Head Injury as Risk Factor for Psychiatric Disorders: A Nationwide Register-Based Follow-Up Study of 113,906 Persons With Head Injury

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Objective: Studies investigating the relationship between head injury and subsequent psychiatric disorders often suffer from methodological weaknesses and show conflicting results. The authors investigated the incidence of severe psychiatric disorders following hospital contact for head injury.

Method: The authors used linkable Danish nationwide population-based registers to investigate the incidence of schizophrenia spectrum disorders, unipolar depression, bipolar disorder, and organic mental disorders in 113,906 persons who had suffered head injuries. Data were analyzed by survival analysis and adjusted for gender, age, calendar year, presence of a psychiatric family history, epilepsy, infections, autoimmune diseases, and fractures not involving the skull or spine.

Results: Head injury was associated with a higher risk of schizophrenia (incidence rate ratio [IRR]=1.65, 95% CI=1.55–1.75), depression (IRR=1.59 95% CI=1.53–1.65), bipolar disorder (IRR=1.28, 95% CI=1.10–1.48), and organic mental disorders (IRR=4.39, 95% CI=3.86–4.99). This effect was larger than that of fractures not involving the skull or spine for schizophrenia, depression, and organic mental disorders, which suggests that the results were not merely due to accident proneness. Head injury between ages 11 and 15 years was the strongest predictor for subsequent development of schizophrenia, depression, and bipolar disorder. The added risk of mental illness following head injury did not differ between individuals with and without a psychiatric family history.

Conclusions: This is the largest study to date investigating head injury and subsequent mental illness. The authors demonstrated an increase in risk for all psychiatric outcomes after head injury. The effect did not seem to be solely due to accident proneness, and the added risk was not more pronounced in persons with a psychiatric family history.

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The possible development of psychiatric disorders as a consequence of head injury has been investigated for decades with greatly varying results. A recent meta-analysis (1) suggested that onset of schizophrenia appears more frequently following head injury; however, the included studies showed significant heterogeneity. Two of the most robust studies based on the Scandinavian registers did not seem to find an overall increased risk of schizophrenia (2, 3) but found only a small increase in risk among male patients with schizophrenia (3) and in nonaffective nonschizophrenia psychosis (2). Depression seems to be the most common psychiatric disorder following head injury (4). However, although one study (5) found the risk of depression to be highly increased when a head-injury group was compared with a noninjured control group, another study (6), comparing a head-injury group with persons who had other injuries, did not find a significantly increased risk. Bipolar disorder has been suggested to be the most uncommon mood disorder following head injury (7). Nonetheless, the largest study found a moderately increased risk of postinjury bipolar disorder (8), while others did not observe a significantly increased risk (5). Several hypotheses have been proposed about the association between mental illness and head injury, addressing aspects such as the location of the injury, postinjury changes in the brain (4, 9–12), and the ability of the brain to recover through neuroplasticity (13). The potentially harmful inflammatory response in the CNS after a head injury (14, 15) may also have an impact on the subsequent risk of mental illness.

Use of the Danish registers to investigate the link between head injury and mental illness offers advantages in overcoming many limitations of previous studies: elimination of recall bias, comparison of the head-injury cohort with the background population, and adjustment for various confounders. To consider the possibility of greater accident proneness among persons who received psychiatric diagnoses after head injury, we additionally controlled for non-CNS-related fractures, a factor included in few other studies (3, 8). In line with recent immunological hypotheses, we investigated the possible interaction between head injury and infections or autoimmune diseases.

