Comorbidity and Childhood Epilepsy: A Nationwide Registry Study

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abstract

BACKGROUND AND OBJECTIVE: Children with epilepsy are at increased risk of other disorders and difficulties, preceding, cooccurring with, or after the diagnosis of epilepsy. Risk estimates vary, few studies are population-based, and few provide comprehensive assessments of comorbidities. We used nationwide registry data to describe frequencies of medical, neurologic, developmental, and psychiatric conditions occurring before and after children are diagnosed with childhood epilepsy.

METHODS: Data were obtained from the Norwegian Patient Registry, which is an administrative database recording *International Classification of Diseases, 10th Revision* diagnoses from all government-funded specialist health services in Norway (outpatient consultations and hospitalizations). We included data from the years 2008 through 2013 for all children born in Norway between 1996 and 2013 (0–17 years of age at the end of follow-up). Children with epilepsy were compared with the general child population, adjusting for sex and age. We also compared children with complicated epilepsies (ie, epilepsies with additional neurologic and/or developmental disorders) to children with uncomplicated epilepsies.

RESULTS: The study population included 1 125 161 children. There were 6635 (0.6%) children with epilepsy. Nearly 80% of children with epilepsy had ≥1 comorbid disorder. All types of disorders were more frequent in children with epilepsy, with additional medical disorders recorded in 55%, neurologic disorders in 41%, and developmental/psychiatric disorders in 43%. Children with complicated epilepsies had the highest overall levels of comorbidity, but the risk of medical and psychiatric comorbidities was also substantial among children with uncomplicated epilepsies.

CONCLUSIONS: The overall frequency of comorbid disease is high in children with epilepsy, including children with presumably uncomplicated epilepsies.

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Dr Aaberg conceptualized and designed the study, conducted the data analyses, and drafted the initial manuscript; Dr Bakken contributed to the study design, the acquisition, analysis, and interpretation of the data, and the drafting of the manuscript; Drs Surén and Chin contributed to the study design, the analysis and interpretation of the data, and the drafting of the manuscript; Drs Lossius, Søraas, and Stoltenberg contributed to the analyses and interpretation of the data and reviewed and revised the manuscript; Dr Håberg contributed to the acquisition, analyses, and interpretation of the data and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Children with epilepsy are at risk for a wide range of comorbid disorders, but few risk estimates are available from population-based samples, and few studies have assessed a broad range of medical, neurologic, developmental, and psychiatric comorbidities in these children.

WHAT THIS STUDY ADDS: This nationwide, registry-based study shows that children with epilepsy are at increased risk of almost all types of medical, neurologic, developmental, and psychiatric disorders. Elevated risks are observed across all types of epilepsy, even for presumably uncomplicated epilepsies.

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There is an increasing focus on comorbid disorders in people with epilepsy, and new definition proposals have sought to frame epilepsy as not just a seizure disorder, but as a disorder with a wide range of neurobiological, cognitive, psychological, and social aspects.[1]

Comorbid disorders may share causes or risk factors with epilepsy, or even be the actual cause of epilepsy. They may also be consequences of seizures, epileptic activity, or antiepileptic treatment.[2–4] Consequently, these other conditions may precede, cooccur with, or follow the diagnosis of epilepsy.[2] Comorbid disorders contribute to the disease burden experienced by patients and their families and influence their quality of life and long-term outcome.[2–11]

Most studies of comorbidity in childhood epilepsy have focused on neurocognitive, behavioral, social, and psychiatric disorders or difficulties.[12–21] Knowledge about other medical comorbidities is limited, and only a couple of studies have investigated this in children specifically.[22,23] Most studies of medical comorbidities have included only adults or subjects of all ages and primarily reported findings in adults.[24–34] Some studies have focused on specific diagnoses rather than an extensive range.[35–38] For all categories of comorbid conditions, the prevalence estimates vary widely depending on the study design, methodology, and population under study.[5,39,40] Only a few studies of children with epilepsy (CWE) have been able to compare with the general child population.[12,14,20,21,23,41–43]

To improve our knowledge about comorbidities in CWE, we have used nationwide registry data to:

1. Estimate the proportions of medical, neurologic, developmental, and psychiatric disorders in CWE compared with the general child population.
2. Compare comorbidity patterns in CWE with and without additional neurologic and/or developmental disorders.
3. Examine differences in comorbidity patterns by age and sex in CWE.

