Long-term prognosis after childhood convulsive status epilepticus: a prospective cohort study

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Summary

Background The prognosis of convulsive status epilepticus (CSE), a common childhood medical neurological emergency, is not well characterised. We aimed to investigate the long-term outcomes in a cohort of participants who previously had CSE.

Methods In this prospective study, we followed up a population-based childhood CSE cohort from north London, UK (the north London convulsive status epilepticus surveillance study cohort; NLSTEPSS). We collected data from structured clinical neurological assessment, neurocognitive assessment (Wechsler Abbreviated Scale of Intelligence), brain MRI, medical records, and structured interviews with participants and their parents to determine neurological outcomes, with adverse outcome defined as presence of one or more of epilepsy (active or in remission), motor disability, intellectual disability, or statement of special educational needs. We applied multiple imputation to address missing data and performed binary logistic regression analyses on complete-case and imputed datasets to investigate sociodemographic and CSE factors associated with adverse outcomes.

Findings Of 203 survivors (90% of inception cohort), 134 (66%) were assessed at a median follow-up of 8·9 years (IQR 8·2–9·5). The cumulative incidence of epilepsy was 24·7% (95% CI 16·2–35·6), with most (89%) emerging within 18 months after CSE. The cumulative incidence of epilepsy was lower in patients with prolonged febrile seizures (14·3%, 6·3–29·4) and survivors of acute symptomatic CSE (13·3%, 3·7–37·9) than in those of remote symptomatic CSE (45·5%, 21·3–72·0) and unclassified CSE (50·0%, 25·4–74·6). One participant (2·9%, 0·5–14·5) in the prolonged febrile seizures group developed temporal lobe epilepsy with mesial temporal sclerosis. The absence of fever at CSE was the only predictor of incident epilepsy (odds ratio [OR] 7·5, 95% CI 2·25–25·1). Motor and intellectual disability was seen predominantly in participants who had idiopathic and cryptogenic CSE (seven [36·8%, 95% CI 19·1–59·0] and 16 [84·2%, 62·4–94·5] of 19, respectively) and remote symptomatic CSE (33 [62·3%, 48·8–74·1] and 40 [75·5%, 62·4–85·1] of 53), and most of these participants had pre-existing disabilities. Pre-existing epilepsy was the only predictor of intellectual disability (OR 8·0, 95% CI 1·1–59·6). 51·5% (95% CI 43·1–59·8) of those followed up had a statement of special educational needs.

Interpretation Childhood CSE is associated with substantial long-term neurological morbidity, but primarily in those who have epilepsy, neurological abnormalities, or both before the episode of CSE. Survivors without neurological abnormalities before CSE have favourable outcomes.

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Introduction

Convulsive status epilepticus (CSE), a common childhood medical neurological emergency, is associated with increased mortality and morbidity, but there is considerable variability in reported frequency of adverse outcomes.[1,2] Between 11% and 45% of patients develop new-onset epilepsy within 5 years after CSE, but most studies do not separate motor and cognitive sequelae. Although some evidence suggests that short-term hippocampal injury and developmental or memory impairments occur after febrile status epilepticus, whether these changes lead to development of mesial temporal sclerosis is uncertain.[2–5] Most outcome studies are constrained by methodological shortcomings such as hospital-based or retrospective designs, unclear definition of outcomes, lack of formal neurocognitive assessment and neuroimaging, small sample size, and short follow-up (usually only up to 5 years). Thus, prognosis after childhood CSE is not well characterised.[2]

We did the first population-based study focused on childhood CSE, the north London convulsive status epilepticus surveillance study (NLSTEPSS), and described incidence, cause, and short-term outcomes.[1] We followed up these participants in this Status Epilepticus Outcomes Study (STEPSOUT). Having previously published data for risk and predictors of death,[6] we aimed to comprehensively assess this cohort to investigate their

Research in context

Evidence before this study

A previous systematic review on outcomes of childhood convulsive status epilepticus (CSE) included papers published up to May, 2006. We performed an additional search on PubMed for original articles on outcomes after childhood CSE published between June 1, 2006, and July 31, 2017, with the search terms "status epilepticus" combined with the terms "outcome", "morbidity", "prognosis", "recurrence", "mesial temporal sclerosis", "hippocampal sclerosis", and "cognition". Searches were repeated with "prolonged febrile convulsion", "prolonged febrile seizure", and "lengthy febrile seizure". Only studies that included patients aged between 1 month and 18 years at the time of status epilepticus were considered. The search identified 32 relevant additional articles. From the results of the systematic review and more recent studies it is clear that childhood CSE is associated with increased mortality and morbidity; however, there is considerable variability in reported frequency of adverse outcomes, primarily because of methodological differences. Also, evidence suggests short-term hippocampal injury and developmental or memory impairments after febrile status epilepticus, but whether these changes lead to development of mesial temporal sclerosis is uncertain. Most previous studies are hospital based or retrospective and have a small sample size or short follow-up (up to 5 years); therefore, whether the existing literature can be generalised to understand the natural history and prognosis following childhood CSE is uncertain.

