Physical and mental health comorbidities of epilepsy: population-based cross-sectional analysis of 1.5 million people in Scotland

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1. Introduction

Epilepsy is the second commonest chronic neurological disorder in developed countries with an estimated prevalence of around 9.7 per 1000 population and an incidence of 0.55 per 1000 per year.[1] Other United Kingdom studies have suggested a prevalence of 7.7 per 1000 population and 5.6 per 1000 population.[2 3] There is a consistent association between epilepsy and socioeconomic status with a higher prevalence and incidence in the less affluent.[2] People with epilepsy are known to have more physical ill-health than the general population, but previous studies examining this have not usually accounted for higher rates of socioeconomic deprivation in people with epilepsy and have studied less comorbidities.[3-5] Lower socioeconomic status is also strongly associated with multimorbidity, with people living in the most deprived areas having more multimorbidity than those living in the most affluent areas, and on average developing multimorbidity 10-15 years earlier.[6] The observed association between epilepsy and the presence of other conditions may therefore partly or entirely reflect that people with epilepsy are less affluent.

Mental illness, particularly depression, is also commonly recognised in people with epilepsy, and rates of depression and anxiety are higher than in the general population.[7] A recent large cohort study concluded there was a bidirectional relationship between epilepsy and depression and the authors proposed that a common neurobiology to account for the association.[8] An alternative explanation however is that higher prevalence of depression in people with epilepsy reflects the increasing burden of deprivation and physical ill health and that they suffer and this is not unique to epilepsy but occurs with many other chronic illnesses.

The aim of this study was to compare the prevalence of comorbid physical and mental health conditions in those with and without epilepsy aged 14 and over after accounting for age, gender and social deprivation, and to examine the prevalence of depression in people with

epilepsy compared to people with other physical conditions after accounting for the total burden of comorbid physical disease.

2. Methods

The design was secondary analysis of a cross-sectional analysis of an established database for 1,510,742 people aged 14 and over who were registered with 314 primary care practices in Scotland, United Kingdom on 31st March 2007. The original dataset was created for a study of the epidemiology of multimorbidity, and counted 40 common physical and mental health conditions including epilepsy.

The UK National Health Service (NHS) requires registration with a single primary care practice, and 98% of people in Scotland are registered with a general practice. All Scottish general practices use electronic medical records, and the record is transferred between practices when people move. The data covers approximately one third of the Scottish population, and has previously been shown to be representative of the whole Scottish population in terms of age, sex and socioeconomic deprivation.[9] In the UK National Health Service (NHS), epilepsy is diagnosed in secondary care by a specialist who writes to the patient's general practitioner who then records the diagnosis in the medical record. The medical record belongs to the NHS and when patients move their record follows them, meaning that a lifelong primary care record exists.

People were defined as having epilepsy if their record included a Read Code for epilepsy recorded ever AND they had been prescribed an antiepileptic drug (AED) in the last 12 months.[10] The full case definition is included in appendix 1, and matches that of 'active epilepsy' used in the UK Quality and Outcomes Framework programme which incentivises practices to maintain disease registers for selected conditions including epilepsy.[11] The focus of the study was on people aged 14 years of age and above since this is the approximate

age at which people with epilepsy begin to be transferred to adult services in the UK (although the actual age of transition varies by locality and, reflecting national guidance, may involve joint clinics for adolescents).[12]

Data on 31 other common and important physical conditions and 8 mental health conditions were also extracted as described in previous publications, although these were defined in relation to the original study rather than pre-specified as being relevant to epilepsy (appendix 2).[6] Finally, data on age, sex, and socioeconomic status measured using the Carstairs' deprivation score were extracted. The Carstairs' score is a measure of neighbourhood socioeconomic deprivation assigned to individuals based on their postcode of residence, and has been widely used in healthcare research.[13 14]