We have defined comorbidity as the cooccurrence of conditions in the same individual irrespective of temporal or causal relations, as proposed by Feinstein in 1970.[44]

METHODS

Data and Population

The study is based on the Norwegian Patient Registry (NPR), an administrative database containing data from all hospitals and outpatient clinics owned and/or reimbursed by the Norwegian government. Reporting to the NPR is mandatory. Diagnoses are coded by physicians according to the *International Classification of Diseases, 10th Revision* (ICD-10).[45] Individual-level research data are available from 2008 on.

We included data from 2008 to 2013 on children born between 1996 and 2013 (0–17 years at the end of follow-up). Epilepsy was defined as having ≥2 registrations with ICD-10 codes G40 and/or G41. The NPR provided all ICD-10 codes registered in the study period in CWE, plus information about sex and year of birth. To enable comparisons with the general child population, the NPR provided an additional anonymized data file that included ICD-10 codes, sex, and year of birth for all Norwegian children born in 1996 to 2013, including CWE. The total number of individuals in the population, by sex and year of birth, were obtained from Statistics Norway (www.ssb.no).

We included data from all government-owned health services. Private practices receiving government reimbursements are also obliged to report to the NPR, but reporting was incomplete before 2013, and we did not include data from private practices in our study. The NPR data from 2013 showed that 24 CWE had epilepsy diagnoses recorded only in private practices that year. Consequently, the number of missed diagnoses is low and unlikely to affect the overall estimates of comorbidity in CWE.

Disease Categories

Our aim was to capture and categorize all comorbid conditions that were chronic or long-lasting and likely to have a significant effect on overall health and quality of life. Transient conditions (eg, infectious episodes) and conditions unlikely to occur in children (eg, varices) were excluded. Comorbid conditions were divided into 3 main categories–medical, neurologic, and developmental/psychiatric–and further subdivided into disease categories based on the ICD-10. The study was not designed to investigate causal relations, and some categories contain comorbid diagnoses that are potential causes of epilepsy, such as brain neoplasms and malformations, metabolic disorders, and chromosomal abnormalities.

The exact codes included in each category are listed in Supplemental Table 3. In general, the categories correspond to the individual ICD-10 blocks, but in some cases, we added codes from the R block ("Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified"). Norwegian physicians often use these codes when diagnostic conclusions have not yet been made. For example, ICD-10 code R62 ("Lack of expected normal physiological development") is often used to denote significant developmental delay, which is

why we have included R62 in our definition of developmental disorders.

To study how comorbidity patterns vary by the complexity of the epilepsy, we divided CWE into 2 subgroups based on the presence or absence of comorbid neurologic and/or developmental disorders. Complicated epilepsy (CWE+) included CWE with any additional diagnoses of neurologic disorders, intellectual disability (F70–79), autism or other disorders of psychological development (F80–89), and/or lack of expected normal physiologic development (R62). Uncomplicated epilepsy (CWE–) included CWE with no such additional diagnoses.

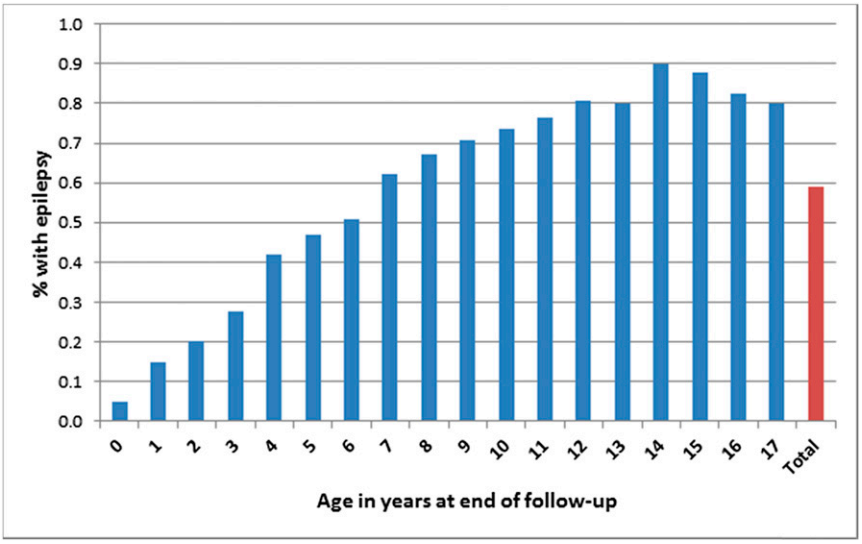

FIGURE 1
The distribution of epilepsy diagnoses by age at end of follow-up. Data are from the NPR 2008–2013 and include Norwegian children born 1996–2013.

