Directionality of the Association Between Epilepsy and Depression

A Nationwide Register-Based Cohort Study

Eva Bølling-Ladegaard, MD, Julie Werenberg Dreier, PhD, Lars Vedel Kessing, MD, DrMedSci,
Esben Budtz-Jørgensen, MSc, DrSci, Kasper Lolk, MEc, and Jakob Christensen, MD, DrMedSci

Correspondence
Dr. Bølling-Ladegaard
eva@clin.au.dk

Abstract

Background and Objectives

Epilepsy and depression share a bidirectional relationship; however, its magnitude and long-term temporal association remain to be elucidated. This study investigates the magnitude and long-term association between epilepsy and depression, comparing with the risks of the 2 disorders after another chronic medical illness (asthma).

Methods

In a nationwide register-based matched cohort study, we identified all individuals who received a first diagnosis of epilepsy, depression, and asthma from January 1, 1980, to December 31, 2016. We used a Cox regression model to estimate the risk of epilepsy after depression and vice versa and the risk of epilepsy or depression after asthma, compared with healthy references matched on age and sex, adjusting for medical comorbidity, substance abuse, and calendar time. Results were stratified by epilepsy subtype. We furthermore investigated the risk of admission with acute seizures for persons with epilepsy who became depressed.

Results

In a population of 8,741,955 individuals, we identified 139,014 persons with epilepsy (54% males, median age at diagnosis 43 years [inter quartile range (IQR) 17–65 years]), 219,990 persons with depression (37% males, median age at diagnosis 43 years [IQR 29–60 years]), and 358,821 persons with asthma (49% males, median age at diagnosis 29 years [IQR 6–56 years]). The adjusted hazard ratio (aHR) of depression after epilepsy was 1.88 (95% CI 1.82–1.95), and the aHR of epilepsy after depression was 2.35 (95% CI 2.25–2.44). The aHR of depression after asthma was 1.63 (95% CI 1.59–1.67) and that of epilepsy after asthma, 1.48 (95% CI 1.44–1.53). The risk of depression was highest in the few years preceding and after an epilepsy diagnosis, and vice versa, but remained elevated during the entire follow-up period for both directions of the association. There was no evidence of a stronger association with depression for any epilepsy subtype. Receiving a diagnosis of depression subsequent to an epilepsy diagnosis was associated with a 1.20-fold (95% CI 1.07–1.36) increased HR of acute hospital admission with seizures.

Discussion

We identified a long-term bidirectional relationship between depression and epilepsy in a large-scale cohort study. Risk estimates were higher than those of epilepsy or depression after asthma.

Glossary

aHR = adjusted HR; **aOR** = adjusted OR; **CCI** = Charlson comorbidity index; **DCPR** = Danish Central Psychiatric Register; **DNPR** = Danish National Patient Registry; **HR** = hazard ratio; *ICD-8* = International Classification of Diseases, eighth revision; *ICD-10* = International Classification of Diseases, 10th revision; **OR** = odds ratio; **PPV** = positive predictive value.

Depression is the most frequent psychiatric comorbidity in people with epilepsy[1] with prevalence of active depression ranging from 13% to 37%,[2-4] an estimate 2–5 times higher than in the background population.[5] The clinical and therapeutic implications of this comorbidity are significant; for example, comorbid mood disorders are among the strongest predictors of poor quality of life,[6,7] suicidal ideation, and premature death[8-10] in people with epilepsy and has been associated with higher frequency and severity of seizures and poor response and adherence to antiseizure medication.[11-14]

Historically, the view has been widely held that epilepsy and depression had a cause-consequence relationship; that is, depressive symptoms were adaptive phenomena reactive to the seizure disorder. However, over the past 2 decades, epidemiologic studies have established that not only are persons with epilepsy at a greater risk of experiencing depression, but patients with primary depression also have a 1.45- to 7-fold higher risk of developing epilepsy.[13,15-18] Theories of common pathogenic mechanisms operant in both conditions have been suggested and are supported by shared features in the principal theories of epilepsy and depression pathogenesis, including imbalances of common neurotransmitters[19]; structural and functional disturbances of common brain regions, such as the hippocampus and amygdala[20]; and endocrine and inflammatory disturbances.[21]

Yet, studies on the co-occurrence of epilepsy and depression have shown substantial disparity, possibly owing to heterogeneity in study designs and methods (e.g., differences in study populations and case definitions). Few large-scale, population-based studies have been conducted on this matter, and most have compared risks to healthy individuals rather than to individuals with other chronic diseases.[4,13,15,16] The latter is relevant to address the facts that experiencing a chronic disabling disease may increase the risk of depression per se and inherently increase the frequency of medical contacts and thereby the likelihood of obtaining a second diagnosis. Thus, among references, there may be more cases of unidentified depression because these persons are less often screened by a doctor—and the association may be overestimated when merely comparing the risk of, for example, depression between persons with epilepsy and persons without epilepsy. This form of selection bias is known as the Berkson bias.[22]

Although the association between epilepsy and depression has been compellingly established and is currently the subject of massive attention of researchers, its magnitude, consequences

at a population level, and temporal aspects need further elucidation. We therefore used data from nationwide registers to study the relationship between depression and epilepsy and addressed the potential impact from the Berkson bias by comparing the risks in patients with another chronic medical illness, asthma. Furthermore, we assessed whether specific epilepsy subtypes are particularly associated with depression, whether severity of depression is associated with risk of epilepsy, and whether comorbid depression is associated with risk of treatment failure in patients with epilepsy.

