Associations between antiepileptic use and hypogammaglobulinaemia: Findings from a population-based case-control study using data linkage.

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Abstract

Background and objectives

Increased mortality in epilepsy due to infections (other than pneumonia) has been demonstrated. Small case series of people on antiepileptic drugs (AEDs) have described hypogammaglobulinaemia, which may predispose to infections. It is unclear whether hypogammaglobulinaemia is more frequent in people on AEDs, what AEDs it is associated with, or what clinical impact it has. In this population-based study, we aimed to determine whether AEDs were associated with hypogammaglobulinaemia, which AEDs were associated, and whether the associations may be causal.

Methods

We conducted an unmatched case-control study using data linkage of routinely-collected biochemistry, prescribing, and morbidity datasets in North-East Scotland from 2009-2021. Cases were participants with immunoglobulin levels less than the reference range. Controls were those with normal/high immunoglobulin levels. Logistic regression was used to investigate associations between AED exposure and any hypogammaglobulinaemia, adjusting for age, sex and comorbidity. We also analysed low IgA, IgM and IgG separately. We analysed 'any AED' exposure and common individual drugs separately. Cumulative exposure data were used to determine whether an exposure-response relationship was present.

Results

18,666 cases and 127,157 controls were identified. Use of any AED was associated with increased risk of hypogammaglobulinaemia (adjusted odds ratio [aOR] 1.20 [95% CI 1.15-1.25]). Phenytoin use was strongly associated with low IgA (aOR 5.90 [95% CI 3.04, 10.43]). Carbamazepine and

lamotrigine were also associated with low IgA. Apart from topiramate, which was associated with a non-significant decrease in odds of hypogammaglobulinaemia, there was a consistent increase in odds of hypogammaglobulinaemia across most AEDs studied. Panhypogammaglobulinaemia was associated with any AED use, carbamazepine, lamotrigine, gabapentin and multiple AED use. There was evidence of an exposure-response relationship between any AED use and any hypogammaglobulinaemia, low IgA and low IgG. Carbamazepine and probably lamotrigine also had an exposure-response relationship with any hypogammaglobulinaemia.

Discussion

AEDs may increase hypogammaglobulinaemia risk. Specific classes of immunoglobulins are differentially affected, and the exposure-response analysis suggests this may be causal. Further work should investigate the clinical impact of these findings. Clinicians should check immunoglobulin levels if unusual or recurrent infections occur in patients treated with AEDs.

Introduction

Approximately 50 million people worldwide have epilepsy, which is associated with a higher risk of mortality than in people without epilepsy.[1] Previous authors have classified cause of death in epilepsy into those related to epilepsy (e.g. causes of epilepsy such as tumours and consequences of seizures such as aspiration pneumonia) and those not related to epilepsy.[2] However, some causes of death not conventionally thought to be epilepsy-related are increased, including infections other than pneumonia, and we do not have a good understanding about why this is.[1]

We previously treated a patient with longstanding epilepsy on carbamazepine who developed hypogammaglobulinaemia (HGG) and progressive multifocal leukoencephalopathy (PML) without known immunosuppression. After discontinuation of carbamazepine, hypogammaglobulinaemia and the PML resolved. We therefore considered whether there is an increased risk of HGG in people with antiepileptic drugs (AEDs) that may explain some of the increased infection mortality risk in epilepsy, which could potentially be preventable.

Previous case reports have associated AEDs, namely carbamazepine,[3–13] phenytoin,[14–23] lamotrigine[24,25] and levetiracetam,[24,26] with transient HGG. Although these case reports and small studies suggest AEDs are associated with HGG, there are no population-based studies that have investigated this and we are therefore unaware of the frequency of HGG in people taking AEDs, or whether this association is causal.[5–8,27]

We therefore aimed to determine the association between AEDs and HGG, whether associations are specific to individual immunoglobulins, and whether an exposure-response relationship exists.

Materials and methods

Data source

Data for this study were obtained from data linkage of three routinely-collected healthcare datasets in NHS Grampian, which provides health care for a population of 586,000 in North-East Scotland, UK. These datasets were (i) the NHS Grampian laboratories dataset, containing all laboratory testing from primary care and hospitals in the area; (ii) Prescribing Information System (PIS), containing all primary care prescriptions in the area; and (iii) the Scottish Morbidity Record (SMR) 01, containing co-morbidity data derived from hospital discharge coding. The merged dataset included all people with immunoglobulins tested in Grampian from 01/01/2009 to 30/04/2021, with data on their immunoglobulin values, AED prescriptions, and co-morbidities. Linkage was performed in the Grampian Data Safe Haven (DaSH) platform. Data were linked using unique patient identification numbers and pseudonymised.

Standard protocol approvals, registrations, and patient consents

There was no direct participant recruitment for this study and ethical approval was obtained from the North Node Privacy Advisory Committee.[28]

Study design

A retrospective unmatched case-control study was performed. For the primary analysis, cases were defined as those with low levels of any one of IgA, IgG, or IgM and controls as those with normal/high levels of all these immunoglobulins between 2009 and April 2021. Low immunoglobulins were defined as any measurement below the respective reference range. We also performed secondary analyses, where cases and controls were defined by type of immunoglobulin separately (low IgA versus normal IgA, low IgG versus normal IgG, and low IgM versus normal IgM). Where there were multiple measurements of immunoglobulins in individuals, cases were defined as

those with any low immunoglobulin measurement. We used SMR 01 comorbidity data to exclude individuals with known causes of HGG (diagnosis of a primary immunodeficiency disorder, haematological malignancy, or treated with chemotherapy [ICD-10 codes: D80-D89, C81-C96, Z51.1, Z51.2, Z54.2]) from all analyses to reduce confounding.