Added value of this study

After reporting the incidence, cause, and short-term outcomes from children in the north London convulsive status epilepticus surveillance study (NLSTEPSS), we prospectively followed up this cohort to determine their long-term outcomes. To our knowledge, this is the first prospective population-based study to comprehensively describe the natural history and the long-term outlook after childhood CSE due to all causes. Our results showed that although morbidity is considerable after childhood CSE, this is seen primarily in those with symptomatic causes and pre-existing neurological abnormalities. Previously neurologically normal children have a favourable outcome with low incidence of epilepsy, motor disability, and intellectual disability after CSE. CSE recurrence occurs predominantly in those with previous neurological abnormalities. We also showed that temporal lobe epilepsy and mesial temporal sclerosis can be seen after all forms of childhood CSE, not just prolonged febrile seizures, but are uncommon. Our data suggest that CSE characteristics such as seizure duration are not major predictors of outcome independently of cause.

Implications of all the available evidence

Collectively, the available data are reassuring and suggest favourable outcomes in previously neurologically normal children, and the direct contribution of CSE in the development of neurological sequelae seems less than previously thought. However, whether CSE results in subtle neurocognitive deficits or behavioural difficulties in previously neurologically normal children is uncertain and needs investigation. Studies comparing outcomes after short seizures with seizures lasting 30 min or longer might also help to determine whether early cessation of seizures might improve outcomes. Development of strategies for early identification of those at high risk of neurocognitive sequelae and appropriate support at school and behavioural support might reduce the long-term negative effects of childhood CSE and improve quality of life. In addition to improvements in acute management of seizures, reducing childhood CSE incidence through preventive measures such as universal immunisation and optimal management of epilepsy, particularly in resource-poor settings, offers the best opportunity to reduce the morbidity and mortality associated with childhood CSE.

long-term epilepsy, motor, intellectual, and educational outcomes after CSE.

Methods

Study design and participants

Recruitment for NLSTEPSS has previously been reported.[1] In summary, between May 1, 2002, and April 30, 2004, using a multitiered notification system set up within a collaborative network of 21 hospitals in north London (UK), 226 participants with CSE were enrolled. Clinical and demographic data were shared with the central research team using linked anonymisation.

For STEPSOUT, participants were recruited through their local paediatricians, who used individual unique NLSTEPSS identification to recall patient identifiable information and determine survival status.[6] All surviving participants from NLSTEPSS were eligible for inclusion. Local paediatricians sent an invitation letter to these participants or their parents (if participant was still younger than 18 years) on behalf of the research team, with study information and consent forms, asking them to consent for study participation. Non-responders were sent reminders before being considered lost to follow-up.

We obtained written informed consent from all participant's parents or guardians, and consent or assent from each participant. STEPSOUT was approved by the UCL Institute of Child Health and Great Ormond Street Hospital Research Ethics Committee. We report our study findings according to STROBE guidelines.

Procedures

For each participant, background demographic, medical, and developmental data before CSE, and clinical details about CSE were obtained from the NLSTEPSS database.

To investigate prognosis and predictors of adverse outcomes after CSE, we retained the NLSTEPSS CSE classification.[1,7] Baseline motor functioning was determined from clinical neurological assessment at hospital discharge after initial CSE. Because formal cognitive assessment could not be performed at CSE for pragmatic reasons, we used parental report on development milestones before CSE occurred. We defined baseline cognition as abnormal if there was previously diagnosed intellectual disability, or if there was developmental delay documented in two or more domains: motor, speech or language, cognition, social or personal, or activities of daily living.[8]

Participants and their parents were interviewed, using a structured pro forma to ensure systematic and consistent enquiry for presence of seizures or epilepsy (before and after CSE and at follow-up), seizure semiology and epilepsy course, CSE recurrence, cognitive and motor development, behavioural problems, and schooling. Interviews were supplemented with review of hospital records. Participants underwent structured clinical neurological assessment (done by SSP) and neurocognitive assessment using the Wechsler Abbreviated Scale of Intelligence (WASI; done by MMM), and were invited to have brain MRI on an Avanto 1.5 Tesla scanner (Siemens, Erlangen, Germany). A single consent was used for all assessments including MRI. All participants were encouraged to undergo MRI but parents had the option to opt out if they did not wish to have MRI. Conventional MRI sequences, fluid attenuated inversion recovery (FLAIR), and three-dimensional fast low angle shot (3D-FLASH) sequences were acquired for detailed visualisation of mesial temporal structures. Mesial temporal sclerosis was defined radiologically as the presence of definite hippocampal atrophy, increased T2 signal in the hippocampus, and disturbed internal architecture.[9] All scans were visually analysed and reported by experienced paediatric neuroradiologists, as per standard clinical practice. All scans were further reviewed by another experienced paediatric neuroradiologist (WKKC), who was masked to clinical details.