The characteristics of people with and without epilepsy were compared in terms of sex, age, socioeconomic status measured by quintiles (equal fifths of the Scottish population) of the Carstairs score, and the number of comorbid conditions they had. The prevalence of the 31 physical conditions in people with and without epilepsy was then compared, using both unadjusted and adjusted prevalence odds ratios (pOR). Adjustment was carried out using a logistic regression model with the presence or absence of the comorbid condition as the binary outcome variable, and adjusted for characteristics including age, sex and deprivation. The same analysis was carried out for the prevalence of the eight comorbid mental health conditions, but the number of physical conditions (excluding epilepsy) was included in the adjustment, reflecting that physical disease burden is known to be strongly associated with the presence of depression in particular.[6 15] Data was analysed using SPSS version 22 and differences tested for statistical significance using t-tests assuming unequal variances for continuous data and chi-squared tests and confidence intervals for the difference between proportions for categorical variables. The NHS Grampian Research Ethics Service had previously approved the anonymous use of these data for research purposes.

3. Results

Of the 1,510,742 people included in the dataset, 12,720 had epilepsy (prevalence 8.4 per 1000 population, 95% CI 8.3 to 8.5). The prevalence of epilepsy rose with age from 4.9 per 1000 in 14 to 24 year olds to a peak of 10.3 per 1000 in 65 to 84 years, falling slightly to 8.4 per 1000 in people aged 85 years and over. There was a social gradient in prevalence, rising from 6.4 per 1000 in people living in the most affluent fifth of areas to 10.7 per 1000 for those living in the most deprived. 69.9% of people with epilepsy had one or more of the 39 other conditions examined, compared to 46.9% of the general population who did not have epilepsy. People with epilepsy had a mean of 0.81 (95% CI 0.78 to 0.85, $p<0.001$) more comorbid conditions than people without, with 1.02 (95% CI 0.99 to 1.06, $p<0.001$) more physical and 0.26 (95% CI 0.25 to 0.27, $p<0.001$) more mental health conditions. (Table 1).

Of the comorbid physical health conditions 29 out of 31 had statistically significantly increased unadjusted odds of occurring in people with epilepsy compared to people without epilepsy. After adjustment for differences in age, gender and deprivation the number of statistically significantly increased odds ratios fell to 24 of the 31 comorbid physical health conditions studied. The strongest adjusted associations were with constipation (prevalence OR [pOR] 4.83 for prevalence in people with epilepsy compared to those without), stroke or transient ischaemic attack (TIA) (pOR 4.58), blindness (pOR 3.38), chronic liver disease (pOR 2.57) and migraine (pOR 2.36). Of the two conditions with statistically significantly lower crude prevalence in people with epilepsy, adjustment for age, sex and deprivation rendered the association with chronic sinusitis non-significant (adjusted pOR 0.90, 95% CI 0.71 to 1.14) whereas the association with hypertension remained statistically significant but clinically small (adjusted pOR 0.94, 95% CI 0.89 to 0.99).(Table 2).

All eight of the mental health conditions studied were more common in people with epilepsy, and these associations remained statistically significant after adjustment for deprivation, age

and gender, and after additionally adjusting for number of physical health conditions. The strongest association was with the presence of learning disabilities (adjusted pOR 29.1, 95% CI 27.1 to 31.3 for people with epilepsy vs those without). Depression was the most prevalent mental health condition for people with and without epilepsy, but occurred significantly more often in people with epilepsy (16.3% vs 9.5%, unadjusted pOR 1.85, 95% CI 1.77 to 1.82; fully adjusted pOR 1.57, 95% CI 1.49 to 1.65) (Table 3).

The prevalence of comorbid depression in people with epilepsy rose steadily with both the number of comorbid physical conditions and with increasing socioeconomic deprivation (Figure 1). These relationships persisted after adjustment in a logistic regression model for age, sex as well as the number of physical conditions and deprivation (adjusted pOR for depression for those with four or more physical comorbidities vs none 5.82, 95% CI 4.90 to 6.91; and for the most deprived vs the most affluent of 1.51, 95% CI 1.27 to 1.79). Similar patterns of increasing prevalence of comorbid depression with increasing physical comorbidity were seen for a range of other physical conditions, with the prevalence of depression given the presence of other physical disease not strikingly different for epilepsy than other conditions. (Figure 2).

