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Psychiatric comorbidity in relation to clinical characteristics of epilepsy: A retrospective observational study

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ABSTRACT

Purpose: Prevalence of psychiatric disorders in people with epilepsy is high. However, diagnostic validity and information about the nature of the seizure disorders are often poor in population-based studies. In a well validated and classified patient sample, we investigated psychiatric comorbidity according to clinical characteristics.

Method: Participants in The Trøndelag Health Study (HUNT) with ≥ 2 diagnostic epilepsy codes during 1987–2019 were identified. Medical records were reviewed, and epilepsy was validated and classified according to ILAE. Psychiatric comorbidity was defined by ICD-codes.

Results: In 448 individuals with epilepsy, 35% had at least one psychiatric disorder (anxiety and related disorders 23%, mood disorders 15%, substance abuse and personality disorders 7%, and psychosis 3%). Comorbidity was significantly higher in women than in men ($p = 0.007$). The prevalence of psychiatric disorders was 37% in both focal and generalized epilepsy. In focal epilepsy, it was significantly lower when etiology was structural ($p = 0.011$), whereas it was higher when the cause was unknown ($p = 0.024$). Comorbidity prevalence was 35% both in patients achieving seizure freedom and in those with active epilepsy but 38% among 73 patients with epilepsy resolved.

Conclusion: Just over one third of people with epilepsy had psychiatric comorbidities. The prevalence was equal in focal and generalized epilepsy but was significantly higher in focal epilepsy of unknown cause compared to lesional epilepsy. Comorbidity was independent of seizure control at last follow-up but was slightly more common in those with resolved epilepsy, often having non-acquired genetic etiologies possibly linked to neuropsychiatric susceptibility.

1. Introduction

The epidemiological link between epilepsy and psychiatric disease is well established. Virtually all psychiatric disorders are more common in people with epilepsy than in those without. A recent review based on meta-analyses of population-based studies, affirms that people with epilepsy are burdened by a high prevalence of the major psychiatric disorders, including depression (23%), anxiety (20%) and psychosis

Abbreviations: HUNT, The Trøndelag Health Study; ASMs, antiseizure medications; ICD-9/ICD-10, The 9th/10th revision of the International Classification of Diseases; ILAE, International League Against Epilepsy; FTC, focal to bilateral tonic clonic seizure; IGE, idiopathic generalized epilepsy; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; GTCA, generalized tonic-clonic seizures alone.

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(5–7%) [1].

The risk for developing psychiatric comorbidity in epilepsy is complex. Various factors may interact in the same patient. The psychosocial consequences of the diagnosis of epilepsy, such as stigma and uncontrolled seizures along with negative psychotropic effects of antiseizure medications (ASMs) have traditionally been considered the most important underlying factors [2,3]. However, observational data also indicate bidirectional relationships, corroborating shared neurobiological mechanisms between epilepsy and psychiatric disease [1,4–7]. Nevertheless, large registry studies are often hampered by insufficient validity of the epilepsy diagnoses as well as scarce information about the clinical features of the various seizure disorders [8]. Therefore, studies with comprehensive and validated clinical information are needed to further elucidate the relationship between psychiatric comorbidity and individual epilepsy characteristics.

We aimed to investigate the nature of the associations between epilepsy and psychiatric disorders in a well validated and classified sample of patients with epilepsy. We specifically considered epilepsy type, age of seizure onset, etiology, and seizure prognosis.

2. Material and methods

2.1. Study population

This was a retrospective observational study using data from The Trøndelag Health Study (HUNT) [9], which is one of the largest epidemiological health studies conducted. It provides a unique database of information gathered from inhabitants of Trøndelag county in Norway. All inhabitants of the study area aged 20+ years were invited to participate in the HUNT2 (inclusion 1995–1997) and HUNT3 (inclusion 2006–2008). A total of 65,237 adults participated in HUNT2 (69.5% of those invited), 50,807 (54.1%) in HUNT3, rendering a total of 69,634 unique subjects with complete participation (including biological sampling) available for this study. Individuals with epilepsy diagnostic codes (ICD-10 G40.x or ICD-9 345.x) on at least two separate neurologic or pediatric outpatient appointments during 1987–2019 were identified.

2.2. Epilepsy validation and classification

Clinical information from medical records was reviewed between 2021 and 2022 to validate and classify the seizure disorders according to the current definition of epilepsy and the revised classification of the epilepsies by the International League Against Epilepsy (ILAE) [2,10]. The ascertainment procedure was supervised by an experienced clinical epileptologist (E.B.). Epilepsy characteristics were recorded, including age of onset, seizure types, etiology, and seizure control according to the most recent neurological follow-up. Active epilepsy was defined as seizures within the last five years [11]. Epilepsy resolved was defined as seizure freedom for $>$ 10 years with no ASMs for $>$ 5 years [2].

