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# Is traumatic brain injury a risk factor for schizophrenia? A meta-analysis of case-controlled population-based studies.

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## BRIEF REPORT

### **Is Traumatic Brain Injury a risk factor for psychosis? A systematic review and meta-analysis**

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**Abstract**

**Background:** Traumatic brain injury (TBI) is known to lead to a range of neuropsychiatric and cognitive sequelae. However the question of whether TBI is a risk factor for psychosis remains controversial.

**Methods:** We carried out a systematic review of the literature on TBI and psychosis in order to identify all studies which provide estimates of risk for psychosis following TBI. Odds ratios were combined using fixed effects meta-analysis with the data presented in forest plots. Heterogeneity among studies was estimated.

**Results:** Our literature search yielded 162 studies which were considered to be potentially relevant. From these we identified 8 studies which provided estimates of risk in the form of odds ratios. The pooled analysis revealed a significant association between TBI and psychosis (adjusted odds ratio=1.15, 1.04-1.26), but with significant heterogeneity between the studies. Pooled data from the two family studies show an increased risk of schizophrenia after TBI in individuals who have a family history of psychosis (adjusted odds ratio=1.43, 1.14-1.8) with no heterogeneity.

**Conclusion:** We report a pooled 15% increased risk of psychosis following TBI. The risk is larger (43%) among individuals who have a family history of psychosis. Our findings point to the importance of gene-environment interaction in the etiology of psychosis following TBI.

## Introduction

Schizophrenia is the most common form of psychotic illness with a prevalence of 0.6-2.0% in the population depending on how broadly it is defined (1). Both genetic and environmental factors are important in the etiology of schizophrenia (2). Traumatic brain injury (TBI) has long been implicated in the development of a range of neuropsychiatric disturbances, such as cognitive impairments, mood disorders, anxiety disorder and behavioural problems (3). However the question of whether TBI is a risk factor for psychosis remains somewhat controversial. Davison & Bagley (4) in their classic review of eight studies on this topic published between 1917 and 1964 concluded that, among individuals who had experienced a TBI, *“the observed incidence [of psychosis] over 10 to 20 year periods is 2 to 3 times the expected incidence”*. Subsequently Achte *et al* (5) published a 22 year follow-up study of 3532 Finnish soldiers who had suffered brain injury in World War 2 and reported that 8.9% had an onset of psychosis after the brain injury. However, David and Prince (6) reviewed the literature on head injury and psychosis up to 2004, and came to a different conclusion: *“...given the available published data, one must conclude that it is unlikely that head injury causes schizophrenia”*. To help clarify the evidence we conducted a systematic review and meta-analysis of the literature on risk of psychosis among individuals who have suffered TBI. To our knowledge this is the first meta-analysis on this topic.

## Method

## **Literature Search**

Standard methods for systematic review were used in this paper . The following databases were searched from their inception to March 2009: MEDLINE, EMBASE & the Cumulative Index to Nursing and Allied Health Literature (CINAHL) on OVID and PsycINFO on WEbSPIRS. We searched using the format “[psychosis OR schizophrenia OR psychotic disorder OR delusional disorder OR delusions OR non-affective psychosis OR psychiatric illness OR psychiatric disorder] AND [traumatic brain injury OR cerebral trauma OR head injury OR cranio-cerebral injury OR concussion OR open head injuries OR closed head injuries OR skull fractures]” using text words and indexing (MeSH) terms.

## **Inclusion Criteria**

We included published papers that reported on

- 1) the risk of psychosis among individuals who have suffered traumatic brain injury compared to the risk of psychosis in a non-brain injured population-based control group

or

- 2) allowed calculation of a risk estimate from data provided in the paper.

Traumatic brain injury was not limited by severity.

## **Exclusion Criteria**

Studies were excluded if they were (a) reviews, (b) case reports or case series, (c) abstracts only & no further information available, d) if there was no population-based comparison group or insufficient information to calculate risk estimates.

### **Study Selection & Data Extraction**

Two investigators (CM and MC) examined all titles and abstracts and, following this, obtained full texts of potentially relevant studies. These papers were read to determine whether they met inclusion criteria. We searched reference lists of included studies.

