

PSYCHOSIS FOLLOWING HEAD INJURY: A CRITICAL REVIEW

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Schizophrenia is the most common form of psychotic mental disorder, with a point prevalence generally estimated to lie between 0.6–1.0%. Genetically informative studies have indicated a multifactorial aetiology, with an important heritable (genetic) component, but with environmental exposures also undoubtedly relevant. The “neurodevelopmental hypothesis” has informed a body of research that fairly consistently identifies birth complications as a risk factor for the later onset of schizophrenia.^{1 2}

Injury to the head or brain after birth and beyond has been posited as a risk factor for psychosis for many decades but has enjoyed little systematic research (see Lishman,³ van Reekum *et al*,⁴ and Fujii and Ahmed⁵ for reviews). The purpose of this article is to review this information systematically. Computerised databases including Medline and PsychInfo were searched using head/brain injury and psychosis or schizophrenia as search terms, covering the period from 1966 to end 2003. Citations from published reviews were also retrieved and yielded important articles and monographs, some published more than two decades ago, not included in these databases.

Four types of study design have been used to assess the relation between head injury and schizophrenia: the case report; the long term follow up of series of head injured persons; the cross sectional survey; and the case-control study.

CASE REPORTS

Case reports document individual unusual clinical events or episodes. The report from O’Callahan and colleagues⁶ is a good recent case in point. The striking circumstance here was the onset of schizophrenia in a previously well 16 year old, with no other risk factors, two years after a significant head injury involving a blow to the left frontotemporal region. His parents commented that “he was never the same since the accident”. However, it is possible that the onset of schizophrenia was incidental to the head injury, and that the family had made a link between the two events because of an understandable need to make sense of the fate that had befallen their child. On the other hand, the observation may indeed highlight a direct causal link between the trauma and psychosis.

Fujii and Ahmed⁷ carried out a systematic review of case studies of “psychotic disorder due to traumatic brain injury” (PDTBI), a diagnostic category proposed under the *Diagnostic and statistical manual*, 4th revision (DSM-IV), covering the period 1971 to 1994, identifying 39 articles describing a total of 69 cases. In doing so they applied, retrospectively, the DSM-IV PDTBI criteria, namely:

- 1) presence of hallucinations or delusions
- 2) evidence that the psychosis is a direct consequence of traumatic brain injury
- 3) psychosis is not better accounted for by another mental disorder
- 4) psychosis does not occur exclusively during a state of delirium.

In 89% of cases there was loss of consciousness, and in 22 of the 29 for whom data were available the head injury was classified as moderate or severe. The interval between head injury and onset of psychosis varied between 0–34 years with a mean of 4.1 years. However 38% of onsets were within one year and more than half had their onset within two years. The authors comment, correctly, that reporting bias may have led to selective reporting of cases with a relatively short latency between head injury and onset of psychosis. Only 14% of patients experienced negative symptoms of schizophrenia (apathy and withdrawal), much lower than the figure generally reported for schizophrenia (cited variously to lie between 25–84%). The authors do not give details of how they applied the key second criterion, although they focus in their analysis upon focal electroencephalogram (EEG) abnormalities and neuroimaging evidence of temporal lobe and ventricular enlargement. These changes are not specific, occurring also in schizophrenia in the absence of a history of traumatic brain injury. Case reports are rather low on the “hierarchy of evidence” and will not be considered further in this review.

LONG TERM FOLLOW UP OF HEAD INJURED COHORTS

Cohort studies can clarify the temporal sequence between exposure and outcome, with minimal information bias. Long term follow up of head injured cohorts are effectively one half of a cohort

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study, in which there is an exposed group but no directly observed reference unexposed group. The incidence rate of the outcome (in this case schizophrenia) is then observed. Where the exposure is rare, it may be reasonable to use the incidence rate in the general population (if known) as an estimate of the incidence rate among the unexposed for purposes of comparison. However, the characteristics of the exposed population may differ from those of the general population, hence introducing a form of bias into the estimate of the association between risk exposure and disease outcome. Thus, for example, those experiencing a head injury are typically young and male. Such discrepancies are generally dealt with by standardisation. Age and sex are commonly standardised for, as they are strongly associated with many disease outcomes (including schizophrenia), and outcome rates for both the exposed group and/or the reference group are often available for different age bands, separately for men and women.

