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Cardiovascular, thromboembolic and renal outcomes in IgA vasculitis (Henoch-Schönlein purpura): a retrospective cohort study using routinely collected primary care data

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Abstract

Background: IgA vasculitis (IgAV, Henoch-Schönlein purpura) is a small-vessel vasculitis most common in children but also occurring in adults. Case series have suggested that IgAV may be associated with cardiovascular disease and venous thromboembolism, but this has not been evaluated in population-based studies. Renal disease and hypertension are possible complications of the disease with unknown incidence.

Methods: Using a large United Kingdom primary care database, we conducted an open retrospective matched cohort study of cardiovascular, venous thrombotic and renal outcomes in adult-onset and childhood-onset IgAV. Control participants were selected at a 2:1 ratio, matched for age and sex. Adjusted hazard ratios (aHRs) were calculated using Cox proportional hazards models.

Results: 2,828 patients with adult-onset IgAV and 10,405 patients with childhood-onset IgAV were compared with age- and sex-matched controls. There was significantly increased risk of hypertension (adult-onset aHR 1.42, 95%CI 1.19-1.70, $p<0.001$; childhood-onset aHR 1.52, 95% CI 1.22-1.89, $p<0.001$) and stage G3-G5 chronic kidney disease (adult-onset aHR 1.54, 95%CI 1.23-1.93, $p<0.001$; childhood-onset aHR 1.89, 95%CI 1.16-3.07, $p=0.010$). There was no evidence of association with ischaemic heart disease, cerebrovascular disease or venous thromboembolism. All-cause mortality was increased in the adult-onset IgAV cohort compared to controls (aHR 1.27, 95%CI 1.07-1.50, $p=0.006$).

Conclusions: Patients with IgAV are at increased risk of hypertension and CKD compared to individuals without IgAV; analysis restricted to adult-onset IgAV patients showed increased mortality. Appropriate surveillance and risk factor modification could improve long-term outcomes in these patients.

Introduction

IgA vasculitis (IgAV), also termed Henoch-Schönlein purpura, is a small-vessel vasculitis most frequently affecting children[1]. IgAV is the commonest childhood vasculitis in the United Kingdom, with estimated annual incidence of 20/100,000 children under the age of 17 years according to the largest regional study[2]. However, incidence rates vary widely between study populations, and, furthermore, these may represent underestimates of true incidence[3]. The epidemiology of adult-onset IgAV is less well-studied, but hospital-based studies indicate an estimated annual incidence of 0.8-1.8/100,000 population[3].

IgAV may be complicated by glomerulonephritis[4] and it is thought that adult-onset IgAV is associated with increased risk and severity of renal involvement compared to childhood disease[5,6]. However, long-term health outcomes of adult-onset IgAV are not well characterised. Most evidence regarding complications of IgAV in adults derives from case reports and case series[7]; there is need for controlled epidemiological studies to address this question.

Other outcomes associated with IgAV are unknown. Multiple case reports have raised the possibility of associations between IgAV and venous thromboembolism (VTE), hypertension and ischaemic heart disease (IHD) in both children and adults[8-19]. However, many cases involved patients with additional risk factors, making the role of IgAV unclear. To date, the incidence of these outcomes has not been examined in a large cohort study. Furthermore, there is emerging evidence that patients with other vasculitides have increased incidence of cardiovascular disease[20,21] and receive inadequate management of cardiovascular risk[22].

This study aims to calculate incidence of IgAV in adults and children, and to quantify risk of important complications in adult and childhood-onset disease, in particular, risk of cardiovascular, thrombo-embolic and renal outcomes. These data will facilitate prognostication in such patients, thus informing strategies for surveillance and risk factor modification in routine care.

Methods

Study design

Incidence and prevalence of IgAV

To calculate IgAV incidence, annual cohort studies were performed between 1st January 2005 and 31st December 2016. To estimate prevalence, sequential cross-sectional studies were carried out on 1st January each calendar year from 2005 to 2016.

Chronic outcomes

An open retrospective matched cohort study was performed to compare long-term cardiovascular, venous thromboembolic and renal outcomes in adults and children diagnosed with IgAV and randomly-selected age- and sex-matched controls without a diagnosis. The study period was 1st January 1995 to 15th May 2017.

Data source

Data were extracted from The Health Improvement Network (THIN) database, which comprises anonymised medical records for 3.6 million active patients from >675 general practices, as previously reported[23,24]. Patient data are derived from practices using Vision electronic medical record software, which stores information in a hierarchical system of clinical (Read) codes[25]. THIN includes information on patient demographics, diagnoses, prescriptions, and investigations. THIN

has previously been validated for studies of cardiovascular and renal outcomes[26,27], and for studies of VTE risk[28]. It is broadly representative of the UK population in terms of demographics, disease prevalence and mortality rates[23]. To maximise data quality, general practices were only included in this study from the latest of one year after they began using Vision software and one year after their acceptable mortality recording (AMR) date[24]. Diagnosis was based on Read codes which registered a clinical diagnosis of Henoch Schonlein Purpura, and not IgA deposition within tissues.

Study population

Incidence and prevalence of IgAV

Adults and children with no record of a IgAV diagnosis at the beginning of each one-year study period were included in the annual incidence cohorts. The eligible populations were followed from 1st January every year until the earliest of the following dates: IgAV diagnosis, patient left the practice, death, or 31st December of that year. Annual prevalence is reported per 100,000 population.

Chronic outcomes

In the adult-onset IgAV cohort, patients were eligible for inclusion if they had a clinical code for IgAV recorded at age ≥16 years. Inclusion in the childhood-onset IgAV cohort was restricted to patients with recorded diagnosis of IgAV before the age of 16 years. For each patient with IgAV, two age and sex-matched control patients were randomly selected from a pool of eligible controls. All patients were required to be registered with their general practice for at least one year before study entry.