This article is featured in this month's AJP Audio and is the subject of a CME course (p. 475)

TABLE 1. Risk of Psychiatric Disorders Associated With Hospital Contact for Head Injury[a]

	Schizophrenia Spectrum Disorders					Unipolar Depression	
Head Injury Contact and Severity	N	IRR	95% CI	IRR[b]	95% CI[b]	N	IRR
No hospital contact for head injury (reference)	9,303	1.00		1.00		21,793	1.00
Hospital contact for head injury	1,304	1.65	1.55–1.75	1.48	1.40–1.57	2,812	1.59
Mild head injury	1,156	1.64	1.54–1.74	1.47	1.38–1.56	2,539	1.59
Skull fracture	52	1.28	0.96–1.66	1.15	0.86–1.49	107	1.27
Severe head injury	96	2.16	1.75–2.62	1.83	1.49–2.23	166	1.77

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.
[b] Further adjusted for fractures not involving the skull or spine, a family history of psychiatric disorders, epilepsy, and infections.
[c] Because of low case numbers, IRRs were adjusted only in the basic model.

To our knowledge, this is the largest study to date to investigate the association between head injury and psychiatric disorders.

Method

The Registers

The Danish Civil Registration System (16), established in 1968, contains demographic data and allows identification of parents. It assigns all Danish residents a unique identification number that permits linkage between the national registers. Inpatient psychiatric contacts are registered in the Danish Psychiatric Central Register (17), which was computerized in 1969. In 1995, outpatient psychiatric and emergency department contacts were also included. The Danish National Hospital Register (18) has contained information on somatic inpatient hospital contacts since 1977 and outpatient and emergency department contacts since 1995. All registered diagnoses are defined according to ICD codes; ICD-8 was used until 1993 and ICD-10 from 1994 onward.

Study Population

The national registers enabled us to create a cohort of individuals born in Denmark between January 1, 1977, and December 31, 2000. These individuals were identified by their identification number and followed until death, emigration, or December 31, 2010. All individuals were followed in the Danish National Hospital Register for diagnoses of head injury and linked to the Danish Psychiatric Central Register for the included psychiatric outcomes. We used the first-time psychiatric diagnoses of each outcome after the 10th birthday during the period 1987–2010. Persons who had psychiatric diagnoses before injury, including substance use disorders, were excluded.

Data Collection

We acquired data on four general outcomes from the Danish Psychiatric Central Register: schizophrenia spectrum disorders, unipolar depression, bipolar disorder, and organic mental disorders (diagnostic codes are listed in the data supplement that accompanies the online edition of this article). The organic mental disorders are characterized by a known physical etiology to the psychiatric symptoms. Some of the organic disorders included diagnoses that imply a previous head injury diagnosis. Hence, we performed subanalyses with the definition restricted to diagnoses that do not necessarily presuppose head injury and with symptoms similar to those in the schizophrenia and mood disorder spectrum. We collected the parental history of psychiatric disorders (including substance use disorders) identified in the Danish Psychiatric Central Register and the Danish National Hospital Register. The Danish National Hospital Register provided the exposure diagnoses of head injury, which were categorized according to a three-level hierarchy (19): mild head injury, skull fracture, and severe head injury. The occurrence of more than one head injury diagnosis for the same patient within 14 days was considered a coding error and thus recorded as the same event according to this hierarchy. The definition of mild brain injury used in Denmark is that of the American Congress of Rehabilitation Medicine (19) and involves a direct trauma to the head resulting in a change of brain function. Any loss of consciousness cannot exceed 30 minutes, and any posttraumatic amnesia cannot exceed 24 hours; after 30 minutes, the Glasgow Coma Scale score cannot be <14. If these criteria are exceeded, the brain injury is defined as severe. Skull fracture can be present alone or combined with other types of head injury. In the present study, a total of 6,452 persons had hospital contacts for skull fracture; of these, 2,749 individuals (43%) also had a mild head injury and 1,501 individuals (23%) also had a severe head injury. From the Danish National Hospital Register, we obtained diagnoses of fractures not involving the skull or spine. These were included as an indicator of accident proneness prior to the head injury potentially due to an undiagnosed psychiatric disorder. Individuals diagnosed with both head injury and such fractures entered the study as part of the head-injury cohort. We collected diagnoses of autoimmune disease and infections leading to hospital contact in order to investigate the possible added risk of mental disorders in persons with concomitant head injury. Our definition of infections excluded diagnoses of AIDS/HIV and ICD-8 diagnoses with the modification code "suspected" or "not found" and similar codes in ICD-10. We also obtained the first-time diagnoses of epilepsy.

