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Doctoral thesis

**NTNU**
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
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Department of Neuromedicine and Movement Science

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**Psykiske lidelser hos pasienter med epilepsi**

Epilepsi er et paraplybegrep som omfatter en rekke tilstander med forskjellige årsaker, ytringsform og prognose. Fellesnevneren er spontane, uprovoserte epileptiske anfall som skyldes en vedvarende tilstand i hjernen som disponerer for gjentagende anfall. Epilepsi er i tillegg assosiert med økt forekomst av psykiske lidelser, som kan påvirke prognose og behandling av epilepsien.

Denne avhandlingen omfatter fire studier som har undersøkt forholdet mellom epilepsi og psykiske symptomer. Vi brukte populasjonsbaserte registerdata for å undersøke forekomst og direksjonalitet mellom epilepsi og psykiske lidelser (Artikkel I og III). Vi har også inkludert en kasuistikk som illustrerer det komplekse forholdet mellom epileptiske anfall og psykiske symptomer (Artikkel II). Til slutt har vi gjennomført en studie hvor vi så på hvilke pasienter med epilepsi som hadde størst risiko for psykiatrisk samsykelighet (Artikkel IV).

Basert på tall fra Norsk pasientregister og Reseptregisteret fant vi at hhv 0.9% og 0.8% av befolkningen hadde fått en epilepsidiagnose (Artikkel I og III). Pasienter med epilepsi hadde en høyere risiko for rusmiddellidelser, bipolare lidelser og psykoselidelser. Forekomsten var høyere uavhengig av aldersgruppe og kjønn (Artikkel I). I Artikkel III bekreftet vi et bidireksjonalt forhold mellom epilepsi og psykose (gjensidig økt risiko), men noe overraskende fant vi at over halvparten av pasientene med begge lidelser hadde blitt behandlet for psykose først (56%).

I Artikkel II beskriver vi hvordan epileptiske anfall med psykoselignende symptomer kan arte seg. Ut fra anfallsbeskrivelse og undersøkelsesfunn foreslår vi at komplekse bilaterale visuelle hallusinasjoner med gjenkjennbare elementer kan være knyttet til epileptisk aktivitet i nevronale cellenettverk som kobler visuell informasjon med navigering, stedsans og hukommelse.

I Artikkel IV gikk vi gjennom journalene til deltagere i Helseundersøkelsen i Trøndelag som hadde hatt epilepsioppfølging minst 2 ganger. Blant 448 pasienter med bekreftet epilepsi hadde 35% minst en psykisk lidelse i tillegg. Forekomsten var lik hos de med fokal epilepsi og de med generalisert epilepsi, men lavere hos de med ukjent type epilepsi. Hos de med fokal epilepsi fant vi en høyere risiko blant kvinner, de med ukjent årsak til epilepsien, de med yngre alder ved debut og de med anfall som utviklet seg til bilaterale tonisk-kloniske anfall. Vi fant også at anfallsfrie pasienter hadde minst like høy forekomst sammenlignet med pasienter med aktiv epilepsi. Våre funn støtter at det kan foreligge en felles underliggende sårbarhet for å utvikle begge tilstander.

Denne avhandlingen bidrar til økt innsikt i forekomst av psykiske lidelser ved epilepsi, og økt kunnskap om risikofaktorer for slik samsykelighet. Kunnskapen kan bidra til bedre helhetlig og tverrdisiplinær behandling som kan påvirke disse pasientenes livskvalitet.

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## List of papers

Paper I | **Substance use disorders and psychotic disorders in epilepsy: A population-based registry study**

Bakken, I.J., Revdal, E., Nesvåg, R., Brenner, E., Knudsen, G.P., Suren, P., Ghaderi, S., Gunnes, N., Magnus, P., Reichborn-Kjennerud, T., Camilla, S., Trogstad, L.I., Haberg, S.E. and Brodtkorb, E. Substance use disorders and psychotic disorders in epilepsy: A population-based registry study. *Epilepsy Res* 2014; **108**:1435-1443.

Paper II | **Experiential seizures related to the hippocampal-parahippocampal spatial representation system**

Revdal, E., Arntsen, V., Doan, T.P., Kvello-Alme, M., Kvistad, K.A., Bråthen, G. and Brodtkorb, E. Experiential seizures related to the hippocampal-parahippocampal spatial representation system. *Epilepsy & Behavior Reports* 2020; **14**:100386.

Paper III | **Bidirectionality of antiseizure and antipsychotic treatment: A population-based study**

Revdal, E., Morken, G., Bakken, I.J., Bråthen, G., Landmark, C.J. and Brodtkorb, E. Bidirectionality of antiseizure and antipsychotic treatment: A population-based study. *Epilepsy Behav* 2022; **136**:108911.

Paper IV | **Psychiatric comorbidity in relation to clinical characteristics of epilepsy: A retrospective observational study**

Revdal, E., Kolstad, B.P., Winsvold, B.S., Selmer, K.K., Morken, G. and Brodtkorb, E. Psychiatric comorbidity in relation to clinical characteristics of epilepsy: A retrospective observational study. *Seizure* 2023; **110**:136-143.

## Acronyms and abbreviations

| | |
|---|---|
| APDs: | Antipsychotic drugs |
| ASMs: | Antiseizure medications |
| ATC code: | Anatomical Therapeutic Chemical code |
| CAE: | Childhood absence epilepsy |
| DDD: | Defined Daily Doses |
| DEE: | Developmental and epileptic encephalopathies |
| DSM: | Diagnostic and Statistical Manual of Mental Disorders |
| EEG: | Electroencephalography |
| FTC: | Focal to bilateral tonic clonic seizures |
| GAD-7: | Generalized Anxiety Disorder-7 |
| GTC: | Generalized tonic-clonic seizures |
| GTCA: | Generalized tonic-clonic seizures alone |
| GWAS: | Genome-wide association study |
| HUNT: | The Trøndelag Health Study |
| ICD-9/ICD-10: | The $9^{th}$/$10^{th}$ revision of the International Classification of Diseases |
| ICPC-2: | The $2^{nd}$ edition of the International Classification of Primary Care |
| IDD: | Interictal dysphoric disorder |
| IGE: | Idiopathic generalized epilepsies |
| ILAE: | International League Against Epilepsy |
| JAE: | Juvenile absence epilepsy |
| JME: | Juvenile myoclonic epilepsy |
| MRI: | Magnetic resonance imaging |
| NorPD: | The Norwegian Prescription Database |
| NPR: | Norwegian Patient Registry |
| NPV: | Negative predictive value |
| PPV: | Positive predictive value |
| TLE: | Temporal lobe epilepsy |

## Summary

Epilepsy is a disease of the brain defined by recurrent epileptic seizures with various clinical presentations. The disorder has neurobiological, cognitive, psychological, and social consequences. Many of the epilepsies are associated with comorbidities with a potential to affect the course and treatment of the disorder. Over the last couple of decades there has been increasing awareness of an association between psychiatric disorders and epilepsy. Psychiatric symptoms in epilepsy were long regarded as mere consequences of the epilepsy and its treatment. However, research has revealed a bidirectional relationship between seizures and psychiatric disorders, meaning that the presence of one increases the risk of developing the other.

This thesis comprises four studies on the relationship between epilepsy and psychiatric symptoms. Paper I and III are population-based retrospective observational studies investigating prevalence and directionality. Paper II is a case report illustrating the complexity of ictal psychiatric symptoms and Paper IV is a retrospective case-control study where clinical epilepsy predictors of psychiatric comorbidity are in focus.

In Paper I, we used diagnostic codes from the specialist health care services to compare the proportion and age and sex distribution of substance use disorders and psychotic disorders among adults with epilepsy to the population without epilepsy. Overall, 0.9% of Norwegian adults had been registered with epilepsy in somatic hospitals during 2008-2012. We found an elevated adjusted relative risk for substance use disorders, bipolar disorders, and psychoses in people with epilepsy. The prevalence of these disorders was higher in all age-groups and both sexes of people with epilepsy compared to the population without epilepsy, it was also higher when compared to patients with diabetes, another chronic disorder.

Paper II is a case report where we explored ictal psychiatric symptoms in the form of complex visual pseudo-hallucinations. The ictal symptoms ranged from simple, unilateral visual phenomena of flickering light to bilateral scenic visions of places feeling familiar. Ictal electroencephalography (EEG) findings and seizure semiology corresponded to a lesion in

the posterior section of the right parahippocampal gyrus which is part of the neuronal network responsible for linking visual information with memory and spatial mapping and navigation. The findings suggest that this particular network is crucial for the semiology of experiential seizures with visual hallucinations and elements of recall.

In Paper III, we investigated the directionality of epilepsy and psychosis by using prescription data. The prevalence of epilepsy in the adult population of Norway was 0.8%, the same as for psychosis. Moreover, the prevalence of psychosis in epilepsy was 2.8% and that of epilepsy in psychosis was 3.1%. Our study confirmed a bidirectional relationship, but surprisingly, we found that a larger portion of subjects (56%) had started antipsychotic treatment prior to onset of epilepsy treatment than the other way around.

In Paper IV we aimed to study the prevalence of psychiatric comorbidity according to clinical epilepsy characteristics in a sample of 448 HUNT-participants with validated and classified epilepsy. We found that 35% had at least one psychiatric disorder. The prevalence was equal in focal and generalized epilepsy but was significantly lower in those with an unknown epilepsy type. In focal epilepsy, unknown etiology, presence of focal to bilateral tonic clonic (FTC) seizures, a younger age at epilepsy onset, and being female were characteristics associated with an increased prevalence of psychiatric comorbidity. Structural etiology and age at epilepsy onset ≥ 60 years were features accompanied by a reduced risk. Interestingly, those with epilepsy resolved at final follow-up had a slightly higher prevalence of psychiatric comorbidity compared to those with active epilepsy. The findings show that prevalence varies according to clinical characteristics of epilepsy and support a potential shared susceptibility for epilepsy and psychiatric disease.

The present studies provide clinically relevant knowledge about prevalence and risk factors of psychiatric comorbidity in people with epilepsy in Norway. Future research should further explore the multifactorial mechanisms behind this association.

# 1 Introduction

*«Like etiology, it is important that the presence of comorbidities be considered for every patient with epilepsy at each stage of classification, enabling early identification, diagnosis, and appropriate management»*
*I.E. Scheffer et al., International League Against Epilepsy (ILAE) Position Paper, Epilepsia 2017 [1].*

## 1.1 Epilepsy

Epilepsy is a brain disorder causing sporadic unprovoked seizures and is one of the most common neurological disorders worldwide affecting between 4 to 10 per 1000 people [2, 3]. In Norway, previously reported prevalence rates have ranged between 0.5-0.8% [4-7]. Sudden excessive electrical brain activity due to a transient imbalance between excitation and inhibition in neuronal networks causes epileptic seizures when the abnormal activity crosses a certain individual threshold [8]. Onset and propagation of epileptic discharges can be focal or generalized, and semiology varies according to location of the abnormal electrical impulses and the function of the seizure generating area. Seizures are classified by the onset of the epileptic activity as focal, generalized, or unknown, and can be further characterized by symptoms. Focal seizures affect limited areas of one side of the brain, while epileptic discharges in generalized seizures are widespread and involve networks in both brain hemispheres (Figure 1).

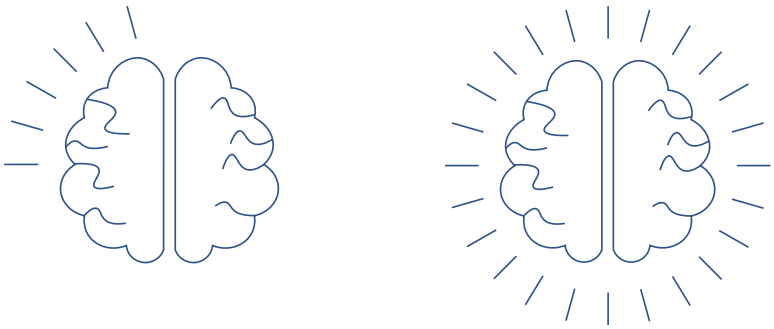

**Figure 1** Epileptic activity in focal and generalized seizures respectively.
*Illustration: Eline Revdal*

### 1.1.1 Definition and classification of epilepsy

In 2014, ILAE proposed a new diagnostic definition of epilepsy based on three possible criteria [9]:

1) Two epileptic seizures separated by at least 24 hours
2) One seizure and an increased risk of recurrence based on clinical information or findings
3) Criteria of an epilepsy syndrome diagnosis fulfilled

Once diagnosed, the epilepsy should be classified according to a three-level classification based on seizure type, epilepsy type or epilepsy syndrome, and etiology as well as comorbidity should be incorporated along each level of classification (Figure 2) [1]. Patient history, seizure semiology and magnetic resonance imaging (MRI)- or electroencephalography (EEG)-findings are the pillars of epilepsy diagnostic workup and classification.

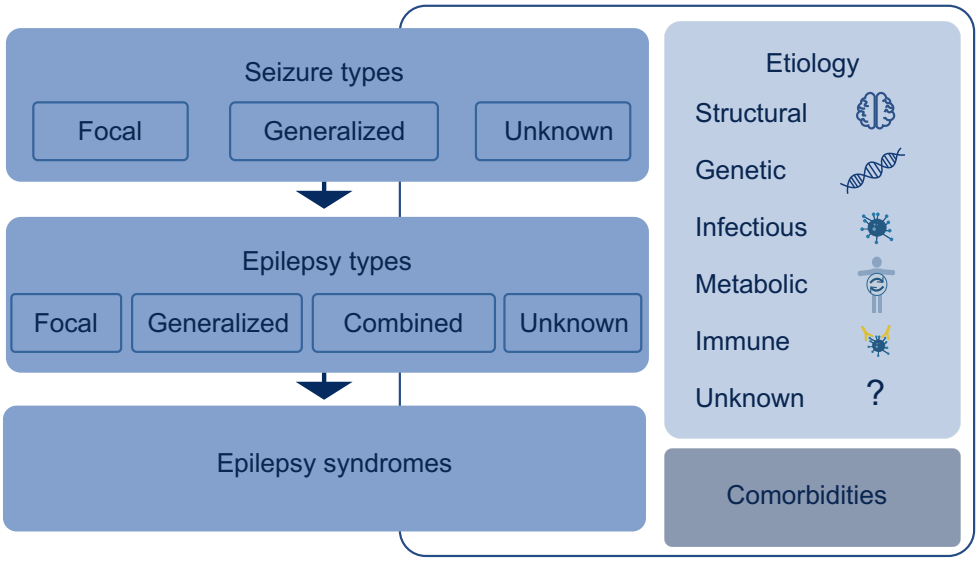


**Figure 2** Framework for the classification of the epilepsies.

*Illustration: Eline Revdal, adapted from Scheffer et al. [1]*

### 1.1.2 Management

Antiseizure medications (ASMs) are the initial choice of treatment in almost all patients diagnosed with epilepsy. These drugs reduce the propensity to excessive neuronal discharges, and complete seizure control is achieved in approximately 70% of patients [2, 10]. However, the recent adaption of the term “epilepsies” reflects the acknowledgement of epilepsy as a complex, multifaceted spectrum disorder reaching beyond seizures [1, 11]. Neuronal network defects and more subtle changes in network function may contribute to cognitive impairment and psychiatric comorbidity in people with epilepsy [12, 13]. The ILAE has recognized the need for comprehensive management encompassing all aspects of epilepsy [1]. Hence, the appropriate individual treatment is based on several factors: epilepsy or seizure type, age and sex of the patient, comorbid conditions, potential adverse or beneficial drug side effects and interactions.

## 1.2 Psychiatric comorbidity in epilepsy

*"Melancholics ordinarily become epileptics, and epileptics, melancholics:*
*what determines the preference is the direction the malady takes;*
*if it bears upon the body, epilepsy, if upon the intelligence, melancholy."*
*Hippocrates, 400 BC [14].*

This quote by Hippocrates demonstrates that the comorbidity between epilepsy and psychiatric disorders has long been acknowledged. Comorbidity is a complex term referring to an association between two diseases co-existing in one patient at a higher rate than expected by coincidence [15, 16].

### 1.2.1 General aspects of psychiatric disorders in epilepsy

Psychiatric disorders are mental illnesses that disturb cognition, emotional regulation, or behavior. The symptoms of these disorders reflect underlying psychobiological irregularities and are associated with distress and/or impaired functioning [17]. The 10$^{th}$ revision of the international classification of diseases (ICD-10) categorizes these disorders into 11 main groups:

1) Organic mental disorders
2) Substance use disorders
3) Psychotic disorders
4) Mood disorders
5) Neurotic disorders
6) Behavioral disorders
7) Personality disorders
8) Intellectual disability
9) Neurodevelopmental disorders
10) Behavioral and emotional disorders of childhood and adolescence
11) Unspecified mental disorders

More than 1/3 of people with epilepsy have psychiatric comorbidity, and common psychiatric disorders often occur at rates 2-3-fold that of the population without epilepsy [18, 19]. In addition, various psychiatric symptoms can be directly related to epileptic seizures and are classified according to their temporal relation to seizure occurrence (Figure 3) [20-22]:

- **Pre-ictal:** Psychiatric symptoms precede the seizure in the form of prodromes (days) or auras (seconds/minutes). Prodromes are symptoms or behaviors occurring up to 3 days before a seizure. Mood and behavioral changes, "funny feeling", dysphoria, irritability or anxiety are common prodromal symptoms [23]. Auras represent the first part of some focal seizures and are subjective phenomena. They are short-lasting and usually appear just before the main part of a seizure take place but can also occur alone. They may include psychiatric symptoms like anxiety or panic, hallucinations, and transient delusions.
- **Ictal:** Brief symptoms representing focal ictal discharges, typically stereotyped. Ictal cognitive, emotional, and psychiatric symptoms can be déjà vu/jamais vu, flash backs, slow motion, dreamy states, anxiety or panic, dysphoria, or hallucinations.
- **Post-ictal:** The postictal phase can manifest with confusion, anxiety and mood changes lasting for hours or days. Distinct psychiatric symptoms such as psychosis can appear after a seizure or typically a cluster of seizures, often with a lucid interval of up to one week [24, 25]. The symptoms can last for a few days or weeks, but usually resolve within two weeks.
- **Interictal:** Psychiatric symptoms appear independently of seizures and are randomly related in time to seizure occurrence. Interictal psychiatric symptoms may be similar to symptoms of primary psychiatric disorders in people without epilepsy.
- **Alternative:** Psychiatric symptoms emerge when uncontrolled seizures suddenly resolve. It refers to a clinical phenomenon of a reciprocal relationship between epilepsy and psychiatric disorders. The behavioral symptoms are polymorphic, usually with paranoid or affective features. Alternative psychosis is a classic example of this phenomenon [26].

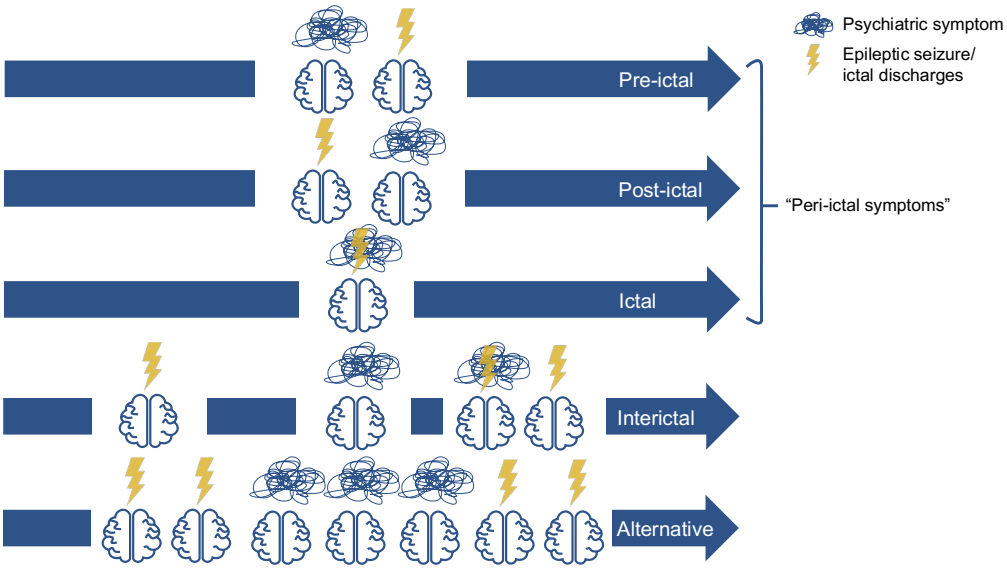


**Figure 3** Psychiatric symptoms classified according to temporal relation to seizures.
*Illustration: Eline Revdal*

Several factors may explain the co-occurrence of epilepsy and psychiatric disorders, and both unidirectional and bidirectional elements of this relationship have been explored. A unidirectional association between diseases suggests a causal effect of one disorder on the other, as implied in the conceptual definition of epilepsy as a disorder not only characterized by the predisposition to generate seizures but also by non-seizure manifestations such as the neurobiological, cognitive, psychological, and social consequences of the condition [27]. In addition, a bidirectional association between epilepsy and psychiatric comorbidity has been presented, meaning that the presence of either one disease increases the risk of the other [18, 28, 29]. Such a relationship might suggest a shared susceptibility due to common underlying pathological mechanisms of disease development [30, 31]. Sometimes both temporal patterns are present, reinforcing one another, leading to multifaceted clinical situations.