Classification and definition of AED exposure

For most of the analyses, AED exposure was considered a binary variable: no AED exposure prior to the index immunoglobulin measurement versus AED exposure prior to immunoglobulin measurement. Where individuals had multiple immunoglobulin test dates, either the first test that was normal/high was used for controls and the test with the lowest result was used for cases. The drugs studied and British National Formulary (BNF) codes are listed in the Supplementary Material Table S1. Exposure groups included: (i) treatment with any AED; (ii) treatment with specific AEDs – a) carbamazepine, b) phenytoin, c) sodium valproate, d) lamotrigine, e) levetiracetam, f) gabapentin, g) pregabalin, h) topiramate, i) other AEDs; (iii) treatment with multiple AEDs; and (iv) no AED use prior to immunoglobulin measurement.

In the exposure-response analysis, for each subject with any AED prescription, the duration of treatment from the first available prescription date in the PIS to the index immunoglobulin measurement date was calculated. Cumulative treatment duration was categorised as no exposure, <1 year, 1-<2, 2-<4, 4-6, >6+ years.

Covariates

Age, sex, and Charlson Comorbidity Index (CCI, derived from SMR 01 data) were included in statistical modelling as potential confounders. AED choice varies by sex and age,[29] and limited data suggest immunoglobulin levels in men and women may be differentially affected by AED exposure.[24] Higher comorbidity status is associated with both prescriptions for AEDs and rates of HGG.[30,31] We

were unable to adjust for other potential confounders (e.g. we lacked systematic data about the presence of a diagnosis of epilepsy, because the comorbidity data available were only from inpatient diagnoses).

Statistical analysis

Descriptive statistics were used to summarise the cases and controls. The following analyses were undertaken:

1. Associations between use of AEDs and any HGG

In this primary analysis, logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) for the associations between exposure to any, multiple and specific AEDs and any HGG (any low immunoglobulin result), with adjustment for age, sex and CCI.

2. Associations between use of AEDs and specific HGG

The above analysis was repeated, but associations between AED use and (i) low specific immunoglobulins (IgA, IgG and IgM) and (ii) panhypogammaglobulinaemia (PanHGG), defined as IgA, IgG and IgM levels all less than the normal range were investigated.

3. Exposure-response relationship between AEDs and HGG

To determine if an exposure-response relationship exists, ORs and 95% CI were calculated for the AED exposure durations listed above compared with the reference category of no exposure. Cases and controls were limited to those with PIS data from 2013 onwards to ensure AED exposure time was accurate because PIS data from before 2013 was incomplete and thus absence of a previous prescription before this time may not reliably indicate the start of AED use. We firstly investigated the exposure-response relationship in an exposure group including any AED shown to be associated with HGG in the primary analysis (for any and specific low immunoglobulin subclasses). Given sample size constraints, we secondly examined the exposure-response relationship between only two specific agents (carbamazepine and lamotrigine) and any HGG. These agents had adequate

sample sizes, were associated with each immunoglobulin subtype, and had been identified in previous reports of AED-induced HGG.[3–13,24,25] Forest plots were used to visually examine for trend.

4. Sensitivity analysis

Two sensitivity analysis were undertaken where low immunoglobulin status was redefined as less than the median in those with immunoglobulins below the normal range, where immunoglobulin subclasses were analysed separately. All analyses were adjusted for age, sex and CCI.

All data cleaning and statistical analyses were undertaken using RStudio v1.4.1106[32] except that the forest plots were made using GraphPad Prism v9.1.22.[33] Results were held to be significant at the $p<0.05$ level. Cell values of less than 5 were denoted as '<5' to ensure compliance with the *Study Statistical Disclosure Control Guidance.*[34] Post-hoc power calculation showed that the primary analyses were over-powered (100% power for identifying a odds ratio of 1.3 assuming $\alpha=0.05$) but power for individual associations between AEDs and low immunoglobulin subclasses was lower and varied widely between different associations studied.

Data availability

Investigators may request access to the pseudonymised datasets used in this study from the Grampian Data Safe Haven (DaSH), with access to be granted within the secure safe haven environment. Prior to data access, proposals will require permission from the relevant approval providers (e.g., NHS Grampian Caldicott, NHS Grampian Research Development and Ethics). Data agreements may also be required. Access to these datasets must be within five years of the initial study completion and there may be costs associated with the hosting of the data.

Results

Descriptive statistics: Cases and controls

154,286 participants were initially identified who had immunoglobulins tested and 8,463 participants (5.5%) were excluded based on SMR 01 data ICD-10 codes for identifiable causes of HGG. Of 145,823 without identifiable causes of HGG, there were 18,666 (13%) HGG cases (any low immunoglobulin measurement) and 127,157 controls (87%). Characteristics of cases and controls are listed in Table 1. The median (IQR) age at the time of immunoglobulin testing was 65 (45-77) years in cases and 48 (31-65) in controls. Approximately 40% of participants were male in each case group, with the exception of the IgM group where males constituted 55% of cases. Cases with low IgG and IgM were older, on average, than controls (median age 67 vs 59 and 69 vs 58), although median age of IgA cases was much lower than in controls (19 vs 51). Nearly 70% of controls had a CCI of zero, compared to 50% of cases. The cases group had a higher burden of comorbidities, with 23% having a CCI of greater than two compared to 11% in the control group.