The Danish Data Protection Agency approved the study.

Statistical Analysis

Survival analysis was performed in SAS, version 9.2 (SAS Institute, Cary, N.C.), and the incidence rate ratios (IRRs) were estimated by log-linear Poisson regression. All analyses were adjusted for gender, age, and calendar year in the basic model. In the fully adjusted model, we included non-CNS-related fractures, psychiatric family history, epilepsy, and infections. We investigated for multiplicative interaction between head injury and psychiatric family history, infections, and autoimmune disease. The risk of mental illness following head injury was evaluated in different age groups divided into 5-year intervals and estimated according to time since head injury. All variables except gender were treated as time dependent.

Results

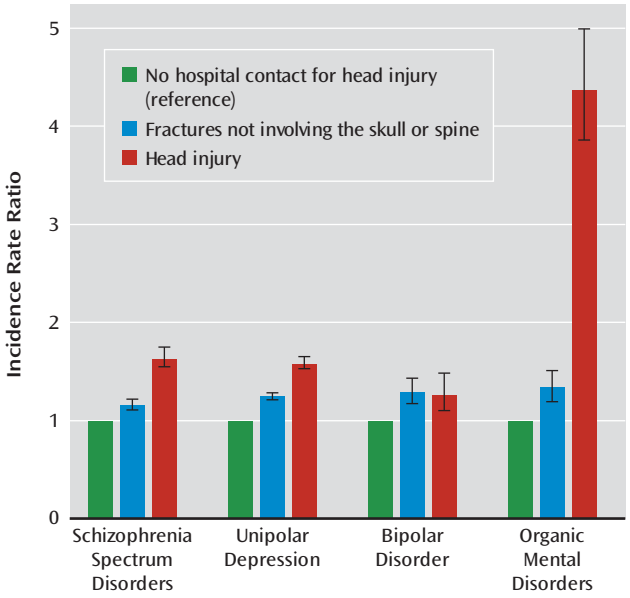
During the period 1977–2000, a total of 1,438,339 individuals were born in Denmark, of whom 113,906 had a hospital contact for head injury between 1977 and 2010. All individuals with a hospital contact for head injury were followed for

Unipolar Depression			Bipolar Disorder[c]			Organic Mental Disorders[c]		
95% CI	IRR[b]	95% CI[b]	N	IRR	95% CI	N	IRR	95% CI
	1.00		1,668	1.00		877	1.00	
1.53–1.65	1.46	1.40–1.51	191	1.28	1.10–1.48	322	4.39	3.86–4.99
1.53–1.66	1.46	1.40–1.52	180	1.35	1.16–1.57	155	2.38	2.00–2.82
1.04–1.52	1.16	0.95–1.39	5	0.67	0.24–1.43	22	5.63	3.58–8.38
1.51–2.05	1.56	1.33–1.81	6	0.72	0.29–1.47	145	36.22	30.23–43.09

the included psychiatric outcomes from their 10th birthday in the period 1987–2010. During this period, 38,270 individuals were diagnosed with any of the included psychiatric disorders, amounting to 16,269,924 person-years of follow-up. Out of these, a total of 10,607 persons had a diagnosis of schizophrenia, of whom 1,304 (12%) had previously been exposed to head injury; 24,605 persons had a depression diagnosis, of whom 2,812 (11%) had a previous head injury; 1,859 persons had a bipolar disorder, of whom 191 (10%) had a previous head injury; and 1,199 persons had an organic mental disorder, of whom 322 (27%) had a previous head injury. Of all persons with head injury, a total of 4,629 (4%) were subsequently diagnosed with one of the included severe psychiatric disorders.