Psychiatric comorbidity in epilepsy has been extensively researched during recent years. However, knowledge gaps still exist. Studies have been heterogeneous, and estimates have varied considerably dependent on study population, sources of ascertainment and

diagnostic definitions. Further, few studies have had the data to substantiate the bidirectional relationships, especially between epilepsy and psychosis, and whole population-based studies have been requested [32, 33]. Conversely, studies on prevalence of psychiatric comorbidity according to detailed and validated clinical epilepsy characteristics are needed to further disentangle the multifaceted relationship and to identify patients at risk of unfavorable outcomes.

### 1.2.2 Temporal lobe epilepsy

The limbic system is an aggregation of brain structures that are involved in various cognitive processes such as spatial memory, learning, motivation, social and emotional processing, and essential parts of the limbic system are located within the temporal lobe [34]. Approximately 60% of all epilepsies are focal, and temporal lobe epilepsy (TLE) is the most common type of focal epilepsy [35]. It is also the most common type of epilepsy refractory to ASM treatment. Several psychiatric symptoms in people with epilepsy have been linked to TLE in particular [32, 36-40]. Structural alterations of the amygdala, hippocampus and parahippocampus of the limbic system have been associated with psychiatric disorders, and some authors have suggested that larger network dysfunctions may be involved when people with epilepsy have psychiatric ictal symptoms [34, 41-46]. Makhalova et al. found that the level of depression correlated to the extent of amygdala enlargement in patients with drug-resistant epilepsy and psychiatric comorbidity, and suggested that the amygdala was a hub within functionally altered complex fronto-temporo-limbic networks involved in depression of people with epilepsy [41].

Ictal psychiatric symptoms represent focal seizures and can have lateralizing and localizing value [22]. In a review from 2014, Mula suggested that ictal symptoms of panic, mania, depersonalization, psychosis and aggressive behavior are symptoms mainly arising from the non-dominant hemisphere and auditory hallucinations from the dominant hemisphere [22]. There were no uniform data on the origin of symptoms of ictal depression and a specific localizing value of psychiatric symptoms has been more controversial, but temporal lobe and limbic structures are often involved.

### 1.2.3 Idiopathic generalized epilepsy

Idiopathic generalized epilepsy (IGE) is a subtype of genetic generalized epilepsies that is usually treatment responsive. This group accounts for approximately 15-20% of all epilepsy cases [47, 48]. IGE refers to four epilepsy syndromes: childhood absence epilepsy (CAE); juvenile absence epilepsy (JAE); juvenile myoclonic epilepsy (JME); and generalized tonic-clonic seizures alone (GTCA), of which JME is the most common type. Studies have suggested a particular association between JME and frontal lobe impairment and specific cognitive traits such as impaired planning and organizing ability as well as higher impulsivity and risk-taking behavior [49-52]. These personality traits have even been found in seizure-free JME patients and the literature has highlighted a poorer social and socioeconomic outcome in many patients, but the condition is heterogeneous [49, 53]. Psychiatric disorders have also been linked with CAE, an epilepsy type commonly associated with a good prognosis of achieving seizure remission [54, 55]. In a study on outcome of IGE in adults, Gesche et al. found an increased risk of psychiatric comorbidities in those with drug-resistant IGE [48].

### 1.2.4 Atypical symptoms

The symptom clusters of psychiatric disorders in people with epilepsy may be atypical and many studies have found that common diagnostic manuals or screening tools fail to identify psychiatric disorders in people with epilepsy [21, 56, 57]. Neither the ICD nor the Diagnostic and Statistical Manual of Mental Disorders (DSM) systems classify seizure-related symptoms as detailed as listed in Figure 3. A study investigating prevalence of psychiatric comorbidities in patients with drug-resistant focal epilepsy found that approximately 15% fulfilled the criteria for mood disorders according to non-specific screening tools like the Mini international Mental Interview, while a clinical approach focusing on epilepsy-specific symptoms of interictal dysphoric disorder (IDD) revealed a rate of 22% [37]. Similarly, using a specific screening scale for anxiety that has been validated in epilepsy (Generalized Anxiety Disorder-7, GAD-7) disclosed a prevalence of 38%, compared to 11-29% using scales with non-specific criteria (Mini international Mental Interview and State-Trait Anxiety scale), while clinical evaluation revealed that as many as 53% had anticipatory anxiety of seizures

[37]. Others have also highlighted that the lack of established diagnostic criteria for epilepsy-specific anxieties such as anticipatory anxiety of seizures limits the likelihood of identifying these phenomena in clinical practice [58]. This underscores the importance of clinical awareness of the atypical phenotypes of psychiatric conditions in epilepsy. However, it should be noted that any screening tool is better than none, as it has been found that many neurologists do not screen for psychiatric symptoms at all [59-61]. The Neurological Disorder Depression Inventory for Epilepsy and GAD-7 have been suggested as useful tools in epilepsy management [62-64]. An international consensus from 2011 suggested that screening for psychiatric symptoms should be carried out at least once a year for all patients with epilepsy [64].

### 1.2.5 Specific psychiatric disorders in epilepsy

#### *1.2.5.1 Mood disorders*

Mood disorders are the most frequent psychiatric comorbidities in people with epilepsy and occur in approximately 1 in 3 patients [65]. Depression is most common and has been reported to occur in up to half of patients with refractory epilepsy [66, 67]. Symptoms of interictal depressive episodes can be identical to those of primary mood disorders as described in diagnostic manuals but may also present as intermittent dysphoric symptoms. Vaaler et al. found that patients presenting with the rapidly fluctuating symptoms of acute unstable depressive syndrome had a higher prevalence of seizures, epilepsy and pathologic EEG-findings than patients with major depressive disorders [68]. An atypical presentation of depression in people with epilepsy was first described by Kraepelin in 1923 and then Bleuler in 1949, and later labelled “interictal dysphoric disorder” (IDD) by Blumer in 2000 [56, 69]. IDD is portrayed as a pleomorphic affective disorder in people with epilepsy characterized by the presence of at least three out of eight key features: depressive mood, lack of energy, pain, insomnia, fear, anxiety, paroxysmal irritability, and euphoric moods. Severe IDD may also present with psychotic features resembling interictal psychotic disorders [70]. Interestingly, some authors have suggested that IDD is not only an epilepsy-related mood disorder, as it has also been found in patients with migraine [71]. A recent review concluded that its validity as a distinct diagnostic category is difficult to establish, but highlights the

value of recognizing this clinical pattern in the management of epilepsy patients [72]. Prodromal irritability or dysphoric symptoms are not rare and can cause significant impairment in patients, and postictal tiredness, depressed mood or irritability can be prolonged or unusually severe [21, 62, 69]. Kanner et al. found that 43 out of 100 consecutive patients with refractory focal epilepsy reported symptoms of depression postictally, whereas 22 reported postictal manic symptoms [24].

Bipolar disorder is characterized by recurrent episodes of mania (type I) or hypomania (type II) alternating with depression and is considered a mood disorder according to diagnostic systems. Bipolar disorder is far less common among people with epilepsy than depression. Still, two separate studies reported a relatively high prevalence of bipolar symptoms in epilepsy, and Ettinger et al. also concluded that rates in people with epilepsy were higher compared to rates in controls as well as in people with other chronic disorders [73, 74].

#### *1.2.5.2 Anxiety*

Anxiety disorders are the second most common psychiatric disorders in people with epilepsy and are often associated with mood disorders [56, 75, 76]. Interictal anxiety may present similarly to anxiety disorders in people without epilepsy or as more epilepsy-specific, for instance as anticipatory anxiety of seizures [21]. Rates of depression-anxiety-comorbidity in epilepsy may be distorted by misdiagnosed symptoms of anxiety, as fear and anxiety may be part of an IDD and should be diagnosed as such if other (at least two) IDD-features are present [21]. Anticipatory anxiety of seizures, fear of accidents, agoraphobia or social phobia may develop as a direct result of having recurrent, unpredictable seizures. Ictal anxiety is the most frequent ictal psychiatric manifestation [22] and postictal symptoms of anxiety are relatively common [24, 64]. A feeling of panic is the most typical symptom of ictal fear, and the diagnosis of primary panic attacks can sometimes be difficult to differentiate from seizures [38]. A duration of less than two minutes, a stereotypic presentation and a post-episodic confusion are clinical characteristics in support of an epileptic origin [77]. An aura of fear is also quite common and has been reported in 10-20% of patients with TLE [77].

#### *1.2.5.3 Psychosis*

The introduction of electroconvulsive therapy by the Hungarian neuropsychiatrist Ladislas Meduna in 1934 originated from speculations about a possible antagonistic association between schizophrenia and epilepsy [78]. This inverse relationship between seizure control and psychotic symptoms was later described as “forced normalization” by Landolt in 1953 [79], and reflects a sudden disappearance or reduction of ictal discharges on EEG-recordings that can trigger behavioral or psychiatric symptoms [80]. Accordingly, any successful epilepsy treatment causing rapid seizure control may potentially induce psychosis in susceptible patients [81]. The pathophysiology of this phenomenon remains uncertain, but noteworthy, initiation of antipsychotic drugs as treatment is inferior to ASM adjustments [26].

As with mood disorders and anxiety, symptoms of psychosis in epilepsy can be somewhat atypical compared to psychosis in people without epilepsy. Interictal psychosis is often termed “schizophrenia-like” due to its resemblance to primary schizophrenic disorders, but negative symptoms and deteriorations in personality can be less prominent, and patients may often remain emotionally responsive [82]. In a systematic review and meta-analysis, Clancy et. al reported a pooled prevalence of psychosis in epilepsy of 5.6%, of which interictal psychosis was the most common with a prevalence of 5.2% [32]. The prevalence of postictal psychosis was 2%; however, this has been described as the most common form of psychosis in epilepsy by others. Postictal psychoses often involve conspicuous violent and religious elements implying danger to the patients themselves and others [83]. Ictal psychoses typically manifest as stereotyped hallucinations perceived as unreal by the patients (pseudo-hallucinations), unlike hallucinations of primary psychoses, and may appear in relation to non-convulsive status epilepticus [84].

#### *1.2.5.4 Intellectual disability*

Nearly a quarter of people with epilepsy have intellectual disability, and the prevalence of epilepsy among people with intellectual disability is about the same [85, 86]. In patients with severe communication deficits, specific psychiatric diagnoses may remain obscure. The behavioral phenotype of neurogenetic disorders associated with intellectual disability often includes psychiatric comorbidity. The concept of developmental and epileptic

encephalopathies (DEE), where epileptiform abnormalities contribute to a progressive disturbance of cerebral function, has recently been acknowledged [1]. This group is characterized by severe drug-resistant epilepsy with onset in childhood and neurodevelopmental comorbidities in the form of attention deficit hyperactivity, autism spectrum disorder, mood instability and sleep disturbances. Classical examples are electroclinical syndromes such as Lennox Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex [87, 88]. An expanding discovery of novel genetic etiologies may introduce a replacement of the term DEE with gene-specific names as phenotypic traits often correlate with genetic variants [1]. However, specific etiologies in the large bulk of adult patients within this category has remained undetermined. The management of these patients represent a substantial multi-professional challenge, and they exhibit a particular vulnerability to psycho-behavioral side effects from ASMs [88]. Patients with DEE are usually treated in community care and excluded from common psychiatric services.

### 1.2.6 Effects of psychiatric comorbidity

Epilepsy stigma is still a major challenge, even in western countries [89, 90], and the "double stigma" of additional psychiatric comorbidity may lead to vicious circles promoting social disadvantages and isolation [91]. Psychiatric comorbidities can impact the quality of life of patients with epilepsy to a greater extent than frequency and severity of seizures [92-94]. In addition, the risk of premature death in people with epilepsy is higher than in the general population [95]. In fact, a Danish population-based study found that people with epilepsy live on average 10-12 years shorter than the general population [96] and a Swedish study found an adjusted odds ratio of premature death of 11.1 compared to controls without epilepsy [97]. Interestingly, in the Swedish study, psychiatric comorbidity in epilepsy was found to increase this difference [97]. An increased risk of attempted or completed suicide or suicidal ideation has also been found among people with epilepsy [76, 98-100]. Psychiatric comorbidity increases this risk as well, but factors related to severity of epilepsy, such as a higher ASM drug load or frequency of seizures seem to be independent risk factors [101, 102]. In 2008, the US Food and Drug Administration issued a much debated class-wide warning about a link between suicide risk and ASMs regardless of indication, as a meta-analysis had revealed an odds ratio of 1.8 of suicidal ideation and/or behavior with ASMs

compared to placebo [103]. The ASMs included were carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. Among patients with epilepsy specifically, the relative risk was 3.6, while it was lower for patients with psychiatric disorders treated with ASMs (1.6). However, several have highlighted the complex nature of suicidality in people with epilepsy, underlining the multifactorial aspects of the relationship, and a reduced risk of drug-related suicidality has been reported with newer ASMs suggesting a class-effect is a major simplification [104-106]. Although a mutually increased risk of accidents, substance abuse and suicide may influence the association between epilepsy and premature death, a 5-fold risk of sudden unexpected death in epilepsy (SUDEP) has also been found among women with epilepsy and psychiatric disorders compared to those with epilepsy alone [107].

Epilepsy has been associated with a substantial economic burden on individuals and society [108]. An American study found that costs related to psychiatric comorbidities were significantly higher in patients with epilepsy compared to patients without epilepsy [109].

Considering the overall impact of psychiatric disorders in epilepsy, it should be obvious that these comorbidities must be addressed. Nonetheless, psychiatric comorbidity in people with epilepsy is still often underrecognized and undertreated [110-114].

# 2 Objectives


**Figure 4** Aims and objectives.

The overall aim of this thesis was to explore and elucidate the complex association of epilepsy and psychiatric disorders. We hope that better knowledge and increased awareness about this association can ultimately improve comprehensive management of people with epilepsy. We wanted to study the prevalence of psychiatric comorbidity in epilepsy and the directionality of the disorders. We further aimed to investigate risk factors of psychiatric disease in people with epilepsy by examining the clinical characteristics of the seizure disorders in relation to psychiatric comorbidity in detail.

Paper I | **Substance use disorders and psychotic disorders in epilepsy: A population-based registry study**

To compare the proportion and age and sex distribution of substance use disorders and psychotic disorders among adults with epilepsy to the general population by using data from the Norwegian Patient Registry (NPR).

Paper II | **Experiential seizures related to the hippocampal-parahippocampal spatial representation system**

To highlight the multifaceted relationship between epilepsy and psychiatric symptoms by presentation of a special case with ictal experiential symptoms in the form of focal repetitive seizures with simple and complex visual pseudo-hallucinations.

Paper III | **Bidirectionality of antiseizure and antipsychotic treatment: A population-based study**

To study the prevalence and directionality of psychosis in epilepsy by means of prescription data from the Norwegian Prescription Database (NorPD), and to explore prescription patterns in people with both disorders.

Paper IV | **Psychiatric comorbidity in relation to clinical characteristics of epilepsy: A retrospective observational study**

To investigate whether some epilepsy characteristics are associated with a higher prevalence of psychiatric comorbidity in a cohort of patients with validated epilepsy.

# 3 Materials and methods

## 3.1 Study design

We investigated the association between epilepsy and psychiatric comorbidity on a population-based level using registry data in two retrospective observational cohort studies (Paper I and III), as well as in more detail from medical records in one case report (Paper II) and one case-control study (Paper IV) (Figure 5). Cohort studies can be retrospective or prospective and are valuable in investigation of rare exposures and comparison of prevalence of disease in exposed and unexposed individuals over time [115]. Case-control studies can be very valuable in research trying to identify possible associations between an exposure, for instance different clinical traits of epilepsy, and an outcome. They are suitable for identifying risk/predictors, but they do not demonstrate causation [116].

Population-based studies have the obvious advantage of covering the entire population and are valuable contributions in prevalence research. We investigated the prevalence of psychiatric disorders among those with epilepsy ("exposed"). Large sample sizes and long time-spans provided opportunity to examine rare diseases such as epilepsy and psychosis and directionality of disorders [117]. The NPR and NorPD are both validated sources of data in epidemiological research [7, 118, 119]. To study the relationship between epilepsy and psychiatric disorders in more detail, we chose to perform a case-control study on subjects with validated epilepsy in Paper IV. Clinical features of epilepsy were examined and compared in subjects with and without psychiatric comorbidity to learn more about this intricate relationship and to potentially uncover unknown associations.

**Figure 5 A**

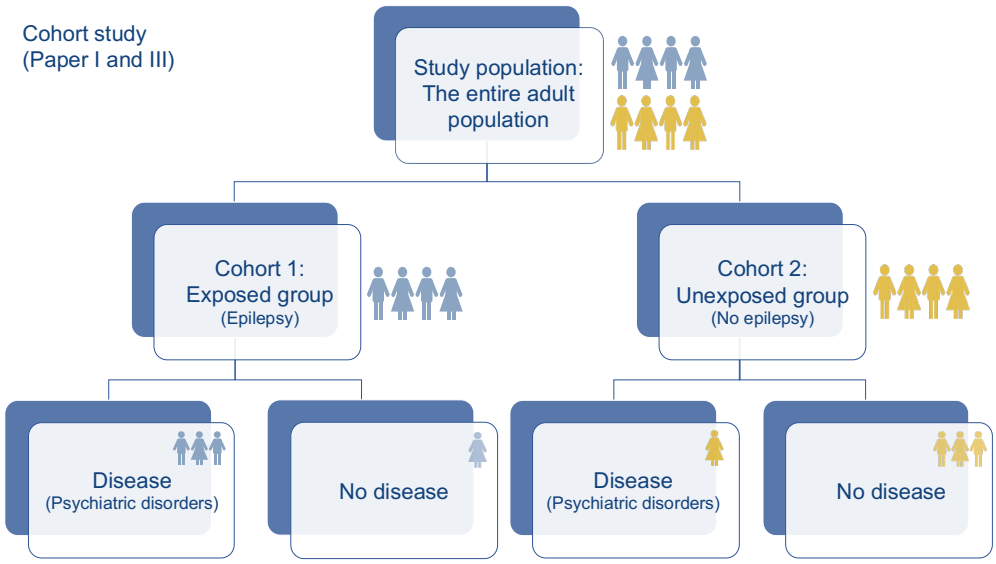


**Figure 5 B**

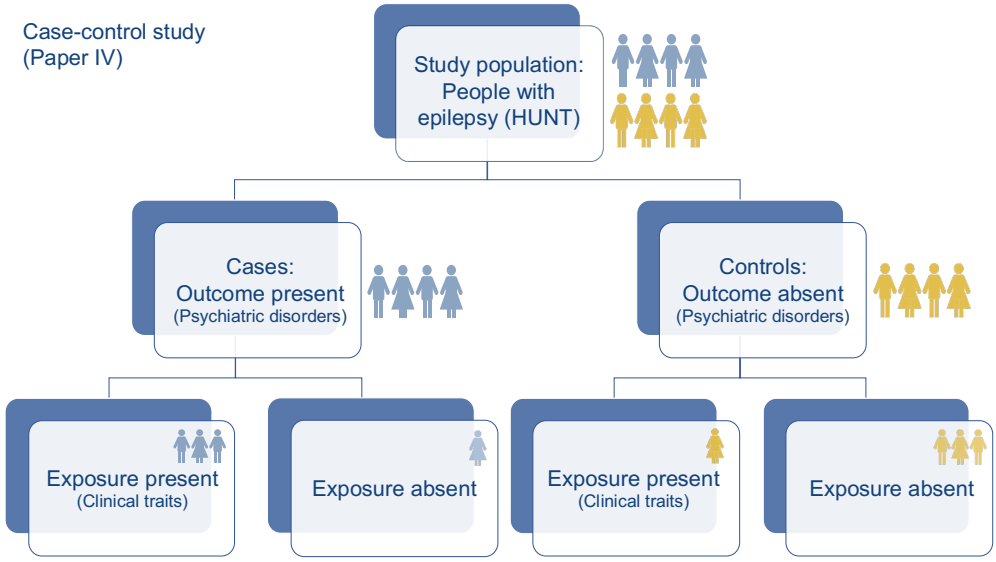


**Figure 5** Study design. A Cohort study; B Case-control study.

*Illustration: Eline Revdal, adapted from Song and Chung [115]*

## 3.2 Diagnostic criteria for epilepsy

The ILAE diagnostic definition of epilepsy [9] is applied in Paper IV, where we used medical records to validate the epilepsy diagnosis. In population-based registry studies however, there are no general guidelines describing the most appropriate method for including true cases of disease. Hence, the decision-making lies with the research group and is usually based on previous publications and clinical experience. The chosen criteria of disease can greatly impact results, as demonstrated by Christensen et al. in a study on epilepsy prevalence in Denmark [120], and can also affect the comparability of a study to others within the same field of research.