Index date in the exposed group was the date of first documentation of IgAV after study entry for incident cases (newly diagnosed patients), or date of study entry for prevalent cases (patients with an existing diagnosis). To avoid immortal time bias[29], controls were assigned the same index date as their corresponding exposed patient. Participants were followed up until the earliest of the following dates: outcome event, death, patient left practice, practice stopped contributing to the database, and study end.

Outcomes

In patients with adult-onset IgAV, primary outcomes were IHD, VTE, stroke/TIA, hypertension, stage G3-G5 CKD and all-cause mortality. IHD, VTE, stroke/TIA and hypertension were defined by clinical (Read) codes; stage G3-G5 CKD was defined by new-onset estimated glomerular filtration rate (eGFR) <60mls/min/1.73m^2 on two consecutive measurements separated by at least 90 days[30]. Clinical codes were selected based on QOF business rules and previously published studies[31,32].

For hypertension, a sensitivity analysis was performed using a lag period of one year to test whether this represented a chronic outcome or was solely related to the acute illness.

In the childhood-onset IgAV cohort, primary outcomes were hypertension, VTE and CKD. IHD, stroke/TIA and mortality were not studied in this cohort due to low incidence in this age group and short follow-up period.

Analysis

Annual incidence rates (IR) of IgAV were calculated by dividing the number of newly diagnosed IgAV patients by person-years at risk for adults and children separately.

Cox proportional hazards models were used to calculate crude hazard ratios (HR) and adjusted hazard ratios (aHR) for each outcome in IgAV compared to controls. Breslow's method was used to handle tied survival times where required. All models were adjusted for the following covariates: age, sex, BMI category, Townsend deprivation quintile, and smoking status. Additionally, the models for IHD and stroke/TIA were adjusted for baseline diabetes, hypertension, and lipid-lowering drug prescription; the model for hypertension was adjusted for baseline diabetes and lipid-lowering drug prescription; the model for CKD was adjusted for baseline diabetes and hypertension; and the model for all-cause mortality was adjusted for lipid-lowering drug prescription and Charlson co-morbidity index (CCI). For childhood-onset IgAV, BMI category, lipid-lowering drug prescription and smoking status were not included in the models. BMI recorded closest to index date was categorised as '<25 kg/m^{2}', '25-30 kg/m^{2}' (overweight) and '>30 kg/m^{2}' (obesity); smoking status was categorised as 'smoker', 'ex-smoker' and 'non-smoker'. Social deprivation was categorised according to Townsend deprivation quintile[33]. CCI was categorised as '0', '1', '2', or '>2'[34]. Separate categories were created for missing data, which were included in the regression analyses.

Baseline renal function was not adjusted for in the primary analysis due to limited availability of creatinine measurements before the index date. A sensitivity analysis was performed in which all models were adjusted for baseline eGFR.

For the adult- and childhood-onset studies, all patients without a record of the outcome under study at baseline were included in the primary analysis. For the CKD study, primary analysis included only patients with an eGFR >60mls/min/1.73m^{2} at baseline. Sensitivity analyses were performed in which: 1) patients with missing baseline eGFR values were included and categorised as having normal renal function; and 2) all patients were included regardless of baseline eGFR, assuming that baseline eGFR might reflect transient residual renal impairment.

To ensure that results are applicable to disease of adult onset, a sensitivity analysis was performed using incident (newly diagnosed, definite adult-onset) adult IgAV cases only.

Analyses were performed using STATA 14.0. Statistical significance was set at $p<0.05$.

Results

Incidence of IgAV in adults and children

Between 2005 and 2016, incidence of childhood-onset IgAV was 27.22 per 100,000 person-years; incidence of adult-onset IgAV was 2.20 per 100,000 person-years (Fig. 1; baseline characteristics are summarised in Table S2). Mean (SD) age at diagnosis was 6.68 years (3.41) years for children and 38.1 (18.8) years for adults. Whilst IgAV incidence remained stable, prevalence of both adult- and childhood-onset IgAV increased over the study period. Between 2005 and 2016, prevalence of adult-onset IgAV increased from 34 to 44 per 100,000 population; prevalence of childhood-onset IgAV increased from 621 to 846 per 100,000 population.

Outcomes in adult-onset IgAV

Baseline characteristics

There were 2,828 patients with adult-onset IgAV and 5,655 controls. Median (IQR) follow-up was similar in both cohorts: 4.91 (2.07-9.08) years in the IgAV cohort and 4.99 (2.18-9.05) years in the control cohort.

Mean age at study entry was 43 years in both exposed and unexposed cohorts. Both cohorts had 48.4% males. At baseline renal impairment (eGFR <60mls/min/1.73m^2) was more common in patients with IgAV (6.86% vs. 4.05% in unexposed). Similar differences between those with and without IgAV were observed for hypertension (18.5% vs. 13.0%), diabetes mellitus (5.3% vs. 3.7%), VTE (1.8% vs. 1.1%), lipid-lowering drug prescription (11.1% vs. 5.0%) and CCI (15.28% vs. 7.35% with ≥2 comorbidities). Patients with IgAV were less likely to be current smokers (18.5% vs. 22.8%). The cohorts were similar with respect to BMI and Townsend deprivation quintile (Table 1).

Hypertension

196 IgAV patients (6.93%) received a diagnosis of hypertension, compared to 315 (5.57%) controls (Table 2); incidence was 15.26 and 11.18 per 1,000 person-years respectively: aHR 1.42 (95%CI 1.19-1.70). Cumulative hazard curves are shown in Fig. 2. Results were robust in two sensitivity analyses restricting outcome to hypertension diagnosed at least one year after the index date and restricting to incident IgAV cases and their matched controls (Table S2).

