Childhood seizures and risk of psychiatric disorders in adolescence and early adulthood: a Danish nationwide cohort study

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Summary

Background Paediatric seizures have been linked to psychiatric disorders in childhood, but there is a paucity of large-scale population-based studies of psychiatric comorbidity in later life. We aimed to examine the relation between childhood seizures and the risk of psychiatric disorders in adolescence and early adulthood.

Methods We did a register-based cohort study of all individuals born in Denmark in 1978–2002. Using diagnostic information from the Danish National Patient Register, all cohort members were categorised according to occurrence of febrile seizures and epilepsy, before entering the follow-up period on their 10th birthday. Individuals were followed up until onset of mental illness, death, emigration, or the end of the study period on Dec 31, 2012. Cox regression analyses were used to estimate the risk of five predefined groups of psychiatric disorders (substance abuse disorders, schizophrenia, mood disorder, anxiety, and personality disorder), separately and combined. Models were adjusted for relevant confounders.

Findings Between Jan 1, 1978, and Dec 31, 2002, 1 291 679 individuals were born in Denmark and followed up in our population cohort (approximately 15 million person-years). 43 148 individuals had a history of febrile seizures, 10 355 had epilepsy, and 1696 had both these disorders. 83 735 (6%) cohort members were identified with at least one of the psychiatric disorders of interest. The risk of any psychiatric disorder was raised in individuals with a history of febrile seizures (hazard ratio [HR] 1·12, 95% CI 1·08–1·17), epilepsy (1·34, 1·25–1·44), or both disorders (1·50, 1·28–1·75). Excess risk of psychiatric illness associated with childhood seizures was present across a range of different disorders, most notably schizophrenia but also anxiety and mood disorders. Associations did not differ between males and females (p=0·30) but increased with a growing number of admissions for febrile seizures (p<0·0001) and with later onset of childhood epilepsy (p<0·0001).

Interpretation Children with epilepsy and febrile seizures—with and without concomitant epilepsy—are at increased risk of developing a broad range of psychiatric disorders in later life. Clarification of the underlying mechanisms attributable to these associations is needed to identify potential options for prevention.

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Introduction

Paediatric seizures—including febrile seizures and epilepsy—affect 4–5% of all children and are, thereby, some of the most common neurological conditions in childhood.[1] Febrile seizures have generally been considered to have a favourable prognosis, with little or no long-lasting implications for child development.[2] However, epilepsy has been associated with an increased risk of adverse neuropsychiatric development. Particularly in the youngest children, associations between epilepsy and psychiatric disorders have been seen, including attention deficit hyperactivity disorder (ADHD)[3,4] and autism spectrum disorders.[5–7] In older children and younger adults, psychiatric comorbidity encompasses a broad spectrum of conditions, including behavioural disorders, mood disorders, personality disorders, anxiety disorders, and psychotic disorders.[8–10]

The nature of the relation between seizures in early childhood and psychiatric disorders is poorly understood. Some hypotheses have evolved around direct effects of the seizures themselves, whereas others suggest that psychiatric disorders might arise because of the psychosocial disadvantage of having to live with the condition.[11] Many studies have reported a bidirectional relation between seizures and psychiatric illness, which suggests that associations arise from a shared underlying genetic susceptibility and pathophysiology.[12] Psychiatric comorbidity is a driving factor of premature mortality among individuals with epilepsy;[13] thus, it is important to clarify whether a similar psychiatric comorbidity—that might also be associated with premature mortality—is seen in children with febrile seizures.

So far, studies have generally been based on clinical or small population samples,[14–16] and large-scale studies

Research in context

Evidence before this study

We searched Medline and the Web of Science for articles published before Oct 1, 2018, using the MeSH terms and keywords "Seizures, Febrile", "Epilepsy", "Mental disorders", and "Comorbidity", with no restrictions on date or language. Furthermore, we used a snowballing technique in which we perused references of references to detect reports of studies not identified in the database search. Details of the literature search are provided in the appendix (p 1). Epidemiological and clinical studies show that children with epilepsy frequently will develop comorbid psychiatric disease over the life course, but febrile seizures are thought to have little or no long-lasting implications for the development of the child. However, large-scale population-based studies addressing the long-term risk of psychiatric comorbidities are scarce.

See Online for appendix

Added value of this study

We followed up a population-based cohort of children for more than 15 million person-years, including those with a history of febrile seizures, epilepsy, or both. We calculated relative and cumulative risks of developing psychiatric disorders in adolescence and early adulthood. Children who have seizures during childhood had an excess risk of developing a broad range of psychiatric disorders in later life, such as anxiety, mood disorders, psychotic disorders, and personality disorders. We also provided new evidence that the risk of psychiatric comorbidity increases in children with febrile seizures who later develop epilepsy.

Implications of all the available evidence

Compared with previous reports, the extent of the psychiatric comorbidity in children with seizures reported in our study was more modest. Much of the existing evidence is based on studies using clinical samples that comprise more severe cases, whereas our findings most likely reflect the risk of psychiatric disorders in the general population of people with epilepsy and febrile seizures. In our study, children with febrile seizures—in particular those with recurrent febrile seizures—seemed to have a higher risk of a wide range of psychiatric comorbidities, similar to children with epilepsy (although less pronounced). Moreover, children experiencing seizures in the first 10 years of life seemed to be more susceptible to mental disorders throughout adolescence and early adulthood. These findings confirm and extend the range of psychiatric disorders previously associated with childhood epilepsy and document a novel association with febrile seizures without epilepsy, which increase in strength with recurrent febrile seizures.

examining the full range of psychiatric comorbidities after childhood seizures are scarce. We did a large population-based study to examine the relation between febrile seizures and childhood epilepsy and subsequent risk of a broad spectrum of psychiatric comorbidities in adolescence and early adulthood.

Methods

Study design and participants

This study was undertaken as a population-based follow-up study. Using data from the Danish Civil Registration System, we established a cohort of all children born in Denmark between 1978 and 2002 and followed them up from their 10th birthday. The Danish Civil Registration System includes virtually all individuals living in Denmark and contains continuously updated information on vital status and place of residence (including emigrations and immigrations). Every individual in the register is assigned a unique personal identification number, which enables accurate linkage between a range of nationwide health and social registries. The study population was restricted to children who were alive and residing in Denmark on their 10th birthday and whose parents were both also born in Denmark.

