Functional / dissociative seizures: Epidemiological and clinical aspects

Thesis

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by

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Antonia Villagrán

Abbreviations

ALE adverse life events

ASQ Attachment Style Questionnaire

BRI Behavioral Regulation Index

BRIEF Behavior Rating Inventory of Executive Function

CI confidence interval

DES Dissociative Experience Scale

DS dissociative seizures

DSM Diagnostic and Statistical Manual of Mental Disorders

EEG electroencephalography

EF executive function

FND functional neurological disorder

FDS functional/dissociative seizures

FS functional seizures

HQoL Health-related quality of life

ICD International Classification of Diseases

ILAE International League Against Epilepsy

IR incidence rate

MI metacognition Index

MRI magnetic resonance imaging

NEA nonepileptic attacks

NEAD non-epileptic attack disorder

NEC Norwegian Epilepsy Center

NES non-epileptic seizures

NPR Norwegian patient registry

PBI Parental Bonding Instrument

PNEA psychogenic nonepileptic attacks

PNEE psychogenic nonepileptic events

PNES psychogenic nonepileptic seizures

PPV positive predictive value

PTSD post-traumatic stress disorder

RAVLT Rey Auditory and Verbal Learning Test

SDQ Somatoform Dissociation Questionnaire

TEC Traumatic Experience Checklist

WAIS Wechsler Adult Intelligence Scale

WASI Wechsler Abbreviated Scale of Intelligence

WHO World Health Organization

List of publications

Paper I

Villagrán A, Eldøen G, Duncan R, Aaberg KM, Hofoss D, Lossius MI. Incidence and prevalence of psychogenic nonepileptic seizures in a Norwegian county: A 10-year population-based study. Epilepsia. 2021 Jul;62(7):1528-1535.

Paper II

Villagrán A, Lund C, Duncan R, Lossius MI. The effect of attachment style on long-term outcomes in psychogenic nonepileptic seizures: results from a prospective study. Epilepsy Behav 2022;135: 108890.

Paper III

Villagrán A, Lund C, Duncan R, Ingvar Lossius M. Adverse life events in patients with functional seizures: Assessment in clinical practice and association with long-term outcome. Epilepsy Behav. 2023 Oct 5;148:109456.

Paper IV

Villagrán A, Hessen E, Torgersen H, Alfstad KÅ, Lossius MI. Negative impact of self-reported executive problems on the long-term outcome in patients with functional/dissociative seizures: results from a prospective observational study. In preparation.

Additional publication

Villagrán A, Duncan R, Hofoss D, Lossius MI. Response: The true prevalence of psychogenic nonepileptic seizures is much higher than this Epilepsia. 2021 Nov;62:2877.

Summary in English

Patients with functional/dissociative seizures (FDS) are commonly seen in neurological practice. FDS superficially resemble epileptic seizures, but are not associated with epileptiform activity. FDS is regarded as a functional neurological disorder. Misdiagnosis is frequent and healthcare pathways for patients with FDS are often characterized by repeated emergency-room visits, hospital admissions, and extended investigations. FDS is associated with high rates of disability and economic stagnation, and the prognosis is presumably rather poor. Epidemiological data on FDS are scarce.

The articles included in this thesis provided, to the best of our knowledge, the first population-based estimates of the prevalence of FDS in a particular population. Based on a systematic review of the medical records of patients who were resident in Møre and Romsdal County, Norway registered with diagnostic codes of F44.5 “dissociative seizures” and R56.8 “convulsions, not elsewhere classified” in the period January 2010 to January 2020, we found a FDS prevalence of 23.8/100 000 (95% confidence interval [CI] = 17.9–29.6). The highest prevalence was found in the age group 15–19 years, at 59.5/100 000 (95% CI = 22.6–96.3). Our estimates of occurrence of FDS were in line with previous estimates from non-population-based data.

In our prospective cohort from the National Center for Epilepsy, the long-term prognosis of FDS was poor. At follow-up (mean duration of almost 6 years), 61% of patients diagnosed with FDS continued to experience seizures. We found that attachment anxiety, female gender, and self-rated executive dysfunction were risk factors for persistent FDS.

Poor health-related quality of life at follow-up was associated with antecedent adverse life events (ALE). A substantial proportion of the ALE identified by a self-report questionnaire had not been documented in the clinical records.

Knowledge about the occurrence, long-term outcomes, and risk factors for the persistence of FDS are important both for the patients and the clinicians involved with this patient group, as well as for planning of healthcare services.

Summary in Norwegian

Pasienter med funksjonelle/dissosiative anfall (FDS) er ofte sett i nevrologisk praksis. FDS ligner overfladisk epileptiske anfall, men er ikke assosiert med epileptiform aktivitet. FDS regnes som en funksjonell nevrologisk lidelse. Feildiagnostisering er hyppig og behandling av pasienter med FDS er ofte preget av gjentatte kontakter med akuttmottak, gjentatte sykehusinnleggelser og undersøkelser. FDS er assosiert med høye forekomster av økonomisk inaktivitet og forhøyet risiko for å falle utenfor arbeidsliv. Prognosen er antatt å være dårlig. Det finnes lite epidemiologiske data om FDS.

Artiklene inkludert i denne avhandlingen ga, så vidt vi vet, de første populasjonsbaserte tall for forekomst av FDS. Basert på en systematisk journalgjennomgang av pasienter bosatt i Møre og Romsdal, registrert med diagnosekoder F44.5 «dissosiative anfall» og R56.8 «kramper, ikke andre steder klassifisert» i perioden januar 2010 til januar 2020 fant vi en FDS-prevalens på 23,8/100 000 (95 % konfidensintervall [KI] = 17,9–29,6). Høyest prevalens ble funnet i aldersgruppen 15–19 år, på 59,5/100 000 (95 % KI = 22,6–96,3). Våre estimater av FDS-prevalens var i tråd med tidligere estimater fra ikke-populasjonsbaserte data.

I vår prospektive kohort fra Spesialsykehus for epilepsi (SSE) var langtidsprognosen for FDS dårlig. Etter oppfølging (gjennomsnittlig nesten 6 år) fortsatte 61 % å ha anfall. I vår studie var engstelig tilknytning (attachment anxiety), kvinnelig kjønn og selvvurdert eksekutiv dysfunksjon risikofaktorer for vedvarende FDS.

Dårlig helserelatert livskvalitet ved oppfølging var assosiert med forutgående belastende livshendelser (adverse live events). En betydelig andel av de potensielt belastende livshendelsene identifisert gjennom et selvrapporteringsskjema var ikke dokumentert i de kliniske journalene.

Kunnskap om forekomst, langsiktig utfall og risikofaktorer for persistens av FDS er viktig både for klinikere involvert i denne pasientgruppen, samt for planlegging av helsetjenester.

Contents

1. Introduction

Functional/dissociative seizures - a functional neurological disorder

Functional/dissociative seizures (FDS) are considered to be a functional neurological disorder (FND). Patients with an FND have neurological symptoms in the absence of neurological disease. (1) FDS is characterized by seizures that superficially resemble epileptic seizures, but are not associated with epileptiform activity. (2) FND, especially FDS, are one of the most common disorders in patients attending neurological clinics (3) and cause a substantial burden for the patients, their families, and healthcare systems. (4)

Terminology and classification

Within clinical practice and research there have been several different diagnostic labels for this disorder, such as functional seizures (FS), psychogenic nonepileptic seizures (PNES), and dissociative seizures (DS). There are also terms that avoid including the words seizures and/or psychogenic, such as nonepileptic attacks (NEA), psychogenic nonepileptic attacks (PNEA), and psychogenic nonepileptic events (PNEE).

Which term is the most appropriate is still under debate and there is no widely accepted consensus. (5-9) Nonetheless, the choice of terminology is important, not merely of academic interest, as it affects both patients' and caregivers' responses to the diagnosis. (9) Although to my knowledge, there is not yet an official publication, the International League against Epilepsy (ILAE) Functional / Dissociative Seizure Task Force advocates the new term of functional/dissociative seizures (FDS). With that background, I have chosen to use the recommended term, functional/dissociative seizures (FDS), in this thesis. Previously, PNES has been the most frequently used term in Norway, at least in the last decade. As the nomenclature is under debate, we have also used different terms in our articles (PNES in articles 1 and 2, FS in article 3, and FDS in article 4).

In the current classification systems, FDS do not have a distinct place. They are classified as dissociative disorders in the International Classification of Diseases (ICD) — 10th edition (ICD-10) (10), whereas they are categorized as a somatoform disorder in the Diagnostic and Statistical Manual of Mental Disorders —Fifth Edition (DSM-5) (2).

In Europe, the ICD is the classification system used. Surveys among healthcare professionals in European countries indicate that only a minority of clinicians use the ICD-10 code for DS F44.5 when diagnosing FDS. (11, 12) Instead, in clinical practice, a variety of nonspecific codes are commonly chosen when coding for FDS, including the nonspecific ICD-10 code for seizures R 56.8.

Diagnosis of FDS

FDS is one of the main differential diagnoses in patients assessed for transient loss of consciousness. (13) Clinical features, such as long duration and a fluctuating course of the seizure, with waxing and waning, are clues that should raise the suspicion of FSD. (14) However, the differential diagnosis is challenging, and a long diagnostic delay is common. (15) Healthcare practitioners often report uncertainty regarding the diagnosis, and a fear of making diagnostic errors. (16) Making an erroneous diagnosis both ways, that is, misdiagnosing FDS as epilepsy, or erroneously diagnosing epilepsy as FDS, exposes patients to ineffective and potentially harmful (mis)treatment.

In 2013, the ILAE Nonepileptic Seizures Task Force published a paper stating an agreement on the minimum requirements for a diagnosis of FDS (then referred to as PNES). Based on these recommendations, the combination of a history indicative of FDS and ictal recordings on video-electroencephalography (EEG) is considered the diagnostic gold standard. (17) The diagnosis of FDS should be established based on information about patient history, seizure semiology, and EEG-findings. Depending on clinical and electrophysiological information, the diagnosis of FDS can be made at one of four levels of certainty; see Table 1.

Diagnostic level	**History**	**Witnessed event**	**EEG**
Possible	Consistent with FDS	By witness of self- report	No epileptiform activity on interictal EEG
Probable	Consistent with FDS	By clinician in person or reviewed video recording	No epileptiform activity on interictal EEG
Clinically established	Consistent with FDS	By clinician experienced in seizure disorders (in person or on video)	No epileptiform activity on routine or ambulatory ictal EEG during a typical event
Documented	Consistent with FDS	By clinician experienced in seizure disorders (in person or on video) while on video EEG	No epileptiform activity immediately before, during or after a typical event captured on ictal video EEG

Table 1. Diagnostic levels of certainty for the diagnosis of functional/dissociative seizures, adapted from La France Jr., et al (2013). (17)

Occurrence of FDS

As mentioned above, FDS is one of the main differential diagnoses for transient loss of consciousness. In patients assessed in emergency settings for suspected seizures, FDS account for 11-

27% of the diagnoses made. (18, 19) Among patients seen for prolonged seizures or suspected status epilepticus, the proportion diagnosed with FDS is even higher, accounting for up to 50% of the cases. (19, 20)

Women are disproportionately affected by FSD, with around 70% of patients being female in most larger studies. (21) However, the female preponderance is less pronounced in several subgroups, such as the elderly or persons with intellectual disabilities. (21-23)

Detailed knowledge about the background, composition, and magnitude of the population with FDS is crucial for planning and providing healthcare. Given the challenges related to the diagnosis and misdiagnosis of FDS, terminology and codes used, and the heterogeneity of the population with FDS, reliable data on the occurrence of FDS are scarce. The prevalence and incidence of FDS may vary. depending on, for example, geographical region, age, and socio-economic status. Existing data are of poor quality, usually with limitations due to the studied populations and study designs.

The ILAE Epidemiology Commission has published a report on standards for epidemiological studies and surveillance of epilepsy. (24) There is no similar standard for FDS. How to define, for example, whether a given person has active FDS, and thereby should be counted as a prevalent case, is not commonly agreed upon. This illustrates just one of the many obstacles that are met when conducting epidemiological studies on FDS.

Prevalence of FDS

The prevalence of FDS indicates the proportion of persons with FDS in a given population. The prevalence of FDS has not been directly measured previously. Based on the numbers of patients with FDS attending epilepsy centers, the prevalence has been estimated to be 2–50/100 000. (6, 25)

Incidence of FDS

The incidence of FDS describes the frequency of new cases of FDS in a given population over a specified period. Incidence rates (IR) of FDS of between 1.4 and 4.9/100 000/year have been reported from different adult populations. (26-28) A nationwide study in a Danish pediatric population showed an incidence of 2.4/100 000/year. (29)

Etiology

The etiology of FDS is multifactorial and generally explained on the basis of a biopsychosocial model, often taking into account possible predisposing, precipitating, and perpetuating factors. (30)

Risk factors or predisposing factors include a history of adverse life events (ALE) in childhood and adulthood, family dysfunction, genetic vulnerability, cognitive deficits, emotional instability, and

health problems. The latter includes other functional disorders, such as chronic pain. Precipitating factors may include physical trauma, injury or illness, emotional distress, and bereavement. Social isolation, misdiagnosis, and mistreatment are common examples of maintaining or perpetuating factors. (31)

Attachment styles

Attachment theory may provide an explanatory framework for the interplay of family dysfunction, ALE, and other risk factors with the development and clinical course of FDS. According to attachment theory, early childhood interactions with parents or other primary caregivers result in distinct patterns of thoughts, beliefs, emotions, and behaviors regarding self and others. These are referred to as attachment styles. (32, 33) Attachment disturbances have been linked to several mental disorders. (34) In patients with FDS, fearful attachment (35) and insecure attachment (36) have been found to be predominant. Attachment styles have also been associated with outcome in psychotherapy. (37)

Adverse life events

As mentioned above, a history of ALE is considered a common risk factor for FND in general, and for FDS in particular. (15) Patients with FND report stressful life events, including trauma and neglect, around four to eight times more frequently than healthy controls. (1) It is important to note, however, that some patients with FND do not have a history of ALE. There are indications for an association between the severity of experienced ALE and symptom severity in patients with FND. (38) In patients with FDS, earlier seizure onset and seizure severity have been related to antecedent sexual abuse. (39) Sexual abuse has also been linked to poor outcome in FND. (40) A history of antecedent ALE might play a role in the outcome for patients with FDS as well, but data about this topic are scarce.

Comorbidity

Patients with FDS may suffer from several other comorbidities. A high proportions of comorbid psychiatric disorders, such as dissociative and somatoform disorders, post-traumatic, depressive and anxiety disorders, as well as personality disorders, have been reported in FDS patients. (15) More recent findings have also indicated elevated rates of other diseases, such as neurological and metabolic diseases. (41) In particular, comorbidity with epilepsy has been described in several studies. (42) Newer studies not only report high rates of morbidity in patients with FDS compared to the general population, but also increased mortality. (43, 44)

Neuropsychological finding in FDS

Patients with FDS commonly report cognitive deficits. Subjective cognitive problems are linked to reduced health-related quality of life (HQoL). Studies of cognitive function in patients with FDS have yielded mixed results. When there is impairment, it often shows as general dysfunction, affecting multiple domains. (45) The most consistent findings are alterations in attention and executive function (EF). EF involves the ability to control and regulate cognition and behavior, and to adapt to changing situations. It is considered crucial for goal-directed behavior. (46) EF may therefore play an important role in engagement with, and adherence to, treatment plans for patients with FDS.

Treatment and outcomes in FDS

Internationally accepted treatment guidelines for FDS are lacking, but psychotherapy is generally considered the treatment of choice for patients with FDS. (47, 48) Long-term outcome is regarded to be poor, with approximately two-thirds of newly diagnosed adults with FDS continuing to have seizures years after receiving their diagnosis. It should be noted, however, that previous studies have some methodological weaknesses, as they were mainly retrospective in nature and have had low responder rates. (49-51)

2. Aims of the study

The main aim of the present research project was to map the occurrence and long-term outcomes of FDS among selected populations in Norway. A secondary aim was to examine the role of a variety of prognostic factors for long-term outcome.

These research objectives were explored through the following specific aims:

I. To assess the incidence and prevalence of FDS in the County of Møre and Romsdal, applying the definition of FDS/PNES used by the ILAE Nonepileptic Seizures Task Force.
II. To assess the long-term seizure outcome in a FDS cohort, recruited from the Norwegian Epilepsy Center (NEC) and examine the role of attachment styles on outcome.
III. To investigate the impact of ALE on long-term outcomes in patients with FDS and the degree of assessment of ALE in clinical practice.
IV. To explore neuropsychological profiles in the same cohort of patients with FDS from the NEC in Norway and investigate the role of neuropsychological characteristics on long-term outcome.

3. Methods

The articles included in this thesis are based on data from two different cohorts. Article 1 presents data from a population-based cohort from the Norwegian county of Møre and Romsdal, whereas Articles 2, 3, and 4 are based on a clinically well-described prospective cohort recruited from the NEC.

The Møre and Romsdal study population

Located in the western region of Norway, the county of Møre and Romsdal has a total area of 14 356 km^2. Møre and Romsdal had a population of 265 238 on January 1, 2020 (135 213 men, 130 025 women), which is an increase of 5.6% from the population at the start of our study in 2010 and represents roughly 4.9% of the Norwegian population. Around 12% of the county's population in 2020 were immigrants born abroad, primarily in Central Europe. The most common immigrant ethnicities were German, Polish, and Lithuanian. Around 4% of the population were non-European immigrants, primarily from Thailand, Eritrea, and Syria. In 2020, 2.6% of the population of Møre and Romsdal was under the age of 20 years, around 57% was between the ages of 20 and 64 years, and the remaining 20% 65 years or older. According to Statistics Norway, the socioeconomic status, level of urbanization, distribution of ages, and access to healthcare of Møre and Romsdal's population are comparable to those of Norway as a whole. (52) Neurological inpatient and outpatient treatments are located in two hospitals, each of which has an EEG division. Three hospitals offer pediatric services.

