

Traumatic Stress Disorders and Risk of Subsequent Schizophrenia Spectrum Disorder or Bipolar Disorder: A Nationwide Cohort Study

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Objective: Traumatic stress disorders are prevalent in patients with schizophrenia and bipolar disorder. However, there is a lack of prospective longitudinal studies investigating the risk of severe mental illness for people diagnosed with traumatic stress disorders. We aimed to assess if patients with acute stress reaction (ASR) or post-traumatic stress disorder (PTSD) are at increased risk of schizophrenia spectrum disorders or bipolar disorder. **Methods:** We performed a prospective cohort study covering the entire Danish population including information on inpatient and outpatient mental hospitals over 2 decades. Predictors were in- or outpatient diagnoses of ASR or PTSD. We calculated incidence rate ratios (IRR) with 95% CIs of schizophrenia, schizophrenia spectrum disorder, and bipolar disorder. **Results:** Persons with a traumatic stress disorder had a significantly increased risk of schizophrenia (IRR 3.80, CI 2.33–5.80), schizophrenia spectrum disorder (IRR 2.34, CI 1.46–3.53), and bipolar disorder (IRR 4.22, CI 2.25–7.13). Risks were highest in the first year after diagnosis of the traumatic stress disorder and remained significantly elevated after more than 5 years. Mental illness in a parent could not explain the association. **Conclusion:** Our findings support an association between diagnosed traumatic stress disorders and subsequent schizophrenia spectrum disorder or bipolar disorder. If replicated, this may increase clinical focus on patients with traumatic stress disorders.

Key words: post-traumatic stress disorder/acute stress reaction/schizophrenia/schizophrenia spectrum disorder/bipolar disorder

Introduction

Traumatic experiences may have long-term effects on the structure and function of the human brain¹ and it

is hypothesized that these changes might lead to mental illness,² including mood disorders and psychosis.³ Studies have confirmed a high comorbidity between post-traumatic stress disorder (PTSD) and schizophrenia and bipolar disorder respectively. Compared to a prevalence of PTSD in the general population of 7.8%,⁴ a meta-analysis found a mean prevalence rate of PTSD on 12.4% in people with schizophrenia⁵ and of 16% in people with bipolar disorder.⁶ Another meta-analysis compared data from heterogeneous studies and found a crude estimated prevalence of PTSD of 29% in people with schizophrenia.⁷

However, the relationships of traumatic experiences, traumatic stress disorders, and severe mental illness remain complex and poorly understood. For example, a large proportion of people with PTSD develop psychotic symptoms,⁸ but psychosis has also been reported to cause traumatic-like experiences. Also, traumatic stress disorders and severe mental illness may both be on a spectrum precipitated by traumatic experiences.⁹

Our dataset enabled us to investigate clinically relevant questions: What is the prognosis of people diagnosed with traumatic stress disorder? Does this population have a higher risk of developing severe mental illness? And if so, is this risk sufficiently large to be clinically relevant? And finally, how does the risk changes over time from when a person is diagnosed with a traumatic stress disorder?

Much research on traumatic stress disorders and severe mental illness has focused on PTSD and psychosis, and research on the association between acute stress reaction (ASR) and severe mental illness is scarce. The diagnostic criteria of PTSD and ASR both require the experience of a trauma, such as assault, rape, war, or natural disaster.^{10,11} Thus, we hypothesize that a diagnosis of ASR is

equally associated with an increased risk of severe mental illness. Furthermore, in Denmark, ASR is approximately 3 times as prevalent as PTSD.¹² This adds to the clinical relevance of investigating the prognosis of people diagnosed with ASR.

Most research has focused on the association of traumatic stress disorders and psychosis, and research on the relationship of traumatic stress disorders and bipolar disorder remain limited. Traumatic experiences in childhood has been associated with an increased risk of developing bipolar disorder and schizophrenia.^{13,14} Whether this relationship holds true for traumatic stress disorders diagnosed in adulthood is currently unknown.

Lastly, it has both theoretical and clinical relevance to elucidate how a family history of severe mental illness may affect the association of traumatic stress disorders and severe mental illness.