Outcomes

Our primary objective was to assess epilepsy, motor, intellectual, and educational outcomes in survivors after childhood CSE. The secondary objectives were to estimate cumulative incidence, incidence, predictors, and spectrum of new-onset (incident) epilepsy; describe prevalence of epilepsy (active and in remission) and predictors of active epilepsy; estimate cumulative incidence, incidence, and predictors of incident motor and intellectual disability; describe prevalence of motor and intellectual disability, and educational difficulties; determine CSE recurrence; and characterise brain MRI findings.

Data from interviews, medical records, and neurology and neurocognitive assessments were used to determine outcomes. Adverse neurological outcomes were defined as having one or more of the following: epilepsy (active or in remission), motor disability, intellectual disability, or a statement of special educational needs (table 1). We adopted the International League Against Epilepsy (ILAE) guidelines for epilepsy definitions and classification, and an adaptation of the 2001 WHO Global Burden of Disease (GBD) project for definitions of motor and cognitive outcomes.[10,11] Need for special educational support determined educational outcomes.

	Definition
Seizures or epilepsy	
Epilepsy	Two or more unprovoked seizures occurring at least 24 h apart
Terminal remission	Seizure-free and off drug treatment in the preceding 2 years
Active epilepsy	Seizures within the past 2 years or currently on drug treatment for epilepsy
CSE recurrence	Recurrence of one or more episodes of CSE during follow-up (ie, between entry into NLSTEPSS and end of follow-up in the current study)
Motor functioning	
Minor impairment	Isolated hypotonia, gait, or coordination difficulties
Motor disability	Spasticity or paresis of one or more limbs (eg, cerebral palsy, hemiparesis)
Intellectual functioning	
Normal	Full-scale IQ score of 85 or above on WASI
Borderline intellectual functioning	Full-scale IQ score between 71 and 84 on WASI
Intellectual disability	Full-scale IQ score of 70 or lower on WASI, or untestable because of profound impairment
Educational difficulties	
Additional support in mainstream class	Special educational needs met effectively within mainstream settings through additional support (eg, School Action or School Action Plus)
Statement of special educational needs	Children with a statutory statement of special educational needs requiring substantial additional support in school because of learning, medical, or behavioural difficulties

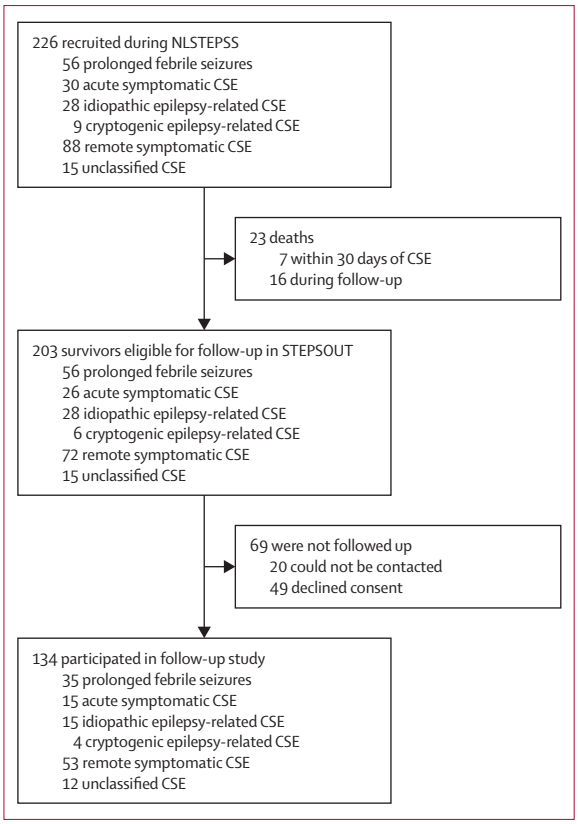
CSE=convulsive status epilepticus. NLSTEPSS=the north London convulsive status epilepticus surveillance study. WASI=the Wechsler Abbreviated Scale of Intelligence.

Table 1: **Definitions for clinical outcomes at follow-up**

Statistical analysis

Analyses were done by two authors (SSP and MC-B) using R software environment for statistical computing (version 3.0.1) for multiple imputation, SPSS (version 21.0) for subsequent statistical analyses, including Kaplan-Meier analysis, and StatXact (version 4, Cytel Software) to calculate the exact difference in proportions in characteristics between study participants and those lost to follow-up.