Methods

Study Design and Data Sources

Data were obtained by linking the following Danish nationwide registers[23]: the Danish National Patient Registry (DNPR)[24] with information on all patients treated at somatic hospitals (i.e., all hospitals that primarily take care of patient with nonpsychiatric illnesses) in Denmark since 1977 (outpatient and emergency room contacts since 1995), the Danish Central Psychiatric Register (DCPR)[25] with information on all psychiatric admissions in Denmark since 1970 (outpatient and emergency room contacts since 1995), the Danish Civil Registration System,[26] containing information on vital and emigration status on all individuals living in Denmark since 1969, and the Income Statistics Register,[27] containing information on the income composition of the entire Danish population since 1970. From 1977 to 1993, diagnostic information in the DNPR and the DCPR was based on the Danish version of the *International Classification of Diseases, eighth revision* (*ICD-8*) and from 1994 on the *International Classification of Diseases, 10th revision* (*ICD-10*).[24,25] This study was designed as a nationwide register-based matched cohort study.

Study Population

We identified all persons who were alive and resident in Denmark at some point during the study period from January 1, 1980, to December 31, 2016. From this population, we defined 3 cohorts with first-time diagnoses of epilepsy, major depression, and asthma. Persons diagnosed with epilepsy or asthma were identified from the DNPR, and persons with major depression were identified from the DCPR. Persons with epilepsy were subdivided into the following categories of epilepsy subtypes: epilepsy with focal-onset seizures, epilepsy with generalized seizures, and other/unspecified epilepsy. Persons diagnosed with major depression were subdivided into the following categories of severity[28]: mild, moderate, severe, or unspecified. Main and auxiliary diagnoses were used for the identification of patients. Diagnostic codes of all

disorders and subclassifications are listed in eTable 1 (links. lww.com/WNL/C491).

The time of disease onset was defined as the first day of the first hospital contact with each of these diagnoses (index date). To minimize inclusion of prevalent cases, we excluded individuals diagnosed before January 1, 1980. We sampled a reference population for each cohort, by matching 5 persons to each person with the disorder by sex and age at diagnosis, among those who were alive and did not have neither the exposure nor the outcome disorder at the index date (i.e., the day the index person was diagnosed with the index diagnosis). Exposure density sampling was used for the matching process.[29] According to the diagnostic hierarchy in ICD-8 and ICD-10, schizophrenia and bipolar disorder rank higher than depression; that is, if diagnosed with either of the former, any cases of depression would be considered to fall under the higher ranked disease and the person would not be considered to experience depression or be at risk of depression. Therefore, in analyses with depression as exposure or outcome, persons were excluded if diagnosed with schizophrenia or bipolar disorder before index date and censored if diagnosed with these disorders after the index date (for diagnostic codes, see eTable 1, links.lww.com/WNL/C491).

The cohorts of persons with newly diagnosed epilepsy, major depression, or asthma and their respective reference cohorts were followed up from the index date until a diagnosis of interest (epilepsy or major depression), death, emigration, censoring, or the end of follow-up on December 31, 2016, whichever came first.

Statistical Analysis

We used a Cox regression model to estimate the hazard ratio (HR) and corresponding 95% CI of depression after an epilepsy diagnosis, compared with the matched reference group without epilepsy. Time since the index date was used as the underlying time scale. Persons in the reference groups were censored in case of diagnosis with the index diagnosis. We performed the analyses for epilepsy diagnoses combined and by epilepsy subtype (at first registered diagnosis of epilepsy) in a stratified analysis. In addition, we performed the analysis for the entire study period and population combined and analyses stratified by time since diagnosis and by age groups (age at index date 0–19 years, 20–39 years, 40–59 years, 60–79 years, and 80+ years).

In a similar manner, we estimated the HR of epilepsy in persons with diagnosis of depression compared with matched persons without depression. This was performed for the depression diagnoses combined and by depression severity (at first registered diagnosis) for the subset of persons diagnosed from 1994 and onward. Finally, we estimated HRs of depression and epilepsy after an asthma diagnosis, compared with matched persons without asthma, in a manner similar to that described earlier.

In all analyses, a multivariable Cox regression model was performed with full adjustment for Charlson comorbidity index (CCI) score on the index date, substance abuse, and calendar year. The ICD-8 and ICD-10 codes used to define CCI score are listed in eTable 2 (links.lww.com/WNL/C491). Substance abuse was defined as having a main or auxiliary diagnosis of alcohol or drug abuse in the DNPR or the DCPR (for diagnostic codes, see eTable 1) on or before the index date. Calendar year was included in the model as a time-varying covariate (divided into 8 periods: 1980–1984, 1985–1989, 1990–1994, 1995–1999, 2000–2004, 2005–2009, 2010–2014, and 2015–2016).

We estimated the cumulative incidences of depression in the epilepsy group and the matched population without epilepsy, and vice versa, using competing risk regression with death and emigration as competing events and time since index date as the underlying time scale. To visualize the temporal correlation between epilepsy and depression onset, we plotted the incidence rate of major depression diagnoses over time in people with epilepsy, and vice versa, against the rate in matched references, on time axes from 20 years before to 20 years past index date.

To evaluate whether comorbid depression affected the risk of treatment failure in persons with epilepsy, we examined the risk of an acute hospital admission with seizures (for diagnostic codes, see eTable 1, links.lww.com/WNL/C491) as a proxy for treatment failure in people with and without comorbid depression, after allowing an initial 6-month stabilization period after epilepsy diagnosis. To account for socioeconomic status, we performed a sensitivity analysis in which we included equated household income from the Income Statistics Register (disposable income of a household weighted by number of household members, available in the register from 1987 and onward) as a covariate, on a subset of cohorts with index dates from 1987 and onward. In another sensitivity analysis, we performed the main analyses of risk of depression after epilepsy and vice versa, without censoring for bipolar disorder or schizophrenia.