We used a prospective cohort design to investigate if patients with traumatic stress disorder were at higher risk of developing a schizophrenia spectrum disorder or bipolar disorder, while adjusting for mental illness in parents. Elucidating the temporal relationship of the disorders may add both to our understanding of how traumatic experiences could contribute to the development of severe mental illness, but also provide valuable clinical information on periods of high-risk. Thus, we investigated the potential temporal effect of traumatic stress disorder on the subsequent risk of psychosis. As such, this is the first high-powered, nationwide longitudinal study on traumatic stress disorder and severe mental illness.

Methods

Study Population

Using the Danish Civil Registration System,¹⁵ we established a population-based cohort including all individuals born in Denmark between 1985 and 2004, who were alive on their 10th birthday, and with both parents born in Denmark ($N = 1\,005\,021$). In Denmark, all live-born children and new residents were assigned a unique personal identifier, which can be used to link information within and across the nationwide computerized Danish registers. The Civil Registration System was established in 1968, and all persons alive and living in Denmark were registered for administrative use. With regards to individuals born in Denmark in 1960 or later, it contains information on maternal identity. It furthermore contains complete information on immigrations and emigrations from 1971 onwards. The prevalence of Danish citizens missing in the registers is low (0.3%) and data accuracy is ensured by a number of control mechanisms at various levels, including registration required by law, electronic and personal validation. Also the data are continuously used by the administrative system in Denmark which corrects errors whenever they are encountered.¹⁶

Psychiatric Diagnoses

Psychiatric diagnoses were obtained from the Danish Psychiatric Central Research Register,¹⁷ which contains information on all psychiatric inpatient admission dates and diagnoses since 1969, and all outpatient contact dates and diagnoses since 1995. Psychiatric diagnoses are based on the International Classification of Diseases 8th revision¹⁸ for admissions between 1969 and 1993, and the International Classification of Diseases 10th revision¹⁰ for psychiatric contacts from 1994 onwards. There are no private inpatient psychiatric facilities in Denmark and all treatment is free, which ensures extensive coverage of psychiatric contacts. Private outpatient contacts, however, are not registered. The study population was linked to the Danish Psychiatric Central Research Register using the unique personal identifier to determine the date of the first diagnosis of the 2 predictors: ASR (ICD-10 code F43.0) and PTSD (ICD-10 code F43.1). Similarly, we obtained the date of the first diagnosis of the 3 outcomes: Schizophrenia (ICD-10 code F20), schizophrenia spectrum disorder (ICD-10 codes F20-29), and bipolar affective disorder (ICD-10 codes F30-31). We included diagnoses given during admission, outpatient contact or emergency clinic visits. Disease onset was defined as the date of the first psychiatric contact leading to the diagnosis of interest. Recent Danish studies on the validity of ASR, PTSD, schizophrenia, and schizophrenia spectrum disorders conclude that the Danish registers serve as a valid and comprehensive source for research on these disorders.¹⁹⁻²¹

Study Design

We followed the cohort from their 10th birthday or January 1, 1995, whichever occurred last, until the date of their first diagnosis of interest, death, emigration from Denmark, disappearance or January 1, 2014, whichever occurred first. By following individuals from age 10 we exclusively included persons at risk of the psychiatric diagnosis of interest, ie, persons with a history of the disorder before their 10th birthday were excluded. The year 1985 was chosen as the cut-off limit to ensure incident cases of traumatic stress disorder (introduced in the ICD-10), and to include outpatient diagnoses which were included from 1995.

Statistical Analyses

Survival analyses were conducted using Poisson regressions with the logarithm of person-years as an offset variable. This method is equivalent to the Cox regression under the assumption of piecewise constant incident rates according to the time-scale (age).^{22,23} Incidence rate ratios were estimated using the GENMOD procedure in SAS software version 9.3 (SAS Institute Inc). P -values and 95% CIs were based on Likelihood Ratio tests ($P < .05$ was considered statistically significant). Age,