Paper I and III are registry studies where the choice of diagnostic criteria was thoroughly discussed. Table 1 gives an overview of prevalence rates according to different criteria considered (Paper I, III, IV). Limitations are discussed in more detail under section 5.3 "Methodological considerations".

**Table 1** Prevalence rates of epilepsy in Norway based on different criteria for diagnosis

| **Definition of epilepsy** | **N** | **Period prevalence[a] (%)** |
|---|---|---|
| *Paper I (2008-2012, NPR)* | | |
| **At least one epilepsy diagnostic code registered** | **33,571** | **0.90** |
| At least two epilepsy diagnostic codes registered | 23,177 | 0.62 |
| At least five epilepsy diagnostic codes registered | 10,824 | 0.29 |
| *Paper III (2004-2017, NorPD)* | | |
| One unique prescription of ASMs for epilepsy | 74,163 | 1.96 |
| Two unique prescriptions of ASMs for epilepsy | 64,095 | 1,69 |
| Four unique prescriptions of ASMs for epilepsy | 56,193 | 1.48 |
| Ten unique prescriptions of ASMs for epilepsy | 44,724 | 1,18 |
| **Four unique prescriptions of ASMs for epilepsy, at least one prescribed in specialist health care services** | **31,289** | **0.83** |
| Four unique prescriptions of ASMs for epilepsy, at least one prescribed by a *specialist* in neurology or pediatrics | 23,058 | 0.61 |
| *Paper IV (1987-2019, HUNT)* | | |
| At least two epilepsy ICD-diagnostic codes registered | 516 | 0.74 |
| **Validated epilepsy by medical record review** | **448** | **0.64** |

[a] Paper I N=3,751,256; Paper III N=3,790,620; Paper IV N=69,634

## 3.3 Paper I

**Substance use disorders and psychotic disorders in epilepsy: A population-based registry study**

All Norwegian hospitals and outpatient clinics receiving governmental reimbursement must report data, including diagnostic codes according to ICD-10, to the NPR. Since 2008, the information provided has been linked to an 11-digit personal identification number assigned to all inhabitants of Norway, enabling individual-based research on medical disorders in the population. Substance abuse treatment facilities have reported to the NPR from 2009 onwards.

The NPR provided whole-population data files for comparison of proportions of psychiatric disorders in people with epilepsy to the population without epilepsy for the study period 2008-2012. Norwegian residents born 1930-1994 (18-82 years by the end of follow-up) were included in the study. To also include those with well-controlled epilepsy and therefore more sporadic hospital contacts, people with epilepsy were identified by at least *one* registration of an epilepsy diagnostic code (G40.x). Data on sex, year of birth and psychiatric ICD-10 codes were also provided. In this Paper, we defined alcohol use disorder by ICD-10 code F10.x, non-alcohol drug use disorder by F11.x-F19.x, psychotic disorders by F20.x-F31.x, F32.3, or F33.3, schizophrenia spectrum disorders by F20.x, F21.x, F22.x, or F25.x, and bipolar disorder by F30.x or F31.x registered at least once during 2008-2012.

To test the validity of our findings, stricter definitions of epilepsy were applied in some of the analyses, where subjects with at least two or five diagnostic codes for epilepsy were included (Table 1). We also compared the results to people with diabetes type I (ICD-10 code E10.x), another chronic disorder.

All statistical analyses were performed by the first author, Inger Johanne Bakken. Stata software package, Version 11.2 (StataCorp. 2009, Stata Statistical Software: Release 11, College Station, TX: StataCorp LP) was used for the data analysis. Prevalence of epilepsy according to sex and age group was obtained by dividing number of patients by average number of sex-and age-matched residents in Norway during 2008-2012. Chi-Square test was applied for differences by sex within the epilepsy group. Fitted log-binomial regression

models were used to estimate adjusted (for sex and age-group) and unadjusted relative risks (RRs) with associated 95% confidence intervals of people with epilepsy compared to the population without epilepsy.

## 3.4 Paper II

**Experiential seizures related to the hippocampal-parahippocampal spatial representation system**

Medical records were reviewed by the candidate and discussed with the main supervisor (E.B.). MRI-findings were reviewed by an experienced radiologist (K.A.K.), and EEG-findings by an experienced clinical neurophysiologist (V.A.). Basic neurobiological aspects were specifically considered by one of the co-authors with expertise in functional neuroanatomy (T.P.D.). The interaction of the hippocampal-parahippocampal spatial navigation systems with visuo-spatial networks and the presented symptoms was discussed with Nobel Prize laureate Professor Edvard Moser, Kavli institute for Systems Neuroscience, NTNU. Relevant information regarding epilepsy history, clinical findings and the current episodes of experiential ictal symptoms were presented and discussed.

## 3.5 Paper III

**Bidirectionality of antiseizure and antipsychotic treatment: A population-based study**

The NorPD provided individual-based information on all antiseizure medications (ASMs) defined by the Anatomical Therapeutic Chemical code (ATC code) N03A and antipsychotic drugs (APDs) defined by ATC code N05A dispensed from Norwegian pharmacies during 2004-2017. Treatment for chronic disorders is reimbursed by the government according to diagnosis-specific codes for each prescribed drug. The ICD-10 and the 2nd edition of the International Classification of Primary Care (ICPC-2) were implemented from 2008. Subjects were 18+ years of age by the end of the study period.

The dataset included pseudonymous patient identification numbers, information on sex and year of birth, ATC code (version 2018), date of dispensation, number of defined daily doses (DDDs) per prescription, and reimbursement codes.

Subjects were categorized into two diagnostic groups based on ATC- and reimbursement codes: (1) epilepsy and (2) psychosis. To avoid including subjects with incorrectly coded reimbursement, four unique prescriptions of ASMs for epilepsy or APDs for psychosis were required for inclusion, of which at least one had been issued with an ICD-10 reimbursement code from the specialist healthcare services (Table 1).

Directionality according to the first dispensation of ASMs and APDs was analyzed in those with epilepsy and psychosis comorbidity as defined by prescription data. We argued that most subjects with chronic disorders such as epilepsy and psychosis would not go as long as four years without any treatment and employed a four-year comorbidity-free period to reduce bias of undisclosed prevalent comorbidity at first registered dispensation. Hence, no subjects had collected treatment for *both* disorders during 2004-2008.

We identified which ASMs had been collected during the 12 months leading up to the first treatment for psychosis, and which APDs before the first epilepsy-treatment. We also analyzed the number of unique ASMs or APDs used during this year. The overall distribution of drugs in the comorbidity group compared to those without comorbidity was presented and mean DDDs/patient/day of both drugs in those with and without comorbidity were calculated by summarizing all DDDs per year of each of the drugs divided by the total number of users and further divided by 365 days.

Statistical analyses were performed by the candidate. Stata software package, Version 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for the data analysis. The alpha-level was set at 0.05. Chi-Square test was used to test for significant association between groups of comorbidity or non-comorbidity and prescribed medication. The continuous data of the variable DDD/patient/day deviated from a normal distribution, hence the non-parametric two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare means.

## 3.6 Paper IV

**Psychiatric comorbidity in relation to clinical characteristics of epilepsy:**

**A retrospective observational study**

In this retrospective observational case-control study we used data from the Trøndelag Health Study (HUNT) [121]. HUNT is one of the largest epidemiological health studies conducted, and the HUNT database contains information from four cross-sectional surveys. All inhabitants of Nord-Trøndelag county in Norway aged 20+ years were invited to participate in HUNT2 (inclusion 1995-97) and HUNT3 (inclusion 2006-08). Participation was based on voluntary enrollment, and data were collected from self-reported questionnaires and biological samples. A total of 65,237 adults participated in HUNT2 (participation rate 69.5%), 50,807 in HUNT3 (54.1%), rendering 69,634 unique subjects with complete participation available for this study. Among these, 516 subjects had been registered with at least two separate epilepsy hospital contacts (neurologic or pediatric department) during 1987-2019. Medical records were reviewed and the epilepsy diagnosis was validated and classified according to the revised classification of the ILAE from 2017 [1].

A case report form was used to collect pre-specified clinical details of interest, including age of epilepsy onset, sex, seizure type, MRI-findings, and etiology, as well as ASM treatment and seizure control within the past one or five years at last registered neurological follow-up. Epilepsy resolved was defined as seizure freedom for more than 10 years with no use of ASMs for at least 5 years [9]. Most of the medical record reviews were performed by trained medical students as part of two student thesis projects at NTNU supervised by Eylert Brodtkorb, where 347 of the patients were included. The remaining medical records (n = 169) were reviewed by the first (E.R), second (B.P.K.) or last author (E.B.).

Psychiatric comorbidity was defined by ICD-codes of psychiatric disorders registered in psychiatric specialist health care services in Trøndelag county during 1987-2022 (ICD-10: F06-F69 and F80-F99; ICD-9: 291-319). 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 systems. Prevalence of psychiatric disorders in relation to the various epilepsy characteristics was analyzed. The number of psychiatric outpatient appointments and

hospital admissions, and the durations of in-patient care were used to assess the overall psychiatric health care consumption in each subject, and averages were calculated according to epilepsy type.

Statistical analyses were performed by the candidate. Stata software package, Version 17.0 (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC) was used for the data analysis. The alpha-level was set at 0.05. The absolute (n) and relative (%) frequencies of nominal variables were calculated and presented. Chi-Square (2x2) tests were used to compare prevalence of psychiatric comorbidity according to various epilepsy characteristics if cell counts (n) were > 5. Risk difference (RD) was calculated as an effect measure of significantly different results. We used binary linear regression with psychiatric comorbidity as the dependent variable, and the relevant predictors as covariates, unadjusted, and adjusted for 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 if they deviated from a normal distribution and two-sample t-tests if not.

## 3.7 Ethics

The studies were approved by the Regional Committee for Medical and Health Research Ethics, Central (Paper II and Paper III) and South-East Norway (Paper I and Paper IV). A written consent by the reported patient was obtained for Paper II (case report).

# 4 Synopsis of results

Paper I | **Substance use disorders and psychotic disorders in epilepsy: A population-based registry study**

Based on data from the NPR, a total of 33,571 individuals (0.90% of the population) born in 1930-1994 were registered with epilepsy at least once during the study period (2008-2012). The prevalence of alcohol use disorder among people with epilepsy was 5.74% compared to 1.29% in the population without epilepsy, with an adjusted RR of 4.42 (95% CI [4.22, 4.62]). For drug use disorders, the corresponding figures were 4.32% and 1.22% (adjusted RR 3.86, 95% CI [3.67, 4.06]). Psychotic disorders, by a broad definition, were registered in 3.75% of people with epilepsy compared to 1.31% in the population without epilepsy (adjusted RR 2.96, 95% CI [2.80, 3.12]). The overall distribution of disorders according to sex and age within the group of people with epilepsy was similar to that in the population without epilepsy.

Paper II | **Experiential seizures related to the hippocampal-parahippocampal spatial representation system**

This case report presents a patient with temporal lobe epilepsy treated with lamotrigine who presented complex ictal experiential symptoms evolving into prolonged and recurrent pseudo-hallucinations during pregnancy. Ictal symptoms of heterogeneous character ranged from simple unilateral visual phenomena to more complex bilateral hallucinations with elements of recall. Ictal EEG-findings along with semiology and MRI-findings pointed to the parahippocampal region of the brain as being crucial in experiential seizures with this type of complex bilateral visual hallucinations. The report highlights the complexity of psychiatric symptoms in epilepsy.

Paper III | **Bidirectionality of antiseizure and antipsychotic treatment: A population-based study**

During the study period (2004-2017), a total of 31,289 subjects had collected an ASM for epilepsy at least four times and 28,889 an APD for psychosis. The prevalence rates of

treatment for epilepsy and of treatment for psychosis were both 0.8%. Further, 891 individuals had been treated for both conditions, giving a prevalence of 2.8% of psychosis in epilepsy and 3.1% of epilepsy in psychosis. Among the 558 subjects included in the analyses of directionality, 56% had collected APD-treatment before the first ASM. Levetiracetam, topiramate or zonisamide, drugs known to have psychiatric side effects, had been used to treat the epilepsy during the last year in approximately 40% of those developing psychosis, whereas olanzapine and quetiapine were most used before starting epilepsy treatment in patients with psychosis; clozapine was used by 13%.

Paper IV | **Psychiatric comorbidity in relation to clinical characteristics of epilepsy: A retrospective observational study**

A total of 516 out of 69,634 participants of the HUNT2 and 3 studies had been registered with epilepsy diagnostic codes from neurologic or pediatric departments on at least two occasions. The epilepsy diagnoses were confirmed by medical record review in altogether 448/516 patients (87%), resulting in a prevalence of validated epilepsy of 0.64% in this HUNT-cohort. Psychiatric comorbidity was registered in 35% of these patients (anxiety and related disorders in 23%, mood disorders in 15%, substance abuse and personality disorders both in 7%, and psychosis in 3%). Comorbidity was significantly higher in women than in men ($p = 0.007$), with a risk difference of 12% (95% CI [-0.24, -0.01). The prevalence of psychiatric disorders was 37% in both focal and generalized epilepsy. In focal epilepsy, it was significantly less common when etiology was structural ($p = 0.011$) with an absolute RD of 13% (95% CI [-0.24, -0.03]) and more common when the cause was unknown ($\chi 2$ (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. Comorbidity prevalence was 35% both in patients achieving seizure freedom and in those with active epilepsy but 38% among 73 patients with epilepsy resolved.

# 5 Discussion

## 5.1 Main findings

This thesis explores the complex relationship between epilepsy and psychiatric comorbidity by a variety of different study designs, collectively providing valuable knowledge about the association.

### 5.1.1 Prevalence of psychiatric comorbidity in epilepsy

It is well established that psychiatric disorders are more frequent among people with epilepsy than in the general population [18, 19]. Alfstad et al. investigated prevalence of psychiatric symptoms in Norwegian children and youth with epilepsy compared to controls using health profile questionnaires, and found such symptoms in a significantly higher proportion of those with epilepsy (38% vs 17%) [122]. Similar differences were reported in a Danish population-based study (37% vs 16%) [120]. Prevalence of developmental/psychiatric disorders in children aged between 0-17 years differed even more in a Norwegian population-based registry study, revealing a rate of 43% among those with epilepsy compared to only 7% within the general child population [6]. The proportion of psychiatric comorbidity in people with epilepsy in Paper IV was in line with this previous research (35%).

A strong association between psychiatric disorders and TLE has been highlighted in the literature [37, 39]. We could not exactly determine the prevalence of TLE in our study (Paper IV), as the specific location of ictal onset had not been identified in a large proportion of patients. However, we found no difference in prevalence of psychiatric disorders in focal compared to generalized epilepsy (37%). Psychiatric disorders were more common in women than in men, reflecting the distribution in the general population [123-126]. Depression and anxiety have been reported to be the most common psychiatric disorders in people with epilepsy at prevalence rates of 23% and 20%, respectively [18], and these conditions have received the most scientific attention [65]. In comparison, we found anxiety to be the most frequent psychiatric disorder among people with focal epilepsy (26%) and mood disorders the second most common (16%) (Paper IV). Anxiety and depression were

equally frequent in generalized epilepsy (both 18%) and in epilepsy of unknown type (both 9%).

An association with psychotic disorders has also been demonstrated in several studies, but bias due to sample selection from tertiary referral centers has been highlighted as a major limitation [32]. Our population-based studies confirmed a higher prevalence of psychotic disorders (Paper I and Paper III), as well as of bipolar disorders and alcohol- and drug use disorders in people with epilepsy (Paper I), with relative risks ranging between 2.2-4.5. Others have found comparable results [127], but assessing the prevalence of psychiatric conditions is difficult and estimates vary substantially.

Table 2 displays a summary of all prevalence rates from Paper I, III, IV of this thesis compared to rates reported in a recent review (Paper I included in some of the analyses) [65]. We found similar prevalence rates of psychosis in epilepsy in all three papers (2.8-3.7%). Our estimates of psychosis were low compared to the review, even in Paper I, where we applied a broader definition of psychoses. The estimates of mood disorders were also lower, conceivably due to methodological differences. Another recent systematic review and meta-analysis of 17 studies on the prevalence of bipolar symptoms or disorder in epilepsy (Paper I included) reported a pooled prevalence somewhat closer to our estimate (4.5%) [128]. Interestingly, Mula et al. found that although bipolar disorders were prevalent in 11.8% of patients with epilepsy according to diagnostic criteria, only 1.4% were considered to have bipolar disorders unrelated to IDD, seizures (peri-ictal symptoms) or ASM treatment [73]. This illustrates the considerable influence of methodological differences. In accordance with this, Scott et al. found diagnostic methodology to be the only significantly influencing effect on the pooled prevalence of anxiety in a meta-analysis of 27 studies [75]. Many psychiatric conditions, particularly mood disorders, or peri-ictal and otherwise short-lasting or more unspecific psychiatric symptoms will be managed solely in primary care. Prevalence estimates based on diagnostic codes from specialist health care excludes such cases.

**Table 2** Prevalence rates of psychiatric disorders in epilepsy

| ICD diagnoses | Paper IV | Paper III | Paper I | Review Lu et. al 2021 |
|---|---|---|---|---|
| **Organic etiology** | 8.0 | | | |
| **Substance use** | 6.7 | | 8.6 | 7.9 |
| Alcohol | | | 5.7 | 4.4* |
| Drugs | | | 4.3 | 6.1* |
| **Psychotic disorders** | 3.3 | 2.8 | 3.7 | 5.2 |
| Schizophrenia | | | 1.7 | 1.7* |
| **Mood disorders** | 15.4 | | | 35.0 |
| Depression | | | | 25.1 |
| Bipolar disorders | | | 1.5 | 6.2* |
| **Anxiety disorders** | 22.5 | | | 25.6 |
| **Personality disorders** | 6.7 | | | |
| **Other** | 7.6 | | | |

*Paper I included in review

### 5.1.2 Overlapping clinical symptoms

Comorbid conditions may have overlapping and complex clinical features, sometimes leading to differential diagnostic challenges or “diagnostic overshadowing”. Diagnostic overshadowing is a judgement bias where health care professionals mistakenly attribute new symptoms to clinical manifestations of a preexisting disorder. This concept has received much attention in people with mental illness developing somatic disease [129, 130]. Overshadowing of psychiatric disorders in people with epilepsy has historically also been insufficiently acknowledged in clinical practice. Psychosocial issues and psychiatric symptoms have largely been ascribed to the consequences of the seizure disorder [27]. Common causes of diagnostic and treatment overshadowing include lack of knowledge on the part of the care providers, lack of symptom recognition and unavailability of relevant clinical assessment and management. Psychiatric symptoms are often misinterpreted and neglected in people with epilepsy and should be brought out of the shadows. On the other hand, epileptic manifestations may mimic psychiatric disease. Seizures can manifest with ictal and peri-ictal emotional and experiential phenomena, sometimes misinterpreted, resulting in unfavorable therapeutic approaches [20].

In Paper II we reported a patient with ictal pseudo-hallucinations and experiential phenomena. The patient had been acutely admitted to a psychiatric hospital when presenting with psychiatric symptoms after a nocturnal FTC. When these symptoms resolved, she reported repetitive and nearly continuous, stereotypical, and elementary unilateral hallucinations and more diffusely distributed, bilateral and complex non-stereotypical visual hallucinations related to places recognized as familiar. Ictal visual hallucinations can arise from both temporo-occipital pathways and temporal localizations. Occipital ictal activity provides elementary visual symptoms restricted to one visual field, while visual symptoms reflecting ictal activity in the temporal/parietal lobe may be more complex and experiential covering both visual fields [131].

