Paediatric traumatic brain injury as a risk factor for psychosis and psychotic symptoms: a systematic review and meta-analysis

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Abstract

Psychosis is one of the most disabling psychiatric disorders. Paediatric traumatic brain injury (pTBI) has been cited as a developmental risk factor for psychosis, however this association has never been assessed meta-analytically. A systematic review and meta-analysis of the association between pTBI 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. We identified 10 relevant studies and 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 pTBI 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. In conclusion, we report cautious meta-analytic evidence for a positive association between pTBI and future psychosis. New evidence will be key in determining long-term reliability of this finding.

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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 (pTBI) and psychosis is plausible given what we know 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;

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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 to determine the association between paediatric TBI and later psychotic disorders or symptoms of psychosis. 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

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Paediatric traumatic brain injury 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 when 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 psychotic disorders 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 psychosis-risk syndromes, psychotic symptoms and psychotic-like experiences. We only included studies where the onset of the psychotic disorder/symptoms occurred after the TBI. We excluded studies reporting only broad neuropsychiatric outcomes (such as behavioural difficulties) without any specific assessment of psychosis.

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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 S1 for 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 & psychotic 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, 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. 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, hallucination, paranoia, psychosis-risk syndromes, and psychotic-like experiences. Diagnoses of schizophrenia, psychosis, hallucination, and paranoia 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 psychotic disorders or symptoms, anytime time point was 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

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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. 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 ($\leq$ 54), moderate (55–74), and high ($\geq$ 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 conclusion 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 or sub-threshold symptoms of psychosis), (iv) type of outcome measurement (i.e. clinical

diagnosis vs 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 de-

duplication 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
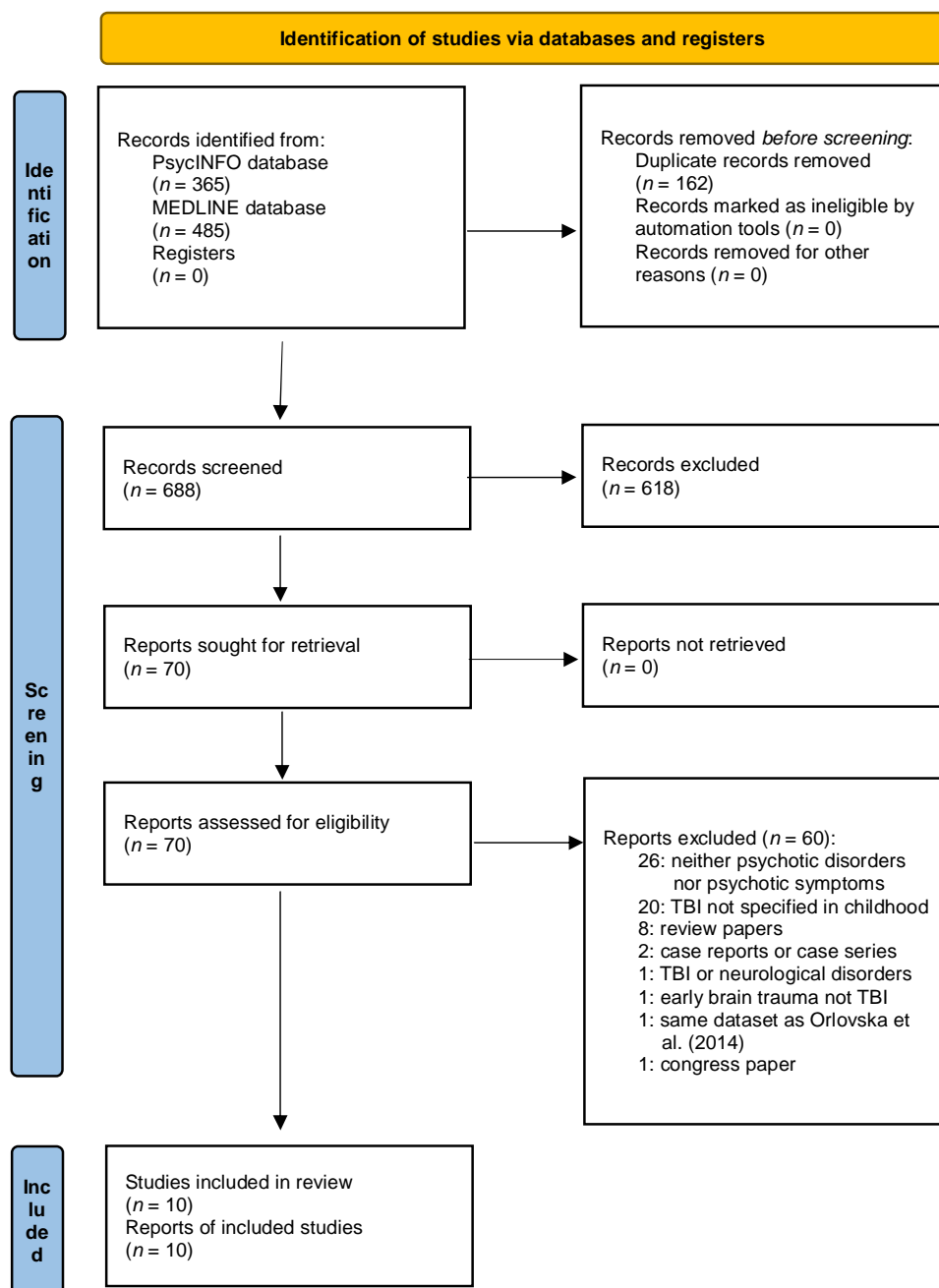
Study characteristics