2.3. Psychiatric disorders

Psychiatric comorbidity was defined as disorders severe enough to need follow-up in psychiatric specialist health care services. ICD-codes from psychiatric departments in Trøndelag county registered in the period 1987–2022 were identified (ICD-10: F06-F69 and F80-F99; ICD-9: 291–319) for all patients with validated epilepsy. Diagnostic codes for intellectual disability (ICD-10: F70-F79; ICD-9: 317–319) and dementias (ICD-10: F01-F05; ICD-9: 290) were excluded as these conditions mainly receive services outside the specialist psychiatric health care. Psychiatric disorders were analyzed in relation to the various epilepsy characteristics. Number of psychiatric outpatient appointments and hospital admissions, and the durations of inpatient care were used to assess the overall psychiatric health care consumption in each subject.

2.4. Statistical analysis

Stata software package, Version 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for the data analysis. Descriptive analyses of the absolute (n) and relative (%) frequencies were calculated from nominal variables. Chi square (2×2) tests were used to compare epilepsy characteristics of the groups with and without psychiatric comorbidity. Analyses of significance were limited to subgroups with cell counts $>$ 5. Where relevant, risk difference (RD) was calculated as an effect measure. We used binary linear regression with psychiatric comorbidity as the dependent variable, and the relevant predictors as covariates, unadjusted, and adjusted for potential confounders (sex and age of onset of epilepsy), one at a time. The two-sample Wilcoxon rank-sum (Mann–Whitney U) test was used to compare continuous data deviating from a normal distribution and two-sample t-tests when not. A p-value $<$ 0.05 was considered significant.

2.5. Ethics

The study was approved by the Regional Committee for Medical Research Ethics, South East Norway (2018/1623).

3. Results

A total of 516 participants with diagnostic codes for epilepsy at a minimum of two occasions were identified from the 69,634 available participants of the HUNT2 and 3 studies. Sixty-eight patients (13%) were excluded due to apparent/suspected misdiagnosis of epilepsy or missing relevant medical data. Altogether 448 patients were included for analysis, giving a 0.64% period prevalence of validated epilepsy among the HUNT2 and 3 participants.

3.1. Distribution of psychiatric comorbidity in relation to epilepsy characteristics

Table 1 displays the distribution of sex, seizure onset age, epilepsy type and degree of achieved seizure control at last follow-up in relation to psychiatric comorbidity of included individuals. Any psychiatric disorder was recorded in 35% of patients during the study period (1987–2022). Fifteen percent were registered with only one psychiatric disorder, 10% were registered with two, 6% with three and 4% of patients were registered with more than three unique diagnoses. The rate of patients with psychiatric disorders was highest in those with seizure onset $<$ 18 years (40%) and those with onset between 40 and 59 years (40%) and was significantly lower in those diagnosed after 60 years (25%) (χ^2 (1) = 4.05, p = 0.044) with an absolute RD of 12% (95% CI [−0.24, −0.01]). A significantly larger proportion of women had psychiatric comorbidity as compared to men (χ^2 (1) = 7.16, p = 0.007), RD 12% (95% CI [0.03, 0.21]). The prevalence of comorbidity was similar in focal and generalized epilepsy (37%) but was significantly lower in those with an unknown epilepsy type (15%) (χ^2(1) = 9.01, p = 0.003) with an absolute RD of 22% (95% CI [−0.33, −0.11]). Proportion of psychiatric comorbidity was equal in patients achieving seizure freedom and in those with active epilepsy. A large part of patients with complete seizure control during the last five years had epilepsy resolved (73/206, 35%). Psychiatric comorbidity was recorded in 38% of these patients.

Table 2 shows the frequency and distribution of psychiatric ICD-codes according to epilepsy type among all patients. Anxiety and related disorders were most common (23%), followed by mood disorders (15%), substance abuse and personality disorders (both 7%), and psychosis (3%). While not significantly different, anxiety disorders were slightly more frequent in focal epilepsy than in generalized epilepsy, whereas personality disorders were more common in generalized epilepsy.

Table 1
Psychiatric comorbidity according to epilepsy characteristics.