We found that the long-lasting, abundant, and non-stereotypical visual phenomena in our patient was associated with ictal EEG-activity corresponding to an MRI-detected volume increase of a right sided parahippocampal lesion proving to represent a ganglioglioma grade 1. This area of the brain contains neurons involved in spatial cognition and episodic memory [132, 133]. The case-report illustrates how psychiatric and neurological phenomena can manifest through common pathophysiological mechanisms within overlapping brain circuits [131, 134]. We relate our findings to the Nobel Prize-awarded discovery of the brain network harboring specific neuronal place- and grid-cells in the parahippocampus by John O´Keefe, Edvard and May-Britt Moser [135]. These structures are involved in the sense and memory of place which is perceived without laterality. The findings add to the understanding of the experiential semiology of TLE as these parahippocampal neuronal populations and adjacent network pathways appear to be involved in the symptomatology of experiential seizures with visual pseudo-hallucinations and elements of scenic familiarity. Due to its non-lateralizing or -localizing nature, this form of ictal “psychosis” may easily be misinterpreted as primary psychiatric symptoms.

## 5.2 Mechanisms of psychiatric comorbidity in epilepsy

There may be several mechanisms involved in the co-existence of diseases [136, 137]. Figure 6 is an illustration of potential pathways to comorbidity:

- Diseases occur together by chance.
- Diseases occur together due to causal association (unidirectional relationships).
- Diseases occur together due to shared risk factors such as common pathological mechanisms (bidirectional relationships).

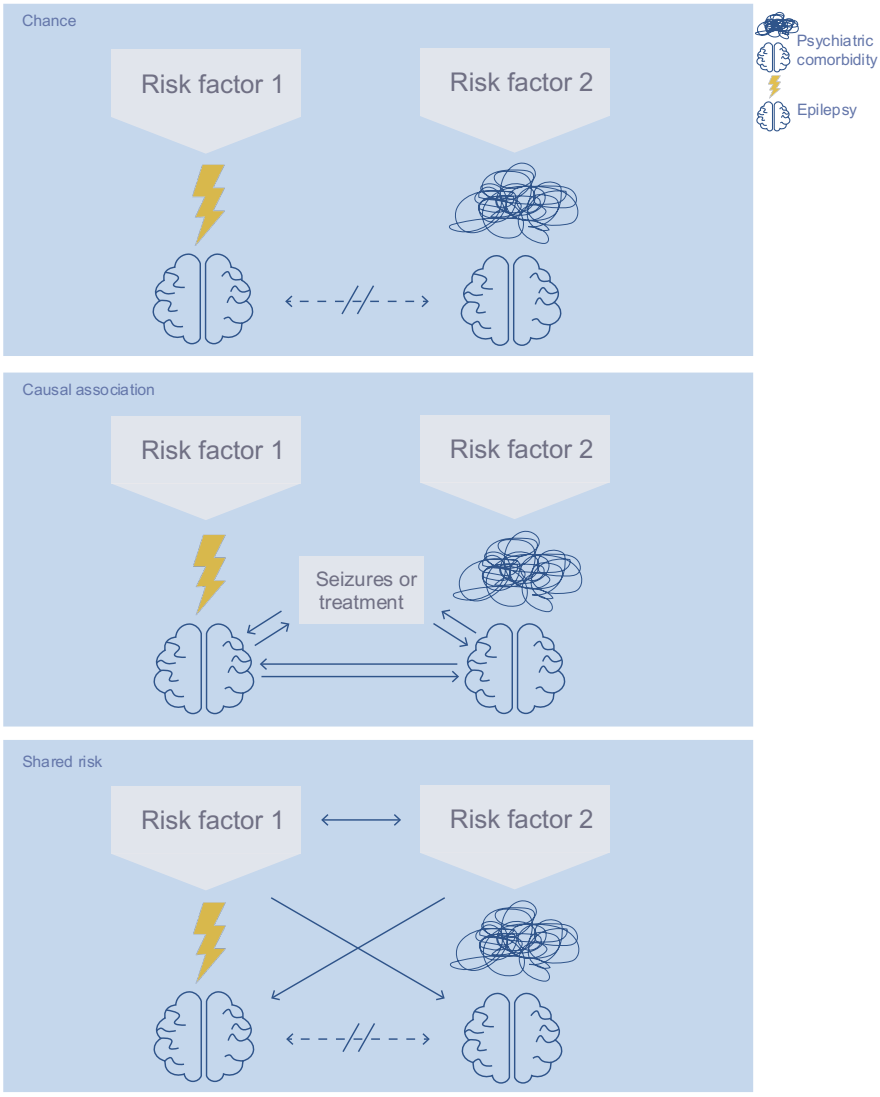


**Figure 6** Potential mechanisms of association between epilepsy and psychiatric comorbidity.
*Illustration: Eline Revdal*

### 5.2.1 Co-occurrence by chance

Chance occurrence refers to a situation where the *true* prevalence of a condition is the same in the index disease (the disease under study) as in the general population [136]. Various sources of bias discussed in section 5.3 “Methodological considerations” can influence investigated prevalence rates. However, it is a long-established fact that psychiatric disorders are overrepresented in people with epilepsy compared to the population without epilepsy.

### 5.2.2 Causal comorbidity

Causative mechanisms may be at play if the prevalence of the comorbid condition is significantly increased among those with the index disease.

#### *5.2.2.1 Epilepsy preceding psychiatric disorders*

Psychosocial consequences of living with an unpredictable chronic neurological disorder, as well as the emotional impact of stigma, can sometimes be causal factors for the development of psychiatric disease in people with epilepsy.

Causal associations can also be indirect. Seizures can cause postictal psychiatric symptoms, and various ASMs are known to have adverse psychiatric side effects such as psychotic symptoms, irritability, aggression, depression, or anxiety [138, 139]. Topiramate, zonisamide and levetiracetam are some of the ASMs most commonly involved [81, 138, 140, 141]. In Paper III, at least one of these ASMs had been used by approximately 40% of subjects with comorbid epilepsy and psychosis during the 12 months prior to the first APD treatment. Kanemoto et. al found that 45 among 132 patients with interictal psychosis and epilepsy had recently either increased the dose of ASMs or added new ASMs at the time of psychotic onset, suggesting potential adverse reactions [142]. However, adverse effects may be difficult to sort out in people susceptible to psychiatric disorders by other causes. Noteworthy, patients with a history of mental illness have an increased risk of such adverse effects compared to those without [143]. Interestingly, 18% (41/231) of those with epilepsy preceding psychosis had not collected any ASM during these 12 months. Non-adherence is associated with psychiatric disorders [144, 145], especially schizophrenia, and emerging

psychotic symptoms could possibly explain the large proportion of subjects that had not collected any ASM prior to onset of APD treatment. Conversely, some ASMs have beneficial effects on psychiatric symptoms and are used to treat psychiatric disorders on a regular basis [146, 147]. Discontinuation of such drugs in epilepsy treatment can also unmask psychiatric symptoms.

Psychiatric disorders have been associated with long-standing severe and uncontrolled epilepsy [113, 148-150], and historically psychiatric comorbidity was mainly regarded as complications of the seizure disorder [151]. It has been suggested that neuropsychiatric symptoms in people with epilepsy may be facilitated by repeated harmful effects of ictal discharges on brain networks by so-called "kindling" [152, 153]. The neuropsychiatric and cognitive symptoms of epileptic encephalopathies may be interpreted as a result of kindling-like mechanisms.

Consistent with these theories, the reported age of onset of primary psychosis is late adolescence or early twenties [154], while interictal psychosis usually presents later in life [155]. Correspondingly, in Paper III we found a mean age at first collection of APD for psychosis of 39 years in subjects with established epilepsy treatment. Further, in Paper IV we found that early onset of epilepsy was related to psychiatric comorbidity. The difference in mean age of onset was close to significant in the overall group and significant in the group of focal epilepsies. This could support a kindling mechanism, as an earlier onset of epilepsy may correspond to a larger exposure to seizure activity. In accordance with this, we also found that in focal epilepsies, having FTC seizures, implying involvement of larger areas of the brain and more exposure to possible harmful ictal effects, was correlated to a higher prevalence of psychiatric comorbidity. Yet, the risk difference was only 8% when adjusted for onset age. A recent Chinese multicenter study found similar results; an increased risk of anxiety and depression related to having FTC seizures (OR 1.5) and a decreased odds of 3.8% for developing depression by every 1-year increment of age [156]. Early onset epilepsy has also been associated with an increased risk of interictal psychosis in patients with temporal lobe epilepsy (TLE) [142], and others have suggested that psychosis in epilepsy could be related to the extent of brain-involvement during seizures [157]. We also found that subjects with an unknown type of epilepsy had a significantly lower risk of psychiatric comorbidity (Paper IV). It is not unlikely that the uncertainty of diagnostic classification

represents a lack of EEG-findings possibly reflecting a reduced frequency of epileptic discharges. Interestingly, patients with generalized epilepsy had a higher mean number of psychiatric outpatient follow-ups, hospital admissions as well as days of hospitalization due to psychiatric disorders than patients with focal epilepsy, however, the difference was not significant. Although prevalence of psychiatric comorbidity was equal in focal and generalized epilepsy, a possible tendency to more severe psychiatric disorders in generalized epilepsy should be further investigated. Different pathophysiological consequences of the two types of epilepsy may produce phenotypic differences of psychiatric comorbidities.

#### *5.2.2.2 Psychiatric disorders preceding epilepsy*

A range of common seizure precipitating circumstances may be involved when psychiatric disorders precede epilepsy. Severe stress, lack of sleep, alcohol, or substance abuse as well as non-adherence are issues heavily associated with mental illness, and psychiatric disorders in people with epilepsy are known to exacerbate severity and seizure frequency [33, 61, 158-164]. In Paper I, we found an increased prevalence of substance use disorders among people with epilepsy compared to those without. Other studies have also revealed increased rates of alcoholism and drug abuse among people with epilepsy [165, 166]. This association is especially problematic due to the direct pharmacodynamic effect of such substances on seizure threshold [167]. Also, it yields diagnostic difficulties between acute symptomatic seizures due to either intoxication or withdrawal and epilepsy [168, 169].

Psychotropic drugs are known to lower the seizure threshold as well [170]. Clozapine and chlorpromazine stand out as the APDs with the highest seizure-provoking potential, maprotiline and clomipramine among the antidepressants, but the effect is considered related to dose and titration [170-172]. In Paper III we found that clozapine had been used by close to 15% of the patients treated for psychosis at epilepsy onset. Olanzapine and quetiapine, APDs with moderate seizure-triggering effects [172, 173], had both been used by 30%. Epileptic seizures in patients with psychiatric disorders were traditionally regarded as consequences of the proconvulsant effects of psychotropic drugs, but research now suggests that other mechanisms are also involved [174]. This is supported by the findings of Paper III, where as many as 27% of those with psychosis predating epilepsy had not

collected an APD during the last 12 months before epilepsy onset. Noteworthy, some studies have found a higher rate of seizures in epilepsy patients with psychiatric symptoms given placebo or not receiving treatment compared to those treated with appropriate psychotropic drugs [172, 175]. This suggests a potential protective effect of treatment in individuals with psychiatric comorbidity, probably by ameliorating seizure precipitating factors. Unwarranted fear of seizure breakthrough may lead clinicians to withhold effective psychiatric treatment. Nevertheless, the potential impact on seizure threshold needs to be considered when prescribing psychotropic drugs to patients with epilepsy [176].

### 5.2.3 Shared risk

#### *5.2.3.1 Bidirectional mechanisms*

A bidirectional relationship indicates reciprocal effects where each condition can cause the other. Multiple studies have confirmed bidirectional relationships between epilepsy and most psychiatric conditions, indicating that the association between epilepsy and these disorders may result from shared risk factors.

Epilepsy and psychiatric disorders are both regarded as network disorders of the brain, meaning that symptoms of disease originate from a disturbance of the complex interconnection of various brain structures that are functionally and/or structurally linked [177], and research has disclosed several overlapping components that may explain the bidirectional relationship [13, 178, 179]. Shared pathological mechanisms may induce processes that make neuronal networks predisposed to both seizures and psychiatric symptoms [12], for instance by a hyperactive hypothalamic-pituitary-adrenal axis, by higher glutamatergic and lower GABAergic and serotonergic concentrations or by increased levels of certain proconvulsive cytokines [174]. Common pathological factors causing structural and functional changes like altered cortical thickness, cell density of neurons, interneurons, and glial cells, or even network connectivity or neurotransmitter bindings may also be involved [12, 174]. Research has even indicated that neuropsychiatric stressors can induce harmful effects on neuronal network function as well, suggesting that kindling-mechanisms can also be involved when psychiatric disorders precede epilepsy or when psychiatric symptoms exacerbate the epilepsy [61, 149, 151-153, 158, 159, 161, 180-182]. An earlier

onset of epilepsy in those with psychiatric comorbidity may support the phenomenon of kindling but can also indicate a genetic etiology or susceptibility. Genetic predisposition may even account for some inter-individual differences in vulnerability to kindling-like effects [183, 184].

Keezer et al. argue that a reciprocal temporal sequence is not sufficient to verify true bidirectionality, since an observed effect as such could result from shared risk factors and random temporal sequence of disease onset as well [136]. We confirmed a bidirectional relationship between epilepsy and psychosis in Paper III, and surprisingly, we found that as many as 56% of those with epilepsy and psychosis had been treated with APDs for psychosis before onset of epilepsy treatment. However, the pathophysiology of the epileptogenic process should be considered in evaluations of directionality and causative mechanisms of epilepsy and psychiatric comorbidity. Epileptogenesis is the gradual process by which the brain becomes functionally altered and predisposed to generate seizures, and/or by which the epilepsy continues to progress [185]. Hence, the diagnostic measure of onset of epilepsy, the first or second seizure, does not in fact reflect the onset of the pathophysiological processes involved in development of epilepsy. The onset of epileptogenesis can sometimes be determined by specific triggering events such as cerebral trauma or inflammation but is often unidentifiable. Thus, the true temporal sequence of the epileptic process and psychiatric comorbidity can be difficult to determine.

Due to the nature of the relationship between epilepsy and psychiatric disorders, there is increasing interest in possible genetic links [30]. In fact, a recent extensive genome-wide association study (GWAS) revealed considerable genetic overlap between epilepsy and psychiatric disorders, indicating a complex genetic association between the two [31]. Another GWAS also investigating co-localization and polygenic risk score recently revealed a genetic association between impulsivity and JME [186]. In Paper IV, we found comparable rates of psychiatric comorbidity in people with active epilepsy and those with seizure freedom or epilepsy resolved. In fact, approximately half of the patients with resolved IGE or resolved childhood onset epilepsy had psychiatric disorders. A high load of psychiatric comorbidity has also previously been associated with the usually self-limiting childhood epilepsies, underlining that seizure remission does not ensure a good outcome in adulthood [54, 55, 187, 188]. The manifestation of the genetic pattern of these patients could be age

dependent, and psychiatric symptoms in some patients may appear as alternate expressions of neuronal network dysfunction even after epilepsy remission.

A high prevalence of psychiatric disorders in seizure-free patients was recently presented in a Brazilian study as well [189]. In fact, an increasing number of publications highlight that psychiatric comorbidity is not necessarily related to seizure frequency or to the most severe types of epilepsy. A study investigating school dropout, anxiety and depression in patients with IGE found that epilepsy severity as illustrated by drug resistance, polytherapy and active generalized tonic clonic seizures (GTCs) was not associated with school dropout or total score of the Hospital Anxiety and Depression Scale [190]. Severity and seizure control did also not affect the prevalence of depression or anxiety in the meta-analysis by Scott et al. [75] and others have found unfavorable psychosocial outcome in people with seizure freedom as well [55, 188, 191, 192]. In Paper III, we found a similar mean DDD of ASMs in patients with epilepsy and psychosis compared to those without psychosis (1.07 compared to 1.03, respectively), possibly indicating similar disease-severity in the two groups. This high rate of psychiatric comorbidity even in those with well-controlled epilepsy or epilepsy resolved no longer affected by psychosocial factors related to the seizure disorder or by the possible adverse effects associated with ASMs, support a shared genetic susceptibility. Interestingly, a family history of mental illness has been linked to an increased risk of psychiatric adverse reactions to ASMs [193] and studies have even found that a vulnerability to unfavorable neuropsychiatric reactions to levetiracetam can be linked to specific genetic variants [194, 195], suggesting an inherent biological susceptibility even to unwanted responses to ASM treatment [196, 197]. In line with previous research [198], we also found that an unknown etiology of those with focal epilepsy was related to higher rates of psychiatric comorbidity, while structural causes were related to lower rates (Paper IV). This suggests a stronger background of unidentified factors of neuropsychiatric susceptibility in these patients.

In summary, numerous potential mechanisms acting in concert form the basis of the association of epilepsy and psychiatric disorders, and certain genetic patterns may promote a shared predisposition to both conditions.

## 5.3 Methodological considerations

Paper I, III and IV were all observational studies, meaning that the investigator observes without intervention [199], and assesses the strength of the relationship between disease and exposure [115]. Bias can occur in any research and can reduce the generalizability of study results. Bias can be defined as a systematic error that results in an outcome failing to reflect the true value of the measure investigated [199]. Several relevant issues need to be considered.

Prevalence estimates may vary according to the sources of diagnostic information. Epilepsy is only diagnosed and often managed in specialist health care, whereas the management of psychiatric symptoms can be limited to primary health care. In Paper I, III and IV, prevalence estimates were based on diagnostic codes from specialist health care services and rates, especially those of psychiatric conditions, might therefore be underreported in all these studies. The World Health Organization concluded that 35-50% of people with severe and debilitating psychiatric disorders in developed countries had not seen a health care professional at all in the previous year [200]. Further, diagnostic codes from medical records and registry databases only represent those conditions that are observed and documented in a clinical setting depending on patients choosing to seek professional help. Fear of stigma may keep people from reporting psychiatric symptoms, probably leaving many with undiagnosed psychiatric conditions. Diagnoses based on questionnaires and interviews may detect many patients with symptoms never diagnosed in a clinical setting [199].

### 5.3.1 Observational studies

By using population-based registry data and a validated source of diagnostic information such as the ICD classification system, we ensured a standardized method of disease identification in both people with epilepsy and the general population. Using population-based data should ideally balance the amount of unreported comorbid disease in the two groups. However, in 1946 Berkson described one form of selection bias where patients within the health care follow-up systems (such as those with epilepsy or psychiatric disorders) are more likely to acquire any additional diagnosis compared to the general population simply because of their interaction with health care facilities [201]. In Paper I we

investigated this further by comparing prevalence of psychiatric conditions in people with epilepsy to those with another chronic disorder, type I diabetes. The overall proportions registered with psychiatric comorbidity were still considerably higher in those with epilepsy. On the other hand, the phenomenon of diagnostic overshadowing, discussed in section 5.1.2, may conceal the presence of psychiatric comorbidities in epilepsy, particularly when being less severe. We also acknowledge that participants included only from the specialist health care, may represent a selected group of patients with more severe disease and potentially a higher susceptibility to comorbidity.

Further, prevalence estimates may be influenced by inaccuracies in the identification of those with true epilepsy or psychiatric disorders. However, a review of validation studies evaluating the accuracy of administrative healthcare data in identifying epilepsy concluded that using registry data in epidemiological research of epilepsy is valuable, and the studies included tended to accomplish high estimates (>80%) of positive predictive values (PPVs), negative predictive values (NPVs), sensitivity and specificity [202]. The accuracy of *specific* psychiatric codes, however, is reported to be lower [203]. A review of the validity of these codes found an overall median PPV of 76%, but the 39 studies included were heterogeneous and had a wide range of outcomes (PPVs between 10-100%) [204]. Noteworthy, the PPV of psychotic illness recorded in specialist health care was quite high, 80-90% [204]. Also, a Norwegian study evaluating the quality of severe mental disorder diagnoses in the NPR found a high diagnostic consistency and accuracy of schizophrenia and bipolar disorder [205].