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 symptom, 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 supplementary Table S1. A summary of included

study characteristics are presented in Table 2. Details of the quality assessment ratings are

reported in supplementary Table S2, with seven studies rated as demonstrating high quality of

evidence, one moderate, and two low.

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Table 2. *Comparison data for probability of psychotic disorders or 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, 1987[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

[e]Schizophrenia was chosen over non-affective psychosis due to more precise measurement of psychotic disorder

[f]Both concussion and head traumas were chosen and aggregated

[g]Raw data on number of participants in relation to psychosis reported in the supplemental materials were used

[h]Data provided by the original author

[i]3-year follow-up was chosen due to primary analysis of the original study

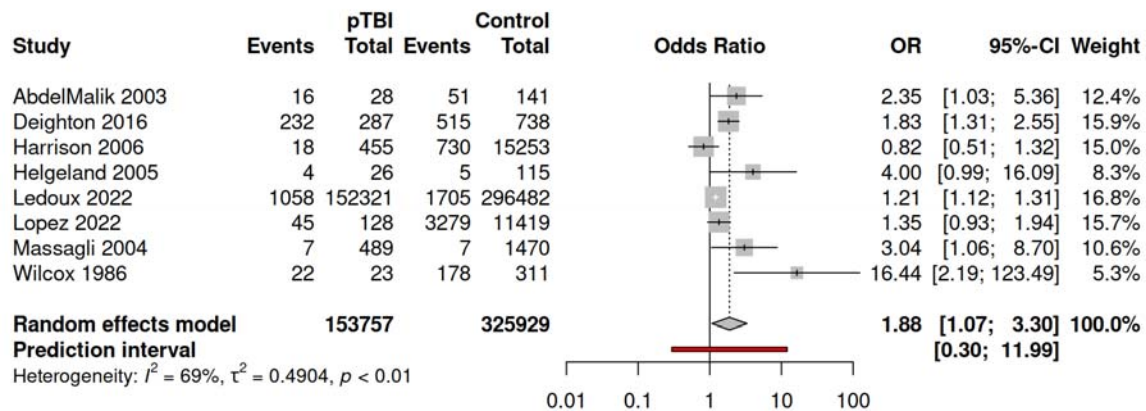[j]Hospital contacts for head injury from 0-15 years old were chosen

[k]Surgical control was chosen due to primary analysis of the original study

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 pTBI

group; 325,929 in the control group), there was an overall significant positive association

between exposure to paediatric TBI and outcomes of psychotic disorders or 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	pTBI Events	pTBI Total	Control Events	Control 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 analysis

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 disorder/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 Figures S1–S5 in the supplementary material.