This study was approved by the Danish Data Protection Agency. According to Danish legislation, no further ethics approval or collection of informed consent is required for research projects entirely based on public administrative registries.

Procedures

Information on diagnoses of febrile seizures and epilepsy in childhood was obtained by linkage to the Danish National Patient Register. This register covers all admissions to hospitals in Denmark from 1977, and all outpatient and emergency room contacts are included from 1995 onwards. Diagnoses are based on WHO's International Classification of Diseases, 8th revision (ICD-8) from 1977 to 1993, and on the 10th revision (ICD-10) from 1994 until the end of the study period in 2012. We considered a child to have epilepsy if he or she received any epilepsy diagnosis before the age of 10 years (ICD-8, 345 [excluding 345.29]; ICD-10, G40). We judged a child to have had a febrile seizure if the diagnosis was made between the age of 3 months and 5 years (ICD-8, 780.21; ICD-10, R56.0) and if no recorded diagnosis of epilepsy (ICD-8, 345 [excluding 345.29]; ICD-10, G40), cerebral palsy (ICD-8, 343.99 and 344.99; ICD-10, G80), intracranial tumour (ICD-8, 191 and 225; ICD-10, C70–C71 and D32–D33), severe head trauma (ICD-8, 851 and 854; ICD-10, S06.1–S06.9), or intracranial infection (ICD-8, 320 and 323; ICD-10, G00–G09) had been made before the febrile seizure.[17] We categorised children into four groups depending on the occurrence of seizures before the child's 10th birthday: history of neither febrile seizures nor epilepsy; history of febrile seizures only; history of epilepsy only; and history of febrile seizures and subsequent epilepsy. We defined the number of hospital contacts with febrile seizures as none, one, two, or three or more. We

distinguished between febrile seizures occurring before or after the median age at onset (16 months), and additionally defined a group of late-onset febrile seizures (ie, ≥3 years of age).[18] For epilepsy, we defined four distinct categories of age at onset, of roughly equal size (<1 year, 1 year to <3 years, 4 years to <7 years, and 7 years to <10 years).

Information on incident psychiatric diagnoses in all cohort members was obtained by linkage to the Danish Psychiatric Central Research Register. This register covers all admissions to mental hospitals and psychiatric departments in Denmark from 1970, and from 1995 it also includes all outpatient and emergency room contacts. Individuals in this register, thus, represent patients with psychiatric disorders treated in secondary care. To avoid issues related to bidirectionality, we did not consider disorders such as ADHD or autism spectrum disorders, which are frequently diagnosed in the early years of childhood—ie, in the same period we assessed febrile seizures and epilepsy. Instead, we focused on disorders that typically do not develop until adolescence or early adulthood.[19] For all cohort members, we considered mental and behavioural disorders due to psychoactive substance abuse (ICD-10, F10–F19), schizophrenia and related disorders (ICD-10, F20–F29), mood disorders (ICD-10, F30–F39), anxiety, stress-related and somatoform disorders (ICD-10, F40–F48), and specific personality disorders (ICD-10, F60–F60.9). Equivalent ICD-8 codes are provided elsewhere.[19] For subgroupings of psychiatric disorders, the following classification of disorders was used (x represents any digit unless otherwise stated): mental and behavioural disorders due to alcohol use (ICD-10, F10; ICD-8, 291.x9, 303.x9, 303.20, 303.28, and 303.90); mental and behavioural disorders due to cannabis use (ICD-10, F12; ICD-8, 304.59); schizophrenia (ICD-10, F20; ICD-8, 295.x9 [excluding 295.79]); schizoaffective disorder (ICD-10, F25; ICD-8, 295.79 and 296.89); bipolar disorders (ICD-10, F30–F31; ICD-8, 296.19, 296.39, and 298.19); single and recurrent depressive disorder (ICD-10, F32–F33, ICD-8, 296.09, 296.29, 298.09, and 300.49); recurrent depressive disorder (ICD-10, F33; ICD-8, 296.09, 296.29, 298.09, and 300.49b); obsessive compulsive disorder (ICD-10, F42; ICD-8, 300.39); and borderline personality type (ICD-10, F60.31; ICD-8, 301.84). Individuals with multiple disorders were included in the analyses of each specific disorder. The date of onset for each of the disorders was defined as the first date of the first contact.

Statistical analysis

Cox regression models were used to estimate hazard ratios (HRs) and corresponding 95% CIs for psychiatric disorders according to history, number, and age at onset of seizures. Analyses were done for each group of psychiatric disorders, and combined (any psychiatric disorder). In all models, the child's age was used as the underlying time scale. Follow-up of children at risk—ie, children with no previous diagnosis of the psychiatric disorder of interest—began on their 10th birthday and continued until diagnosis, emigration from Denmark, death, or end of follow-up on Dec 31, 2012, whichever came first. All models were stratified by sex, allowing for different baseline hazards in boys and girls. The proportionality assumption was tested using Schoenfeld-scaled residuals and was satisfied for all main exposures. To account for possible confounding, we further adjusted all HRs for a range of perinatal, demographic, and socioeconomic factors. Covariates included in the analyses were birthweight, gestational age, Apgar score at 5 min, and parental age at birth. Further adjustment was made for maternal education (highest completed) and paternal income in the year the child turned 10 years old. We considered these two different measures of maternal and paternal socioeconomic status because we believed these covariates would each be stable across the childhood years. Continuous variables were categorised because none of the associations could be more adequately described by a linear model. Parental psychiatric disorders were treated as time-varying covariates, estimated as time since first diagnosis (unexposed, and subsequently time since diagnosis in intervals increasing from 1 month to 5 years).

