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Medication burden in epilepsy: Exploring the impact of non-epilepsy concomitant drugs load

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ABSTRACT

Purpose: To determine the burden of non-epilepsy drugs on people with epilepsy, using administrative health care data.

Methods: The Achmea Health Insurance Database (AHID) contains health claims data from 25 % of the Dutch population. From the AHID, we selected all policyholders with coverage for at least one full calendar year between 2006 – 2009. We included adults with diagnostic codes for epilepsy and randomly selected two frequency-matched controls per case. We labeled drugs dispensed at least twice per calendar year as chronic and excluded antiseizure medications. We estimated and compared the prevalence of chronic medication use, number of chronic medications used, number of prescriptions dispensed, Rx Risk comorbidity index, and drug burden index (DBI) between people with epilepsy and controls.

Results: Non-epilepsy chronic medication use was more frequent in people with epilepsy than controls (67 % versus 59 %, $p < 0.001$). People with epilepsy had an increased DBI (average 0.19 versus 0.10, $p < 0.001$), used more chronic medications (median 2 versus 1, $p < 0.001$) and had more prescriptions dispensed (median 7 versus 3, $p < 0.001$). The DBI and number of unique chronic medications were higher among older (> 60 years) than younger (< 60 years) subjects in cases and controls. Non-epilepsy chronic medication use was more prevalent in people with epilepsy across all therapeutic drug classes and most comorbidities measured using the Rx Risk score.

Conclusion: Chronic non-epilepsy medication use is more prevalent among people with epilepsy. The medication burden is higher among elderly with epilepsy and could partially explain the lower quality of life of people with epilepsy with comorbidities.

1. Introduction

Epilepsy is a serious chronic neurological disorder associated with an increased risk of psychiatric comorbidity and premature mortality. Accumulating evidence suggests that somatic comorbidity is markedly increased in people with epilepsy compared to the general population [1–6]. These comorbidities have a substantial detrimental effect on the quality of life in people with epilepsy [7–11]. The precise determinants for the comorbidities are yet unknown, but may include the use of medications for epilepsy or other indications [12,13]. Polypharmacy is a special concern among the elderly with epilepsy [14,15].

Dutch health insurance databases are a potentially useful source in research, as the Netherlands health care system has mandatory universal insurance [16]. In the Dutch system physicians include all diagnoses, pharmacists log all prescriptions dispensed and the insurer keeps the data. The Achmea Health Insurance Database (AHID) reflects health care use of the Dutch population with regard to age, gender and socioeconomic status [17]. It has also been validated for identifying people with epilepsy using Diagnostic Treatment Protocol (DTP) codes [18]. We used the AHID to determine the burden of concomitant non-antiseizure medications in both young and older people with epilepsy.

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2. Methods

2.1. Population and setting

Data retrieved from the AHID contained retrospective figures including information about policyholders' demographics and health care use over the period 2006 − 2009. During this period, the yearly average number of people ≥ 18 years in the AHID was 3,247,887.

We included all adults with at least one diagnostic code for epilepsy and who had coverage for at least one full calendar year in the same period. We then randomly selected a control group, i.e. people without a DTP for epilepsy, from the same database on an approximately 2:1 ratio, frequency matched for age, sex, and area code.

The study was approved by the Medical Ethics Committee of Leiden University Medical Center and by Achmea's Scientific and Privacy Committee.

2.2. Data collection

The database included demographics; sex, birth and death year (if applicable), duration of coverage, and health care use. This included information about visits to primary, secondary and tertiary care providers, diagnoses (as DTP codes), information on drug prescriptions (Anatomic Therapeutic Chemical (ATC) [19] codes) and the number of daily defined doses (DDD) dispensed at any one time.

2.3. Definitions

Medication use was labelled as chronic if a drug was dispensed at least twice per calendar year per individual. We removed the ATC codes for 'antiepileptics' (N03XXXX). We also removed the ATC data for Diazepam (N05BA01), for which the DDD is 10 mg, if 5 DDDs or fewer were dispensed, to avoid contamination with rescue medication for epilepsy, and for Clobazam (N05BA09) as this is also often prescribed for seizures.