Characteristics	Total	Without psychiatric comorbidity	With psychiatric comorbidity	p-value
N (%)	448 (100)	293 (65)	155 (35)	
Mean age at start of HUNT2[a], years ±SD	39.4 ± 16.7	41.6 ± 17.2	35.4 ± 15.1	***<0.001***
Median onset age[b], years (IQR)	26 (13–54)	29 (14–56.5)	21 (12–50)	0.056
Distribution of onset age, n (%)				
< 18 years	159 (39)	95 (60)	64 (40)	0.065
18–39 years	93 (23)	66 (71)	27 (29)	0.182
40–59 years	80 (20)	48 (60)	32 (40)	0.277
≥ 60 years	73 (18)	55 (75)	18 (25)	***0.044***
Sex, n (%)				***0.007***
Women	204 (46)	120 (59)	84 (41)	
Men	244 (54)	173 (71)	71 (29)	
Epilepsy type, n (%)				
Focal	337 (75)	213 (63)	124 (37)	0.088
Generalized	60 (13)	38 (63)	22 (37)	0.717
Combined	4 (1)	2 (50)	2 (50)	
Unknown	47 (11)	40 (85)	7 (15)	***0.003***
Seizure control at last follow-up, n (%)				
Seizures last five years	186 (42)	121 (65)	65 (35)	0.896
Seizures last year	99 (22)	64 (65)	35 (35)	0.858
Seizure free > 5 years	206 (46)	133 (65)	73 (35)	0.731
Epilepsy resolved	73 (16)	45 (62)	28 (38)	0.460
Unknown	56 (13)	39 (70)	17 (30)	0.476

Statistics: Chi-square (2×2) tests were used to calculate all p-values except for comparison of age.
[a] Normal distribution, two sample *t*-test.
[b] Non-normal distribution, Mann-Whitney U test. Onset age available in 405/448 patients: $n = 264$ without psychiatric comorbidity; $n = 141$ with psychiatric comorbidity.

Table 2
Distribution of psychiatric ICD-diagnoses according to type of epilepsy.

ICD diagnoses	All $n = 448$ (%)	Focal $n = 337$ (%)	Generalized $n = 60$ (%)	Combined $n = 4$ (%)	Unknown $n = 47$ (%)
Organic etiology[a]	36 (8)	30 (9)	4 (7)	1 (25)	1 (2)
Substance use[b]	30 (7)	24 (7)	3 (5)		3 (6)
Psychotic disorders[c]	15 (3)	11 (3)	3 (5)		1 (2)
Mood disorders[d]	69 (15)	53 (16)	11 (18)	1 (25)	4 (9)
Anxiety disorders etc.[e]	101 (23)	86 (26)	11 (18)		4 (9)
Personality disorders[f]	30 (7)	22 (7)	7 (12)		1 (2)
Other[g]	34 (8)	23 (7)	9 (15)		2 (4)

Psychiatric comorbidity was present in 155 (35%) patients, several were registered with more than one psychiatric disorder.
[a] ICD-10: F06-F09; ICD-9: 293, 294, 310.
[b] ICD-10: F10-F19; ICD-9: 291, 292, 303–305.
[c] ICD-10: F20-F29; ICD-9: 295, 297, 298.
[d] ICD-10: F30-F39; ICD-9: 296, 311.
[e] ICD-10: F40-F48; ICD-9: 300, 306, 308, 309.
[f] ICD-10: F60-F69; ICD-9: 301, 302.
[g] ICD-10: F50-F59, F80-F89, F90-F99; ICD-9: 316, 299, 307, 312–316.

3.2. Focal epilepsy

Table 3 gives an account of focal epilepsy characteristics in relation to psychiatric comorbidity. In this group, age of seizure onset was significantly lower in those with psychiatric comorbidity ($z = 2.10$, $p = 0.035$); in childhood onset epilepsy, comorbidity occurred in 45%. Psychiatric disorders were significantly less common in the group of patients with the highest age at seizure onset (RD 13%, 95% CI [−0.26, −0.01]). Moreover, they were significantly less common in those with structural etiology (χ^2 (1) = 6.51, $p = 0.011$) with an absolute RD of 13% (95% CI [−0.24, −0.03]) and more common when the cause was unknown (χ^2 (1) = 5.10, $p = 0.024$), RD 12% (95% CI [0.02, 0.22]). The RDs were substantially unchanged when adjusted for sex and onset age of epilepsy. In childhood onset epilepsy, 28 of 55 patients with unknown etiology had psychiatric comorbidity (51%) in contrast to 8 of 24 patients with structural abnormalities (33%) (non-significant).

The occurrence of focal to bilateral tonic clonic seizures (FTC) was also significantly associated with psychiatric comorbidity compared to

Table 3
Psychiatric comorbidity in patients with focal epilepsy.