4. Discussion

This study found that people with epilepsy have more other physical and mental health conditions than the general population even after adjusting for age, gender and socioeconomic deprivation. Over two-thirds of people with epilepsy had at least one other of the 39 conditions examined, and almost one in five had four or more other conditions. The associations between epilepsy and the presence of all the mental health conditions examined were weakened by adjustment for age, gender, deprivation and physical ill health, but remained statistically and are usually clinically significant. The prevalence of depression in people with epilepsy increased with increasing levels of physical comorbidity and deprivation, and the strength of association for the same total burden of physical disease and deprivation was similar to that observed for people with a number of other chronic physical conditions including asthma, coronary heart disease, chronic obstructive pulmonary disease, peripheral vascular disease and diabetes.

Many of the somatic and psychiatric associations identified within this study can be explained by biologically plausible mechanisms proposed in previous studies. These state that the association is likely to reflect a direct causal association, an example of shared genetic or environmental factors, or a result of epilepsy and its treatment. It is well established that stroke is a cause of epilepsy, particularly for large infarcts. 23% of all epilepsy over the age of 65 and almost 10% overall is considered to be secondary to cerebrovascular disease.[16] The association between epilepsy and other structural brain disorders has been identified in previous studies, notably for multiple sclerosis and Parkinson's Disease,[17-19]and neurodegenerative disorders are believed to account for 25% of all epilepsy in older people.[16] Epilepsy secondary to another pathology is the probable explanation of why people with epilepsy are older than people without epilepsy in this study.

Migraine has also been consistently associated with epilepsy and this is likely to reflect common genetic and environmental factors.[20 21] Epilepsy and a number of other conditions may also share a common aetiology. For example, alcohol dependency is commonly associated with epilepsy, peptic ulcer disease and chronic liver disease. Some conditions are likely to result from adverse effects of both epilepsy and or its treatment such as the association with dermatological disorders (although genetic factors clearly contribute) and constipation.[22 23] The association between epilepsy and depression has led to interest in whether a common neurobiological mechanism may predispose to both.[4 7] Although the cross-sectional nature of this study does not allow direct exploration of causality, the finding that the prevalence of depression is similar in epilepsy as the prevalence in many chronic physical health conditions with disparate aetiologies is consistent with depression being significantly driven by the experience of chronic ill health and stigma in addition to any common neurobiological mechanism unique to epilepsy and depression.[24-27] Additionally, the prevalence of depression in people with epilepsy is strongly associated with an increasing physical comorbidity burden, again consistent with the experience of chronic ill health being a significant driver of depression. This study cannot examine this directly because it is cross-sectional, but the only large longitudinal study in this area found that the association between epilepsy and depression is bidirectional (people with epilepsy are at a higher risk of depression and vice versa).[8] Further longitudinal studies of this would be helpful.

A strength of this study is the method by which people with active epilepsy were selected to only include people coded as having epilepsy who were receiving current drug treatment. This ensures that those with a historical diagnosis of epilepsy who were no longer taking medication were excluded. A limitation is that like all such routine data studies, this study is reliant on the accuracy of clinical coding. At the time of data extraction, general practices were financially incentivised to create and maintain an accurate register of people with

epilepsy, and this was subject to external audit and inspection.[28 29] The prevalence of epilepsy in this study (8.4 per 1000) was higher than the 5.6 per 1000 found in an older study using similar UK primary care electronic medical record data from before epilepsy registers were incentivised.[3] A recent population study using data linkage techniques and a validated gold standard cohort found a similar prevalence (7.7 per 1000, CI 7.6 to 7.9),[2] and previously it has been suggested that the prevalence of epilepsy is 9.7 per 1000 increasing confidence in the completeness of recording.[1] However, a limitation is that like other cross-sectional routine data studies, GP registers do not accurately record type of epilepsy, and it is only possible to examine associations rather than directly explore causality.[30] Routine data studies of comorbidity could also be subject to a type of surveillance bias, in that people with epilepsy may attend primary care more often than the general population, resulting in the increased identification of comorbidities.[31 32] However, this proposition is not supported by studies using direct methods of case ascertainment such as household surveys. For example, a Canadian population study relying on household surveys also found higher prevalence of comorbidity in people with epilepsy compared to general population controls.[5]