15.1% (22,072) of participants were prescribed AEDs during the exposure period. The proportion of HGG cases prescribed any AED was higher than the proportion of controls prescribed any AED in the IgG and IgM subgroups, although not in the IgA subgroup. The most commonly prescribed AED was gabapentin (54.0% of participants with at least one AED prescription), and 29.8% of the participants exposed to AEDs used multiple agents. Average length of AED exposure was longer among cases than controls.

1. Associations between use of AEDs and any HGG

Use of AEDs was associated with an increased risk of any HGG (adjusted odds ratio [aOR] 1.20 [95%CI 1.15, 1.25], p<0.001) (Table 2). All individual AEDs were significantly associated with increased risk of any HGG, with the exception of topiramate which had a non-significant reduction in

risk of HGG (aOR 0.84, 95%CI 0.69, 1.01, p=0.06). Results from this primary analysis are depicted in Table 2. Removal of topiramate from the 'any AED' category did not make a substantial difference to the association with any HGG: aOR (95%CI) 1.21 (1.16, 1.26). Relative risk was calculated and found to be very similar to the unadjusted ORs.

2. Associations between use of AEDs and specific HGG/panHGG

Results from analyses of associations between AEDs and specific HGG are shown in Table 3. Carbamazepine, phenytoin, lamotrigine and 'other AEDs' were significantly associated with low IgA. Phenytoin use was strongly associated with low IgA (aOR 5.90 [95% CI 3.04, 10.43]). All AEDs were significantly associated with low IgG and IgM to varying degrees (Table 3), with the exception of phenytoin, levetiracetam, topiramate and 'other AEDs', although phenytoin, levetiracetam and 'other AEDs' had similar aORs to the other significantly-associated AEDs and lack of power due to small number in these analyses may explain why these drugs were not significantly associated. Any AED, carbamazepine, lamotrigine, gabapentin and multiple AED use were all significantly associated with panhypogammaglobulinaemia.

3. Exposure-response relationship between AEDs and specific HGG

Results of the exposure-response analysis are shown in Figure 1. There was evidence of a trend of increased odds of any HGG with increasing duration of AED exposure (excluding topiramate). While confidence intervals overlapped, the confidence interval for the <1 year duration period did not overlap the aOR estimate for the 4-6 year or >6 years exposure groups. As exposure time on any AED (except topiramate) increased, the odds of HGG generally increased for IgA, IgG and IgM, with a clearer trend present with IgA and IgG that with IgM. For IgA, the confidence interval of the <1 year exposure group did not overlap with aOR estimate of 2-4 years, 4-6 years, and >6 years exposure groups. Similarly for IgG, the confidence interval of the <1 year exposure group did not overlap with the aOR estimate for the 4-6 year and >6 year exposure groups. For both IgA and IgG the confidence

intervals for the <1 year exposure group and the >6 years exposure group did not overlap. For IgM there was little increase in OR after 2 years' exposure. Thus, there is good evidence for a dose-response relationship low IgA and low IgG, but not for IgM. We lacked sufficient numbers to investigate dose-response relationships for individual drugs except carbamazepine and lamotrigine. While numbers in individual groups were small, there was a clear trend of increased risk of any HGG with increasing duration of CBZ and a possible trend with increasing duration of exposure to lamotrigine.

4. Sensitivity analyses

The sensitivity analyses results are shown in Tables 4 and 5. The redefinition of cases to those with very low immunoglobulin levels reduced number of cases and hence power. There was consistency between these analyses and the main analysis of individual immunoglobulin types in that the ORs were generally above 1 for associations, with the exception of topiramate.

Discussion

Main Findings

In this large populated-based case-control study, exposure to most AEDs was associated with increased risk of any HGG, independent of age, sex, and comorbidity. Phenytoin had a strong association with low IgA with nearly six-fold increased odds, which was a much stronger association than any other identified in this study. Carbamazepine and lamotrigine were the only other individual drugs with a clear association with low IgA. Differences between AEDs were less clear for low IgM and low IgG, with exception of topiramate which was associated with a non-significant reduced risk of each type of HGG. Any AED use, carbamazepine, lamotrigine, gabapentin and multiple AED use were associated with PanHGG. Our data also demonstrated an exposure-response relationship may exist for some of the commonly-used AEDs, which provides some evidence that this association may be causal.

Comparison with previous studies

To our knowledge, this is the first population-based study of hypogammaglobulinaemia in people taking AEDs. Several small studies have previously investigated immunoglobulins in people taking specific anticonvulsants. Callenbach and colleagues studied 127 consecutive children with epilepsy and found that carbamazepine significantly decreased IgA, IgG and IgM levels, after 9-18 months of treatment.[35] Svalheim and colleagues studied 211 patients with epilepsy on AEDs and 80 controls aged 18-45 years and found carbamazepine was associated with low IgG only, lamotrigine was associated with low IgA, IgG and IgM, and no significant association existed between levetiracetam and low immunoglobulins after six months of treatment.[24] Ashrafi and colleagues studied 33 patients with epilepsy before and six months after carbamazepine initiation found 24.2% had a significant reduction in IgA levels.[36] Gilhus and colleagues investigated 49 phenytoin-treated patients with epilepsy and 19 untreated controls and about 5% of phenytoin-treated patients developed IgA

deficiency.[37] A further 15% had sub-normal IgA levels. El-Shimi and colleagues found that IgA and IgM were lower than in 50 children with epilepsy treated with carbamazepine than in 15 controls.[38] In one longitudinal study of 19 patients with epilepsy, zonisamide was unlikely to affect immunoglobulin levels, but this study had low power.[39] Other drugs have had little previous research into their effects on immunoglobulins. Oxcarbazepine has been reported to induce low immunoglobulins in a case report.[40]