Statistical Methods

We used SPSS version 22 (IBM SPSS Statistics, IBM Corporation) and Stata version 13.1 (Stata Corp, College Station, TX). CWE were compared with the general child population by logistic regression analyses adjusted for sex and year of birth. Because of the large number of comparisons conducted, we used 99% confidence intervals (CIs) for the odds ratios (ORs).

Ethics

The study was approved by the Regional Committee for Medical and Health Research Ethics for South East Norway, reference 2010/2583. The study data were derived from health registries mandated by Norwegian law, for which individual consent is not required.

RESULTS

The study population included 1 125 161 children, of whom 9215 were registered with a diagnosis of epilepsy. Of these 9215, 6635 had ≥2 recordings of ICD-10 codes G40/G41 and were defined as having epilepsy. The proportions increased by age to a maximum of 0.9% in 14-year-olds (Fig 1). For the study population as a whole, the proportion of CWE was 0.6%. The mean age at the end of follow-up was higher in CWE than in the general child population (11.7 vs 9.1 years) and the proportion of boys was also higher (54.3% vs 51.2%).

Overall Frequencies of Comorbidity

Overall, 78.3% of CWE had ≥1 comorbid disorders recorded, whereas the similar proportion was 30.3% in the general child population. Multiple comorbidities were common, and 13.4% of CWE had diagnoses within all 3 main categories of comorbidity (medical, neurologic, and developmental/psychiatric).

All medical conditions were more frequent in CWE than in the general child population (Table 1). The most frequent, both in CWE and the general child population, were gastrointestinal disorders (most commonly constipation and gastroesophageal reflux), which were recorded in 19.1% of CWE versus 5.4% in the general child population. Other frequent disease categories in CWE were congenital malformations outside of the central nervous system (18.2%), musculoskeletal disorders (15.3%), chronic lower respiratory disorders (mainly asthma) (10.3%), and malnutrition and/or eating difficulties (10.1%). The largest relative increases in CWE (the highest ORs) were observed for visual impairments (OR = 30.6), chromosomal abnormalities (OR = 19.6), malnutrition and/or eating difficulties (OR = 16.1), sleep disorders (OR = 13.0), immune disorders (OR = 8.6), nutritional deficiencies (OR = 7.4), and metabolic disorders (OR = 7.3).

For neurologic disorders (Table 1), the most frequent in CWE were cerebral palsy (13.9%), headache conditions (6.6%), and congenital neurologic malformations (6.5%). Both the absolute and the relative increases were large, with ORs >25 for all types of neurologic disorders except headache conditions.

Developmental and/or psychiatric disorders were registered in 42.9% of CWE overall, compared with 6.6% in the general population (Table 1). The relative increase in CWE was particularly large for developmental disorders, with intellectual disability in 17.0% (OR = 41.0), disorders of psychological development in 21.3% (OR = 11.6),

TABLE 1 Comorbid Disorders (Including Potentially Causative Comorbid Disorders) in Children With Epilepsy (CWE) compared with the General Child Population (GCP)