Cases of FDS were identified through the Norwegian Patient Registry (NPR). This is a mandatory administrative registry containing discharge diagnosis data from those hospitals and outpatient clinics that are owned or reimbursed by the Norwegian government; these account for more than 99% of health services in Norway. Diagnoses are coded using the ICD-10.

Based on our clinical experience, indicating a lack of consensus regarding a diagnostic code for FDS and the finding that many clinicians use the nonspecific code R56.8 “convulsions, not elsewhere classified” rather than F44.5 “conversion disorder with seizures or convulsions”, we decided to include all patients registered with a primary diagnosis of ICD-10 code F44.5 or R56.8 in the period from January 1, 2010 to January 1, 2020 at the hospitals in the county of Møre and Romsdal.

Data collection in the population-based study

All potential FDS diagnoses in the Møre and Romsdal study were validated through medical record reviews. Data collection was done by Antonia Villagrán using a data collection protocol. For each case, a minimum dataset was reviewed. This included demographic data and clinical information about the medical history, seizure assessment, EEG, magnetic resonance imaging (MRI), blood samples, treatment, and other relevant information. Medical record reviews were performed for 1241 cases registered with ICD codes F44.5 (n=25) or R56.8 (n=1216) during the study period.

Validation of FDS diagnoses in the population-based study

FDS cases were validated by applying the approach to diagnosing FDS proposed by the ILAE in 2013. According to the ILAE proposal, FDS diagnoses can be established on the base of information about clinical history, witnessed events, and EEG findings. The ILAE defined four diagnostic levels of certainty for FDS, namely: (1) possible, (2) probable, (3) clinically established, and (4) documented (see Table 1). Time of onset of FDS was defined as the year of onset of seizure symptoms suggestive of FDS.

All cases were validated and classified by the PhD student and first author of Article 1, Antonia Villagrán. A random subsample of 124 cases (10% the study sample) was rated independently by the main supervisor and last author of Article 1, Morten I. Lossius. In instances when consensus was lacking, the medical records were reviewed again, cases were discussed, and consensus was reached.

Definition of comorbid epilepsy and psychiatric disorders

Comorbid epilepsy was defined as confirmed when there was a history of at least two unprovoked seizures consistent with epileptic seizures and at least one EEG showed epileptiform activity. We considered comorbid epilepsy as probable when one of the above criteria (epileptiform activity or clinical information) were indicative for epilepsy.

Psychiatric comorbidity was registered as mentioned in the medical record (e.g., depressive symptoms, anxiety, post-traumatic stress disorder (PTSD)).

Measuring the occurrence of FDS

For the calculation of incidence and prevalence of FDS in Article 1, we included all persons living in the county of Møre and Romsdal until death or end of follow-up on January 1, 2020 as the source population. Persons with FDS according to the ILAE definition of FDS were included in the calculation of incidence and prevalence of FDS presented in Article 1. As discussed above, there is no commonly accepted definition of active FDS. We considered persons who had at least one documented FDS

during the past 5 years as prevalent cases. Figures based on FDS within the past 2 years are also presented.

The prevalence rate was calculated as the total number of cases per 100 000 inhabitants using ascertained cases as the numerator and the 2020 census on January 1, 2020 for the county of Møre and Romsdal (265 238) as the denominator.

Cases were considered incident if the FDS diagnosis had been made between January 1, 2010 and December 31, 2019. Annual incidence rates were estimated using the population of Møre and Romsdal on January 1 of each year as the denominator and the number of subjects diagnosed with FDS during that year as a numerator.

In Article 1, in addition to the IR and prevalence of active FDS, we also estimated positive predictive values (PPVs) and the sensitivity of the registered diagnostic ICD-10 codes F44.5 and R56.8. The PPV for F44.5 was calculated by dividing the number of patients with verified FDS (registered with the code F44.5) by all patients registered with F44.5. The PPV for R56.8 was calculated respectively. The sensitivity for the diagnoses were estimated using the proportion of subjects with verified FDS registered with either F44.5 or R56.8 as a denominator and the number of all subjects with FDS after our validation as a numerator.

Statistical methods.

Analyses were conducted using IBM SPSS Statistics 22 (Armonk, NY: IBM Corporation).

Clinical data with continuous variables were summarized by the median and range, categorical variables by frequencies and percentages. In order to compare differences between age groups (children/adolescents ≤19 years old vs. adults ≥20 years old), the chi-squared test was used for categorical variables and the Mann–Whitney U test for continuous variables. Fisher's exact test was calculated in the event of less than five cases per cell.

Ethics

The Møre and Romsdal study was approved by the Regional Committee for Medical Research Ethics, Norway, Regional Ethical Committee Central (ethical agreement 2018/24712). Data were retrieved retrospectively from the NPR and from clinical files, which means that all data had originally been obtained for clinical and administrative purposes. Individual consent was therefore not required. The possible benefits from our increase in knowledge about the occurrence of FDS were considered to outweigh the possible disadvantage for study participants, which overall appear to be negligible.

The Cohort from the Norwegian Epilepsy Centre

The clinical cohort from the NEC consisted of consecutive patients, aged 16 years and older, included during the period from September 2009 to October 2017. Due to organizational changes at the center, there were periods (during 2010, 2013, and 2016) with no patient inclusion. Patients were recruited to the study either at the end of a diagnostic stay, when a FDS diagnosis was confirmed, or during a follow-up stay.

Clinical setting

Patients are referred to the NEC by neurologists, pediatricians, and general practitioners when the diagnosis of a seizure disorder is uncertain. When FDS is considered as possible diagnosis, patients undergo a diagnostic work-up consisting of a clinical evaluation, observation, revision of MRI of the brain, video-EEG, and psychological evaluation. When a diagnosis of FDS is confirmed, the diagnosis is explained to the patient and relatives by the physician. Patients and families are provided with further information on FDS by a staff nurse and are then usually invited to a follow-up stay of 2–4 weeks duration for further psychoeducation on FDS from a multidisciplinary team. This team is composed of epileptologists (neurologists or pediatricians), psychologists, nurses, a social worker, an occupational therapist, and a physical therapist. Patients are then referred to their local psychiatry outpatient department or to the local community psychiatric health team.

Inclusion and exclusion criteria

Inclusion criteria were documented FDS, diagnosed by an experienced epileptologist at the NEC, with a history indicative for FDS and witnessed events while on video–EEG, consistent with the highest degree of certainty according to criteria from the ILAE (17) and 16 years of age or older. Patients with comorbid epilepsy, estimated low (<70) IQ, and patients with severe medical and/or psychiatric conditions expected to be unable to undergo the planned assessment were excluded.

All patients were interviewed and baseline demographic and medical data were prospectively collected by Caroline Lund, Antonia Villagrán, and Morten I. Lossius. A total of 62 patients were invited to join the study, four of whom declined. A further two did not meet our study criteria after thorough examination of the records. One patient died during the study, and as undiagnosed concomitant epilepsy was thought possible, she was also excluded. Two patients withdrew their consent during the study, leaving 53 participants for the analyses. All participants, or both the participants and their parents for those under the age of 18 years, gave their informed written consent.

Psychometric assessment

All participants were invited to complete the following self-report questionnaires at baseline: The Attachment Style Questionnaire (ASQ), Parental Bonding Instrument (PBI), Traumatic Experience Checklist (TEC), Dissociative Experience Scale (DES), Somatoform Dissociation Questionnaire (SDQ-20), and a visual analog health thermometer (EQ-VAS). Other than EQ-VAS, none of the Norwegian versions of these questionnaires has been clinically validated.

Attachment style Questionnaire (ASQ)

The ASQ (53) is a self-reporting measure of adult attachment dimensions containing 40 items that are rated on a 6-point Likert scale, (from 1 (totally disagree) to 6 (totally agree)). The following attachment dimensions were derived: ‘‘confidence in relationships” that assesses secure attachment, ‘‘discomfort with closeness” and ‘‘relationships as secondary” both of which assess aspects of attachment avoidance, and ‘‘need for approval” and ‘‘preoccupation with relationships” that are both aspects of attachment anxiety. A higher score indicates a greater amount of the attachment construct measured. Consistency coefficients (Cronbach’s alpha) showed good reliability for the five dimensions presented in Article 2 (ranging from 0.80 to 0.84).

Parental bonding instrument (PBI)

We used the Norwegian version (54) of PBI (55) to assess maternal and paternal parenting styles recalled from the first 16 years of each participant’s life. The PBI comprises 25 items answered on a 4-point Likert scale (from 1 (very like) to 4 (very unlike)), and measures two fundamental dimensions of interpersonal relationships, including parental behavior: ‘care’ and ‘protection’. By combining these two dimensions the participant’s parents can be aligned into one of the four categories: affectionless control (low care, high protection), affectionate constraint (high care, high protection), neglectful (low care, low protection), and optimal parenting (high care, low protection). Previous studies of PBI have shown satisfactory reliability and validity estimates. (56) Our data on the four PBI subscales, presented in Article 2, showed excellent internal reliability, with Cronbach’s alpha ranging from 0.87 (subscale paternal protection) to 0.93 (subscale maternal care).

Traumatic experience checklist (TEC)

The TEC (57) is a 29-item self-report questionnaire assessing potentially traumatic experiences, including emotional abuse, emotional neglect, sexual harassment, sexual abuse, physical abuse, threat to life/bizarre punishment/intense pain, as well as family-related items, e.g., family poverty, and alcohol or drug abuse by family members. Events are further evaluated according to the participant’s age when they happened (0–6 years, 7–12 years, 13–18 years, and above 18 years), how long they lasted (more or less than 1 year), the subjective impact (none, slight, moderate, severe, or

extreme), and the support received (none, some, or good support). The TEC renders a total score, representing the number of potentially traumatic adverse events experienced throughout the life span, and additionally distinguishes between five subscales: emotional neglect, emotional abuse, threat to body or life, sexual harassment, and sexual abuse, which reflect trauma severity. Previous studies have shown satisfactory reliability and validity. (58)

Dissociative experience scale (DES)

The DES (59) is a self-report inventory of dissociative phenomena containing 28 items. It provides a total score and three subscales: depersonalization–derealization, amnestic dissociation, and absorption and imaginative involvement. It is reported to be reliable, internally consistent, and temporally stable. (60) Our data, presented in Article 2, show good reliability for the three subscales with consistency coefficients (Cronbach's alpha) ranging from 0.78 to 0.84.

Somatoform dissociation Questionnaire (SDQ-20)

The SDQ-20 (61) measures the severity of somatoform dissociation and consists of 20 items, that are to be rated on a 5-point Likert scale (from 1 (not at all) to 5 (extremely)). The scores across the items are summed to an index of symptom levels (total index ranges from 20 to 100). Our results, presented in Article 2, indicate good reliability with Cronbach's alpha of 0.79.

Health related quality of life (HRQoL)

We assessed HRQoL using a visual analog scale similar to a thermometer, which is part of the EuroQol (EQ-5D) instrument, (62) ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

Reports of adverse life events (ALE) assessed from the medical records

In Article 3, we examined participants' medical records for any reported disclosure of experiences of ALE at their entry into the NEC. Criteria for identification of the various forms of ALE were determined prior to the retrospective chart review. These criteria were aligned with the criteria for traumatic experiences, as stated in the TEC; see Table 2. The records reviewed included referrals and records from the stay at the NEC from physicians, psychologist, and nurses involved in the routine diagnostic work-up.

Adverse life events	**TEC items**
Household Challenges includes: Household substance abuse Household mental illness Family financial problems Divorce of the parents Having to look after parents and siblings	1, 2, 7
Loss of a family member	3, 4
Threat to life from illness, an operation or an accident, serious injury	5, 6
Own divorce	8
Bodily threat	9, 10, 23
War time experience, incl. second generation war-victim	11, 12
Witnessing others undergo trauma	13
Emotional neglect	14, 15, 16
Emotional abuse includes bullying	17, 18, 19
Physical abuse	20, 21, 22
Sexual harassment	24, 25, 26
Sexual abuse	27, 28, 29

Table 2. Categories of potential ALE aligned according to items in the TEC.

Neuropsychological assessment

Of the study cohort consisting of 53 participants, a subgroup of 36 participants underwent a comprehensive neuropsychological assessment.

Different cognitive domains, including global cognitive functioning, memory, attention, and EF were assessed by cognitive tests. The behavioral aspects of executive dysfunction were additionally assessed by a self-report questionnaire. The various instruments used are described briefly below:

We estimated intelligence by the short version of Wechsler Abbreviated Scale of Intelligence (WASI subtests: Word comprehension and Matrix reasoning). (63) Immediate and delayed recall from the Rey Auditory and Verbal Learning Test (RAVLT) and immediate and delayed reproduction from the Rey Complex Figure Test were used to assess learning and memory. (64-66) Commonly used tests were employed to assess aspects of EF: We measured divided attention by the Trail Making B test, (67) working memory by the Number-Letter Switching task from WAIS (Wechsler Adult Intelligence Scale) -IV, (68) and selective attention/response inhibition by the Stroop Neuropsychological Screening Test. (69) Attention and processing speed were measured using the Digit span and Digit symbol subtests from WAIS-IV, as well as the Trail Making Test-A. (67)

To assess behavioral and cognitive aspects of EF, we used the Behavior Rating Inventory of Executive Function – Adult version (BRIEF-A) (70) for participants aged 18 years or above and the Behavior Rating Inventory of Executive Function - Self Report Version (BRIEF-SR) for adolescents (71) for participants younger than 18 years. These standardized ratings scales have been developed to capture everyday behaviors associated with specific domains of EF in adults and adolescents. They are summed into two major indexes: the Behavioral Regulation Index (BRI) and the Metacognition Index (MI). The BRI is supposed to measure the ability to maintain appropriate regulatory behavioral control and emotional responses. Appropriate behavioral regulation is thought to be a likely precursor to efficient metacognitive problem solving. The MI reflects the ability to initiate activity, to sustain working memory, to plan and organize problem-solving approaches in a variety of contexts, and to organize belongings.

Selected test from this neuropsychological battery, with the main focus on EF, were included in the analysis of data in Article 4.

Follow-up

At a mean of 71 months (SD 29.0, range 22–130 months) and a median of 66 months after inclusion, participants were contacted by telephone. Following a structured interview guide, they were asked about current medical status (e.g., FDS frequency, FDS-related contact with a physician, FDS-related

hospital admissions), employment status, and psychiatric/psychological interventions (e.g., psychotherapy, other non-pharmacological interventions).

Statistical methods

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 26, IBM). Missing items were replaced with the mean of the answered items in the subscale, provided that at least half of that subscale had been answered.

Diagnostic delay was defined as time from seizure onset to time of diagnosis of FDS. FDS status at follow-up was defined as: FDS free (when the participant reported no FDS within the last year), 50% FDS reduction (when FDS frequency was lower than 50% of FDS frequency reported at baseline), or continuing to experience FDS at follow-up.

For the neuropsychological assessment all raw scores were converted to T-scores. We chose a T-score of 35 or below (or a percentile of 6.68 or below) equivalent to 1.5 SD below normative mean to represent the cutoff between normal and abnormal neuropsychological function. This is a commonly used impairment cutoff inneuropsychology.72, 73

BRIEF-scores are standardized based on a normal distribution, with a mean of 50 and SD of 10. T-scores ≥65 were considered abnormal, according to recommendations in the test manual.

Cronbach's coefficient alpha was calculated to determine the internal consistency of the employed questionnaires. It was calculated by correlating the score from each scale item t with the total score for each observation.

Descriptive statistics were used to explore the occurrence of demographic clinical data, attachment styles, parental bonding categories, ALE, and symptom severity measures, as measures of dissociation (DES and SDQ-20).

Group comparisons (e.g., between patients who were seizure free at follow-up and those continuing to experience FDS at follow-up, and utilization vs. non-utilization of healthcare at follow-up) were tested using Student’s t-test for continuous and normally distributed variables, Mann–Whitney U-tests for ordinal or skewed variables, and chi-square tests or Fisher’s exact tests for categorical data. All hypothesis testing was two-tailed. To correct for multiple comparisons when assessing group differences on baseline and follow-up characteristics (>20 variables) in Article 2, we considered p-values of <0.01 as statistically significant, otherwise p values of <0.05 were considered statistically significant.

Relationships between HRQoL, SDQ-20, DES, other symptom severity parameters (e.g., age at FS onset, diagnostic delay), outcome measures (e.g., FS status, hospital admissions, HRQoL at follow-up), and TEC subscale scores and records on adverse events from the medical journals were examined by partial correlation analysis, controlling for age, sex, and time to follow-up.

To determine potential predictors for achieving cessation of FDS by time of follow-up, and potential risk factors for reduced HRQoL at follow-up we performed multivariate logistic regression analysis.

To examine the extent of agreement between reports on ALE from medical records and from the self-report questionnaire we used Cohen's Kappa. Agreement was rated as follows: <0 no agreement, 0–0.2 slight agreement, 0.21– 0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 substantial agreement, and 0.81–1 almost perfect agreement. (72, 73)

Ethics

The study was approved by the Regional Committee for Medical Research Ethics, South-East Norway (2009/1078/REC South-East). Participation in the study was voluntary and informed written consent was obtained from the participants, or from both the participants and their parents for those under the age of 18 years. Participants underwent additional examinations, with the neuropsychological assessment being the most time consuming, and they gave consent to receiving a telephone call for follow-up. Apart from time usage, the risks and possible disadvantages for study participants was considered to be low.

4. Results

Paper I:

Villagrán A, Eldøen G, Duncan R, Aaberg KM, Hofoss D, Lossius MI. Incidence and prevalence of psychogenic nonepileptic seizures in a Norwegian county: A 10-year population-based study. Epilepsia. 2021 Jul;62(7):1528-1535.