The frequency of comorbid conditions in epilepsy highlights the need for increased vigilance within primary and secondary care. A finding that almost 50% of people with epilepsy have multiple comorbidities highlights the complexity faced by the primary care physician who is expected to manage such comorbidity without compromising seizure control, and by specialists who will need to account for important comorbidities when deciding on treatment. This is particularly important because comorbid epilepsy and mental health conditions are associated with reduced quality of life and increased mortality.[33 34] The reason for this remains unclear but commonly used medications for mood disorders, anxiety and psychosis such as tricyclic antidepressants, selective serotonin reuptake inhibitors and antipsychotics

are known to potentially lower the “seizure threshold”.[35 36] Concerns about psychotrophic medication reducing seizure threshold could also potentially lead to poorly treated depression which would contribute to observed lower quality of life in people with epilepsy and comorbid mental health conditions.[34] The evidence provided highlights that those with epilepsy are potentially challenging to primary care physicians who are faced with the complex balance between seizure control and treating comorbid conditions which can potentially lead to inadequate treatment for associated mental illness.

Given the socioeconomic patterning of epilepsy, this highlights the importance of equitable access to primary care a strength currently found in the United Kingdom healthcare system. In addition, adequate funding for the training and retention of primary care physicians with a special interest in common chronic health conditions (“the expert generalist”) including epilepsy may provide a solution to managing this complex group within a community setting, although further research is required to determine the optimum management of this group of patients.[37-40]

5. Conclusion

This study demonstrates that those with epilepsy have greater levels of comorbidity than the general population but the influence that comorbidity and poly-pharmacy have on outcome remains unclear. Research in well-described population clinical cohorts is needed to determine the relative importance of intrinsic factors (epilepsy type, genetics, significant clinical factors) and external factors (such as comorbidity, polypharmacy, and socioeconomic status), to inform the development of stratified health care to be applied to those with complex epilepsy.

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Conflict of interest

All authors have no conflicts of interest to disclose.

Authorship statement

BG and SWM conceived and led the study which created the dataset on which this analysis is based. All authors contributed to the design of this study, with analysis led by CJW supported by BG. CJW wrote the first draft of the paper, with all authors contributing to redrafting and approving the final version.

Table 1: Characteristics of people aged 14 years and over with and without epilepsy in the dataset

	People with epilepsy (≥14 years) No. (%) N=12720	People without epilepsy (≥14 years) No. (%) N=1498022	Prevalence of epilepsy Prevalence per 1000 population (95% CI)
Sex			
Male	6415 (50.4)	737567 (49.2)	8.6 (8.4 to 8,8)
Female	6305 (49.6)	760455 (50.8)	8.2 (8.0 to 8.4)
Age Group (years)			
14 to 24	1171 (9.2)	236886 (15.8)	4.9 (4.6 to 5.2)
25 to 44	3918 (30.8)	504471 (33.7)	7.7 (7.5 to 7.9)
45 to 64	4701 (37.0)	468426 (31.3)	9.9 (9.6 to 10.2)
65 to 84	2623 (20.6)	251977 (16.8)	10.3 (9.9 to 1.1)
85 and over	307 (2.4)	36262 (2.4)	8.4 (7.5 to 9.4)
Deprivation (quintiles)			
Q1 (least deprived)	1852 (14.6)	286337 (19.1)	6.4 (6.1 to 6.7)
Q2	2356 (18.5)	320417 (21.4)	7.3 (7.0 to 7.6)
Q3	2897 (22.8)	338906 (22.6)	8.5 (8.2 to 8.8)
Q4	2728 (21.4)	285080 (19.0)	9.5 (9.2 to 9.9)
Q5 (most deprived)	2887 (22.7)	267282 (17.8)	10.7 (10.3 to 11.1)
			Difference in % with comorbidity (95% CI)
No. of comorbidities			
None	3824 (30.1)	794708 (53.1)	-23.0 (-22.2 to -23.8)
One	2939 (23.1)	308679 (20.6)	2.5 (1.8 to 3.2)
Two	2105 (16.5)	162848 (10.9)	5.7 (5.0 to 6.3)
Three	1482 (11.7)	97196 (6.5)	5.2 (4.6 to 5.7)
Four or more	2370 (18.6)	134591 (9.0)	9.6 (9.0 to 10.3)
No. of physical comorbidities			
None	5093 (40.0)	874288 (58.4)	-18.3 (-17.5 to -19.2)
One	3174 (25.0)	299187 (20.0)	5.0 (4.2 to 5.7)
Two	1895 (14.9)	147627 (9.9)	5.0 (4.4 to 5.7)
Three	1166 (9.2)	82638 (5.5)	3.6 (3.2 to 4.2)
Four or more	1392 (10.9)	94282 (6.3)	4.6 (4.1 to 5.2)
No. of mental health comorbidities			
None	8428 (66.3)	1280682 (85.5)	-19.2 (-18.4 to -20.1)
One	3280 (25.8)	181406 (12.1)	13.7 (12.9 to 14.5)
Two	840 (6.6)	30901 (2.1)	4.5 (4.1 to 5.0)
Three or more	172 (1.4)	5033 (0.3)	1.0 (0.8 to 1.2)