A hospital contact for head injury was associated with an increased risk of schizophrenia, depression, bipolar disorder, and organic mental disorders (IRRs, 1.65, 1.59, 1.28, and 4.39, respectively) (Table 1). The risks of schizophrenia and depression were still significantly elevated in the full model (IRRs, 1.48 and 1.46), which adjusted for several confounders, including epilepsy. For schizophrenia, depression, and organic mental disorders, the risk was highest after exposure to severe head injury (IRRs, 2.16, 1.77, and 36.22). A trend in the hierarchy of head injury severity was present only in relation to the organic disorders (p=0.51) but not to schizophrenia (p=0.01) or depression (p=0.006). Trend analyses could not be performed for bipolar disorder because of low case numbers. There was no interaction between gender and risk of schizophrenia, depression, bipolar disorder, or organic mental disorders. Non-CNS-related fractures increased the risk of all outcomes (schizophrenia: IRR=1.16, 95% CI=1.11–1.22; depression: IRR=1.25, 95% CI=1.21–1.28; bipolar disorder: IRR=1.29, 95% CI=1.17–1.43; and organic mental disorders: IRR=1.34, 95% CI=1.19–1.51) (Figure 1). However, the effect of head injury was significantly greater than the effect of these fractures with respect to schizophrenia, depression, and organic mental disorders (p values <0.001) but not with respect to bipolar disorder. When the analyses of organic mental disorders were restricted to diagnoses with symptoms included in the schizophrenia and mood disorder spectrum (394 persons, of whom 88 had hospital contacts for head injury), the risk after exposure to head injury was still significantly increased (IRR=3.26, 95% CI=2.54–4.13).

FIGURE 1. Risk of Psychiatric Disorders Associated With Hospital Contact for Head Injury and Fractures Not Involving the Skull or Spine[a]



[a] Adjusted for gender, age, and calendar year. Error bars indicate 95% confidence interval.

There was significant interaction between head injury and time since head injury for organic mental disorders, schizophrenia, and depression (p values <0.001) but not for bipolar disorder.

The risk increased with temporal proximity to the head injury, with the highest risk found during the first year after injury for organic mental disorders, schizophrenia, and depression (IRRs, 9.47, 2.26, and 1.95) (Table 2). Among all age groups, head injury between 11 and 15 years of age was the strongest predictor of the subsequent development of schizophrenia, depression, and bipolar disorder (IRRs, 1.86, 1.60, and 1.30) (Table 3). The risk of schizophrenia and depression in this age group was significantly larger than the risk found in the group of persons 6–10 years of age (p<0.001 and p=0.002) and in the group of persons older than 15 years of age (p values <0.001).

Individuals with a psychiatric family history might be expected to be more accident prone than others; however,

TABLE 2. Risk of Psychiatric Disorders, by Time Since Hospital Contact for Head Injury[a]

Time Since Hospital Contact for Head Injury	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No hospital contact for head injury (reference)	9,303	1.00		21,793	1.00		1,668	1.00		877	1.00	
<1 year	89	2.26	1.82–2.76	151	1.95	1.66–2.28	6	1.09	0.43–2.21	35	9.47	6.63–13.08
1–5 years	319	1.87	1.67–2.08	650	1.87	1.73–2.02	39	1.48	1.06–2.01	84	5.31	4.21–6.60
6–10 years	356	1.72	1.54–1.91	733	1.60	1.48–1.72	56	1.51	1.15–1.95	90	4.58	3.66–5.66
11–15 years	285	1.53	1.36–1.72	647	1.52	1.41–1.65	42	1.21	0.88–1.62	59	3.56	2.70–4.59
>15 years	255	1.35	1.19–1.53	631	1.36	1.26–1.47	48	1.05	0.78–1.39	54	3.02	2.26–3.96

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.