The aim of this study was to assess the incidence and prevalence of active FDS in the Norwegian county of Møre and Romsdal. The study population included 265 238 eligible participants. We identified 1241 patients who had been registered with a diagnosis of either F44.5 (conversion disorder with seizures or convulsions, twenty-five patients) or R56.8 (convulsions, not elsewhere classified, 1216 patients) in the period January 2010 to January 2020. After case validation, 101 patients were classified as FDS cases, 21 registered with F44.5 and 80 with R56.8.

The PPV of the ICD diagnosis F44.5 for dissociative seizures was 83.3%. The PPV for the unspecific diagnosis of R56.8 “convulsions, not elsewhere classified” was 6.6%. Sensitivity for the diagnostic codes of F44.5 and R56.8 were 20.8% and 79.2%, respectively.

Prevalence

By investigation of patients with FDS during the previous 5 years, we found 63 cases with this diagnosis on on January 1, 2020. Based on this value, the point prevalence for FDS in this population was calculated to be 23.8/100 000 (95% CI= 17.9–29.6). Of these 63 prevalent cases, 44% (n = 28) had documented FDS or clinically established FDS, 30% (n = 19) had probable FDS, and 22% (n = 14) had possible FDS. The prevalence of documented FDS (the highest level of diagnostic certainty) was 10.6/100 000 (95% CI = 6.7–14.5).

The highest prevalence was found in the age group 15–19 years, with 59.5/100 000 persons (95% CI = 22.6–96.3). The female:male sex ratio was 3.2:1, with a female prevalence of 36.9/100 000 (95% CI = 26.5–47.4), significantly higher than the male prevalence of 11.1/100 000 (95% CI = 5.5–16.7).

When patients with FDS during the previous 2 years only were included, 30 cases were recognized as prevalent on January 1, 2020, resulting in a point prevalence of FDS of 11.3/100 000 (95% CI = 7.3–15.4). Of these, 37% (n = 11) had documented FDS, 7% (n = 2) had clinically established FDS, 37% (n = 11) had probable FDS, and 20% (n = 6) had possible FDS. Including only the highest level of certainty of diagnosis with documented cases of FSS, the prevalence was 4.1/100 000 (95% CI = 1.7–6.6).

The highest prevalence was found in the age group 15–19 years, with 23.8/100 000 (95% CI = 0–256.8). The female:male sex ratio was 3.3:1, with a female prevalence of 17.7/100 000 (95% CI = 10.5–24.9) and a male prevalence of 5.2/100 000(95% CI = 1.3–9.0).

Incidence rates (IR)

Seventy-nine cases of FDS were diagnosed during the study period, resulting in a mean annual IR (between 2010 and 2019) of 3.1/100 000/year (95% CI = 2.4–3.7). We found no clear trend in the annual incidence rates over the study period. The IR was highest in 2010, with 4.4/100 000/year, and lowest in 2011, with 1.2/100 000/year. The female:male ratio was 3.3:1, with a mean annual IR for females of 4.7/100 000/year (95% CI = 1.0–8.6) and 1.4/100 000/year (95% CI = 0–4.3) for males. The age-specific incidence peaked at 15–19 years with 9.81/100 000/year (95% CI = 0–24.7).

Clinical and demographic data of the FDS cohort are shown in Table 3.

	FDS cohort, incident and prevalent cases (n=84)
Female sex (%)	65 (77.4)
Age at diagnosis in years, median (range)	27 (11-78)
ICD-10 code	
F44.5	20 (23.8)
R56.8	64 (76.2)
Diagnosis at type of hospital/department (%)	
Pediatric department	12 (14.3)
Neurologic department	49 (58.3)
NEC	23 (27.4)
Diagnostic delay in years, mean (range)	3.2 (0-24)
Diagnostic certainty (%)	
Possible	22 (26.2)
Probable	25 (29.8)
Clinically established	2 (2.4)
Documented	35 (41.7)
Comorbid epilepsy (%)	
Confirmed	6 (7.1)
Probable	5 (6.0)
Psychiatric comorbidity (%)	52 (61.9)

Table 3. Clinical and demographic data for the FDS cohort (incident and prevalent cases) in Møre and Romsdal County, Norway

Paper II:

Villagrán A, Lund C, Duncan R, Lossius MI. The effect of attachment style on long-term outcomes in psychogenic nonepileptic seizures: results from a prospective study. Epilepsy Behav 2022;135: 108890.

In this article we investigated associations between long-term clinical outcome in patients with FDS, parenting and attachment styles, and demographic, clinical, and neuropsychiatric factors.

Fifty-three patients were included in the study, 51 (96 %) provided follow-up data. Most (84.9 %) patients were female, and the mean age of PNES onset was 25.6 years, with a mean diagnostic delay of 5.6 years. Thirty-two (60 %) of the 53 participants had a prior psychiatric history of anxiety or depression and 45 (85 %) had experienced at least one traumatic life event.

Our patients with FDS showed significantly lower levels of attachment confidence (security) ($p < 0.0001$) and higher levels of attachment insecurity than a normative sample. (74) The mean confidence score for our cohort was 32.3 (SD = 7.3), whereas the mean confidence score of a normative adult population sample was 44.8 (SD = 5.1). (74) Twenty-nine (56 %) of our patients with FDS had a confidence score below 34.6, which is 2 standard deviations below the normative mean.

Thirteen participants (25 %) rated their mothers as having been an optimal parent and 19 (36 %) provided this rating for their fathers. Comparisons between the dimensions care and control of the parental bonding in our FDS sample and the general population, showed no significant differences in levels of maternal and paternal care and control. (75)

At follow-up, 20 patients (39 %) were free of FDS (within the last year). Patients that had achieved FDS remission at follow-up had significantly lower levels of attachment anxiety ($p = 0.01$) at baseline, compared with those still suffering from FDS.

Seizure freedom at follow-up was predicted by male gender, younger age at FDS onset, and less attachment anxiety.

Paper III:

Villagrán A, Lund C, Duncan R, Ingvar Lossius M. Adverse life events in patients with functional seizures: Assessment in clinical practice and association with long-term outcome. Epilepsy Behav. 2023 Oct 5;148:109456.

In the third article we explored the association of ALE with long-term outcome parameters other than seizure (FDS) freedom, and the extent to which ALE are detected and documented in clinical work, as compared to detection by self-report questionnaires.

Fifty-three patients with FDS aged 16–62 years were included. Symptom severity, HRQoL, and antecedent ALE were assessed at baseline. Medical records were examined for records of reporting of ALE. At a mean of 70.45 (SD 29.0, range 22–130) months after inclusion, participants were contacted and asked about their FDS status, FDS-related healthcare utilization, and HRQoL.

A history of emotional abuse documented in the medical record was an independent risk factor for worse HRQoL at follow-up. Participants with a history of emotional abuse rated their HRQoL at follow-up at 17.5 points lower, on average, than those without such a history.

When correcting for age, sex, and duration of follow-up, there was no significant correlation between a history of ALE and FDS-related healthcare utilization in the year prior to follow-up.

The prevalence of ALE documented in medical records was lower than the rates measured by a self-report questionnaire.

Paper IV:

Villagrán A, Hessen E, Torgersen H, Alfstad KÅ, Lossius MI. Negative impact of self-reported executive problems on the long-term outcome in patients with functional/dissociative seizures: results from a prospective observational study. In preparation.

In the fourth article we investigated EF and its impact on long-term outcome in a subgroup of patients with FDS from our prospective sample from the NEC. Thirty-five inpatients (age range: 16-62 years) with FDS underwent neuropsychological assessment for both tested and self-reported EF at baseline. Participants were evaluated for their medical status at a mean of 5.5 years (SD 2.4, range 1.9-10.9 years) after inclusion. At follow-up, 15/35 (43%) of the participants were FDS-free.

Two participants had a full-scale IQ below 70 and were therefore excluded, leaving 33 for the final analyses. Among the participants, 11.1% scored below cutoff on the full-scale IQ and 16.7% were below cutoff on the executive score. Concerning behavioral measures for EF, 27.8% scored above cutoff on the BRI and 33.3% scored above cutoff on the MI of the BRIEF.

Patients who continued to suffer from FDS at follow-up, had more frequently reported executive problems above the cutoff level, as assessed by the MI ($p = 0.02$). For IQ measures and tested EF, we found no significant group-level differences between patients who had become FDS-free and those who had not.

Self-reported executive dysfunction was an independent risk factor for ongoing FDS at follow-up, with an odds ratio (OR) of 10.47 (CI: 1.04-106.02, $p= 0.047$).

5. Discussion

Incidence and prevalence of FDS

Article 1 provided, to the best of our knowledge, the first population-based measurement of the prevalence of FDS in a geographically selected population. Previous estimates have been based on patients with FDS seen at epilepsy centers and did not state how "prevalent" was defined. (6, 25) In our study, we gave a population-based estimate based on hospital coding. As standards for epidemiological studies in FND or FDS are lacking, we chose to report prevalences based on both 2-year and 5-year timeframes, in keeping with ILAE recommendations on standards for epidemiological studies and surveillance of epilepsy. (24) Our overall 5-year prevalence figure, at 23.8/100 000, was around midrange of previous estimates, and the 2-year figure (11.3/100 000) was substantially lower. (6, 25) Our definition of having FDS, and thereby being counted as a prevalent case, required the patient to present to healthcare with indicative symptoms. Previous investigations suggest that many patients with FDS cease to seek medical care at some point after diagnosis. (76) As up to two thirds of patients may experience FDS for many years after diagnosis, but do not present to healthcare with them, (77) our 5-year prevalence figure might be more accurate, but is still likely to be an underestimate of the actual FDS prevalence.

There are several other factors that might have contributed to the fact that our prevalence figures most likely underestimate the true prevalence of FDS. Even when a diagnosis of FDS or epilepsy is made by a clinician with appropriate expertise, there will inevitably be some erroneous diagnoses and some cases in which FDS is missed. In our study we did not review cases coded as epilepsy, and thereby we are likely to have missed some FDS cases. We might have missed further patients with FDS who had been primarily diagnosed by psychiatrists; for example, patients with PTSD and / or dissociative episodes who were not referred to a neurologist. Some patients with mild or few seizures (FDS) might have remained in primary care. Due to a lack of consensus regarding use of diagnostic codes for FDS, some cases might have been registered under other diagnostic codes, such as Z03.3 "observation for suspected nervous system disorder" or R55 "syncope and collapse"; these were not included in our study, and therefore any cases registered with these codes would also have been missed. The number of such cases that we failed to identify is difficult to estimate.

We found a mean annual incidence rate of 3.1/100 000/year. There is some speculation regarding whether there is an increasing incidence of FDS and other FND. FND has been referred to as a "silent epidemic". (78) Data from a relatively recent Danish study in a pediatric population, including children and adolescents 5–17 years of age, indicated the potential for an increasing incidence, but reported a lower IR than ours, at 2.4/100 000/year. (29) It is uncertain whether the reported

increasing IR from the Danish study reflects a true increase in Danish pediatric FDS cases, or whether the increase in the data, may be due, at least partially, to changes in the coding system. A new category R56.8 G for "Other and Unspecified Convulsions, Non-Epileptic Seizures" was introduced to the Danish registry in 2010. In our cohort, we found no consistent pattern of change in the annual IR over the study period.

There are a few other studies reporting on the incidence of FDS: A US study (28) including adults and a Scottish study (26) that included cases aged 13 years and older reported IR of 3.0 and 4.9/100 000/year, respectively. These are relatively similar to our incidence figure. However, these studies included only video-EEG-confirmed cases, and the Scottish study excluded cases with comorbid epilepsy. Our comparable IR (video-EEG-confirmed cases) was only 1.26/100 000/year. Inclusion of only video-EEG-confirmed cases is likely to underestimate incidence, and therefore, there seems to be a true difference between the Scottish and US populations and ours, although differing diagnostic practices might also contribute. A nationwide Icelandic study (27) from the 1990s that included subjects aged 15 years and older, reported a much lower IR of 1.4 per 100 000/year. However, this estimate was based on only 14 incident cases, of whom seven had comorbid epilepsy.

Diagnostic coding

As already mentioned, there is a general lack of consensus on coding and terminology for FDS. Surveys among healthcare professionals have indicated that only a minority use the ICD-10 code F44.5 when diagnosing FDS. In a study among Danish pediatricians, only 31% stated that they used the code F44.5. (11) Among UK healthcare professionals, mainly neurologists, even fewer (18%) reported using the term dissociative seizures. (12) This haphazard coding practice not only hampers clear communication with patients and between clinicians, but also presents a considerable obstacle for epidemiological studies. In our cohort, only 24% of the patients were diagnosed with "dissociative seizures" (F44.5), and more than 75% were registered under the non-specific code R56.8. Even among those with video-EEG-confirmed diagnosis, that is those with the highest level of diagnostic certainty, the proportion registered with a diagnosis of "dissociative seizures" was only slightly higher, being only 32%. The low proportion of patients given the diagnosis of "dissociative seizures" and the corresponding ICD code, is also reflected in the low sensitivity for the diagnostic code F44.5 in our cohort (20.8%). Using the code F44.5 to identify persons with FDS in registry-based studies, may therefore result in a substantial proportion of individuals with FDS not being identified and may lead to inclusion bias. One example is a recently published Swedish study (79) that reported on mortality in FDS patients and was based on diagnoses registered in the Swedish NPR. In this Swedish study (79) only patients registered with the code F44.5 were included and diagnoses were not

verified. The authors probably missed a substantial proportion of true FDS cases who had been registered with other, non-specific codes.

Patterns of clinical evaluation and referrals

Around one third (27%) of the patients diagnosed with FDS from the County of Møre and Romsdal had been at the NEC; all the others were examined and diagnosed at the local pediatric or neurological services. This is important to note when discussing the generalizability of results based on patients with FDS recruited from epilepsy centers, as in our Articles 2-4. Based on our findings from the population-based cohort, as described in Article 1, it is apparent that in our population, most FDS patients are not referred to a tertiary epilepsy center for diagnostic evaluation. Results from such specialist center-based cohorts may therefore not be representative for the whole group of patients with FDS. Further population-based studies are needed to gain more insights into this heterogenic group.

Seizure outcome in FDS

In Article 2, we present data from our prospective cohort study on the seizure outcome of FDS. At follow up following diagnosis after an average of 5.8 years, 61% of the patients continued to be suffering from FDS. Our results were based on follow-up data from 96% of the initially enrolled cohort. Our high follow-up rate, especially compared to previous studies on outcomes in FDS, might partially reflect the high trust that patients have in the Norwegian healthcare system, in general, and, specifically, our center's structured diagnostic and follow-up procedures. (80) Previous studies have been mainly retrospective in nature and/or have had low responder rates. (49-51, 76, 81) One prospective study from Scotland reported that 66% of patients still had FDS after 3 years, which is in line with our results. However, in the Scottish study, over half of the initially enrolled cohort was lost to follow-up. (82) Our results indicate, despite methodological differences, previous estimates of outcome may have been realistic. However, as stated above, our data is based on a cohort from a tertiary epilepsy center and results may not be generalizable to the whole group of FDS patients.

Factors associated with seizure outcome in FDS

As reported in Articles 2 and 4, attachment anxiety, self-reported executive dysfunction, female gender, and older age at FDS onset were all found to be risk factors for persistent FDS at follow-up. Recollection of parenting styles, illness duration, work and educational status, marital status, ALE burden, and levels of dissociation were not associated with seizure outcome in our cohort.

Attachment

Insecure and disorganized attachment styles have been linked to psychiatric conditions, (83) including FND. (84) Fearful (35) and insecure attachment (36) have also been found to be the predominant attachment styles in patients with FDS. There are some indications that attachment patterns might play a role in the therapeutic process and influence outcome. Patients with anxious attachment often present with chaotic and contradictory representations of self and others, and have been described as being difficult to treat. (37) In patients with borderline personality disorder, it has been shown that those with a preoccupied attachment style were less likely to respond to intervention. It has been argued that a preoccupied attachment style might complicate engagement in the therapeutic treatment and the alliance with the therapist. (85) It might, therefore, be useful to explore attachment patterns in patients with FDS and to tailor therapeutic strategies accordingly.

Executive Dysfunction

In Article 4, we report that self-rated executive dysfunction was an independent risk factor for ongoing FDS at follow-up (a mean of 5.5 years after diagnosis). In contrast, there were no significant differences between patients who had become FDS free at follow-up and those who had not, regarding objective measures for IQ or objective measures of EF. As EF encompasses multiple domains, such as planning, inhibition, set shifting, self-monitoring, organization, and initiating and sustaining mental activity, and is crucial for goal achievement, a negative association between executive dysfunction and the long-term outcome in patients with FDS seems plausible. The MI reflects the ability to solve problems and to monitor success and failure; both these traits are important for achieving a therapeutic goal and for following, or adapting and then following, a therapeutic plan.

A lack of correlation between self-reported EF and performance on tests for EF has previously been described for patients with epilepsy (86) and for neuropsychiatric disorders. (87) It has been argued that complex functions, such as EF, may be challenging to assess by structured neuropsychological tests that only resemble the complexities of everyday life situations to a limited extent. Neuropsychological tests may therefore be of restricted validity when assessing EF. (88) This report of a weak correlation between tested and self-reported EF (87, 89) has led to the conclusion that tests and self-reports reflect different aspects of EF.

Discrepancies between subjective and objective measures of distress, arousal, and symptom burden in patients with FDS, have also been reported previously. A meta-analysis found no correlation between subjective and objective measures in most of the included studies, raising the question of whether subjective or objective measures are more meaningful. (90) The authors concluded that

subjective and objective measures assess different, but equally valid, constructs and argue that both might be meaningful in understanding and exploring different aspects of FDS further. (90) Subjective reports of stress have been linked to long-term outcomes, such as morbidity and mortality, in other cohorts. (91) We are not aware of previous studies in which subjective measures of impaired EF in patients with FDS have been linked to long-term outcome.