Characteristics	Focal epilepsy			
	Total	Without psychiatric comorbidity	With psychiatric comorbidity	p-value
N (%)	337 (100)	213 (63)	124 (37)	
Mean age at start of HUNT2[a], years ±SD	41.9 ± 16.3	44.1 ± 16.9	38.2 ± 14.6	***0.001***
Median onset age[b], years (IQR)	36.5 (16–57)	39 (17–61)	30 (14–53)	***0.035***
Distribution of onset age, n (%)				
< 18 years	87 (29)	48 (55)	39 (45)	0.064
18–39 years	71 (24)	49 (69)	22 (31)	0.249
40–59 years	76 (25)	44 (58)	32 (42)	0.263
≥ 60 years	68 (21)	50 (74)	18 (26)	***0.046***
Sex, n (%)				***0.045***
Women	158 (47)	91 (58)	67 (42)	
Men	179 (53)	122 (68)	57 (32)	
Epilepsy etiology, n (%)				
Structural	172 (51)	120 (70)	52 (30)	***0.011***
Acquired other	12 (4)	6 (50)	6 (50)	0.334
Non-acquired genetic[c]	6 (2)	4 (67)	2 (33)	
Unknown	147 (44)	83 (56)	64 (44)	***0.024***
Seizure type, n (%)				***0.034***
Only focal	108 (32)	77 (71)	31 (29)	
FTC	229 (68)	136 (59)	93 (41)	
Seizure control at last follow-up, n (%)				
Seizures last five years	148 (44)	95 (64)	53 (36)	0.740
Seizures last year	79 (23)	52 (66)	27 (34)	0.581
Seizure free > 5 years	137 (41)	83 (61)	54 (39)	0.409
Epilepsy resolved	39 (12)	22 (56)	17 (44)	0.349
Unknown	52 (15)	35 (67)	17 (33)	0.505

FTC, focal to bilateral tonic-clonic seizure.
Statistics: Chi-square (2×2) tests were used to calculate all p-values except for comparisons of age.
[a] Normal distribution, two sample *t*-test.
[b] Non-normal distribution, Mann-Whitney U test. Onset age available in 302/337 patients: $n = 191$ without psychiatric comorbidity; $n = 111$ with psychiatric comorbidity.
[c] 5/6 Self-limited focal epilepsies; 1/6 Autosomal dominant sleep-related hypermotor epilepsy.

those with focal seizures alone (χ^2 (1) = 4.47, p = 0.034). The RD of 12% was not confounded by sex but was reduced to 8% when adjusted for onset age. Of the 39 patients with epilepsy resolved, 44% had psychiatric comorbidity compared to 36% of the 148 patients with active epilepsy.

3.3. Generalized epilepsy

Table 4 displays epilepsy characteristics of generalized epilepsy according to psychiatric comorbidity. Median epilepsy onset age was 13 years, and childhood seizure onset occurred in 85% of patients, of which 39% had psychiatric disorders. Idiopathic generalized epilepsies (IGE) occurred in 73% of those with generalized epilepsy. The highest occurrence of psychiatric comorbidity was found in childhood absence epilepsy (CAE) (54%), followed by juvenile absence epilepsy (JAE) (43%), juvenile myoclonic epilepsy (JME) (29%) and the lowest rate was found in generalized tonic-clonic seizures alone (GTCA) (20%).

Table 4
Psychiatric comorbidity in patients with generalized epilepsy.

Characteristics	Generalized epilepsy			
	Total	Without psychiatric comorbidity	With psychiatric comorbidity	p-value
N (%)	60 (100)	38 (63)	22 (37)	
Median age at start of HUNT2[a], years (IQR)	26 (17–34.5)	29 (18–38)	22 (13–30)	0.062
Median onset age[b], years (IQR)	13 (7–16)	13.5 (6.5–16.5)	12.5 (9–14)	0.765
Distribution of onset age, n (%)				0.757
< 18 years	49 (85)	30 (61)	19 (39)	
≥ 18 years	9 (15)	6 (67)	3 (33)	
Sex, n (%)				0.051
Women	31 (52)	16 (52)	15 (48)	
Men	29 (48)	22 (76)	7 (24)	
Epilepsy syndrome, n (%)				
IGE	44 (73)	28 (64)	16 (36)	0.936
CAE	13 (22)	6 (46)	7 (54)	0.146
JAE	7 (12)	4 (57)	3 (43)	
JME	14 (23)	10 (71)	4 (29)	
GTCA	10 (17)	8 (80)	2 (20)	
Other[c]	3 (5)	1 (33)	2 (67)	
Unknown	13 (22)	9 (64)	5 (36)	0.933
Seizure type, n (%)				
Only motor	31 (52)	22 (71)	9 (29)	0.205
Only absence	10 (17)	4 (40)	6 (60)	
Both motor and absence	18 (30)	11 (61)	7 (39)	0.815
Unknown	1 (2)	1 (100)		
Seizure control at last follow-up, n (%)				
Seizures last five years	24 (40)	16 (67)	8 (33)	0.662
Seizures last year	11 (18)	7 (64)	4 (36)	
Seizure free for > 5 years	35 (58)	21 (60)	14 (40)	0.526
Epilepsy resolved	16 (27)	9 (56)	7 (44)	0.492
Unknown	1 (2)	1 (100)		

