of paediatric TBI and mental health. This construct consists of:

(i)   internalising problems (i.e., anxiety, depression, posttraumatic stress, and withdrawal; Gornall et al., 2021);

(ii)   externalising problems (i.e., aggression, conduct problems, hyperactivity, inattention, and risk-taking; Gornall et al., 2021);

(iii)   overall mental health difficulties (i.e., novel psychiatric diagnoses post-injury and total problem subscales of validated behavioural and emotional inventories; Gornall et al., 2021); and/or

(iv)   neurocognitive deficits (i.e., cognitive fatigue; Riccardi & Ciccia, 2021; executive function, learning and memory, complex attention, language, perceptual–motor function, and social cognition; Goh et al., 2021).

Existing Findings and Research Gaps

Regarding internalising, externalising, and overall mental health difficulties, the most recent meta-analysis reported that the paediatric concussion (i.e., mild TBI) group experienced significantly higher levels of these three areas of mental health difficulties across acute (0–3 months post-injury), persisting (3–12 months post-injury), and chronic (more than 12 months post-injury) timepoints compared with the control group (Gornall et al., 2021). Specifically, another meta-analysis found a significant association with an increased risk for ADHD in children with severe TBI at T1 (one year or less post-injury) and T2 (more than one year post-injury), after controlling for pre-injury ADHD (Asarnow et al., 2021). In determining recovery from concussion, post-concussive symptoms (PCS) might be used to classify children with paediatric TBI into experiencing persistent PCS or full recovery. PCS are defined as somatic (e.g., fatigue, headache), cognitive (e.g., forgetfulness, inattention, slow processing speed), and emotional (e.g., disinhibition, irritability) complaints following a concussion (Yeates, 2010).

Indeed, a meta-analysis identified the prevalence rate of persistent PCS to be 35.1%, with a higher rate for older and female children presented at concussion clinics rather than emergency departments (Chadwick et al., 2022). However, the authors identified a lack of standardised diagnostic criteria for measuring persistent PCS, warranting further research on comparing various measurements of persistent PCS to establish reliable and valid criteria for the construct (Chadwick et al., 2022). Although it is now known that pre-injury mental health difficulties are a reliable predictor of paediatric post-concussion mental health outcomes, the relationship between PCS and post-injury mental health symptoms remains poorly understood (Gornall et al., 2021). Moreover, when considering the wider context and the potential contribution of non-injury variables to mental health outcomes, the roles of

psychological resilience and family characteristics (e.g., family living arrangement, parent education) remain largely unexplored and warrant further investigation (Gornall et al., 2021).

Regarding neurocognitive deficit outcomes, a meta-analysis reported statistically higher levels of cognitive fatigue (i.e., mental tiredness after prolonged mental activities) in the paediatric TBI group than the control group (Riccardi & Ciccia, 2021). Another meta-analysis reported a dose–response relationship between TBI severity and neurocognitive outcomes in children, including executive function as well as learning and memory, at 0–3 months post-injury; with the persistence of the post-severe-TBI neurocognitive outcomes lasted for more than 24 months, suggesting long-term detrimental effects of severe TBI on several cognitive domains (Goh et al., 2021). Although the study attempted to examine all six post-injury neurocognitive domains, including executive function, learning and memory, complex attention, language, perceptual–motor function, and social cognition, some of these domains were less explored at the time of the research. For example, only two studies were included in the meta-analysis stratified by social cognition (Goh et al., 2021). Later, On et al. (2022) specifically investigated post-injury social cognition outcomes, which include specific dimensions such as emotion recognition, theory of mind, pragmatic language, moral reasoning, and social problem-solving. Their meta-analysis found that the paediatric TBI group performed significantly worse than the control group on higher-order aspects of social cognition, including theory of mind and pragmatic language (On et al., 2022). However, when considering both injury-related (e.g., TBI severity, location of the head injury) and non-injury-related factors (e.g., family environment, socioeconomic status), it remains unclear whether these factors are moderators of post-injury social cognition (On et al., 2022).