	Any psychiatric disorder (n)	Hazard ratio (95% CI)*		Cumulative incidence at age 30 years (95% CI)
		Basic adjustment	Full adjustment†	
All individuals				
Total	83 735	..	..	11·6% (11·6–11·7)
Neither febrile seizures nor epilepsy	79 676	1·00	1·00	11·5% (11·4–11·6)
Febrile seizures	2954	1·17 (1·12–1·21)	1·12 (1·08–1·17)	13·4% (12·9–13·9)
Epilepsy	934	1·55 (1·45–1·65)	1·34 (1·25–1·44)	17·0% (15·8–18·2)
Febrile seizures and epilepsy	171	1·74 (1·50–2·02)	1·50 (1·28–1·75)	18·8% (15·9–21·8)
Females‡				
Neither febrile seizures nor epilepsy	47 896	1·00	1·00	13·9% (13·8–14·1)
Febrile seizures	1664	1·18 (1·12–1·24)	1·14 (1·08–1·20)	16·8% (16·0–17·7)
Epilepsy	510	1·48 (1·36–1·62)	1·30 (1·18–1·42)	20·9% (19·0–22·8)
Febrile seizures and epilepsy	89	1·64 (1·33–2·02)	1·37 (1·10–1·70)	22·4% (17·9–27·3)
Males‡				
Neither febrile seizures nor epilepsy	31 780	1·00	1·00	9·2% (9·1–9·3)
Febrile seizures	1290	1·15 (1·09–1·21)	1·10 (1·04–1·17)	10·7% (10·1–11·4)
Epilepsy	424	1·64 (1·49–1·81)	1·41 (1·27–1·56)	13·7% (12·4–15·2)
Febrile seizures and epilepsy	82	1·86 (1·50–2·31)	1·66 (1·32–2·09)	15·6% (12·4–19·7)

*All analyses are stratified by sex and adjusted for calendar year. †Further adjusted for birthweight, gestational age at delivery, Apgar score (5 min), maternal education, paternal income, parental age at birth, and parental psychiatric disease. The number of individuals included in the fully adjusted analysis was 1 198 831 because of missing information for covariates in 92 938 individuals. ‡p value for interaction between sex and childhood seizures, p=0·30.

Table 1: **Relative and absolute risks of any psychiatric disorder associated with a history of seizures among 1 291 769 children born in Denmark (1978–2002)**

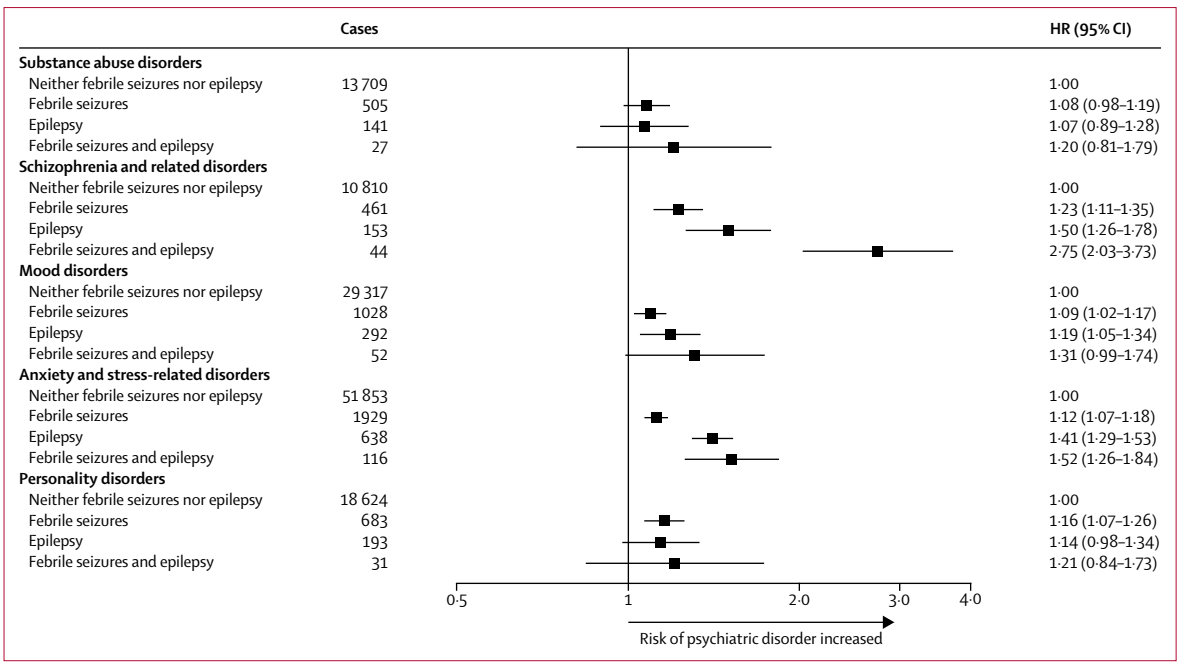

Figure 1: **Adjusted relative risks of psychiatric disorders associated with a history of febrile seizures and epilepsy in childhood among 1 291 769 children born in Denmark (1978–2002)**

All analyses are adjusted for sex, calendar year, birthweight, gestational age at delivery, Apgar score (5 min), maternal education, paternal income, parental age at birth, and parental psychiatric disease.

Similarly, calendar time during follow-up was split into intervals of 3–4 years to account for calendar period effects. All other covariates were considered time-independent. Analyses were done as complete case analyses and robust SEs were used to correct for dependency between (maternal) siblings in the population. To estimate cumulative incidences of psychiatric disorders, we used competing risk regression.

We did sensitivity analyses excluding children with status epilepticus (ICD-8, 345.29; ICD-10, G41), seizure onset in the neonatal period (first 28 days after birth), and potentially structural causes of epilepsy (head trauma, intracranial infections, intracranial bleedings, cerebral palsy, and intracranial tumours). Children younger than 10 years with epilepsy without these structural lesions will include a relatively high proportion of children with an unknown cause of epilepsy—ie, idiopathic epilepsy.[20–22] We also examined the association separately for epilepsies with focal and generalised onset. To account for epilepsy with onset after the beginning of follow-up (ie, in adolescence and adulthood), we did a further sensitivity analysis in which epilepsy was treated as a time-varying exposure. Furthermore, because anxiety, stress-related disorders, and somatoform disorders can be diagnosed before age 10 years,[19] some children with very early onset of these disorders were excluded in the main models because they were not at risk of incident disease at the beginning of follow-up. In a sensitivity analysis, we ignored all diagnoses of anxiety and stress-related disorders made between age 5 years and age 10 years, and we followed up these children from age 10 years until the first diagnosis made after this point. In this way, we allowed children who were diagnosed in early childhood (ie, younger than 10 years) and who were later admitted to a psychiatric department or outpatient clinic (ie, aged 10 years or older) to also be included in the risk estimates. Finally, as an alternative to the complete case analysis, which might induce some selection in the fully adjusted models, we included a missing category in the variables without complete coverage (birthweight, gestational age, Apgar score, maternal education, paternal income) so we could include the entire study population in the analyses.