Category	CWE (N = 6635)		GCP (N = 1 125 161)		CWE vs GCP
Disorders	N	%	N	%	OR (99% CI)
Medical disorders	3627	54.7	286 361	25.5	3.5 (3.3–3.7)*
Gastrointestinal disorders	1264	19.1	60 840	5.4	4.3 (3.9–4.6)*
Congenital nonneurologic malformations	1206	18.2	81 289	7.2	3.4 (3.1–3.7)*
Musculoskeletal disorders	1018	15.3	49 934	4.4	3.3 (3.0–3.6)*
Chronic lower respiratory disorders	683	10.3	45 431	4.0	2.8 (2.5–3.1)*
Malnutrition/eating difficulties	670	10.1	9398	0.8	16.1 (14.4–17.9)*
Skin disorders	480	7.2	42 329	3.8	2.0 (1.8–2.3)*
Chromosomal abnormalities	355	5.4	3245	0.3	19.6 (16.9–22.7)*
Hearing impairment/deafness	342	5.2	12 716	1.1	4.6 (4.0–5.3)*
Endocrine disorders	307	4.6	12 627	1.1	3.6 (3.1–4.2)*
Urinary tract disorders	272	4.1	13 483	1.2	3.3 (2.8–3.9)*
Genital disorders	212	3.2	21 899	2.0	1.5 (1.2–1.8)*
Cardiovascular disorders	200	3.0	7379	0.7	4.3 (3.6–5.2)*
Sleep disorders	192	2.9	2491	0.2	13.0 (10.6–15.8)*
Hematologic conditions	188	2.8	7676	0.7	4.4 (3.6–5.4)*
Benign neoplasms	171	2.6	15 506	1.4	1.8 (1.5–2.2)*
Metabolic disorders	129	1.9	2750	0.2	7.3 (5.8–9.2)*
Visual impairment/blindness	125	1.9	652	0.1	30.6 (23.7–39.5)*
Obesity	123	1.9	5173	0.5	3.2 (2.5–4.0)*
Nutritional deficiency	62	0.9	1477	0.1	7.4 (5.3–10.4)*
Malignant neoplasms	56	0.8	1613	0.1	5.2 (3.7–7.4)*
Immune disorders	42	0.6	834	0.1	8.6 (5.7–13.0)*
Neurologic disorders	2743	41.3	27 596	2.5	25.0 (23.4–26.8)*
Cerebral palsy	920	13.9	2932	0.3	55.9 (50.4–62.0)*
Headache conditions	437	6.6	11 375	1.0	5.4 (4.8–6.2)*
Neurologic congenital malformations	434	6.5	2106	0.2	39.7 (34.5–45.8)*
Hydrocephalus	234	3.5	1225	0.1	33.9 (28.1–41.0)*
Cerebrovascular diseases	129	1.9	681	0.1	35.9 (27.8–46.2)*
CNS neoplasms	105	1.6	607	0.1	25.9 (19.7–34.1)*
Other neurologic disorders	1754	26.4	12 891	1.2	28.3 (26.2–30.5)*
Developmental/psychiatric disorders	2847	42.9	74 086	6.6	9.4 (8.7–10.0)*
Disorders of psychological development (including autism)	1414	21.3	21 787	1.9	11.6 (10.7–12.6)*
Autism	516	7.8	7104	0.6	10.7 (9.5–12.1)*
Intellectual disability	1126	17.0	4583	0.4	41.0 (37.3–45.0)*
ADHD	801	12.1	21 872	1.9	5.4 (4.8–5.9)*
Behavioral/emotional disorders (except ADHD)	698	10.5	28 941	2.6	3.6 (3.2–3.9)*
Unspecified developmental delay	494	7.5	11 834	1.1	8.2 (7.3–9.3)*
Anxiety	99	1.5	5463	0.5	2.3 (1.8–3.0)*
Depression	72	1.1	4873	0.4	1.8 (1.4–2.5)*

Data are from the NPR 2008–2013 and include Norwegian children born 1996–2013. CNS, central nervous system.
* $P < .01$.

and unspecified developmental delay (ICD-10 code R62) in 7.5% (OR = 8.2). Of the disorders of psychological development, autism accounted for 7.8% (OR = 10.7). Attention-deficit/hyperactivity disorder (ADHD) was the most common psychiatric diagnosis in CWE, occurring in 12.1% (OR = 5.4). There were few cases of comorbid anxiety or depression in CWE, probably because emotional disturbances in children are mostly coded under the ICD-10 section for childhood behavioral and emotional disorders (F90–98). A total of 10.5% of CWE had diagnoses from this section (OR = 3.6).

Complicated Versus Uncomplicated Epilepsy

Of the 6635 CWE, 3883 (58.5%) were defined as CWE+ and 2752 (41.5%) as CWE–. In general, all medical and psychiatric conditions were more frequent in CWE+ than in CWE– and more frequent in CWE– than in the general child population (Table 2).

Medical disorders were recorded in 65.9% of CWE+ and 38.8% of CWE–. ORs for CWE+ versus CWE– are not included in Table 2, but the largest relative differences between CWE+ and CWE– were observed for visual impairments (OR = 14.3), malnutrition/eating difficulties (OR = 13.7), and chromosomal abnormalities (OR = 9.8). Psychiatric disorders were also common in both groups, with the highest proportions in CWE+.