In Paper IV, we carefully reviewed medical records to validate the epilepsy diagnosis. Among those with at least two diagnostic epilepsy codes from either a neurological or pediatric appointment 87% were confirmed to have true epilepsy as defined by ILAE. Other Norwegian studies validating epilepsy diagnoses have found similar results [7, 206]. We investigated potential epilepsy-related predictors of psychiatric comorbidity to identify patients with increased risk in a case-control study. To ensure that cases and controls represented the same population, we sampled both groups from a pool of participants through the HUNT studies introducing a more random selection of cases and controls [199]. By including a random sample of cases and controls, we could not match by sex and age; however, these confounders were adjusted for in the statistical analyses of risk differences

of significant variations in proportion. Further, we recognize that participation bias/non-response bias may occur when participation is based upon active involvement. Factors such as severity of disease or psychiatric comorbidities associated with social withdrawal, lack of energy, lack of motivation/interest, cognitive ability, dependence on others or other incapacitating features, may influence participation and shift the true relation of the conditions towards those with less severe disease. The relatively low number of patients with JME may reflect such bias, as some might have personality traits that can render them less likely to sign up for study participations [49].

Moreover, as demonstrated in Table 1, prevalence estimates can vary with the methodological approach used to classify the study-participants as "diagnosed". By applying stricter definitions for inclusion many individuals with misdiagnosed epilepsy will be left out, but some true patients will also be missed.

In Paper III, we used prescription data to investigate directionality. Although the data in that study covered a long period (14 years), we acknowledge that the true onset of treatment is difficult to determine. We selected a comorbidity-free period of four years to increase internal validity [207] of estimated directionality, but we could not rule out the possibility of previously treated epilepsy or psychosis. We also recognize that the onset of treatment does not necessarily reflect onset of disorder.

# 6 Concluding remarks

This thesis provides clinically relevant knowledge about prevalence and risk factors of psychiatric comorbidity in people with epilepsy in Norway. It confirms that psychiatric illness is overrepresented in epilepsy as compared to the general population. We found that this is true also for substance use disorders, psychosis, and bipolar disorders which have been less investigated compared to mood and anxiety disorders. Our findings also support a bidirectional relationship between epilepsy and psychosis. Surprisingly, more than half of comorbid patients had been treated for psychosis prior to onset of ASM treatment. The high proportion of patients with psychiatric disorders even among those with epilepsy resolved support the understanding that the association between psychiatric disorders and epilepsy represent more than just psychosocial issues related to having a current seizure disorder or adverse effects from ASMs. Diagnostic overshadowing in people with epilepsy needs to be addressed and prevented by dissemination of relevant knowledge among professionals providing comprehensive epilepsy care.

In line with previous research, we found that risk factors vary according to clinical epilepsy characteristics. Being female, having FTC seizures or an unknown etiology were risk factors of psychiatric comorbidity in people with focal epilepsy. Although there were no significant predictors among those with generalized epilepsy, a notably large proportion of patients with childhood absence epilepsy had psychiatric comorbidity, but the number of patients was small.

Psychiatric comorbidity represents a substantial burden for people with epilepsy. Despite the obvious influence of these co-occurring disorders on the lives of people with epilepsy, epilepsy care tends to focus mostly on the seizure frequency and antiseizure treatment. Screening tools and standardized guidelines for epilepsy follow-up that include comorbid psychiatric disease should be incorporated in clinical care to ensure appropriate multi-disciplinary and evidence-based management of people with epilepsy, aiming to improve the overall outcome and quality of life of the patients. Psychiatric services should be readily available for people with epilepsy.

# 7 Future research

Future research should further explore the multifactorial mechanisms behind the association between epilepsy and psychiatric disease. Phenotypic differences in psychiatric disorders of people with epilepsy compared to those without epilepsy might be explained by differences in network involvement directly related to the epilepsy. Moreover, specific neurological symptoms can often be linked to lesions of specific functional areas of the brain, but the localization of psychiatric symptoms has been more ambiguous. Linking psychiatric symptoms to brain circuits rather than anatomical regions has been a suggested approach [208]. Psychiatric disorders are typically associated with considerable clinical heterogeneity, and Segal et al. found that regional brain alterations of patients with the same psychiatric diagnosis were located in the same anatomic area in less than 7% of 1,294 subjects [209]. However, these abnormalities involved shared functional brain circuits in almost 60% of the cases, suggesting that phenotypic differences within psychiatric conditions may be a result of deviation in regional localization, while similarities may reflect involvement of common network dysfunctions [209]. Future research on the mechanisms and causative factors underlying psychiatric comorbidity in epilepsy should focus on smaller phenotypic symptom clusters and their association to specific epilepsy types or even syndromes to be able to investigate the complex relationship between these disorders and the possibility of common genetic variants. A better comprehension of network correlates of neuropsychiatric comorbidities in epilepsy would probably benefit the understanding of the causative mechanisms involved. Future research may reveal that psychiatric symptoms are in fact sometimes integral parts of the epilepsy, associated by common underlying network alterations due to genetic susceptibility, underpinning the need for genetic research and further exploration of shared pathophysiological mechanisms. Moreover, studies must evaluate the effectiveness of targeted approaches and early intervention of psychiatric comorbidity in epilepsy.

# 8 References


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# PAPER I

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# Substance use disorders and psychotic disorders in epilepsy: A population-based registry study

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**Summary**
*Background:* Epilepsy affects around 70 million people worldwide. Psychiatric comorbidity may add to the burden of the disease. We studied substance use disorders and psychotic disorders among people with epilepsy from a population-based perspective.
*Methods:* Norwegian specialist health services (hospitals and outpatient clinics) report diagnoses for individual patients to the Norwegian Patient Register. We used information on subjects born in 1930–1994 who were registered with a diagnosis of epilepsy at least once during the five-year period of 2008–2012. We compared the proportion of people with epilepsy registered with substance use disorders (alcohol use disorders or non-alcohol drug use disorders) and psychotic disorders (schizophrenia spectrum disorders or bipolar disorder) with similar figures in the population without epilepsy. We applied chi-square tests and log-binomial regression for analysis.

*Abbreviations:* NPR, Norwegian Patient Register; ICD-10, International Classification of Diseases Version 10.

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*Results:* Overall, 0.90% of the Norwegian adult population was registered with epilepsy in somatic hospitals during 2008—2012. The total proportion registered with alcohol use disorder was 5.74% among people with epilepsy and 1.29% in the population without epilepsy (age- and sex-adjusted relative risk [RR]: 4.42, 95% confidence interval [CI]: 4.22—4.62). The corresponding figures were 4.32% and 1.22% (RR 3.86 [95% CI: 3.67—4.06] for drug use disorder, 1.72% and 0.60% (RR 2.94 [95% CI: 2.71—3.19]) for schizophrenia spectrum disorders, and 1.50% and 0.68% (RR 2.29 [95% CI: 2.10—2.49]) for bipolar disorder.
*Conclusion:* People with epilepsy were more often registered with substance use disorders and psychotic disorders than people without epilepsy. Psychiatric comorbidity requires particular attention in both diagnostic work-up and management of epilepsy, and creates complex medical challenges that require close cooperation between neurologists and psychiatrists. These findings may have implications for the organization and further development of comprehensive epilepsy care.


## Introduction

Epilepsy is one of the most common neurological disorders, affecting nearly 3 million people in Europe alone (Wittchen et al., 2011) and around 70 million people worldwide (Ngugi et al., 2010). In the Global Burden of Disease Study 2010, epilepsy was ranked as the world's 16th leading cause of disability-adjusted life-years, indicating that epileptic disorders contribute significantly to premature mortality and severe morbidity (Murray et al., 2012).

Psychiatric comorbidities are often seen in epilepsy and add further burden to these patients in terms of inadequate response to treatment, contribution to poor quality of life, and increased mortality (Lin et al., 2012). Despite the high prevalence of psychiatric disorders in epilepsy, such conditions often remain unrecognized and undertreated (de Boer et al., 2008; Karouni et al., 2013). While a bidirectional relationship between depression and epilepsy is well established, the association with bipolar disease is less clear and the increased risk of schizophrenia has varied in different studies (Kanner and Hesdorffer, 2012). The interaction between substance use disorders and seizure disorders has to our knowledge not been addressed in large population-based studies using the general population as the reference group. The Norwegian Patient Register (NPR) is a nationwide registry containing diagnostic information assigned by Norwegian specialist health services (hospitals and outpatient clinics in somatic and mental health care). Data from this registry have previously been used to determine the proportion of children aged 0—11 years with diagnoses of epilepsy, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD), and cerebral palsy (Suren et al., 2012).

A thorough understanding of the multifaceted challenges met by people with seizure disorders is important for providing comprehensive epilepsy management. The aim of the current study was to compare the proportion and age and sex distribution of substance use disorders and psychotic disorders among adults with epilepsy by using data from the NPR.

## Methods

### The Norwegian Patient Register

The NPR is an administrative database to which it is mandatory for all Norwegian hospitals and outpatient clinics receiving governmental reimbursement to report. The NPR receives data from hospitals and outpatient clinics, substance use treatment facilities, and specialists in private practice contracted by the health authorities. Diagnoses are reported to the NPR according to the World Health Organization's International Classification of Diseases, Version 10 (ICD-10). The 11-digit personal identification number unique to every inhabitant in Norway has been reported to the NPR from 2008 onwards. Substance use facilities have reported to the NPR from 2009 onwards.

### Data material

All individuals born in 1930—1994 (aged 18—82 years by the end of follow-up) who were registered at least once in somatic hospitals during 2008—2012 with a diagnosis of epilepsy, as defined by ICD-10 codes G40.0—G40.9 (G40.x), were eligible for the study (people with epilepsy). The NPR provided data on sex, year of birth, and all ICD-10 codes registered during 2008—2012 in somatic and psychiatric hospitals and outpatient clinics, and in substance use treatment facilities.

We defined alcohol use disorder by ICD-10 code F10.x, non-alcohol drug use disorder by F11.x—F19.x, psychotic disorders by F20.x—F31.x, F32.3, or F33.3, schizophrenia spectrum disorders by F20.x, F21.x, F22.x, or F25.x, and bipolar disorder by F30.x or F31.x registered at least once during 2008—2012 in NPR. The ICD-10 codes F11.x—F19.x refer to mental and behavioural disorders due to a broad range of specified drugs (opioids, cannabinoids, sedatives, cocaine, and other psychoactive substances). In the remaining text we use the term ''drug use disorder'' for non-alcohol use disorder.

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We obtained whole-population data files from the NPR for comparison of people with epilepsy with the population without epilepsy. Population figures were obtained from Statistics Norway (www.ssb.no).

To test the validity of our findings, we repeated the analyses using people registered at least once during 2008—2012 with a diagnosis of diabetes type 1 (ICD-10 code E10.x) as an alternative comparison group. The NPR provided the same kind of data for people with diabetes type 1 as for people with epilepsy. Analyses were finally repeated with more strict case definitions of epilepsy, first with at least two registrations with epilepsy as the criterion and subsequently with at least five registrations with epilepsy as the criterion.

### Statistical analysis

The proportion of the population registered with epilepsy in different sex and age categories was obtained by dividing the number of patients by the average number of sex- and age-matched residents in Norway during 2008—2012. We applied Pearson's chi-square test to test for differences by sex. In all other analyses, people with epilepsy were compared to the population without epilepsy. We used fitted log-binomial regression models to estimate relative risks (RRs) with associated 95% confidence intervals (CIs) (Deddens and Petersen, 2008). RRs were adjusted for sex and age (categorized into in 10-year age groups).

Stata software package, Version 11.2 (StataCorp. 2009, Stata Statistical Software: Release 11, College Station, TX: StataCorp LP) was used for the data analysis.

### Ethical approval

The study was approved by the Regional Committee for Medical and Health Research Ethics, South-East Region, Norway.

## Results

### Distribution of epilepsy by sex and age

In the five-year period of 2008—2012, a total of 33,571 individuals (0.90% of the population) born in 1930 through 1994, were registered at least once with a diagnosis of epilepsy in somatic hospitals. The overall proportion was significantly higher among men (0.93%) than among women (0.87%), with $p < 0.001$. For both men and women, the proportion was highest in the oldest age groups, and slightly higher in the youngest age groups than for middle-aged individuals (Figure 1). The difference between men and women was most pronounced in the oldest age groups.

### Substance use disorders in epilepsy

The overall proportion registered with substance use disorders (alcohol use disorder and/or drug use disorder) among people with epilepsy was 8.61% (2892/33,571). There was considerable overlap between these conditions; 25.16% (485/1928) of people with epilepsy who were registered with alcohol use disorder were also registered with drug use disorder, and 33.47% (485/1449) of people with epilepsy who were registered with drug use disorder were also registered with alcohol use disorder.

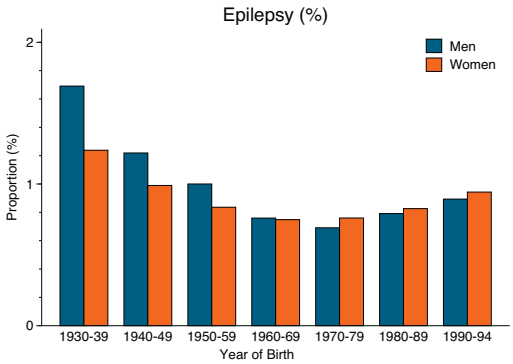


**Figure 1** Proportion of people registered with epilepsy during 2008—2012, by sex and year of birth. Data from the Norwegian Patient Register.

The total proportion registered with alcohol use disorder was 5.74% among people with epilepsy and 1.29% in the population without epilepsy, with an adjusted RR of 4.42 (95% CI: 4.22—4.62) (Table 1). In people with epilepsy, the proportion registered with alcohol use disorder peaked among men born in 1950—1959 at 13.02% (Figure 2, upper panel). In the population without epilepsy, the proportion registered with alcohol use disorder also peaked among men born 1950—1959, but at a much lower level (2.48%) (Figure 2, upper panel).

Similarly, the total proportion registered with drug use disorder was 4.32% in people with epilepsy and 1.22% in the population without epilepsy (adjusted RR: 3.86 [95% CI: 3.67—4.06]) (Table 1). Both in people with and without epilepsy, the highest proportion registered with drug use disorder was observed among people born in 1980—1989 (Figure 2, lower panel). Among people with epilepsy in this age group, 9.78% of men and 5.54% of women were registered with drug use disorder, while the corresponding figures in the population without epilepsy were 2.94% and 1.49%, respectively.

### Psychotic disorders in epilepsy

The proportion registered with psychotic disorders was 3.75% in people with epilepsy and 1.31% among people without epilepsy (adjusted RR 2.96 [95% CI: 2.80—3.12]) (Table 1).

We observed a higher proportion registered with schizophrenia spectrum disorders among people with epilepsy compared with the population without epilepsy (1.72% vs. 0.60%), with an adjusted RR of 2.94 (95% CI: 2.71—3.19) (Table 1). The sex and age distributions of schizophrenia spectrum disorders among people with and without epilepsy are shown in Figure 3 (upper panel).

The proportion registered with bipolar disorder was more than twice as high among people with epilepsy (1.50% vs. 0.68%), with an adjusted RR 2.29 (95% CI: 2.10—2.49). The

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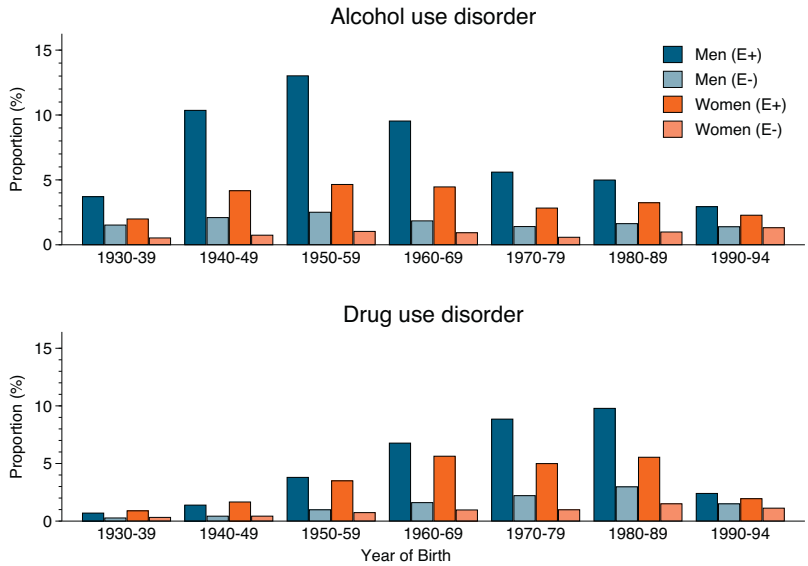


**Figure 2** Proportion of people registered with alcohol use disorder (upper panel) and drug use disorder (lower panel), among people with epilepsy (E+) and without epilepsy (E−) during 2008–2012, by sex and year of birth. Data from the Norwegian Patient Register.

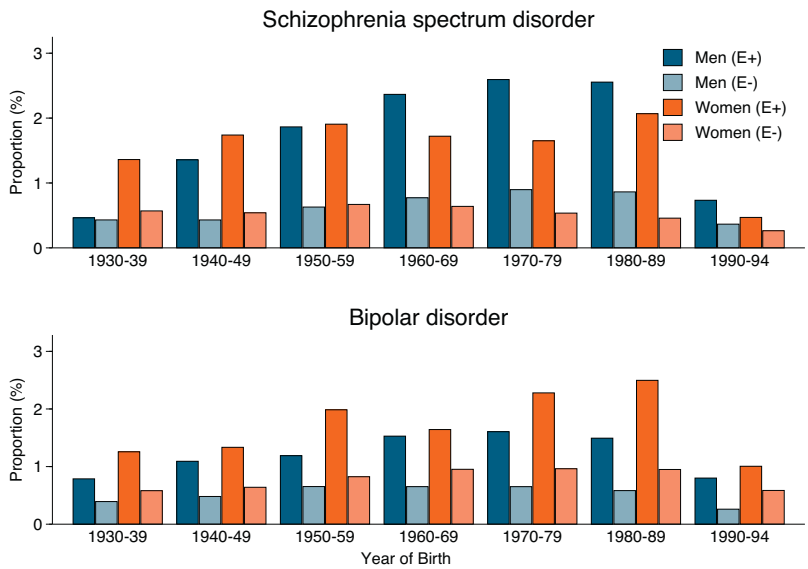


**Figure 3** Proportion of people registered with schizophrenia spectrum disorders (upper panel) and bipolar disorder (lower panel), among people with epilepsy (E+) and without epilepsy (E−) during 2008–2012, by sex and year of birth. Data from the Norwegian Patient Register.

highest proportion (2.50%) was observed among women with epilepsy born in 1980–1989 (Figure 3, lower panel), while the corresponding figure among women in the same age group without epilepsy was 0.94%.

## Overlapping psychiatric comorbidities in epilepsy

Among people with epilepsy, 11.34% (3808/33,571) were registered with substance use disorders and/or psychotic

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**Table 1** Relative risks for alcohol use disorder, drug use disorder, schizophrenia spectrum disorders, and bipolar disorder registration in specialist health care services, people with epilepsy[a] compared to people without epilepsy. Data from the Norwegian Patient Register 2008–2012.

| | People with epilepsy ($N = 33,571$) | | People without epilepsy ($N = 3,705,938$) | | Unadjusted RR[b] (95% CI) | Adjusted RR[c] (95% CI) |
|---|---|---|---|---|---|---|
| | Cases ($n$) | Proportion (%) | Cases ($n$) | Proportion (%) | | |
| Alcohol use disorder[d] | 1928 | 5.74 | 47,742 | 1.29 | 4.46 (4.26–4.66) | 4.42 (4.22–4.62) |
| Drug use disorder[e] | 1449 | 4.32 | 45,068 | 1.22 | 3.54 (3.37–3.74) | 3.86 (3.67–4.06) |
| All psychoses[f] | 1259 | 3.75 | 48,375 | 1.31 | 2.87 (2.72–3.04) | 2.96 (2.80–3.12) |
| Schizophrenia spectrum[g] | 576 | 1.72 | 22,201 | 0.60 | 2.86 (2.64–3.11) | 2.94 (2.71–3.19) |
| Bipolar disorder[h] | 504 | 1.50 | 25,284 | 0.68 | 2.20 (2.02–2.40) | 2.29 (2.10–2.49) |

[a] Epilepsy was defined by at least one registration with ICD-10 code G40.x in a somatic hospital during 2008–2012.
[b] Relative risk.
[c] Adjusted RR was calculated by general linear modeling using the log-binominal distribution as the link function.
[d] At least one registration with ICD-10 code F10.
[e] At least one registration with ICD-10 codes F11–F19.
[f] At least one registration with ICD-10 codes F20–F31, F32.3, F33.3.
[g] At least one registration with ICD-10 codes F20, F21, F22, F25.
[h] At least one registration with ICD-10 codes F30, F31.

disorders. We found that 7.59% (2549/33,571) were registered with substance use disorders, but no psychotic disorders. Furthermore, 2.73% (916/33,571) of people with epilepsy were registered with psychotic disorders, but no substance use disorders. The remaining 1.02% (343/33,571) of people with epilepsy were registered with *both* substance use *and* psychotic disorders.