Future Research Directions

To summarise, some of the unanswered research questions related to paediatric TBI and mental health outcomes are as follows:

1. What are the psychometric properties of measures of persistent post-concussive symptoms (PCS)?

2. What is the relationship between persistent PCS and post-concussion mental health outcomes?

3. Are psychological resilience and family characteristics predictors of post-concussion mental health outcomes?

4. Do non-injury-related factors (such as family environment) moderate social cognitive outcomes after paediatric TBI?

5. What are the effects of injury-related factors (such as paediatric TBI severity) on the longitudinal recovery trajectories of social cognition after the injury?

I have decided to seize this opportunity of writing this critical appraisal to formulate potential research questions that I might focus on during my future research and clinical academic career. For example, I could incorporate some of these research questions into my research proposal when applying for a clinical fellowship position. By answering these research questions, I believe we can develop a better understanding of tracking the recovery of children and young people with TBI, managing their post-injury mental health, and designing family-based treatments for improved mental health outcomes.

Conclusions

Before embarking on this research project, I had no relevant prior experience working with children with TBI. However, the research process has undoubtedly ignited my enthusiasm and passion for contributing to the assessment and treatment of mental health outcomes associated with paediatric TBI. After all, paediatric TBI is not just a medical

condition with physical concerns, but also one with evident mental health difficulties that we, as clinicians and researchers, have a responsibility to address.

References

Adams Nejatbakhsh, N., Dawson, D., Hutchison, M., & Selby, P. (2023). Association between pediatric TBI and mental health and substance use disorders: A scoping review. *Brain Injury*, 1–9. https://doi.org/10.1080/02699052.2023.2184871

Asarnow, R. F., Newman, N., Weiss, R. E., & Su, E. (2021). Association of attention-deficit/hyperactivity disorder diagnoses with pediatric traumatic brain injury: A meta-analysis. *JAMA Pediatrics*, *175*(10), 1009–1016. https://doi.org/10.1001/jamapediatrics.2021.2033

Babikian, T., Merkley, T., Savage, R. C., Giza, C. C., & Levin, H. (2015). Chronic aspects of pediatric traumatic brain injury: Review of the literature. *Journal of Neurotrauma*, *32*(23), 1849–1860. https://doi.org/10.1089/neu.2015.3971

Bell, V. (2017). Open science in mental health research. *The Lancet Psychiatry*, *4*(7), 525–526. https://doi.org/10.1016/S2215-0366%2817%2930244-4

Blackburn, H., Hanley B., & Staley K. (2010). *Turning the pyramid upside down: Examples of public involvement in social care research*. INVOLVE, Eastleigh. https://www.invo.org.uk/wp-content/uploads/2011/06/INVOLVETurningthe-pyramidOct2010.pdf

Chadwick, L., Sharma, M. J., Madigan, S., Callahan, B. L., & Owen Yeates, K. (2022). Classification criteria and rates of persistent postconcussive symptoms in children: A systematic review and meta-analysis. *The Journal of Pediatrics*, *246*, 131–137.e2. https://doi.org/10.1016/j.jpeds.2022.03.039

Di Battista, A., Soo, C., Catroppa, C., & Anderson, V. (2012). Quality of life in children and

    adolescents post-TBI: A systematic review and meta-analysis. *Journal of*

    Neurotrauma, *29*(9), 1717–1727. https://doi.org/10.1089/neu.2011.2157

Emery, C. A., Barlow, K. M., Brooks, B. L., Max, J. E., Villavicencio-Requis, A.,

    Gnanakumar, V., Robertson, H. L., Schneider, K., & Yeates, K. O. (2016). A

    systematic review of psychiatric, psychological, and behavioural outcomes following

    mild traumatic brain injury in children and adolescents. *Canadian Journal of*

    Psychiatry, *61*(5), 259–269. https://doi.org/10.1177/0706743716643741

Goh, M. S. L., Looi, D. S. H., Goh, J. L., Sultana, R., Goh, S. S. M., Lee, J. H., & Chong, S. -

    L. (2021). The impact of traumatic brain injury on neurocognitive outcomes in

    children: A systematic review and meta-analysis. *Journal of Neurology, Neurosurgery*

    and Psychiatry, *92*(8), 847–853. https://doi.org/10.1136/jnnp-2020-325066

Gornall, A., Takagi, M., Morawakage, T., Liu, X., & Anderson, V. (2021). Mental health

    after paediatric concussion: A systematic review and meta-analysis. *British Journal of*