IGE, idiopathic generalized epilepsy; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; GTCA, generalized tonic clonic seizures alone.
Statistics: Chi-square (2×2) tests were used to calculate all p-values except for comparisons of age.
[a] Non-normal distribution; Mann-Whitney U test.
[b] Non-normal distribution; Mann-Whitney U test. Onset age available in 58/60 patients: n = 36 without psychiatric comorbidity; n = 22 with psychiatric comorbidity.
[c] Jeavons syndrome, myoclonic-atonic, myoclonic-absence.

3.4. Psychiatric health care consumption

In Table 5, we attempted to grade the severity of psychiatric comorbidity according to psychiatric health care consumption. Mann-Whitney U tests showed no significant differences between focal and generalized epilepsy. However, > 50 outpatient visits during the study period indicate severe and longstanding psychiatric problems in 15% of patients with focal epilepsy and comorbidity and 27% of patients with generalized epilepsy. This corresponds to a higher mean number of hospital admissions and longer durations of inpatient care in generalized epilepsies.

3.5. Epilepsy resolved

Table 6 provides an overview of the 73 patients with epilepsy resolved. The majority had childhood onset seizures (69%), of which 45% had psychiatric comorbidity. Structural etiology was seen in 10 of those with focal epilepsy, five had psychiatric comorbidity. Six had received successful resective epilepsy surgery (3 low grade tumors, 2 vascular malformations, 1 hippocampal sclerosis/focal cortical dysplasia, 1 temporal lobe cyst); two had psychiatric comorbidity. Twenty-one had focal epilepsy with unknown etiology, of which nine had comorbidity. Five patients were classified with presumed genetic epilepsy in the form of self-limited focal epilepsy of childhood, only one had been diagnosed with a psychiatric disorder in the form of adjustment disorder with anxiety.

Psychiatric comorbidity was found in half of the patients with resolved IGE (7/14); 6/9 with CAE and 1/3 with JAE. There were no psychiatric disorders recorded in the two patients with either resolved JME or GTCA.

Thirty-four of the 47 patients with an unknown type of epilepsy had been seizure free for > 5 years (72%); epilepsy was resolved in 18 (38%).

4. Discussion

Based on diagnostic codes in the specialist health care services, our findings are consistent with previous estimates of one third of patients with epilepsy having some form of psychiatric comorbidity [1]. In a recent Danish registry study, comorbidity was identified in 37% of people with epilepsy based on ICD-10 codes or prescriptions of drugs for psychiatric disorders during a 5-year period, compared to 16% in the general population [8]. In the present study, 35% were recorded with psychiatric comorbidity (excluding intellectual disability and dementia), of which anxiety disorders were most common (23%), followed by mood disorders (15%), substance use (7%), personality disorders (7%), and psychosis (3%). Our findings corroborate that psychiatric illness in epilepsy is more common in women than in men [12] reflecting the distribution in the general population [13–16]. Our data further demonstrate that age of seizure onset in focal epilepsy is lower in those with comorbidity compared to those without. In a nationwide Norwegian registry study taking place from 2008 to 2013, only 16% of children with "uncomplicated" epilepsy (leaving out neurological/developmental disabilities) had been diagnosed with psychiatric comorbidity, with a different distribution of the disorders (ADHD 8%, other behavioral/emotional disorders 7%, anxiety and depression 2%) [17]. Taken together, this suggests that an increased rate of overt psychiatric illness may manifest with age in people with early onset epilepsy.

4.1. Epilepsy type

The prevalence of psychiatric illness was equal in focal and generalized epilepsy, but lower in the smaller group with epilepsy of unknown type. Some patients classified with epilepsy of unknown type may have

Table 5
Severity of psychiatric comorbidity based on psychiatric health care consumption.