A *p* value of less than 5% indicated significance throughout all the analyses (2-sided). Interaction was tested by including interaction terms and using likelihood ratio tests. The proportional hazard assumption for the Cox regression model fits was tested with the *cox.zph* function in R's "*survival* package"[30]; the assumption was violated for the main exposures of the main analyses; when stratified by follow-up time, proportionality was fulfilled within each stratum. All analyses were performed with statistical software programs (SAS version 9.4; R version 4.0.4).

Standard Protocol Approvals, Registrations, and Patient Consents

The study was based on pseudoanonymized data, and the study involved no individual patient contact. The study was therefore exempt form ethical review and approval according to Danish law. The study was approved by the Danish Data Protection Agency.

Data Availability

The raw data that support the findings of this study are not publicly available due to the legislation of Statistics Denmark and the Danish Act on Processing of Personal Data.

Results

We identified 8,741,955 individuals alive and resident in Denmark at some point between January 1, 1980, and December 31, 2016 (Figure 1). We excluded 53,007 persons diagnosed with epilepsy, major depression, bipolar disorder, or schizophrenia before January 1, 1980, leaving 8,688,948 persons in the source population, from which the epilepsy, depression, and matched reference cohorts were identified (Figure 1; for the generation of the asthma cohorts see eFigure 1, links.lww.com/WNL/C491). Characteristics of the 3 patient cohorts and their respective reference groups are summarized in Table 1. Persons with asthma had a lower median age at index date (28.0–28.9 years) than those with index diagnoses of epilepsy (42.6 years) or depression (43.0 years), $p < 0.001$. Persons with epilepsy generally experienced more comorbid disorders (CCI score ≥2: 18.9% vs 11.0% in the depression and 8.6%–8.7% in the asthma cohorts, $p < 0.001$), while persons with index diagnoses of depression were at a greater risk of being substance abusers (15.7% vs 10.5% in the epilepsy and 3.3%–3.7% in the asthma cohorts, $p < 0.001$) (Table 1).

The rate of developing depression was nearly 2-fold increased in persons with epilepsy compared with the matched population without epilepsy (adjusted HR [aHR] 1.88, 95% CI 1.82–1.95) (Table 2). The HRs were highest in the first months and years after primary diagnosis, declined over time, yet remained significantly elevated compared with those for the matched references throughout the observation period. The highest rate of depression after epilepsy was found in those aged 40–59 years (aHR 1.98, 95% CI 1.85–2.13) and lowest for those aged 0–19 years (aHR 1.80, 95% CI 1.70–1.90) at first epilepsy diagnosis (Table 2). In the analysis stratified by epilepsy subtype, there was no evidence of a stronger association with depression for any epilepsy subtype because all CIs overlapped; the highest rate of depression was found in the "other/unspecified" group (aHR 1.93, 95% CI 1.86–2.02) (Table 2).

The rate of epilepsy was more than 2-fold increased in persons with incident depression compared with the matched population without depression (aHR 2.35, 95% CI 2.25–2.44) (Table 3). As in the opposite analysis, the HRs were highest in the first months and years after depression diagnosis and declined over time. The rate of epilepsy was highest among the youngest, that is, those aged 0–19 years (aHR 3.69, 95% CI 3.12–4.34) at time of first depression diagnosis (Table 3), whereas the lowest rate was found among those aged 80 years or more (aHR 1.51, 95% CI 1.26–1.84) at first depression diagnosis (Table 3). In the analysis stratified for depression severity, the highest rate of epilepsy was found for those diagnosed with "mild" depression at first ever depression diagnosis (aHR 2.79, 95% CI 2.51–3.11) (Table 3) and the lowest rate of epilepsy was found for those diagnosed with "moderate" depression (aHR 2.32, 95% CI 2.16–2.50), although all CIs overlapped.

The rates of depression and epilepsy in persons with asthma were 1.63-fold (95% CI 1.59–1.67) and 1.48-fold (95% CI 1.44–1.53) increased respectively, compared with matched populations of persons without asthma (eTables 3 and 4, links.lww.com/WNL/C491). Additional analyses on the reverse associations are summarized in eTable 5.

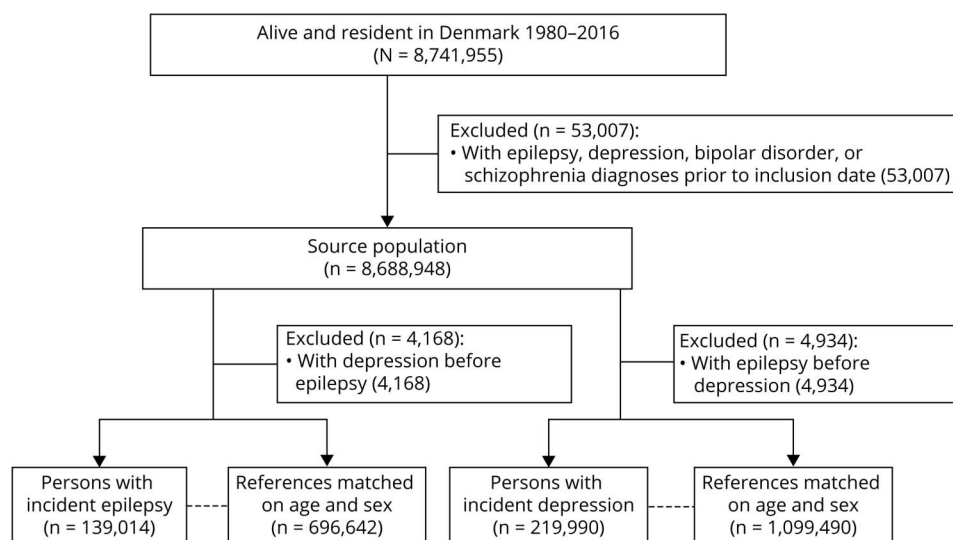**Figure 1** Generation of the Source and Study Populations