Davison and Bagley⁸ reviewed eight such studies published between 1917 and 1964 reporting cumulative incidence rates for schizophrenia of between 0.07–9.8%, with a median cumulative incidence of 1.35%. Two studies had a follow up of two years or less; the others covered periods of 10–20 years. Most were cohorts of brain injured servicemen. Only one recruited victims of head injury during peacetime, and this reported a cumulative incidence of 0.7% (95% confidence intervals (CI) 0.5% to 0.9%) among 4807 head injured persons. The authors comment that “with an expectation of developing schizophrenia in the general population of 0.8% over a 25 year risk period (age 15 to 40 years), the observed incidence over 10 to 20 year periods is 2 to 3 times the expected incidence”. The source of the expected rate in the general population is not referenced. Only one small study permitted age standardisation—the expected incidence of schizophrenia in the brain injured cohort would have been two cases, compared with the 11 observed among the 415 who were exposed. Davison and Bagley’s review is authoritative, and for its time exceptionally well conducted. The authors were aware of problems with defining the outcome (schizophrenia), and operationalised this as far as possible to meet the 1957 World Health Organization criteria which were current at the time. It is impossible to be certain that the investigators in the individual studies reviewed were applying diagnoses either (1) in a similar way to each other, or (2) according to the WHO criteria, or (3) in a way that would be analogous to that used to estimate the 0.8% cumulative incidence in the general population between the ages of 15–40 years, cited as a comparator.

The study of Achte and colleagues⁹ (not included in Davison and Bagley’s review) is in many ways a definitive, and much cited, example of the genre. This was a 22–26 year follow up of 3552 Finnish men who had suffered brain injuries during the second world war. As war injuries, these were atypical of head injuries occurring in peace time: 42% were open injuries with exposure of dura or brain tissue, and 98.8% were caused by injury from shrapnel or bullets. Hospital records were examined for ascertainment of psychosis post-injury. One hospital (the Rehabilitation Institute for Brain-Injured Veterans) was responsible for providing all medical care for this group of patients; the authors therefore argued that relatively complete ascertainment of onset of psychosis was likely. Overall, 317 persons, constituting 8.9% of the brain injured cohort, were considered to have had an onset of psychosis after the brain injury. The method for establishing these diagnoses is not

described and is unlikely to have been standardised. Several of the categories (for example, hypochondriacal psychoses, amniform psychoses, psychoses with intoxication) are no longer recognised and are unlikely to meet modern criteria for schizophrenia. The two categories of schizophrenic psychoses (2.1%) and paranoid psychosis (2.0%) are most directly comparable, accounting for an overall cumulative incidence of 4.1% within this cohort. Even the 4.1% cumulative incidence for the narrower group of schizophrenia related psychosis exceeds by some margin the 1% lifetime risk that most authorities would now accept (despite the lack of standardisation for age and sex; note that young men have a higher incidence of schizophrenia in general). Although the authors do not provide a standard error for their estimate of 4.1% incidence, this can be calculated as 0.33%. Therefore, given the sample size of 3553, within 95% confidence intervals, the precision of the estimate is ± 0.65 , thus the true incidence should lie somewhere between 3.5–4.7%. Therefore, on the face of it this study would appear to provide strong evidence for a prospective association between head injury and schizophrenia and schizophreniform psychoses.

However, there are some concerns. First, the diagnoses do not seem to have been made using structured standardised methods, and clearly would not have been made blind to the knowledge that those involved had experienced a head injury. This creates clear potential for observer bias which may have artificially inflated the extent of the association. Second, as previously mentioned, the nature of the head injuries in this cohort were highly atypical, and it is therefore doubtful whether findings from this cohort can be generalised to the peacetime context; however, the incidence of psychosis was similar for those experiencing closed and open head injuries. Third, potential confounding factors have not been considered; the most important of these is psychological combat trauma. By definition, all of those injured will have been in combat, and the considerable stresses may have acted as a strong predisposing factor in those otherwise vulnerable to psychotic decompensation. It is perhaps significant in this respect that 20.5% of patients were considered to be “psychically deviant” pre-injury (it is unclear how the authors arrived at this judgement). A better designed study would have included non-head injured soldiers with similar combat experience as a non-exposed comparison cohort. Fourth, the close scrutiny of the brain injured cohort through the special medical services provided for them by the state may have led to a more complete ascertainment of psychoses (particularly those of mild severity or brief duration) than would be the case for the general population with whom the incidence rates in this cohort are being compared.

De Mol and colleagues¹⁰ studied, retrospectively, 530 brain injured patients who had undergone neuropsychological assessment in a tertiary referral neurosurgical centre in Brussels between 1968 and 1980, with a follow up period of between 1–10 years. Again, no details are given of ascertainment procedures for the presence of psychosis, and in the absence of evidence of structured approaches, observer bias is a distinct possibility. DSM-III criteria were used. The overall cumulative incidence was 3.4% (18 out of 530 patients, comprising 6 with paranoid disorders, 6 with schizophrenic disorders, 3 with a manic episode, 2 with brief reactive psychosis, and 1 with a major depressive episode). The incidence of schizophrenic or schizophreniform disorders was therefore 12/530 or 2.3%, with a standard error (not provided by the authors) of 0.65. The precision of this estimate would

therefore be $\pm 1.3\%$. De Mol and colleagues' study is unusual in that apparently 83% of all onsets of psychosis occurred within six months of the head injury, and the majority were apparent from the time of recovery of consciousness in the immediate aftermath of the injury. This compares with 42% of Achte's cohort with an onset more than 10 years after the injury. De Mol reported that 83% of those who developed psychoses had a deviant pre-morbid personality, based upon dubious projective tests. He concluded that, "...the trauma itself could not be considered as a cause of the psychosis... the trauma precipitated or aggravated a pre-psychotic or psychotic premorbid personality". In summary, this paper does not provide convincing evidence for an association between head injury and subsequent onset of psychosis.