The prevalence of executive dysfunction in patients with FDS is not well established. As presented in Article 4, we found that around 17% of participants with FDS exhibited executive deficits, based on cognitive tests, whereas about 33% had executive dysfunction based on self-report. Impaired EF, as assessed by neuropsychological examination in patients with FDS, has been previously described. One study showed reduced performance on the "Trail Making Test" and "Digit Span Test Forward and Backward" in 40 patients with FDS, indicating lower working memory and set-shifting ability than in healthy controls. (92, 93)

Self-reported executive dysfunction was associated with a history of anxiety and depression in our study. There is evidence that mood disorders are frequently accompanied by a range of cognitive deficits. (94, 95) Deficits in EF have been linked to depressive states, both active (96) and in remission, (97) and also to anxiety disorders. (98)

Gender

As described in Article 2, being male was the strongest predictor of an FDS-free outcome in our cohort. However, our numbers were small, with only 8 males in the cohort and the results have wide confidence intervals, indicating low precision of the OR. Whether gender may, nevertheless, influence FDS outcome is debatable; previous studies have yielded contradictory results. In accordance with our results, one study found that male gender was predictive of a favorable outcome (77), whereas another study reported that female gender was predictive of a good outcome. (99) Men are under-represented in most studies of FDS and therefore insufficiently studied. From studies that have examined gender differences, we know that men experience significantly less sexual traumas and show lower levels of dissociation than women. (100) Both these factors could play a role in FDS severity and outcome.

Health-related quality of life (HQoL) in FDS

As shown in Article 2, self-reported HQoL assessed with the health thermometer was low in our cohort compared to the general population in Norway. (101) This indicates poor HQoL in patients with FDS, as has previously been shown in reports from larger FDS cohorts. (102)

Factors associated with HQoL at follow-up in FDS

There has been some debate on treatment goals and outcome measures for patients with FDS and FND in general. Outcome measures, other than achievement of FDS freedom or improvements in FND core symptoms, might also be important. It has been proposed that it would be of value to assess other measures of physical and psychological symptoms, as well as quality of life. (103) HQoL, might be an especially relevant metric to explore, as it has been linked to both morbidity and mortality. (104, 105)

As described in Article 2, the persistence of FDS at follow-up in our study was associated with poor HQoL at follow-up. The difference between those continuing to have FDS and those that had become seizure free was around 17 points (p=0.02). A reduction in seizure frequency >50 % at follow-up was not associated with improved HQoL.

Adverse life events (ALE)

In Article 3 we looked at the relation between HRQoL at follow-up and reports about antecedent ALE. We found that HRQoL at follow-up was inversely correlated with reports about emotional abuse, antecedent physical abuse, and the experience of ‘‘threat to life”. In the multiple linear regression analysis, a history of ALE was a risk factor for lower HRQoL at follow-up (occurring, on average, almost 6 years after diagnosis). There is limited information in the literature regarding the potential influence of abuse and other ALE on long-term outcomes. One study found no predictive effect of sexual abuse, physical abuse, and other psychological trauma on outcomes, such as healthcare use and employment, at 5–10 years after diagnosis. (106) Another study on a cohort with mixed FND did not identify an association between clinical outcomes, thereunder HRQoL and ALEs in childhood or across the lifespan. (107) It has been reported that patients with FDS and childhood abuse have reduced adherence rates to psychotherapy, (108) which, again, is likely to have an impact on long-term outcomes.

Thorough information about the burden of prior ALE is valuable for clinicians involved in diagnosing patients with suspected FDS, as there is a known, considerable treatment gap for patients with FDS. (109) Patients with FDS often present acutely to the emergency department. Their healthcare pathway has been described as “looping”, with repeated presentations in emergency settings, but low rates of documented diagnosis and referral for psychological treatment. (110) Evolving a common understanding of relevant predisposing, precipitating, perpetuating, and protective factors, including ALE, together with the clinician and the patient, might be crucial to break that loop and help more patients into treatment. With this in mind, in Article 3 we explored the rate of detection of ALE in clinical practice.

Assessment of ALE in clinical practice

As reported in Article 3, we found that a substantial proportion of the ALE identified within our research project via the self-report questionnaire (TEC) had not been documented in the clinical records. This result is in concordance with studies from mental healthcare that report that less than one-third of abuse and neglect identified by researchers is documented in clinical records. (111) Substantial under-recording of maltreatment and abuse has also been reported from primary care. (112) The rates of ALE, as assessed by the TEC in our study, are similar to results from a previous meta-analysis of studies on childhood trauma in FDS. (113) The meta-analysis also found lower rates of ALE when the data were collected during clinical investigation, as compared with self-report questionnaires. (113) The fact that correlations between ALE and clinical data were improved by the use of TEC data supports the view that the additional disclosures elicited by the questionnaire are unlikely to be spurious.

Our findings suggest that clinicians involved in the diagnostic work-up of patients with FDS, even at a tertiary epilepsy center, may not systematically assess and document ALE. The reason for this is unclear. It is possible that neurologists, pediatricians, epileptologists, and even psychologists, working at an epilepsy center may not feel appropriately trained to inquire about ALE. The results of a recent survey among neurology residency-program directors and neurology-residency graduates are consistent with this suggestion, indicating that most programs lacked curriculum material on FDS (and FND in general). (114) Neurology-training curricula should address ALE inquiry in patients with (suspected) FDS. In addition, supplementation of history taking with a self-report questionnaire on ALE might be valuable in clinical practice. However, it is important to emphasize, once again, that a proportion of patients may not report ALE regardless of how the question is asked, and that a history of ALE is not mandatory for the diagnosis of FDS (in DSM-5, as well as in clinical practice).

Strengths and limitations of the studies

The main strength of the Møre and Romsdal study, published in paper 1, was the population-based design, including all age groups. Another strength was that diagnoses from the NPR register were systematically validated using definitions of FDS recommended by the ILAE. By including patients registered with the specific diagnostic code, F44.5, and the non-specific code for seizures, R56.8, we were able to identify a substantial proportion of all true FDS cases; however, as discussed above, we probably did not identify all cases.

We found that only the minority of patients with FDS were registered under ICD-code of F44.5 “dissociative seizures”. It would not have been sufficient to review only those patients registered with this diagnosis in the NPR. With the background of our clinical experience, we decided to include

also the non-specific code R56.8. Other codes, such as R55 “syncope”, could also have been included, but would have increased the volume of medical records that had to be reviewed, while probably only contributing a small number of additional cases. Validating the two diagnoses that we chose, meant reviewing more than ten medical records in order to identify a single FDS case. As already discussed, the inconsistent use of a specific diagnostic code for FDS by clinical pediatricians and neurologists poses an obstacle against using registry-based studies of FDS. Case validation, which seems necessary in order to identify true FDS cases, might simply be unfeasible in larger registry-based cohorts, such as investigations on a national scale.

The major strength of the NEC study, with results presented in articles 2-4, is the prospective design and the follow-up after a prolonged period, with a very low rate of patients lost to follow-up. Only patients with documented FDS, according to the ILAE recommendations, were included in our study.

The studies included in this thesis also have various limitations. One limitation of the Møre and Romsdal study is that we were unable to include and review patient records registered with epilepsy codes. It is known that some patients with FDS are initially diagnosed (erroneously) with epilepsy. By not reviewing those with records with registered epilepsy diagnoses, we were unable to identify any FDS that had been misdiagnosed with epilepsy. As with all registry-based studies, the quality of our data and our diagnostic conclusions are dependent on the quality and completeness of the primary recorded clinical data. In our study, we reviewed files from neurology and pediatric departments with good general knowledge on seizure disorders, but that were not specialized on FDS. Erroneous diagnoses and coding might, as in all clinical practice, have occurred. As discussed above, this might have contributed to us underestimating the true incidence and prevalence of FDS.

The NEC study also has limitations. In particular, the relatively small number of participants included and the fact that the cohort was recruited from a single tertiary epilepsy center are limitations that restrict the generalizability of our findings. Many patients with FDS are likely to be diagnosed and treated locally and never referred to a tertiary center, as seen in the results from our population-based study described in article 1.

6. Concluding remarks and future aspects

We conclude that our population-based estimate of the prevalence of FDS was within the range of estimates reported in the literature and based on non-population-based data. Both incidence and prevalence values were strikingly high in adolescents. The current diagnostic term for FDS in ICD-10, “dissociative seizures,” is applied only to the minority of patients with FDS, even in those with the highest level of diagnostic certainty. As there is no substantial change in the upcoming 11th revision

of the ICD-11 regarding dissociative neurological symptom disorders, the challenge remains of finding a term that is accepted and used by all, or the majority of, clinicians globally.

The long-term outcomes for FDS in our prospective cohort from the NEC is poor, with the majority still experiencing seizures around 6 years after diagnosis. In our cohort, insecure attachment style, female gender, and self-rated executive dysfunction were all risk factors for persistence of seizures.

In clinical management of FDS patients, it seems important that a common understanding of relevant factors contributing to FDS is developed. We believe that this could be of value for both the patient and the clinician, in order to assist in breaking the otherwise common loop of repeated emergency room presentations and (unnecessary) investigations, and also to increase the proportion of patients referred to, and enrolling in, therapy.

Increasing our knowledge about the occurrence and clinical characteristics of FDS by interdisciplinary and international collaborations, exploring larger cohorts, and generating more robust results, remains important for minimizing the impact, and reducing the occurrence, of FDS.

7. Papers I – IV

Paper I

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Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Incidence and prevalence of psychogenic nonepileptic seizures in a Norwegian county: A 10-year population-based study

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Abstract

Objective: This study was undertaken to measure the incidence and prevalence of active psychogenic nonepileptic seizures (PNES) in a Norwegian county.

Methods: Using the Norwegian patient registry, we identified patients in Møre and Romsdal County in Norway diagnosed with F44.5 (conversion disorder with seizures or convulsions) or R56.8 (convulsions, not elsewhere classified) in the period January 2010 to January 2020. A review of the patients' medical records and an assessment of diagnostic validity were performed. PNES were diagnosed according to the recommendations by the International League Against Epilepsy Nonepileptic Seizures Task Force. Point prevalence of PNES on January 1, 2020 and incidence rates for the period 2010–2019 were determined.

Results: Based on PNES within the past 5 years, we found a PNES prevalence of 23.8/100 000 (95% confidence interval [CI] = 17.9–29.6), including all levels of diagnostic certainty. For the highest level of diagnostic certainty (video-electroencephalographically confirmed), the prevalence was 10.6/100 000 (95% CI = 6.7–14.5). The highest prevalence was found in the age group 15–19 years, at 59.5/100 000 (95% CI = 22.6–96.3). The mean annual incidence rate between 2010 and 2019 was 3.1/100 000/year (95% CI = 2.4–3.7).

Significance: We report for the first time a population-based estimate of the prevalence of PNES. Our findings suggest that the prevalence of PNES is within the range of estimates from non-population-based data. We found a strikingly high prevalence of PNES in the 15–19-year age group.

KEYWORDS

adolescents, diagnostic coding, epidemiology, psychogenic nonepileptic seizures

1 | INTRODUCTION

Psychogenic nonepileptic seizures (PNES) are among the most common functional neurological disorders,[1] seen frequently in various clinical contexts. In epilepsy clinics, up to one third of patients are diagnosed with PNES.[2] PNES are categorized as a dissociative (conversion) disorder in International Classification of Diseases, 10th revision (ICD-10) or conversion (functional neurological symptom) disorder in Diagnostic and Statistical Manual of Mental Disorders, 5th edition.[3,4]

PNES may affect many aspects of life for patients and their families. Many patients are first misdiagnosed with epilepsy, exposing them to potentially harmful and unnecessary treatment.[5] Health care costs are high, mainly due to frequent emergency room visits, hospital admissions, including intensive care units, and repeated, extended investigations.[6] Diagnosing PNES can be difficult, and health care practitioners often report uncertainty regarding the diagnosis.[7] The combination of ictal recordings on video-electroencephalography (EEG) and a history indicative of PNES is considered the diagnostic gold standard.[8]

Epidemiological data on PNES are scarce.[9] Incidence rates of between 1.4 and 4.9/100 000/year have been reported from different adult populations.[10–12] A recent nationwide study in a Danish pediatric population showed an incidence of 2.4/100 000/year.[13]

PNES prevalence is difficult to determine and has not been directly measured. A long delay from onset to diagnosis and patients with PNES disengaging from medical follow-up are considerable obstacles for epidemiological studies.[9] Based on numbers of patients with PNES attending epilepsy centers, the prevalence has been estimated at 2–50/100 000.[9,14]

Epidemiological studies that provide good estimates of the occurrence of PNES are crucial for health care planning. We therefore investigated the incidence and prevalence of PNES during the past decade in a Norwegian county.

Key Points

- Epidemiologic data on PNES are scarce
- In this 10-year population-based study that included all age groups and a systematic case validation using definitions recommended by the ILAE Nonepileptic Seizures Task Force, we investigated incidence rates and prevalence of PNES
- Prevalence of PNES was 23.8/100 000 including all levels of diagnostic certainty
- This is the first population-based estimate of prevalence of PNES; the obtained prevalence was within estimates from the literature based on non-population-based data

2 | MATERIALS AND METHODS

2.1 | Data source

Participants were identified through the Norwegian Patient Registry (NPR). This is a mandatory administrative registry containing discharge diagnosis data from hospitals and outpatient clinics owned or reimbursed by the Norwegian government, which account for more than 99% of health services in Norway.[15] Diagnoses are coded by physicians according to ICD-10.[3]

Based on our clinical experience indicating a lack of consensus for a diagnostic code for PNES and the finding that many clinicians use the nonspecific code R56.8 "convulsions, not elsewhere classified" rather than F44.5 "conversion disorder with seizures or convulsions," we decided to include all patients registered with a primary diagnosis of ICD-10 code F44.5 or R56.8 in the period from January 1, 2010 to January 1, 2020 at the hospitals in the county of Møre and Romsdal, Norway. Other diagnostic codes that might apply for PNES (e.g., Z03.3 "observation for suspected nervous system disorder") are not commonly used and were therefore not included.

The Regional Committee for Medical Research Ethics, Norway, Regional Ethical Committee Central (ethical agreement 2018/24712) approved this study. This study followed the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline.

2.2 | Design

This is a population-based, cross-sectional study of the incidence and prevalence of PNES in the county of Møre and Romsdal, Norway between January 1, 2010 and January 1, 2020.

2.3 | Study population

Norway has a well-developed public health care system that provides comprehensive health services to everyone. In primary health care, every inhabitant has an assigned general practitioner. Specialist health care is provided by hospital services run and owned by the state.

Møre and Romsdal is a county in the western part of Norway covering an area of 14 356 km². At the end of the study, on January 1, 2020, Møre and Romsdal had a population of 265 238 (135 213 men, 130 025 women), which is a 5.6% increase on the population at the beginning of the

study, and constitutes approximately 4.9% of the Norwegian population. Immigrants born outside of Norway, primarily from Central Europe, constituted 11.7% of the population of the county. The prevailing immigrant nationalities were from Poland, Lithuania, and Germany. Non-European immigrants mainly from Syria, Eritrea, and Thailand accounted for 4.4% of the total population. Regarding age, 2.6% of the population in Møre and Romsdal was younger than 20 years, 56.7% was between 20 and 64 years, and 19.7% was 65 years or older. According to Statistics Norway, demographic data in Møre and Romsdal, such as socioeconomic status, degree of urbanization, age distribution, and access to health care, are similar to those in Norway as a whole.[16]

Inpatient and outpatient neurological services are centered in two hospitals, each with an EEG department. Pediatric services are located in three hospitals. No private neurologists or pediatricians practice in the county.

Norwegian guidelines specify that all patients suspected of having seizures or epilepsy are referred to a neurologist or pediatrician for clinical evaluation and EEG.[17] These patients are therefore seen at one of the hospitals in the county and registered in the NPR. Norway has one tertiary center for epilepsy care, the National Center for Epilepsy at Oslo University Hospital, which is a referral resource for difficult cases.

2.4 | Medical record data

For each case identified by diagnostic code (F44.5/R56.8) in the NPR, the medical history, seizure assessment, EEG, magnetic resonance imaging, blood samples, treatment, and other relevant information were reviewed. A minimum dataset, including demographic and clinical information, was recorded in a database.

Cases were validated and classified by the first author (A.V.). A random subsample of 124 participants (10% of the study sample) was rated independently by the last author (M.I.L.). Both are senior consultants in neurology and epileptologists at the National Center for Epilepsy. In instances of nonconsensus, the medical records were reviewed again, cases were discussed, and consensus was reached.

PNES was defined as the occurrence of events clinically resembling epileptic seizures, but not caused by ictal epileptiform activity, and having psychological basis and causes.[9] Cases were validated using the approach to diagnosing PNES proposed by the International League Against Epilepsy (ILAE) in 2013.[8] Based on history, witnessed events, and EEG findings, the ILAE defined four diagnostic levels of certainty for PNES, namely: (1) possible, (2) probable, (3) clinically established, and (4) documented (Table 1).

Time of onset was defined as the year of onset of symptoms suggestive of PNES. We defined comorbid epilepsy as confirmed when there was a history of at least two unprovoked seizures consistent with epileptic seizures and at least one EEG showed epileptiform activity. Comorbid epilepsy was considered as probable when one of the above criteria (epileptiform activity, clinical information) were indicative for epilepsy. Psychiatric comorbidity was registered as mentioned in the medical record (e.g., depressive symptoms, anxiety, posttraumatic stress disorder [PTSD]).

People living in Møre and Romsdal County on January 1, 2020, fulfilling the ILAE criteria mentioned above, and having had at least one documented PNES during the past 5 years were defined as prevalent cases. Figures based on PNES within the past 2 years are also presented. The prevalence rate was calculated as the total number of cases per 100 000 inhabitants using ascertained cases as the numerator and the 2020 census on January 1, 2020 (265 238) as the denominator.