Table 1 Characteristics of the Patient and Reference Populations

	Epilepsy	Reference group[a]	Depression	Reference group[b]	Asthma[c]	Reference group[d]	Asthma[e]	Reference group[f]
N	139,014	696,642	219,990	1,099,490	347,319	1,736,595	350,224	1,751,120
Sex, female (%)	46.5	46.5	62.8	62.8	50.3	50.3	50.7	50.7
Age, y, median (quartiles)[g]	42.6 (16.7–65.2)	42.6 (16.7–65.2)	43.0 (28.8–59.7)	43.0 (28.8–59.7)	28.0 (4.9–56.2)	28.0 (4.9–56.2)	28.9 (5.0–56.6)	28.9 (5.0–56.6)
Follow-up time, y, mean (SD)	11.3 (9.6)	13.2 (9.6)	9.1 (7.5)	10.2 (7.9)	11.5 (8.4)	12.3 (8.4)	11.5 (8.5)	12.3 (8.4)
Charlson comorbidity index score (%)[h]								
0	64.7	84.1	75.9	84.3	81.2	90.1	80.9	90.0
1	16.4	8.0	13.1	8.4	10.2	4.8	10.4	4.8
2	8.9	4.7	6.2	4.6	4.8	3.3	4.9	3.3
3	4.6	1.7	2.4	1.4	2.0	1.0	2.0	1.0
4+	5.4	1.5	2.4	1.3	1.8	0.9	1.8	0.9
Substance abuse (%)	10.5	1.9	15.7	2.6	3.3	1.5	3.7	1.7

[a] Persons without epilepsy at index date matched on sex and age at index date.
[b] Persons without depression at index date matched on sex and age at index date.
[c] Asthma cohort 1 with no depression before inclusion date.
[d] Persons without asthma at index date matched on sex and age at index date.
[e] Asthma cohort 2 with no epilepsy before inclusion date.
[f] Persons without asthma at index date matched on sex and age at index date.
[g] Age at the index date.
[h] Charlson comorbidity index score by group: 0 points, 1 point, 2 points, 3 points, 4 points, or more.

For the epilepsy cohort, there was a higher rate of an acute admission with seizures (aHR 1.20, 95% CI 1.07–1.36) in those who received a depression diagnosis after the onset of epilepsy compared with those who did not (Table 4).

We analyzed whether the risk of epilepsy and depression varied with sex, comorbidity, substance abuse, and calendar year and summarized interaction parameters in eTables 6 and 7 (links.lww.com/WNL/C491). There was no significant interaction with sex in the rate of depression after epilepsy (p = 0.47) or vice versa (p = 0.68). There was significant interaction with comorbidity score (p = 0.007), substance abuse ($p < 0.001$), and calendar year ($p < 0.001$) for the rate of depression after epilepsy and for epilepsy after depression ($p < 0.001$ for all 3 interaction parameters). The elevated rate of depression after epilepsy and vice versa held significant across all strata of the covariates.

Sensitivity analyses with additional adjustment for socioeconomic status yielded an aHR of 1.76 (95% CI 1.68–1.83) (eTable 8, links.lww.com/WNL/C491) for depression after epilepsy compared with matched references without epilepsy and an aHR of 2.30 (95% CI 2.20–2.41) (eTable 8) for epilepsy after depression, compared with matched individuals without depression.

Sensitivity analyses without censoring for bipolar disorder or schizophrenia yielded slightly higher aHRs for depression after epilepsy compared with matched references without epilepsy (aHR 1.91, 95% CI 1.85–1.98) and for epilepsy after depression (aHR 2.41, 95% CI 2.31–2.50) compared with matched individuals without depression (eTable 9, links.lww.com/WNL/C491).

Figure 2A illustrates the cumulative incidence of depression after epilepsy diagnosis compared with the matched population without epilepsy. The cumulative incidence of depression at 5 and 35 years of follow-up in the epilepsy cohort was 1.37% (95% CI 1.33–1.41) and 6.05% (95% CI 5.81–6.19) respectively, compared with 0.59% (95% CI 0.58–0.61) and 3.92% (95% CI 3.84–4.00) at 5 and 35 years of follow-up in the reference population (Gray test for group difference: $p < 0.001$). The curve had a slightly steeper slope over the first few years, leveling off to a steady increase with increasing follow up-time. Similarly, the cumulative incidence of epilepsy after a major depression diagnosis was increased compared with the matched population without depression (Figure 2B), with a cumulative incidence of epilepsy in the depression cohort of 1.10% (95% CI 1.08–1.12) at 5 years of follow-up and 4.19% (95% CI 3.95–4.38) at 35 years of follow-up, compared with 0.32% (95% CI 0.31–0.33) and 2.06% (95% CI 1.99–2.12) at the same time points in the reference population (Gray test for group difference: $p < 0.001$).