Age Differences

Most of the medical conditions were more commonly registered

TABLE 2 Comorbid Disorders (Including Potentially Causative Comorbid Disorders) in Children With Complicated Epilepsy (CWE+) and Children With Uncomplicated Epilepsy (CWE–) Compared With the General Child Population (GCP)

Category	CWE+		CWE–		CWE+ vs GCP	CWE– vs GCP
Disorders	*N*	%	*N*	%	OR (99% CI)	OR (99% CI)
Medical disorders	2559	65.9	1068	38.8	5.6 (5.1–6.1)*	1.8 (1.7–2.0)*
Gastrointestinal disorders	999	25.7	265	9.6	6.3 (5.7–6.9)*	1.9 (1.6–2.3)*
Congenital nonneurologic malformations	959	24.7	247	9.0	5.1 (4.6–5.6)*	1.5 (1.3–1.8)*
Musculoskeletal disorders	840	21.6	178	6.5	5.0 (4.5–5.6)*	1.2 (1.0–1.5)
Chronic lower respiratory disorders	470	12.1	213	7.7	3.4 (3.0–3.8)*	2.1 (1.7–2.5)*
Malnutrition/eating difficulties	630	16.2	40	1.5	27.9 (24.8–31.4)*	2.1 (1.4–3.2)*
Skin disorders	326	8.4	154	5.6	2.3 (2.0–2.7)*	1.5 (1.2–1.9)*
Chromosomal abnormalities	329	8.5	26	0.9	31.9 (27.3–37.3)*	3.3 (2.0–5.5)*
Hearing impairment/deafness	287	7.4	55	2.0	6.7 (5.7–7.9)*	1.7 (1.2–2.5)*
Endocrine disorders	256	6.6	51	1.9	5.3 (4.5–6.3)*	1.4 (1.0–2.0)
Urinary tract disorders	214	5.5	58	2.1	4.6 (3.8–5.5)*	1.7 (1.2–2.3)*
Genital disorders	137	3.5	75	2.7	1.6 (1.3–2.0)*	1.3 (1.0–1.8)
Cardiovascular disorders	138	3.6	62	2.3	5.1 (4.0–6.4)*	3.2 (2.3–4.4)*
Sleep disorders	154	4.0	38	1.4	17.9 (14.4–22.2)*	6.1 (4.0–9.4)*
Hematologic conditions	147	3.8	41	1.5	5.9 (4.8–7.4)*	2.3 (1.5–3.5)*
Benign neoplasms	117	3.0	54	2.0	2.1 (1.6–2.7)*	1.3 (0.9–1.9)
Metabolic disorders	113	2.9	16	0.6	11.1 (8.6–14.2)*	2.2 (1.1–4.1)*
Visual impairment/blindness	119	3.1	6	0.2	50.3 (38.7–65.3)*	3.5 (1.2–10.1)*
Obesity	76	2.0	47	1.7	3.3 (2.5–4.5)*	2.9 (2.0–4.2)*
Nutritional deficiency	49	1.3	13	0.5	10.0 (6.9–14.7)*	3.7 (1.8–7.7)*
Malignant neoplasms	46	1.2	10	0.4	7.3 (5.0–10.8)*	2.3 (1.0–5.1)
Immune disorders	35	0.90	7	0.25	12.3 (7.9–19.2)*	3.5 (1.3–9.3)*
Developmental/psychiatric disorders	2413	62.1	434	15.8	22.8 (20.8–25.0)*	2.1 (1.8–2.4)*
Disorders of psychological development (including autism)	1414	36.4	NA	NA	25.6 (23.3–28.1)*	NA
Autism	516	13.3	NA	NA	19.5 (17.1–22.2)*	NA
Intellectual disability	1126	29.0	NA	NA	84.0 (75.9–93.0)*	NA
ADHD	581	15.0	220	8.0	6.8 (6.1–7.7)*	3.4 (2.8–4.1)*
Behavioral/emotional disorders (except ADHD)	500	12.9	198	7.2	4.4 (3.9–5.0)*	2.4 (2.0–2.9)*
Unspecified developmental delay	494	12.7	NA	NA	14.9 (13.1–16.9)*	NA
Anxiety	64	1.7	35	1.3	2.6 (1.8–3.6)*	1.9 (1.2–3.0)*
Depression	52	1.3	20	0.7	2.3 (1.6–3.4)*	1.2 (0.7–2.1)

Data are from the NPR 2008–2013 and include Norwegian children born 1996–2013. CWE+, CWE with additional recordings of neurological and/or developmental disorders; CWE-, CWE without recordings of neurological and/or developmental disorders; NA, not applicable because the presence of these comorbid disorders is part of the definition of CWE+.