Only one study has previously reported an exposure-response relationship between AED exposure and HGG. El-Shimi and colleagues found that IgG levels (but not IgA or IgM levels) were lower in children treated for longer with carbamazepine but this analysis was hindered by a low sample size (only 50 children).[38]

Although the mechanisms by which AEDs cause HGG are unclear, low immunoglobulin subclass concentrations in children treated with carbamazepine or sodium valproate has been attributed to the effect of AEDs on B cell maturation or regulatory T lymphocytes, which directly affect immunoglobulin isotype production.[35,41] Dosch et al. observed that AEDs impacting immunoglobulin concentrations block sodium channels, therefore it may be possible that this mode of action causes the observed side effect.[14] However, topiramate also blocks sodium channels[42] and was found to be the only AED not associated with an increased risk of HGG in our study and, conversely, we found some AEDs which do not act on sodium channels (e.g. gabapentin and pregabalin) were associated with HGG. AEDs have also been postulated to trigger an underlying common variable immunodeficiency (CVID), which may have appeared at some stage in life regardless of AED exposure.[24] However this theory is not a plausible frequent mechanism of HGG: case reports suggest HGG is transient and immunoglobulins normalise following AED cessation,[3,5,6,14,17,18] whereas CVID is a genetic, non-reversible condition, and is much rarer than the observed frequency of HGG in AED-users.[43]

Strengths

This study has several strengths. We used a large population-based dataset, at low risk of selection bias, covering all immunoglobulin results from a population of over 580,000, with no age restriction. Access to comprehensive prescribing data covering approximately 10 years allowed us to investigate exposure to all common AEDs.[44] We also excluded participants with specific co-morbidities associated with HGG using ICD-10 codes, to reduce confounding. Additionally, we analysed different levels of HGG, both any low measure and a measurement lower than the median of low Ig measurements. Furthermore, we had comprehensive population-wide assessment of AED use. In the UK, AEDs can only be obtained with a medical prescription and all community prescriptions are included in the PIS database. Lastly, our analyses were adjusted for potential confounders.

Limitations

Inevitably, this study also has several limitations. First, many people on AEDs will not have their immunoglobulins routinely checked so we are likely to have underestimated the true incidence of HGG. However, this is unlikely to bias the associations we examined as this will be similar across all exposure groups. Second, we will not have excluded all participants with co-morbidities which cause HGG. SMR01 is derived from hospital discharge coding, so individuals who were not admitted to hospital with these conditions between 2009 and 2021 would not have been excluded. Potential residual confounding may also exist as CCI only measures specific comorbidities. We were unable to adjust for other conditions may impact on HGG risk – such as protein-losing enteropathies or nephrotic syndrome.[45] Third, there were limitations relating to incomplete prescribing data. The earlier years of the PIS database were incomplete so AED start dates before 2012 were unreliable, which limited the sample size for analysis of the exposure-response relationship. PIS does not include hospital prescriptions of AEDs, but these will usually be short-term so we will have captured most long-term AED use. Our data were based on medications being dispensed and we lacked

measures of patient concordance. Fourth, although this was a population-based study with a large sample size, numbers in analyses of some specific AEDs, particularly when stratifying the dataset into IgA, IgG and IgM and exposure durations led to small sample sizes. Fifth, we investigated multiple comparisons which increases risk of chance findings. We did not adjust for multiple comparisons because many of the associations we examined were not independent of each other (e.g. analysis of any HGG and specific HGGs were not independent and multiple AEDs may she common mechanisms for HGG). However, we have seen consistency between analysis with similar results for many AEDs and the exposure-response analysis gives evidence that these findings are not just due to chance. We also did not have data available on IgG subclasses. Lastly, we have calculated odds ratios rather than relative risks, so the measures of association may be biased slightly away from unity.

Association or Causation?

While we can prove that AEDs cause hypogammaglobulinaemia there are several strands to suggest that these associations may be causal. The exposure-response relationship suggests that there may be a duration effect or a cumulative dose effect and provides evidence for causation. There have also been case reports[5,6,26,46] reporting reversibility of HGG with discontinuation of particular drugs, again providing evidence for causality.

Clinical relevance

Many people with low immunoglobulins do not develop frequent or unusual infections,[47] so many with HGG associated with AEDs may not have a serious clinical consequences. However, it is likely that some of those with AED-associated HGG will go on to develop significant infections as a result. This may be of particular importance for certain patient groups, such as those who already have immune deficiencies or who are on immunosuppressant drugs, or those with progressive neurological disease who are more vulnerable to infection. Further work to investigate the clinical

impact is urgently needed. In the meantime, evaluation of immunoglobulin levels should be considered in individuals taking AEDs who suffer from recurrent or unusual infections. If HGG is identified in this context, switching to an alternative AEDs could be considered. It may be that topiramate should be the preferred AED in this context, but this requires more research.

Further research

Although our findings demonstrate an association between AED exposure and risk of HGG, more studies are required to understand the underlying mechanisms whereby AEDs influence immunoglobulin production. Our data showed reduction of risk of HGG in people on topiramate with borderline statistical significance (p=0.06) so another study is needed to confirm this. Our data on the exposure-response relationship in specific AEDs was limited by small numbers so replication in a larger population or with longer duration is needed. To determine the clinical impact of our findings, it is important to investigate whether AED use is associated with higher risk of infection using prospective analysis, and how frequently AED-induced HGG leads to serious infections. If AED-associated HGG is associated with an increased risk of infection, research will also be needed to evaluate mitigation or management strategies.