All analyses were done using Stata, version 13.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 1978, and Dec 31, 2002, 1 291 679 children were born in Denmark and were alive at their 10th birthday. In this population cohort, 43 148 (3%) children had been diagnosed with febrile seizures, 10 355 (1%) had a history of epilepsy, and 1696 (<1%) had both disorders. The proportion of boys was higher among children with febrile

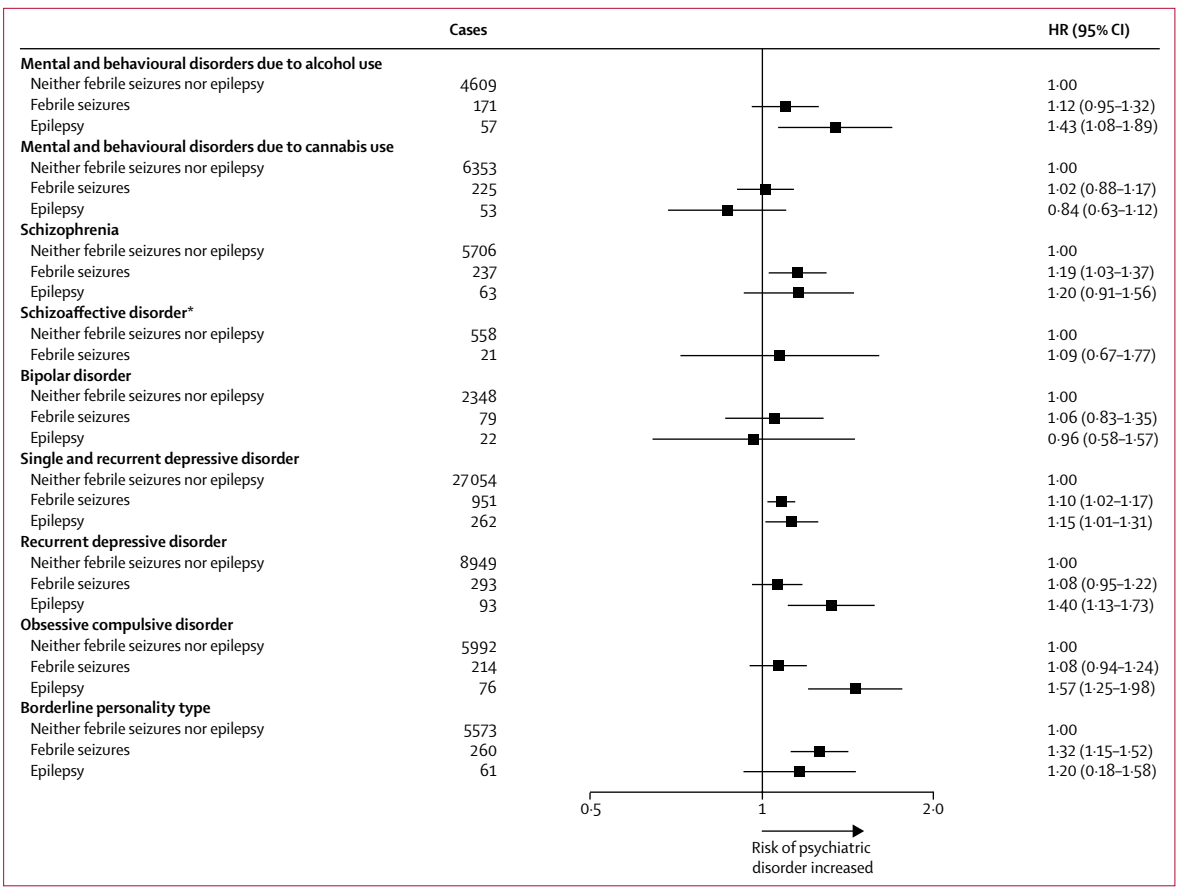

Figure 2: **Adjusted relative risks of subgroupings of psychiatric disorders associated with a history of febrile seizures and epilepsy in childhood among 1 291 769 children born in Denmark (1978–2002)**

For recurrent depression, onset was defined as the second admission that occurred at least 8 weeks after the last discharge with a relevant ICD-8 code. All analyses are adjusted for sex, calendar year, birthweight, gestational age at delivery, Apgar score (5 min), maternal education, paternal income, parental age at birth, and parental psychiatric disease. *There were too few cases of schizoaffective disorder among individuals with childhood epilepsy to analyse.

seizures and epilepsy than among those without, and children with seizures generally had worse perinatal and sociodemographic characteristics. Similarly, at the beginning of follow-up, the children with seizures were more likely to have a diagnosis of ADHD and autism spectrum disorders (appendix p 2). The cohort was followed up for more than 15 million person-years, and median age at the end of follow-up was 21·2 years (10th percentile 12·5 years, 90th percentile 32·3 years).

During follow-up, 83 735 (6%) cohort members were registered with at least one of the psychiatric disorders of interest (table 1). Compared with children without childhood seizures, the risk of developing a psychiatric disorder was marginally increased for children with a history of febrile seizures (adjusted HR 1·12, 95% CI 1·08–1·17) and moderately raised for those with childhood epilepsy both with (1·50, 1·28–1·75) and without (1·34, 1·25–1·44) febrile seizures. The association with febrile seizures remained unchanged when we accounted for epilepsies with onset after the beginning of follow-up (HR 1·12, 95% CI 1·08–1·17; appendix p 3). In children with no childhood seizures, the risk of having at least one psychiatric diagnosis by age 30 years was 11·5% (95% CI 11·4–11·6). By comparison, corresponding risks among children with febrile seizures, epilepsy, or both febrile seizures and epilepsy were 13·4% (95% CI 12·9–13·9), 17·0% (15·8–18·2), and 18·8% (15·9–21·8), respectively. The cumulative incidence of psychiatric disorders was higher among females than among males, but the effect of childhood seizures was independent of sex (p=0·30 for interaction).