TABLE 3. Risk of Psychiatric Disorders, by Age at Hospital Contact for Head Injury[a]

Age at Hospital Contact for Head Injury	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No hospital contact for head injury (reference)	9,303	1.00		21,793	1.00		1,668	1.00		877	1.00	
0–5 years	226	1.35	1.18–1.54	511	1.36	1.24–1.48	27	0.95	0.63–1.36	56	3.51	2.65–4.56
6–10 years	242	1.33	1.16–1.50	522	1.34	1.23–1.46	27	0.88	0.59–1.26	52	3.00	2.24–3.93
11–15 years	334	1.86	1.66–2.07	637	1.60	1.48–1.74	40	1.30	0.93–1.75	55	3.28	2.47–4.27
>15 years	502	1.14	1.04–1.25	1,142	1.26	1.19–1.34	97	1.23	0.99–1.50	159	3.67	3.08–4.34

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.

as shown in Table 4, head injury actually added significantly more to the risk of schizophrenia, bipolar disorder, and organic mental disorders in persons without a psychiatric family history. The risk of depression after head injury was the same regardless of psychiatric family history. Infections and autoimmune disease have previously been shown to act as independent risk factors for psychiatric disorders (20, 21), and they could interact with the effect of head injury. Nonetheless, head injury contributed significantly more to the risk of organic mental disorders in individuals without infections compared with individuals with infections (p=0.008). This was not the case for the risk of schizophrenia, depression, or bipolar disorder. In persons with and without autoimmune disease, head injury did not add significantly more to the risk of schizophrenia, depression, bipolar disorder, or organic mental disorders.

Discussion

In the largest population-based study to date, we found an increased risk of schizophrenia, depression, bipolar disorder, and organic mental disorders following head injury. The findings regarding schizophrenia, depression, and organic mental disorders could not altogether be attributed to accident proneness, since the effect of head injury exceeded the effect of non-CNS-related fractures. The risk seemed to be largest after exposure to severe head injury, even though the expected dose-response relationship of head injury severity was present only for organic mental disorders. The added risk did not differ in those with and without a psychiatric family history.

Our results demonstrated a 65% increase in the risk of schizophrenia following head injury, which is in line with results of a recent meta-analysis (1) and several previous studies (1, 22–24), although several other studies did not find a strong association (2, 3, 25, 26). In a Taiwanese follow-up study (22), the risk of schizophrenia was found to be doubled after traumatic brain injury, but the authors could not rule out preinjury mental illness. A smaller Danish register study (3) found only a slight increase in the risk of schizophrenia among men when accident proneness was taken into account. The incidence of nonaffective nonschizophrenia psychoses, but not of schizophrenia, was increased in a Swedish register study (2) after adjustment for birth-related data and socioeconomic status.

In this study, we found the risk of depression to be increased by 59% after a head injury. This is supported by some previous studies (5, 23, 27) but not by others (6, 28). A study relying on retrospective self-report (27) among U.S. soldiers found exposure to mild head injury to increase the risk of depression more than threefold compared with exposure to other types of injury. Another study (28), however, compared 437 persons exposed to mild head injury to otherwise injured controls and did not find the prevalence of depression to be significantly increased.

We found the risk of bipolar disorder following head injury to be increased by 28%, while previous prevalence rates ranged widely from 2% to 17% (29). A Danish register study (8) found the risk of bipolar disorder to be approximately

TABLE 4. Risk of Psychiatric Disorders Associated With Head Injury in Persons With and Without a Family History of Psychiatric Disorders, a Hospital Contact for Infection, and Autoimmune Disease[a]