Ischaemic heart disease and cerebrovascular disease

53 patients (1.87%) with adult-onset IgAV and 104 (1.84%) controls were diagnosed with IHD, corresponding to IRs of 3.32 and 3.20 per 1,000 person-years respectively. There was no evidence of association between IgAV and risk of IHD (aHR 1.08, 95%CI 0.77-1.52). 52 patients with IgAV (1.84%) and 109 controls (1.93%) experienced a stroke/TIA, with IRs of 3.14 and 3.26 per 1,000 person-years respectively. There was no evidence of association between IgAV and risk of stroke/TIA (aHR 0.95, 95%CI 0.68-1.32).

Venous thromboembolism

28 patients with adult-onset IgAV (0.99%) and 46 controls (0.81%) were coded with a VTE event; incidence was 1.67 and 1.36 per 1,000 person-years respectively. Crude and adjusted HRs were not statistically significant: aHR 1.21 (95%CI 0.76-1.95).

Chronic kidney disease

There were 134 incident cases of CKD stages G3-5 (5.11%) in the adult-onset IgAV cohort, compared to 185 (3.42%) in controls; incidence was 8.72 and 5.75 per 1,000 person-years respectively: aHR 1.54 (95%CI 1.23-1.93). This association remained significant in all sensitivity analyses, including adjustment for baseline eGFR (Table S2).

All-cause mortality

There were 238 deaths (8.42%) in the adult-onset IgAV cohort and 348 (6.15%) in the control cohort, corresponding to mortality rates of 13.93 and 10.12 per 1,000 person-years respectively. In the primary analysis, all-cause mortality was significantly increased in the adult-onset IgAV cohort compared to controls: aHR 1.27 (95%CI 1.07-1.50). However, in a sensitivity analysis using incident cases and their controls only, the effect was not statistically significant (aHR 1.09, 95%CI 0.83-1.42).

Adjusting for baseline eGFR did not affect the results for any outcome (Table S3).

Outcomes in childhood-onset IgAV

Baseline characteristics

10,405 patients with incident or prevalent childhood-onset IgAV were identified and matched to 20,810 controls without IgAV. Mean (SD) age at diagnosis for the IgAV cohort was 6.68 (3.4); mean age at study entry was 17.6 (13.1) years and 53% were male in both cohorts. Median (IQR) follow-up was similar: 4.86 (2.06-9.08) years in the IgAV cohort and 4.98 (2.17-9.86) years in controls. At baseline, more patients with IgAV had hypertension (1.78% vs. 1.13%) and VTE (0.28% vs 0.18%) compared to controls (Table 1). The cohorts were also similar with respect to baseline renal function, Townsend deprivation quintile and smoking status.

Hypertension

139 patients with IgAV (1.34%) and 193 controls (0.93%) had hypertension (Table 3); incidence was 2.29 and 1.57 per 1,000 person-years respectively: aHR 1.52 (95%CI 1.22-1.89). This association remained significant in all of the sensitivity analyses performed (Table S3). Cumulative hazard curves are shown in Fig. 3.

Venous thromboembolism

In the childhood-onset IgAV cohort, 25 patients (0.24%) experienced VTE, compared to 46 controls (0.22%); incidence was 0.40 and 0.37 per 1,000 person-years respectively. There was no evidence of association between childhood-onset IgAV and VTE (aHR 1.10, 95%CI 0.68-1.79).

Chronic kidney disease

There were 32 incident cases of CKD (0.31%) in patients with IgAV compared to 34 (0.16%) in the controls; incidence was 0.51 and 0.27 per 1,000 person-years respectively: aHR 1.89 (95%CI 1.16-3.07; see Table S3).

Discussion

In this population-based study, we show that, compared to an age- and sex-matched control population, childhood and adult-onset IgAV is associated with increased risk of hypertension and CKD. Adult-onset IgAV was not associated with IHD, cerebrovascular disease or VTE.

Annual IgAV incidence from 2005 to 2016 in children (27.22 per 100,000 person-years) and adults (2.20 per 100,000 person-years) was marginally higher than previously reported (20 and 0.8-1.8 per 100,000 person-years in children and adults respectively), likely due to the different case-finding strategies employed[2,3]. Previous studies likely underestimated IgAV incidence as they had access to less comprehensive datasets. Whilst incidence remained stable over the study period, prevalence of adult- and childhood-onset IgAV increased. This could be explained by improved documentation of existing IgAV diagnoses, or may reflect increased patient survival. The former explanation is more likely given the short time period over which this increase occurred.

To our knowledge, this is the first controlled study examining incidence of IHD, stroke/TIA and VTE in adult patients with IgAV. Despite evidence from case series suggesting that IgAV confers increased risk of these outcomes[8–19], we found no evidence of association between IgAV and IHD, stroke/TIA or VTE. We note that incidence of VTE was low in this cohort (1.67 per 1,000 person-

years). VTE may be an isolated acute event unrecorded in general practice records, and therefore this result should be interpreted with caution.

Although hypertension has been associated with poor outcomes in some patients with IgAV[35], incidence of hypertension in childhood- and adult-onset IgAV was previously unknown. This study revealed similar risk for children and adults. The effect could be explained by renal manifestations of IgAV or by use of medications such as non-steroidal anti-inflammatory drugs and corticosteroids. The association remained significant in a sensitivity analysis using only hypertension recorded at least one year post-index date, suggesting that it is not solely an acute feature of the disease.