### Additional analyses

In the alternative comparison group (patients registered with diabetes type 1 in somatic hospitals during 2008–2012), the overall proportions registered with alcohol use disorder, drug use disorder, and psychotic disorders were 2.80%, 1.78%, and 2.16%, respectively. These figures were lower than in people with epilepsy but higher than in the main comparison group (people without epilepsy) (Table 1).

We finally repeated the analyses with stricter definitions of epilepsy. Among patients with two or more registrations with epilepsy ($N = 23,177$), the overall proportions registered with alcohol use disorder, drug use disorder, and psychotic disorder were 5.00%, 4.32%, and 3.75%, respectively. The corresponding figures for people with five or more registrations with epilepsy ($N = 10,824$) were 4.38%, 3.65%, and 3.64%. These figures were similar to what was found when using a single registration with epilepsy as the criterion (Table 1).

## Discussion

We observed a strong association between substance use disorders and epilepsy, and between psychotic disorders and epilepsy in individuals treated in the specialist health care system. A considerable proportion of people with epilepsy, more than one in 10, were registered with substance use disorders and/or psychotic disorders. Also, one in 100 people with epilepsy were registered with both conditions. To the best of our knowledge, this is the first population-based study to assess the relationship between substance use disorders and epilepsy using the general population as the reference group and among the largest studies of the relationship between psychotic disorders and epilepsy.

### Distribution of epilepsy

We found that 0.90% of the population had been registered with a diagnosis of epilepsy over the five-year study period (2008–2012). Although previously reported estimates of the prevalence of epilepsy from other countries have varied substantially due to differences in sampling frames and study designs (Banerjee et al., 2009; Ngugi et al., 2010), interpreting this figure as an estimate of the prevalence in the general population corresponds reasonably well with previous findings (Karouni et al., 2010; Kessler et al., 2012; Qin et al., 2005; Rai et al., 2012; Tellez-Zenteno et al., 2005).

### Substance use disorders in epilepsy

Alcohol use disorder and drug use disorder were considerably more frequently registered in people with epilepsy

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compared to the population without epilepsy. The proportion registered with substance use disorders was particularly high among young (mainly drug use disorder) and middle aged men (mainly alcohol use disorder) both among those with and without epilepsy.

Increased prevalence of substance use disorder among people with epilepsy has previously been reported only from surveys (Kessler et al., 2012; Tellez-Zenteno et al., 2007). Recently, higher proportions of alcoholism and drug abuse have been shown among people with epilepsy than among people with migraine or lower extremity fracture in a registry study from the USA (Selassie et al., 2014).

People with substance use disorders are at high risk of developing seizures, but the magnitude of this complication is difficult to ascertain (Leach et al., 2012). Depending on the pharmacodynamic properties of the substance, acute symptomatic seizures may be precipitated by either intoxication or withdrawal. When a pharmacological action is the sole mechanism of a seizure, epilepsy is, by definition, not present. A range of other seizure-precipitating life-style factors, including sleep deprivation and stress, may accompany substance use disorders. Furthermore, the association between substance use and seizures may also result from indirect mechanisms. Related intracranial lesions may entail acute as well as remote causes of seizures, such as traumatic brain injury and stroke (Leach et al., 2012; Rathlev et al., 2002). An epileptogenic effect of chronic alcohol ingestion has also been suggested (Samokhvalov et al., 2010).

Comorbidity between two disorders does not need to be the result of direct causal mechanisms (Neale and Kendler, 1995). The association between substance use and epilepsy can also reflect a non-causal relationship caused by common underlying risk factors (genetic or environmental) influencing both disorders.

Alcohol is a major seizure precipitant. In a prospective study on patients acutely hospitalized with seizures, 35% were identified with recent hazardous alcohol consumption (Brathen et al., 1999). Among these patients, two in three were considered to have withdrawal seizures, and 51% were considered to have focal onset seizures by clinical evaluation including EEG and brain imaging. These findings reflect the difficulties in differentiating between acute symptomatic seizures and breakthrough seizures precipitated by alcohol as part of epilepsy (Beghi et al., 2010; Rathlev et al., 2002). One can presume that epilepsy is over-diagnosed in subjects with substance use disorders. If abuse is unidentified, recurrent seizures precipitated by abuse are liable to be perceived as epilepsy. Also, the threshold for referrals to substance abuse treatment facilities might be lower for people with epilepsy, which also might influence the observed association. On the other hand, alcohol abuse has been shown to be under-reported in people with epilepsy, due to denial of its presence (Brathen et al., 1999). The current study indicates that the association between substance use disorders and seizure disorders is a substantial problem that needs more clinical as well as scientific focus.

Management of patients affected by both seizure disorders and substance use disorders can be challenging. These patients may receive inadequate assessment of their seizure disorder in psychiatric and substance use treatment settings. Also, dually affected patients may not receive appropriate epilepsy care due to non-compliance with regard to life-style, clinical appointments, and prescribed drug treatment.

## Psychotic disorders in epilepsy

We found that psychotic disorders were more frequently registered in people with epilepsy than in the population without epilepsy, in agreement with previous results. Mental health problems in people with epilepsy have previously been assessed in clinical samples (Dalmagro et al., 2012; Henning and Nakken, 2010; Jones et al., 2007; Mula et al., 2008), in surveys carried out in the general population (Kessler et al., 2012; Rai et al., 2012; Stefanello et al., 2010; Tellez-Zenteno et al., 2007), and in registry studies (Bredkjaer et al., 1998; Fazel et al., 2013; Hesdorffer et al., 2012; Karouni et al., 2010; Qin et al., 2005; Selassie et al., 2014). Registry-based studies from Denmark have investigated incidence of psychotic disorders in epilepsy (Bredkjaer et al., 1998; Qin et al., 2005) and report a two- to three-fold increased incidence rate of psychosis spectrum disorders and schizophrenia-like psychosis in people with epilepsy compared with the general population (Bredkjaer et al., 1998; Qin et al., 2005). Interestingly, in a smaller registry study from the UK, patients registered with epilepsy in the General Practice Database had higher incidence rates of psychosis and other mental health problems both before and after the epilepsy diagnosis (Hesdorffer et al., 2012). Similarly, increased rates of psychiatric comorbidity predating and succeeding seizure onset have been reported from a Swedish a registry-based case-control study (Adelow et al., 2012). In a Norwegian study based on drug prescription patterns, the total prevalence of psychiatric comorbidity in epilepsy was estimated to be 32% (Karouni et al., 2010). That study also showed that antipsychotics were used 5.8 times more frequently among patients taking antiepileptic drugs for epilepsy than in the general population. Furthermore, the odds of suicide has been shown to be significantly elevated in people with epilepsy, indicating that psychiatric disorders may play an important role in the premature mortality seen in epilepsy (Fazel et al., 2013).

The clinical and pharmacological relationships between seizure disorders and psychotic disorders are complex. Psychosis may be temporally related to seizures in various ways, either postictally or interictally, and usually occurs in people with chronic, uncontrolled epilepsy (Nadkarni et al., 2007). Antiepileptic drugs may precipitate psychiatric symptoms, either by specific pharmacodynamic effects or in the form of alternative psychosis when seizures are suppressed. The potential seizure-inducing properties of antipsychotic drugs need to be considered (Brodtkorb and Mula, 2006). Reciprocal medical interactions are challenging to both neurologists and psychiatrists.

Recent studies have suggested that the association between epilepsy and schizophrenia spectrum disorders could reflect a non-causal relationship being explained by common underlying neurobiological mechanisms (Chang et al., 2011; Clarke et al., 2012). Shared genetic predispositions to neurodevelopmental disorders (including autism spectrum disorders, schizophrenia spectrum disorders, epilepsy, and intellectual disability) represented by pathogenic copy number variants have also been detected

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(Grayton et al., 2012). These findings challenge the traditional view that psychiatric comorbidities exclusively are complications to or consequences of the underlying seizure disorder (Kanner, 2013).

### Strengths and limitations

The main strength of the current study is the utilization of registry data covering the entire population over a five-year study period. We had access to diagnostic data from all hospitalizations and outpatient visits in somatic and mental health care institutions, substance treatment facilities, and private practitioners in the field of psychology and psychiatry.

As in other studies based on observational, routinely collected data, a major limitation is the lack of validity testing of the diagnoses. However, preliminary results from an ongoing validity study indicate that approximately 80% of diagnoses with the ICD-10 code G40.x in the NPR are correct for children younger than 14 years (work in progress). In a study from Canada, the positive predictive value of the ICD-10 codes for epilepsy in specialist health care administrative databases was found to be as high as 98.6%.

As alcohol and drug use disorders are characterized by a high risk of occasional acute symptomatic seizures (Brathen et al., 1999; Leach et al., 2012; Rathlev et al., 2002), the differential diagnosis between unprovoked and withdrawal seizures may be difficult. Thus validity might represent a particular problem in the current study. We therefore repeated all analyses with more strict case definitions of epilepsy, first with at least two registrations with epilepsy as the criterion and subsequently with at least five registrations with epilepsy as the criterion. The proportion registered with substance use or psychotic disorders remained higher in people with epilepsy also when stricter definitions of epilepsy were applied.

The presumed lower threshold for referral of people with epilepsy to substance use treatment facilities might also have inflated the observed association between epilepsy and substance use disorders. Furthermore, treatment in the specialist health care system for one condition (in our case, epilepsy) may increase the chance for registration of a second condition (in our case, substance use disorder or psychosis), both due to potentially increased referral rates and registration practices. Such mechanisms might give the impression that the second condition occurs more frequently among patients with the first condition than in a general population, even if this is not the case. In order to investigate this further, we repeated all analyses described here for patients registered in somatic hospitals with diabetes type 1. In this patient group, the overall proportions registered with alcohol use disorder, drug use disorders, and psychotic disorders were higher than in the general population, but considerably lower than in people with epilepsy. Thus, also when using another group of patients with a chronic disease as the reference group, we found an elevated proportion of substance use disorders and psychotic disorders among patients with epilepsy. However, we cannot rule out that the high comorbidity rates observed in our study could be influenced by selection bias. It is well known that subjects with more than one disorder are more likely to be part of a clinical sample (Berkson, 1946), and therefore the comorbidity rates observed in treatment-seeking samples can be inflated compared to the general population.

Another limitation of the current study is the restricted time frame available for research. As the NPR has included individual-level data only from 2008, it has not been operative long enough to allow estimation of incidence rates or to investigate time patterns.

### Conclusions

The current study reveals a strong association between substance use disorders and epilepsy and between psychotic disorders and epilepsy among patients in specialist health care. A high clinical awareness of these complex associations is needed. Our observations highlight the need for a proficient psychiatric service as part of the comprehensive management of people with epilepsy, and demonstrate the importance of highly specialized and interacting multidisciplinary services to this often dually or even multiply affected patient group.

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# PAPER II

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Case Report

# Experiential seizures related to the hippocampal-parahippocampal spatial representation system

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ABSTRACT

Ictal visual hallucinations may have occipital as well as temporal lobe origin. We report a patient with clustering of focal aware seizures with visual hallucinations. Ictal EEG findings and seizure semiology with alternating contralateral elementary visual phenomena and non-lateralizing experiential hallucinations (visual scenes, memory flashbacks, spatial distortion) corresponded to a lesion in the posterior part of the right parahippocampal gyrus. This area is part of the hippocampal-parahippocampal system for mapping allocentric space. Within this system, the parahippocampal cortex encodes information about visual environmental scenes in concert with functionally defined neurons relevant for episodic memory and spatial cognitive processes (place, grid, border and head direction cells, as well as neurons tracking the passage of time). These functions are tightly linked to visual exploration.

We suggest that the hippocampal-parahippocampal spatial navigation system is a crucial part of the networks responsible for the semiology of experiential seizures with complex visual hallucinations and elements of recall.



## 1. Introduction

Hallucinations in people with epilepsy can be divided as ictal, postictal and interictal according to their relationship to seizure events [1]. Ictal symptoms are determined by the function of the seizure-generating area in the brain, i.e. the area of ictal onset and propagation in synaptically connected network areas. Ictal visual hallucinations may have occipital as well as temporal lobe origin. In occipital lobe epilepsy, they consist of elementary sensory symptoms restricted to one visual field. In temporal lobe epilepsy, they may be elementary and lateralized, as well as complex and experiential without confinement to any visual field. Experiential seizures may encompass vivid memory-like hallucinations, such as scenes from the past [2–8].

We present a case of focal epilepsy and prolonged bouts of mixed elementary and complex visual hallucinations due to a lesion in the right parahippocampal cortex. The neuronal correlates of spatial cognition and episodic memory in relation to visual representations are discussed with respect to the hippocampal-parahippocampal systems for mapping allocentric space [9]. The present case study illustrates the value of systems neuroscience to examine how psychiatric and neurological symptoms can manifest through comparable pathophysiological mechanisms within overlapping neural networks [10].

## 2. Case history

### 2.1. Background

Since her mid-twenties, this right-handed woman presented focal to bilateral tonic–clonic seizures (FTCS) during sleep. EEG showed right-sided temporal slow activity, and MRI demonstrated an abnormality in the posterior part of her right parahippocampal gyrus initially interpreted as gliosis (Fig. 1, upper part).

She was treated with lamotrigine (LTG), but still had occasional nocturnal FTCS. She became pregnant at age 31. Adjustments of LTG doses according to declining serum concentrations failed to maintain pre-pregnancy levels. In the last months of gestation, she reported episodes of déjà vu

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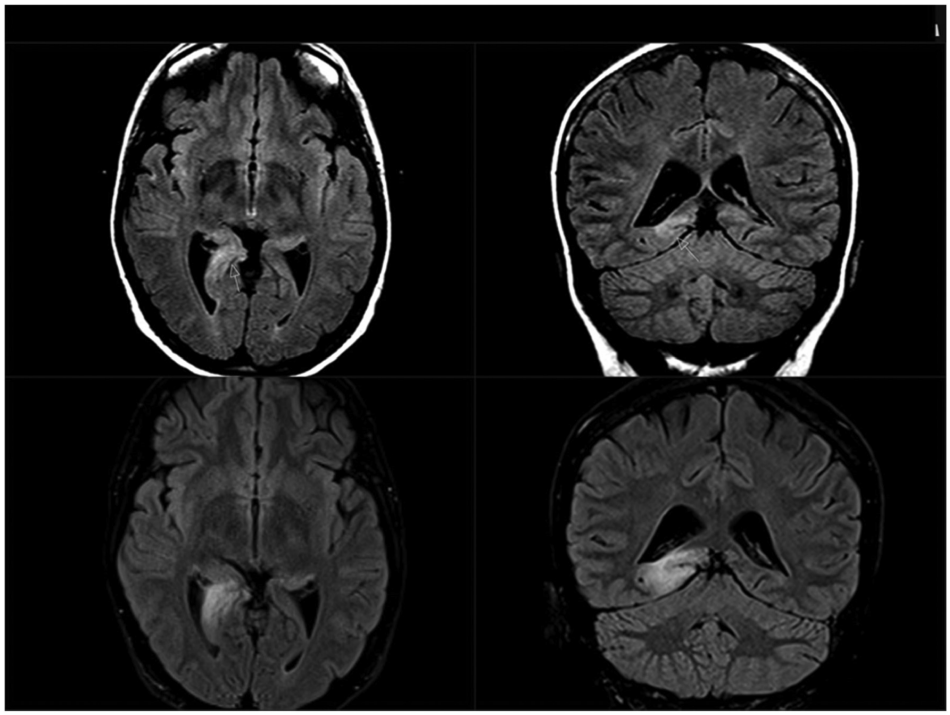

**Fig. 1.** MRI findings. FLAIR images (axial plane, left; coronal plane, right). Upper: Prior to serial seizures with complex hallucinations. Lesion in the posterior part of the right parahippocampal gyrus and in the hippocampal tail. Lower: During serial seizures. Substantial volume increase of the lesion with extension toward the occipital cortex.

followed by visual phenomena in her left visual field. These included flashing lights as well as seeing a mirror reflection of herself (autoscopy).

### 2.2. Ictal hallucinations

After another nocturnal FTCS in gestational week 36, she became confused and agitated. She screamed, ran around, and tried to jump off her balcony. A psychosis was suspected, and she was acutely admitted to psychiatric hospital. These symptoms quickly resolved. She had amnesia for the entire episode. Later, she reported recurrent flashing lights evolving to vivid complex visual hallucinations perceived as revivals of previous dreams and experiences. Interictal EEG showed epileptiform discharges in her right posterior temporal area.

Eight days after the acute event, MRI showed a substantial volume increase of the lesion in her right posterior temporal lobe toward the corresponding posterior horn of the lateral ventricle and retrosplenial cortex. The changes were interpreted as cytotoxic oedema and included the hippocampus as well as the parahippocampal cortex (Fig. 1, lower part).

After delivery by caesarean section, clinical examination revealed a complete left-sided homonymous hemianopia. Frequent series of episodic visual hallucinations continued. The various semiological features are reported in Table 1. The symptoms were recognized as imaginary, precluding true psychosis. Interictally, she reported an odd feeling of spatial disorientation.

Long-term video-scalp EEG was performed during episodic visual hallucinations and demonstrated corresponding ictal activity in the

**Table 1**
Reported visual perceptions during focal aware serial seizures.

| |
|---|
| Repetitive, stereotypical and elementary visual hallucinations in the left visual field: |
| - Bright flickering light, partly as intense sunshine |
| - Mirror reflection of myself |
| Diffusely distributed complex, moving and non-stereotypical visual hallucinations and illusions in the entire visual field, sometimes with left-sided predominance: |
| - Difficulty reading and writing, letters change form and position, transform to strange signs, resembling hieroglyphics – cannot control where my pen hits |
| - The room turning smaller and darker and then larger and brighter |
| - Familiar sceneries of landscapes, trees, running water, rivers |
| - Beaches and cottages/boathouses by the sea, reminiscent of previously visited holiday locations |
| - People with shopping bags passing at the local supermarket |
| - Distortion of people's faces turning purple; blood |
| - Hair growing in people's faces, covering only parts of the face or the entire face, as if people turn into werewolves |
| - Moving purple spots and stains of oil – colourful – to the left – also all over the room – difficult to explain |
| - Crawling bugs and spiders |

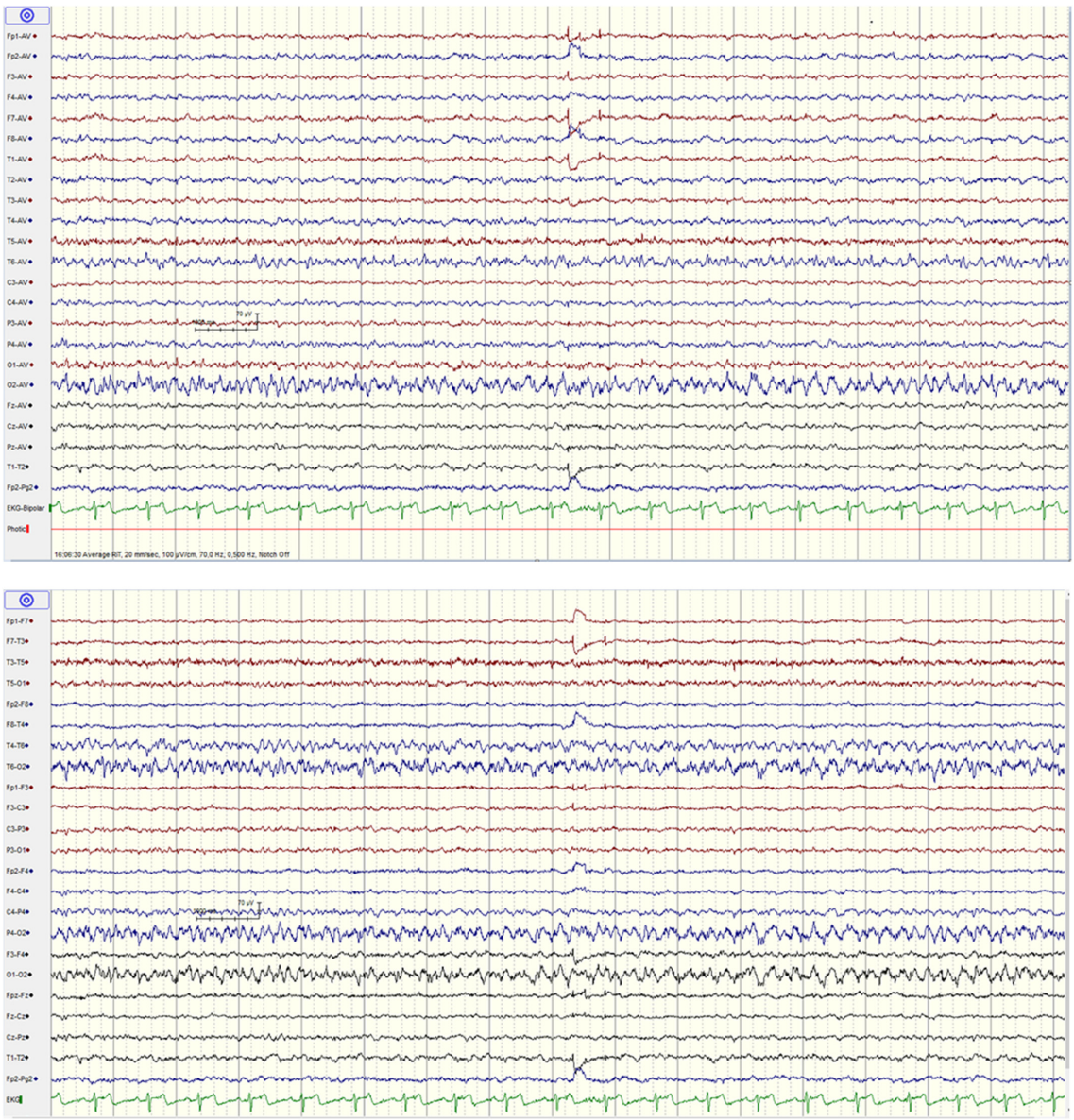


**Fig. 2.** Stereotypical ictal EEG activity associated with non-lateralizing visual hallucinations with spatial distortion during long-term monitoring (time 04.06.30 PM, see Table 2). Montage: average, upper; bipolar longitudinal, lower. Electrographic seizures begin with slow 3-Hz delta activity in the right occipital and posterior temporal region (leads O2 and T6), evolve to spiky rhythmic 8-Hz activity; midway, the frequency declines to 4-Hz theta activity.

right temporo-occipital area (Fig. 2). Subclinical ictal activity was recorded during sleep. In Table 2, ictal experiences during long-term EEG are reported *verbatim* as written by the patient, seemingly hampered by visual and spatial disturbances. During the first recorded cluster, four clinical seizures occurred within 16 min.