2.4. Outcome measures

We analyzed the burden of chronic medication use as the percentage of people who used any non-epilepsy chronic medication (in total, split into ATC groups, and split into age groups of under and over 60 years old). We also estimated the drug burden index (DBI) for people with epilepsy and controls (in total and split into age groups of under and over 60 years old). The DBI is an index to quantify the burden of medications with anticholinergic and/or sedative effects [20]. It is calculated as the sum of the daily doses taken of the relevant medications (D) divided by the minimum recommended dose added (δ) to the daily dose (D);

$$DBI = \sum \frac{D}{D+\delta}$$

We estimated the DBI for medications in chronic use, using a previously validated list of medications and minimal doses [21]. The daily dose of a relevant medication was estimated by dividing the number of DDDs prescribed at the first dispensing by the number of days between the first and second dispensing. We analyzed the number of unique chronic medications and the number of prescriptions dispensed by the pharmacy. Lastly, we evaluated the Rx Risk comorbidity index, an index that categorizes ATC codes [22]. Most categories relate to common comorbidities, while some relate to drug indications (e.g. alcohol dependency and smoking cessation) or medication groups (e.g. antiplatelets and anticoagulants). The Rx Risk comorbidity index has been shown to be accurate and can be used in the prediction of mortality [23,24].

2.5. Statistical analysis

We present baseline demographics and chronic medication use in people with a diagnosis of epilepsy and controls using descriptive statistics. To avoid data skewing based on differences in duration of insurance coverage, we split our dataset into four groups for each of the years from 2006 to 2009. In each group only people who were insured for that full year were included. We used t-tests, Mann-Whitney U tests and Chi-square tests where appropriate. For the overall prevalence of medication use and Rx Risk scores we calculated the average percentages over the four-year period. We reported the odds ratios and confidence intervals for each of these four years. Despite the asymmetrical distribution of duration of insurance coverage and the DBI, we report means and standard deviations as the median, 25th and 75th percentile were equal, i.e. 48 months for duration of insurance coverage and 0 for the DBI.

Given the large number of people in the database, only p-values below 0.001 were considered significant.

Statistical analyses were performed with IBM SPSS Statistics for Windows, version 26.

3. Results

We included 24,185 people with epilepsy and 46,861 controls who were insured by Achmea for at least one full calendar year. Each year healthcare use, as reflected by general practitioner visits and number of DTPs, was significantly higher in people with epilepsy than controls. Cases had a longer duration of insurance coverage than the controls (46.3 versus 41.9 months; $p < 0.001$). The DBI was significantly higher for people with epilepsy than for controls in each year, showing a higher use of medications with anticholinergic or sedative effects (Table 1).

Chronic non-epilepsy medication use was more frequent among people with epilepsy than controls (66.6 % versus 59.4 %). When stratified by ATC category groups, the proportion of chronic medication users was higher among cases than controls for all groups and reached significance in every year in all but five groups. The highest significant odds ratios were found in the ATC groups blood and blood forming organs, nervous system, and systemic hormonal preparations (Table 2).

The highest odds ratios according to the Rx Risk index which were significant every year for people with epilepsy versus controls were found for alcohol dependency, psychotic illness, incontinence, liver failure, and anxiety. The most common medical conditions for both groups were hyperlipidaemia, gastrooesophageal reflux disease, use of antiplatelet drugs, and ischaemic heart disease: hypertension (Table 3).

People with epilepsy used more unique chronic medications than controls (median 2 versus 1; $p < 0.001$), and there were fewer people with epilepsy than controls who did not use other medications chronically (19.3 % versus 27.6 %) (Fig. 1). There was also a difference in the number of prescriptions for chronic medication dispensed on average per year between people with epilepsy (median 7 prescriptions per year) and controls (median 3 ($p < 0.001$)).

Compared to younger subjects (age < 60 years), the proportion of chronic medication users and the DBI was higher in older subjects (> 60 years) for both cases and controls. The finding of an increased prevalence of chronic medication use and a higher DBI among people with epilepsy remained significant when comparing cases and controls per age group (Table 4).

4. Discussion

Our data suggest that people with epilepsy are more likely to use medications chronically, use more unique medications and have more medications dispensed than the general population. The DBI, reflecting the burden of anticholinergic and sedative medications, was also higher for people with epilepsy. Medication use for psychiatric disorders, such

Table 1
Baseline characteristics.