An excess risk of psychiatric illness associated with childhood seizures was present across a range of different disorders (figure 1). The strongest associations were recorded for schizophrenia and related disorders in children with a history of febrile seizures (adjusted HR 1·23, 95% CI 1·11–1·35), epilepsy (1·50, 1·26–1·78) and febrile seizures and epilepsy (2·75, 2·03–3·73). Similar—although less pronounced—associations with childhood seizures were present for mood disorders and anxiety and stress-related disorders. Risk estimates for anxiety and stress-related disorders were largely unaffected

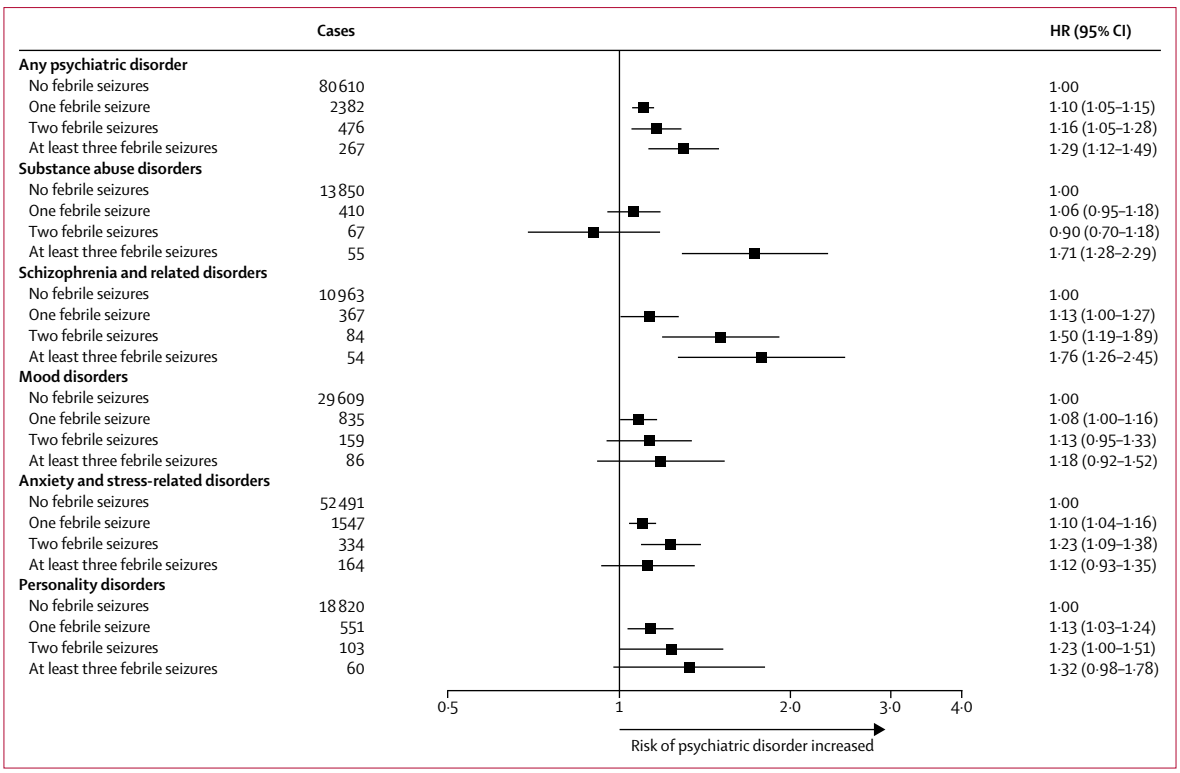

Figure 3: **Adjusted relative risks of psychiatric disorders according to number of admissions with febrile seizures among 1 291 769 children born in Denmark (1978–2002)**

All analyses are adjusted for sex, calendar year, birthweight, gestational age at delivery, Apgar score (5 min), maternal education, paternal income, parental age at birth, and parental psychiatric disease.

when children with a previous diagnosis of these disorders (n=2175) were included in the analyses (appendix p 4). The risk of substance abuse disorders was not increased for any groups of children with childhood seizures, and the association with febrile seizures was significant for personality disorders only. Children with a history of both febrile seizures and epilepsy generally had the highest risk for all the psychiatric disorders considered in this study. However, in view of the few children in this group, these estimates are associated with a high degree of uncertainty.

Figure 2 shows associations between childhood seizures and risk for subgroups of substance abuse disorders, schizophrenia and related disorders, mood disorders, anxiety and stress-related disorders, and specific personality disorders. These findings are largely consistent with those presented in figure 1 but show slight differences in how childhood seizures are associated with risks for specific diagnoses. For example, risk for substance abuse disorders due to alcohol use was increased for those with childhood epilepsy (adjusted HR 1·43, 95% CI 1·08–1·89), but risk was not increased for substance abuse disorders due to cannabis use (0·84, 0·63–1·12). Moreover, for mood disorders, overall associations were driven more by depressive disorders than by bipolar disorders.

For epilepsy, no association was recorded between number of admissions and later development of psychiatric disorders (data not shown). However, risk for psychiatric disorders generally rose progressively with increasing number of hospital contacts for febrile seizures, with growing risk for psychiatric disorders after one (adjusted HR 1·10, 95% CI 1·05–1·15), two (1·16, 1·05–1·28), and three or more (1·29, 1·12–1·49) febrile seizures (figure 3; p<0·0001 for trend).

The association between child's age at seizure onset and risk for psychiatric disorders was examined for febrile seizures and epilepsy (table 2). Median age at onset for febrile seizures in our population cohort was 16 months (10th percentile 9 months, 90th percentile 3 years) and for epilepsy it was 4·5 years (6 months to 9 years). For children with febrile seizures, no difference in risk of developing psychiatric disease was noted between onset of seizures in children younger than 16 months (adjusted HR 1·10, 95% CI 1·04–1·17) and in those aged between 16 months and younger than 3 years (1·11, 1·04–1·17). However, higher risk was seen in children in whom the first febrile seizure did not occur until age 3 years or older (adjusted HR 1·25, 95% CI 1·12–1·41). Similarly, for epilepsy, higher age at onset of epilepsy was associated with higher risk for psychiatric disorders (p<0·0001 for trend).