* $P < .01$.

in the young CWE, except some conditions that were fairly evenly distributed across age groups, such as neoplasms, endocrine, urinary, and genital conditions, or increased by age, such as obesity and musculoskeletal conditions. Neurologic conditions were also more common in the youngest children, except for headache conditions, which increased by age, and cerebral palsy and cerebral neoplasms, which were fairly stable across age groups. These age differences probably reflect a genuine decline in medical and neurologic comorbidity by age, but there is also likely to be some underascertainment of medical and neurologic disorders among the older children because of the lack of data before 2008.

The proportions of CWE with developmental disorders in total were relatively stable across ages. The unspecified developmental delay diagnoses (R62) appear to be replaced by specific diagnoses as the children grow older, as shown in Fig 2. For psychiatric diagnoses, the proportions increased by age.

Sex Differences

Proportions of comorbid conditions in CWE distributed by sex are shown in Supplemental Table 4. We found no sex differences in CWE that were not apparent in the general child population as well. Both among CWE and other children, boys had an increased risk of most developmental disorders and ADHD, whereas girls had an increased risk of depression.

DISCUSSION

The aim of this study was to assess comorbidities in children with epilepsy. Our main findings do not pertain to specific disorders, but the overall burden of disease and the patterns of comorbidity observed. Nearly 80% of CWE had ≥1 comorbid disorders, and multiple comorbidities were common. These consisted not only of additional disorders affecting brain development and functioning, but a wide range of medical and psychiatric conditions. The increase in disease risk also

included presumably uncomplicated epilepsies.

The increase in risk of disorders originating in the brain (ie, neurologic, developmental, and psychiatric conditions) is well known in CWE. Our findings for those conditions are in line with previous studies.[12–14,21,22,46–48] Some of the comorbid neurologic, chromosomal, and metabolic disorders are likely to represent causes of epilepsy. The high proportions of medical disorders were a more surprising finding. Some of the specific medical diagnoses, such as asthma, have been investigated in other studies,[22,23] and found to be increased in CWE. However, few previous studies have assessed a broad range of medical disorders in CWE, so we will focus on this in the remainder of the discussion.

Gastrointestinal disorders were the most frequent type of comorbid disorders. These were mostly treatable conditions, such as constipation and gastrointestinal reflux, occurring among younger CWE. More alarming were the high proportions of malnutrition and eating difficulties, which were found in 1 out of 6 CWE overall, and increased in both CWE+ and CWE–. Nutritional deficiencies were also considerably more frequent in CWE relative to the general child population. An increased risk of nutritional deficiencies in epilepsy has been demonstrated in a study that included subjects of all ages,[31] and our findings support that this is a considerable problem in CWE. In many cases, particularly for CWE+, nutritional difficulties are likely to result from the underlying cause of epilepsy, such as chromosomal disorders or cerebral palsy, rather than the epilepsy itself.

Sleep disorders were registered in 2.9% of CWE, which is 13 times more often than in the general child population. Sleep disorders are often not recorded, especially in children who are not in regular contact with specialist health services. There is likely to be considerable underreporting of sleep disorders in our data, and more so for children without epilepsy. Sleep disturbances may influence the outcome of epilepsy, as well as the health-related quality of life and the psychological functioning of the patients,[35,49–54] and it has been shown that diagnosing and improving sleep may have a positive impact in CWE.[35,51–56]