    Sports Medicine, *55*(18), 1048–1058. https://doi.org/10.1136/bjsports-2020-103548

Keightley, M. L., Côté, P., Rumney, P., Hung, R., Carroll, L. J., Cancelliere, C., & Cassidy,

    J. D. (2014). Psychosocial consequences of mild traumatic brain injury in children:

    Results of a systematic review by the International Collaboration on Mild Traumatic

    Brain Injury Prognosis. *Archives of Physical Medicine and Rehabilitation*, *95*(3 Suppl

    2), S192–S200. https://doi.org/10.1016/j.apmr.2013.12.018

Laliberté Durish, C., Pereverseff, R. S., & Yeates, K. O. (2018). Depression and depressive

    symptoms in pediatric traumatic brain injury: A scoping review. *The Journal of Head*

    Trauma Rehabilitation, *33*(3), E18–E30.

    https://doi.org/10.1097/HTR.0000000000000343

Max, J. E. (2014). Neuropsychiatry of pediatric traumatic brain injury. *The Psychiatric*

    Clinics of North America, *37*(1), 125–140. https://doi.org/10.1016/j.psc.2013.11.003

On, Z. X., Ryan, N. P., Konjarski, M., Catroppa, C., & Stargatt, R. (2022). Social cognition

    in paediatric traumatic brain injury: A systematic review and meta-analysis.

    Neuropsychology Review, *32*(1), 127–148. https://doi.org/10.1007/s11065-021-

    09488-2

Riccardi, J. S., & Ciccia, A. (2021). Cognitive fatigue in pediatric traumatic brain injury: A

    meta-analysis and scoping review. *The Journal of Head Trauma Rehabilitation*,

    36(4), 226–241. https://doi.org/10.1097/HTR.0000000000000644

Ritchie, K. A., & Slomine, B. S. (2022). Neuropsychological and neuropsychiatric recovery

    from mild traumatic brain injury. *Current Opinion in Psychiatry*, *35*(2), 83–89.

    https://doi.org/10.1097/YCO.0000000000000776

Schachar, R. J., Park, L. S., & Dennis, M. (2015). Mental health implications of traumatic

    brain injury (TBI) in children and youth. *Journal of the Canadian Academy of Child*

    and Adolescent Psychiatry, *24*(2), 100–108.

Yau, K. -C., Revill, G., & Bell, V. (2022) A systematic review of paediatric traumatic brain

    injury as a risk factor for psychotic experiences. *PROSPERO, CRD42022360772*.

    https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360772

Yau, K. -C., Revill, G., Blackman, G., Shaikh, M., & Bell, V. (2023). *Paediatric traumatic*

    brain injury as a risk factor for psychosis and psychotic symptoms: A systematic

    review and meta-analysis. medRxiv. https://doi.org/10.1101/2023.02.17.23286118

Yeates, K. O. (2010). Mild traumatic brain injury and postconcussive symptoms in children

    and adolescents. *Journal of the International Neuropsychological Society*, *16*(6), 953–

    960. https://doi.org/10.1017/S1355617710000986

Appendices

Appendix S1: Pre-registration of the review

Citation

King-Chi Yau, Grace Revill, Vaughan Bell. A systematic review of paediatric traumatic brain injury as a risk factor for psychotic experiences. PROSPERO 2022 CRD42022360772 Available from:
https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022360772

Review question
This systematic review aims to determine the association between preceding paediatric traumatic brain injury (pTBI) and subsequent presence of psychotic experiences.

Searches
The databases of PsycINFO (Ovid) (from 1806 onwards) and MEDLINE (Ovid) (from 1946 onwards) will be searched based on the main terms of (i) traumatic brain injury, (ii) psychotic experiences, and (iii) child. We will include all peer-reviewed primary studies published in English language with no publication date restrictions applied. The search will last from 1/10/2022 to 1/12/2022, to be carried out by reviewers (KCY, GR). Prior to the final analysis searches will be re-run to identify any further studies that can be included in the review.