Table 2: Prevalence of comorbid physical conditions in people with and without epilepsy

Physical Condition	People with epilepsy No. (%) N=12720	People without epilepsy No. (%) N=1498022	Unadjusted Prevalence OR (95% CI)	Adjusted for age, sex, deprivation Prevalence OR (95% CI)
Constipation	1317 (10.4)	35302 (2.4)	4.79 (4.52 to 5.07)	4.83 (4.54 to 5.15)
Stroke or TIA	1245 (9.8)	35328 (2.4)	4.49 (4.23 to 4.77)	4.58 (4.29 to 4.89)
Blindness	268 (2.1)	8430 (0.6)	3.80 (3.36 to 4.30)	3.38 (2.99 to 3.83)
Chronic liver disease	67 (0.5)	2547 (0.2)	3.11 (2.44 to 3.97)	2.57 (2.02 to 3.28)
Migraine	187 (1.5)	9319 (0.6)	2.38 (2.06 to 2.76)	2.36 (2.04 to 2.73)
Multiple sclerosis	73 (0.6)	3777 (0.3)	2.28 (1.81 to 2.88)	2.23 (1.77 to 2.82)
Viral hepatitis	19 (0.1)	1157 (0.1)	1.94 (1.23 to 3.05)	1.83 (1.16 to 2.88)
Parkinson’s disease	48 (0.4)	2695 (0.2)	2.10 (1.58 to 2.80)	1.82 (1.36 to 2.43)
Dyspepsia (treated)	1247 (9.8)	78128 (5.2)	1.98 (1.86 to 2.10)	1.77 (1.67 to 1.88)
Pain	1845 (14.5)	124456 (8.3)	1.87 (1.78 to 1.97)	1.65 (1.57 to 1.74)
Bronchiectasis	41 (0.3)	2798 (0.2)	1.73 (1.27 to 2.35)	1.53 (1.12 to 2.08)
Psoriasis or eczema	144 (1.1)	10570 (0.7)	1.61 (1.37 to 1.90)	1.50 (1.27 to 1.77)
Deafness	756 (5.9)	55940 (3.7)	1.63 (1.51 to 1.75)	1.45 (1.35 to 1.57)
Thyroid disorders	880 (6.9)	71267 (4.8)	1.49 (1.39 to 1.59)	1.41 (1.32 to 1.52)
Heart Failure	243 (1.9)	18667 (1.2)	1.54 (1.36 to 1.75)	1.33 (1.17 to 1.52)
Asthma (currently treated)	998 (7.8)	90557 (6.0)	1.32 (1.24 to 1.41)	1.32 (1.24 to 1.41)
COPD	678 (5.3)	53224 (3.6)	1.53 (1.41 to 1.65)	1.29 (1.19 to 1.40)