### **Data Analysis**

Estimates of risk of psychosis associated with TBI were extracted from the relevant studies or calculated from data available in the paper. Data was obtained from authors if necessary. Odds ratios were combined using fixed-effects meta-analysis, with the data presented in forest plots (7). Heterogeneity among studies was estimated using Cochran Q and the  $I^2$  statistic, the latter describing the percentage of variation among studies that is due to heterogeneity rather than chance (8). Heterogeneity was indicated by a Q statistic (reported with a  $\chi^2$  value) with  $p < .10$ , and  $I^2$  values of 25%, 50%, and 75% can be taken to indicate low, medium and high levels of heterogeneity respectively (9). All of the analyses were undertaken with STATA statistical software package, version 10 (Stata Corp 10)(10).

### **Results**

Our literature search and search of reference lists yielded 9131 references. After reviewing the titles, 162 were considered to be potentially relevant. From these, we identified 8 studies which met our inclusion criteria, of which two were nested case-

control studies (13,18) , one was a large cross-sectional survey (silver), three were cohort studies (11,14,16,17) and two were family studies (family-based case-control design) (12,15).Two studies (16,17) reported from the same cohort but presented data on different age groups and therefore both were included in this analysis. A summary of the 8 studies are presented in Table 1.

The overall pooled analysis revealed a significant association between TBI and subsequent psychosis (adjusted odds ratio=1.15, 1.04-1.26). (See Fig 1). However there was significant heterogeneity between the studies (Heterogeneity  $\chi^2= 30.70$  (d.f. = 7)  $p = 0.000$ ;  $I^2=77.2\%$ ) Therefore,we examined the family studies and case-control/cohort studies separately.

Pooled data from the 6 population-based cohort, cross-sectional and case-control studies (11, 14, 16, 17, 13, 18)showed an increased risk of development of schizophrenia or psychotic disorder in individuals who had been exposed to TBI (adjusted odds ratio=1.1, 1.005-1.231) . However there was notable heterogeneity between the studies (Heterogeneity  $\chi^2= 26.43$  (d.f. = 5);  $p < 0.000$ ;  $I^2=81.1\%$ ).

Pooled data from the two family studies (12, 15)show an increased risk of schizophrenia after TBI in individuals who have a family history of schizophrenia (adjusted odds ratio=1.43, 1.14-1.8). There was no significant heterogeneity between the two studies (Heterogeneity  $\chi^2= 0.15$  (d.f. = 1)  $p = 0.7$ ;  $I^2 = 0.0\%$ ).



## Discussion

In contrast with the previous review on this topic, (5) we report an significant increased risk of psychosis following TBI (in the order of about 10%). The risk is greater among individuals who have a family history of schizophrenia or psychosis - a 43% increase. The results from the two family studies are remarkably similar with no heterogeneity evident between these studies, but we found significant heterogeneity among the population-based cohort and case-control studies in this analysis. This heterogeneity may be attributed to a number of reasons:

a) Duration of follow-up: There is marked variability in the duration of follow-up, ranging from a 3-year follow-up (16) up to 31 years ( 14) and no consensus on which is the greatest period of risk for psychosis.

b) Source of information about head injury: Studies used either self-report data or hospital admission data to provide information about head injury. Self –report of head injury is open to the possibility of recall bias, although, in many cases, efforts were made to supplement patient report with previous medical records and collateral history from family members. The use of hospital data is not affected by recall bias but has the disadvantage of not allowing investigation of the risk of psychosis after mild head injuries which do not require admission.

We propose that the debate should now move from establishing whether TBI is a risk factor for psychosis to refining which aspects and characteristics of the TBI confer this increase in risk. In particular the following issues require clarification:

- 1) Age at TBI: Some authors (Abdel-Malik and Massagli) have proposed that head injuries occurring during childhood are associated with an increased risk of psychosis but others (Harrison) have not found such an association.
- 2) Location of TBI: Davison and Bagley (4) proposed that temporal and frontal lobe lesions were more likely to lead to psychosis and this was supported by two case-series of patients with psychosis following TBI (19, 20). However the classic study by Achte et al. (1969) (21) reported no association between location of injury and the subsequent development of psychosis. This issue remains unresolved and is difficult to study using hospital admission data which typically does not provide detail on location of brain injury.
- 3) Severity of TBI: There is some suggestive evidence that psychosis is more likely to occur after mild brain injury (21) and this is borne out by two studies in our paper (15,16) but is also difficult to study using population based hospital admission data.
- 4) Comorbid epilepsy None of the studies included in this review provided information on epilepsy. This could be a potential confounder of the association as head injury can cause epilepsy (3) and epilepsy is associated with an increased risk of psychosis (22,23).