The incidence rate of depression peaked around the time of epilepsy diagnosis in individuals with epilepsy (Figure 3A), with an elevated rate in the years before and after epilepsy

Table 2 aHRs of Depression After Epilepsy Compared With Matched Reference Populations

	Persons in cohort, n	IR of depression (95% CI)[a]	HR (95% CI)[b]	aHR (95% CI)[c]
No epilepsy[d]	696,642	14.3 (14.1–14.6)	1 (ref)	1 (ref)
Epilepsy	139,014	30.3 (29.4–31.2)	2.12 (2.05–2.19)	1.88 (1.82–1.95)
Time since epilepsy diagnosis	Persons with epilepsy, n			
			1 (ref)	1 (ref)
0 to <3 mo	139,014	73.5 (64.6–83.3)	6.88 (5.68–8.33)	5.75 (4.69–7.05)
3 to <6 mo	132,008	48.5 (41.2–56.7)	4.27 (3.46–5.27)	3.49 (2.79–4.37)
6 mo to <1 y	127,871	36.4 (31.8–41.5)	3.39 (2.88–4.01)	2.65 (2.21–3.17)
1 to <5 y	121,531	27.8 (26.3–29.5)	2.47 (2.31–2.65)	2.04 (1.89–2.20)
5 to <10 y	90,487	24.2 (22.7–25.8)	1.85 (1.72–1.99)	1.61 (1.49–1.73)
10 to <20 y	64,943	31.9 (30.3–33.6)	1.91 (1.80–2.02)	1.71 (1.61–1.82)
≥20 y	29,135	31.2 (28.8–33.8)	1.62 (1.49–1.77)	1.47 (1.35–1.61)
Age group, y[e]				
			1 (ref)	1 (ref)
0–19	39,882	25.1 (23.9–26.3)	1.86 (1.76–1.97)	1.80 (1.70–1.90)
20–39	26,074	36.3 (34.5–38.2)	2.30 (2.17–2.45)	1.97 (1.82–2.10)
40–59	29,732	31.8 (29.9–33.8)	2.56 (2.38–2.75)	1.98 (1.85–2.13)
60–79	33,240	31.9 (29.4–34.6)	2.07 (1.89–2.27)	1.71 (1.55–1.88)
80+	10,086	35.8 (29.2–43.5)	1.44 (1.16–1.77)	1.40 (1.13–1.73)
Epilepsy subtype[f]				
			1 (ref)	1 (ref)
Focal epilepsy	24,418	27.50 (25.59–29.52)	1.90 (1.75–2.08)	1.74 (1.59–1.91)
Generalized epilepsy	16,903	24.06 (22.28–25.94)	1.95 (1.78–2.13)	1.77 (1.60–1.94)
Other/unspecified epilepsy	97,693	32.64 (31.57–33.74)	2.22 (2.14–2.32)	1.93 (1.86–2.02)

Abbreviations: aHR = adjusted HR; HR = hazard ratio; IR = incidence rate.
[a] IR of depression per 10,000 person-years.
[b] Unadjusted.
[c] Adjusted for Charlson comorbidity index, substance abuse, and calendar year.
[d] Persons without epilepsy at index date matched on sex and age at index date.
[e] Age at index date.
[f] Epilepsy subtype classification based on first epilepsy diagnosis ever registered.

diagnosis, when compared with the matched reference group. Similarly, in individuals with depression, the incidence rate of epilepsy peaked around the time of depression diagnosis (Figure 3B) and remained elevated in the following years, when compared with that in the reference group.

Discussion

In this study, we used Danish nationwide registers to demonstrate the increased risk of depression after incident epilepsy and increased risk of epilepsy after incident depression. The association between the 2 disorders was robust and persisted after adjusting for medical comorbidity, calendar year, substance abuse, and socioeconomic status. Disease rates peaked in the years just before and after the primary diagnosis

but remained elevated throughout follow-up time. Using admission with seizures as a proxy for treatment failure, we found increased risks of treatment failure in persons with epilepsy who were diagnosed with depression.

Overall, we found relative risk estimates that were in line with that found in population-based studies of comparable design and sample size. In a recent, large-scale Canadian study,[13] incident epilepsy was associated with an increased HR for depression of 2.04 (95% CI 1.97–2.09), and incident depression was associated with an increased HR for developing epilepsy of 2.55 (95% CI 2.49–2.60). In a recent meta-analysis[31] of 4,195 participants, the overall odds ratio (OR) of lifetime depression in persons with epilepsy compared with that in healthy individuals was 2.20 (95% CI 1.07–4.51). In a

Table 3 aHRs of Epilepsy After Depression Compared With Matched Reference Populations