Risk for psychiatric disorders after epilepsy remained unchanged when we excluded individuals with status

epilepticus (adjusted HR 1·35, 95% CI 1·25–1·44), seizure onset in the neonatal period (1·35, 1·26–1·44), and potentially structural causes (1·40, 1·30–1·49). Furthermore, the association did not seem to differ in epilepsies with focal (adjusted HR 1·42, 95% CI 1·25–1·62) and generalised (1·36, 1·19–1·56) onset. Finally, when children with missing values in covariates were included in the fully adjusted models, the association between psychiatric disorders and febrile seizures (adjusted HR 1·13, 95% CI 1·08–1·17), epilepsy (1·35, 1·26–1·44), and both febrile seizures and epilepsy (1·46, 1·25–1·70) did not change.

	Individuals (n)	Hazard ratio (95% CI)*	
		Basic adjustment	Full adjustment†
Febrile seizures			
None	1 246 925	1·00	1·00
Age at onset, <16 months	20 706	1·13 (1·07–1·19)	1·10 (1·04–1·17)
Age at onset, 16 months to <3 years	19 975	1·16 (1·10–1·23)	1·11 (1·04–1·17)
Age at onset, ≥3 years	4163	1·33 (1·19–1·49)	1·25 (1·12–1·41)
Epilepsy			
None	1 279 718	1·00	1·00
Age at onset, <1 year	2247	1·37 (1·17–1·60)	1·20 (1·01–1·42)
Age at onset, 1 year to <4 years	3279	1·43 (1·25–1·63)	1·17 (1·01–1·35)
Age at onset, 4 years to <7 years	3132	1·61 (1·42–1·83)	1·40 (1·22–1·59)
Age at onset, 7 years to <10 years	3393	1·69 (1·51–1·89)	1·52 (1·35–1·71)

*All analyses are stratified by sex and adjusted for calendar year. †Further adjusted for birthweight, gestational age at delivery, Apgar score (5 min), maternal education, paternal income, parental age at birth, and parental history of psychiatric disease.

Table 2: **Risk of psychiatric disorder after age 10 years in 1 291 769 children born in Denmark (1978–2002), according to age at onset of childhood seizures**

Discussion

In this large nationwide follow-up study, individuals who had seizures during childhood were at increased risk of developing psychiatric disease in adolescence and early adulthood. Febrile seizures were generally associated with a low-to-moderate excess risk of psychiatric morbidity, whereas epilepsy seemed to confer a somewhat greater risk. These findings thereby suggest not only that children having seizures are susceptible to mental illnesses in childhood[3–7] but also that this susceptibility carries on into later stages of life.

These findings contribute to the growing body of evidence on comorbidity between epilepsy and psychiatric disorders.[8,9,23] In our study, people with childhood-onset epilepsy were at a higher risk of a range of different disorders in later life, including schizophrenia, mood disorders, and anxiety and stress-related disorders. However, although we generally reported no more than a 1·5-fold excess risk of psychiatric disease in people with childhood epilepsy, meta-analyses have frequently reported much higher risk ratios,[23] suggesting that people with epilepsy have a twofold to threefold excess risk of depression[24] and a nearly eightfold increased risk of psychotic illness.[25] By contrast with our sample, which was a population-based cohort, much of the current evidence on psychiatric comorbidity in individuals with epilepsy stems from studies using clinical samples. It is possible that the association with psychiatric comorbidity is more pronounced in such samples, since they tend to include more severe cases of epilepsy. Our findings, on the other hand, might reflect more accurately the risk among the general population of people with epilepsy. Furthermore, the association between epilepsy and mental illness was also stronger in the analyses in which epilepsy with onset after age 10 years was considered, suggesting that later-onset epilepsy might be associated with a greater risk of psychiatric comorbidity.

We furthermore found that children with childhood epilepsy were at higher risk of mental disorders due to alcohol use but not cannabis use. Substance abuse disorders have previously been linked to epilepsy,[26] but the reason for the difference between alcohol-related and cannabis-related substance abuse disorders noted in our study is not entirely clear. These findings need further replication.

Much evidence suggests that the relation between epilepsy and psychiatric disorders is bidirectional.[26] In our study, we aimed to estimate the psychiatric risk after seizures (and not vice versa). We, therefore, exclusively studied seizures happening during early childhood and psychiatric disorders arising in later life to clearly separate in time the onset of seizures from the onset of psychiatric disorders. We used the date of the first diagnosis to define onset of the disorders. Although this date is likely to be accurate in measuring onset of febrile seizures, when admission happens directly in relation to the seizure, it is probably less precise for epilepsy and psychiatric disorders. For these disorders, a delay often takes place between onset of symptoms and time of diagnosis. In analyses of age at onset, we noted that the association between epilepsy and psychiatric disorders seemed to become stronger with later onset of epilepsy—ie, the highest risk was seen in epilepsies with onset at age 7–9 years. We cannot exclude bidirectionality, since some individuals with epilepsy might have had psychiatric symptoms (that were not yet diagnosed) preceding epilepsy onset in this age group. However, this is unlikely to be the case for febrile seizures and for epilepsies with onset at early age.

The psychiatric comorbidity of febrile seizures has been studied less frequently than for epilepsy, possibly because febrile seizures have been judged largely benign with a favourable prognosis in terms of further neurocognitive development and mortality.[2,27] In our study, we have shown that children with febrile seizures do seem to be at slightly higher risk of developing psychiatric disorders as teenagers and young adults, even in the absence of subsequent epilepsy. This excess risk was present across a range of different disorders—eg, schizophrenia, mood, anxiety, personality, and stress-related disorders. These findings are in line with other register-based studies, suggesting that children with febrile seizures had a 1·3-fold (95% CI

1·2–1·4)[3] and 1·5-fold (0·9–2·4)[5] increased risk of ADHD, a 2·5-fold (1·5–4·1) amplified risk of autism spectrum disorders,[5] and a 1·4-fold (1·1–2·0) augmented risk of schizophrenia,[28] which could not be accounted for by concomitant epilepsy. On the contrary, multiple studies of neurocognitive and behavioural outcomes suggest that individuals with a history of febrile seizures have similar results to those without febrile seizures in several cognitive and behavioural assessments.[11,14,15,29] We noted that the association with mental illness was strongest in individuals with recurrent febrile seizures and with onset of febrile seizures after the age of 3 years. It is possible either that the excess risk of psychiatric disease we recorded is attributable mainly to a subset of individuals with febrile seizures—eg, individuals with prolonged or otherwise complex febrile seizures and individuals with genetic predisposition—or that we were simply able to detect more subtle differences than most other studies because our study was well powered, particularly in the analyses of febrile seizures.