Types of study to be included
The following types of design will be included: randomised or non-randomised controlled trials, retrospective or prospective cohort studies, and case-control studies (including nested case-control and family studies). We will exclude meta-analyses, systematic reviews, literature reviews, cross-sectional studies, case reports or case series, qualitative studies, opinion pieces, editorials, comments, newsletters, book chapters, and congress papers.

Condition or domain being studied
Paediatric traumatic brain injury. Psychotic experiences.

Participants/population
We will include participants of any age or gender with a diagnosis of paediatric traumatic brain injury.

Intervention(s), exposure(s)
Paediatric traumatic brain injury (pTBI) will be defined as an onset of traumatic brain injury (TBI) before adulthood (i.e., < 18 years old). pTBI can be determined by the age of the study population (e.g., children or adolescents with TBIs) or the time of the onset of TBI (e.g., adults with a history of pTBI). We will include participants with a diagnosis of pTBI based on screening tools, structured clinical interviews, medical records reviews, or clinical diagnosis. TBIs with severity ranging from mild (including concussion) to severe will be included. For exclusion, we will not select studies when the occurrence of pTBI cannot be determined and psychotic experiences have not been measured. In addition, we will not include studies when exposure to TBI cannot be differentiated from other non-TBI conditions within a single group.

Comparator(s)/control
Studies with and without comparison groups will be included, with no exclusion criteria to be applied.

Context
There will be no restrictions by country or care setting.

Main outcome(s)
The main outcome of interest will be presence of psychotic experiences based on screening tools, psychometric measures, structured clinical interviews, medical records review, or clinical diagnosis. Psychotic experiences will include schizophrenia, psychosis, hallucination, paranoia, psychosis-risk syndromes, and psychotic-like experiences. We will only include studies indicating that the onset of psychotic experiences was after, instead of before, TBI. We will exclude studies reporting only the more general neuropsychiatric outcomes.

Measures of effect

Odds ratio (OR) or standardised mean difference (SMD) as appropriate with 95% confidence interval (CI).

Additional outcome(s)

Not applicable.

Data extraction (selection and coding)

Study Selection Process

Two reviewers (KCY, GR) will independently screen the titles and abstracts of all the records retrieved after removal of duplicates by Ovid's automatic de-duplication feature. In case of disagreement, discussion will be held. A third reviewer (VB) will be consulted if a consensus cannot be reached. Then, the two reviewers will independently screen the full-text reports, and similar processes of discussion between the two reviewers and consultation with the third reviewer, in the case of disagreement, will be held.

Data Extraction Process

A data extraction excel sheet will be developed. Two reviewers (KCY, GR) will use it to independently extract study characteristics and outcomes, and data will be compared. In cases of conflicts, discussion will be held or the third reviewer (VB) will be consulted.

Data Items

Outcomes

We will primarily extract the number of participants experiencing psychotic experiences after TBI. For a particular study, there may be a multiplicity of results, and we will follow a priori defined rules of decision to select data. (i) When both the raw number of participants experiencing psychotic experiences and the calculated statistics (e.g., odds ratios) are available, we will extract the raw number. (ii) When descriptive statistics of interval measures of psychotic experiences and the calculated statistics (e.g., p values or effect sizes) are available, we will extract the descriptive statistics. (iii) When both non-imputed and imputed data are reported, we will choose the imputed.

Exposures

We will primarily extract the number of participants experiencing TBI. If there is a multiplicity of results, and we will follow a priori defined rules of decision similar to those listed for outcome data (i.e., extracting raw values).

Study Characteristics

We will extract the (i) year and location of the study, (ii) study design, and (iii) participant characteristics (in the exposure and control groups [if any]).

Risk of bias (quality) assessment

Two reviewers (KCY & GR) will independently assess the quality of included studies using a 14-item checklist (Kmet et al., 2004) on a 3-point scale (0 = criteria not met; 1 = partially met; 2 = fully met), generating a summary score (total sum / total possible sum) ranging from 0 to 100, to categorise the low (0-49), moderate (50-74), and high (75-100) study quality. All disagreements will be resolved by consensus.