Coronary heart disease	987 (7.8)	80484 (5.4)	1.48 (1.39 to 1.58)	1.26 (1.17 to 1.35)
Glaucoma	191 (1.5)	15741 (1.1)	1.44 (1.24 to 1.66)	1.25 (1.08 to 1.45)
New diagnosis of cancer diagnosis in last 5 years	512 (4.0)	43428 (2.9)	1.41 (1.29 to 1.54)	1.24 (1.14 to 1.36)
Irritable bowel syndrome	547 (4.3)	51908 (3.5)	1.25 (1.15 to 1.36)	1.23 (1.13 to 1.34)
Atrial fibrillation	280 (2.2)	23699 (1.6)	1.40 (1.24 to 1.58)	1.22 (1.08 to 1.38)
Inflammatory bowel disease	103 (0.8)	9721 (0.6)	1.25 (1.03 to 1.52)	1.19 (0.98 to 1.44)
Peripheral vascular disease	267 (2.1)	23063 (1.5)	1.37 (1.21 to 1.55)	1.16 (1.02 to 1.31)
Diabetes	814 (6.4)	74515 (5.0)	1.31 (1.22 to 1.40)	1.12 (1.04 to 1.20)
Diverticular disease	338 (2.7)	33482 (2.2)	1.19 (1.07 to 1.33)	1.05 (0.94 to 1.18)
Prostate	168 (1.3)	15067 (1.0)	1.29 (1.11 to 1.51)	1.05 (0.89 to 1.23)
Chronic kidney disease	324 (2.5)	33243 (2.2)	1.15 (1.03 to 1.29)	1.01 (0.90 to 1.14)
Hypertension	2199 (17.3)	232156 (15.5)	1.14 (1.09 to 1.19)	0.94 (0.89 to 0.99)
Rheumatoid arthritis, other inf. poly-arthropathies including gout and systemic connective tissue disorders	518 (4.1)	57810 (3.9)	1.06 (0.97 to 1.16)	0.93 (0.85 to 1.01)
Chronic sinusitis	72 (0.6)	9139 (0.6)	0.93 (0.74 to 1.17)	0.90 (0.71 to 1.14)

Table 3: Prevalence of comorbid mental health conditions in people with and without epilepsy

Mental	People with epilepsy No. (%) N=12720	People without epilepsy No. (%) N=1498022	Unadjusted Prevalence OR (95% CI)	Adjusted for age sex and deprivation Prevalence OR (95% CI)	Adjusted for age, sex, deprivation and number of physical conditions (excluding epilepsy) Prevalence OR (95% CI)
Learning disability	995 (7.8)	4147 (0.3)	30.6 (28.5 to 32.8)	30.5 (28.4 to 32.8)	29.1 (27.1 to 31.3)
Dementia	266 (2.1)	11441 (0.8)	2.78 (2.45 to 3.14)	2.83 (2.48 to 3.22)	2.77 (2.43 to 3.16)
Anxiety and other neurotic, stress related and somatoform disorders	1255 (9.9)	54764 (3.7)	2.89 (2.72 to 3.06)	2.64 (2.49 to 2.81)	2.40 (2.26 to 2.56)
Alcohol problem	979 (7.7)	41660 (2.8)	2.92 (2.73 to 3.11)	2.58 (2.41 to 2.76)	2.44 (2.28 to 2.61)
Schizophrenia and related non-organic psychosis or bipolar disorder	262 (2.1)	12238 (0.8)	2.55 (2.26 to 2.89)	2.36 (2.09 to 2.67)	2.29 (2.03 to 2.60)
Other psychoactive substance misuse	832 (6.5)	41754 (2.8)	2.44 (2.27 to 2.62)	2.17 (2.02 to 2.33)	1.96 (1.82 to 2.11)
Anorexia or bulimia	89 (0.7)	5311 (0.4)	1.98 (1.61 to 2.44)	2.15 (1.74 to 2.65)	1.99 (1.61 to 2.46)
Depression	2067 (16.3)	142182 (9.5)	1.85 (1.77 to 1.94)	1.73 (1.65 to 1.82)	1.57 (1.49 to 1.65)

Figure 1: Prevalence of comorbid depression in people with epilepsy by the number of comorbid physical conditions and socioeconomic deprivation