We calculated cumulative incidence for each adverse outcome by dividing total new-onset (incident) cases by the total number of cases without adverse outcome at baseline and available for follow-up. We determined incidence by dividing total incident cases by person-years in the population without adverse outcome at baseline and available for follow-up. We calculated 95% CIs on the basis of the Poisson distribution. Because most participants were at preschool age (1 month to 5 years) at CSE presentation, we did not calculate incidence for adverse educational outcomes. We calculated prevalence



See Online for appendix

Figure 1: **Study flow diagram**
CSE=convulsive status epilepticus. NLSTEPSS=the north London convulsive status epilepticus surveillance study. STEPSOUT=Status Epilepticus Outcomes Study.

of each outcome as the proportion of the cohort with adverse outcome at follow-up.

To investigate predictors of incident epilepsy, active epilepsy, incident motor disability, and incident intellectual disability, we used a complete-case approach for participants with complete baseline and follow-up data. We applied multivariate imputation by chained equations (MICE) to address missing data and minimise potential bias.[12] We performed binary logistic regression analyses on complete-case and imputed datasets. We used univariable analyses to identify factors reaching statistical significance of p≤0·1, which were then assessed in multivariable analyses. Factors not significant on univariable analyses were included in final models to identify factors associated with adverse outcomes only after adjustment for other clinically relevant variables. Sociodemographic variables included age at CSE, sex, prematurity (gestation <37 weeks), family history of epilepsy, and Index of Multiple Deprivation 2004 (IMD 2004) scores as indicators of socioeconomic status. Clinical variables were previous febrile seizures, first-ever (incident) versus previous CSE, febrile (temperature >38°C) versus afebrile CSE, whether prehospital treatment for CSE was given, interval between onset and first treatment for CSE, duration of CSE (continuous and categorical variable), intermittent versus continuous, type of seizure onset (focal *vs* generalised), and epilepsy, motor disability, or abnormal cognition at baseline.

Role of the funding source

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

Results

Of 203 surviving participants (90% of inception cohort in NLSTEPSS), 20 (10%) could not be contacted, 49 (24%) declined consent, and 134 (66%) were followed up (figure 1). 67 (50%) participants in the follow-up study were boys and 67 (50%) were girls, median age was 2·7 years (IQR 1·1–5·1) at CSE and 11·6 years (9·8–14·3) at follow-up. Median CSE duration was 70 min (IQR 45–100), and median follow-up was 8·9 years (IQR 8·2–9·5). There was no significant difference in clinical or demographic characteristics between STEPSOUT participants and dropouts (appendix). At follow-up, all 134 participants had in-person neurological examination; 94 underwent neurocognitive evaluation and the remaining 40 were not assessable using WASI due to profound cognitive impairment and were therefore categorised as having intellectual disability. MRI data were available for 106 (79%) participants. The rest were either unable to co-operate for MRI scan because of intellectual disability or behavioural problems, or declined consent.

The cumulative incidence of epilepsy was 24·7% (95% CI 16·2–35·6) and incidence was 28·8 (95% CI 17·1–45·6) per 1000 person-years (table 2). Cumulative incidence was lower in prolonged febrile seizures (14·3%, 95% CI 6·3–29·4) and acute symptomatic CSE (13·3%, 3·7–37·9) than in remote symptomatic CSE (45·5%, 21·3–72·0) and unclassified CSE (50·0%, 25·4–74·6). All incident epilepsies emerged within 5 years after CSE, 89% within 18 months (figure 2). In the complete-case analysis, absence of fever at CSE was the only predictor of incident epilepsy (odds ratio [OR] 7·5, 95% CI 2·25–25·1) and results were similar in the multiple imputation analysis (appendix)

Of the five participants with prolonged febrile seizures and with incident epilepsy, one developed temporal lobe epilepsy (4·5 years later) and had mesial temporal sclerosis (appendix). Two participants with unclassified CSE and one with remote symptomatic CSE developed temporal lobe epilepsy, and all except one (who declined MRI) had mesial temporal sclerosis. Thus, one (2·9%) of 35 participants with prolonged febrile seizures and four (5·5%) of 73 participants with no epilepsy before CSE

developed temporal lobe epilepsy, with or without mesial temporal sclerosis, after CSE.

Prevalence of epilepsy was 59·0% (95% CI 50·5–66·9) (table 3). Active epilepsy was present in 55 (41%) participants, primarily in those who had idiopathic and cryptogenic CSE, remote symptomatic CSE, and none who had prolonged febrile seizures (table 3). All five participants in the prolonged febrile seizures group who developed epilepsy after CSE were seizure free and off drug treatment in the preceding 2 years before the follow-up visit. In complete-case multivariable analysis, having epilepsy before CSE was the only predictor of active epilepsy at follow-up (OR 8·4, 95% CI 1·8–39·0), with similar results in the multiple imputation analysis (appendix). No one with prolonged febrile seizures was later diagnosed with Dravet syndrome.