		People with epilepsy	Controls	p-value[a]
Overall				
	N	24185	46861	
	Male (%)	12917 (53.4)	24930 (53.2)	0.60
	Mean age in years in index year[b] (± SD)	49.8 (± 18.5)	49.8 (± 18.3)	0.80
	Mean duration of insurance coverage from 2006 – 2009 in months (± SD)[c]	46.3 (± 5.0)	41.9 (± 12.0)	< 0.001
Per year				
2006	**N**	23234	39837	
	Male (%)	12419 (53.5)	21089 (52.9)	0.21
	Mean age in years in index year[b] (± SD)	50.1 (± 18.5)	50.9 (± 18.4)	< 0.001
	Median number of general practitioner consultations (IQR)	7 (11)	4 (8)	< 0.001
	Median number of DTP codes (IQR)	2 (5)	0 (2)	< 0.001
	Number of people using medications with anticholinergic and/or sedative effects (%)	5065 (21.8)	6043 (15.2)	< 0.001
	Mean DBI (± SD)[d]	0.19 (± 0.48)	0.11 (± 0.34)	< 0.001
2007	**N**	23819	39887	
	Male (%)	12721 (53.4)	21148 (53.0)	0.34
	Mean age in years in index year[b] (± SD)	50.0 (± 18.5)	50.6 (± 18.3)	< 0.001
	Median number of general practitioner consultations (IQR)	8 (13)	5 (9)	< 0.001
	Median number of DTP codes (IQR)	2 (4)	0 (2)	< 0.001
	Number of people using medications with anticholinergic and/or sedative effects (%)	5493 (23.1)	6235 (15.6)	< 0.001
	Mean DBI (± SD)[d]	0.21 (± 0.50)	0.12 (± 0.35)	< 0.001
2008	**N**	23159	39430	
	Male (%)	12339 (53.3)	20890 (53.0)	0.47
	Mean age in years in index year[b] (± SD)	49.4 (± 18.3)	50.2 (± 18.2)	< 0.001
	Median number of general practitioner consultations (IQR)	9 (13)	5 (9)	< 0.001
	Median number of DTP codes (IQR)	2 (3)	0 (2)	< 0.001
	Number of people using medications with anticholinergic and/or sedative effects (%)	5340 (23.1)	6237 (15.8)	< 0.001
	Mean DBI (± SD)[d]	0.20 (± 0.49)	0.11 (± 0.35)	< 0.001
2009	**N**	22045	42205	
	Male (%)	11739 (53.3)	22406 (53.1)	0.70
	Mean age in years in index year[b] (± SD)	48.8 (± 18.1)	49.5 (± 17.9)	< 0.001
	Mean number of general practitioner consultations (± SD)	9 (13)	5 (10)	< 0.001
	Median number of DTP codes (IQR)	2 (4)	0 (2)	< 0.001
	Number of people using medications with anticholinergic and/or sedative effects (%)[e]	3967 (18.0)	4684 (11.1)	< 0.001
	Mean DBI (± SD)[d]	0.15 (± 0.42)	0.08 (± 0.27)	< 0.001

Abbreviations: SD = standard deviation; DTP = diagnostic treatment protocol; IQR = interquartile range; DBI = drug burden index.
[a] chi-squared test p-value for difference in proportions (i.e. male and number of people using medications with anticholinergic and/or sedative effects), unpaired *t*-test p-value for difference in normally distributed means (i.e. mean age), and Mann-Whitney U *t*-test for means with a skewed distribution (i.e. duration of insurance coverage, mean number of DTP codes, mean number of general practitioner consultations, and mean DBI) [b] index year is 2006 [c] despite the fact that the distribution of the data is asymmetrical, we have chosen to report the means to quantify the effect size as the median, 25th and 75th percentile were all 48 [d] despite the fact that the distribution of the data is asymmetrical, we have chosen to report the means to quantify the effect size. This is because median, 25th and 75th percentile were all 0 [e] the drop in prevalence of anticholinergic and/or sedative medication use coincides with a policy change enforced in 2009 in which reimbursement for benzodiazepines was substantially restricted.

as alcohol dependence, anxiety, and depression, was more prevalent amongst people with epilepsy. This reflects previous studies and provides further evidence of an increased prevalence of psychiatric comorbidities in people with epilepsy [2,3,5,6].

Health insurance in the Netherlands is mandatory and healthcare is universally accessible which makes these results representative, assuming there is no bias in insurance use between people with and without epilepsy. In the Netherlands, physicians register diagnostic codes thus avoiding remote coding by dedicated coders based on discharge summaries, which may introduce inaccuracies [25–27].