IgAV is thought to have a poorer renal prognosis in adult patients than in children[5,6,36]. In patients with adult-onset IgAV, incidence of stage G3-5 CKD was 8.72 per 1,000 person-years, with a 54% increase in risk compared to controls. In patients with childhood-onset IgAV, incidence of CKD was much lower (0.51 per 1,000 person-years) but with a similar HR. The increased incidence of CKD in adults compared to children may be explained by a higher burden of co-morbidity and renal impairment at baseline.

A 35% increase in all-cause mortality was observed in adult-onset IgAV patients compared to controls. However, this effect was no longer statistically significant in a sensitivity analysis including only incident cases of IgAV. This may be explained by reduced length of follow-up when only incident cases are considered.

Strengths and limitations

Definition of exposure status depended on accurate coding of IgAV diagnosis in primary care medical records. These records do not include information on whether IgAV was diagnosed based solely on clinical criteria, or whether biopsy findings were used. We are unable to identify patients with renal involvement at diagnosis and recognise that there may be stronger associations with the outcomes if the cohort is restricted to patients with biopsy-proven IgAV, as previously shown in patients with biopsy-proven Henoch-Schönlein nephritis[37].

Alternatively, other vasculitides, such as microscopic polyangiitis (MPA), may have been misdiagnosed as IgAV in the absence of histological investigation. Inclusion of such patients could increase the incidence of complications such as CKD. Although widespread testing for anti-neutrophil cytoplasm autoantibodies has been available since the 1990s, we have no data on ANCA testing and cannot exclude that this diagnosis may have been missed in some cases.

It is possible that patients with greater disease severity were selectively coded in primary care, leading to overestimation of effect size. However, our incidence and prevalence estimates were similar, if not slightly higher than previously reported. Similarly, inaccurate coding of outcomes is a potential source of error. CKD is likely to be under-diagnosed in primary care[38], so practice records may underestimate its incidence. To minimise this risk, CKD was defined by eGFR criteria not clinical codes.

A further caveat is uncertainty regarding classification of IgAV as adult-onset. In the primary analysis, all adult IgAV patients with coded date of diagnosis after their 16th birthday were included. However, some cases may have been inappropriately defined as adult-onset, for example if coded when the patient moved to a new practice. Nevertheless, results were replicated in sensitivity analyses using incident adult IgAV cases only, showing that our findings are robust to stricter definitions of adult-onset IgAV.

When considering cardiovascular outcomes in patients with adult-onset IgAV, it should be noted that the affected population was relatively young (mean age 43.3 years at study entry). Therefore, it is possible that length of follow-up in this study was insufficient to detect increased risk of IHD.

Finally, this study could be influenced by surveillance bias. Patients with IgAV may receive closer monitoring of blood pressure and renal function in primary care. This may contribute to the higher CCI scores observed in patients with adult-onset IgAV compared to controls.

Despite these limitations, a strength of this population-based study design is its external validity. Patients with IgAV and control participants were included from a primary care database which is broadly representative of the UK population in terms of ethnicity, chronic disease prevalence and mortality rates[23].

Conclusion

This retrospective cohort study demonstrates associations between IgAV and hypertension and CKD. These findings emphasise the importance of blood pressure and renal function monitoring in patients with IgAV. Our data also suggest that IgAV should not be considered a “single hit” disease, but that clinicians should monitor for long-term sequelae. Further research is required to clarify the cause of hypertension in patients with IgAV, and to investigate whether such patients suffer from additional long-term sequelae than that are currently unrecognised.

Contributions

AT, LH and KN conceived the work. AT contributed to the analysis and interpretation of data, drafting the manuscript and revising for intellectual content. AS and KN contributed to the acquisition, analysis and interpretation of data, and drafting the manuscript. NJA contributed to data analysis and interpretation, and writing the manuscript. LH contributed to drafting the manuscript and revising for intellectual content. PC, CF and SB contributed to revising the manuscript for intellectual content. All authors approved the final version to be submitted for review.

Ethics

The THIN data collection scheme and research carried out using THIN data were approved by the NHS South-East Multicentre Research Ethics Committee in 2003; under the terms of this approval, studies must undergo independent scientific review. Approval for this analysis was obtained from the Scientific Review Committee (for the use of THIN data) in April 2018 (SRC reference number 18THIN016).

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Key points

What is already known about this subject?

• IgAV is recognised to occur in both children and adults however the incidence and prevalence, especially in adults, is unknown in large populations based in primary care

• IgAV is associated with long-term complications including chronic kidney disease. Small case series have previously suggested a predisposition to ischaemic heart disease and venous thromboembolism in some patients.

What does this study add?

• The risk of hypertension and CKD is significantly increased in adult-onset and childhood-onset IgAV compared to the general population

• IgAV is not significantly associated with ischaemic heart disease or venous thromboembolism in this study. The young age of most patients and short follow-up in this study mean longer follow-up is required to address the risk of ischaemic heart disease.

How might this impact on clinical practice?

• Clinicians looking after patients who have had IgAV should routinely monitor for hypertension and CKD

Tables

Baseline summary characteristics table

Table 1: Baseline characteristics of the adult- and childhood-onset IgAV cohorts with corresponding controls. Adult-onset patients include all incident and prevalent IgAV cases with a date of diagnosis after the age of 16 years. Childhood-onset patients include all incident and prevalent IgAV cases with a date of diagnosis before the age of 16 years. Controls were age- and sex-matched in a 2:1 ratio.