year, time since traumatic stress disorder, and parental history of mental illness were treated as time-dependent variables whereas all other variables were treated independent of time. We defined the variables sex, age in 1-year bands, calendar time in 1-year bands, place of birth (capital, suburb of capital, provincial city >100 000 inhabitants, provincial town 10 000–100 000 inhabitants, and rural areas), and maternal and paternal age at birth (<20, 20–24, 25–29, 30–34 and >35).²⁴ Maternal and paternal history of mental illness was constructed as 3 binary variables for each parent describing a history of any mental disorder (F00-99), schizophrenia spectrum disorders (F20-29), and mood disorders (F30-39). We examined the long term effect (+5 y) of traumatic stress disorder by estimating incidence rate ratios for the 3 outcomes in 3 different adjustment scenarios. As a basic adjustment we included sex, age, and year. As a second adjustment we added place of birth and maternal and paternal age at birth. And as the third adjustment we included maternal and paternal history of mental illness. Additionally, we studied the effect of time since the first diagnosis of traumatic stress disorder. Finally, we looked at the interactions between the long-term effect (5+ y) of stress and sex, family history of psychiatric diagnosis, mother's and father's age at birth, place of birth and age for the outcomes schizophrenia and schizophrenia spectrum disorder. Regarding bipolar disorder, we lacked sufficient power to consider these potential effect modifications. We also looked at the long-term effect (more than 5 y ago) of stress disorder on the outcome of interest in those who at time of outcome only had had an outpatient contact compared to those who had had an inpatient contact (or both).

This study was approved by the Danish Data Protection Agency and the Danish Health Data Authority.

Results

Stress Disorder

The study population consisted of 1 005 021 individuals born in Denmark between 1985 and 2004. Of these,

488 996 (49%) were women and 516 025 (51%) were men. We identified 4283 individuals registered with a first-time diagnosis of traumatic stress disorder: 64% women and 36% men. Of these, 3168 (74%) had a diagnosis of ASR, 1203 (28%) a diagnosis of PTSD and 88 (2%) both diagnoses.

Risk of Severe Mental Illness

During follow-up, 3852 individuals developed schizophrenia, 7819 schizophrenia spectrum disorder, and 1510 bipolar affective disorder. We found a significant long-term effect of a diagnosis of traumatic stress disorder on the risk of all outcomes: Schizophrenia, schizophrenia spectrum disorder, and bipolar affective disorder. This increased risk remained significant after adjusting for sex, age, calendar year, place of birth, maternal and paternal age at child birth, and maternal and paternal history of mental illness (table 1). The risk of developing schizophrenia, schizophrenia spectrum disorder, and bipolar affective disorder was more than 15-fold increased in the first year after incident traumatic stress disorder (table 2). Over time, the risk decreased but remained significant even after 5 years. Risks were larger for patient who experienced an admission compared to patients who only had outpatient contact to the mental health system (supplementary table 1).

Potential Effect Modifiers of the Effect of Stress Disorder

We found a significant interaction between the long-term effect of stress and family history of psychiatric disorders for both schizophrenia ($P = .0098$) and schizophrenia spectrum disorder ($P = .0135$). For schizophrenia we also found an interaction between stress and age ($P = .0415$), which was not the case for schizophrenia spectrum disorder ($P = .1552$). We did not see an interaction between the long-term effect of stress and sex, mother's and father's age at birth and place of birth for neither schizophrenia nor schizophrenia spectrum disorder. Regarding bipolar

Table 1. Long-Term Risk of Schizophrenia and Bipolar Disorder Following a Diagnosis of Traumatic Stress Disorder

Outcome	Stress Disorder		
	Adjustment 1	Adjustment 2	Adjustment 3
	IRR (95% CI)	IRR (95% CI)	IRR (95% CI)
Schizophrenia	5.85 (3.59;8.91)	5.15 (3.16;7.85)	3.80 (2.33;5.80)
Schizophrenia spectrum	3.82 (2.38;5.75)	3.23 (2.01;4.86)	2.34 (1.46;3.53)
Bipolar disorder	5.83 (3.11;9.83)	5.63 (3.00;9.50)	4.22 (2.25;7.13)

Note: IRR, incidence rate ratio. Adjustment 1; sex, age, year. Adjustment 2; additionally place of birth and both parents' age at birth. Adjustment 3; additionally parental history of mental illness. The long-term effect was delineated as more than 5 years after onset with a stress disorder (F43.0+F43.1). Thereby, the long-term effect is less influenced by potential biases due to misdiagnosis and referral bias. All effect sizes by time since first diagnosis with stress disorder are shown in table 2.