Our study has limitations. Only prescribed medications are recorded, thus excluding over the counter drugs. We do not know whether there are differences in self-medicating rates between people with epilepsy and controls. The availability of over the counter drugs is, however, restricted in the Netherlands [28] so this should have minimal impact on our results. We only analyzed data on dispensed medication without substantiating adherence. This may have introduced bias but we found no evidence that adherence significantly differs between people with epilepsy and the general population. It is also possible that some of the medications identified were prescribed for epilepsy rather than for a comorbidity; this could have caused overestimation of medication use in those with epilepsy. We tried to minimize this by excluding benzodiazepines used frequently for the regular treatment of epilepsy. We excluded all prescriptions for Clobazam. The route of administration is not provided, so excluding rescue medication was difficult; we chose to exclude only low doses of Diazepam. We did not exclude Midazolam as the nasal spray was not available during our timeframe [29]. People with epilepsy had a significantly longer duration of insurance coverage than controls which suggests that they may be less likely to switch providers. Reasons for this are unclear, as health insurance is mandatory and switching providers is possible at any time. Insurers are not allowed to refuse cover based on medical history. To minimize potential bias introduced by this we therefore estimated findings per calendar year, including only individuals covered for the whole year. We assessed a large population based cohort, which carries the risk of reporting significant effects but with small effect sizes. We therefore adjusted the significance level and only considered p-values below 0.001 to be significant. Two aspects might affect the generalizability of our findings; the first is the Dutch health care setting with an uniform and mandatory insurance policy. Studies in other countries without universal health care systems may yield different results. Besides this medication consumption may differ per country. The second factor relates to the studied time period (2006 – 2009) as medication consumption and profiles may change over time. We chose to use the general population as a control group. An alternative approach could be to compare our epilepsy cohort with a cohort with another chronic disease. We did not choose to do so as comparing people with epilepsy with people with other conditions like stroke, rheumatoid arthritis or schizophrenia will likely yield contrasting results as the comorbidity profiles of these conditions differ. We therefore believe that our

Table 2
Chronic medication use (excluding antiseizure medications) per ATC group.

	Average % of people with epilepsy using these across 2006 – 2009	Average % of controls using these across 2006 – 2009	OR 2006 (95 % CI)	OR 2007 (95 % CI)	OR 2008 (95 % CI)	OR 2009 (95 % CI)
All medications, excl. antiseizure medications	66.6	59.4	1.36 (1.32 – 1.41)*	1.38 (1.33 – 1.42)*	1.35 (1.31 – 1.40)*	1.36 (1.31 – 1.40)*
Blood and blood forming organs	23.6	14.9	1.68 (1.61 – 1.75)*	1.81 (1.74 – 1.89)*	1.78 (1.71 – 1.85)*	1.79 (1.72 – 1.86)*
Nervous system, excl. antiseizure medications	25.6	16.7	1.63 (1.57 – 1.70)*	1.69 (1.63 – 1.76)*	1.69 (1.62 – 1.75)*	1.91 (1.83 – 1.99)*
Various[a]	0.3	0.2	1.23 (0.89 – 1.70)	1.57 (1.17 – 2.10)	1.66 (1.22 – 2.26)	1.53 (1.13 – 2.07)
Systemic hormonal preparations, excl. sex hormones and insulins	7.1	5.0	1.42 (1.32 – 1.52)*	1.48 (1.38 – 1.58)*	1.46 (1.36 – 1.56)*	1.46 (1.37 – 1.56)*
Anti-infectives for systemic use	9.0	6.5	1.29 (1.21 – 1.37)*	1.41 (1.32 – 1.49)*	1.46 (1.38 – 1.55)*	1.47 (1.38 – 1.56)*
Alimentary tract and metabolism	27.1	21.2	1.32 (1.27 – 1.38)*	1.39 (1.34 – 1.44)*	1.39 (1.34 – 1.44)*	1.42 (1.37 – 1.47)*
Dermatologicals	10.0	7.5	1.31 (1.24 – 1.39)*	1.34 (1.26 – 1.42)*	1.38 (1.31 – 1.46)*	1.42 (1.34 – 1.50)*
Antineoplastic and immunomodulating agents	2.1	1.6	1.27 (1.12 – 1.44)*	1.40 (1.24 – 1.57)*	1.33 (1.18 – 1.49)*	1.20 (1.07 – 1.35)
Musculo-skeletal system	13.1	10.8	1.24 (1.18 – 1.30)*	1.25 (1.19 – 1.31)*	1.26 (1.20 – 1.32)*	1.26 (1.20 – 1.33)*
Antiparasitic products, insecticides and repellents	0.4	0.3	1.22 (0.92 – 1.62)	1.12 (0.86 – 1.46)	1.23 (0.96 – 1.59)	1.34 (1.04 – 1.74)
Cardiovascular system	32.1	28.5	1.18 (1.14 – 1.23)*	1.20 (1.16 – 1.24)*	1.18 (1.14 – 1.22)*	1.19 (1.15 – 1.23)*
Sensory organs	7.6	6.6	1.12 (1.05 – 1.19)	1.15 (1.08 – 1.22)*	1.17 (1.10 – 1.25)*	1.19 (1.12 – 1.27)*
Respiratory system	13.6	12.2	1.15 (1.09 – 1.20)*	1.13 (1.08 – 1.19)*	1.14 (1.09 – 1.19)*	1.11 (1.06 – 1.17)*
Genito-urinary system and sex hormones	10.8	10.4	1.05 (0.99 – 1.11)	1.09 (1.03 – 1.15)	1.04 (0.99 – 1.09)	1.05 (1.00 – 1.10)