Baseline Characteristics (Standard Deviation or Percentage)				
	Adult-onset IgAV		**Childhood-onset IgAV**	
	Exposed	**Unexposed**	**Exposed**	**Unexposed**
Number of patients	2,828	5,655	10,405	20,810
Median follow-up period (years)	4.91 (IQR 2.07-9.08)	4.99 (IQR 2.18-9.05)	4.86 (IQR 2.06-9.08)	4.98 (IQR 2.17-9.86)
Mean age at study entry (years)†	43.33 (18.8)	43.33 (18.7)	17.57 (13.12)	17.59 (13.13)
Mean age at IgAV diagnosis	38.09 (18.8)	N/A	6.68 (3.41)	N/A
Gender (Male)	1,370 (48.4%)	2,739 (48.4%)	5,545 (53.29%)	11,090 (53.29%)
Gender (Female)	1,458 (51.6%)	2,916 (51.6%)	4,860 (46.71%)	9,720 (46.71%)
Mean body mass index (BMI)	26.9 (6.1)	26.2 (5.5)	N/A	N/A
Smoking status				
Current smoker	522 (18.5%)	1,289 (22.8%)	1,178 (11.32%)	2,102 (10.10%)
Ex-smoker	525 (18.6%)	845 (14.9%)	528 (5.07%)	904 (4.34%)
Non-smoker	1,525 (53.9%)	2,825 (50.0%)	2,751 (26.44%)	5,427 (26.08%)
Not available	256 (9.05%)	696 (12.31%)	5,948 (57.16%)	12,377 (59.48%)
Hypertension	523 (18.5%)	734 (13.0%)	185 (1.78%)	236 (1.13%)
Diabetes mellitus	149 (5.3%)	210 (3.7%)	66 (0.63%)	133 (0.64%)
VTE	52 (1.8%)	61 (1.1%)	29 (0.28%)	37 (0.18%)
IHD	139 (4.9%)	220 (3.9%)	N/A	N/A
Stroke and TIA	68 (2.4%)	107 (1.9%)	N/A	N/A
eGFR category				

>90 ml/min per 1.73 m^2	639 (22.60%)	856 (15.14%)	116 (0.56%)	100 (0.96%)
60-90 ml/min per 1.73 m^2	697 (24.65%)	1,160 (20.51%)	121 (0.58%)	157 (1.51%)
30-59 ml/min per 1.73 m^2	164 (5.80%)	209 (3.70%)	1,339 (6.43%)	707 (6.79%)
<30 ml/min per 1.73 m^2	30 (1.06	20 (0.35%)	1,358 (6.53%)	642 (6.17%)
Not available	1,298 (45.90%)	3,410 (60.30%)	17,876 (85.90%)	8,799 (84.57%)
Lipid regulating medication use	313 (11.1%)	506 (5.0%)	N/A	N/A
Current contraceptive use*	336 (23.1%)	572 (19.6%)	799 (16.44%)	1,432 (14.73%)
Townsend deprivation quintile				
(Least deprived) 1	622 (22.0%)	1,231 (21.8%)	2,216 (21.30%)	4,529 (21.76%)
2	542 (19.2%)	1,161 (20.5%)	1,927 (18.52%)	3,863 (18.56%)
3	557 (19.7%)	1,080 (19.1%)	1,968 (18.91%)	4,055 (19.49%)
4	476 (16.8%)	955 (16.9%)	1,856 (17.84%)	3,633 (17.46%)
5	334 (11.8%)	670 (11.9%)	1,293 (12.43%)	2,614 (12.56%)
Not available	297 (10.5%)	558 (9.9%)	1,145 (11.0%)	2,116 (10.17%)
Charlson co-morbidity index				
0	1,806 (63.86%)	4,176 (73.85%)	N/A	N/A
1	590 (20.86%)	1,063 (18.80%)	N/A	N/A
2	259 (9.16%)	258 (4.56%)	N/A	N/A
> 2	173 (6.12%)	158 (2.79%)	N/A	N/A

†Note that many patients had a IgAV diagnosis prior to study entry – prevalent cases

*Current contraceptive use percentage reported for females only.

Summary of adult-onset IgAV outcomes

Table 2: Summary of primary outcomes in adult-onset IgAV cases and corresponding controls.

	Hypertension		Ischaemic heart disease		Stroke/TIA		Venous thrombo-embolism		Chronic kidney disease		All-cause mortality	
	IgAV	**Control**	**IgAV**	**Control**	**IgAV**	**Control**	**IgAV**	**Control**	**IgAV**	**Control**	**IgAV**	**Control**
Number of Patients	2,305	4,921	2,689	5,435	2,760	5,548	2,776	5,594	2,487	5,225	2,828	5,655
Numbers of Outcomes	196	315	53	104	68	107	28	46	134	185	238	348
Person-years	12,847.60	28,174.46	15,974	32,542.38	16,552.39	33,468.58	16,771.07	33,813.95	15,359.92	32,167.31	17,085.13	34,391.52
Incidence Rate (per 1,000 person-years)	15.26	11.18	3.32	3.20	3.14	3.26	1.67	1.36	8.72	5.75	13.93	10.12
Crude Hazard Ratio (95% CI)	1.36 (1.14-1.63)		1.04 (0.75-1.44)		0.96 (0.69-1.34)		1.22 (0.76-1.96)		1.52 (1.22-1.90)		1.37 (1.17-1.62)	
***p*-value**	0.001		0.829		0.814		0.401		<0.001		<0.001	
Adjusted Hazard Ratio (95% CI)	1.42 (1.19-1.70)		1.08 (0.77-1.52)		0.95 (0.68-1.32)		1.21 (0.76-1.95)		1.54 (1.23-1.93)		1.27 (1.07-1.50)	
***p*-value**	<0.001		0.637		0.758		0.424		<0.001		0.006	

Summary of childhood-onset IgAV outcomes

Table 3: Summary of primary outcomes in childhood-onset IgAV cases and corresponding controls.