	Persons in cohort, n	IR of epilepsy (95% CI)[a]	HR (95% CI)[b]	aHR (95% CI)[c]
No depression[d]	1,099,490	7.3 (7.1–7.4)	1 (ref)	1 (ref)
Depression	219,990	20.3 (19.7–20.9)	2.82 (2.71–2.92)	2.35 (2.25–2.44)
Time since depression diagnosis	Persons with depression, n			
			1 (ref)	1 (ref)
0 to <3 mo	219,990	43.9 (38.3–50.4)	6.99 (5.74–8.49)	5.63 (4.57–6.88)
3 to <6 mo	214,007	34.3 (29.5–39.6)	5.61 (4.56–6.95)	4.45 (3.56–5.55)
6 mo to <1 y	209,643	28.4 (25.3–31.9)	4.13 (3.54–4.82)	3.19 (2.72–3.77)
1 to <5 y	200,897	20.7 (19.7–21.8)	3.33 (3.11–3.54)	2.59 (2.41–2.80)
5 to <10 y	141,591	16.4 (15.2–17.4)	2.58 (2.38–2.79)	2.06 (1.90–2.24)
10 to <20 y	83,376	17.4 (16.2–18.6)	2.26 (2.08–2.46)	1.87 (1.71–2.05)
≥20 y	18,940	18.9 (17.7–22.1)	2.03 (1.76–2.34)	1.93 (1.65–2.24)
Age group, y[e]				
			1 (ref)	1 (ref)
0–19	21,361	17.1 (15.1–19.9)	3.86 (3.29–4.55)	3.69 (3.12–4.34)
20–39	76,862	16.8 (15.9–17.8)	4.01 (3.75–4.33)	3.21 (2.97–3.48)
40–59	67,540	20.9 (19.9–22.1)	2.98 (2.79–3.17)	2.20 (2.06–2.36)
60–79	39,343	27.9 (26.3–30.1)	2.21 (2.03–2.38)	1.91 (1.76–2.07)
80+	14,884	25.0 (20.0–28.4)	1.55 (1.30–1.88)	1.51 (1.26–1.84)
Depression severity[f]				
			1 (ref)	1 (ref)
Mild	33,803	21.0 (19.5–22.8)	3.52 (3.19–3.89)	2.79 (2.51–3.11)
Moderate	84,044	19.2 (18.2–20.2)	2.93 (2.74–3.13)	2.32 (2.16–2.50)
Severe	35,436	22.1 (20.4–23.8)	3.11 (2.82–3.42)	2.58 (2.33–2.86)
Unspecified	49,922	21.3 (19.7–23.0)	3.32 (3.04–3.64)	2.69 (2.44–2.95)

Abbreviations: aHR = adjusted HR; HR = hazard ratio; IR = incidence rate.
[a] IR of epilepsy per 10,000 person-years.
[b] Unadjusted.
[c] Adjusted for Charlson comorbidity index, substance abuse, and calendar year.
[d] Persons without depression at index date matched on sex and age at index date.
[e] Age at index date.
[f] Depression severity classification based on first depression diagnosis ever registered.

Table 4 aHRs of Antiepileptic Treatment Failure Defined by Acute Admission With Seizures in Epilepsy Patients With Depression Compared With Epilepsy Patients Without Depression

	Persons in cohort, n	IR of failure (95% CI)[a]	HR (95% CI)[b]	aHR (95% CI)[c]
No depression	123,612	87.2 (85.6–88.8)	1 (ref)	1 (ref)
Depression[d]	4,801	100.1 (92.6–106.9)	1.32 (1.16–1.50)	1.20 (1.07–1.36)

Abbreviations: aHR = adjusted HR; HR = hazard ratio; IR = incidence rate.
[a] IR of acute hospital admission with seizures, per 10,000 person-years.
[b] Unadjusted.
[c] Adjusted for Charlson comorbidity index, substance abuse, and calendar year.
[d] Exposure defined as an incident diagnosis of depression after epilepsy diagnosis.

Figure 2 Cumulative Incidences of Depression After Incident Epilepsy and Vice Versa, Compared With Matched Reference Populations
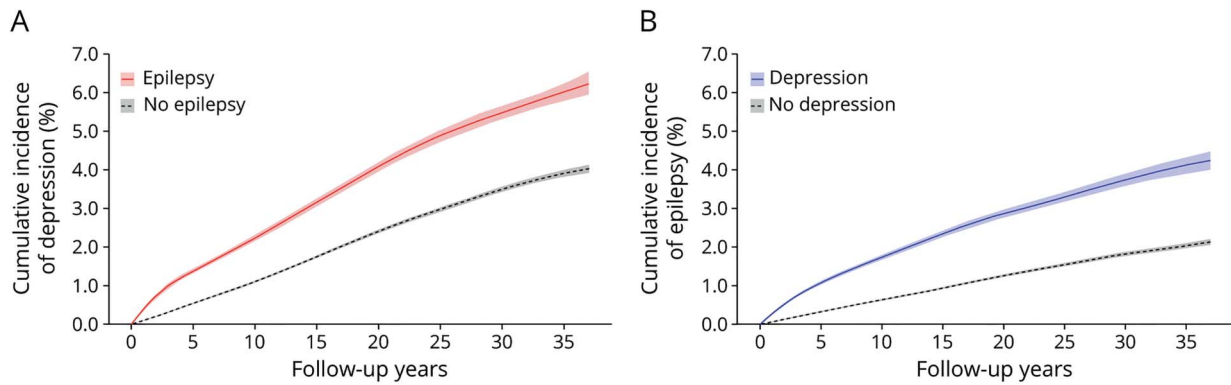

(A) Cumulative incidence of depression in people with epilepsy vs a reference population without epilepsy, matched on sex and age during epilepsy diagnosis. (B) Cumulative incidence of epilepsy in people with depression vs a reference population without depression, matched on sex and age during depression diagnosis.

community-based Swedish study[16] from 1990, cases of incident epilepsy had 7-fold increased odds of having a history of depression compared with sex-matched and age-matched controls (OR 7.03, $p = 0.003$). This study had a small sample size (n = 83), and information on prior depression was obtained through retrospective interviews, with risk of recall bias. In another small-scale (n = 435) matched case-control study,[15] a 4-fold increased risk of incident, unprovoked seizures was found for those with a history of major depression (adjusted OR [aOR] 3.7, 95% CI 0.8–17.0). This study was limited to adults older than 54 years, and risk was not adjusted for alcohol or drug abuse, a considerable confounder for the risk of epilepsy after depression.[32] Indeed, our estimates were substantially attenuated after adjustment for substance abuse.

Our results add to existing evidence by reliably confirming the bidirectional association between epilepsy and depression with high precision estimates, provided by a large study sample, a long and complete follow-up of the entire Danish population, and detailed studies of the association across a broad range of analysis types.