In conclusion, our systematic review and meta-analysis has found that there is an increased risk of psychosis following traumatic brain injury. This increase in risk is small – in the order of 10% but it is an association which deserves further attention. In particular, we found a higher risk associated with head injury among individuals with a genetic predisposition to psychosis (as indexed by a positive family history of schizophrenia). Therefore our findings could be interpreted as a further example of

gene-environment interaction in psychosis (24,25). Further investigation in large samples is warranted , incorporating data on severity and location of the TBI and age at injury. Examination of the interaction between TBI and known candidate genes for schizophrenia may be a fruitful line of enquiry.

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No conflicts of interest to declare

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**Table 1.0 Summary of Studies included in Systematic Review**

Authors	Type of Study	Country	Number of subjects	Number of Patients developing Psychosis	Study Population	Source of information about psychosis	Source of Information about HI*
<b>Silver (2001)</b> <sup>11</sup>	Cohort	US	Total N= 5034 N=361 with history of TBI	Schizophrenia OR=1.86 (95% CI =1.04-3.29)	Probability sample of adults from New Haven portion of the NIMH Epidemiologic Catchment Area programme	Diagnostic Interview Schedule	Patient report of history of severe TBI
<b>Malaspina (2001)</b> <sup>12</sup>	Family	US	N= 1840 members of multiplex schizophrenia and bipolar disorder pedigrees	OR = 1.50 (95% CI=0.93-2.43)	National Institute of Mental Health Genetics for Schizophrenia & Bipolar Disorders	Diagnostic interview for genetic studies	Patient report- Diagnostic Interview for Genetic Studies question on HI
<b>Nielsen (2002)</b> <sup>13</sup>	Nested Case-Control	Denmark	N= 8288 persons admitted with schizophrenia and 82880 controls	OR= 0.899 (95% CI= 0.78-1.036)	National Patient Register – date of first psychiatric admission		Hospital admission
<b>Timonen (2002)</b> <sup>14</sup>	Cohort	Finland	10,934 people	OR= 1.105 (95% CI= 0.413-2.95)	Northern Finland 1966 Birth Cohort Study		Hospital discharge registers and case notes of outpatient clinics
<b>AbdelMalik (2003)</b> <sup>15</sup>	Family	Canada	67 patients with narrowly defined schizophrenia compared with 102 of unaffected siblings from multiply affected families	OR = 1.49 (95% CI= 1.14-1.94)	Ongoing study of familial schizophrenia-genetic linkage of narrowly defined schizophrenia		From SCID-1 & supplemented by collateral information from family & medical records
<b>Massagli (2004)</b> <sup>16</sup>	Cohort	US	490 children who sustained a mild TBI in 1993	OR= 3.006 (95% CI= 1.06-8.52)	Computerised records of patients in a large staff model health maintenance organisation		Mild TBI* diagnoses at emergency department, hospital or outpatient clinic

<b>Fann (2004)</b> <sup>17</sup>	Cohort	US	939 health plan members diagnosed with TBI	Psychotic disorder OR= 1.84 (95% CI= 1.22-2.76)	TBI diagnosis at hospital in 1993 Psychiatric diagnosis in year prior to & 3 years following reference date	TBI* diagnosis at emergency department, hospital or outpatient clinic in 1993
<b>Harrison (2006)</b> <sup>18</sup>	Nested Case-Control	Sweden	N= 731,305	Schizophrenia OR=1.10 (95% CI=0.82-1.47)  Non-affective psychosis OR=1.35 (95% CI= 1.14-1.6)	Individuals born in Sweden between 1973 and 1980	Hospital admission registers

**Abbreviations:** HI: Head Injury; TBI: Traumatic brain injury

**Figure 1: Forest plot showing adjusted odds ratios and 95% CI for psychosis**



