The Incidence, Prevalence and Mortality of Granulomatosis with Polyangiitis in the UK Clinical Practice Research Datalink.

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ABSTRACT

Objectives: To estimate the incidence, prevalence and mortality of Granulomatosis with polyangiitis (GPA) in the United Kingdom.

Methods: We conducted a historical cohort study using data from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES). We calculated incidence rate ratios, adjusted for age, gender and ethnicity, using Poisson regression.

Results: We identified 462 cases diagnosed between 1997 and 2013. Our overall estimate of incidence was 11.8 (95% CI 10.7-12.9)/million person-years. Incidence in children (aged <16 years) was 0.88 (95% CI 0.40-1.96), and adults 14.0 (95% CI 12.8-15.4). The incidence was lower in females (adjusted IRR 0.68; 95% CI 0.56-0.81) and highest in the 55-69 year age-group (adjusted IRR 9.5, 95% CI 6.9-13.0; reference group 0-39 years). Incidence was not significantly different in the Black / Minority Ethnic population compared to the white population (adjusted odds ratio 0.78, 95% CI 0.53-1.13, p=0.13). The prevalence in 2013 was 134.9 (121.3-149.6) /million. Mortality was 13.6% at 1-year, and higher in HES than CPRD-identified cases (Hazard ratio 3.16, 95% CI 2.19-4.56, p<0.001).

Conclusions:

By combining primary and secondary care datasets we have found the incidence and mortality of granulomatosis with polyangiitis to be higher than previously reported. We predict that at present each year in the UK there will be approximately 700 new cases of whom 95 will die within 12 months.

INTRODUCTION

Previous estimates of incidence and prevalence of Granulomatosis with polyangiitis (GPA, formerly known as Wegener's granulomatosis) vary widely and have mainly been from small studies with low numbers of cases.[1] In addition, there are few data on influence of ethnic group, gender and age on incidence.

To improve the evidence base, a large study is needed that captures the full spectrum of people with this illness. Studies of disease incidence based on hospital case series in specialist centres may miss the mildest and most severe cases, as they may never be referred to the specialist centre, or may die before referral can be arranged. Studies based in primary care have the potential to reduce such referral bias, but may miss the most severe cases that are diagnosed in hospital and die before accessing primary care services again. Ideally, a cohort is needed with case ascertainment in both primary and secondary care.

The aim of this study is to estimate the incidence, prevalence and mortality of Granulomatosis with polyangiitis in a UK population-based cohort, using both GP and hospital records contained within the CPRD and HES datasets, during 1997-2013.

PATIENTS AND METHODS

Study design and study population

This is a historical cohort study containing the 398 practices in the CPRD with data linked to HES (approximately 65% of patients in the whole CPRD).

The CPRD is a longitudinal database of anonymised medical records from general practitioners. Patients are broadly representative of the UK population in terms of age, sex and ethnicity.[2] HES contains records of all inpatient stays and day case attendances in England. Primary and secondary diagnoses from each admission are coded using ICD-10.

We included people contributing data to CPRD-HES between 1 April 1997 and 31 December 2013. Patients were eligible for periods of time where their CPRD records were deemed to be of acceptable standard for research by the CPRD.[2]

Case definition

Cases had a diagnosis of Granulomatosis with polyangiitis by either Read code in the CPRD or ICD-10 code in HES. To select relevant diagnosis codes, the Read code and ICD-10 dictionaries were searched using the terms "Granulomatosis with polyangiitis" and the condition's former name "Wegener's Granulomatosis". This identified only one relevant and specific code in each: Read code G754, and ICD-10 code M31.3, both for "Wegener's granulomatosis". The Read code has previously been validated[3], and work had previously been undertaken locally to validate the ICD-10 code as described in the discussion. The diagnosis date was taken as first occurrence of a code for 'Vasculitis' or 'Granulomatosis with polyangiitis', in a patient with a CPRD or ICD-10 code for Granulomatosis with polyangiitis, as we considered it unlikely that two types of vasculitis would co-exist in the same person. Incident cases had a first record of a code for Granulomatosis with polyangiitis during the study period, and included only patients with at least 1 year of follow up from practice registration prior to diagnosis to try to minimise the number of prevalent cases misclassified as incident[4].