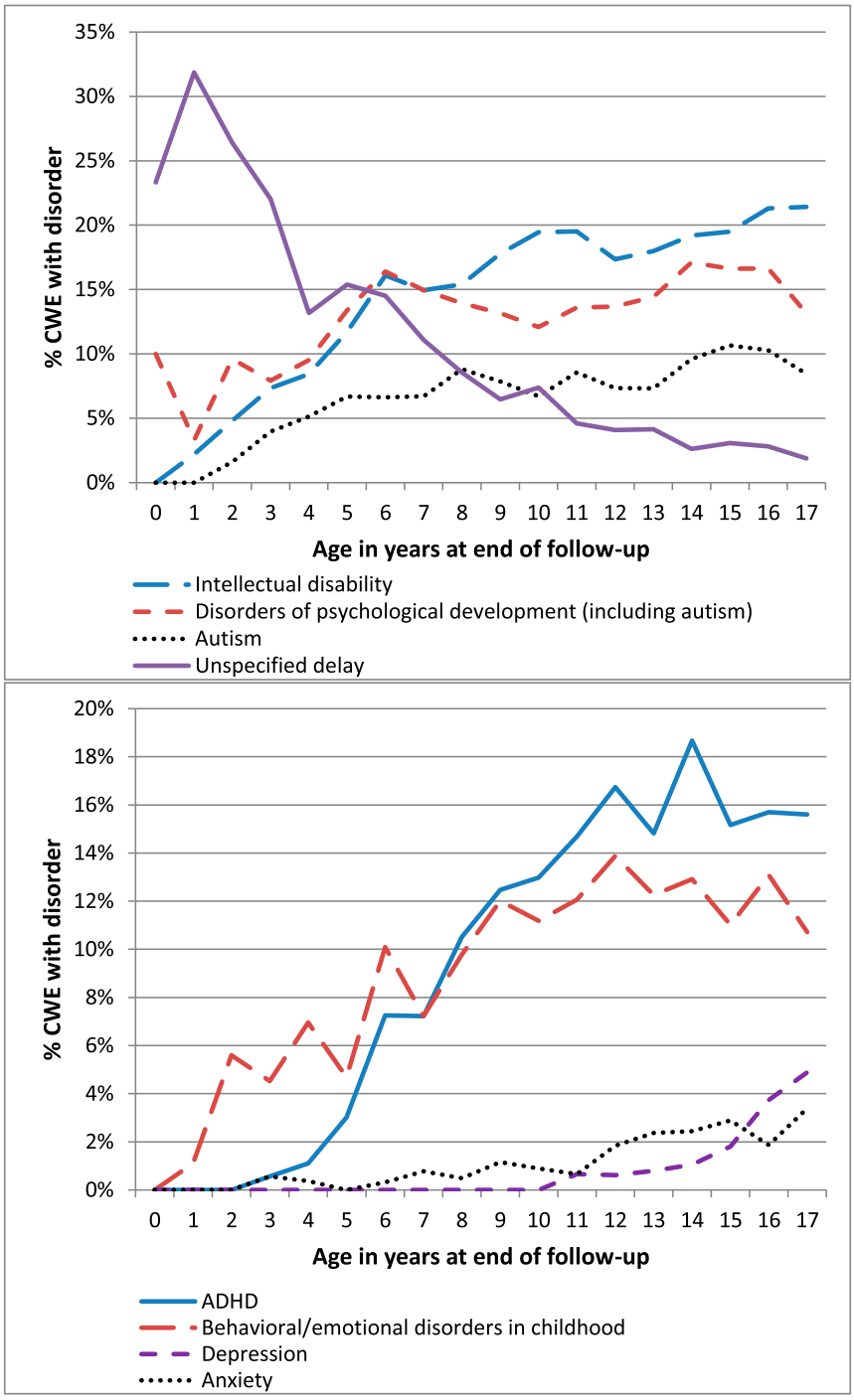

FIGURE 2
The distribution of developmental and psychiatric disorders by age at end of follow-up in CWE. Data are from the NPR 2008–2013 and include Norwegian CWE born 1996–2013.

The relative risk of visual impairments in CWE was high, especially in CWE+. This has also been shown in other studies, with proportions ranging from 3.4% to 5%.[31,48,57] Our proportion of 1.9% was lower, possibly because not all children needing glasses are examined by ophtalmologists, and therefore not captured by the registry.[58]

Although the absolute risk is low, the finding of a high relative risk of immune disorders in CWE is interesting, because the interaction between epilepsy and the immune system is currently debated, both with regards to the pathogenesis of epilepsy[59–61] and antiepileptic treatment.[8,62] It is known that antiepileptic drugs may affect the immune system,[63,64] and immune-modulating therapies are used in treatment.[65,66] Some rare forms of epilepsy are even caused by neuronal autoantibodies.[62,65]