	Hypertension		**Venous thrombo-embolism**		**Chronic kidney disease**	
	IgAV	**Control**	**IgAV**	**Control**	**IgAV**	**Control**
Number of Patients	10,220	20,574	10,376	20,773	10,370	20,763
Numbers of Outcomes	139	193	25	46	32	34
Person-years	60,753.91	123,318.1	62,333.31	125,359.3	62,185.31	125,362.3
Incidence Rate (per 1,000 person-years)	2.29	1.57	0.40	0.37	0.51	0.27
Crude Hazard Ratio (95% CI)	1.46 (1.17-1.81)		1.08 (0.66-1.75)		1.90 (1.17-3.08)	
***p*-value**	0.001		0.762		0.009	
Adjusted Hazard Ratio (95% CI)	1.52 (1.22-1.89)		1.10 (0.68-1.79)		1.89 (1.16-3.07)	
***p*-value**	<0.001		0.697		0.010	

Figures

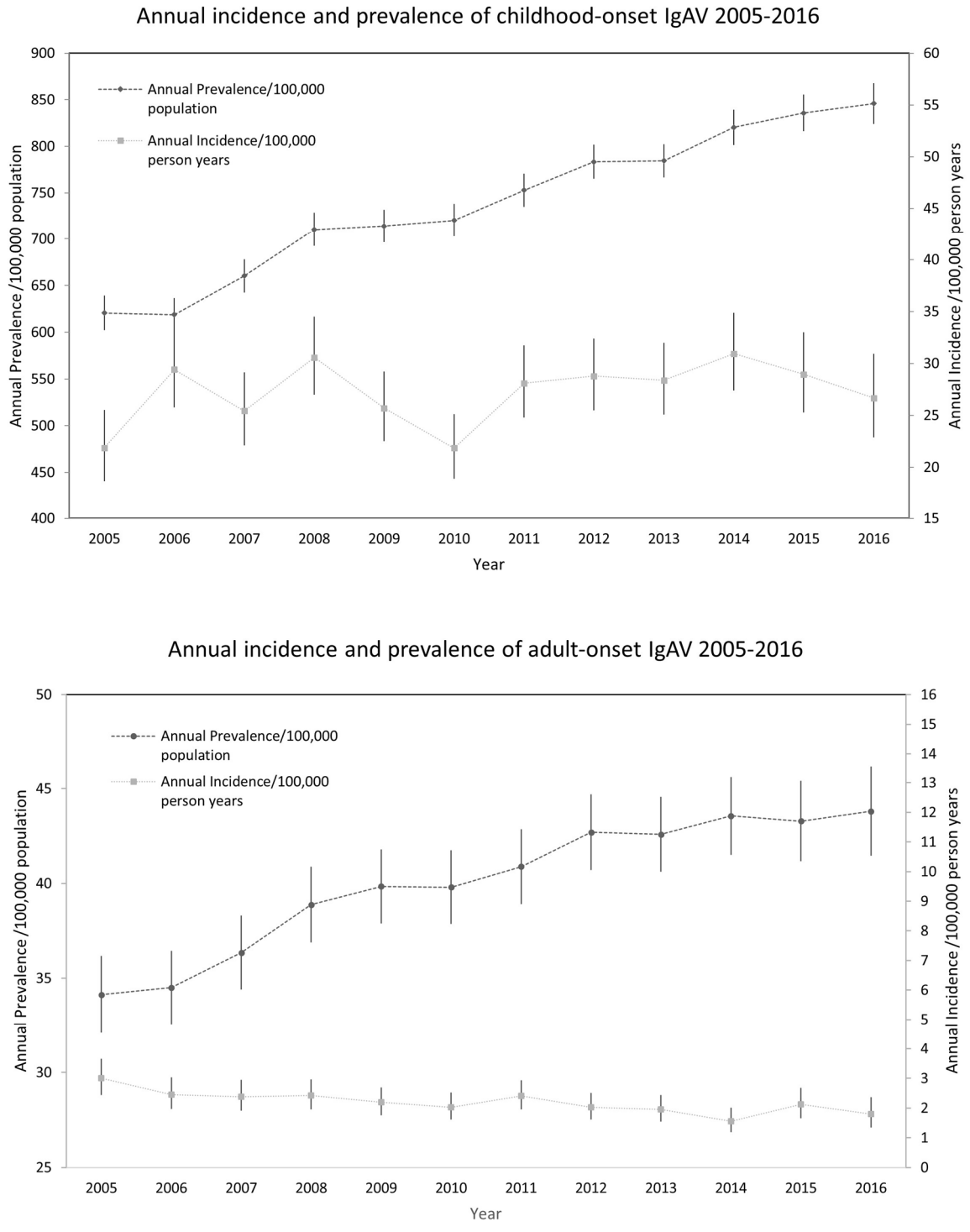

Figure 1: Annual incidence and prevalence for childhood-onset and adult-onset IgAV from 2005 to 2016.

1A) Annual incidence (squares) and prevalence (circles) for childhood-onset IgAV (95% confidence intervals shown). 1B) Annual incidence (squares) and prevalence (circles) for adult-onset IgAV (95% confidence intervals shown).