Strategy for data synthesis

We will estimate the meta-analytic odds ratio (OR) or meta-analytic standardised mean difference (SMD) as appropriate with 95% confidence interval (CI) of psychotic experiences associated with preceding pTBI among the included studies using the R package meta. We will use funnel plots and Egger's test to examine potential publication bias.

If there are enough studies providing data for calculation or extraction of ORs or SMDs, we will first use the

metaviz package in R to visualise small study effects and publication bias by a funnel plot. Afterwards, we will use the R metaprop package to compute the I^2 statistic to measure heterogeneity among the included studies and we will use a random-effects model if heterogeneity is sufficiently high. We will conduct a leave-one-out sensitivity analysis to examine if the exclusion of any particular study would change the conclusions.

We will make a post-hoc decision to decide whether to carry out subgroup analyses based on subgroups of study design (e.g., case-control, cohort studies), study location, and diagnosis (e.g., schizophrenia, psychosis, psychotic-like experiences). If there are insufficient data for any meta-analyses, we will conduct a narrative synthesis based on ESRC guidelines (Popay et al., 2006). The focus of the narrative synthesis will be the relationship between preceding pTBI and subsequent psychotic experiences.

Analysis of subgroups or subsets
We will make a post-hoc decision to decide whether to carry out subgroup analyses based on subgroups of study design (e.g., case-control, cohort studies), study location, and diagnosis (e.g., schizophrenia, psychosis, psychotic-like experiences).

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Type and method of review
Meta-analysis, Narrative synthesis, Systematic review

Anticipated or actual start date
01 October 2022

Anticipated completion date
30 September 2023

Funding sources/sponsors
Not applicable.

Conflicts of interest

Language
English

Country
England

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Brain Injuries, Traumatic; Child; Humans; Risk Factors

Date of registration in PROSPERO

22 September 2022

Date of first submission
22 September 2022

Stage of review at time of this submission
The review has not started

Stage	Started	Complete
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions
22 September 2022

PsycINFO (from 1806) and MEDLINE (from 1946) databases were searched via Ovid.

1. Brain Injuries/

2. Traumatic Brain Injury/

3. Brain Concussion/

4. Psychosis/

5. Schizophrenia/

6. (TBI or traumatic brain injur* or brain injur* or head injur* or cerebral trauma or craniocerebral injur* or concussion* or skull fracture*).ab,id,ti.

7. (psychosis or psychotic or psychotic disorder* or psychotic exp* or psychotic?like exp* or schizophreni* or delusional disorder* or delusion* or hallucinat* or psychiatric illness* or psychiatric disorder*).ab,id,ti.

8. (infan* or baby* or babies or toddler* or preschool* or child* or pediat* or paediat* or prepubescen* or prepuberty* or puberty or pubescen* or teen* or young* or youth* or minors* or underag* or juvenile* or preadolesc* or adolesc*).ab,id,ti.

9. (childhood birth 12 yrs or preschool age 2 5 yrs or school age 6 12 yrs or adolescence 13 17 yrs).ag.

10. 1 or 2 or 3 or 6

11. 4 or 5 or 7

12. 8 or 9

13. 10 and 11 and 12

14. Brain Injuries/

15. Brain Injuries, Traumatic/

16. Brain Concussion/

17. Psychotic Disorders/

18. Schizophrenia/

19. Infant/

20. Child, Preschool/

21. Child/

22. Adolescent/

23. (TBI or traumatic brain injur* or brain injur* or head injur* or cerebral trauma or craniocerebral injur* or concussion* or skull fracture*).ab,kw,ti.

24. (psychosis or psychotic or psychotic disorder* or psychotic exp* or psychotic?like exp* or schizophreni* or delusional disorder* or delusion* or hallucinat* or psychiatric illness* or psychiatric disorder*).ab,kw,ti.

25. (infan* or baby* or babies or toddler* or preschool* or child* or pediat* or paediat* or prepubescen* or prepuberty* or puberty or pubescen* or teen* or young* or youth* or minors* or underag* or juvenile* or preadolesc* or adolesc*).ab,kw,ti.

26. 14 or 15 or 16 or 23

27. 17 or 18 or 24

28. 19 or 20 or 21 or 22 or 25

29. 26 and 27 and 28

30. 13 or 29

31. remove duplicates from 30