Robustness and sensitivity analyses

For the assessment of publication bias, visual inspection of the funnel plot (Figure 3)

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

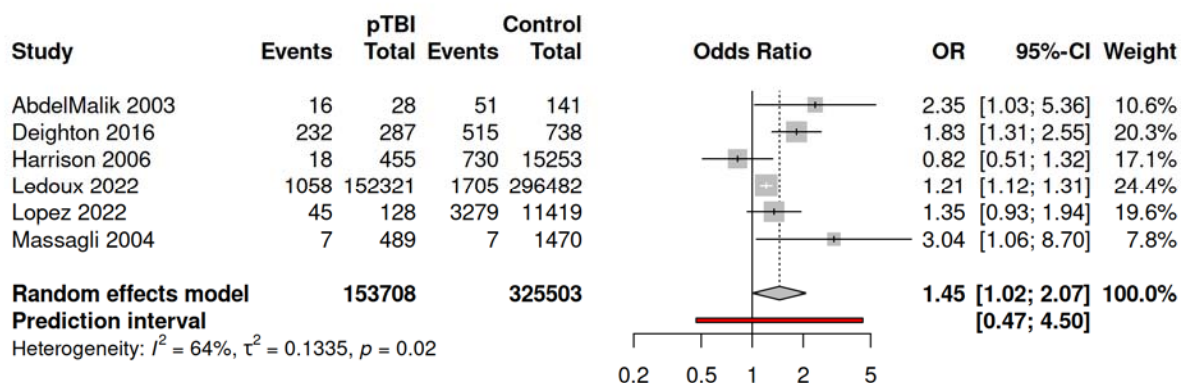publication bias (Ioannidis & Trikalinos, 2007).

Figure 3. Funnel plot of standard error by odds ratio in meta-analysis
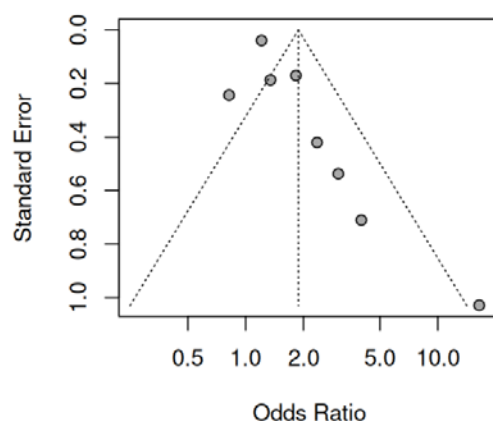
No studies were identified as outliers and no studies were identified as excessively

influential using Viechtbauer and Cheung's (2010) outlier and influential diagnostics. A

leave-one-out sensitivity analysis revealed only minor changes to the estimated odds ratio 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]).

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A meta-regression analysis indicated that the quality of evidence summary score predicted the association between pTBI 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 4) remained significant with narrower confidence intervals suggesting a more accurate estimate (OR = 1.45, 95% CI [1.02, 2.07]) and slightly reduced heterogeneity ($I^2 = 64\%$, $\tau^2 = 0.13$, $p = 0.02$).

Figure 4. 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

		pTBI		Control			OR	95%-CI	Weight
Study	Events	Total	Events	Total	Odds Ratio				
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: $I^2 = 64\%$, $\tau^2 = 0.1335$, $p = 0.02$

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

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focussed on the association between preceding paediatric TBI and the broad outcomes of

mental disorders, Molloy et al. (2011) contacted the original authors and reported no

association between paediatric TBI and the subsequent development of schizophrenia (odds

ratio [OR] = 1.1, 95% CI [0.41, 2.96]) although 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 pTBI 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

were identified in the systematic review which 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 pTBI and psychosis. Consequently, we conclude that

this analysis provides additional evidence for an association between pTBI and psychosis.

However, concerns remain about the long-run reliability of this estimate remain 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 pTBI and psychosis. Developmental models of psychosis suggest that pTBI could be a plausible risk factor for psychosis, given that the full spectrum of pTBI (from mild pTBI 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 pTBI 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 pTBI, psychotic symptoms, and any potential confounders and/or mediators.

Nevertheless, given the concordance between the findings reported here and developmental models of psychosis (Howes & Murray, 2014; Murray et al., 2017), this may suggest that history of pTBI may be a useful addition when taking a history of patients with psychosis and that public health that prevent pTBI 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 measured outcomes design (case control vs cohort), outcome (symptoms vs disorder), outcome measure (clinical diagnosis vs validated measure) and life-stage of measured psychosis outcome (adulthood vs 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 than subgroups typically included 3-4 studies. However, the heterogeneity of studies reflects the fact that many were not primarily designed to assess the association with pTBI and psychosis spectrum phenomena, and more focused 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 potentially useful evidence.

Based on the above discussions, it is recommended that future research focus on specifically assessing the association between pTBI 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 pTBI, 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 and type of injury, would enhance our understanding of the presence/absence of an aetiological relationship between

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pTBI and psychosis. Lastly, future reviews should consider including non-English language databases.

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

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None

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