Conclusion

In conclusion, our study shows that AEDs are associated with increased risk of HGG, with all drugs except topiramate associated with HGG. Specific classes of immunoglobulins appear to be differentially affected, with IgA deficiency in particular associated with phenytoin use. Our data suggest an exposure-response relationship so the associations may be causal. Further research is urgently needed to establish the clinical impact of these findings. In the meantime, we recommend that immunoglobulins should be checked in patients on AEDs with unusual or recurrent infections.

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Table 1: Characteristics of cases and controls.

Variable		**All participants *N* (%)**		**IgA *N* (%)**		**IgG *N* (%)**		**IgM *N* (%)**		**PanHGG *N* (%)**		**Excluded participants[a]**
		Cases Low Ig	**Controls** Normal Ig	**Cases** Low IgA	**Controls** Normal IgA	**Cases** Low IgG	**Controls** Normal IgG	**Cases** Low IgM	**Controls** Normal IgM	**Cases** Low IgM	**Controls** Normal IgM	
Number of participants		18666	127157	4617	140994	3982	88360	12882	79232	391	145432	8463
Age (years) at date of Ig test: median (IQR)		65 (45, 77)	48 (31, 65)	19 (4, 57)	51 (32, 67)	67 (50, 77)	59 (43, 72)	69 (57, 79)	58 (41, 71)	59 (5, 75)	50 (31, 67)	63 (49, 73)
Male sex		9374 (50.2)	50493 (39.7)	1957 (42.4)	57827 (41.0)	1611 (40.5)	39200 (44.4)	7098 (55.1)	33619 (42.4)	210 (53.7)	85888 (59.1)	4015 (41.4)
Charlson Comorbidity Index: median (IQR)		0 (0, 2)	0 (0, 1)	0 (0, 0)	0 (0, 1)	1 (0, 3)	0 (0, 2)	1 (0, 3)	0 (0, 2)	0 (0, 2)	0 (0, 1)	3 (2, 5)
Immunoglobulin measure (g/L): median (IQR)[b]				0.57 (0.33, 0.70)	2.40 (1.78, 3.20)	5.30 (4.60, 5.70)	10.40 (8.86, 12.30)	0.39 (0.31, 0.45)	1.04 (0.77, 1.44)			
Exposure to antiepileptic medication	None	15103 (80.9)	108648 (85.4)	4115 (89.1)	119455 (84.7)	3037 (76.3)	72082 (81.6)	10178 (79.0)	64749 (81.7)	313 (80.1)	123438 (84.9)	7296 (64.6)
	Any	3563 (19.1)	18509 (14.6)	502 (10.9)	21539 (15.3)	945 (23.7)	16278 (18.4)	2704 (21.0)	14483 (18.3)	78 (19.9)	21994 (15.1)	3990 (35.4)
	Carbamazepine	388 (2.1)	1782 (1.4)	70 (1.5)	2094 (1.5)	111 (2.8)	1569 (1.8)	284 (2.2)	1389 (1.8)	11 (2.8)	2159 (1.5)	632 (7.5)
	Phenytoin	36 (0.2)	106 (0.1)	12 (0.3)	130 (<0.1)	10 (0.3)	120 (0.1)	25 (0.2)	105 (0.1)	<5 (<1.0)	140 (0.1)	237 (2.8)
	Sodium valproate	187 (1.0)	962 (0.8)	31 (0.7)	1116 (0.8)	54 (1.4)	781 (0.9)	131 (1.1)	702 (0.9)	<5 (<1.0)	1145 (0.8)	739 (8.7)
	Lamotrigine	202 (1.1)	974 (0.8)	53 (1.1)	1122 (0.8)	54 (1.4)	792 (0.9)	138 (1.1)	705 (0.9)	8 (2.0)	1168 (0.8)	710 (8.4)
	Levetiracetam	83 (0.4)	350 (0.3)	14 (0.3)	418 (0.3)	26 (0.7)	336 (0.4)	61 (0.5)	300 (0.4)	<5 (<1.0)	430 (0.3)	558 (6.6)
	Gabapentin	1940 (10.4)	9980 (7.8)	239 (5.2)	11661 (8.3)	557 (14.0)	9095 (10.3)	1474 (11.4)	8156 (10.3)	49 (12.5)	11871 (8.2)	1148 (13.6)
	Pregabalin	1801 (9.6)	9173 (7.2)	238 (5.2)	10726 (7.6)	493 (12.4)	8221 (9.3)	1364 (10.6)	7337 (9.3)	38 (9.7)	10936 (7.5)	969 (11.4)

	Topiramate	123 (0.7)	1286 (1.0)	37 (0.8)	1369 (0.9)	31 (0.8)	804 (0.9)	73 (0.6)	757 (1.0)	<5 (<1.0)	1408 (1.0)	184 (2.2)
	Other	165 (0.9)	697 (0.5)	29 (0.6)	830 (0.6)	43 (1.1)	661 (0.7)	126 (1.0)	575 (0.7)	6 (1.5)	856 (0.6)	436 (5.2)
	Multiple agents	1086 (5.8)	5500 (4.3)	169 (3.7)	6404 (4.5)	337 (8.5)	4951 (5.6)	793 (6.2)	4479 (5.7)	35 (9.0)	6551 (4.5)	184 (2.2)
Average length of exposure period (years): median (IQR)		1.9 (0.4, 6.1)	0.9 (0.2, 3.7)	2.1 (0.5, 6.1)	1.4 (0.2, 5.0)	1.8 (0.2, 5.1)	1.3 (0.2, 5.1)	1.8 (0.3, 5.5)	1.0 (0.2, 4.9)	4.2 (0.4, 6.4)	0.3 (0, 3.1)	6.5 (1.0, 8.0)

[a] Reasons for exclusion: Primary immunodeficiency disorder, haematological malignancies, or treated with chemotherapy

[b] Normal range: IgA 0.8-4.0g/L; IgG 6.0-16.0; IgM 0.5-3.0

Abbreviations: N, number; Ig, immunoglobulins; PanHGG, panhypogammaglobulinaemia; IQR, interquartile range

Table 2: Primary analysis showing associations between antiepileptic drug use and any hypogammaglobulinaemia, unadjusted and adjusted for confounders.