Febrile seizures have been associated with premature mortality in children with complex febrile seizures in the first few years after the onset of febrile seizures. This excess mortality was accounted for partly by underlying neurological disorders, including epilepsy.[27,30] We followed up children from age 10 years and, thus, only included children who survived until that age. However, only very few children died; thus, mortality is unlikely to affect the association between febrile seizures and psychiatric disorders in adults.

The mechanisms that cause the observed associations between childhood seizures and psychiatric disorders are not clear. It is possible that the seizures (febrile and afebrile) themselves or their associated treatment harm the developing brain and thereby predispose individuals to mental illness in later life.[10,31,32] However, the relation described between seizures and many psychiatric disorders seems to be bidirectional, which suggests that common underlying causal factors might exist. Although we adjusted all analyses for a range of perinatal and sociodemographic characteristics, it is possible that residual or unmeasured confounding could account for our findings, in part or in whole. In particular, genetic factors might cause functional or structural neuronal changes, leading to both seizures and subsequent mental illness. Important priorities for future research are to elucidate the extent to which a shared genetic basis could account for our findings and to find out if there might be mediating or modifying conditions—eg, parental mental illness, cognitive function, or educational attainment.[33]

Several important strengths and limitations of our study are worth noting. We designed the study as a population-based follow-up study and included all children born in Denmark during a 25-year period. In view of this large population size, we were able to address a broad spectrum of psychiatric comorbidities in adolescence and early adulthood associated with childhood seizures. The study was based entirely on information from nationwide registries, and owing to the virtually complete coverage of the population registers, bias arising from sampling and attrition was kept to a minimum. The proportion of children with missing values for covariates included in analyses was generally very low (<2%), except for gestational age (4–5%). However, more than 85% of missing values for gestational age were for children born at the beginning of the study period (1978–81), during which time changes in reporting were implemented. The distribution of gestational age in that period is similar to that in other periods, and children without information for gestational age were similar to those with that information, in terms of birthweight.[34] Thus, there does not seem to be any systematic pattern in the missingness of gestational age data in that period, which reduces the risk of bias. Furthermore, the results of our study did not change in the sensitivity analysis when children with missing values were included, suggesting that the complete case analyses were not biased by this issue in any substantial manner.

In our study, psychiatric diagnoses were retrieved from the Danish Psychiatric Central Research Register. This register contains information for individuals treated in secondary mental health care. Some individuals with mental illness might not need treatment in a secondary health-care facility and might be seen in primary care only, particularly if the prognosis is mild. These individuals will not show in the register. However, because the threshold for admission to secondary mental health care services is not likely to depend on seizure history, misclassification would most likely be non-differential and bias our estimates towards the null. Nevertheless, cumulative incidences are probably conservative estimates of the actual risk of developing mental health problems.

The Danish National Patient Register was used to identify children with febrile seizures and epilepsy. Validation studies have shown high positive predictive values for diagnoses of febrile seizures (93%, 95% CI 89–96)[35] and epilepsy (81%, 75–87),[36] but these values were much lower for epilepsy subtypes.[36] We were unable to identify a risk difference between focal epilepsy and generalised epilepsy, which could possibly be attributable to uncertainty of epilepsy subtype classification and differences in terminology used. The distinction between generalised epilepsies and focal epilepsies is made on clinical grounds, typically supported by findings on neuroimaging and interictal electroencephalogram (EEG) discharges.[22] However, imaging and clinical findings are typically insufficient to classify the type of epilepsy. Moreover, children with generalised epilepsy might have EEGs with focal features and incidental focal findings on MRI. Accordingly, differentiation between the two main types of epilepsy is associated with some degree of uncertainty. Further, the classification and terminology used in ICD-8 and ICD-10 do not match that used by the International League Against Epilepsy,[20,22,36] and ICD-8 and ICD-10 do not list causes in any detail.[21]

Both registration and diagnosis of psychiatric disorders, febrile seizures, and epilepsy changed during the study period—ie, the ICD-10 classification system was introduced in 1994 and outpatient and emergency room contacts were included from 1995 and onwards. Issues arising from such changes were addressed by adjusting all analyses for calendar period effects. In the analyses, we also treated all continuous variables—including age at onset of febrile seizures and epilepsy—as categorical variables. However, categorising continuous variables (eg, age at onset) inevitably leads to loss of information. There is rarely consensus about the choice of exact cutoffs, which might limit generalisability of our findings.

Finally, our study was limited by a paucity of important clinical information. For instance, it would have been of interest to examine in more detail how associations varied with duration or frequency of seizures, whether children later became seizure-free, or whether children had side-effects of medication.

The findings of our large, prospective, population-based study show that individuals with febrile seizures and epilepsy in childhood are at excess risk of developing a broad range of psychiatric disorders in later life, such as anxiety, mood disorders, and psychotic disorders. Although our findings quantify psychiatric comorbidity in the general population of individuals with childhood seizures, further research is needed to clarify the underlying mechanisms.

Contributors

JWD, CBP, CC, and JC contributed to the idea for the study, study design, the analytical strategy of the study, and critically reviewed and revised the report. JWD did statistical analyses and drafted the initial report. All authors approved the final version of the report.

Declaration of interests

JWD and JC report grants from the Novo Nordisk Foundation, the Danish Epilepsy Association, and the Central Denmark Region, during the conduct of the study. JC also reports personal fees for giving lectures for UCB Nordic and Eisai, outside of the submitted work. CBP reports grants from the Lundbeck Foundation and Stanley Medical Research Institute, during the conduct of the study. CC declares no competing interests.

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References

1 Friedman MJ, Sharieff GQ. Seizures in children. *Pediatr Clin North Am* 2006; **53:** 257–77.

2 Nelson KB, Ellenberg JH. Prognosis in children with febrile seizures. *Pediatrics* 1978; **61:** 720–27.

3 Bertelsen EN, Larsen JT, Petersen L, Christensen J, Dalsgaard S. Childhood epilepsy, febrile seizures, and subsequent risk of ADHD. *Pediatrics* 2016; **138:** e20154654.