Abbreviations: ATC = anatomical therapeutic chemical; OR = odds ratio; CI = confidence interval; excl. = excluding.
[a]residual group, consisting of the subcategories; allergens, all other therapeutic products, diagnostic agents, general nutrients, all other non-therapeutic products, contrast media, diagnostic radiopharmaceuticals, therapeutic radiopharmaceuticals, and surgical dressings.
*p = < 0.001.

approach provides the best snapshot to quantify the medication burden in epilepsy.

Not all medications with anticholinergic and/or sedative effects are included in the DBI as the DDD has not been defined for some drug combinations. The Rx Risk index was constructed to increase understanding and description of the chronic disease burden in the population [22]. It has limitations as it cannot assess comorbidities untreated with medication. This will underestimate the prevalence of certain commonly undertreated comorbidities, particularly psychiatric ones, such as depression [30,31]. It also only takes the primary use of drugs into account, so diseases treated with off-label medication might be misclassified. Only a limited number of conditions are included in the score. A strength of the Rx Risk index, however, is that it is based on objective drug dispensing information rather than clinical coding which carries the risk of underestimation. Comorbidities are often underreported in hospital databases, especially for diagnoses for which hospitalization is not always necessary, e.g. asthma, hypertension and some psychiatric disorders [32,33]. Coding also often requires a clinic visit while some comorbidities are primarily treated outside hospitals. Another drawback of using clinical coding to assess comorbidities is that one clinic visit for multiple problems usually results in one code.

Research on medication use other than antiseizure medications in epilepsy is limited. A lower estimate of chronic medication use apart from antiseizure medications (40 %) was reported in a survey at a tertiary outpatient clinic in Poland [34]. This can be partially explained by the difference in definition of chronic medication (medication that was used on a daily or weekly basis versus medication for which at least two prescriptions were dispensed in one calendar year), and the study method (questionnaires versus insurers' dispensing information). Questionnaires are more prone to bias, whereas insurance data is complete and objective. In a Norwegian study using a similar method to ours to assess autoimmune comorbidity in epilepsy using prescription dispensing information from a large health registry database, a higher prevalence of medication for diabetes mellitus type I, hypothyroidism, myasthenia gravis, and multiple sclerosis was found [35]. We found an increased burden of non-epilepsy drugs among elderly with epilepsy. This is concordant with an American study using a pharmaceutical claims database [36]. Statins, calcium channel blockers and selective serotonin reuptake inhibitors (SSRIs) were the most commonly used concomitant medications. In a Finnish study on comorbidities in elderly people with newly diagnosed epilepsy using hospital registry data, extreme polypharmacy of more than 10 concomitant medications was reported in 27 percent of cases [37]. Hypertension, dyslipidaemia and ischaemic stroke were the most prevalent indications for non-epilepsy medication use. This is not surprising as in newly diagnosed epilepsy in elderly concomitant disease can be the cause of epilepsy [38]. Polypharmacy in epilepsy is recognised as a risk factor for poor quality of life but most studies focus only on (over)treatment with antiseizure medications [11,14,15]. Polypharmacy is a particular concern in the frail elderly in view of impaired tolerance and altered pharmacokinetics [38,39]. Cognitive side effects of antiseizure medications are important as they may be amplified by the use of other medications. We found that people with epilepsy have an increased DBI, so have an increased anticholinergic and sedative drug burden. The DBI was highest in older people with epilepsy. A higher DBI is associated with several negative outcomes, including hospitalization and physical and cognitive dysfunction [40].

Anticholinergic medications are especially associated with poor cognitive function [41]. Rational deprescribing of psychotropic agents may decrease the number of falls and improve cognition [42]. Chronic medication use may also amplify other common side effects of antiseizure medications, e.g. dizziness as a frequent side effect of antihypertensive medications. Chronic use of non-epilepsy drugs concomitantly with antiseizure medication may increase the risk of other comorbidities in epilepsy, e.g. osteoporosis due to chronic use of antidepressants or antipsychotics [43]. The framework for assessing frailty

Table 3
Assessment of comorbidities in health insurance data according to the Rx Risk index [20].