A somewhat similar civilian cohort is described in a monograph by Roberts.¹¹ He attempted to study long term outcome in a consecutive series of 479 patients admitted to the Radcliffe Infirmary, Oxford between 1948–61, following a head injury with subsequent post-traumatic amnesia of > 1 week (that is, severe), which was a subset of 7000 head injury admissions. Follow up was between 10–24 years. Of 291 survivors who could be examined or who had sufficient clinical records, seven were labelled "paranoid dementia" and a further two had a "schizophrenia-like" psychosis ($9/291 = 3.09\%$, 95% CI 1.4% to 5.8%). Standardised assessments of psychopathology were not used. The latter two were said to have prominent affective features and their disorders arose nine and 17 years post-injury. Roberts concludes: "Evidence that schizophreniform illness in the absence of dementia was likely to be precipitated by severe head injury was slight" (page 182).¹¹

Also included here for completeness is the study by Thomsen¹² who reported a 10–15 year follow up of a cohort of 40 people (28 males) with "very severe blunt head trauma" personally assessed by the author, a Danish neurologist. Most had motor, speech, social, and cognitive deficits. The author describes eight as suffering from "post-traumatic psychoses", six of whom had a late or delayed onset. None had previously been admitted to psychiatric hospital. Of the descriptions given, none clearly conveys a

schizophrenia-like disorder; rather the problems comprise aggression, mood disturbance, and disinhibition.

A more recent study examined the onset of psychiatric syndromes among 196 adults hospitalised with traumatic brain injury admitted to a general hospital in Cardiff,¹³ with loss of consciousness, a Glasgow coma score of < 15 , or radiological evidence of brain assault. Psychiatric interview was completed approximately one year after the injury and index admission. Sixty two patients screened positive on the general health questionnaire (GHQ), of whom 45 (73%) consented to more detailed assessment using the schedules for clinical assessment in neuropsychiatry (SCAN). The advantage of this study is that a validated, structured assessment for mental health outcomes was used. Unfortunately, those screening negative on the GHQ were not interviewed, with the implicit assumption that the GHQ is completely sensitive as a screening instrument, which it is not. Secondly, those who screened positive but could not be interviewed were assumed to have been free of psychiatric pathology, again a most unlikely eventuality. The reported incidence rates are therefore best viewed as estimates of the minimum incidence. The prevalence of depressive episode and panic disorder were nevertheless considerably higher than had been observed in the UK national psychiatric morbidity survey (NPMS). Only one patient had developed schizophrenia, indicating an *annual incidence* of 0.8% compared with a *prevalence* of around 0.4% seen in the NPMS. Despite the weaknesses of this study, there is at least some evidence of non-specific effects of head injury upon risk for mental disorder.

Taken overall, long term follow up studies suggest a higher incidence of schizophrenia among those who have experienced a significant head injury than in the general population. It is not as easy as it might seem, for purposes of comparison, to arrive at a suitable estimate of the cumulative incidence of schizophrenia in the general population. One reasonable estimate is that taken from the UK 1946 birth cohort, followed up intensively from birth to the age of 43 years (that is, until 1989).¹⁴ Cases were identified from records of all hospital and general practitioner contacts, by cross referencing with the mental health enquiry for England (1974–86,

Table 1 Quantitative summary of cohort studies of head injured people

Author (year)	Number at risk	Years of follow up	Cumulative incidence (95% CI)	Relative risk*
Brain injured cohorts				
<i>Studies reviewed by Davison and Bagley⁸</i>				
Poppelreuter (1917)	3000	2†	0.1 (0.0 to 0.2)	0.2
Feuchtwanger (1938)	1564	15	1.7 (1.1 to 2.3)	2.8
Aita and Reitan (1948)	500	0.25†	0.4 (0.0 to 1.0)	0.7
Hillbom (1951)	1821	10	1.2 (0.7 to 1.7)	2.0
Meinertz (1957)	1110	15	1.5 (0.7 to 2.3)	2.5
Lobova (1960)	1168	15	9.8 (8.0 to 11.6)	16.3
Hillbom (1960)	415	20	2.6 (1.0 to 4.2)	4.3
Liberman (1964)	4807	15	0.7 (0.5 to 0.9)	1.2
<i>Subsequent studies</i>				
Achte (1967)	3552	22–36	4.1 (3.5 to 4.7)	6.8
Roberts (1979)	291	10–24	3.1 (1.4 to 5.8)	5.1
De Mol (1987)	530	1–10	2.3 (1.0 to 3.6)	3.8
Population cohort comparison				
Jones <i>et al</i> (1994)	4746	43	0.6 (0.4 to 0.9)	1

*Risks relative to those in the general population using Jones *et al* (1994)¹⁴ as a comparison. Relative risks have been calculated by dividing the cumulative incidence in the exposed cohorts by that in the general population comparator (0.6%).