### 2.3. Outcome

Add-on valproate controlled the seizures for several weeks. Another MRI after seven weeks showed a complete return to pre-pregnancy state, suggesting that the changes represented post-ictal phenomena (Fig. 1). Clinically, the visual field defect had also resolved.

Later, focal aware seizures recurred. This time, the initial phenomena consisted of déjà vécu with an idea that looking at a random object induced seizures. Visual symptoms were limited to simple left-sided phosphenes with a perception of the surroundings turning unique and spectacular, along with anxiety, palpitations and abdominal discomfort. She developed drug-resistant epilepsy, and she was eventually referred for epilepsy surgery assessment three years later. A depth electrode EEG recording (now in the absence of ictal scalp EEG activity) demonstrated

**Table 2**
Ictal EEG activity and clinical symptoms recorded during long-term monitoring.

| Scalp EEG | Digital time PM | Time PM, recorded by patient | Ictal symptoms *verbatim* reported in writing |
|---|---|---|---|
| Ictal activity | 03:48:41–03:49:54<br>1 m, 11 s | 03:50 | *Reading and writing*: Difficulties; the letters rearrange. |
| EEG not saved | | 3:55 | *Writing SMS*: Difficult, letters appear misplaced; they look like different signs. |
| EEG not saved | | 04:02 | *Reading book*: Letters change place; move – understand the word, but misspelt. |
| Ictal activity | 04:05:58–04:07:06<br>1 m, 8 s | 04:06 | Visions, predominantly to the left, but then all over the table in front of me/to the side/the room looks different – also some flashings, just lasting ½ min. |
| Ictal activity | 04:21:59–04:22:39<br>38 s | 04:20 | *Awakening from nap*: Very strong sunshine up to the left. Water, beach, boathouses, beautiful places. Everything within 1 min. Difficult to read what I am writing now. |
| Ictal activity | 05:40:36–17:41:39<br>1 m, 3 s | | Seizure not reported |
| Ictal activity | 07:14:13–19:15:32<br>1 m, 19 s | 07:15 | Visions, seeing myself in bed – up to the left – boathouses, less than 1 min.<br>*Watching TV*: Lots of flashings up to the left; first visions on the screen; the notepaper looks different.<br>Visions on the wall lasting about 1 min. My sight is very poor; cannot read what I am writing. |
| No ictal activity | | 07:35 | *Watching TV/looking out of the window*: Poor vision, as if I am not wearing lenses, but they are both in place. |
| No ictal activity | | 08:30 | Lots of hallucinations in my entire visual field; scenery etc.; mixed with what is actually in the room. I know what is real, as I recall how it looked like a couple of minutes ago. The room changes – gets smaller and darker, then bigger and brighter, but I know what is real. The hallucinations last less than 1 min, but come and go with short intervals. Poor vision makes me unable to control my spelling. |
| Ictal activity | 10:59:43–11:01:14<br>1 m, 31 s | 11:00 | *Surfing on the mobile*: Hallucinations appear as soon as I start reading. See many things on the walls for about 30 s. My eyesight gets worse. Difficult to read, even large font. |

SMS, short message service (cell phone).

ictal onset related to the lesion in her right parahippocampal gyrus. A lesionectomy was performed. Histological examination revealed a ganglioglioma grade 1. Following the surgery, she was left with aware seizures with an initial odour followed by déjà vu sensations. FTCS and complex hallucinations have not recurred.

Ethical approval other than collection of written informed consent was not required by the Regional Committee for Ethics in Research.

## 3. Discussion

The patient developed an enduring state of relapsing and remitting ictal symptoms lasting several days, approximating focal status/"aura continua" [11,12]. The excessive focal seizures appeared to cause a visual field deficit corresponding to an increase of MRI FLAIR signal in the vicinity of the lesion, likely caused by sustained cerebral hypoperfusion [13,14]. Presumably, these transitory changes enhanced ictal activity and propagation causing further neuronal damage, which may have contributed to subsequent drug-resistance [15].

Ictal visual symptoms may present as elementary hallucinations (seeing bright spots or simple geometrical figures) typically originating in the primary visual cortex, whereas complex hallucinations, such as seeing whole scenes, have been suggested to involve the visual association areas in the temporal/parietal lobes [16]. A series of surgically treated patients with ictal visual symptoms clearly demonstrated that elementary hallucinations can also occur with temporal lobe onset (anteromedially and posteriorly), similarly to the present patient, while complex hallucinations never occurred in distinct occipital lobe onset seizures [17]. In that study, elementary visual hallucinations were confined to the contralateral visual field, whereas a lateralization of complex hallucinations was not reported. Still, in all cases, ictal EEG activity was localized to a lesion demonstrated by MRI or to its neighbouring regions [17]. Elliott and Shorvon claim that complex hallucinatory experiences in epilepsy cannot be well localized, and the more elementary they are, the more localized they tend to be [6]. Noteworthy, simple autoscopic mirror images are likely to be lateralized [18].

In the present patient, non-lateralizing, abundant and non-stereotypical experiential phenomena were associated with ictal temporo-occipital scalp EEG activity corresponding to a parahippocampal lesion. This constellation calls for further explanation. The lesion was located within the posterior portion of the medial temporal lobe corresponding to the parahippocampal cortex where both functional MRI signal and single unit recordings have revealed neurons encoding visual scenes selectively [19,20]. This particular area is part of the hippocampal-parahippocampal system for mapping allocentric space. It contains several functionally specific neurons associated with spatial cognition and episodic memory, such as place, grid, border and head direction cells [9,21], as well as neurons tracking the passage of time [22,23]. In rodents, these functionally defined neuronal types are phylogenetically preserved across mammals and have also been reported in primates, including humans [24–26]. Although associated with visual phenomena, this spatial navigation system does not relate to any visual field lateralization. Based on single hippocampal neuron recordings during episodic memory recall in humans [27], it might be speculated whether activation of subsets of these specific cell populations could elicit experiential phenomena related to recollection of previously experienced scenarios and situations (landscapes, moving elements, faces) in the form of a "mental diplopia". Consistent with this hypothesis, it has been reported that electric stimulation of the parahippocampal place-selective area elicited various topographical visual hallucinations with qualities of déjà vu [28]. Conceivably, these functionally defined neurons act in concert with synaptically connected areas within various "visual streams" and epileptic pathways. A complex functional connectivity based on multiple and bidirectional epileptic propagation within these subcortical networks may confuse the relationship between the epileptogenic and symptomatogenic zones and thus explain the abundant and variable semiology [29]. Advanced stereo-EEG recordings during experiential seizures might further map the responsible neuronal networks [28,30].

These recent findings now add to the understanding of experiential phenomena in people with temporal lobe epilepsy, so wonderfully described and discussed in detail by Penfield [2,3] and Gloor [4] several decades ago. The medial temporal lobe navigation system seems to shape our visual experience [31]. We believe that the present example illustrates the relevance of a more precise delineation of the principal symptomatogenic zones and networks responsible for this seizure type. A lateralizing value of experiential seizures is dubious, as these phenomena have been recorded or elicited from both hemispheres [2–5,8,28], although intuitively, visuo-spatial phenomena may be thought to predominate from the non-dominant hemisphere [3].

## 4. Concluding remarks

The electroclinical features in our patient alternated between contralateral elementary and non-lateralized complex hallucinations in the form of visual scenes due to a lesion in the right parahippocampal

cortex. We hypothesize that activation of the hippocampal-parahippocampal spatial navigation systems causes experiential hallucinations by interaction with visuospatial networks. Specific neuronal populations associated with spatial cognition and episodic memory may be responsible for the symptomatology, conceivably together with propagation to pathways with neocortical cognitive and sensory functions. These networks may be part of the anatomical substrate for experiential seizures.

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## Declaration of competing interest

None.

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# PAPER III

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# Bidirectionality of antiseizure and antipsychotic treatment: A population-based study

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ABSTRACT

*Purpose:* To study the prevalence and directionality of comorbid epilepsy and psychosis in Norway.
*Methods:* The Norwegian Prescription Database (NorPD) provided individual-based information on all antiseizure medications (ASMs) and antipsychotic drugs (APDs) dispensed during 2004–2017. Subjects were ≥18 years of age at the end of the study period. Diagnosis-specific reimbursement codes from the 10th revision of the International Classification of Diseases/2nd edition of the International Classification of Primary Care (ICD-10/ICPC-2) combined with ATC codes were used as indicators of diagnosis. Subjects had collected ASMs for epilepsy or APDs for psychosis at least four times, at least once issued with an ICD-10 code from the specialist healthcare service. Directionality was analyzed in subjects receiving both treatments. To reduce prevalent comorbidity bias, we employed a four-year comorbidity-free period (2004–2007). The use of specific ASMs and APDs was analyzed.
*Results:* A total of 31,289 subjects had collected an ASM for epilepsy at least four times, 28,889 an APD for psychosis. Both the prevalence of treatment for epilepsy and of treatment for psychosis was 0.8%. Further, 891 subjects had been treated for both conditions; 2.8% with epilepsy had been treated for psychosis, and 3.1% with psychosis had been treated for epilepsy. Among 558 subjects included in the analyses of directionality, 56% had collected the first APD before an ASM, whereas 41% had collected an ASM first. During the last year prior to comorbidity onset, levetiracetam, topiramate, or zonisamide had been used for epilepsy by approximately 40%, whereas olanzapine and quetiapine were most used in patients with psychosis, and clozapine in 13%.
*Conclusion:* The proportion of patients with prior antipsychotic treatment at onset of epilepsy is higher than previously acknowledged, as demonstrated in this nation-wide study. Apart from a shared neurobiological susceptibility, the bidirectionality of epilepsy and psychosis may be influenced by various environmental factors, including the interaction of pharmacodynamic effects. APDs may facilitate seizures; ASMs may induce psychiatric symptoms. In patients with combined treatment, these potential drug effects should receive ample attention, along with the psychosocial consequences of the disorders. A prudent multi-professional approach is required.


*Abbreviations:* NorPD, The Norwegian Prescription Database; ASMs, antiseizure medications; APDs, antipsychotic drugs; ICD-10, The 10th revision of the International Classification of Diseases; ICPC-2, The 2nd edition of the International Classification of Primary Care; DDD, Defined Daily Doses; ATC code, Anatomical Therapeutic Chemical code.

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## 1. Introduction

During recent years, there has been much focus on the comorbidity of psychiatric disorders in people with epilepsy. Psychosocial and neurobiological factors are at play. Virtually all psychiatric disorders seem to occur in a higher proportion of subjects with epilepsy than in those without, and observational studies have indicated a bidirectional relationship [1]. However, estimates have varied considerably across studies dependent on settings, sources of ascertainment, and diagnostic criteria. In a recent survey of patients acutely submitted to a psychiatric hospital, the life-time prevalence of epilepsy was 3.9% [2]. An extensive meta-analysis of 58 studies of psychosis in epilepsy showed a pooled prevalence of 5.6% (range 0.02–27%). There was substantial heterogeneity across individual studies, and further population-based research was requested [3].

Historically, psychosis in epilepsy has been attributed to the consequences of having seizures and the psychosocial burden of the diagnosis [4]. Less attention was given to the onset of epilepsy in people with prior psychosis [5]. In roughly the last 10 years, growing evidence of a reciprocal relationship also for psychosis has been found in selected populations, but few studies have had the data to substantiate this bidirectionality.

Some evidence has been documented in selected samples from various countries: A Japanese study from tertiary centers of 312 patients fulfilling the diagnostic criteria for both disorders identified 23 patients diagnosed with a psychotic disorder predating the diagnosis of epilepsy, whereas the majority developed interictal psychosis in the course of confirmed epilepsy [6]. In a Swedish case–control study of 1,885 subjects from the Stockholm Epilepsy Register, the risk for developing epilepsy after hospitalization for psychosis was increased by 2.3 compared to controls [7]. A similar retrospective cohort study of hospital admissions in the UK found an elevated risk of epilepsy of 2.1 and 3.0 in two different study materials including one covering the whole of England [8]. Another study from the UK using data from a general practice research database also demonstrated an increased rate of prior psychiatric disorders, including psychosis, in people with newly diagnosed epilepsy [9]. Likewise, two US studies of elderly subjects (>65 years), suggested that premorbid psychosis was an independent risk factor for late-onset epilepsy [10,11]. A recent literature review suggests that the incidence of epilepsy in patients with schizophrenia is 4–5 times higher than that of the general population [5]. Notwithstanding, scarce scientific attention has been given to the group of subjects with established psychosis at epilepsy onset, and the extent of this group is still not determined [3].

Hence, we set out to investigate the prevalence and directionality of comorbid epilepsy and psychosis in a population-based study of subjects receiving combined antipsychotic and antiseizure treatments using The Norwegian Prescription Database (NorPD) covering all Norwegian pharmacies. We wanted to assess the proportions of subjects first starting with either antipsychotic drugs (APDs) prescribed for psychosis or antiseizure medications (ASMs) prescribed for epilepsy.

## 2. Material and methods

This was a retrospective population-based observational study using pharmacoepidemiologic data from the NorPD.

### 2.1. Data material

The NorPD contains individual-based information on all drugs dispensed from Norwegian pharmacies from 2004. Diagnosis-specific codes reflect reimbursable indications, such as epilepsy and psychiatric disease. The 10th revision of the International Classification of Diseases (ICD-10) and the 2nd edition of the International Classification of Primary Care (ICPC-2) were implemented from 2008.

We obtained NorPD-data with information on all ASMs defined by the Anatomical Therapeutic Chemical code (ATC code) N03A and APDs defined by ATC code N05A collected from 2004 through 2017 in subjects ≥18 years of age at the end of the study period. The dataset included pseudonymous patient identification numbers, information on sex and year of birth, ATC code (version 2018), date of dispensation, number of defined daily doses (DDDs) per prescription, and reimbursement codes.

The adult population of Norway in the years 2004–2017 was collected from Statistics Norway [12].

### 2.2. Identification of diagnostic groups

Subjects were categorized into two diagnostic groups based on reimbursement codes: (1) epilepsy and (2) psychosis, limited to schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders (Table 1). Four unique prescriptions of ASMs for epilepsy or APDs for psychosis were required for inclusion, of which at least one had been issued with an ICD-10 reimbursement code from the specialist healthcare service.

### 2.3. Directionality

In subjects with prescriptions of both ASMs and APDs (epilepsy and psychosis comorbidity), we analyzed the directionality of treatments according to the first date of dispensation of each drug. To reduce prevalent comorbidity bias, we employed a four-year comorbidity-free period for those included in the analysis of directionality, meaning that no subjects had collected treatment for both disorders during these years.

### 2.4. Antiseizure and antipsychotic treatment

For each subject in the comorbidity groups, we identified unique ASMs and APDs prescribed during the last twelve months before onset of treatment for each condition. We also analyzed the number of ASMs used for epilepsy and APDs for psychosis during these twelve months. Finally, we analyzed the distribution of ASMs and APDs used both by subjects with and without comorbidity during the entire study period. We calculated mean DDD/patient/day for both ASMs and APDs prescribed for epilepsy and psychosis, respectively, according to subjects with or without comorbidity. The total DDDs per year of each drug was divided by total number of users, and further divided by 365 days.

**Table 1**
Diagnostic group based on ATC code and reimbursement codes according to ICD-10 and ICPC-2.

| Diagnostic group | ATC code | Reimbursement codes | |
|---|---|---|---|
| | | ICD-10 | ICPC-2 |
| 1 Epilepsy | N03A[a] | G40 | N88 |
| 2 Psychosis | N05A[b] | F20-F29, -F2[c] | P72, P98, -72[c] |

ATC code, Anatomical Therapeutic Chemical code; ICD-10, International Classification of Diseases; ICPC-2, International Classification of Primary Care.
[a] ATC code N03A: Antiseizure medication.
[b] ATC code N05A: Antipsychotics.
[c] Reimbursement codes defined by The Norwegian Medicines Agency 1.9.2008: -F2/-72 "Psychosis and psychotic symptoms in psychiatric disorders".

### 2.5. 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. Chi Squared ($\chi^2$) test was used to test for significant association between groups of comorbidity or non-comorbidity and prescribed medication. The continuous data of the variable DDD/patient/day deviated from a normal distribution, hence the non-parametric two-sample Wilcoxon rank-sum (Mann–Whitney) test was used to compare means. A $p$-value $\leq$0.05 was considered significant.

### 2.6. Ethics

The use of registry data for this study was approved by the Regional Committee for Medical and Health Research Ethics, Central Norway (2016/56 and 2018/629).

## 3. Results

### 3.1. Epilepsy

A total of 31,289 subjects had collected an ASM with a reimbursement code for epilepsy four times or more: 15,430 (49%) women and 15,859 (51%) men. The prevalence of treatment for epilepsy in the adult population of Norway was 0.8% (Table 2). By the end of the study period 4209 (13%) of the subjects had been without epilepsy treatment for more than 5 years, suggesting epilepsy in remission.

### 3.2. Psychosis

An APD for psychosis had been prescribed at least four times to 28,889 subjects: 13,863 (48%) women and 15,026 (52%) men. The prevalence of treatment for psychosis was also 0.8% (Table 2). By the end of the study period 4335 (15%) had not collected APDs for psychosis for at least 5 years.

### 3.3. Comorbid conditions

A total of 891 subjects were treated for both epilepsy and psychosis, 0.02% of the adult population. This gives a prevalence of APD treatment for the defined psychotic disorders in people also treated for epilepsy of 2.8%, and a prevalence of ASM treatment for epilepsy in people with psychosis of 3.1% (Table 2). There were 426 (48%) women and 465 (52%) men among the subjects with comorbid epilepsy and psychosis.

### 3.4. Directionality

The order of ASM and APD treatment in people with both epilepsy and psychosis is shown in Table 3. There were 558 subjects included in the analysis of directionality after the clean period 2004–2007. In 56% of the cases, the first APD was collected prior to the first ASM, whereas an ASM was collected first in 41%.