Medicine	**Cases *N* (%)**	**Controls *N* (%)**	**Unadjusted analyses**	**Adjusted analyses[a]**
			OR (95% CI)	**OR (95% CI)**
Any AED	3563 (19.1)	18509 (14.6)	1.38 (1.33, 1.44)	1.20 (1.15, 1.25)
Carbamazepine	388 (2.1)	1782 (1.4)	1.49 (1.34, 1.66)	1.36 (1.21, 1.52)
Phenytoin	36 (0.2)	106 (0.1)	2.32 (1.57, 3.35)	1.65 (1.11, 2.40)
Sodium valproate	187 (1.0)	962 (0.8)	1.33 (1.13, 1.55)	1.24 (1.05, 1.45)
Lamotrigine	202 (1.1)	974 (0.8)	1.41 (1.21, 1.65)	1.41 (1.20, 1.64)
Levetiracetam	83 (0.4)	350 (0.3)	1.62 (1.26, 2.05)	1.30 (1.01, 1.66)
Gabapentin	1940 (10.4)	9980 (7.8)	1.36 (1.29, 1.43)	1.15 (1.09, 1.21)
Pregabalin	1801 (9.6)	9173 (7.2)	1.37 (1.30, 1.45)	1.21 (1.14, 1.27)
Topiramate	123 (0.7)	1286 (1.0)	0.65 (0.54, 0.78)	0.84 (0.69, 1.01)
Other	165 (0.9)	697 (0.5)	1.62 (1.36, 1.91)	1.27 (1.06, 1.50)
Multiple agents	1086 (5.8)	5500 (4.3)	1.37 (1.28, 1.46)	1.23 (1.14, 1.31)

[a] Adjusted for age, sex and CCI

Abbreviations: N, number; OR, odds ratio; CI, confidence interval; AED, antiepileptic drug

Table 3: Secondary analysis showing associations between antiepileptic drug use and low IgA, IgG, IgM, and panHGG[a] adjusted for confounders[b].

	Low IgA			Low IgG			Low IgM			Panhypogammaglobulinaemia		
Medicine	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**
Any AED	502 (10.9)	21539 (15.3)	1.02 (0.92, 1.12)	945 (23.7)	16278 (18.4)	1.22 (1.13, 1.31)	2704 (21.0)	14483 (18.3)	1.18 (1.13, 1.24)	78 (20.0)	21994 (15.1)	1.40 (1.08-1.79)
Carbamazepine	70 (1.5)	2094 (1.5)	1.58 (1.23, 2.00)	111 (2.8)	1569 (1.8)	1.50 (1.23, 1.82)	284 (2.2)	1389 (1.8)	1.27 (1.11, 1.45)	11 (2.8)	2159 (1.5)	2.00 (1.03-3.47)
Phenytoin	12 (0.3)	130 (<0.1)	5.90 (3.04, 10.43)	10 (0.3)	120 (0.1)	1.71 (0.83, 3.12)	25 (0.2)	105 (0.1)	1.14 (0.72, 1.75)	2 (0.5)	140 (0.1)	5.19 (0.85-16.43)
Sodium valproate	31 (0.7)	1116 (0.8)	1.00 (0.68, 1.41)	54 (1.4)	781 (0.9)	1.47 (1.10, 1.92)	131 (1.1)	702 (0.9)	1.23 (1.01, 1.49)	4 (1.0)	1145 (0.8)	1.25 (0.39-2.93)
Lamotrigine	53 (1.1)	1122 (0.8)	1.59 (1.19, 2.09)	54 (1.4)	792 (0.9)	1.44 (1.08, 1.88)	138 (1.1)	705 (0.9)	1.32 (1.09, 1.58)	8 (2.0)	1168 (0.8)	2.50 (1.13-4.71)
Levetiracetam	14 (0.3)	418 (0.3)	1.25 (0.70, 2.07)	26 (0.7)	336 (0.4)	1.43 (0.93, 2.10)	61 (0.5)	300 (0.4)	1.18 (0.88, 1.56)	3 (0.8)	430 (0.3)	2.32 (0.57-6.10)
Gabapentin	239 (5.2)	11661 (8.3)	0.95 (0.83, 1.09)	557 (14.0)	9095 (10.3)	1.25 (1.14, 1.37)	1474 (11.4)	8156 (10.3)	1.10 (1.04, 1.17)	49 (12.5)	11871 (8.2)	1.61 (1.17-2.17)
Pregabalin	238 (5.2)	10726 (7.6)	1.97 (0.84, 1.11)	493 (12.4)	8221 (9.3)	1.22 (1.11, 1.35)	1364 (10.6)	7337 (9.3)	1.20 (1.13, 1.28)	38 (9.7)	10936 (7.5)	1.30 (0.91-1.81)
Topiramate	37 (0.8)	1369 (0.9)	0.74 (0.52, 1.01)	31 (0.8)	804 (0.9)	0.89 (0.61, 1.26)	73 (0.6)	757 (1.0)	0.94 (0.73, 1.19)	1 (0.3)	1408 (1.0)	0.27 (0.02-1.18)
Other	29 (0.6)	830 (0.6)	1.51 (1.01, 2.16)	43 (1.1)	661 (0.7)	1.23 (0.88, 1.66)	126 (1.0)	575 (0.7)	1.20 (0.98, 1.46)	6 (1.5)	856 (0.6)	2.46 (0.97-5.07)
Multiple agents	169 (3.7)	6404 (4.5)	1.13 (0.96, 1.32)	337 (8.5)	4951 (5.6)	1.40 (1.24, 1.57)	793 (6.2)	4479 (5.7)	1.16 (1.07, 1.26)	35 (9.0)	6551 (4.5)	2.05 (1.42-2.88)