Psychiatric profile	Type of epilepsy				
	All $n = 155$ (%)	Focal $n = 124$ (%)	Generalized $n = 22$ (%)	Combined $n = 2$ (%)	Unknown $n = 7$ (%)
Number of outpatient visits					
1–10	77 (50)	67 (54)	7 (32)	2 (100)	1 (14)
11–50	50 (32)	36 (29)	9 (41)		5 (71)
> 50	26 (17)	19 (15)	6 (27)		1 (14)
Mean ±SD	31.3 ± 61.0	29.2 ± 63.3	44.2 ± 58.5	4.5	35.1 ± 14.6
Median (IQR)	10 (2–36)	8 (2–29)	23 (3–69)	4.5 (1–8)	36 (25–45)
Number of hospital admissions					
At least one	47 (30)	35 (28)	9 (41)		3 (43)
1–3	31 (20)	22 (18)	7 (32)		2 (29)
> 3	16 (10)	13 (11)	2 (9)		1 (14)
Mean ±SD	1.2 ± 3.1	1.1 ± 2.5	2.0 ± 5.6		1.1 ± 1.9
Median (IQR)	0 (0–1)	0 (0–1)	0 (0–1)		0 (0–2)
Average duration of hospitalizations (days)					
Mean ±SD	18.2 ± 14.5	17.6 ± 14.4	23.5 ± 16.0		10.0 ± 6.2
Median (IQR)	13.6 (6–27)	12.7 (6–27)	23.4 (18–27)		12 (3–15)

Table 6
Psychiatric comorbidity in patients with epilepsy resolved.

Characteristics	Epilepsy resolved			
	Total	Without psychiatric comorbidity	With psychiatric comorbidity	p-value
N (%)	73 (100)	45 (62)	28 (38)	
Median age at start of HUNT2[a], years (IQR)	28 (18–40)	28 (18–41)	28.5 (16.5–39.5)	0.763
Median onset age[b], years (IQR)	12 (7–21.5)	13.5 (9–24)	9.5 (7–16)	0.131
Distribution of onset age, n (%)				
< 18 years	47 (69)	26 (55)	21 (45)	0.102
≥ 18 years	21 (31)	16 (76)	5 (24)	
Sex, n (%)				0.130
Women	31 (42)	16 (52)	15 (48)	
Men	42 (58)	29 (69)	13 (31)	
Epilepsy type, n (%)				
Focal	39 (53)	22 (56)	17 (44)	0.325
Structural	10 (14)	5 (50)	5 (50)	
Acquired other	3 (4)	1 (33)	2 (67)	
Non-acquired genetic/SeLFE	5 (7)	4 (80)	1 (20)	
Unknown etiology	21 (29)	12 (57)	9 (43)	0.615
Generalized	16 (22)	9 (56)	7 (44)	0.616
IGE	14 (19)	7 (50)	7 (50)	0.319
CAE	9 (12)	3 (33)	6 (67)	
JAE	3 (4)	2 (67)	1 (33)	
JME	1 (1)	1 (100)		
GTCA	1 (1)	1 (100)		
Other	2 (3)	2 (100)		
Unknown	18 (25)	14 (78)	4 (22)	

SeLFE, self-limited focal epilepsies of childhood; IGE, idiopathic generalized epilepsy; CAE, childhood absence epilepsy; JAE, juvenile absence epilepsy; JME, juvenile myoclonic epilepsy; GTCA, generalized tonic clonic seizures alone.
Statistics: Chi-square (2×2) tests were used to calculate all p-values except for comparisons of age.
[a] Non-normal distribution; Mann-Whitney U test.
[b] Non-normal distribution; Mann-Whitney U test. Onset age available in 68/73 patients: $n = 42$ without psychiatric comorbidity; $n = 26$ with psychiatric comorbidity.

had IGE in the form of GTCA with absent or inconspicuous EEG abnormalities [10], often having a more favorable seizure and psychosocial outcome than other IGE syndromes [18,19].

In focal epilepsy, localized neurobiological abnormalities and neuropsychological deficits, such as in temporal lobe epilepsy, may cause a vulnerability to developing psychiatric symptoms. Temporal lobe epilepsy is the most common focal epilepsy but could not be strictly identified in this study as standard EEG findings were sometimes ambiguous and defined ictal onset was not available for most patients. Comorbidity in the form of mood disorders, anxiety and psychosis is high and well established, and may altogether affect more than half of the patients with temporal lobe epilepsy [20]. Interestingly, we found that psychiatric comorbidity in focal epilepsy was significantly associated with the occurrence of FTC when compared to only focal seizure semiology, possibly due to involvement of a broader neuronal network.