	Average % of people with epilepsy in these categories across 2006 – 2009	Average % of controls in these categories across 2006 – 2009	OR 2006 (95 % CI)	OR 2007 (95 % CI)	OR 2008 (95 % CI)	OR 2009 (95 % CI)
Alcohol dependency	0.7	0.1	4.44 (3.20 – 6.16)*	5.16 (3.70 – 7.20)*	6.27 (4.45 – 8.75)*	6.41 (4.61 – 8.91)*
Pulmonary hypertension	< 0.01	< 0.01	-[a]	3.35 (0.30 – 36.94)	5.11 (0.53 – 49.11)	7.66 (0.86 – 68.53)
Psychotic illness	4.7	1.6	2.82 (2.55 – 3.13)*	2.95 (2.67 – 3.25)*	2.88 (2.62 – 3.17)*	3.24 (2.94 – 3.58)*
Hyperkalaemia	0.1	< 0.01	2.03 (0.91 – 4.53)	3.22 (1.65 – 6.30)*	3.56 (1.74 – 7.31)*	1.92 (0.98 – 3.75)
Transplant	0.2	0.1	2.49 (1.41 – 4.40)	3.00 (1.71 – 5.26)*	2.58 (1.74 – 3.83)*	2.24 (1.52 – 3.29)*
Incontinence	1.5	0.7	2.31 (1.95 – 2.74)*	2.43 (2.06 – 2.86)*	2.24 (1.91 – 2.64)*	2.30 (1.98 – 2.69)*
Pancreatic insufficiency	0.2	0.1	2.32 (1.49 – 3.62)*	2.52 (1.63 – 3.88)*	1.97 (1.28 – 3.02)	2.48 (1.65 – 3.73)*
Hepatitis B	< 0.01	< 0.01	3.43 (0.63 – 18.73)	2.01 (0.61 – 6.59)	1.70 (0.50 – 5.88)	1.915 (0.55 – 6.61)
Liver failure	1.9	0.9	1.97 (1.71 – 2.28)*	2.10 (1.83 – 2.41)*	2.32 (2.01 – 2.67)*	2.51 (2.17 – 2.90)*
Anxiety	8.6	4.7	1.77 (1.67 – 1.89)*	1.81 (1.70 – 1.92)*	1.80 (1.70 – 1.91)*	3.49 (3.14 – 3.87)*
Malignancies	0.5	0.2	1.68 (1.23 – 2.28)	2.39 (1.82 – 3.14)*	2.73 (2.08 – 3.59)*	2.08 (1.62 – 2.67)*
Parkinson's disease	1.2	0.6	1.77 (1.46 – 2.14)*	1.80 (1.50 – 2.14)*	2.13 (1.79 – 2.52)*	2.23 (1.89 – 2.63)*
Renal disease	1.0	0.6	1.74 (1.42 – 2.13)*	1.80 (1.49 – 2.16)*	1.84 (1.54 – 2.21)*	2.04 (1.70 – 2.45)*
HIV	0.3	0.1	1.68 (1.13 – 2.50)	1.61 (1.10 – 2.37)	1.82 (1.27 – 2.62)	1.83 (1.30 – 2.59)
Hepatitis C	< 0.01	< 0.01	0.74 (0.19 – 2.84)	1.68 (0.49 – 5.79)	2.73 (0.89 – 8.33)	1.60 (0.49 – 5.23)
Anticoagulants	5.4	3.3	1.57 (1.45 – 1.71)*	1.66 (1.53 – 1.79)*	1.68 (1.56 – 1.82)*	1.76 (1.63 – 1.90)*
Antiplatelets	15.9	10.3	1.59 (1.52 – 1.67)*	1.69 (1.61 – 1.78)*	1.66 (1.59 – 1.75)*	1.68 (1.60 – 1.76)*
Steroid responsive disease	3.5	2.2	1.55 (1.40 – 1.72)*	1.67 (1.52 – 1.85)*	1.62 (1.47 – 1.78)*	1.59 (1.44 – 1.75)*
Depression	9.6	6.3	1.50 (1.41 – 1.59)*	1.59 (1.49 – 1.68)*	1.60 (1.51 – 1.70)*	1.65 (1.55 – 1.75)*
Dementia	0.2	0.2	1.51 (0.93 – 2.47)	1.71 (1.13 – 2.60)	1.65 (1.18 – 2.32)	1.45 (1.06 – 2.00)
Pain	6.0	4.1	1.52 (1.40 – 1.64)*	1.52 (1.41 – 1.63)*	1.44 (1.34 – 1.55)*	1.54 (1.43 – 1.65)*
Osteoporosis/Paget's	3.1	2.1	1.38 (1.24 – 1.54)*	1.47 (1.33 – 1.63)*	1.48 (1.34 – 1.63)*	1.56 (1.42 – 1.72)*