†For these two brain injured cohort studies the period of follow up is very short. Only those psychoses with an onset after the injury had been included. It would therefore be expected that the cumulative incidence would be lower than for that over the whole first 43 years of life, the period at risk for the general population cohort.

recording all mental health admissions), and through a short form of the Present State Examination administered to all cohort participants at the age of 36. DSM-III diagnoses were then applied following independent review of all relevant material. Thirty cases of schizophrenia were identified among 4746 persons remaining in the cohort, a cumulative incidence of 0.63% (95% CI 0.41% to 0.86%) over the first 43 years of life. While the follow up period is at first sight longer than the 10–20 years that was the norm for the brain injured cohorts, one must bear in mind that the brain injured participants entered their cohorts around the age of 20–30 years (peak age for injury) and were followed through to roughly 30–50 years of age. Therefore this is an apt comparison (table 1).

There are two major weaknesses of these studies:

- ▶ Most involve servicemen with penetrating skull injuries. It is not clear how far findings from these studies would generalise to those with the non-penetrating concussive head injuries seen more commonly in peacetime. The association may also have been confounded by the combat trauma experienced by the wounded veterans. The large study focusing on peacetime injuries¹⁵ indicated a cumulative incidence very close to what would be expected in the mainly non-injured general population. However, to some extent this weakness is also a strength. It has been suggested that even a prospective association between head injury and schizophrenia may reflect reverse causality—the schizophrenia causes the head injury rather than vice versa, as those in the prodrome of developing the illness are more “accident prone”. While this may explain the high incidence rates of schizophrenia in peacetime cohorts, it is unlikely to do so among those injured in war time where injuries are for the most part neither accidental, nor related to the behaviour or mental state of the injured person.
- ▶ Very few of these studies, conducted in the relatively distant past, used criteria for diagnosing schizophrenia and schizophreniform psychoses that would match well with those applied nowadays. There may be a tendency to over interpret symptoms in those with a brain injury, leading to a biased, overestimated rate of psychotic disorder.

CROSS SECTIONAL SURVEYS

The association between head injury and schizophrenia was assessed in just one large cross sectional survey.¹⁶ Such study designs are not well suited to the study of rare conditions; however, in this instance (the data were collected as part of the US National Epidemiological Catchment Area study, based in New Haven, Connecticut) the sample size of 5034 was adequate. The association between head injury and the range of psychiatric disorders was examined using a structured interview, the diagnostic interview schedule, administered by trained lay interviewers. Diagnoses were based on DSM-III criteria. Traumatic brain injury was defined as a positive response to the question: “Have you ever had a severe head injury that was associated with loss of consciousness or confusion?” Sociodemographic factors, indices of general health and substance use were also recorded. Out of a sample of 5034, 361 were classed as having a head injury (against 4673 without), a raw proportion of 7.2% or 8.5% after weighting. The number in the head injury group who were diagnosed with schizophrenia was 73 (3.4%) versus 1.9% of the non-head injury controls. This difference was not significant at conventional levels ($\chi^2 = 2.8, p = 0.093$)*. On the other hand, head injury was associated with major depression, alcohol abuse/dependence,

and other psychiatric disorders, but not bipolar disorder ($n = 45$).

The strengths of the study were the population base, the large sample size, the systematic rating of psychopathology, and statistical adjustment for potential confounding variables. The main weaknesses are intrinsic to the cross sectional study design. Since outcome (psychiatric disorder) and exposure (head injury) are ascertained at the same time, it is difficult to interpret associations that are observed between the two. These may reflect reverse causality, with the onset of the psychiatric disorder preceding and causing the head injury. The investigators did not gather information on the timing of these events, which might have helped to address this issue. Alternatively information bias may well have been a problem, since those with mental disorders may have been systematically more (or less) likely to recall and report the experience of head injury. The ascertainment of head injury was relatively crude, being based on self report rather than, say, hospital records, although the latter are likely to be an underestimate. On the other hand the overall rate of head injury seems plausible and the association with other psychiatric disorders (and with other factors including male sex, relative youth, lower socioeconomic status, etc) are all according to expectations given what is known about the epidemiology of head injury. The rate of schizophrenia seems to be tending towards an increase over the base rate in this population, but the comparison fails to reach the conventional level of significance at the 5% level. In the context of this, mainly negative, finding it is important to mention that the validity of the lay administered DIS interview has been called into question with respect to the diagnosis of schizophrenia. In the eastern Baltimore ECA study, κ for agreement with the criterion of a clinical diagnosis was found to be only 0.19 (95% CI 0.00 to 0.29), little better than chance.¹⁷ Random misclassification error in the assessment of the outcome will systematically reduce any true association towards the null.