4 Brikell I, Ghirardi L, D'Onofrio BM, et al. Familial liability to epilepsy and attention-deficit/hyperactivity disorder: a nationwide cohort study. *Biol Psychiatry* 2018; **83:** 173–80.

5 Gillberg C, Lundström S, Fernell E, Nilsson G, Neville B. Febrile seizures and epilepsy: association with autism and other neurodevelopmental disorders in the child and adolescent twin study in Sweden. *Pediatr Neurol* 2017; **74** (suppl C): 80–86.

6 Sundelin HEK, Larsson H, Lichtenstein P, et al. Autism and epilepsy. *Neurology* 2016; **87:** 192.

7 Christensen J, Overgaard M, Parner ET, Vestergaard M, Schendel D. Risk of epilepsy and autism in full and half siblings: a population-based cohort study. *Epilepsia* 2016; **57:** 2011–18.

8 Rodenburg R, Stams GJ, Meijer AM, Aldenkamp AP, Dekovic M. Psychopathology in children with epilepsy: a meta-analysis. *J Pediatr Psychol* 2005; **30:** 453–68.

9 Verrotti A, Carrozzino D, Milioni M, Minna M, Fulcheri M. Epilepsy and its main psychiatric comorbidities in adults and children. *J Neurol Sci* 2014; **343:** 23–29.

10 Gaitatzis A, Trimble MR, Sander JW. The psychiatric comorbidity of epilepsy. *Acta Neurol Scand* 2004; **110:** 207–20.

11 Kariuki SM, Newton CR, Prince MJ, Das-Munshi J. The association between childhood seizures and later childhood emotional and behavioral problems: findings from a nationally representative birth cohort. *Psychosom Med* 2016; **78:** 620–28.

12 Berg AT, Altalib HH, Devinsky O. Psychiatric and behavioral comorbidities in epilepsy: a critical reappraisal. *Epilepsia* 2017; **58:** 1123–30.

13 Fazel S, Wolf A, Långström N, Newton CR, Lichtenstein P. Premature mortality in epilepsy and the role of psychiatric comorbidity: a total population study. *Lancet* 2013; **382:** 1646–54.

14 Visser AM, Jaddoe VW, Ghassabian A, et al. Febrile seizures and behavioural and cognitive outcomes in preschool children: the Generation R study. *Dev Med Child Neurol* 2012; **54:** 1006–11.

15 Chang YC, Guo NW, Huang CC, Wang ST, Tsai JJ. Neurocognitive attention and behavior outcome of school-age children with a history of febrile convulsions: a population study. *Epilepsia* 2000; **41:** 412–20.

16 Berg AT, Caplan R, Hesdorffer DC. Psychiatric and neurodevelopmental disorders in childhood-onset epilepsy. *Epilepsy Behav* 2011; **20:** 550–55.

17 Anon. Febrile seizures: long-term management of children with fever-associated seizures. *Pediatrics* 1980; **66:** 1009–12.

18 Annegers JF, Hauser WA, Elveback LR, Kurland LT. The risk of epilepsy following febrile convulsions. *Neurology* 1979; **29:** 297–303.

19 Pedersen CB, Mors O, Bertelsen A, et al. A comprehensive nationwide study of the incidence rate and lifetime risk for treated mental disorders. *JAMA Psychiatry* 2014; **71:** 573–81.

20 Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989; **30:** 389–99.

21 Shorvon SD. The etiologic classification of epilepsy. *Epilepsia* 2011; **52:** 1052–57.

22 Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017; **58:** 512–21.

23 Josephson CB, Jette N. Psychiatric comorbidities in epilepsy. *Int Rev Psychiatry* 2017; **29:** 409–24.

24 Fiest KM, Dykeman J, Patten SB, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology* 2013; **80:** 590–99.

25 Clancy MJ, Clarke MC, Connor DJ, Cannon M, Cotter DR. The prevalence of psychosis in epilepsy: a systematic review and meta-analysis. *BMC Psychiatry* 2014; **14:** 75.

26 Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. Epilepsy, suicidality, and psychiatric disorders: a bidirectional association. *Ann Neurol* 2012; **72:** 184–91.

27 Vestergaard M, Pedersen MG, Ostergaard JR, Pedersen CB, Olsen J, Christensen J. Death in children with febrile seizures: a population-based cohort study. *Lancet* 2008; **372:** 457–63.

28 Vestergaard M, Pedersen CB, Christensen J, Madsen KM, Olsen J, Mortensen PB. Febrile seizures and risk of schizophrenia. *Schizophr Res* 2005; **73:** 343–49.

29 Norgaard M, Ehrenstein V, Mahon BE, Nielsen GL, Rothman KJ, Sorensen HT. Febrile seizures and cognitive function in young adult life: a prevalence study in Danish conscripts. *J Pediatr* 2009; **155:** 404–09.

30 Hesdorffer DC, Crandall LA, Friedman D, Devinsky O. Sudden unexplained death in childhood: a comparison of cases with and without a febrile seizure history. *Epilepsia* 2015; **56:** 1294–300.

31 Bergen DC. Do seizures harm the brain? *Epilepsy Curr* 2006; **6:** 117–18.

32 Farwell JR, Lee YJ, Hirtz DG, Sulzbacher SI, Ellenberg JH, Nelson KB. Phenobarbital for febrile seizures: effects on intelligence and on seizure recurrence. *N Engl J Med* 1990; **322:** 364–69.

33 The Brainstorm Consortium, Anttila V, Bulik-Sullivan B, et al. Analysis of shared heritability in common disorders of the brain. *Science* 2018; **360:** eaap8757.

34 á Rogvi R, Mathiasen R, Greisen G. Defining smallness for gestational age in the early years of the Danish Medical Birth Registry. *PLoS One* 2011; **6:** e16668.

35 Vestergaard M, Obel C, Henriksen TB, et al. The Danish National Hospital Register is a valuable study base for epidemiologic research in febrile seizures. *J Clin Epidemiol* 2006; **59:** 61–66.

36 Christensen J, Vestergaard M, Olsen J, Sidenius P. Validation of epilepsy diagnoses in the Danish National Hospital Register. *Epilepsy Res* 2007; **75:** 162–70.