In general, the disorders and frequencies of comorbid medical conditions in CWE were different from those observed in studies of adults with epilepsy.[2,24–28] However, there is no reason to believe that the consequences are very different. Medical comorbidities have a considerable negative impact on health-related quality of life in adults with epilepsy.[27,32]

The findings of increased levels of comorbidity in CWE+ relative to CWE– is in concordance with previous studies,[12,13,67,68] but it was surprising to find such high levels of medical and psychiatric disorders in CWE– relative to the general child population. Our definition of uncomplicated epilepsy excluded those with any type of additional neurologic disorders or developmental delay, which was strict compared with other studies.[12,13,68] Despite this, there was still a substantial increase in risk of most types of comorbidities in CWE–, indicating that uncomplicated epilepsies are often more complex than the term "uncomplicated" suggests. This general increase in comorbidity in CWE– may relate to various aspects of epilepsy: the seizures, the epileptic activity, the underlying cause, the treatment, and the burden of living with a chronic disease.

The strengths of our study are the assessment of a broad range of comorbid disorders and the size and completeness of the data set. The large numbers allowed us to assess the risk of both rare and common disorders, and the inclusion of the whole child population largely eliminated selection bias, making our findings generalizable to other developed countries as well.

A limitation is the lack of validity data for the epilepsy diagnoses, as well as the other recorded diagnoses. However, previous studies of epilepsy in Norway, based on data from single counties, have found positive predictive values of 80%[69] and 74%[70] for registered diagnoses of epilepsy, indicating a relatively high quality of the data. Another study found a high quality of autism diagnoses in the NPR, with a positive predictive value of 94% (95% CI, 79%–99%).[46] In this study, we chose to err on the side of caution by restricting the CWE definition to those with ≥2 recordings of epilepsy to avoid including children with erroneously recorded epilepsy diagnoses. This may have caused us to lose some true cases of epilepsy, but the overall proportion of epilepsy observed using our definition (0.6%) is in line with estimates from Norway and other countries, which supports our choice of restriction.[48,57,67,69,71–74]

Another limitation is that the proportions of some disorders tend to be underestimated in registry studies.[58] Studies conducting in-person assessments of CWE indicate that psychiatric disorders are often underdiagnosed. For example, Reilly et al[19] found similar proportions to our study of previously diagnosed ADHD, autism, depression, and anxiety, but the proportions increased considerably after in-person assessments had been conducted. Other in-person studies have found high proportions of psychiatric disorders in CWE and that CWE have unmet psychiatric needs.[17,18,75,76] Underdiagnosis of psychiatric disorders is likely to affect the general population, not just CWE. Obesity also appears to be substantially underdiagnosed compared with other studies, both in CWE and the general child population.[23,77–79]

On the other hand, the relative differences between CWE and the general child population may be somewhat inflated because CWE are in regular contact with specialist health services. This regular contact increases the chance of diagnosing any type of comorbid disorder, a type of ascertainment bias often referred to as Berkson's bias.[80] CWE are also likely to undergo thorough investigations of potential causes of epilepsy, which also increase the chances of discovering comorbid disorders. In general, our data are likely to be most accurate for conditions that are serious enough to warrant specialist treatment and follow-up, both in CWE and the general population, whereas less severe conditions and difficulties, such as headache conditions and sleep disorders, are more likely to be captured in CWE than in the general child population.

The lack of data from the NPR before 2008 is also a limitation. As described in the *Results* section, we are likely to have missed some comorbid conditions among the oldest children. This would apply to conditions that children can grow out of, such as

gastroesophageal reflux and asthma. A data set covering all years since birth for the whole study population would have provided better opportunities to study temporal relations between epilepsy and comorbid conditions.

CONCLUSIONS

There are high proportions of comorbidities in CWE, with nearly 80% of CWE having ≥1 additional disorder. Our findings highlight the need for a broad approach in the management of these children, thereby supporting recent recommendations from the World Health Organization.[81] The management should not only focus on the epileptic seizures, but should also include thorough assessments of all aspects of health, including development, psychiatric symptoms, nutrition, growth, and sleep.

ABBREVIATIONS

ADHD: attention-deficit/hyperactivity disorder
CI: confidence interval
CWE: children with epilepsy
CWE+: complicated epilepsy
CWE–: uncomplicated epilepsy
ICD-10: *International Classification of Diseases, 10th Revision*
NPR: Norwegian Patient Registry
OR: odds ratio

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