Table 2. Adjusted Incidence Rate Ratio Estimates of Psychiatric Diagnosis by Time Since Stress Disorder

	Psychiatric Outcomes					
	Schizophrenia		Schizophrenia Spectrum		Bipolar Disorder	
	IRR (95% CI)		IRR (95% CI)		IRR (95% CI)	
Time since diagnosis of stress disorder (F43.0+F43.1)						
0–1 year	19.93	(15.62;24.99)	20.93	(17.56;24.72)	17.99	(12.06;25.66)
1–2 year	8.30	(5.49;11.94)	7.22	(5.20;9.72)	4.32	(1.71;8.78)
2–5 year	5.83	(4.19;7.86)	4.31	(3.22;5.61)	5.19	(3.08;8.11)
5+ year ^a	3.80	(2.33;5.80)	2.34	(1.46;3.53)	4.22	(2.25;7.13)
No F43.0/F43.1	1.00	(ref)	1.00	(ref)	1.00	(ref)

Note: Adjusted for sex, age, calendar time, place of birth, maternal and paternal age at child birth, and maternal and paternal history of mental illness.

^aIdentical to the estimates presented in table 1, adjustment 3.

disorder we had too limited power to consider these effects.

Compared to persons without a history of mental illness in a parent and without a personal history of stress disorder, those with a personal history of stress disorder 5+ years ago had a risk of schizophrenia of 7.43 (3.97; 12.51), those with a history of mental disorder in a parent had a risk of schizophrenia of 2.43 (2.26; 2.60), and those exposed to both extremes had a risk of schizophrenia of 5.41 (2.32; 10.50). For schizophrenia spectrum disorder the estimates were 4.51 (2.41; 7.58), 2.48 (2.36; 2.61) and 3.67 (1.67; 6.83) respectively.

Among persons aged 15–20 years those with stress disorder had an IRR of schizophrenia spectrum disorder of 4.81 (1.72; 10.34). Among persons aged 21+ years it was 2.18 (1.25; 3.49). The comparable estimates for schizophrenia were 11.03 (3.95; 23.76) and 3.38 (1.90; 5.50).

Discussion

This nationwide population-based study demonstrates that individuals experiencing a traumatic stress disorder have an increased risk of schizophrenia, schizophrenia spectrum disorder, and bipolar affective disorder. Our study has 2 main contributions to the literature: Firstly, it confirms the temporal association between traumatic stress disorders and severe mental illness in a nationwide cohort. Secondly, a family history of mental illness could not explain the association between traumatic stress disorder and severe mental illness. Our study includes a high number of cases and we find incidence rate ratios that are large and significant.

The finding that traumatic stress disorder is associated with severe mental illness is consistent with recent findings^{5,7,25–27} and supported by current explanatory theories.^{1–3} Also, the characteristic sex and age distribution of traumatic stress disorder echo findings from comparable Western countries.^{12,28–32} This gender difference is consistent across time and cultures, however it is unclear

whether it reflects different vulnerability to traumatic stress disorders, or that similar traumatic events may be experienced differently by men and women.⁴ A recent and methodologically similar Danish register study found a strong association between traumatic stress disorder and subsequent diagnoses of anxiety and depression, but did not investigate the association of severe mental illness.³²

As expected, both ASR and PTSD increased the risk of both schizophrenia spectrum disorders and bipolar disorder. This unspecific relation between our exposures and outcomes confirms previous findings that traumatic experiences increase the risk of a broad range of mental disorders.²⁶

Schizophrenia spectrum disorders and bipolar disorder are believed to develop from a combination of genetic vulnerability and environmental exposure. We found that a psychiatric history in a parent (ie, predisposition) could not explain the apparent relationship between traumatic stress disorder and severe mental illness. This is coherent with other recent findings.²⁵ Among the environmental exposures traumatic stress seems to be an important risk factor, especially when occurring in childhood or early adulthood.^{26,27} A broad and unspecific range of traumatic experiences seem to increase the risk of severe mental illness, possibly by acting on the genome to shape the adaptability to environmental challenges.^{33,34} Our findings are consistent with this theory.