CASE–CONTROL STUDIES

Wilcox and Nasrallah¹⁸ carried out a classical case–control study in which they used medical records completed on admission to compare previous exposure to head injury *during childhood* among 200 patients with schizophrenia, 122 patients with mania, 203 patients with depression, and 134 “surgical controls”. The participants under study had been admitted to a university hospital in the USA between 1934 and 1944, with a rich historical archive of clinical data. Feighner research criteria were applied (retrospectively) using information from the clinical notes to establish the diagnostic groups. The exposure in this case was self reported head injury with loss of consciousness for more than an hour, or vomiting, confusion or visual changes requiring medical attention. Only reports substantiated (in the notes) by two or more relatives were accepted.

The main results are summarised in table 2. The odds ratios and confidence intervals have been calculated from the data provided. Unfortunately, inclusion and exclusion criteria and selection procedures for cases and controls are not described. Selection bias may well have occurred; there is concern about

* It is not possible to calculate raw numbers of cases from the percentage of the non-head injured subjects given in the paper since they are “weighted” for the sampling strategy (Silver and Greenwald, personal communication). Hence confidence intervals for the proportions and their difference cannot be calculated by the current authors with certainty.

Table 2 Summary of case-control study of head injury and schizophrenia, by Wilcox and Nasrallah¹⁸

	Exposed (HI+)	Not exposed (HI-)	OR (95% CI)
Schizophrenia	22	178	16.6 (2.6 to 689)
Bipolars	6	116	6.9 (0.8 to 321)
Depressives	3	203	2.0 (0.2 to 105)
Surgical controls	1	134	1 (reference group)

CI, confidence interval; HI, head injury; OR, odds ratio.

the suitability of the surgical controls as an unbiased index of exposure in the unaffected general population. Second, rating of the notes for presence or absence of head injury is said to have been carried out blind to diagnostic group, but it is very unclear how this could have been achieved in practice. Third, the problem of recall bias is not properly addressed. The authors insisted on independent confirmation by at least two relatives, presumably to improve the accuracy of recall. In fact, setting this criterion will have tended to accentuate the effect of recall bias ("effort after meaning"). At least two relatives of a person who has gone on to develop schizophrenia are more likely to recall and report a head injury in childhood than would be the case for relatives of surgical patients with appendicitis. Presumably, also, the admitting doctors would be much more likely to go into this kind of developmental history in detail with psychiatric patients than with surgical patients. In summary, there is a strong association observed between schizophrenia and the exposure of reported significant head injury before the age of 10 years. Those with schizophrenia were over 16 times more likely to report this exposure than were surgical controls. However, this study is highly likely to have been subject to bias, the extent and effect of which is impossible to quantify.

Corcoran and Malaspina¹⁹ proposed and tested a more complex model than had been the case with previous studies in this field. They hypothesised that head injury might act in interaction with genetic risk factors in increasing risk for schizophrenia. To test this hypothesis they enquired after a past history of significant head injury (using the diagnostic interview for genetic studies) among 1271 persons from bipolar multiplex pedigrees and 561 persons from multiplex schizophrenia pedigrees, using families collected as part of the National Institute for Mental Health (NIMH) genetics initiative. These families each had two or more first degree relatives affected by schizophrenia or bipolar disorder. The underlying assumption was that the schizophrenia family members would in general have a high genetic risk for that disorder, while the bipolar family members would have a relatively low genetic risk for schizophrenia. Both pedigrees included persons with schizophrenia and their unaffected relatives. The odds of being exposed to a significant head injury was compared between the affected cases and non-affected control groups. For all disorders the odds ratio (OR) was 3.32 (95% CI 1.77 to 6.22), for bipolar disorder the OR was 0.75 (95% CI 0.10 to 5.93), and for schizophrenia the OR was 4.27 (95% CI 1.40 to 13.0).

Therefore overall, people with schizophrenia were over three times more likely to have reported a significant head injury than were unaffected controls. However, the extent of this risk varied between the low genetic risk bipolar pedigree members and the high genetic risk schizophrenia pedigree members. There was in fact no association between head

injury and schizophrenia among the bipolar pedigree members and a fourfold increased risk among those in the high genetic risk schizophrenia pedigrees. The 95% CIs indicate that the association among the schizophrenia pedigrees was significant. The true OR may lie between 1.4–13.0. The absence of an association among the bipolar pedigrees and the strong association among the schizophrenia pedigrees is consistent with the authors' hypothesis that head injury may act in interaction with genetic risk factors increases the risk associated with head injury, and vice versa. Unfortunately the authors did not test this hypothesis more rigorously by testing for the significance of the interaction effect (that is, whether chance alone might have accounted for the different ORs observed in the two pedigrees). Therefore the authors present fairly strong evidence for an association between head injury and schizophrenia among those with strong family histories for schizophrenia, but uncertain evidence as to whether this association is specific to this group.

The main weakness in this study is the method for ascertainment of exposure to head injury. Retrospective enquiry is again likely to be affected by recall. A counter-argument would be that "effort after meaning" would have been just as strong among people with schizophrenia in the multiply affected bipolar pedigrees, yet no association with head injury was observed in this group.