Cumulative incidence of motor disability was 2·1% (95% CI 0·6–7·4) and of intellectual disability was 8·8% (4·3–17·0), and incidence was 2·5 (95% CI 0·3–9·0) per 1000 person-years and 10·2 (4·1–21·1) per 1000 person-years, respectively (table 2). Because only two incident cases occurred, we did not do regression analysis for motor disability. In complete-case analysis, pre-existing epilepsy at CSE was the only predictor of intellectual disability (OR 8·0, 95% CI 1·1–59·6), with similar results in the multiple imputation analysis (appendix). No participants in the prolonged febrile seizure and acute symptomatic CSE groups developed motor disability, and one participant who had prolonged febrile seizures developed intellectual disability.

Motor and intellectual disability was seen predominantly in participants with remote symptomatic CSE and those with idiopathic and cryptogenic CSE. Of 19 participants with idiopathic and cryptogenic CSE, motor disability was seen in seven (36·8%, 95% CI 19·1–59·0) and intellectual disability in 16 (84·2%, 62·4–94·5), reflecting pre-existing disabilities in 36·8% and 68·4%, respectively. Of 53 participants with remote symptomatic CSE, 33 (62·3%, 48·8–74·1) had motor disability and 40 (75·5%, 62·4–85·1) had intellectual disability (table 3), with pre-existing disabilities in 60·4% and 71·7%, respectively. 59 (92·2%, 95% CI 83·0–96·6) of 64 participants with motor disability, intellectual disability, or both, also had epilepsy (appendix).

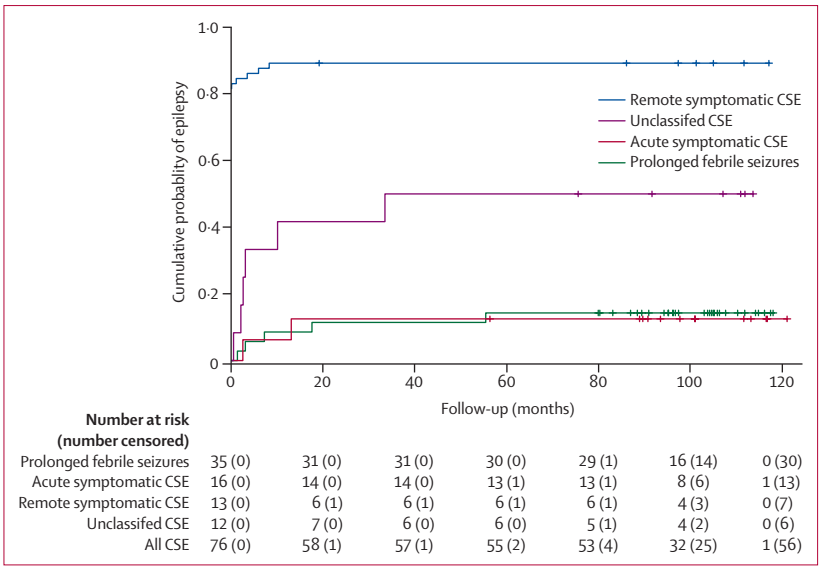
In the entire cohort, 80 (59·7%, 95% CI 51·2–67·6) received educational support, and 69 (51·5%, 43·1–59·8) had a statement of special education needs (appendix). Two (5·7%, 1·6–18·6) participants with prolonged febrile seizures and none (0%, 0–20·4) of those with acute symptomatic CSE had a statement of special educational needs, compared with 17 (89·5%, 68·6–97·1) participants with idiopathic and cryptogenic CSE and 46 (86·8%, 75·2–93·5) participants with remote symptomatic CSE.

Participants who had already had previous CSE at entry to NLSTEPSS were 4·5 times (95% CI 1·8–11·1) more likely to have CSE recurrence during follow-up than those

	Epilepsy				Motor disability				Intellectual disability			
	Incident cases (n/N)	Cumulative incidence (95% CI)	Person-years	Incidence per 1000 person-years (95% CI)	Incident cases (n/N)	Cumulative incidence (95% CI)	Person-years	Incidence per 1000 person-years (95% CI)	Incident cases (n/N)	Cumulative incidence (95% CI)	Person-years	Incidence per 1000 person-years (95% CI)
Prolonged febrile seizures	5/35	14·3% (6·3–29·4)	296	16·9 (5·5–39·4)	0/35	0% (0·0–9·9)	296	0 (0·0–12·5)	1/35	2·9% (0·5–14·5)	296	3·4 (0·1–18·8)
Acute symptomatic CSE	2/15	13·3% (3·7–37·9)	127	15·7 (1·9–56·9)	0/15	0% (0·0–20·4)	127	0 (0·0–29·0)	0/15	0% (0·0–20·4)	127	0 (0·0–29·0)
Idiopathic and cryptogenic CSE	NA	NA		NA	0/12	0% (0·0–24·2)	101	0 (0·0–36·5)	3/6	50·0% (18·8–81·2)	47	63·8 (13·2–186·5)
Remote symptomatic CSE	5/11	45·5% (21·3–72·0)	98	51·0 (16·6–119·0)	1/21	4·8% (0·8–22·7)	189	5·3 (0·1–29·5)	2/15	13·3% (3·7–37·9)	135	14·8 (1·8–53·5)
Unclassified CSE	6/12	50·0% (25·4–74·6)	103	58·3 (21·4–126·8)	1/12	8·3% (1·5–35·4)	103	9·7 (0·2–54·0)	1/9	11·1% (2·0–43·5)	79	12·7 (0·3–70·5)
All CSE	18/73	24·7% (16·2–35·6)	624	28·8 (17·1–45·6)	2/95	2·1% (0·6–7·4)	816	2·5 (0·3–9·0)	7/80	8·8% (4·3–17·0)	684	10·2 (4·1–21·1)