A major strength of our study was the inclusion of a reference group with another chronic disease. The correlation between epilepsy and depression may partly be explained by the fact that a chronic disorder in itself increases frequency of medical visits, thus increasing chances of any additional disorders being caught, compared with healthy persons who have less medical contacts. By taking this issue, known as the Berkson

Figure 3 Incidence Rate of Depression in a Cohort With Epilepsy and Matched References and Incidence Rate of Epilepsy in a Cohort With Depression and Matched References
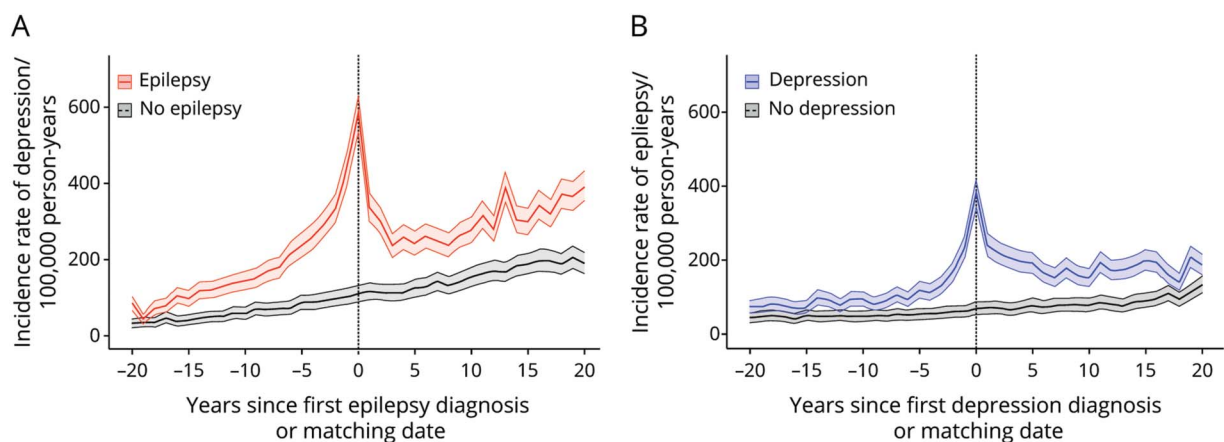
(A). Incidence rate of depression from 20 years before to 20 years after diagnosis of epilepsy (red line) or matching date in the reference population (black line). (B). Incidence rate of epilepsy from 20 years before to 20 years after diagnosis of depression (blue line) or matching date in the reference population (black line).

bias, into account, we strengthen the reliability of the association found. Asthma was chosen as a reference because it shares features with both epilepsy and depression—being fluctuating in intensity and affecting people at a wide distribution of ages—and similar to epilepsy, it is associated with reduced quality of life, emotional stress, sudden unpredictable exacerbations, and fear of fatal episodes.[33] Thus, the analyses of comorbidity with asthma serve dual purposes, indicating that neither the Berkson bias nor the theory of depression being purely reactive to experiencing a chronic encumbering disorder fully explains the associations found. Of note, however, for the majority, the impact of an epilepsy diagnosis on life quality is probably graver than that of a diagnosis with asthma,[34] and in addition, physicians may be more aware of the need for screening for depression in patients diagnosed with the former; thus, residual bias may persist.

The median age at onset was lower in the asthma cohort than in the epilepsy and depression cohorts, a difference that was necessary to take into account because risks of both epilepsy and depression are age dependent.[35,36] We addressed this by presenting HRs stratified by index age group for all main analyses. The estimates for depression after epilepsy were higher than those for depression after asthma across all age groups, although for some age groups (index age groups 0–19, 20–39, and 80+ years), there were overlapping CIs. Similarly, the risk of epilepsy after depression was higher across all age groups than that of epilepsy after asthma, but with overlapping confidence intervals among those oldest (older than 80 years) at index time.

Earlier studies suggested that in persons with both epilepsy and depression, the 2 disorders may often occur in temporal proximity of each other. In a study from Sweden,[17] risk of new onset seizures was presented from >5 years before (OR 2.2, 95% CI: 1.3–3.7) to >2 years after (OR 1.7, 95% CI: 1.0–2.8) debut of depression. In another study of 1,000 adults with epilepsy,[37] HRs of developing psychiatric disorders, compared with controls, were highest in the first year after epilepsy diagnosis (HR 11.4, 95% CI 9.88–13.2), gradually diminishing to nonsignificance after 4 years. In a cohort study of 3,800 epilepsy cases 10–60 years of age,[38] IRRs for depression were 2-fold increased compared with those for controls, in all years from 3 years before to 3 years after epilepsy diagnosis. We were able to add to the existing evidence in both detail and temporal range, showing that the increased risks of depression after epilepsy and vice versa were sustained over a time span from 20 years before to 20 years after index diagnosis, with results presented year by year, across all patient ages. We found that the incidence of depression peaked around the time of epilepsy diagnosis and vice versa. These marked peaks probably partly reflect patients being extra carefully screened by medical professionals in the course of being diagnosed; however, in both directions, the peak extended to several years before and after index time, compellingly giving the impression of a temporal coherence.

We used rate of admission with seizures as a proxy for failure of epilepsy management and found that incident depression was associated with an increased risk of acute admission with seizures. This approach is likely to underestimate the true rate of treatment failure–related events because many patients experience seizures that may not lead to hospital admission. Our result is, however, in accordance with prior findings of decreased adherence to antiseizure medication,[14] increased pharmacoresistance,[11,12] and increased risk of failing to achieve 1-year seizure freedom for epilepsy patients with depression.[13] Thus, many factors may affect chances of successful epilepsy management in those with comorbid depression; our result supports these findings.