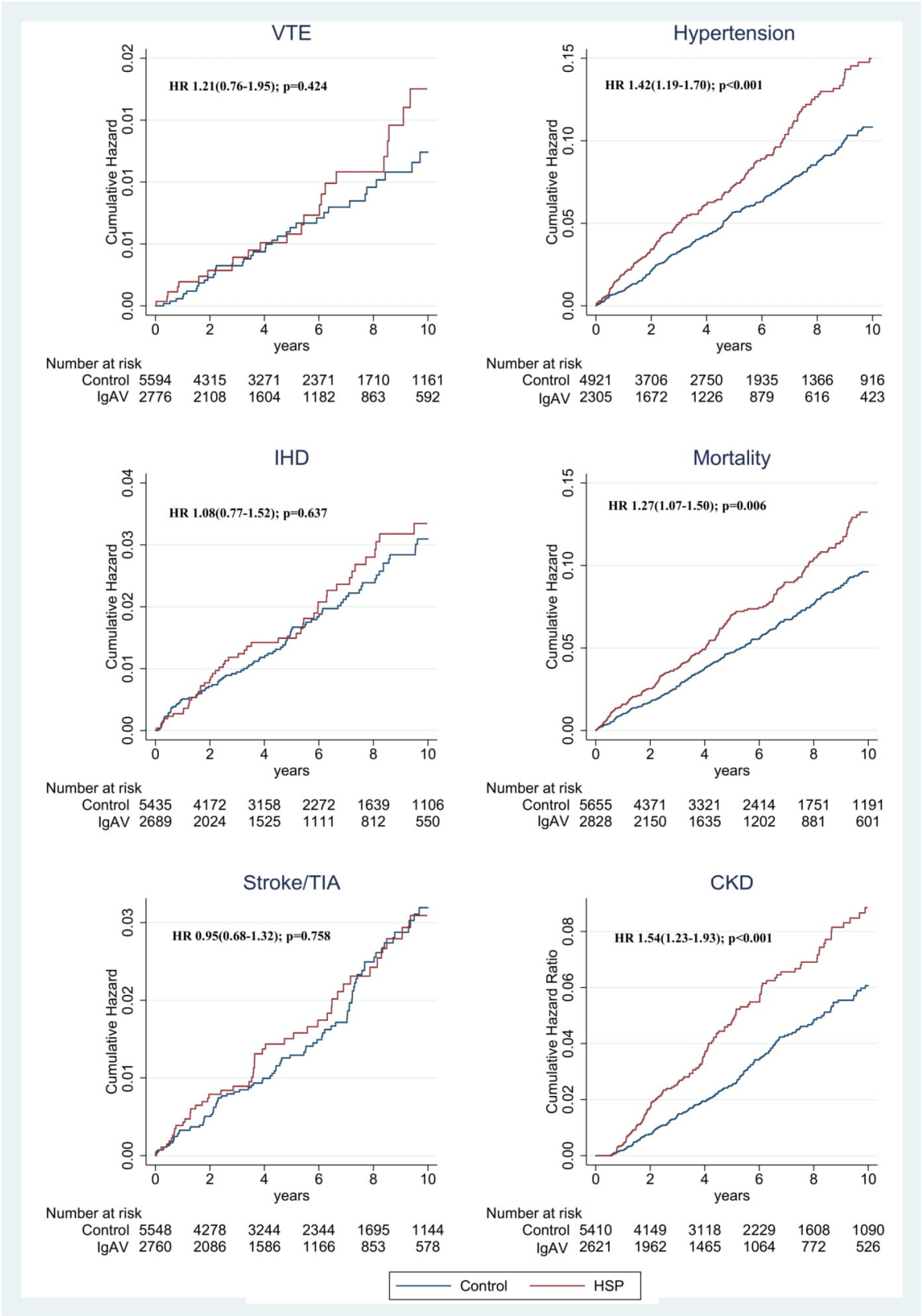

Figure 2: Cumulative hazard curves for outcomes in adult-onset IgAV

Cumulative hazard curves are displayed for each of the six outcomes under study in the adult-onset IgAV cohort.