Head injury as a risk factor for schizophrenia was studied more recently using a retrospective case-control design among 23 Canadian families with multiply affected members.²⁰ Again, the 67 affected family members were cases, and their 102 unaffected relatives were controls. Information on head injury was obtained from the participant during the diagnostic interview, "supplemented where available by collateral information from family members and medical records". The authors report that the proportion of cases and controls with a head injury at any time in their lives was similar. However, the schizophrenia cases had an excess of childhood head injuries, with an OR of 2.34 (95% CI 1.03 to 5.36) for head injuries before the age of 10, and an OR of 1.90 (95% CI 0.95 to 3.79) for head injuries occurring up to the age of 17 years. The authors also report that among those with schizophrenia, the history of a head injury was associated with a significantly earlier age of onset. The median latency between childhood head injury and onset of schizophrenia was 12 years. This paper provides some further evidence that head injury may be a risk factor for schizophrenia among those with a family history of the disorder (and therefore a presumed genetic liability). One difficulty with this research design, focusing upon multiply affected families, is that as with Corcoran's study the findings may only apply to the minority with a family history, and may not generalise to others. It also provides some evidence to support Wilcox and Nasrallah's suggestion that head injury in childhood may be associated with risk for schizophrenia. However, they report, overall, no difference in the frequency of head injuries between schizophrenia cases and controls. It is only when they begin to carry out further analyses limited to head injuries occurring within specific age ranges that the one significant association (with head injury occurring before the age of 10 years) emerges. The danger is that the more analyses are conducted, the greater the chance of committing a type 1 error. One other feature of note is that the

classification of head injury included very mild injuries—for example “minor head injury, with no loss of consciousness and no history of being stunned or dazed”. Inclusion of such minor events will have tended to increase potential for recall bias and are generally excluded from the definition of head injury in other research in this field. Similarly, according to the data presented, the majority of injuries involved no loss of consciousness, or momentary loss of consciousness with either no, or very transient and minor sequelae.

Two studies have assessed risk factors for schizophrenia and related psychoses among people who have suffered traumatic brain injury.^{21, 22} In these case–control studies, the base population consisted of persons with head injuries. Both cases and controls were by definition exposed and it is axiomatic therefore that these studies cannot contribute other than tangentially (see below) to an understanding of the role of head injury in the aetiology of schizophrenia. Nevertheless the papers describe an interesting group of cases with a range of clinical observations and neurological investigations.

Sachdev and colleagues²¹ studied 45 referred patients with schizophrenia-like psychosis (SLP) following brain trauma, matched with 45 head injured patients without SLP (or psychosis, major depression, or drug or alcohol disorder) matched on age (current and at injury) and sex. For those with SLP there was a mean latency of 54 months between injury and onset of psychosis. The specific hypotheses were that SLP was most likely to be associated with a head injury that involved the left temporal lobe, had occurred in an individual aged under 5 years, and “in an individual genetically vulnerable to schizophrenia”. It is noteworthy that the second of these hypotheses was not testable in the study design as described since SLP cases and controls were matched for age at head injury. Multiple statistical comparisons revealed an apparent excess of left temporal and right parietal abnormalities on neuroimaging in SLP cases compared with controls. After Bonferroni correction, none of the observed differences was significant. Other characteristics of the head injury (cause of injury, closed or open injury, loss of consciousness, extent of anterograde or retrograde amnesia) did not differ between SLP cases and controls. Verbal memory, non-verbal memory, and frontal executive function were more impaired in SLP cases than in controls. In a multivariate analysis it appears that the effect of localised brain damage was no longer apparent, and that only family history of schizophrenia was associated with SLP. Although the authors claim that *duration* of loss of consciousness was also significantly and independently associated with SLP in this analysis, the analysis as reported examines the effect of loss of consciousness present or not, and shows no significant association. The safe conclusions to draw from this study would seem to be: (1) a family history of schizophrenia is an important risk factor (just as in those without head injury); and (2) the nature and degree of the head injury seem not to influence risk for schizophrenia (with the important proviso that the study had limited power to detect other than very strong associations, therefore important effects may well have been missed).

Fujii and Ahmed²² conducted a similar case–control study with just 25 cases of PDTBI and 25 controls with traumatic brain injury but no psychosis. To meet criteria for PDTBI cases must have had: (a) no family history of psychotic illness, (b) no prior history of psychotic illness, (c) cognitive deficits, and (d) onset of psychosis after brain injury. It was

not stated whether these criteria (a–c) were also applied to the control group, as they should have been. As with Sachdev and colleagues,²¹ by definition it was not possible to assess directly the role of head injury as a risk factor for schizophrenia; additionally, in this study it was not possible to examine the effect of family history of schizophrenia as those with this exposure were excluded, at least from the case group. None of the characteristics of the index head injury were associated with psychosis. However, the study is too small to exclude completely, real and important effects. The authors emphasise one positive finding—that those with psychosis were more likely to have had either a previous head injury or other evidence of neurological disorder. They use this to support the conclusion that “our findings support the general hypothesis that a pre-existing head injury (probably causing brain injury) or a neurological condition are risk factors for developing a psychosis secondary to TBI”. However, other evidence of neurological disorder seems to have been a heterogeneous and ill defined category including *inter alia* serious traumatic brain injury, febrile seizures, and learning difficulties. Classification seems to have been made from clinical records, and it is not clear that this was done blind.