[a] Panhypogammaglobulinaemia defined as IgA, IgG and IgM levels less than the normal range.

[b] Adjusted for age, sex, and CCI.

Abbreviations: PanHGG, panhypogammaglobulinaemia; N, number; OR, odds ratio; CI, confidence interval; AED, antiepileptic drug

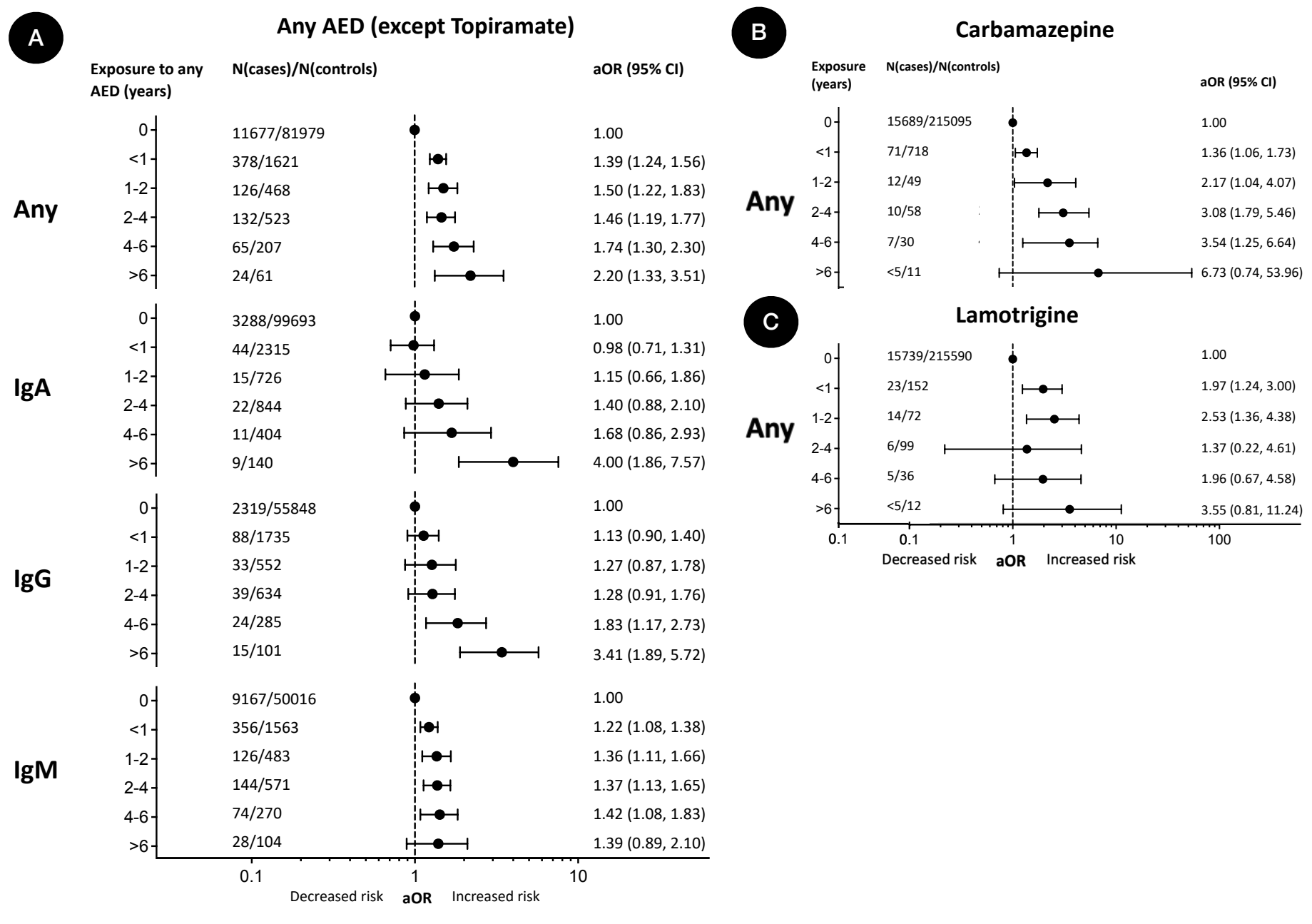
Figure 1: Associations between exposure to antiepileptic medication and hypogammaglobulinaemia over time, adjusted for age, sex and CCI, where immunoglobulins measured before 2013 and prescribing data from before 2013 is excluded.