Cases were considered incident if the PNES diagnosis had been made between January 1, 2010 and December 31, 2019. Annual incidence rates were estimated using the population on January 1 of each year as the denominator and the number of subjects diagnosed with PNES during that year as a numerator.

TABLE 1 Diagnostic levels of certainty for the diagnosis of psychogenic nonepileptic seizures

Diagnostic level	History	Witnessed event	EEG
Possible	Consistent with PNES	By witness of self-report	No epileptiform activity in interictal EEG
Probable	Consistent with PNES	By clinician in person or reviewed video recording	No epileptiform activity in interictal EEG
Clinically established	Consistent with PNES	By clinician experienced in seizure disorders (in person or on video)	No epileptiform activity in routine or ambulatory ictal EEG during a typical event
Documented	Consistent with PNES	By clinician experienced in seizure disorders (in person or on video) while on video-EEG	No epileptiform activity immediately before, during, or after a typical event captured on ictal video-EEG

Note: Adapted from LaFrance et al.[8]

Abbreviations: EEG, electroencephalography; PNES, psychogenic nonepileptic seizures.

2.5 | Statistical analysis

Continuous variables were summarized by the median and range, categorical variables by frequencies and percentages. For comparing differences between age groups (children/adolescents ≤19 years old vs. adults ≥20 years old) the chi-squared test was used for categorical variables and the Mann–Whitney test for continuous variables. Fisher exact test was calculated in the event of less than five expected cases per cell.

3 | RESULTS

In total, 1241 potential PNES cases were identified (Figure 1). Twenty-five patients had an ICD-10 diagnosis of F44.5 and 1216 patients of R56.8 in the NPR. After case validation, 101 patients were rated PNES cases, 21 registered with F44.5 and 80 with R56.8. Among the non-PNES cases, 216 had epilepsy and 924 had other paroxysmal events such as acute symptomatic seizures, febrile seizures, and unspecific paroxysmal symptoms. The interrater reliability test showed an almost perfect agreement[18] between the two raters; Cohen kappa was .88. The positive predictive value of the more specific ICD diagnosis F44.5 was 83.3%, and it was 6.6% for the unspecific diagnosis of R56.8. Sensitivity for the diagnostic codes of F44.5 and R56.8 were 20.8% and 79.2%, respectively.

3.1 | Prevalence

Including all patients with PNES during the previous 5 years, we found 63 cases prevalent on January 1, 2020, resulting in a point prevalence for PNES of 23.8/100 000 (95% confidence interval [CI] = 17.9–29.6). Of these, 44% (n = 28) had documented PNES or clinically established PNES, 30% (n = 19) had probable PNES, and 22% (n = 14) had possible PNES. Including only cases with the highest level of diagnostic certainty (documented PNES), the prevalence was 10.6/100 000 (95% CI = 6.7–14.5). The highest prevalence was found in the age group 15–19 years, with 59.5/100 000 persons (95% CI = 22.6–96.3). The sex ratio was 3.2:1, with a female prevalence of 36.9/100 000 (95% CI = 26.5–47.4) and a male prevalence of 11.1/100 000 (95% CI = 5.5–16.7).

When considering patients with PNES during the previous 2 years, 30 cases with PNES within 2 years were recognized as prevalent on January 1, 2020, resulting in a point prevalence for PNES of 11.3/100 000 (95% CI = 7.3–15.4). Of these, 37% (n = 11) had documented PNES, 7% (n = 2) had clinically established PNES, 37% (n = 11) had probable PNES, and 20% (n = 6) had possible PNES. Including only the highest level of certainty of diagnosis with documented cases of PNES, the prevalence was 4.1/100 000 (95% CI = 1.7–6.6). The highest prevalence was found in the age group 15–19 years, with 23.8/100 000 (95% CI = 0–256.8). The sex ratio was 3.3:1, with a female prevalence of 17.7/100 000 (95% CI = 10.5–24.9) and a male prevalence of 5.2/100 000 (95% CI = 1.3–9.0).

3.2 | Incidence rates

During the study period, 79 cases of PNES were diagnosed. The mean annual incidence rate between 2010 and 2019 was 3.1/100 000/year (95% CI = 2.4–3.7). There was no clear trend in the annual incident rates over the study period. The incidence rate was highest in 2010, with 4.4/100 000/year, and lowest in 2011, with 1.2/100 000/year. The mean annual incidence rate was 4.7/100 000/year (95% CI = 1.0–8.6) for females and 1.4/100 000/year (95% CI = 0–4.3) for males. This gives a female:male ratio of 3.3:1. For age-specific incidence, the rate peaked at 15–19 years, at 9.81/100 000/year (95% CI = 0–24.7). Among the 79 incident PNES cases, 41% (n = 32) had documented PNES, 3% (n = 2) had clinically established PNES, 30% (n = 24) had probable PNES, and 27% (n = 21) had possible PNES.

Prevalence rates and mean annual incidence rates by age groups are shown in Table 2.

3.3 | Clinical characteristics

The median age at diagnosis of PNES was 27 years, and the modal age was 15 years. Most (77%) of the patients were female. Clinical characteristics for the study population are shown in Table 3.

Although the mean diagnostic delay was 3.2 years, for 49% of the cases (n = 41) the diagnosis was made in the same year as the onset of seizures.

Considering patients with documented PNES, 31% (n = 11) were diagnosed with the classification F44.5.

Children and adolescents were more often diagnosed with F44.5 “dissociative seizures” than adults (54% vs. 19%, p = .01), and the diagnostic delay was significantly shorter for children and adolescents (1.3 vs. 4.2 years, p = .03) than for adults aged 20 years or older.

4 | DISCUSSION

We are not aware of any previous measurement of the prevalence of PNES, and previous estimates did not specify a definition of "prevalent."[9,14] Our study was designed to provide a population-based estimate using hospital coding. This implies that part of our definition of having PNES required

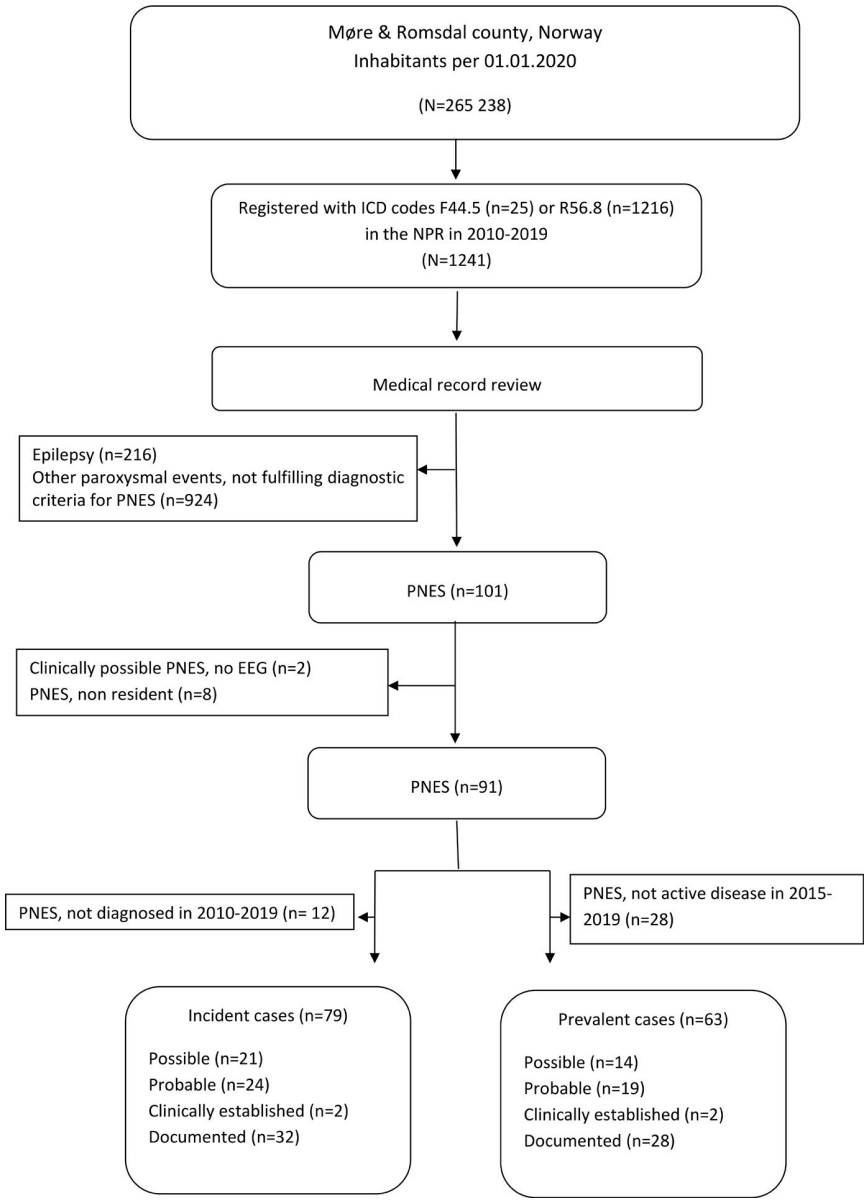

FIGURE 1 Flowchart study participants. EEG, electroencephalogram; ICD, International Classification of Diseases; NPR, Norwegian Patient Registry; PNES, psychogenic nonepileptic seizures

TABLE 2 Mean annual incidence and prevalence of PNES by age groups

	Mean annual incidence		Prevalence, PNES within past 2 years		Prevalence, PNES within past 5 years	
Age groups	*n* (range)	Per 100 000 person-years	*n*	Per 100 000	*n*	Per 100 000
5–14 years	1.0 (0–2)	3.1	1	3.1	1	3.1
15–19 years	1.7 (0–5)	9.8	4	23.8	10	59.5
20+ years	5.3 (2–8)	2.7	25	12.3	52	25.6
All	7.9 (3–11)	3.1	30	11.3	63	23.8

Abbreviation: PNES, psychogenic nonepileptic seizures.

the patient presenting to health care with indicative symptoms. Previous investigations suggest that many patients with PNES cease to access medical care at some point after diagnosis.[19] We chose to report prevalence based on 2-year and 5-year timeframes, in keeping with ILAE recommendations for epilepsy.[20] Our overall 5-year prevalence figure, at

TABLE 3 Clinical and demographic data for the PNES cohort (incident and prevalent cases) in Møre and Romsdal County, Norway

Clinical values	PNES cohort, incident and prevalent cases ($N = 84$)
Female sex, *n* (%)	65 (77)
Age at diagnosis, years, median (range)	27 (11–78)
ICD-10 code, *n* (%)	
F44.5	20 (24)
R56.8	64 (76)
Diagnosis at type of hospital/department, *n* (%)	
Pediatric department	12 (14)
Neurologic department	49 (58)
National epilepsy center	23 (27)
Diagnostic delay, years, mean (range)	3.2 (0–24)
Diagnostic certainty, *n* (%)	
Possible	22 (26)
Probable	25 (30)
Clinically established	2 (2)
Documented	35 (42)
Comorbid epilepsy, *n* (%)[a]	
Confirmed	6 (7)
Probable	5 (6)
Psychiatric comorbidity, *n* (%)[b]	52 (62)

Abbreviations: ICD, International Classification of Diseases; PNES, psychogenic nonepileptic seizures.

[a]Comorbid epilepsy is defined as confirmed when there was a history of at least two unprovoked seizures consistent with epileptic seizures and at least one electroencephalogram showed epileptiform activity. Comorbid epilepsy was considered to be probable when one of the above were indicative for epilepsy.

[b]Psychiatric comorbidity as mentioned in the medical record (e.g., depressive symptoms, anxiety, posttraumatic stress disorder).

23.8/100 000, was around midrange of previous estimates,[9,14] and the 2-year figure (11.3/100 000) was substantially lower. As up to two thirds of patients may experience PNES many years after diagnosis, but do not present to health care with them,[21] our 5-year prevalence figure might be more accurate, but is still most likely an underestimate of the actual PNES prevalence.

Even when a diagnosis of epilepsy is made by a clinician with appropriate expertise, there will inevitably be some cases in which a diagnosis of PNES is missed. Unfortunately, we were unable in the context of the present study to review cases coded as epilepsy. However, other epidemiological studies of PNES have had similar circumstances and did not address diagnostic standards for epilepsy in their base populations.[11,12] The present study has the advantage that our base population has a defined referral pathway for patients with possible epilepsy and has good access to neurological services. The diagnoses of epilepsy were made by clinicians who themselves had unrestricted access to a full range of EEG and imaging investigations. We might have missed further patients with PNES primarily diagnosed by psychiatrists, for example patients with PTSD and dissociative episodes, who were not referred to a neurologist. The question of consistency of use of ICD codes is likely to be an issue in many countries, and was beyond the scope of the present study. Due to a lack of consensus regarding use of diagnostic codes for PNES, some cases might be registered under other diagnostic codes, such as Z03.3 "observation for suspected nervous system disorder" or R55 "syncope and collapse," which were not included in our study. Some incident patients with mild or few seizures might have remained in primary care. The number of such cases is difficult to estimate.

Our study found a mean annual incidence rate between 2010 and 2019 of 3.1/100 000/year, with no consistent pattern of change in the annual incidence rates over the study period. A nationwide Icelandic study that included subjects aged 15 years and older reported a much lower incidence rate of 1.4 per 100 000/year.[11] However, this estimate was based on only 14 incident cases, of whom seven had comorbid epilepsy. A US study including adults[12] and a Scottish study that included cases aged 13 years and older[10] reported PNES incidence rates of 3.0 and 4.9/100 000/year, respectively, which is in approximate agreement with our incidence figure. However, these studies included only video-EEG-confirmed cases, and the Scottish study excluded cases with comorbid epilepsy.[10] Our comparable incidence data

(video-EEG-confirmed cases) was only 1.26/100 000/year. Inclusion of only video-EEG-confirmed cases is likely to underestimate incidence, and therefore, there seems to be a true difference between the Scottish and US populations and ours, although differing diagnostic practices might also contribute.

A Danish study, including children and adolescents 5–17 years of age, reported a lower incidence rate than we found, at 2.4/100 000/year.[13] The inclusion criteria in the Danish study were similar to ours, using a staged approach with different levels of diagnostic certainty. However, the EEG criteria were modified, and EEG information was missing or not performed in 13% of the cases. In the Danish study, the highest incidence rate was found among 16-year-old patients, with a 3.3-fold higher incidence rate at 7.9/100 000/year, which is consistent with our findings.[13]

We found a particularly high prevalence (59.5/100 000/year) and incidence (9.8/100 000/year) in the 15–19 years age group in our study. Our findings should increase the awareness of PNES in adolescents and young adults.

In our cohort, the mean delay was 3.2 years from the first PNES to a confirmed diagnosis. This is consistent with previous findings; the mean diagnostic delay was 1.7 years in the Scottish study and 6.8 years in the US study.[10,12] In a review study, the mean diagnostic delay varied between .6 and 11.18 years,[22] but none of the reviewed reports included children younger than 13 years. We found that the diagnostic delay among children and adolescents was significantly shorter than among adults (1.3 years vs. 4.2 years).

Among our patients, 13% (11 of 84) had either confirmed or probable comorbid epilepsy. Previous studies on the incidence of PNES have found 14.2%–50% with comorbid epilepsy.[11–13] A meta-analysis reported the frequency of epilepsy in patients with PNES to be 22%.[23] The authors discussed that the high frequency of dual diagnoses could reflect that patient recruitment is from specialized epilepsy centers in most studies. The relatively low proportion of comorbid epilepsy among PNES cases in our study is probably due to the population-based inclusion approach, but might to some degree also reflect missing cases with epilepsy and undiagnosed PNES.

The prevalence of psychiatric comorbidity in PNES has been reported to range between 53% and 100%.[24] In our study, 62% of included patients had a psychiatric condition noted in their medical record. This is likely to be an underestimate, as pediatricians and neurologists might not always explore psychiatric issues thoroughly in a busy clinical routine. We did not have access to psychiatric records.

In our cohort, only 24% of the patients had "dissociative seizures" (F44.5) registered as a diagnosis, and more than 75% had a nonspecific diagnosis. Even among those with a video-EEG-confirmed diagnosis, the proportion of those registered with a diagnosis of "dissociative seizures" was only slightly higher, as low as 32%. Surveys among health care professionals have indicated that only a minority use the ICD-10 code F44.5 when diagnosing PNES.[25,26] Our findings are consistent with the known lack of consensus on coding and terminology for PNES. This may hamper clear communication with patients and presents an obstacle for epidemiologic studies. Because there is no substantial change in the upcoming 11th revision of the ICD-11 regarding dissociative neurological symptom disorders,[27] the challenge of finding a more widely accepted term remains.

The main strength of our study was the population-based design, including all age groups, and the systematic case validation using recommended definitions. This approach enabled us to estimate incidence and prevalence values based on ILAE-defined levels of certainty.

However, as discussed above, our method would not identify all PNES cases, and our findings are therefore likely an underestimate. Although inclusion of patients with lower levels of diagnostic certainty provides a more nuanced and complete picture of incidence and prevalence, some inaccurate diagnoses may have been included.

5 | CONCLUSIONS

Our population-based estimate of the prevalence of PNES was within the range of estimates based on non-population-based data available in the literature. We found a strikingly high incidence and prevalence of PNES in adolescents, suggesting the need for further study of this challenging patient group. The current term for PNES in ICD-10, "dissociative seizures," seems to be poorly accepted among clinicians. There is an urgent need for international consensus on a more widely acceptable term. In addition, further work is needed to provide a better understanding of the epidemiology of PNES and to evaluate possible regional differences.