The final case–control study under consideration is technically a nested case–control with incidence density sampling.²³ This design has many methodological advantages, particularly, as shall be described, with respect to minimising selection and information bias. The study relied upon the existence of comprehensive, accurate nationwide registers of healthcare provision, and their accessibility for research. A total of 8288 persons with *International classification of diseases* (ICD)-8 schizophrenia, admitted to a Danish psychiatric hospital between 1978 and 1993, were identified from the Danish Psychiatric Case Register. For each case of schizophrenia, 10 controls were selected from the Central Persons Register (the Danish general population), matched for year of birth, sex, and vital status on the date the case was admitted to psychiatric hospital. Cases and controls were then cross referenced with the National Patient Register, which recorded all admissions to general Danish hospitals, for evidence of an admission with head injury in the period between 1978 and the date of the index psychiatric admission for the case. Evidence of fractures affecting other parts of the body than the head was also sought over a similar period. Associations between head injury and schizophrenia and non-head fractures and schizophrenia were then estimated for three different lag periods for the exposure; in the year before the first admission for the case, in the 1–5 years before the first admission, and in the period more than five years before the admission. The methodological advantages of this approach were as follows:

- ▶ Ascertainment of head injury exposure was made at the time of the injury, and before the onset of schizophrenia in cases. There is no recall involved, and those making the diagnosis of head injury and deciding on admission will have had no way of knowing who would subsequently go on to develop schizophrenia. The two types of information bias, recall and observer bias, which have plagued several of the studies described above are therefore effectively eliminated.
- ▶ Cases comprise all first admissions nationwide over a 15 year period. Controls were matched for the obvious potential confounders of year of birth and age, but were

Table 3 Summary of data from population based Danish study on association between head injury and schizophrenia²³

	Concussion	Severe head injury	Other fractures
No injury	1.0 (reference)	1.0	1.0
Injury	0.94	0.89	0.71*
Head injury, adjusting for fractures	1.37*	1.28*	–
Injury in the period			
<1 year before case admission	2.00*	1.84*	1.10
1–5 years before case admission	0.92	0.71*	0.75*
>5 years before case admission	0.73*	0.78	0.58*

* $p < 0.01$. The authors present p values rather than confidence intervals.

selected at random from among all those with matching characteristics nationwide. Selection bias in such a population based case–control study is highly unlikely.

- ▶ As mentioned earlier, a key consideration is whether any association between head injury and schizophrenia may reflect “reverse causality”—that is, that those in the prodrome of the schizophrenia process may be more accident prone, or may injure themselves with deliberate or suicidal intent. Under those circumstances one would expect there to be a similar association between previous non-head injury and schizophrenia, even though there was no plausible causal mechanism for such a prospective association. Also, the association might be more prominent for injuries occurring in the period immediately before the first admission for the case.

The main findings from this study are summarised in the table 3. The associations between injury and schizophrenia are considered for three exposures—concussion, severe head injury, and other fractures—over each of the three time lag periods. The ORs should be reliable estimates of the relative risk given the incidence density sampling.

Overall, there was no association between either concussion or serious head injury, and schizophrenia (cases and controls were equally likely to have had an admission for these reasons). However, people who developed schizophrenia were *less likely* to have had an admission with a fracture affecting a part of the body other than the head (OR 0.71). As the authors point out, there is no plausible biological mechanism for a protective or risk increasing association between fractured limbs and schizophrenia. This exposure was included to assess the specificity or otherwise of an association with head injury. An increased risk associated with other fractures might suggest reverse causality—that is, that people in the prodrome of schizophrenia were accident prone. In the event, the inverse association presumably suggests that people in the prodrome of schizophrenia are less accident prone perhaps because they are more socially withdrawn and inactive. Nielsen and colleagues took the decision to adjust for experience of other fractures, and having done so showed overall an adjusted modest *increased* risk of schizophrenia associated with concussion (OR 1.37) and severe head injury (OR 1.28). While we understand the authors’ arguments for adjusting for other fractures, technically they were incorrect to do so, having concluded that the apparent protective effect of other fractures was not directly causal, but rather reflected a process of reverse causality, as described above. Further analysis of the association between concussion, head injury, other fractures, and schizophrenia over different lag periods between exposure and onset of schizophrenia indicates that they are generally more likely

than controls to be exposed in the one year before the case’s first psychiatric admission, whereas the reverse is true for the period one or more years before the case’s first admission. The authors present a number of analyses stratified by sex, indicating different patterns of association between head injury and schizophrenia between the two sexes. However, the differences in the size of the effect are generally modest, there has been no testing for the significance of the proposed effect modification by sex, and there is no suggestion that the authors had formulated an a priori hypothesis of different effects of head injury in men and women.