Abbreviations: AED, antiepileptic drug; N, number; aOR, adjusted odds ratio; CI, confidence interval

Table 4: Sensitivity analysis (i) for the associations between antiepileptic drug use and hypogammaglobulinaemia, adjusted for confounders, where cases are redefined as very low immunoglobulin levels.[a]

	Very low IgA			Very low IgG			Very low IgM		
Medicine	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**	**Cases *N* (%)**	**Controls *N* (%)**	**aOR (95% CI)[b]**
Any antiepileptic use	239 (9.7)	21809 (15.2)	0.95 (0.82, 1.09)	484 (22.8)	16739 (17.0)	1.15 (1.03, 1.27)	1409 (21.7)	15778 (18.4)	1.22 (1.15, 1.30)
Carbamazepine	35 (1.4)	2129 (1.5)	1.57 (1.10, 2.17)	57 (2.7)	1623 (1.7)	1.44 (1.09, 1.87)	156 (2.4)	1517 (1.8)	1.37 (1.15, 1.62)
Phenytoin	8 (0.3)	134 (<0.1)	7.56 (3.32, 14.86)	<5 (<0.2)	126 (0.1)	1.25 (0.38, 3.00)	14 (0.2)	116 (0.1)	1.23 (0.67, 2.08)
Sodium valproate	15 (0.6)	1132 (0.8)	0.92 (0.53, 1.49)	28 (1.3)	807 (0.8)	1.38 (0.92, 1.98)	79 (1.2)	754 (0.9)	1.51 (1.19, 1.91)
Lamotrigine	22 (0.9)	1153 (0.8)	1.25 (0.79, 1.87)	31 (1.5)	815 (0.8)	1.51 (1.03, 2.14)	64 (1.0)	779 (0.9)	1.19 (0.91, 1.53)
Levetiracetam	10 (0.4)	422 (0.3)	1.73 (0.86, 3.10)	13 (0.6)	349 (0.4)	1.29 (0.70, 2.16)	37 (0.6)	324 (0.4)	1.43 (1.00, 1.99)
Gabapentin	113 (4.6)	11787 (8.2)	0.90 (0.73, 1.08)	283 (13.3)	9369 (9.5)	1.17 (1.03, 1.33)	761 (11.7)	8869 (10.4)	1.13 (1.04, 1.22)
Pregabalin	105 (4.3)	10859 (7.6)	0.84 (0.68, 1.02)	258 (12.1)	8456 (8.6)	1.18 (1.03, 1.35)	709 (10.9)	7992 (9.3)	1.24 (1.14, 1.35)
Topiramate	12 (0.5)	1394 (1.0)	0.46 (0.25, 0.78)	15 (0.7)	820 (0.8)	0.77 (0.44, 1.24)	36 (0.6)	794 (0.9)	1.03 (0.72, 1.42)
Other	16 (0.7)	843 (0.6)	1.58 (0.92, 2.53)	23 (1.1)	681 (0.7)	1.22 (0.78, 1.81)	72 (1.1)	629 (0.7)	1.33 (1.03, 1.70)
Multiple agents	76 (3.1)	6497 (4.5)	1.00 (0.78, 1.25)	170 (8.0)	5118 (5.2)	1.28 (1.09, 1.50)	418 (6.4)	4854 (5.7)	1.23 (1.11, 1.37)

[a] Very low immunoglobulin levels are defined as immunoglobulin levels less than the median of those with immunoglobulins less than the normal range
[b] Adjusted for age, sex, and CCI.
Abbreviations: N, number; OR, odds ratio; CI, confidence interval; AED, antiepileptic drug


A
Any AED (except Topiramate)
Exposure to any AED (years)
N(cases)/N(controls)
aOR (95% CI)
Any
0 11677/81979 1.00
<1 378/1621 1.39 (1.24, 1.56)
1-2 126/468 1.50 (1.22, 1.83)
2-4 132/523 1.46 (1.19, 1.77)
4-6 65/207 1.74 (1.30, 2.30)
>6 24/61 2.20 (1.33, 3.51)
IgA
0 3288/99693 1.00
<1 44/2315 0.98 (0.71, 1.31)
1-2 15/726 1.15 (0.66, 1.86)
2-4 22/844 1.40 (0.88, 2.10)
4-6 11/404 1.68 (0.86, 2.93)
>6 9/140 4.00 (1.86, 7.57)
IgG
0 2319/55848 1.00
<1 88/1735 1.13 (0.90, 1.40)
1-2 33/552 1.27 (0.87, 1.78)
2-4 39/634 1.28 (0.91, 1.76)
4-6 24/285 1.83 (1.17, 2.73)
>6 15/101 3.41 (1.89, 5.72)
IgM
0 9167/50016 1.00
<1 356/1563 1.22 (1.08, 1.38)
1-2 126/483 1.36 (1.11, 1.66)
2-4 144/571 1.37 (1.13, 1.65)
4-6 74/270 1.42 (1.08, 1.83)
>6 28/104 1.39 (0.89, 2.10)
0.1
1
10
Decreased risk
aOR
Increased risk
B
Carbamazepine
Exposure (years)
N(cases)/N(controls)
aOR (95% CI)
Any
0 15689/215095 1.00
<1 71/718 1.36 (1.06, 1.73)
1-2 12/49 2.17 (1.04, 4.07)
2-4 10/58 3.08 (1.79, 5.46)
4-6 7/30 3.54 (1.25, 6.64)
>6 <5/11 6.73 (0.74, 53.96)
C
Lamotrigine
Any
0 15739/215590 1.00
<1 23/152 1.97 (1.24, 3.00)
1-2 14/72 2.53 (1.36, 4.38)
2-4 6/99 1.37 (0.22, 4.61)
4-6 5/36 1.96 (0.67, 4.58)
>6 <5/12 3.55 (0.81, 11.24)
0.1
0.1
1
10
100
Decreased risk
aOR
Increased risk