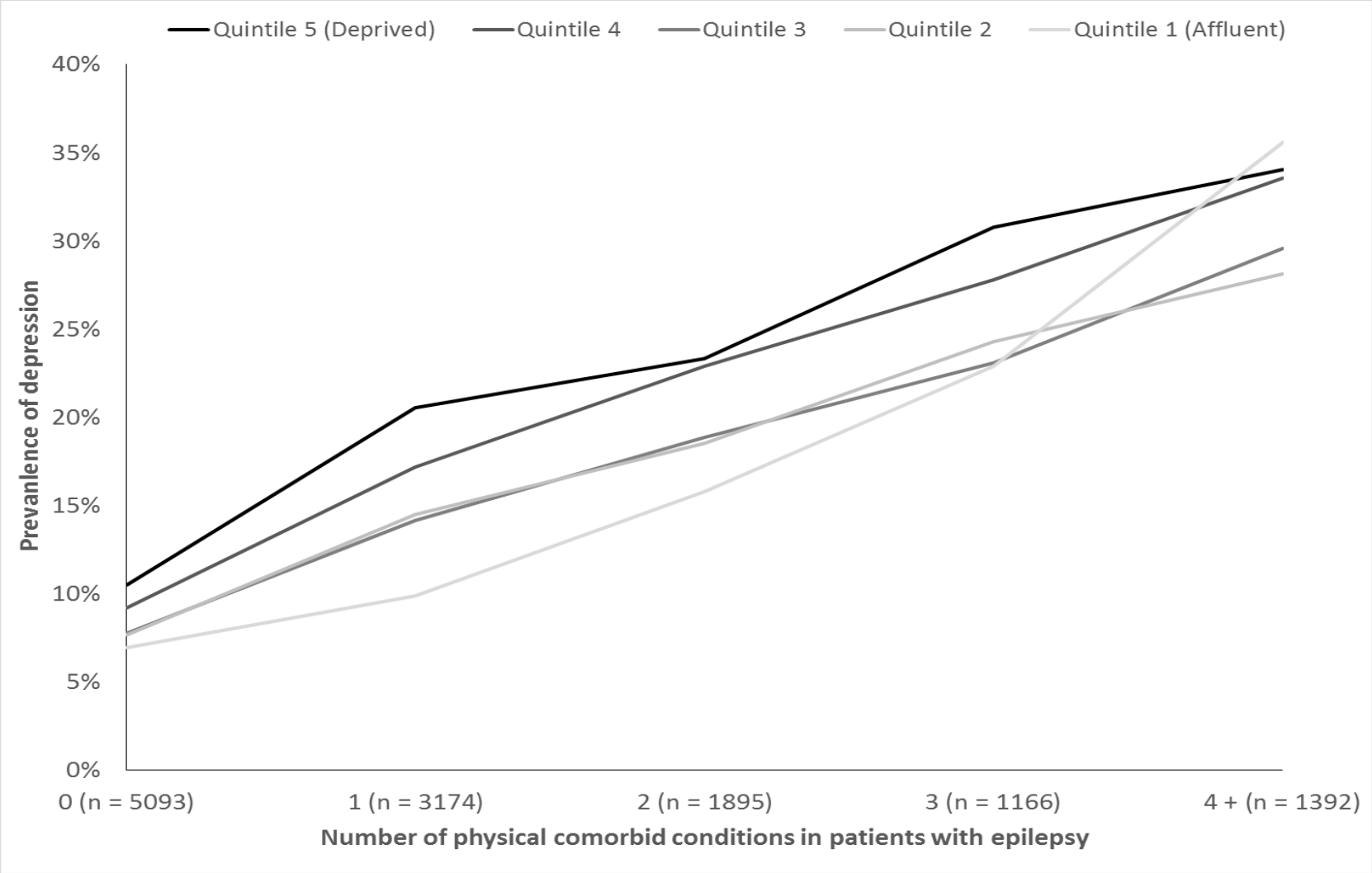
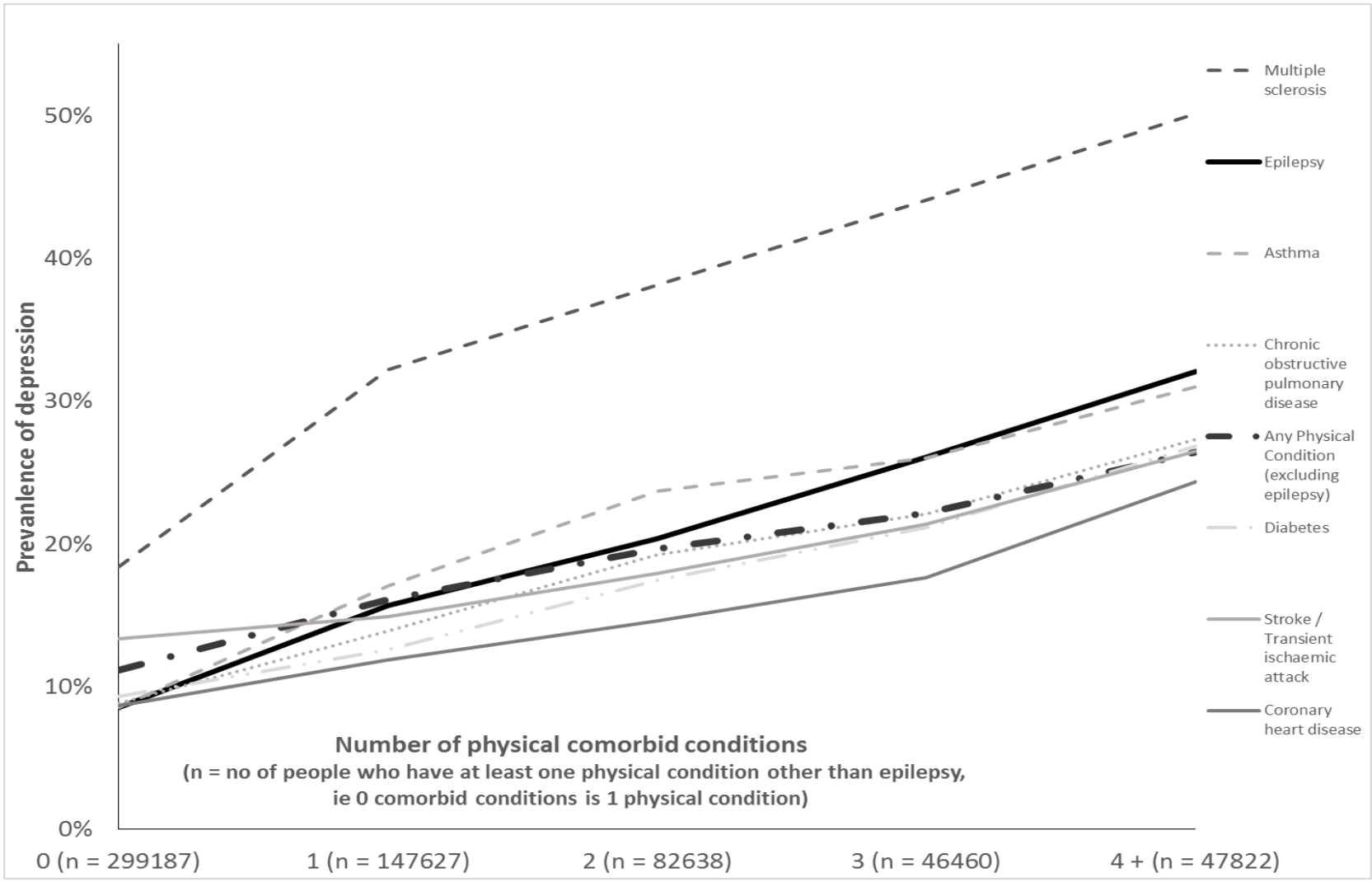


Figure 2: Prevalence of comorbid depression in people with epilepsy and other index conditions


Prevanlence of depression
50%
40%
30%
20%
10%
0%
Multiple sclerosis
Epilepsy
Asthma
Chronic obstructive pulmonary disease
Any Physical Condition (excluding epilepsy)
Diabetes
Stroke / Transient ischaemic attack
Coronary heart disease
Number of physical comorbid conditions
(n = no of people who have at least one physical condition other than epilepsy, ie 0 comorbid conditions is 1 physical condition)
0 (n = 299187)
1 (n = 147627)
2 (n = 82638)
3 (n = 46460)
4 + (n = 47822)

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