	Schizophrenia Spectrum Disorders			Unipolar Depression			Bipolar Disorder			Organic Mental Disorders		
Variable	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI	N	IRR	95% CI
No psychiatric family history												
No head injury (reference)	6,596	1.00		16,298	1.00		1,124	1.00		627	1.00	
Head injury	873	1.65	1.53–1.77	1,939	1.55	1.47–1.62	130	1.37	1.14–1.63	235	4.76	4.09–5.53
Psychiatric family history[b]												
No head injury (reference)	2,707	1.00		5,495	1.00		544	1.00		250	1.00	
Head injury	431	1.41	1.27–1.56	873	1.49	1.39–1.60	61	0.96	0.73–1.24	87	3.10	2.41–3.93
No hospital contact for infection												
No head injury (reference)	5,670	1.00		13,307	1.00		1,010	1.00		438	1.00	
Head injury	690	1.66	1.53–1.79	1,441	1.56	1.47–1.64	100	1.30	1.05–1.58	155	4.93	4.08–5.92
Hospital contact for infection[b]												
No head injury (reference)	3,633	1.00		8,486	1.00		658	1.00		439	1.00	
Head injury	614	1.52	1.39–1.65	1,371	1.51	1.42–1.60	91	1.19	0.95–1.47	167	3.48	2.89–4.16
No hospital contact for any autoimmune disease												
No head injury (reference)	9,100	1.00		21,165	1.00		1,626	1.00		847	1.00	
Head injury	1,259	1.63	1.54–1.73	2,720	1.59	1.53–1.66	185	1.28	1.10–1.48	313	4.45	3.89–5.06
Hospital contact for any autoimmune disease[b]												
No head injury (reference)	203	1.00		628	1.00		42	1.00		30	1.00	
Head injury	45	2.17	1.55–2.97	92	1.46	1.17–1.81	6	1.31	0.50–2.86	9	2.93	1.31–5.92

[a] IRR=incidence rate ratio; adjusted for gender, age, and calendar year.
[b] The main effect of a psychiatric family history, infections, and autoimmune disease is not included.

40% higher after head injury when adjusting for other fractures, while another study (5) did not find an increased risk.

Gender did not seem to interact in our study with the risk of psychiatric illness after head injury. This is in line with several previous findings (2, 9, 30), whereas other studies found an effect of both male (3) and female gender (8, 23). The incidence of schizophrenia and depression in our study was highest the first year after injury and continued to be significantly elevated throughout the following 15 years and beyond, which makes detection bias a somewhat unlikely explanation for these findings. The risk of schizophrenia has previously been shown to be significantly increased the first years (3, 23) and even 30 years (29) after head injury. The latter result was also found for depression (29), suggesting that depression is not merely a transient psychological reaction following head injury, as indicated by previous results (31). The late increase in risk of bipolar disorder in our study contrasts with previous findings (8) and could reflect the fact that many patients with bipolar disorder are initially diagnosed with other psychiatric disorders. Persons exposed to head injury between ages 11 and 15 had the highest risk of a later diagnosis of schizophrenia or depression. A fivefold higher risk of depression was previously found for individuals who suffered traumatic brain injury at 12–14 years of age compared with traumatic brain injury before age 9 (30). A meta-analysis (1) did not find childhood or adolescent head injury to be more strongly associated with schizophrenia. Interestingly, it has been theorized that essential neurodevelopment occurs from 11 to 15 years of age, when deterioration in development can possibly lead to psychosis (32).

The more than fourfold higher risk of organic mental disorders following head injury and 36-fold following severe head injury strongly suggests that some individuals do experience psychiatric symptoms after a head injury. The risk was still more than three times higher for the restricted definition of organic mental disorders, including diagnoses with symptoms similar to those in the schizophrenia and mood disorder spectrum. The inclusion of the organic mental disorders that presuppose a previous head injury served primarily as validation of the expected dose-response relationship of head injury severity, which was presented only for the organic disorders. Only a few studies have observed a dose-response relationship (11, 33), while the majority did not (1, 6, 9, 10, 22, 24, 29, 31). This might be due to fundamental limitations in the assessment of head injury severity (34, 35). Furthermore, the boundaries between the head injury subgroups are most probably subject to diagnostic overlap (19). Also, in our study, not all patients with skull fracture were concomitantly diagnosed with mild (43%) or severe head injury (23%). For the remaining patients, either only the main head injury diagnosis was noted in the medical record or the patients actually experienced less severe cognitive symptoms than the other groups.