We found evidence of a temporal association between traumatic stress disorder and severe mental illness (table 2). However, some studies imply that disposition to severe mental illness and prodromal symptoms might increase the likelihood of experiencing trauma (reverse causality).¹⁴

This study shows a temporal association between adult diagnosis of traumatic stress disorder and subsequent diagnosis of a schizophrenia spectrum disorder or a bipolar disorder. High incidence rates of traumatic stress disorders and association with severe mental illness calls for heightened awareness. A recent review suggests that

trauma-focused psychotherapy could effectively treat reactions to acute traumatic stress.³⁵ Clinical implications include prevention of the initial trauma (eg, by intervening in families at high risk in order to prevent traumatic experiences to the child³), treatment of trauma victims,³⁵ follow-up of patients diagnosed with traumatic stress disorder to ensure early diagnosis and treatment of severe mental illness, and screening and treatment for traumatic stress disorder in patients with severe mental illness.³⁶

Not all traumatized individuals develop traumatic stress disorder. Thus, our study cannot establish whether trauma without traumatic stress disorder is a risk factor of severe mental illness. Further, our study tells nothing of the character (eg, assault, disaster, war) nor the severity of the trauma, and how this may relate to our outcome. However, our finding that patients with previous inpatient contact are at higher risk compared to patients with only outpatient contact, may indicate that severity of traumatic stress disorder is associated with higher risk of schizophrenia and bipolar disorder.

In a methodologically similar study, Meier and colleagues found that psychiatric hospital contacts per se increase the risk of schizophrenia or schizophrenia spectrum disorder.³⁷ We found that the relative risk of severe mental illness persisted more than 5 years after a hospital contact of traumatic stress disorder, indicating that our results are not entirely due to such bias.

As noted, the comorbidity between traumatic stress disorder and severe mental illness is high,^{5,7,38} and the symptoms of traumatic stress disorder may overlap with psychotic disorders and mood disorder.^{39,40} This increases the risk of referral bias and misdiagnosis. The overlap in symptoms may be particularly large in the period immediately following the traumatic experience, which further increase the risk of bias to our findings. On the other hand, we found that that risk of severe mental illness persisted more than 5 years after a diagnosis of traumatic stress disorder. Thus, the long-term effect is likely not influenced by referral bias and misdiagnosis whereas the short-term effect may be. Indeed this was the reason for focusing on long-term effects in [table 1](#) while also presenting estimates in [table 2](#) by time since first onset with stress disorder. In their review article, Morrison and colleagues discuss the evidence that psychosis may cause PTSD, if trauma may cause psychosis and whether psychosis and PTSD could be part of a spectrum of responses to a traumatic event.⁹ They find evidence in support of each of these relationships.

A strength of the study is the prospective design allowing us to calculate incidence rates, examine multiple outcomes to a diagnosis of traumatic stress disorder, and indicate a temporal sequence. Our study population was extensive comprising 1203 cases with a diagnosis of PTSD and 3168 with ASR. Secondly, we were able to adjust for psychiatric comorbidity in parents, ie, the hereditary predisposition for severe mental illness. Thirdly, predictor

diagnosis were recorded independently of outcome diagnosis, thus decreasing the risk of possible recall or selection biases.

Several limitations are associated with the use of registers for case ascertainment. First, diagnoses might differ from the date on which symptoms were first noticed, which could lead to a detection bias.^{19,41} Secondly, our estimate is based on patients seeking treatment which may be different from patients having traumatic stress disorder, as some may not come in contact with mental health services.¹² Thus, our estimates may be affected by disease severity, differing diagnostic standards inter-individually and inter-institutionally, and patient's help seeking behavior.⁴² Of particular note, our estimate probably represents the more severe cases with a higher risk of developing severe mental illness. However we did include both inpatient and outpatient contacts of traumatic stress disorder. Thirdly, the Danish registers do not contain information on diagnoses made outside hospitals, ie, private practitioners and psychologists.

Our findings indicate that a diagnosis of traumatic stress disorders (ASR and post-traumatic stress disorder) is associated with schizophrenia spectrum disorders and bipolar disorder. The study underlines the clinical importance of caring for patients with traumatic stress disorders.

Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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