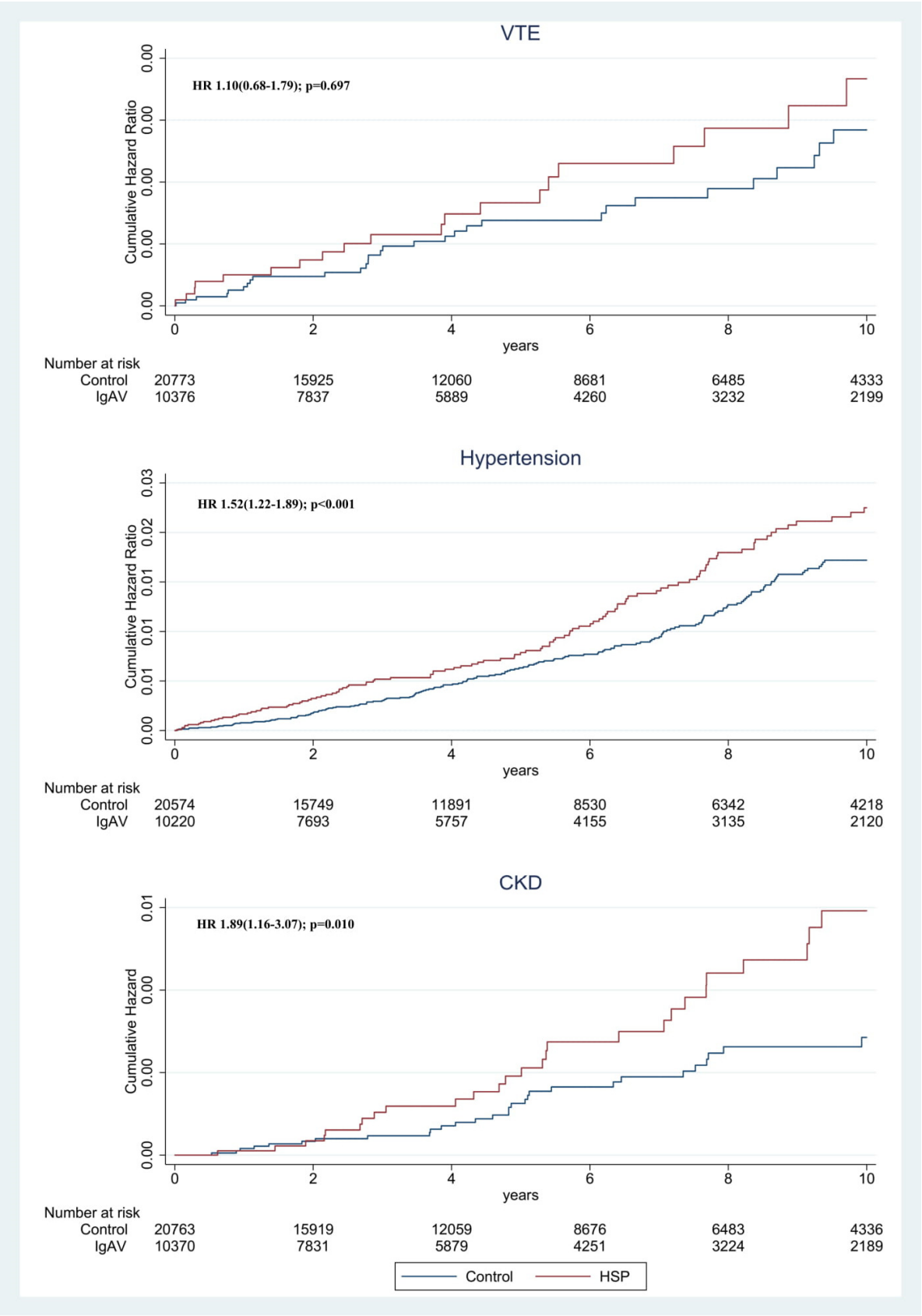

Figure 3: Cumulative hazard curves for outcomes in childhood-onset IgAV

Cumulative hazard curves are displayed for each of the three outcomes under study in the childhood-onset IgAV cohort.

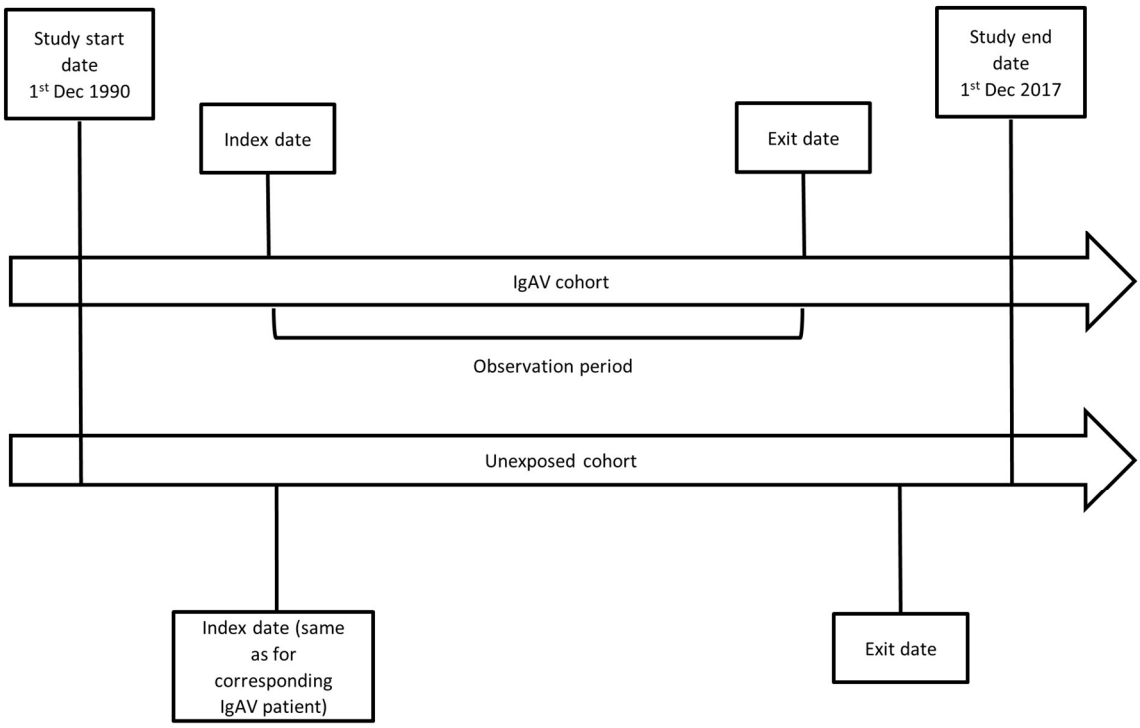

Figure S1 (supplementary): Visual representation of the study timeline and selection process

The exposed cohort were identified by IgAV Read codes, and their controls were matched in a 2:1 ratio for age and sex. The index date for IgAV patients was either the date of diagnosis (for incident cases) or the date on which the patient became eligible to participate (for prevalent cases). Controls were selected at the same index date as their corresponding IgAV patient to mitigate immortal time bias.

To maximise data quality, patients were eligible for participation one year after the latest of the following dates: i) registration at the general practice, ii) introduction of Vision EMR software at the practice, iii) practice acceptable mortality recording (AMR) date, which is an indication of accurate and timely recording of information by the practice. The one-year latent period is applied to give sufficient time for the practice to record all important covariates. The patient exit date is the earliest of the following dates: i) development of outcome under study, ii) date of death, iii) date of transfer from general practice, iv) date of last data collection from general practice.