Gastrooesophageal reflux disease	16.3	12.3	1.33 (1.27 – 1.40)*	1.40 (1.34 – 1.47)*	1.41 (1.35 – 1.47)*	1.41 (1.35 – 1.47)*
Hypothyroidism	3.6	2.7	1.30 (1.18 – 1.44)*	1.31 (1.20 – 1.44)*	1.32 (1.20 – 1.44)*	1.35 (1.23 – 1.47)*
Arrhythmia	3.0	2.4	1.23 (1.12 – 1.37)*	1.31 (1.18 – 1.44)*	1.29 (1.17 – 1.43)*	1.38 (1.25 – 1.53)*
Tuberculosis	< 0.01	< 0.01	1.72 (0.55 – 5.32)	1.68 (0.67 – 4.22)	1.32 (0.49 – 3.56)	0.44 (0.13 – 1.55)
Hyperlipidaemia	16.5	13.7	1.23 (1.17 – 1.28)*	1.26 (1.20 – 1.32)*	1.25 (1.20 – 1.31)*	1.26 (1.21 – 1.32)*
Psoriasis	0.4	0.3	1.17 (0.86 – 1.57)	1.37 (1.03 – 1.83)	1.19 (0.90 – 1.58)	1.17 (0.88 – 1.56)
Benign prostatic hyperplasia	2.6	2.2	1.19 (1.06 – 1.33)	1.23 (1.11 – 1.37)*	1.16 (1.04 – 1.28)	1.12 (1.02 – 1.24)
Glaucoma	1.9	1.6	1.19 (1.05 – 1.35)	1.14 (1.00 – 1.29)	1.12 (0.99 – 1.27)	1.23 (1.09 – 1.39)
Malnutrition	< 0.01	< 0.01	0.86 (0.08 – 9.46)	-[a]	1.70 (0.24 – 12.09)	0.96 (0.18 – 5.23)
Ischaemic heart disease: hypertension[b]	15.3	13.6	1.15 (1.10 – 1.20)*	1.15 (1.10 – 1.21)*	1.14 (1.09 – 1.19)*	1.15 (1.10 – 1.20)*
Migraine	1.1	0.9	1.21 (1.02 – 1.43)	1.21 (1.03 – 1.43)	1.13 (0.97 – 1.33)	1.04 (0.89 – 1.23)
Congestive heart failure	6.2	5.4	1.09 (1.01 – 1.17)*	1.14 (1.06 – 1.22)*	1.16 (1.08 – 1.24)*	1.20 (1.12 – 1.28)*
Inflammation/pain	9.4	8.3	1.17 (1.10 – 1.23)*	1.13 (1.07 – 1.20)*	1.16 (1.10 – 1.23)*	1.10 (1.04 – 1.17)
Chronic airways disease	7.8	6.9	1.14 (1.07 – 1.22)*	1.13 (1.06 – 1.20)*	1.15 (1.09 – 1.23)*	1.11 (1.04 – 1.18)
Allergies	5.9	5.4	1.12 (1.04 – 1.20)	1.10 (1.03 – 1.18)	1.13 (1.05 – 1.21)	1.09 (1.02 – 1.17)
Irritable bowel syndrome	0.5	0.5	1.23 (0.97 – 1.55)	1.15 (0.92 – 1.44)	1.07 (0.84 – 1.36)	0.97 (0.77 – 1.23)
Smoking cessation	< 0.01	< 0.01	-[a]	0.56 (0.06 – 5.37)	1.46 (0.49 – 4.34)	1.23 (0.53 – 2.84)
Ischaemic heart disease: angina	2.2	2.1	0.98 (0.88 – 1.10)	1.11 (1.00 – 1.24)	1.07 (0.96 – 1.20)	1.07 (0.96 – 1.20)
Gout	1.0	0.9	1.09 (0.92 – 1.30)	1.08 (0.92 – 1.27)	1.02 (0.87 – 1.20)	1.00 (0.85 – 1.17)
Hypertension[b]	8.4	8.4	1.05 (1.00 – 1.12)	1.03 (0.97 – 1.09)	0.99 (0.93 – 1.04)	0.97 (0.92 – 1.03)
Bipolar disorder	0.3	0.3	0.83 (0.60 – 1.16)	1.01 (0.74 – 1.38)	0.95 (0.70 – 1.29)	1.09 (0.80 – 1.47)
Diabetes	6.9	7.1	0.96 (0.90 – 1.03)	0.97 (0.91 – 1.04)	0.95 (0.89 – 1.01)	0.96 (0.90 – 1.02)
Hyperthyroidism	0.1	0.1	0.66 (0.35 – 1.24)	0.76 (0.41 – 1.40)	0.82 (0.42 – 1.59)	1.08 (0.55 – 2.14)