This study provides the strongest evidence by far upon which to base an assessment of the likely direction and strength of an association between head injury and schizophrenia. The parsimonious interpretation of the reported findings is that there is no association between either concussion or head injury and the later onset of schizophrenia. The higher odds of exposure to head injury among schizophrenia cases compared with same age and sex controls in the year before their first psychiatric admission is, given the lower odds of exposure in previous years, highly likely to reflect reverse causality. One possible explanation for the findings is that patients presenting with a psychosis in whom there is a clearly identified history of head trauma, may have been placed in the ICD-8 category 293.5—precisely for this purpose. This would lead to an underestimate of “schizophrenia” in people with previous head trauma—a possibility that the authors are not able to discount (PB Mortensen, personal communication). The study is well designed, relatively free of bias, and given the large sample size would have had ample statistical power to have detected even very modest true associations between head injury and schizophrenia. While the study was conducted in Denmark, there is no reason to assume that its findings would not be widely generalisable, including to the population of the UK.

As a general conclusion to this section, case–control studies are difficult to design and conduct, in particular because of problems of potential bias inherent in the retrospective character of the study design. The two studies limited to those with head injuries are essentially irrelevant to the question of whether head injury is a cause of schizophrenia. The study by Silver and colleagues¹⁶ has the strengths of the large sample size (although still relatively small in terms of the rare outcome of schizophrenia) and sound methodology. The study of Nielsen and colleagues²³ stands apart from others in this category of study design, in terms of its size and statistical power, the use of comprehensive contemporaneous records of admission with head injury made before the onset of psychosis in the cases, and in its representative population based selection of schizophrenia cases and suitably matched controls. The discrepancy between

the essentially negative findings of this and the positive associations between head injury and schizophrenia reported in earlier case-control studies is in our opinion most likely explained by biases in the latter.

CONCLUSIONS

The individual case reports can contribute little of evidential value to the question under consideration; whether head injury can be considered to be causally implicated as a risk factor for schizophrenia. The long term follow up studies of head injured cohorts would generally seem to suggest a higher cumulative incidence for schizophrenia than would be expected for the general population, but they each have prominent methodological shortcomings. The classical case-control studies, as described in the preceding section, report apparently irreconcilably different estimates for the association between head injury and schizophrenia. The best designed and conducted study²³ is the most likely to lead to precise and valid estimates of the association between head injury and schizophrenia. One large US cross sectional survey¹⁶ was also essentially negative. The strategy of looking for an interaction between head injury and genetic predisposition or vulnerability to schizophrenia is worth pursuing, perhaps using genetic markers (for example, APOE). However, given the available published data, one must conclude that it is unlikely that head injury causes schizophrenia.

ADDENDUM

An additional (historical) cohort study was published in January 2004.²⁴ This was carried out in a health maintenance organisation covering 4500 members in Washington State, USA. The exposed group consisted of 939 adult patients, diagnosed at an emergency department, hospital, or outpatient clinic as having a traumatic brain injury in 1993. Eighty five per cent of head injuries were classified as mild, 15% as moderate or severe. Three unexposed control patients were selected for each exposed patient, frequency matched for sex, age and enrolment time. Their health records were searched for the period one year before and three years following the head injury date for evidence of psychiatric diagnoses and/or treatment. Forty eight per cent of diagnoses were made by family practitioners. The most striking association was that between moderate to severe head injury and pre-existing psychotic disorder (in the year before the injury): 18/136 (13.2%) of those with moderate to severe head injury had pre-existing psychosis compared with 1.5% of matched unexposed patients (OR 10.0); 2.5% of those with mild head injury had pre-existing psychotic disorder (OR 1.7). For the moderate to severe head injury group, there were similar numbers of psychosis cases (14 (13.0%) in the year after, 8 (9.1%) two years after and 11 (14.5%) three years after)—presumably these were essentially the same cases. Among those with no pre-existing psychiatric illness of any kind with moderate to severe head injury (only 85 cases total), there seemed to be a pronounced elevation in risk for psychotic disorder, in the second and third year after the injury. Compared to those not exposed, the OR in the second year was 5.9 (95% CI 1.6 to 22.1), and in the third year, 3.6 (95% 1.0 to 1.3). The authors conclude that these effects “are consistent with findings from other reports of delayed psychosis after traumatic brain injury”. However, they found a strong association between pre-existing psychosis and head injury, but only searched the health records for this for the

year before the injury. It is likely that relevant diagnoses would have been missed, both because of the restricted period of scrutiny, and because of the reliance upon primary care records. Thus, many of the apparent incident cases of psychosis in the second or third year after head injury may well have occurred in individuals with past histories of psychosis that had been missed. This study was essentially prospective hence information bias in the ascertainment of exposure should not be a problem. Reliance on case notes to ascertain outcome, limited scrutiny for past history of mental illness and the relatively small sample with psychosis are weaknesses. We would conclude that the study provides strong evidence that pre-existing psychosis predisposes to head injury, but only weak evidence for head injury as a cause of psychosis.

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