Some studies have found certain epilepsy subtypes to be associated with an increased risk of depression, most often focal epilepsies,[15,16,39] whereas others found no difference between subtypes.[40] In this study, we failed to detect any differences in the risk of depression between epilepsy subtypes. Our finding may be partly due to a relatively low predictive value for epilepsy subtypes in the DNPR, estimated at 35%–60%.[41] In addition, the stratification was based on first registered diagnosis with epilepsy, thus disregarding potential further subclassification of patients at later admissions.

Of important note, our study sample was limited to hospitalized inpatients or outpatients including emergency room contacts. Persons with epilepsy in Denmark are diagnosed and treated in hospital settings; but for 85%–90% of patients with depression in a Danish study, the first medical treatment took place outside of psychiatric hospitals and three-quarters of persons treated for depression received no hospital care within 5 years.[42] Thus, we might primarily catch those at the severe end of the depression spectrum, which has previously been related to a higher risk of epilepsy,[13] and the result may thus not generalize to cases of depression treated in primary care. The results presented in this study, however, suggest no higher risk of epilepsy in the more severely depressed. Contrarily, there was some indication of a higher risk of epilepsy for the mildly depressed than for those categorized with moderate or severe depression at first registered depression diagnosis; however, it was not statistically significant.

A noteworthy limitation of the study is the somewhat lacking validity of epilepsy, major depression, and asthma diagnoses in the Danish registries, with positive predictive values (PPVs) estimated at 81%,[41] 75%,[43] and 65%,[44] respectively; notably, the PPV of asthma may have been underestimated in the latter study because this was based on conscription records, which may underascertain asthma diagnoses if another medical condition has already been recorded as the reason for exemption, or conscripts wanting to serve may underreport asthma.[44] Nonetheless, misclassification of the registered disorders, especially in the asthma analyses, may cloud the associations. Furthermore, the clinical presentation of depression in persons with epilepsy often does not correspond to the criteria in operationalized classification systems such as ICD-10,[45] and thus, failure to detect depression may occur at a higher rate in those with underlying epilepsy. Such a

differential misclassification could further bias the estimates of the association toward the null.

Another limitation is the diagnostic delay in both epilepsy and depression. In a Spanish study, the mean diagnostic delay from onset of symptoms to a major depression diagnosis was approximately 10 weeks,[46] and hospital-based identification of patients with depression is likely longer. Likewise, in a validation study of the epilepsy diagnosis in the DNPR, delay from index seizure to epilepsy diagnosis was more than a year for 36% of patients.[41] Thus, the capability to address the temporal aspects of the association with the present data is limited. Finally, we did not have access to data on prescriptions or other treatments for this study, preventing us from adjusting for this in the main analyses or inferring on their potential contribution to the correlation.

At present, the nature of the bidirectional relationship between epilepsy and depression remains unclear. Theories of etiologies span from common neurobiological properties, hereditary and psychosocial aspects, negative psychotropic effects of antiseizure medication, and proconvulsant properties of antidepressants.[19,20,45] The latter has been a widely held concern, adding to a reluctance to treat depression in persons with epilepsy,[3] but this has been largely disproven by studies concluding that nearly all antidepressants are safe for persons with epilepsy when administered in proper doses,[47] and the increased risk of epilepsy after depression has been proven robust to adjustment for antidepressant treatment.[15] The present results add to the idea that concurrent depression seems to be associated with worse seizure outcomes for persons with epilepsy, but whether this finding is related to the depression in itself or its treatment cannot be inferred using this study design.

In conclusion, we found a robust association between epilepsy and depression in nationwide Danish registers, strongly supporting previous observations of a bidirectional association between these 2 brain disorders. The results add to the growing amount of evidence, indicating the need for increased clinical awareness of this association and prompt further research to better understand the nature of this association and its consequences.

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Appendix Authors

Name	Location	Contribution
Eva Bølling-Ladegaard, MD	Department of Clinical Medicine, Neurology, Aarhus University, Denmark	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; study concept or design; and analysis or interpretation of data
Julie Werenberg Dreier, PhD	Department of Economics and Business Economics, Business and Social Science, The National Center for Register-Based Research, Centre for Integrated Register-Based Research (CIRRAU), Aarhus University, Denmark	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design
Lars Vedel Kessing, MD, DrMedSci	Department of Clinical Medicine, University of Copenhagen; Copenhagen Affective Disorder Research Center (CADIC), Psychiatric Center Copenhagen, Denmark	Drafting/revision of the article for content, including medical writing for content
Esben Budtz-Jørgensen, MSc, DrSci	Section of Biostatistics, Department of Public Health, University of Copenhagen, Denmark	Drafting/revision of the article for content, including medical writing for content
Kasper Lolk, MEc	Department of Clinical Medicine, Neurology, Department of Economics and Business Economics, Business and Social Science, The National Center for Register-Based Research, Centre for Integrated Register-Based Research (CIRRAU), Aarhus University, Denmark	Drafting/revision of the article for content, including medical writing for content; analysis or interpretation of data
Jakob Christensen, MD, DrMedSci	Department of Clinical Medicine, Neurology, Department of Economics and Business Economics, Business and Social Science, The National Center for Register-Based Research, Centre for Integrated Register-Based Research (CIRRAU), Aarhus University; and Department of Neurology, Aarhus University Hospital, Denmark	Drafting/revision of the article for content, including medical writing for content; major role in the acquisition of data; and study concept or design

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