Abbreviations: OR = odds ratio; CI = confidence interval.
[a]OR could not be calculated as the cases or the controls or both did not use any medications within this group in the given year [b] the difference between the categories of hypertension and ischaemic heart disease: hypertension is the severity of disease estimated by the medications used; the hypertension group is based on diuretic use and the ischaemic heart disease: hypertension group is based on calcium channel blocker and beta blocker use.
*p = < 0.001.

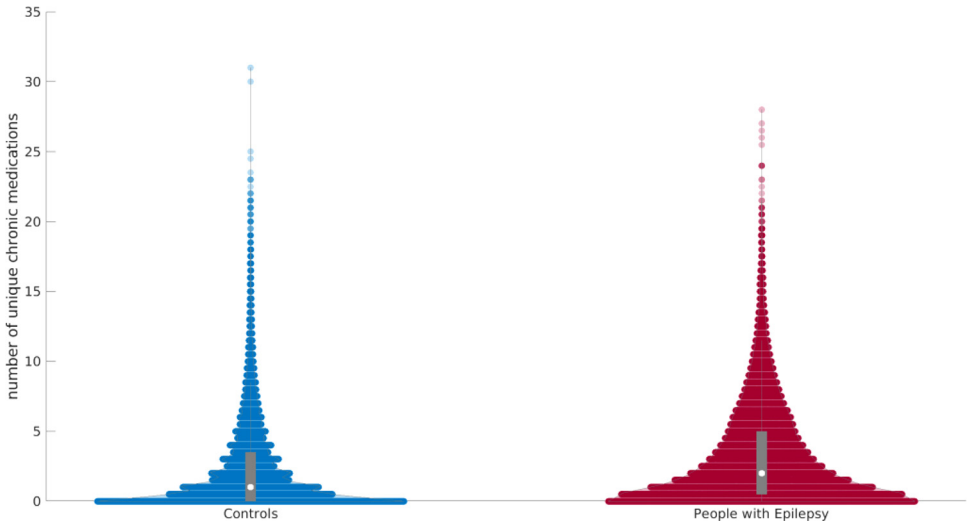

Fig. 1. Overall number of unique chronic medications (excluding antiseizure medications).

Table 4
Chronic medication use (excluding antiseizure medications) and mean DBI per age group.

		Chronic medication use			Mean DBI		
		Cases (%)	Controls (%)	p-value	Cases (SD)	Controls (SD)	p-value
2006	< **60 y.o.**	8561 (54.5)	11937 (45.5)	< 0.001	0.18 (0.49)	0.08 (0.32)	< 0.001
	> **60 y.o.**	6419 (85.3)	10805 (79.4)	< 0.001	0.22 (0.46)	0.16 (0.39)	< 0.001
2007	< **60 y.o.**	9165 (56.8)	12589 (47.5)	< 0.001	0.19 (0.51)	0.09 (0.32)	< 0.001
	> **60 y.o.**	6645 (86.6)	10919 (81.4)	< 0.001	0.23 (0.47)	0.17 (0.39)	< 0.001
2008	< **60 y.o.**	9473 (59.2)	13384 (50.5)	< 0.001	0.19 (0.49)	0.09 (0.32)	< 0.001
	> **60 y.o.**	6231 (86.9)	10622 (82.1)	< 0.001	0.24 (0.48)	0.17 (0.40)	< 0.001
2009	< **60 y.o.**	9218 (59.4)	14724 (50.6)	< 0.001	0.15 (0.44)	0.07 (0.26)	< 0.001
	> **60 y.o.**	5657 (86.5)	10798 (82.4)	< 0.001	0.15 (0.37)	0.09 (0.28)	< 0.001

Abbreviations: DBI = drug burden index; % = percentage of cases or controls; SD = standard deviation; y.o. = years old.

in epilepsy is, however, underdeveloped and there is a paucity of validated strategies for deprescribing non-epilepsy drugs in people with epilepsy. Further work is required to explore how chronic medication use may impact quality of life and the risk of comorbidities. An improved understanding of the mechanisms underlying frailty in epilepsy is a critical next step to developing deprescribing strategies.

Declaration of Competing Interest

JWB and JvdP report no conflict of interest. JWS reports consultancy and lecturing fees from Eisai, UCB and Zogenix, and research support from UCB and GW Pharma, outside this work. RDT reports consultancy and lecturing fees from Theravance Biopharma, Medtronic, UCB and Novartis and research support from Medtronic.

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