NA=not applicable because all individuals in the group, by definition, had epilepsy at CSE presentation. CSE=convulsive status epilepticus.

Table 2: **Cumulative incidence and incidence of epilepsy, motor, and intellectual disability after childhood CSE**



Number at risk (number censored)							
Prolonged febrile seizures	35 (0)	31 (0)	31 (0)	30 (0)	29 (1)	16 (14)	0 (30)
Acute symptomatic CSE	16 (0)	14 (0)	14 (0)	13 (1)	13 (1)	8 (6)	1 (13)
Remote symptomatic CSE	13 (0)	6 (1)	6 (1)	6 (1)	6 (1)	4 (3)	0 (7)
Unclassifed CSE	12 (0)	7 (0)	6 (0)	6 (0)	5 (1)	4 (2)	0 (6)
All CSE	76 (0)	58 (1)	57 (1)	55 (2)	53 (4)	32 (25)	1 (56)

Figure 2: **Kaplan-Meier graph for prevalence of epilepsy at CSE presentation (baseline) and incident epilepsy during follow-up, by CSE category**
All participants in idiopathic and cryptogenic CSE group by definition had epilepsy at CSE presentation, and therefore the line is not visible in the graph. CSE=convulsive status epilepticus.

whose initial CSE was their first episode (appendix). Participants with pre-existing neurological abnormalities were 3·8 times (95% CI 1·8–8·0) more likely to have recurrence than those without. Ten (28·6%) participants with prolonged febrile seizures had recurrence; of these, four had epilepsy after CSE and the other six did not have any further seizures or epilepsy.

Of 59 participants with no pre-existing neurological abnormality, 50 (85%) underwent MRI; and of 75 participants with pre-existing neurological abnormality, 53 (71%) had MRI, either for the study or had had recent MRI for clinical reasons and were adequate for our review. Thus, participants with neurological abnormalities or abnormal MRI are not overrepresented in neuroimaging results.

Of 32 participants with prolonged febrile seizures who had MRIs, two (6·25%, 95% CI 1·7–20·1) had clinically significant abnormalities. One participant with temporal lobe epilepsy had unilateral mesial temporal sclerosis and another participant who was neurologically normal had MRI features of neurofibromatosis type 1. Of 41 participants with remote symptomatic CSE who had MRI, 31 (75·6%, 60·7–86·2) had significant structural abnormalities. 31 (83·8%, 68·9–92·4) of 37 participants with clinically significant MRI abnormalities had epilepsy with or without other neurological comorbidity (appendix).

Discussion

In this prospective study, we investigated long-term seizure incidence and neurological morbidity at a median follow-up of 8·9 years in survivors of a population-based childhood CSE cohort. Our main findings are that most participants with no previous neurological abnormality do not develop epilepsy, motor, or intellectual disability after CSE, and have a favourable outcome. Subsequent temporal lobe epilepsy and mesial temporal sclerosis can be found after all forms of CSE, not just prolonged febrile seizures, but are uncommon. Additionally, participants with epilepsy, neurological abnormality, or both, before CSE had high risk of intellectual disability, and often have active epilepsy at follow-up. The outcome after CSE depends mainly on its cause, and participants with clinically significant abnormal MRIs were at the highest risk for adverse outcomes. Finally, CSE recurrence occured predominantly in those with previous neurological abnormalities, and CSE duration does not have prognostic significance for any of the outcomes.

Cumulative incidence of epilepsy in our cohort (25%) is similar to the 23–36% incidence reported in studies with shorter follow-up.[2,13–15] This result is partly because almost 90% of our cohort who developed epilepsy did so within 18 months after CSE. 10% of children with incident epilepsy present with CSE as their first unprovoked seizure and 80–90% of recurrences happen within 2 years after a first unprovoked seizure.[16,17] Thus, unprovoked CSE, like brief seizures, could be the presentation that leads to the diagnosis of epilepsy within 2 years and a low risk thereafter.