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None.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

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The effect of attachment style on long-term outcomes in psychogenic nonepileptic seizures: Results from a prospective study

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ABSTRACT

Introduction: Insecure and fearful attachment styles have been reported in psychogenic nonepileptic seizures (PNES). We have investigated associations between long-term clinical outcome in PNES, parenting and attachment styles and demographic, clinical, and neuropsychiatric factors.
Material and methods: Patients aged at least 16 years and with documented PNES, according to criteria from the International League Against Epilepsy, were prospectively recruited to this study. They were assessed at baseline to determine clinical characteristics, experience of attachment and perceptions of experienced parenting styles, trauma history, dissociation, and health-related quality of life. At a mean of 70.45 (SD 29.0, range 22–130) months after inclusion, participants were contacted by telephone and asked about their current medical status and psychiatric/psychological interventions.
Results: Of 53 patients included in the study, 51 (96 %) provided follow-up data. Most (84.9 %) patients were female, and the mean age of PNES onset was 25.6 years. At follow-up, 20 patients (39 %) were free of PNES. Those patients that had achieved PNES freedom at follow-up had lower levels of attachment anxiety ($p = 0.01$) and reported to have experienced their fathers as less controlling ($p = 0.02$) and their mothers as more caring ($p = 0.04$) at baseline compared with those patients still suffering from PNES. Seizure freedom at follow-up was predicted by male gender, younger age at PNES onset, and less attachment anxiety.
Conclusion: In our cohort from a tertiary epilepsy center the long-term prognosis of PNES is poor. Attachment anxiety is a risk factor for persistent PNES. It may be of therapeutic relevance to assess attachment patterns in patients with PNES.

1. Introduction

Psychogenic nonepileptic seizures (PNES) is classified as a conversion disorder in DSM-5 [1] and as a dissociative disorder in ICD-10 [2]. Patients with PNES are commonly encountered in neurology clinics [3]. Misdiagnosis, long delays to diagnosis, and inappropriate treatment with anti-seizure medications occur commonly in patients with PNES [4,5]. PNES is associated with high rates of economic inactivity [6] and disability [7]. The prognosis in adults is probably poor: although the quality of follow-up studies is variable, approximately two-thirds of newly diagnosed adults continue to have seizures many years after receiving their diagnosis [8–13].

Individuals with PNES have a high prevalence of traumatic life events, neglect, and family dysfunction [14]. Dysfunctional parenting has been related to personality pathology in adult life [15] and to mental disorders in adolescents [16] and adults [17]. Adults with PNES have been reported to have received less parental care than patients with other conversion disorders [18], whereas a study on children did not find a difference in perceived parenting between children with PNES and their siblings [19].

Attachment theory may provide a link between early traumatic events, family dysfunction, and psychopathological conditions. According to attachment theory, early childhood interactions with primary caregivers result in patterns of thoughts, beliefs, emotions, and behaviors regarding self and others, referred to as attachment styles [20,21]. Attachment disturbances have been associated with several mental disorders [22]. In patients with PNES, a predominance of fearful attachment [23] and insecure attachment [24]

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have been reported. Attachment styles may also influence outcomes in psychotherapy generally [25]. However, in patients with PNES, this potential association has not been investigated.

We conducted a prospective cohort study to investigate clinical outcomes in adult patients with PNES and possible associations between experienced parenting and attachment styles, along with demographic, clinical, and neuropsychiatric factors. We hypothesized that insecure attachment styles, and patient perceptions of poor parental bonding may be associated with a less successful clinical outcome in patients with PNES receiving the usual care and follow-up.

2. Material and methods

2.1. Clinical setting

Patients are referred for diagnosis to the Norwegian Epilepsy Center (NEC) by neurologists, pediatricians, and general practitioners. Patients undergo a diagnostic work-up, clinical evaluation, revision of MRI of the brain, observation, video-electroencephalography (EEG), and psychological evaluation. When a diagnosis of PNES is confirmed, the diagnosis is explained to the patient and relatives by the physician. Patients and families are provided with further information on PNES by a staff nurse and are then invited to a follow-up stay of 2–4 week duration for further psychoeducation from a multidisciplinary team. This team is composed of epileptologists (neurologists and pediatricians), psychologists, nurses, a social worker, an occupational therapist, and a physical therapist. Patients are usually referred to their local psychiatry outpatient department or to the local community psychiatric health team.

2.2. Study sample

From September 2009 to October 2017, we prospectively recruited consecutive patients, aged 16 years and older, from the NEC. Due to organizational changes at the center, there were periods with no patient inclusion during 2010, 2013, and 2016. Patients were recruited to the study either at the end of a diagnostic stay, when a PNES diagnosis was confirmed, or during a follow-up stay. All patients had a documented PNES diagnosis from an experienced epileptologist at the NEC, i.e., a history indicative for PNES and witnessed events while on video–EEG, consistent with the highest degree of certainty of PNES according to criteria from the International League Against Epilepsy [26].

Some authors have claimed that PNES rather than being an entity of its own, has to be regarded as a symptom of underlying psychiatric disorders [27]. In this study, we have chosen to define PNES as a disorder following the classification systems of ICD-10 [2] and DSM-5 [1].

Three experienced neurologists at NEC (CL, MIL, AV) prospectively collected baseline demographic and medical data. The patients were interviewed and medical records were reviewed to ascertain PNES diagnosis, age at PNES onset, and EEG and MRI abnormalities, and to rule out the presence of comorbid epilepsy. Patients with comorbid epilepsy were excluded. Further inclusion and exclusion criteria are listed in Table 1.

A total of 62 patients were invited to join the study, four of whom declined. A further two did not meet our study criteria on review of the records. One patient died during the study, and as undiagnosed concomitant epilepsy was thought possible, she was also excluded. Two patients withdrew their consent during the study, leaving 53 participants for the analyses.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Documented PNES diagnosis according to criteria from the International League Against Epilepsy	Estimated low (<70) IQ
Age 16 years or older	Patients with severe medical and/or psychiatric conditions expected to be unable to undergo the planned assessment

2.3. Psychometric measures

The following self-report questionnaires were used at baseline: The Attachment Style Questionnaire (ASQ), Parental Bonding Instrument (PBI), Traumatic Experience Checklist (TEC), Dissociative Experience Scale (DES), Somatoform Dissociation Questionnaire (SDQ-20), and a visual analog health thermometer (EQ-VAS). Other than EQ-VAS [28], none of the Norwegian versions of these questionnaires has been clinically validated.

2.3.1. Attachment style Questionnaire (ASQ)

The ASQ [29] is a 40-item self-reporting measure of adult attachment dimensions. Items are rated on a 6-point Likert scale (1 (totally disagree) to 6 (totally agree)). A higher score indicates a greater amount of the attachment construct measured. The following attachment dimensions were derived: "confidence in relationships" that assesses secure attachment, "discomfort with closeness" and "relationships as secondary" both of which assess aspects of attachment avoidance, and "need for approval" and "preoccupation with relationships" that are both aspects of attachment anxiety. Consistency coefficients (Cronbach's alpha) showed good reliability for the five dimensions in the present study, ranging from 0.80 to 0.84.

2.3.2. Parental bonding instrument (PBI)

The Norwegian version [30] of PBI [31,32] was used to assess maternal and paternal parenting styles recalled from the first 16 years of each patient's life. It consists of 25 items answered on a 4-point Likert scale (1 (very like) to 4 (very unlike)). The PBI measures two fundamental dimensions of interpersonal relationships, including parental behavior: 'care' and 'protection'. Combining these two dimensions enables sorting of the patient's parents into one of the four categories, including affectionless control (low care, high protection), affectionate constraint (high care, high protection), neglectful (low care, low protection), and optimal parenting (high care, low protection). Previous studies of PBI have shown satisfactory reliability and validity estimates [33]. In our study, the four PBI subscales showed excellent internal reliability, with Cronbach's alpha ranging from 0.87 (subscale paternal protection) to 0.93 (subscale maternal care).

2.3.3. Traumatic experience checklist (TEC)

The TEC [34] is a 29-item self-report questionnaire assessing potentially traumatic experiences, including a wide range of experiences. It has a total score and distinguishes between five subscales: emotional neglect, emotional abuse, threat to body/life, sexual harassment, and sexual abuse. Previous studies have shown satisfactory reliability and validity [35].

2.3.4. Dissociative experience scale (DES)

The DES [36] is a 28-item self-report inventory of dissociative phenomena. It provides a total score and three subscales: depersonalization–derealization, amnestic dissociation, and

absorption and Imaginative Involvement. It is reported to be reliable, internally consistent, and temporally stable [37]. In our study, reliability for the three subscales was good with consistency coefficients (Cronbach's alpha) ranging from 0.78 to 0.84.

2.3.5. Somatoform dissociation Questionnaire (SDQ-20)

The SDQ-20 [38] measures the severity of somatoform dissociation. It includes 20 items that are to be rated on a 5-point Likert scale (1 (not at all) to 5 (extremely)). To obtain an index of symptom levels, the scores across the items are summed (total index ranges from 20 to 100). Cronbach's alpha was 0.79, indicating good reliability.

2.3.6. Visual analog health thermometer (EQ-VAS)

General health was assessed using a visual analog scale similar to a thermometer, which is part of the EuroQol (EQ-5D) instrument [39]. It assesses overall health status, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).

2.4. Follow-up

At a mean of 71 (SD 29.0, 22–130) and a median of 66 months month after inclusion, participants were contacted by telephone and, following a structured interview guide, asked about current medical status (e.g., PNES frequency, employment status, and hospital admissions) and psychiatric/psychological interventions (e.g., psychotherapy, other nonpharmacological interventions).

Statistics based on our hypothesis suggested that insecure attachment would be associated with persistent PNES-seizures at follow-up; the power analysis suggested at least 88 participants each with insecure attachment and with secure attachment to detect a difference in proportions of PNES-free patients at follow-up of 20 % in the group with insecure attachment vs 50 % seizure-free participants at follow-up in the group with secure attachment with a maximum risk of 5 % of committing a type 1-error and a statistical power of 80 %. For the cutoff between secure and insecure attachment, we used 2 Standard Deviations (SD) below the normative mean on the confidence-scale of the ASQ ($\leq$34.6) [40].

Baseline and follow-up characteristics were assessed for differences between patients who were seizure free at follow-up, defined as absence of PNES during the previous year, and not seizure free at follow-up. Student's t-test was used for continuous and normally distributed variables, Mann–Whitney U-test for ordinal or skewed variables, and chi-square tests or Fisher's exact tests for categorical data. In addition, we examined within-group differences according to the secondary outcomes, $\geq$50 % seizure reduction.

All hypothesis testing was 2-tailed. To correct for multiple comparisons when assessing group differences on baseline and follow-up characteristics (>20 variables) (Table 3) we considered p values of $\leq$0.01 as statistically significant, otherwise p values of $\leq$0.05 were considered as statistically significant.

To determine potential predictors of achieving PNES freedom by time of follow-up, we performed multivariate logistic regression analysis. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 26, IBM). Missing items were replaced with the mean of the answered items in the subscale, if at least half of that subscale had been answered.

2.5. Ethics

The present study was approved by the Regional Committee for Medical Research Ethics South East Norway (2009/1078/REC South-east). The study was conducted and reported in accordance with the STROBE checklist.

3. Results

51 (96 %) of the original 53 participants provided data at follow-up, as two participants were lost to follow-up.

Of all 53 patients originally included, 45 (85 %) were female, the mean age at PNES onset was 25.6 years, and the mean age at presentation was 32.1 years, with a mean diagnostic delay of 5.6 years. There was a prior psychiatric history of anxiety or depression in 32 (60 %) of the 53 participants and 45 (85 %) had experienced at least one traumatic life event. For baseline characteristics see Table 2.

Regarding attachment styles, our sample of patients with PNES showed significantly lower levels of confidence (security) ($p < 0.0001$) and higher levels of insecurity on attachment styles than a normative sample. The mean confidence score for our patients with PNES was 32.3 (SD = 7.3) whereas the mean confi-

Table 2
Baseline characteristics of the PNES sample.

Baseline characteristics	Values (n = 53)
Female gender, *n* (%)	45 (84.9)
Age at presentation, y, mean (SD, range)	32.1 (13.4, 16–62)
Age at PNES onset, y, mean (SD, range)	25.6 (11.7, 8–56)
Diagnostic delay in years, mean (SD, range)	5.6 (9.1, 0–50.8)
PNES frequency per month, mean (SD, range)	21.9 (61.8, 0.2–450)
Education in years, mean (SD, range)	13.1 (2.7, 7–22)
Marital status, *n* (%)	
Married/partner	23 (43.4)
Single/separated	30 (56.6)
Employment, *n* (%)	
Employed/student	23 (43.3)
Unemployed	25 (47.2)
Psychiatric history for anxiety or depression, *n* (%)	32 (60.4)
Psychotherapy prior to inclusion, *n* (%)	35 (66.0)
QoL-VAS (*n* = 49), mean (SD, range)	51.9 (19.3, 20–100)
Attachment styles (ASQ), mean (SD, range)	
Confidence	32.3 (7.3, 19–47)
Attachment anxiety	
Need for approval	26.2 (8.2, 10.0–40.6)
Preoccupied with relationships	28.5 (8.6, 11–47)
Avoidant attachment	
Discomfort with closeness	36.6 (9.8, 16.7–55)
Relationships as secondary	17.6 (7.0, 7–39)
Parental bonding (PBI)	
Paternal PBI dimensions, mean (SD, range)	
care	21.7 (9.5, 3–36)
control	13.9 (7.7, 2–36)
Paternal parenting style, n (%)	
affectionless control (low care, high control)	20 (37.7)
affectionate constraint (high care, high control)	5 (9,4)
neglectful (low care, low control)	8 (15,1)
optimal parenting (high care, low control)	19 (35.8)
Maternal PBI dimensions, mean (SD, range)	
care	25.0 (9.3, 6–36)
control	13.8 (8.4, 0–32)
Maternal parenting style, n (%)	
affectionless control (low care, high control)	15 (28.3)
affectionate constraint (high care, high control)	20 (37.7)
neglectful (low care, low control)	3 (5.7)
optimal parenting (high care, low control)	13 (24.5)
Dissociation (DES), mean (SD, range)	
total	15.9 (11.1, 0–46.8)
Amnestic dissociation	8.0 (9.5, 0–45)
Absorption and imaginative involvement	22.8 (15.7, 0–55.6)
Depersonalization and derealization	10.1 (12.2, 0–58.3)
Somatoform dissociation (SDQ-20), mean (SD, range)	32.1 (8.6, 21–58)
Trauma history (TEC), (*n* = 52), *n* (%)	
Emotional trauma	37 (71.2)
Sexual trauma	20 (38.5)
Bodily threat	36 (69.2)
Any trauma	45 (84.9)

dence score of the normative adult population sample was 44.8 (SD = 5.1) for. 29 (56 %) patients had a confidence score ≤ 34.6, that is 2 SD below the normative mean [40].

Among our participants, 13 (25 %) rated their mothers as having been an optimal parent and 19 (36 %) provided this rating for their fathers. Comparisons between the dimensions care and control of the parental bonding in our PNES sample and the general population, indicated similar levels of maternal and paternal care and control [41].

At follow-up, 20 of the 51 patients whom we were able to contact (39 %) were free of PNES and 42 (82 %) had a ≥50 % reduction of seizure (PNES) frequency.

We found significant group-level differences between those patients who had become PNES free and those who had not, concerning reduced healthcare contact (p = 0.001) (Table 3).

Patients who were seizure (PNES) free at follow-up had previously reported lower levels of attachment anxiety than those still having PNES (p = 0.01) (Table 3).

When comparing patients that achieved a seizure-reduction ≥50 % at follow-up to those that did not have a reduction in seizure frequency, there were no significant differences concerning attachment styles or perceived parenting.

We used logistic regression analysis to identify independent factors associated with PNES free outcome. Due to our small sample size, we limited the number of potential predictors and included attachment anxiety (need for approval), sex, and age at PNES onset in the model. Seizure freedom at follow-up was best predicted by male gender; see Table 4.

4. Discussion

In this study, we examined associations between attachment styles and parental bonding, and long-term outcomes among patients with PNES and attempted to identify prognostic factors.

At an average follow up of 5.8 years, 61 % of the patients continued having PNES, based on follow-up data from 96 % of the initially enrolled cohort in our prospective cohort study. The high follow-up rate might reflect the high trust in the Norwegian healthcare system, in general, and, specifically, our center's structured diagnostic and follow-up procedures [42].

Previous studies suggesting poor outcome have been mainly retrospective in nature, some with low responder rates [8–12]. One prospective study reported 66 % of patients still having PNES after 3 years; however, 64 % of the initially enrolled cohort was lost to follow-up [43]. Our data suggest that, despite methodological differences, these previous estimates of outcome may have been realistic.

Table 3
Baseline and follow-up data by PNES outcome, * $p \leq 0.01$.