The majority of patients with generalized epilepsy had IGE. While cognitive abilities are essentially normal in IGE, it is well known that this group of epilepsies can be associated with poor social outcome, including decreased academic achievement, increased risk of psychiatric, emotional, and behavioral problems [19,21–23]. Accordingly, personality disorders were somewhat more common in generalized compared to focal epilepsies. Interestingly, patients with generalized epilepsies tended to have more severe psychiatric disease as judged by the number of psychiatric outpatient appointments and hospital admissions, as well as the duration of inpatient care.

It has been emphasized that young adults with a history of typical absence seizures often have poor psychosocial outcomes leading to the perception of CAE as sometimes “a wolf in sheeps’ clothing” [24]. We found psychiatric comorbidity in 54% of patients with CAE and in 43% with JAE, though the number of individuals was small. A meta-analysis investigating patients with absence epilepsy suggested a strong correlation with depression and anxiety with a bidirectional relationship [25]. In the largest group within IGE, JME, personality features such as impulsivity, risk-taking behavior, and impaired planning and organizing ability are common [26–28]. However, the representation of this syndrome was disproportionally low in the present cohort.

4.2. Seizure control

It has been repeatedly emphasized that patients with active epilepsy have poorer psychosocial outcomes than those achieving seizure control [3,29]. Stigma, ictal effects, and the burden of ASMs are factors which may predispose to psychiatric comorbidity. On the other hand, studies have suggested that pre-existing neuropsychiatric symptomatology is associated with a poor response to ASM treatment [30,31]. Unexpectedly, in this study based on historical data, prevalence of psychiatric comorbidity was equal in patients achieving seizure control for more than five years and in those with active epilepsy. Yet, more surprisingly, epilepsy resolved was even more associated with psychiatric comorbidity. In a recent Brazilian study, the authors were also struck by an increased psychiatric comorbidity in patients with seizure control [32]. An explanation might be that these seizure disorders often represent

non-acquired epilepsies with genetic background harboring a susceptibility to both seizures and psychiatric disease.

More than one third of the present seizure free patients fulfilled the criteria for epilepsy resolved. This study is unique by the identification of a cohort of 73 such cases. The present results support the view that epilepsy and various neuropsychiatric conditions may share pathogenic pathways independent of ictal and ASM adverse effects, which may underlie the bidirectionality of epilepsy and psychiatric illness [4,6].

One may speculate whether the high prevalence of psychiatric comorbidity in individuals with resolved epilepsy might be related to the postulated antagonism between epilepsy and psychiatric disorders. This is thought to underlie the phenomenon of "forced normalization" or alternative psychosis as well as the effect of electroconvulsive therapy in patients with psychiatric disease [33]. However, the exact temporal relationship between seizure control and the onset of psychiatric disorders could not be further explored in the present dataset, but only two of the six patients with resolved epilepsy due to successful resective surgery were recorded with psychiatric comorbidity.

In this study, nearly 70% of patients with epilepsy resolved had seizure onset in childhood. Camfield & Camfield reviewed the adult outcome of various childhood epilepsies and found remission of seizures in 50–75% of the patients. The rate of adult psychiatric comorbidity was high even in patients with normal intelligence, except for those with self-limited epilepsies with centrotemporal spikes which usually have an excellent prognosis, and was largely unrelated to seizure control [34]. Several other studies report that even long resolved epilepsies of childhood may be associated with poor psychosocial and neuropsychiatric outcome in adult life [24,35,36]. Apart from a shared neurobiological susceptibility, disadvantageous psychological and educational consequences of childhood epilepsy may contribute to psychiatric comorbidity.

4.3. The genetic overlap between epilepsy and psychiatric illness

Recent advances in the field of neurobiology are currently underpinning the role of genetic backgrounds for the development of epilepsy [37]. Copy number variants have increasingly been identified across a range of neurodevelopmental and neuropsychiatric disorders, including epilepsy, and the number of single genetic variants in epilepsy syndromes with cognitive and behavioral comorbidities is growing. In many epilepsies, a complex genetic architecture with multiple genetic variants may act in concert [38,39].

Half of the present patients with resolved genetic generalized epilepsies (IGE) developed psychiatric disorders. The genetic expression sometimes appears to be age dependent leading to resolved epilepsy in adolescence. After seizure remission, an alternative expression of dysfunctional neuronal networks in the form of neuropsychiatric symptoms may develop or persist. The high rate of psychiatric comorbidity in our patients with resolved epilepsy no longer afflicted by the stigma and life restrictions of recurrent seizures or the burden of ASM treatment supports this theory.