Our results further support previous data showing good short-term and long-term neurological outcomes in children with prolonged febrile seizures.[2,15,18–23] 14% of participants with prolonged febrile seizure in our cohort developed epilepsy, all with good seizure outcome, and only one participant had intellectual disability. Our findings, together with reports from FEBSTAT showing acute hippocampal injury and subtle cognitive impairment within 1 year.[3–5] suggest the possibility of short-term hippocampal involvement but with minimal long-term consequences. Data are conflicting on the causative role of prolonged febrile seizures in later development of mesial temporal sclerosis and temporal lobe epilepsy.[2,23–26] Our data suggest that temporal lobe epilepsy is not common (3%) in those who develop epilepsy after prolonged febrile seizures, and prevalence of mesial temporal sclerosis is low (3%) within 9 years after prolonged febrile seizures. These findings are consistent with observations from earlier prospective studies suggesting low incidence of temporal lobe epilepsy (<6%) and mesial temporal sclerosis (<7%) after prolonged febrile seizures.[18,22,23,25,26] Although prolonged febrile seizures might increase risk of hippocampal injury in those with pre-existing abnormalities, the direct contribution of prolonged febrile seizures in development of mesial temporal sclerosis, temporal lobe epilepsy, or both, seems less than has long been believed.[4,26]

In our study, prevalence of motor disability was 31% and intellectual disability was 46%. However, disabilities were seen mostly in participants with idiopathic and cryptogenic CSE and those with remote symptomatic

CSE. Additionally, disabilities were present before CSE in most participants, and fewer than 9% were incident. The incidence of motor and intellectual disability in STEPSOUT are broadly consistent with the reported incidence of less than 20%, but there are two notable variances in the subgroup findings.[2,15,18,19,21] One is the seemingly high incidence of intellectual disability in the idiopathic and cryptogenic CSE group, with three of six participants who were reported to be developmentally normal at CSE presentation performing within intellectual disability range on neurocognitive testing. Although the point estimate in this subgroup with modest sample size is high at 50%, the 95% CI is wide (19–81%) and overlaps with results reported in previous literature. Possible reasons for this finding include differences in classification (we classified idiopathic and cryptogenic epilepsy-related CSE and unclassified CSE separately, whereas unclassified CSE are grouped under idiopathic CSE group in most previous studies and therefore the reported outcomes are better); we used a formal cognitive assessment, whereas other studies could have missed some participants who might not have had formal testing; and our study had a longer follow-up compared with other studies and the probability of detection of abnormalities increases with time.[27] The second difference is that our point estimate of 0% for permanent motor and intellectual disability for surviving participants after acute symptomatic CSE is lower than that in some previous studies.[2] Given the width of the 95% CI (0·0–20·4) of this modest sized subgroup (n=15), the true estimate might be more consistent with a higher incidence of disabilities. However, it is equally possible that the true estimate is closer to our point estimate and would be consistent with other studies in which acute symptomatic CSE is associated with increased short-term mortality and the neurological outcome among survivors is favourable.[15,28,29] The 60% of participants who needed educational support were mostly among those who had neurological problems before CSE, and this proportion is similar to the 63% reported in school-aged children with active epilepsy.[27] Taken together, our data suggest that CSE itself might not independently increase the risk of long-term neurocognitive sequelae in a major way.

Our findings provide strong population-based data suggesting the cause of childhood CSE is the main determinant of long-term outcome after the event.[2,15,23] Incidence of neurological sequelae is high in those with symptomatic causes and pre-existing neurological abnormalities, and seemingly low in previously neurologically normal children. In addition to cause, other CSE-related characteristics such as younger age at CSE, absence of fever, focal seizure onset, history of seizures or CSE, and seizure duration have commonly been associated with poor outcomes.[2] However, because it is extremely difficult to separate the effect of CSE itself from its cause, which influences seizure characteristics such as duration, their additional effect on subsequent