	PNES – seizure free (n = 20)	PNES – continued (n = 31)	P value
Baseline			
Female sex, n (%)	14 (70 %)	30 (96.8 %)	0.007*
Age at inclusion, mean (SD, range)	30.0 (11.9, 17–52)	34.2 (14.5, 16–62)	0.24
Follow-up time in years, mean (SD, range)	6.3 (2.3, 3.2–9.6)	5.7 (2.5, 1.9–10.9)	0.39
Age at PNES onset, mean (SD, range)	22.5 (9.7, 9–43)	27.9 (12.8, 8–56)	0.11
Diagnostic delay in years, mean (SD, range)	6.0 (7.2, 0.3–25.3)	5.6 (10.5, 0.0–50.8)	0.43
PNES frequency at baseline, monthly, mean (SD, range)	35.9 (98.7, 1–450)	13.2 (14.5, 0.2–70)	0.21
QoL, mean (SD, range)	56 (20.0, 30–100)	49 (19.4, 0–90)	0.27
Education in years, mean (SD, range)	13.2 (3.6, 7–22)	13 (2.1, 10–17)	0.82
Employed or student, n (%)	10 (55.6)	12 (42.9)	0.4
ASQ Confidence, mean (SD, range)	33.3 (7.4, 21.7–47.0)	31.9 (7.3, 19–44)	0.52
ASQ Attachment anxiety (Need for approval), mean (SD, range)	22.6 (7.3, 10–38)	28.5 (8.3, 10–40.6)	0.01*
ASQ Attachment anxiety (Preoccupied with relationships), mean (SD, range)	26.3 (8.3, 12–45)	30.0 (8.7, 11–47)	0.14
ASQ Avoidant attachment (Discomfort with closeness), mean (SD, range)	36.0 (11.3, 16.7–55.0)	36.6 (9.0, 22–53)	0.84
ASQ Avoidant attachment (Relationships as secondary), mean (SD, range)	15.6 (6.2, 7–28)	19.2 (7.3, 8–39)	0.08
Paternal care, mean (SD, range)	24.8 (8.0, 8–35)	19.6 (10.2,3–36)	0.06
Paternal control, mean (SD, range)	10.9 (7.4, 2–29)	16.1 (7.5, 5–36)	0.02
Maternal care, mean (SD, range)	28.3 (7.6, 9–36)	22.8 (10.2, 6–36)	0.04
Maternal control, mean (SD, range)	12.0 (9.2, 0–31)	14.9 (7.9, 5–32)	0.25
SDQ total, mean (SD, range)	30.6 (6.7, 21–44)	32.7 (9.6, 22–58)	0.41
DES total, mean (SD, range)	13.5 (11.2, 1.4–46.8)	16.6 (10.9, 0–42.5)	0.33
Any trauma in history, n (%)	18 (90)	28 (93)	0.57
Psychotherapy prior to inclusion, n (%)	14 (77.8)	19 (65.5)	0.37
Follow-up			
QoL, mean (SD, range)	74 (18.3, 30–100)	58 (15.5, 0–90)	0.02
Seizure related contact with health care within the last year, n (%)	0	12 (40)	0.001*
Emergency room visits within the last year, n (%)	0 (0)	9 (30)	0.007*
Employed or student, n (%)	10 (50)	14 (45.2)	0.11

Table 4
Potential predictors of PNES-free outcome at follow-up in patients with PNES (multivariate logistic regression analysis), $p \leq 0.05$, Nagelkerke R^2 = 0.46.

	Univariate screen		Multivariate model	
	Odds ratio (Confidence Intervals)	P value	Odds ratio (Confidence Intervals)	P value
Age at PNES onset	0.96 (0.91–1.01)	0.12	0.89 (0.82 – 0.98)	0.01*
Attachment anxiety (Need for approval)	0.91 (0.84–0.98)	0.02*	0.91 (0.83 – 0.99)	0.04*
Male sex	12.82 (1.41–111.11)	0.02*	32.26 (2.20–500)	0.01*

In the present study, gender and attachment anxiety were associated with PNES-free outcome. Illness duration, work and educational status, marital status, adverse life-event burden, and levels of dissociation were apparently not associated with outcome. The non significance of traumatic life events on the prognosis in our study could be due to the high rates of recorded adverse life-event burden in both groups (93 % and 90 %), that could mitigate possible differences.

Nevertheless, levels of secure attachment were significantly lower than those reported from a normative sample [40]. Our findings showed an inverse association between attachment anxiety and remission of PNES at follow-up after a mean of 5.8 years. Attachment anxiety was a negative predictor of a PNES-free outcome in the multivariate regression analysis, but the odds ratio (OR) was low.

Insecure and disorganized attachment styles have previously been linked to psychiatric conditions [44], including functional neurological disorders [45]. In patients with PNES, fearful attachment [23] and insecure attachment [24] have been found to be the predominant attachment styles. Attachment patterns might also play a role in the therapeutic process and influence outcome [25]. Patients with anxious attachment have been described as being difficult to treat, often presenting with chaotic and contradictory representations of self and others [25]. In patients with borderline personality disorder, it has been shown that those having a preoccupied attachment style were more likely to not respond to intervention. It has been argued that preoccupied attachment style might complicate the engagement in the therapeutic treatment and the alliance with the therapist [46].

Another concept that might be closely related is that of defense styles. It has been argued that patients with PNES might have different underlying psychopathology and defense mechanisms which again could influence prognosis [27]. Defense mechanisms are commonly categorized in mature, neurotic, and immature styles [47]. Whereas mature defense style comprises normal and adaptive mechanisms of coping with troubling situations, both neurotic and immature styles are seen as dysfunctional and maladaptive coping strategies [48]. Patients with PNES are likely to use less mature defensive strategies, which again might be associated with insecure attachment patterns [49].

To explore a patient's attachment pattern might be useful for tailoring their therapeutic strategies.

In our study, 35.8 % of our patients with PNES described their fathers as an optimal caregiver during childhood, and even fewer (24.5 %) characterized their mothers as optimal parents. Optimal parenting is delineated by high care and low control. Recollections of parenting style were not found to be associated with remission of PNES seizures at follow-up in our study. It has been shown that the type of parenting received from both the mother and the father influences psychological wellbeing in adulthood [50]. Perceived parental care and control have also been associated with mental disorders in adolescence [16]. A study of a pediatric cohort with PNES found no difference in perceived parenting between patients with PNES and their siblings [19].

In our study, being male was the strongest predictor of a good (i.e., PNES-free) outcome. The numbers were small, with only 8 males in the cohort and the results have large confidence intervals, indicating low precision of the OR. Whether gender may, nevertheless, influence PNES outcome can be debated. Previous studies have yielded contradictory results, with one finding male gender being predictive of a favorable outcome [51], whereas another study found that female gender was predictive of a good outcome [52]. Men are under-represented in most studies of PNES, and therefore may have gender differences in patients with PNES been insufficiently studied. From studies that have examined gender differences, we know that men experience significantly less sexual traumas and show lower levels of dissociation than women [53]. Both these factors could play a role in PNES severity and outcome.

A lower age at PNES onset was not associated with a PNES-free outcome in the univariate analysis in our cohort. In the multivariate analysis, however, it was a predictor of favorable outcome, but with a low OR. Some previous studies have found that younger age at PNES onset is favorable for recovery [8,10]. Different etiopathological mechanisms in pediatric and adult populations with PNES have been hypothesized as being possible reasons for such age-related differences in prognosis.

Self-reported overall health scores (QoL-VAS) were low compared with values from the general population from Norway [28], and in line with reports from other large PNES cohorts [54], indicating poor quality of life (QoL) in patients with PNES. Persistence of PNES at follow-up was associated with poor QoL, whereas patients who were free of PNES at follow-up reported increased scores for QoL although not reaching statistical significance. Nevertheless, reduction in seizure frequency was not associated with improved QoL. Similar findings have been reported from other studies on PNES outcome [8]. There has been some debate on treatment goals and outcome measures for patients with PNES. These findings suggest that the impact of treatments that reduce PNES frequency will be of limited value for quality of life and that cessation of PNES seizures remains an important goal in treatment.

In our whole cohort, including the group of the patients with ongoing PNES at follow-up, contact with healthcare services was reduced over time since diagnosis. Indeed, 60 % of patients with persistent PNES reported not having had contact with healthcare services for PNES-related reasons during the year prior to follow-up. Reduction in healthcare expenses following diagnosis of PNES has been reported previously [55].

4.1. Strengths and limitations

The main strength of our study is the follow-up after a prolonged period, and the very low rate of patients that were lost to follow-up. Only patients with documented PNES, according to the ILAE recommendations, were included in our study and we defined PNES remission as freedom of PNES for the duration of at least one year.

Although we were able to study as many as 53 patients from our national tertiary care center for an average follow-up period of almost six years, our study is under-powered: the number of includable cases fell short of the calculated minimum sample size. The size of our sample also limited the numbers of potential predictors to be studied.

Another limitation in our study is that, although prospective, we were not able to control for all factors/events to which the patients were exposed prior to follow-up. In addition, our cohort was recruited from a single tertiary epilepsy center with an established diagnostic and follow-up pathway for patients with PNES, and this may restrict the generalizability of our findings.

Studies of predictive factors for PNES outcome have shown inconsistent results, and larger prospective (multi-center) studies are necessary to explore this further.

5. Conclusion

The long-term prognosis of PNES in our cohort from a tertiary epilepsy center is poor. Attachment anxiety is a risk factor for persistent PNES. It may be of therapeutic relevance to assess attachment patterns in patients with PNES.

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Declaration of Competing Interest

Author AV has served as a paid consultant for Eisai and Arvelle Therapeutics, unrelated to this study Author RD receives royalties from UpToDate. Author MIL has served as a paid consultant for Eisai, UCB and Arvelle Therapeutics, unrelated to this study. Author CL has no conflicts of interest to disclose.

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Paper III

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Adverse life events in patients with functional seizures: Assessment in clinical practice and association with long-term outcome

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ABSTRACT

Background: A history of adverse life events (ALE) is a risk factor for functional seizures (FS). Their influence on long-term outcome remains unclear. International guidelines recommend assessing ALE in patients presenting with associated disorders. It is not clear to what extent patients evaluated for FS are regularly asked about ALE.

Objectives: We hypothesised that the presence of ALE would relate to worse outcome at follow-up and, that the rate of detection of ALE in clinical work-up would be inferior to that based on self-report questionnaires.

Methods: 53 patients with FS from the National Centre for Epilepsy in Norway, aged 16–62 years were included. Symptom severity, health-related quality of life (HRQoL), and antecedent ALE were assessed at baseline. Medical records were examined for disclosure of ALE. At a mean of 70.45 (SD 29.0, range 22–130) months after inclusion, participants were inquired about FS status, FS-related health care utilization and HRQoL.

Findings: A history of emotional abuse documented in the medical record was an independent risk factor for worse HRQoL at follow-up. Prevalence of ALE documented in medical records was lower compared with rates measured by a self-report questionnaire.

Conclusions: These findings indicate an association between antecedent ALE and HRQoL years after diagnosis. A substantial proportion of the adverse life events by a self-report questionnaire had not been documented in the clinical records.

Clinical implications: The supplemental use of a self-report questionnaire in the diagnostic work-up of patients with FS may be valuable for detecting ALE.

1. Introduction

Adverse experiences in childhood have been associated with increased risk of physical and mental illness and premature mortality [1]. Adverse experiences in adulthood also increase the risk of mental health disorders [2]. Patients with functional neurological disorders (FND) report stressful life events, including trauma and neglect, around four to eight times more frequently than healthy controls [3]. A history of adverse life events (ALE) is considered a common risk factor for functional neurological disorders in general, and for functional seizures (FS), a subtype of functional neurological disorder, also called psychogenic nonepileptic or dissociative seizures, in particular [4]. Studies also indicate an association between the severity of experienced ALE and symptom severity in functional neurological disorders [5]. In patients with FS, earlier onset and seizure severity have been related to reported antecedent sexual abuse [6]. Sexual abuse has also been linked to poor outcome in FND [7]. A history of antecedent ALE might likely impact outcome measures in patients with FS as well, but data about this topic are scarce.

International guidelines, including those from the World Health Organization (WHO), recommend that healthcare providers should ask about adverse life events such as violence and abuse when patients present with associated disorders [8]. As adverse life events are also associated with neurological conditions, there has

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recently been a call to action for trauma-informed neurology [9]. The evidence of a relationship between adverse life events and FS is also reflected in the recommendation by the International League Against Epilepsy (ILAE) Neuropsychobiology Commission that the occurrence of abuse and trauma should be assessed early in the diagnostic work-up of patients with suspected FS [10].

Knowledge about prior potentially traumatic life events is particularly valuable for the clinician evaluating patients with FS, because formulating a synthesis of relevant predisposing, precipitating, perpetuating, and protective factors to developing FS together with the patient, is crucial to tailor treatment plans.

Although it is known that most patients accessing mental healthcare are not asked about adverse life events [11], we are unaware of any existing information regarding the proportion of patients who are being evaluated for FS who are asked about adverse life events.

We hypothesized that a history of ALE would relate to symptom severity as well as to worse outcome at follow-up, as reflected by symptom severity and non-seizure outcome measures, such as quality of life and health care utilization. We also hypothesized that the use of a self-report questionnaire would give added value by identifying ALE in a greater number of patients.

2. Materials and Methods

2.1. Participants

2.1.1. Clinical setting

Neurologists, pediatricians, and general practitioners refer patients to the Norwegian Epilepsy Centre (NEC) for diagnosis. Patients go through a diagnostic work-up including a clinical assessment, observation, revision of the magnetic resonance imaging (MRI), video-electroencephalogram (video-EEG), and psychological assessment. When a diagnosis of FS is confirmed, the physician explains the diagnosis to the patient and their relatives. A staff nurse gives patients and families further information on FS before inviting them to a follow-up stay of 2–4 weeks for psychoeducation by a multidisciplinary team. This team includes neurologists or pediatricians, psychologists, nurses, social workers, occupational therapists, and physical therapists. Patients are then typically referred to the community mental health center or the local outpatient psychiatry department in their area for further treatment.

The selection of participants and the study procedure have been described in detail in Villagrán et al. [12]. Patients admitted to our center between 2009 and 2017 and diagnosed with FS were recruited prospectively for the study. Patients were either recruited at the end of a diagnostic stay, when a diagnosis of FS was confirmed, or during a follow-up stay. During 2010, 2013, and 2016, there were periods with no patient inclusion due to organizational changes at the center.

Inclusion criteria were documented FS, consistent with the highest degree of certainty according to criteria from the ILAE [13] and 16 years of age or older. Patients with comorbid epilepsy, estimated low (<70) IQ, and patients with severe medical and/or psychiatric conditions expected to be unable to undergo the planned assessment were excluded. All patients were interviewed and investigated with gold standard FS work-up (i.e., long-term video-EEG) to ascertain the FS diagnosis, obtain clinical characteristics including information on the history of adverse life events, and rule out the presence of comorbid epilepsy.

2.2. Symptom severity and health-related quality of life self-report measures

At inclusion, participants completed three symptom severity scales: the Dissociative Experience Scale (DES), the Somatoform Dissociation Questionnaire (SDQ-20) and the Visual analogue health thermometer (EQ-VAS). The Norwegian version of the EQ-VAS has been clinically validated [14], but the Norwegian versions of the DES and the SDQ-20 have not.

The DES [15] is a self-reported inventory of dissociative phenomena consisting of 28 item. It provides a total score and three subscales: depersonalization-derealization, amnestic dissociation, and absorption and imaginative involvement. In previous studies, it has been reported to be reliable, internally consistent, and temporally stable [16]. In our study, reliability for the three subscales was good with consistency coefficients (Cronbachs alpha) ranging from 0.78 to 0.84.

The SDQ-20 [17] is a measurement for the severity of somatoform dissociation. It includes 20 items that are to be rated on a 5-point Likert scale (1 (not at all) to 5 (extremely)). The scores across the items are summed (total index ranges from 20 to 100) rendering an index of symptom levels. Cronbach's alpha was 0.79, indicating good reliability. We assessed general overall health status by a visual analogue scale similar to a thermometer, which is part of the EuroQol (EQ-5D) instrument, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state) [18].

2.3. Assessment of adverse life events

In a previous paper in this FS population [12] we acquired data using the Traumatic Experience Checklist (TEC), and found that 85% of patients reported having experienced at least one potentially traumatic life event. Here, we additionally examined the medical records of all participants in the original study for recordings of antecedent traumatic experiences.

2.3.1. Traumatic Experience Checklist

The TEC [19] is a 29-item self-report questionnaire assessing potentially traumatic life events. It covers emotional abuse, emotional neglect, sexual harassment, sexual abuse, physical abuse, threat to life/bizarre punishment/intense pain, as well as family-related items, e.g., family poverty, and alcohol or drug abuse by family members. Events are further evaluated for the age when they happened (0–6 years, 7–12 years, 13–18 years, and above 18 years), how long they lasted (more or less than 1 year), the subjective impact (none, slight, moderate, severe, or extreme), and the support received (none, some, or good support). The TEC renders a total score, representing the number of potentially traumatic adverse events experienced throughout the life span, and additionally distinguishes between five subscales: emotional neglect, emotional abuse, threat to body or life, sexual harassment, and sexual abuse, which reflect trauma severity. Previous studies have found satisfactory reliability and validity [20]. The Norwegian version has not been clinically validated.

2.3.2. Reports of adverse life events from the medical records

Participants' medical records were examined for any reported disclosure of experiences of adverse life events at their entry into the NEC by the first author AV. The records reviewed included referrals to the NEC and records from the stay at the NEC from physicians, psychologist, and nurses involved in the routine diagnostic work-up. Criteria for identification of the various forms of adverse life events were determined prior to the retrospective chart review. These criteria were aligned with the criteria for traumatic experiences as stated in the TEC, see Table 1.

2.4. Follow-up

At a mean of 71 (SD 29.0, range 22–130) months and a median of 66 months after inclusion, participants were contacted by telephone and, after a structured interview guide, asked about their

Table 1
Categories of potential adverse life events aligned according to items in the Traumatic Experience Checklist (TEC).

Adverse life events	TEC items
Household Challenges includes: Household substance abuse Household mental illness Family financial problems Divorce of the parents Having to look after parents, brothers and sisters	1, 2, 7
Loss of a family member	3, 4
Threat to life from illness, an operation or an accident, serious injury	5,6
Own divorce	8
Bodily threat	9, 10, 23
War time experience, incl. second generation war-victim	11, 12
Witnessing others undergo trauma	13
Emotional neglect	14, 15, 16
Emotional abuse includes bullying	17, 18, 19
Physical abuse	20, 21, 22
Sexual harassment	24, 25, 26
Sexual abuse	27, 28, 29

current medical status: self-reported FS frequency, healthcare utilization, HRQoL (EQ-VAS), and other psychosocial issues, e.g., marital status and occupational status. Questions concerning health care utilization were: "Have you had contact with your physician within the last year because of seizure-related issues: yes/no." "Have you had seizure-related admissions to the hospital within the last year: yes/no."