Interestingly, the findings in this study and other studies [24,25] suggest a particular predisposition to psychiatric comorbidity in IGE with absences. Moreover, we found that comorbidity was significantly less common in patients with focal epilepsies with lesional etiology in contrast to those with unknown causes, who had significantly more psychiatric disorders. This could not alone be ascribed to a younger age of seizure onset in patients developing comorbidity. Altogether, these findings indicate a stronger background of unidentified neuropsychiatric susceptibility factors in focal epilepsy of obscure compared to structural etiology, as also previously suggested in patients discharged from psychiatric hospital in Stockholm [40]. An extensive genome-wide association study based on pooled data recently revealed a considerable polygenic overlap between common epilepsies and major psychiatric disorders demonstrating complex genetic relationships, in line with the clinical bidirectionality of these conditions. A stronger association was found for generalized (IGE) than for focal epilepsies in general [39]. Further large-scale collaborative genetic research in well phenotyped individuals is called for.

The predisposition to psychiatric adverse reactions from ASMs may also be genetically driven. One study suggested that levetiracetam-related irritation and aggression are associated with single nucleotide polymorphisms linked to dopaminergic activity [41]. Recently, it has been further shown that the polygenic risk score for schizophrenia is predictive of psychotic reactions from levetiracetam [42]. These studies underscore that combined factors may be involved in the development of psychiatric comorbidity.

4.4. Limitations and strength

Several shortcomings of this study must be addressed. It is limited to a selected part of the population of Nord-Trøndelag, as only individuals who actively signed up for the HUNT2 and 3 surveys were included, likely leaving out many people with epilepsy, cognitive deficits and severe and incapacitating psychiatric comorbidities. The number of patients with generalized epilepsies was surprisingly low, possibly due to the strict reclassification according to the revised 2017 ILAE epilepsy classification, assigning many with only tonic-clonic seizures and inconspicuous EEG and MRI findings to the group with unknown type of epilepsy [10]. The proportion of patients with JME, the most common generalized epilepsy type among adolescents and adults, was particularly low. A subset of these patients is affected by executive function deficits [26], possibly rendering them less prone to partake in voluntary studies, which require planning, organization, and attendance. These personality traits are partly shared by other patients with IGE [19].

This dataset did not allow for an accurate correlation of the timing of seizure remission and the onset of psychiatric comorbidity. We did not have access to psychiatric diagnoses prior to 1987 and could not assess the true onset of psychiatric symptoms based on the first specialist health care diagnostic codes. Moreover, the exact date of the last seizure was sometimes difficult to retrieve from medical records in patients with long-term seizure control. However, the vast majority of patients with resolved epilepsy had seizure onset in childhood. Nevertheless, this study demonstrates a high rate of psychiatric comorbidity in epilepsy with a favorable seizure prognosis.

Finally, the identification of psychiatric comorbidity was based solely on ICD codes from the specialist health services. This method may have low sensitivity for many psychiatric disorders occurring in people with epilepsy [1,8], as they may be treated in primary care only or wrongly considered to be part of the unspecific psychosocial consequences of having an active seizure disorder. Moreover, the presence of acute or chronic precipitating factors could not be investigated, and it is unknown whether some of the psychiatric episodes were triggered by the introduction of specific ASMs or epilepsy surgery.

A strength is the meticulous review of historical medical records excluding individuals with misdiagnosed and non-documented epilepsy, such as acute symptomatic seizures, psychogenic non-epileptic seizures, convulsive syncope, hyperventilation syndrome as well as miscellaneous unclassified paroxysmal events, resulting in a large cohort of well validated and classified patients considered to have true epilepsy.

5. Conclusion

We have confirmed that just over one third of people diagnosed with epilepsy had psychiatric comorbidities. The prevalence in focal and generalized epilepsy did not differ, but it was significantly higher in patients with focal epilepsy of unknown cause compared to those with lesional epilepsy. Surprisingly, we found that psychiatric disorders were equally frequent in patients achieving >5 years of seizure freedom and in those with active epilepsy, and slightly more common in those with epilepsy resolved, a group which often have non-acquired genetic etiology possibly linked to a susceptibility to psychiatric disease.

This study underscores the need for increased clinical awareness of the development of psychiatric comorbidities in people with seizure disorders across the age span. Targeted comprehensive interdisciplinary care is needed. More systematic clinical and genetic research is required to shed light on the vulnerability for psychiatric illness in individuals ever diagnosed with epilepsy.

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Declarations of Competing Interest

The authors have no competing interests to declare.

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