	Epilepsy			Motor functioning			Intellectual functioning*		
	None	Terminal remission	Active	Normal	Minor impairment	Motor disability	Normal	Borderline	Intellectual disability
Prolonged febrile seizures (n=35)	30; 85·7% (70·6–93·7)	5; 14·3% (6·3–29·4)	0; 0·0% (0·0–9·9)	30; 85·7% (70·6–93·7)	5; 14·3% (6·3–29·4)	0; 0·0% (0·0–9·9)	28; 80·0% (64·1–90·0)	6; 17·1% (8·1–32·7)	1; 2·9% (0·5–14·5)
Acute symptomatic CSE (n=15)	13; 86·7% (62·1–96·3)	1; 6·7% (1·2–29·8)	1; 6·7% (1·2–29·8)	14; 93·3% (70·2–98·8)	1; 6·7% (1·2–29·8)	0; 0·% (0·0–20·4)	14; 93·3% (70·2–98·8)	1; 6·7% (1·2–29·8)	0; 0·0% (0·0–20·4)
Idiopathic and cryptogenic CSE (n=19)	0; 0·0% (0·0–16·8)	4; 21·0% (8·5–43·3)	15; 79·0% (56·7–91·5)	3; 15·8% (5·5–37·6)	9; 47·4% (27·3–68·3)	7; 36·8% (19·1–59·0)	2; 10·5% (2·9–31·4)	1; 5·3% (0·9–24·6)	16; 84·2% (62·4–94·5)
Remote symptomatic CSE (n=53)	6; 11·3% (5·3–22·6)	11; 20·8% (12·0–33·5)	36; 67·9% (54·5–78·9)	9; 17·0% (9·2–29·2)	11; 20·8% (12·0–33·5)	33; 62·3% (48·8–74·1)	6; 11·3% (5·3–22·6)	7; 13·2% (6·5–24·8)	40; 75·5% (62·4–85·1)
Unclassified CSE (n=12)	6; 50·0% (25·4–74·6)	3; 25·0% (8·9–53·2)	3; 25·0% (8·9–53·2)	9; 75·0% (46·8–91·1)	2; 16·7% (4·7–44·8)	1; 8·3% (1·5–35·4)	8; 66·7% (39·1–86·2)	0; 0·0% (0·0–24·2)	4; 33·3% (13·8–60·9)
All CSE (n=134)	55; 41·0% (33·1–49·5)	24; 17·9% (12·3–25·3)	55; 41·0% (33·1–49·5)	65; 48·5% (40·2–56·9)	28; 20·9% (14·9–28·5)	41; 30·6% (23·4–38·8)	58; 43·3% (35·2–51·7)	15; 11·2% (6·9–17·6)	61; 45·5% (37·3–54·0)

Data are n; % (95% CI). CSE=convulsive status epilepticus. Terminal remission=seizure-free off drug treatment in the preceding 2 years. *Intellectual functioning was defined as normal if IQ score was 85 or higher, borderline if IQ score was 71–84, and intellectual disability if IQ score was 70 or lower.

Table 3: **Prevalence of epilepsy, motor, and intellectual functioning after CSE in childhood**

outcomes is uncertain.[2] Our findings are consistent with those from earlier studies, and suggest that CSE characteristics such as seizure duration are not major predictors of outcome independent of underlying cause.[14,15,18,26,28,30] However, by definition, only children with seizures longer than 30 min were included in our study.[1,31] This raises the question if earlier cessation of seizures would result in decreased morbidity and mortality.

Data from our group and others suggest that CSE is associated with acute brain injury and short-term cognitive impairment, with at least partial recovery as a result of brain plasticity and reorganisation during follow-up.[3–5,32] We speculate that children with pre-existing brain pathology (structural or genetic) might have less reserve and thus less chance of recovery, which might explain the major contribution of cause to outcomes. Some evidence also suggests that repeated CSE are associated with worse outcomes.[7] Thus, in theory, earlier cessation of seizures might result in better outcomes, particularly in children who already have neurological problems or have had previous CSE. Studies comparing outcomes after short seizures with seizures lasting longer than 30 min might provide useful information, but would still be confounded by the severity of the underlying brain disorder and might not be able to determine the independent effect of CSE on outcomes. Therefore, ready access to emergency treatment, particularly for high-risk groups, should be considered.

Although our study has the advantage of prospective, long-term follow-up of a large population-based cohort, it has limitations. Loss to follow-up is inevitable in epidemiological studies and the reported follow-up rates for cohort studies are typically lower than 60% after 5 years.[33] With our best efforts we could follow up 66% of the original cohort, which is not surprising given the duration of follow-up and population migration for residents in London, and acceptable for this type of study. Our data show no significant difference in the demographic and clinical characteristics of the follow-up cohort and those lost to follow-up (appendix). Additionally, we applied multiple imputation to address missing data and minimise potential bias, and found the results to be consistent using both complete-case and multiple imputation approaches.[12] Therefore, we are confident that the chances that our results are biased are very low. However, multiple imputation is based on the assumption that data are missing at random, and there is no way to know whether outcomes of participants who could not be followed up were systematically different from those that we included in the follow-up. Thus, the potential bias due to multiple imputation cannot be measured. Because the latency to the development of temporal lobe epilepsy and mesial temporal sclerosis after prolonged febrile seizures could be even longer than our follow-up duration, it is possible we might not have captured all cases.[24] Moreover, results from this study, done in a high-income country, might not be generalisable to resource-poor settings where the population have poor access to emergency medical care, suboptimal intensive care facilities, and a different spectrum of CSE causes. For example, the majority of childhood CSE cases in Kenya were caused by infection.[34]

To conclude, the results of our prospective population-based study showed that childhood CSE is associated with substantial long-term neurological morbidity, but primarily in those who have epilepsy or neurological abnormalities before CSE. Children without pre-existing neurological abnormalities who survived CSE have favourable outcomes.

Author contributions

SP, MDH, CG, BGN, RCS, and RFC designed the study. SP and MMM collected data. SP and MC-B did the statistical analysis. WKKC analysed the MRI scans. All authors contributed to interpretation and writing the manuscript. BGN passed away before submission of the manuscript.

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Declaration of interests

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