The wide range in follow-up time was due to challenges in contacting participants and organizational changes at our center.

2.5. Statistics

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, version 26, IBM). Descriptive statistics were used to explore the occurrence of adverse life events and symptom severity measures. Cohen's Kappa was used to examine the extent of agreement between reports on ALE from medical records and from the self-report questionnaire. Agreement was rated as follows: <0 no agreement, 0–0.2 slight agreement, 0.21–0.4 fair agreement, 0.41–0.6 moderate agreement, 0.61–0.8 substantial agreement, and 0.81–1 almost perfect agreement [21,22].

For comparisons between groups regarding categorical data (e.g., utilization of healthcare at follow-up) we used chi-square tests or Fisher's exact test. Student's t-test was used for continuous and normally distributed variables, and the Mann–Whitney U-test for ordinal or skewed variables. Relationships between HRQoL, SDQ-20, DES, other symptom severity parameters (e.g., age at FS onset, diagnostic delay), outcome measures (e.g., FS status, hospital admissions, HRQoL at follow-up), and TEC subscale scores and records on adverse events from the medical journals were examined by partial correlation analysis, controlling or age, sex and time to follow-up.

Diagnostic delay was defined as time from seizure onset to time of diagnosis of FS. FS status was defined as: FS free, when the participant reported no FS within the last year, 50% FS reduction, when FS frequency was lower than 50% of FS frequency reported at baseline.

To determine potential risk factors for reduced HRQoL at follow-up, we performed multiple linear regression analysis. All hypothesis testing was two-tailed. We considered p values of <0.05 as statistically significant. To correct for multiple comparisons we used the Benjamini-Hochberg correction. To reduce the risk of discarding potentially important predictors we decided to apply a false discovery rate of 0.25, reflecting the exploratory nature of our study.

2.6. Ethics

The study was approved by the Regional Committee for Medical Research Ethics South East Norway (2009/1078/REC South-east). It was conducted and reported in accordance with the STROBE checklist.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

3. Results

Of 62 patients who were invited to join the study, four declined. Two patients were excluded as they did not meet our study criteria (one patient did not have video-EEG documented events, and in one patient we could not rule out a comorbid epilepsy). One patient died during the study and was excluded as undiagnosed concomitant epilepsy was thought possible. Another two patients withdrew their consent during the study, leaving 53 participants for the final analyses.

Of the patients included in the study, 45 (85%) were female. The mean age at FS onset was 25.6 years, and the mean age at presentation was 32.1 years (range: 16–62 years). For further demographic and clinical information, see Table 2.

3.1. Assessment of adverse life events

In the medical records of 34/53 (64%) of patients, at least one of the outlined adverse life events had been noted, whereas in the TEC self-report questionnaire 45/52 (87%) of patients reported at least one adverse life event. Nineteen of 53 (36%) reviewed medical records did not give any indication of adverse life events. In 14 of these 19 cases (74%), patients revealed at least one potentially traumatic event by the self-report questionnaire. In 3 out of 7 (43%) cases with no potential traumatic experience in the TEC, there were reports about traumatic events in the medical record. The occurrence of adverse life events as reported in the medical records and in the TEC are summarized in Table 3.

With respect to the different categories of adverse life events, Cohen's kappa calculation found that there was no to fair agreement between most of the categories of self-reported adversities and those documented in patients' journals for all categories, with the exceptions of "threat to life" and "sexual abuse", which reported moderate agreement (Table 3) [21,22]. Rates of adverse events documented in medical records were lower than assessed by the TEC with lowest rates for "sexual harassment" and "bodily threat", see Table 3.

3.2. Relationships between adverse life events and symptom severity

3.2.1. Adverse life events assessed by the TEC

We found the closest correlation between severity of physical abuse and dissociation measured by SDQ-20 ($r = 0.49$, $p < 0.001$) and severity of threat to life and SDQ-20 ($r = 0.45$, $p = 0.005$), for details, see Table 4.

3.2.2. Adverse life events assessed in the routine clinical work-up

As for a history of ALE documented in the medical records, we found the strongest correlations between sexual trauma and dissociation measured by the DES ($r = 0.40$, $p = 0.005$), and sexual trauma and HRQoL ($r = -0.36$, $p = 0.016$). For details, see Table 4.

Table 2
Demographic, clinical information and questionnaire scores in patients with functional seizures. Abbreviations: SD = Standard Deviation, FS = Functional seizures, EQ-VAS = Quality of Life Visual Analogue Scale, SDQ-20 = Somatic Dissociation Questionnaire, DES = Dissociative Experience Scale, TEC = Traumatic Experiences Checklist.

Baseline characteristics	N	Values
Demographics and clinical information		
Female sex, n (%)	53	45 (84.9)
Age at presentation, y, mean (SD, range)	53	32.1 (13.4, 16–62)
Education in years, mean (SD, range)	53	13.1 (2.7, 7–22)
Employment, n (%)	51	
Employed/student		24 (47.1)
Unemployed		27 (52.9)
Psychiatric history for anxiety or depression, n (%)	49	32 (65.3)
Psychotherapy prior to inclusion, n (%)	49	35 (71.4)
Marital status, n (%)	53	
Married/partner		23 (43.4)
Single/separated		30 (56.6)
Severity Measures		
Age at FS onset, y, mean (SD, range)	53	25.6 (11.7, 8–56)
Diagnostic delay in years, mean (SD, range)	53	5.6 (9.1, 0–50.8)
FS frequency per month, mean (SD, range)	53	21.9 (61.8, 0.2–450)
EQ-VAS, mean (SD, range)	49	51.9 (19.3, 20–100)
SDQ-20	51	32.1 (8.6, 21–58)
DES	53	15.9 (11.1, 0–46.8)
Adverse life events		
TEC Overall score, mean (SD, range)	52	6.7 (4.7, 0–18)
TEC Emotional neglect, mean (SD, range)	52	2.6 (4.6, 0–13)
TEC Emotional abuse, mean (SD, range)	52	2.8 (4.3, 0–13)
TEC Physical abuse, mean (SD, range)	52	0.6 (1.6, 0–9)
TEC Threat to life, mean (SD, range)	52	1.4 (2.6, 0–11)
TEC Sexual trauma, mean (SD, range)	52	1.7 (4.3, 0–19)

Table 3
Prevalence of adverse life events disclosed through medical records and Traumatic Experience Checklist (TEC) in patients with Functional Seizures.

	Case note reports of adverse life events n (%)	TEC self-reports of adverse life events n (%)	Cohen's Kappa
Household Challenges	17 (32.7)	39 (75.0)	0.21
Loss of a family member	4 (7.7)	17 (32.7)	0.29
Threat to life from illness, an operation or an accident, serious injury	9 (17.3)	13 (25.0)	0.43
Own divorce	2 (3.8)	7 (13.5)	0.17
Bodily threat	3 (5.8)	36 (69.2)	−0.004
War time experience, incl. second generation war-victim	1 (1.9)	5 (9.6)	0.31
Witnessing others undergo trauma	3 (5.8)	21 (40.4)	0.17
Emotional neglect	8 (16.7)	25 (52.1)	0.31
Emotional abuse	11 (22.4)	30 (61.2)	0.09
Physical abuse	6 (11.5)	19 (36.5)	0.27
Sexual harassment	0 (0)	16 (33.3)	0.0
Sexual abuse	14 (28.6)	19 (38.8)	0.59

3.3. Outcome measures

At follow-up, 31/51 (61%) of the participants were continuing to experience FS. Forty-two out of 51 participants (82%) had a 50% reduction in FS frequency. Twelve out of fifty (24%) of the patients reported having been in contact with a physician for their FS within the last year. Nine out of fifty participants (18%) reported FS-related hospital admissions in the year before contact at follow-up. The reported mean HRQoL at follow-up was 63.8 (SD 24.1, range 0–100).

3.4. Relationships between adverse life events and outcome measures

HRQoL at follow-up was inversely correlated with reports about emotional abuse documented in the medical records ($r = -0.34$, $p = 0.017$) and with the severity of antecedent physical abuse ($r = -0.32$, $p = 0.026$), and the experience of "threat to life" ($r = -0.32$, $p = 0.03$) detected by the TEC.

There was no significant correlation between a history of ALE in any of the aforementioned categories (neither assessed by the TEC nor recorded in the medical record) and FS freedom, 50% FS-reduction at follow-up, FS-related admissions to the hospital at follow-up, nor FS-related contact with a physician in the year prior to follow-up, when correcting for age, sex, and duration of follow-up.

3.5. Risk factor analysis

Having a history of emotional abuse documented in the medical record was an independent risk factor for worse HRQoL at

Table 4
Partial correlation (adjusted for age, sex, and time to follow-up) between symptom severity measures and adverse life events disclosed through Traumatic Experience Checklist and as recorded in the medical journals. P-values adjusted for multiple tests (row-wise Benjamini-Hochberg corrections, FDR 0.25). Significant correlations ($p < 0.05$, FDR 0.25) are marked with *. Abbreviations: FS = functional seizures, EQ-VAS = Quality of Life Visual Analogue Scale, SDQ-20 = Somatic Dissociation Questionnaire, DES = Dissociative Experience Scale, TEC = Traumatic Experiences Checklist, FDR = False Discovery Rate.

	Emotional neglect		Emotional abuse		Physical abuse		Threat to life		Sexual trauma	
	TEC	Medical record	TEC	Medical record	TEC	Medical record	TEC	Medical record	TEC	Medical record
Age at FS onset	−0.18 ($p = 0.23$)	0.05 ($p = 0.72$)	−0.12 ($p = 0.43$)	0.02 ($p = 0.90$)	−0.11 ($p = 0.45$)	−0.07 ($p = 0.65$)	−0.05 ($p = 0.74$)	−0.16 ($p = 0.28$)	−0.27 ($p = 0.06$)	0.03 ($p = 0.86$)
Diagnostic delay	0.23 ($p = 0.12$)	−0.02 ($p = 0.90$)	0.06 ($p = 0.68$)	0.08 ($p = 0.90$)	0.02 ($p = 0.87$)	0.19 ($p = 0.19$)	−0.02 ($p = 0.90$)	0.12 ($p = 0.43$)	0.36 ($p = 0.012$)*	0.042 ($p = 0.89$)
FS frequency per month	0.32 ($p = 0.027$)*	0.0 ($p = 0.99$)	0.15 ($p = 0.32$)	−0.03 ($p = 0.85$)	0.01 ($p = 0.50$)	−0.05 ($p = 0.76$)	0.05 ($p = 0.72$)	−0.06 ($p = 0.70$)	0.09 ($p = 0.54$)	−0.02 ($p = 0.88$)
EQ-VAS	−0.27 ($p = 0.08$)*	−0.26 ($p = 0.08$)*	−0.14 ($p = 0.38$)	−0.32 ($p = 0.03$)*	−0.43 ($p = 0.003$)*	−0.16 ($p = 0.29$)	−0.46 ($p = 0.002$)*	−0.02 ($p = 0.91$)	−0.28 ($p = 0.06$)*	−0.36 ($p = 0.016$)*
SDQ-20	0.26 ($p = 0.08$)*	0.02 ($p = 0.91$)	0.29 ($p = 0.05$)*	0.05 ($p = 0.73$)	0.49 ($p < 0.001$)*	0.06 ($p = 0.69$)	0.45 ($p = 0.002$)*	0.10 ($p = 0.53$)	0.21 ($p = 0.06$)*	0.26 ($p = 0.08$)*
DES	0.25 ($p = 0.09$)*	0.21 ($p = 0.16$)*	0.32 ($p = 0.025$)*	0.22 ($p = 0.14$)*	0.23 ($p = 0.12$)*	0.31 ($p = 0.03$)*	0.33 ($p = 0.025$)*	0.07 ($p = 0.67$)	0.29 ($p = 0.047$)*	0.40 ($p = 0.005$)*

Table 5
Multiple linear regression analysis for HRQoL at follow-up in patients with functional seizures. Significant findings ($p < 0.05$) are marked with *.

Variable	B	95% Confidence Interval	p-values
Emotional abuse documented in the medical records	−17.5	−31.8, −3.2	0.017*
Age	−0.9	−1.3, −0.5	<0.001*
Sex	15.5	−1.3, 32.4	0.07
Time to follow-up	1.0	−1.3, 3.3	0.4

follow-up. Participants with a history of emotional abuse rated their HRQoL at follow-up on average 17.5 points lower than those without such a history, for details, see Table 5.

4. Discussion

In this study, we found that a substantial proportion of the adverse life events identified within our research project via the self-report questionnaire (TEC) had not been documented in the clinical records. This is in concordance with studies from mental healthcare that report that less than one-third of abuse and neglect that is identified by researchers is documented in clinical records [23]. Within primary care, substantial under-recording of maltreatment and abuse has also been reported [24].

The rates of adverse life events as assessed by the TEC in our study are similar to results from previous meta-analysis of studies on childhood trauma in FS [25]. The meta-analysis also reported that lower rates of adverse events were recorded when the data were collected during clinical investigation as compared with self-report questionnaires [25]. The fact that the correlations we found in the present study were improved by the use of TEC data supports the view that the additional disclosures elicited by the TEC are not spurious.

The discrepancy between the prevalence of adverse life events as measured by self-report questionnaire and as documented in the medical records suggests that clinicians involved in the diagnostic work-up of patients with FS even at a tertiary epilepsy center may not systematically assess and document adverse life events. The reason for this is unclear. Neurologists, pediatricians, epileptologists, and even psychologists working at an epilepsy center may not feel appropriately trained to inquire about adverse life events. The results of a recent survey among neurology residency-program directors and neurology-residency graduates are consistent with this, suggesting that most programs lacked curriculum material on communication of the diagnosis of FS [26]. Our data also suggest that a neurology training curriculum should address ALE inquiry in patients with (suspected) FS, and that it may be of value to routinely supplement history taking with a self-report questionnaire on adverse life events. It is nonetheless important to acknowledge that a proportion of patients may not report ALE however the question is asked, and that a history of ALE is not mandatory for the diagnosis of FS (in DSM-5 as well as in clinical practice), however important it might be in subsequent psychological intervention.

Thorough information about the burden of prior ALE is valuable for clinicians involved in diagnosing patients with suspected FS, as there is a known, considerable treatment gap for patients with FS [27]. Patients with FS often present acutely to the emergency department. Their healthcare pathway has been described as a looping pathway, with repeated presentations in emergency settings, but low rates of documented diagnosis and referral for psychological treatment [28]. Evolving a common understanding of relevant predisposing, precipitating, perpetuating and protective factors, including ALE, together with the clinician and the patient might be crucial to break that loop and help more patients into treatment.

In our present study, a history of ALE was a risk factor for lower health-related quality of life at a mean follow-up of almost 6 years. There is limited information in the literature regarding the potential influence of abuse and other adverse life events on long-term outcomes. On study found no predictive effect of sexual abuse, physical abuse, and other psychological trauma on outcomes at 5–10 years after diagnosis [29]. Also, a study on a cohort with mixed FND did not identify an association between clinical outcomes and ALEs in childhood nor across the lifespan [30]. It has been reported that patients with functional seizures and childhood abuse found reduced adherence rates to psychotherapy [31], which again is likely to impact long-term outcome. Self-rated health is regarded to be an important health measurement that has been linked to morbidity and mortality [32,33].

In our cohort, the severity of previous adverse life events assessed with the TEC was significantly associated with measures of dissociation, HRQoL, and clinical measures such as seizure frequency and diagnostic delay. Our findings are in line with reports of a dose-dependent relation between the burden of antecedent ALE and symptom severity. A study from Scotland on patients with FS reported that those who reported sexual abuse had an earlier

onset of FS, a greater delay to diagnosis, and more severe FS semiologic features [6]. For patients with mixed FND [34] and with FS [35], a history of ALE has been linked to gray matter volume changes, suggesting developmental effects of adverse life events. As discussed in previous studies [5], the timing of the adverse life event occurred may also be relevant to its impact on outcomes, for example, whether it happened during formative developmental time in childhood or in adulthood. We did not examine this in the present study.

Our study is limited by our relatively small sample size and its recruitment from an epilepsy center, which increase vulnerability to selection bias, and may limit our findings' generalizability. The retrospective collection of self-report and medical data is also a limitation, as it is another potential source of bias. The wide range and variability of the follow-up time might also have a potential impact on outcome finding, even though we controlled for time-to follow-up in the analysis, this might indirectly influence outcome.

5. Conclusion

Recommendations on management of patients with FS suggest that treatment plans should be tailored on an individual basis [10]. Accurate and complete knowledge about prior adverse life events plays an important part in such tailoring. A common understanding, for the clinician and the patient, of relevant factors contributing to FS might be important to increase the proportion of patients with FS referred to and enrolling in psychological therapy, and thereby break the loop of repeated emergency room presentations. Our results reinforce the importance of ensuring that patients have the opportunity to disclose adverse life events within routine clinical assessment [36], and suggest that the supplemental use of appropriate questionnaires should routinely be part of the assessment process.

Disclosure

Author AV has served as a paid consultant for Arvelle Therapeutics. Author RD receives royalties from UpToDate. Author MIL has served as a paid consultant and lecturer for Arvelle, UCB, EISAI, and JAZZ – pharmaceuticals.

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CRediT authorship contribution statement

Antonia Villagrán: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Caroline Lund:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Roderick Duncan:** Conceptualization, Methodology, Writing – review & editing. **Morten Ingvar Lossius:** Conceptualization, Methodology, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Author AV has served as a paid consultant for Arvelle Therapeutics. Author CL received in 2009 the UCB Nordic Epilepsy Grant as support for this study. Author RD receives royalties from UpToDate. Author MIL has served as a paid consultant and lecturer for Arvelle, UCB, EISAI, and JAZZ – pharmaceuticals. None of the authors have any conflict of interest to disclose.

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Paper IV

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