Persons with psychiatric disorders that are not yet diagnosed might be more prone to accidents (23, 36). However, the observed increased risk of schizophrenia,

depression, and organic mental disorders associated with non-CNS-related fractures was significantly exceeded by the effect of head injury. Nevertheless, accident proneness has been suggested to be associated with prodromal symptoms of psychosis (2, 3) and with decreased attention in patients with depression (36) and even in unaffected individuals predisposed to schizophrenia (24). In line with previous studies (2, 9, 10), we found that head injury did not add more to the risk of mental illness in persons with a psychiatric family history. The finding that persons without a psychiatric family history or infections experienced a greater effect of head injury with regard to some psychiatric outcomes could be due to undiagnosed illness or less severe illness treated outside the hospital. We also used psychiatric family history as a proxy for lower socioeconomic status (4) and lower education levels (6), both of which have been suggested to increase the risk of postinjury psychiatric disorders. Psychiatric family history might also be an indicator of dysfunctional family dynamics, which has been suggested to complicate postinjury recovery and contribute to mental illness (2, 4, 22). Individuals with preinjury psychiatric and substance use disorders were excluded. Physical abuse might also have confounded our results. However, besides adjusting for psychiatric family history, the adjustment for other fractures probably also removed some of this possible effect. Furthermore, individuals with epilepsy might have an increased risk of head injury (37), schizophrenia (38), and bipolar disorder (33), and epilepsy occurs more frequently following head injury (19). Nonetheless, after adjustment in the full model, which included epilepsy, the risks for schizophrenia and depression remained significantly elevated.

Head injury has been shown to increase the permeability of the blood-brain barrier (39) and possibly activate microglia within the brain (14). This might allow immune components from the peripheral blood access to the brain (14), possibly leading to neural dysfunction (39). Additionally, it has been suggested that after injury, brain tissue can be released into the peripheral blood with a possible synthesis of CNS-reactive antibodies (15). Such antibodies might reach the brain during subsequent periods of increased permeability of the blood-brain barrier, in line with the mechanisms by which autoimmune diseases and infections have previously been suggested to increase the risk of schizophrenia and depression (20, 21, 39). Although we did not find significant interaction between head injury and infections or autoimmune disease, they still acted as independent risk factors associated with mental illness, as has been shown previously (20, 21).

However, the most prominent hypotheses of the possible detrimental effect of head injury have been nonimmunological. Studies have found psychosis and mania after head injury to be associated with the anatomical location of the injury (10–12), and postinjury depression has been associated with reduced volumes of certain brain regions (4, 9). Moreover, it has been suggested that diffuse axonal injury disrupts neurotransmitter systems involved in psychosis and mood regulation (35). The outcome after head injury may also depend on the ability of the brain to recover through processes of neuroplasticity, and this ability may depend on age at injury (13), as reflected in the age effect observed in our study. The subsequent mental illness could also be a psychological reaction to the traumatic nature of the accident (2) or to the functional deficits that some individuals experience following a head injury (23, 34).

The large national cohort and the 34-year follow-up period are major strengths of the study. Restricting the cohort to individuals born on or after January 1, 1977, provided complete data on hospital contacts of the persons included, and the prospective design eliminated recall bias, as the outcomes were registered independently of all exposure diagnoses. A validation study (40) examined selected ICD-8 head injury diagnoses from the Danish National Hospital Register in the matched medical records and found correct diagnoses in 88% of the cases. A limitation of our study is that because the oldest cohort members were 33 years old, we may have underestimated the effect of head injury, as some individuals were probably not yet diagnosed with psychiatric disorders. Since our study included severe illness that led to hospital contact, our results are probably not referable to milder illness treated outside hospital settings. Furthermore, it was not possible to adjust for physical abuse as a confounder or to include posttraumatic stress disorder as an outcome.

In summary, we found that head injury increased the risk of all psychiatric outcomes. For schizophrenia, depression, and organic mental disorders, this effect did not seem to be ascribable merely to accident proneness or a psychiatric family history. The risk appeared to be greatest the first year following injury, and for schizophrenia and depression, those in the 11- to 15-year age group were shown to be especially vulnerable to exposure to head injury. This age effect could indicate a particularly sensitive period in neurodevelopment when the impact of a head injury can possibly lead to the development of mental illness.

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