**Table 2**
Distribution and prevalence of epilepsy and psychosis in the adult population of Norway as defined by diagnostic reimbursement codes.

| Diagnostic group | Subjects ($n$) | Prevalence (%) |
|---|---|---|
| Epilepsy | 31,289 | 0.8[a] |
| Psychosis | 28,889 | 0.8[a] |
| Comorbid epilepsy and psychosis | 891 | 0.02[a] |
| Psychosis in epilepsy | | 2.8 |
| Epilepsy in psychosis | | 3.1 |

[a] Prevalence in the adult population of Norway (average population 2004–2017; 3,790,620).

**Table 3**
Directionality of epilepsy and psychosis as assessed by diagnostic reimbursement codes in 558 comorbid patients.

| | Subjects | | Mean age at onset of comorbid condition |
|---|---|---|---|
| | *N* | % | |
| APD first | 310 | 55.6 | 42 (SD 16.9) |
| ASM first | 231 | 41.4 | 39 (SD 19.4) |
| APD ASM same date | 17 | 3.1 | |
| Total | 558 | 100 | |

APD, Antipsychotic drug; ASM, Antiseizure medication.

### 3.5. Antiseizure and antipsychotic drugs

Fig. 1A and B provides an overview of the distribution of ASMs and APDs collected twelve months prior to onset of comorbidity. Out of the 231 subjects collecting ASMs first, 41 (18%) had not

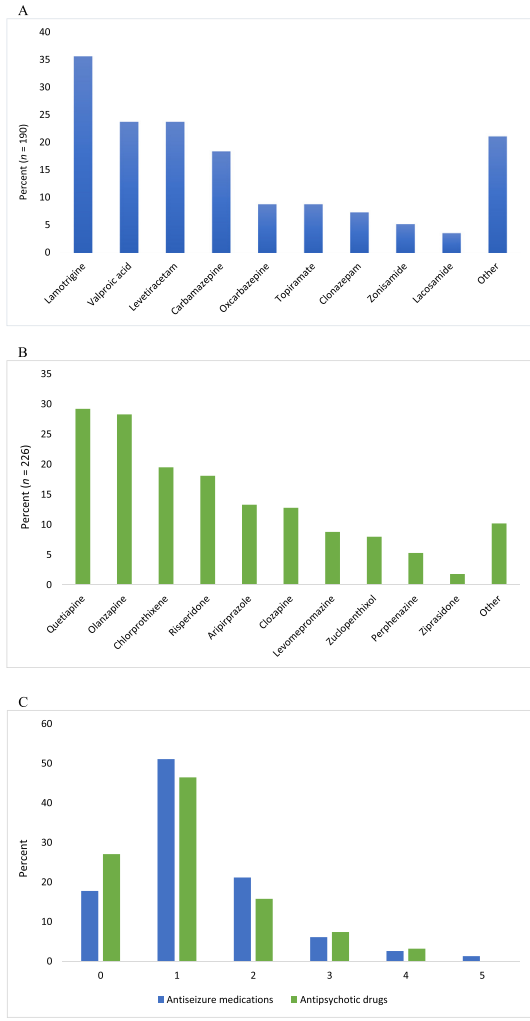



**Fig. 1.** Medications collected during the last year prior to onset of comorbidity; (A) antiseizure medications, (B) antipsychotic drugs, (C) numbers of used antiseizure medications and antipsychotic drugs.

**Table 4**
DDD/patient/day of ASMs and APDs according to groups of comorbidity and non-comorbidity.

| | ASM | | APD | |
|---|---|---|---|---|
| Year | Epilepsy w/psychosis[a] | Epilepsy w/o psychosis[a] | Psychosis w/epilepsy[b] | Psychosis w/o epilepsy[b] |
| 2004 | 1.04 | 1.06 | 0.95 | 0.98 |
| 2005 | 1.02 | 1.09 | 1.01 | 1.02 |
| 2006 | 1.02 | 1.09 | 1.03 | 1.05 |
| 2007 | 1.04 | 1.10 | 1.12 | 1.05 |
| 2008 | 1.07 | 1.07 | 1.03 | 0.96 |
| 2009 | 1.09 | 1.05 | 1.01 | 0.90 |
| 2010 | 1.00 | 1.07 | 0.99 | 0.87 |
| 2011 | 1.02 | 1.06 | 1.05 | 0.89 |
| 2012 | 1.02 | 1.05 | 0.94 | 0.89 |
| 2013 | 0.98 | 1.04 | 0.90 | 0.88 |
| 2014 | 1.00 | 1.06 | 0.93 | 0.88 |
| 2015 | 1.03 | 1.08 | 0.92 | 0.88 |
| 2016 | 0.99 | 1.08 | 0.97 | 0.86 |
| 2017 | 1.07 | 1.12 | 0.96 | 0.89 |
| Mean | 1.03 | 1.07 | 0.99 | 0.93 |
| SD | 0.032 | 0.023 | 0.060 | 0.067 |

ASM, Antiseizure medication; APD, Antipsychotic drug.
[a] $p < 0.001$.
[b] $p = 0.021$.

collected an ASM during the last 12 months before starting an APD for psychosis (Fig. 1C). Ten patients in this group (24%) were ≤18 years of age when first collecting an APD, and 15 had been without ASM treatment for more than 5 years at the end of the study period, suggesting epilepsy in remission. Among the 190 subjects on epilepsy treatment at onset of psychosis, 72 (38%) had used two or more ASMs for epilepsy during the last year.

Olanzapine and quetiapine were the most frequent APDs used during the last twelve months before epilepsy onset. Eighty-four subjects (27%) had not collected an APD for psychosis during this year (Fig. 1C). Among the 226 subjects treated for psychosis the final year before epilepsy onset, 36% had used two or more APDs.

The average DDD/patient/day of ASMs for epilepsy was 1.0 in the epilepsy with psychosis group, compared to 1.1 in the group without comorbid psychosis (SD = 0.032 and 0.023 respectively), $p < 0.001$ (Table 4). For APDs the average DDD/patient/day was 1.0 (SD = 0.060) in the comorbidity group compared to 0.9 (SD = 0.067) in the non-comorbid psychosis group, $p = 0.021$.

During the entire study period, carbamazepine and levetiracetam were both used by a larger proportion of subjects in the non-comorbid epilepsy group, whereas topiramate, clonazepam, and valproic acid were used by more comorbid subjects (Fig. 2A). For APDs levomepromazine, chlorprothixene, risperidone, and clozapine were used by more subjects with comorbidity (Fig. 2B).

## 4. Discussion

To our knowledge this is the first population-based study examining the directionality of ASM and APD treatment in subjects with comorbid epilepsy and psychosis. Based on first time prescriptions among comorbid subjects, the present study suggests that the proportion of people with established psychosis at epilepsy onset is higher than previously recognized [6]. More than half of the patients with comorbid epilepsy and psychosis were already treated with APDs when they started treatment for epilepsy (56%). The findings corroborate the assumption of shared neurobiological mechanisms for these two brain disorders, conceivably due to both structural and genetic traits [13–15]. However, individuals harboring this inherent predisposition may not develop either definite psychosis or manifest epileptic seizures without further exposure to provocative environmental and acquired factors [16]. These factors should receive ample attention in the comprehensive management of people with comorbid epilepsy and psychosis.

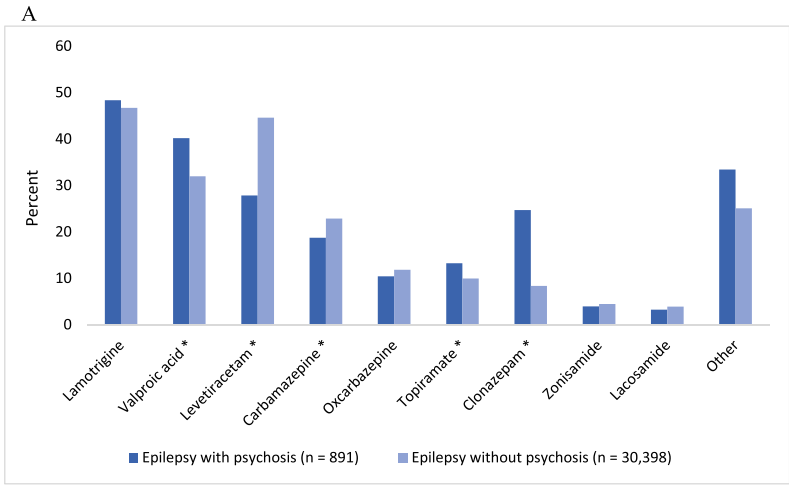
The bidirectionality of the two disorders forms two different clinical scenarios.

### 4.1. Psychosis following epilepsy

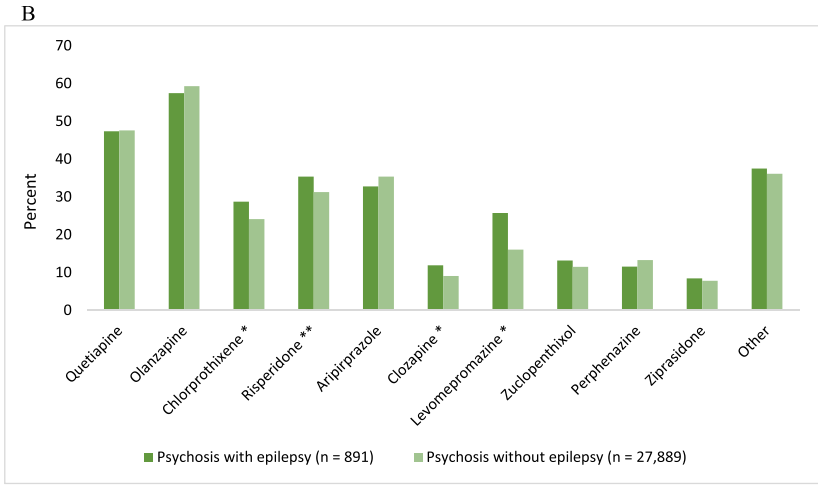
In the current definition of epilepsy by the International League Against Epilepsy, the principal elements of the diagnosis were extended beyond recurrent seizures to also include "the neurobiological, cognitive, psychological, and social consequences of the condition" [17]. This definition highlights the perceived stigma and the restrictions associated with the disease and encompasses a vulnerability to develop psychiatric disorders in people with epilepsy. Apart from the psychosocial impact of the disorder, various disease consequences with potential to induce psychosis have been addressed in the literature.

Postictal and interictal psychosis usually follow long-standing severe and uncontrolled epilepsy [18–20]. Postictal psychosis is a temporary event developing within hours to days after a seizure or a cluster of seizures, particularly in temporal lobe epilepsy, often with conspicuous violent and religious elements [21–23]. The primary treatment is optimization of ASMs rather than long-term APDs [24–26]. Interictal psychosis is usually a chronic disorder resembling nuclear schizophrenia, but negative symptoms are less prominent and emotional responsiveness often preserved [16]. The sum of seizures over time appears to contribute to the vulnerability for this most common form of psychosis in epilepsy [19]. Interictal psychosis usually presents later in life compared to schizophrenia [27]. Consistent with this, in the present study the mean age at first collected APD for psychosis was 39 years in subjects with epilepsy first. It has been suggested that psychotic symptoms may be facilitated by harmful ictal effects on brain function by so-called "kindling" or by vascular factors [14,20,28], or even by subclinical activity in the limbic system undetectable by scalp EEG [29]. Alternative psychosis, or so-called "forced normalization" as reflected in the EEG, may be brought on by abrupt seizure control and could indicate a biological antagonism between psychosis and seizures [18,30]. Accordingly, by this mechanism any successful ASM or other intervention might have the potential to induce psychosis in vulnerable patients [31].

Moreover, several ASMs may cause psychiatric and behavioral pharmacodynamic adverse effects, affecting between 15–20% of




*p < 0.005




*p < 0.005; **p = 0.01

**Fig. 2.** Medications used by subjects with or without comorbidity during the entire study period; (A) antiseizure medications, (B) antipsychotic drugs.

adult patients, of which psychosis was specifically reported in 0.5% in one study [32]. Psychosis has been reported as an adverse effect from various ASMs. The ASMs most commonly involved include ethosuximide, levetiracetam, topiramate, zonisamide, and vigabatrin [31–34]. In the present study, levetiracetam, topiramate, or zonisamide were used by approximately 40% of the patients with epilepsy during the last year prior to APD onset. However, drug effects may be difficult to sort out in people predisposed to psychosis by other factors. Noteworthy, levetiracetam was less used during the entire study period among patients with psychosis compared to those without, probably reflecting avoidance of this drug in patients with psychiatric problems, whereas topiramate was more used. Kanemoto et al. found that 45 among 132 patients with epilepsy and interictal psychosis had added ASMs or increased the dose before psychosis onset, half of these were related to zonisamide [35]. It has been suggested that any ASM may contribute to the development of psychosis in predisposed individuals [36]; however, the daily dose of ASMs has not been significantly associated with psychosis [37]. We did not identify an increased load of ASMs as expressed by mean DDDs in the group of subjects with epilepsy and psychosis.

Interestingly, 18% of the subjects with epilepsy first had not collected any ASM during the last 12 months prior to the first APD for psychosis. A large portion of these subjects were of young age, some possibly with childhood epilepsy in remission. An association even between uncomplicated or self-limited epilepsies and psychiatric disorders has been suggested [2,38,39].

### 4.2. Epilepsy following psychosis

A range of seizure precipitating factors may occur in psychiatric disease, either by endogenous mechanisms in the form of severe emotional stress and lack of sleep, or by exogenous influences due to the exposure to compounds which may lower the seizure

threshold. The pharmacological mechanisms comprise withdrawal effects from alcohol and benzodiazepines and direct neurotoxic effects from various drugs. A high load of APDs may induce seizures and increase the susceptibility to recurrent seizures in predisposed individuals [40]. Moreover, population-based data have shown that people with epilepsy are more often registered with substance use disorders than people without epilepsy, a comorbidity sometimes complicated by psychosis [41,42]. Abuse of various illicit drugs, such as cocaine and psychostimulants frequently precipitate seizures [43,44]. The association of substance use disorders and seizure disorders is a substantial clinical problem, as the borders between epilepsy and acute symptomatic seizures may be blurred [41]. Likewise, people with psychotic disorders may have an increased risk of developing focal epilepsy from various acquired causes, including head traumas associated with violent behavior and self-harm, as well as alcohol and drug intoxications [5,45].

Nearly all patients with long-lasting psychosis are treated with APDs. The impact of the seizure-inducing effects of these drugs in clinical practice has repeatedly been debated. Clozapine stands out as the drug with the most pronounced seizure-triggering effect. Clinical trial data in patients without epilepsy have also shown a higher risk of seizures for olanzapine and quetiapine than for ziprasidone, aripiprazole, and risperidone [26,46]. However, APD treatment, particularly clozapine, may also induce EEG slowing and epileptiform activity [47], leading to an unwarranted suspicion of epilepsy in some patients. Clozapine was used by nearly 15% of the subjects on APD treatment at onset of epilepsy. It had been used by a significantly larger proportion of subjects with epilepsy comorbidity during the entire study period. Clozapine should predominantly be prescribed when other APDs have failed, signifying difficult-to-treat psychosis [48]. Olanzapine and quetiapine were both used by almost 30%, whereas ziprasidone, risperidone, and aripiprazole were less used prior to epilepsy onset. Noteworthy, approximately one quarter of subjects with psychosis antedating epilepsy had not collected any APDs during the last year prior to onset of ASM treatment for epilepsy.

It has been emphasized that appropriate treatment of psychiatric disorders in people with epilepsy has been neglected due to an overestimated risk of seizures associated with APD treatment [1,26]. Some studies have even shown an improved seizure outcome in comorbid patients treated with careful APD regimens, possibly related to achieved control of psychiatric symptoms lessening seizure precipitants, including poor adherence to ASMs [5,40,49]. Nonetheless, data suggest that seizure induction is a dose-dependent class effect of APDs, which varies considerably among the numerous compounds [31,40,46]. A subset of people may be particularly vulnerable to this effect [40], and it is difficult to assess the real magnitude of this phenomenon in clinical practice. This study shows that the overall DDD burden of APDs for psychosis was significantly higher among subjects with epilepsy comorbidity compared to non-comorbid subjects. In some cases, an enzyme-inducing effect on APD serum concentrations from ASMs, such as carbamazepine, may underlie a need for higher doses [1]. The APD-treatment-response of people with epilepsy and psychosis compared to people with schizophrenia is still unknown [26], and psychosis in people with epilepsy might be more difficult to treat. The aim should be to treat people with epilepsy using the minimum effective doses of appropriate drugs [31], carefully considering seizure frequency as well as the total burden of adverse effects in subjects using various CNS-active drugs.

Any of the above discussed factors may worsen seizure control or even directly cause seizures and have to be considered in patients with comorbid seizures and psychiatric disease [28]. Such factors may frequently occur in concert and could conceivably have the potential to unveil a predisposition to developing epilepsy, sometimes with subthreshold effects adding to each other. These factors could explain why psychiatric disorders may lead to a worse response to the treatment of epilepsy [1,50].

### 4.3. Methodological issues

Antiseizure and antipsychotic drugs are used for a wide range of symptoms. The manifestations of epilepsy and its related psychopathology can be atypical and diverse, and most prescriptions in our study were issued in primary care. We acknowledge that the diagnosis of epilepsy is sometimes demanding in people with psychosis due to occasional episodic nonspecific behaviors and intermittent extrapyramidal adverse reactions from APDs. Unfortunately, no information on the classification of epilepsy could be retrieved from the present dataset. Noteworthy, about one quarter of people with epilepsy also have intellectual disability [51]. In these patients, specific psychiatric diagnoses are difficult to identify. In a recent British study addressing polypharmacy in a selected cohort of people with intellectual disability and epilepsy, 27% used APDs, but only 7% had a comorbid diagnosis of psychosis. This suggests not only a higher prevalence of psychosis in people with intellectual disability and epilepsy, but also a higher proportion of APD treatment for non-psychotic conditions, such as unspecific challenging behaviors [52]. However, patients in the present population-based study were strictly selected by reimbursement codes for epilepsy and psychosis, aiming to minimize this potential confounder.

The main strength of this study is the inclusion of the entire adult Norwegian population over a 14-year period, using data from the NorPD, which is a validated source of pharmacoepidemiological studies [53,54]. To ensure long-term treatment, only subjects with ASMs or APDs collected at least four times for the respective diagnoses were included. To further enhance diagnostic validity, the ICD-10 coding system employed by the specialist healthcare services, had been used at least once. By this procedure, the prevalence of patients using ASMs for epilepsy and APDs for psychosis (0.8% for both groups) met fairly well with recent Norwegian population-based prevalence studies both for epilepsy (0.65%) [55], and for psychosis (0.6% for schizophrenia-spectrum disorders) [41]. Prescriptions for affective psychoses were not included. We acknowledge that collected treatment does not necessarily reflect used medication. Also, drugs administered in hospitals or institutions are not included in the NorPD.

An obvious limitation of the study is that we could hardly determine the true onset of treatment in all patients. Selecting a long clean period increases internal validity as pointed out by Roberts et al. [56], but we could not exclude intermittent treatments prior to this period. Nevertheless, this was considered less likely for ASMs than for APDs, as treatment for epilepsy is usually more stable and long-term than for psychosis. Hence, we consider that this possible bias might have influenced the results toward an even higher proportion of onset of treatment for psychosis first.

We also acknowledge that the clinical onset of epilepsy and psychosis may differ from both the time of diagnosis and treatment onset of these disorders. A single seizure may be left untreated until another occurs [57], and the onset of psychosis requiring treatment may obviously be difficult to define [58]. However, the general principles of early symptomatic treatment of psychotic symptoms also apply in epilepsy-related interictal psychoses [31].

## 5. Conclusion

The present study suggests that the proportion of patients with prior antipsychotic treatment at onset of epilepsy is higher than

previously acknowledged. This particular group of patients should receive more clinical and scientific attention. The bidirectional comorbidity of epilepsy and psychosis indicates a shared neurobiological susceptibility, but various environmental factors may also be at play, including the interaction of pharmacodynamic effects. APDs may facilitate seizures, and ASMs may induce psychiatric symptoms. In patients with combined treatment, these potential drug effects should be carefully explored and monitored, along with the psychosocial and life-style consequences of the disorders. A comprehensive multi-professional approach is required. To broaden the understanding of the challenging association between psychosis and epilepsy, joint scientific and educational efforts between the fields of neurology and psychiatry should be reinforced.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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# PAPER IV

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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 ($2\times2$) 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%) ($\chi^2$ (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 ($\chi^2$ (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%) ($\chi^2(1)=9.01$, $p=0.003$) 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 ($\chi^2$ (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 ($\chi^2$ (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 ($\chi^2$ (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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