The denominator was all the people who contributed research standard data to the CPRD-HES during the study dates.[2]

Statistical analysis

We categorised age into groups (0-15 years, 16-39 years, 40-54 years, 55-69 years, 70-84 years, 85+ years). Self-reported ethnicity was coded according to the Office for National Statistics 5+1 categories (White, Mixed, Asian, Black, Chinese or other, and unknown). In addition, to improve statistical power, we recoded ethnicity as white vs Black and Minority Ethnic (BME) vs unknown. We also performed a sensitivity analysis by re-categorising those with unknown ethnicity as white.

We calculated crude annual incidence rates /million person-years, and stratified these by age group, sex and ethnic group. Unadjusted incidence rate ratios (IRR) were obtained by fitting variables individually in separate Poisson regression models. Mutually adjusted IRRs were obtained by fitting age, sex and ethnic group as a priori confounders in a single Poisson model.

We calculated point prevalence /million people on 1 July 2013 and stratified this in the same way as for incidence. We used logistic regression to calculate odds ratios.

We used Kaplan-Meier methods to estimate survival in patients with Granulomatosis with polyangiitis at pre-specified times following diagnosis (30-days, 90 days and 1-year) and stratified mortality rates by source of case identification (CPRD with or without a HES diagnosis vs. identified by HES only), age, sex and ethnicity. We used Cox proportional hazards models to compare hazard ratios.

We used direct standardization of CPRD/HES age and sex specific incidence rates to the age and sex-stratified UK population in 2016, [5] to estimate the number of expected incident cases in the UK, and applied our mortality estimate to predict how many would die within 12 months. We estimated prevalence from the total population of the UK in 2016.

All analyses were performed using Stata 14 statistical software (Statacorp, Texas, USA).

For purposes of comparison with the previous CPRD study,[3] we re-ran our analyses using CPRD-only data (the whole of the CPRD including those people from practices without linked HES data) which we report in a sensitivity analysis.

Ethics

Independent Scientific Advisory Committee (ISAC) for MHRA Database Research approval was obtained for this study on 21/07/2015 (protocol 15_150R).

RESULTS IN CPRD-HES

Overall, we identified 462 incident cases of Granulomatosis with polyangiitis in CPRD-HES (see figure 1). The cohort had a slight male predominance (56.7% male) and mean age at diagnosis 60.0 (SD 15.9) years.

Incidence:

We estimated the overall incidence rate to be 11.8 (10.7-12.9) /million person-years based on 462 cases of Granulomatosis with polyangiitis in 39,286,088 person-years of follow up. The incidence in children (aged <16 years) was 0.88

(95% CI 0.40-1.96)/million person-years, and among adults (≥16 years) was 14.0 (95% CI 12.8-15.4)/million person-years.

Temporal trend:

The incidence by year is shown in table 1. The annual incidence in CPRD-HES appears to increase during the first few years of the study period but there was no significant change from 2000 onwards (IRR /year 1.02, 95% CI 0.99-1.04, p-trend=0.2).

Age, Gender:

Crude incidence rates and adjusted rate ratios are presented in table 2. Incidence was lower among women than men with adjusted IRR 0.67 (95% CI 0.56-0.81, p<0.001). Peak age of incidence was at 55-69 years (IRR 6.8, 95% CI 4.9-9.6, p<0.001, compared with 16-39 years) and similar at 70-84 years (IRR 6.4, 95% CI 4.5-9.1, p<0.001, compared with 16-39 years).

Ethnicity

We identified ethnicity for 90.7% of cases of Granulomatosis with polyangiitis, but only 76.8% of the denominator CPRD-HES linked population (see online supplementary table A). The 'unknown' denominator population was half as large as the white population, and 3 times the size of the BME population. Crude incidence was highest in the white ethnic group (16.2, 95% CI 14.7-17.9) /million person-years, intermediate in the BME group (7.9, 95% CI 5.5-11.3) and lowest in the group with unknown ethnicity (3.7, 95% CI 2.8-5.0). In analysis adjusted for age and sex, the results were similar but slightly attenuated: the incidence rate ratio for BME compared to whites was 0.64 (95% CI 0.44-0.94) and for people of unknown ethnicity compared to whites was 0.30 (95% CI 0.22-0.41).

In the sensitivity analysis, people of unknown ethnicity were re-categorised as white. There was a lower incidence in the BME compared to white populations in crude incidence (IRR0.64, 95% CI 0.44-0.94, p=0.01) but this was partly explained by the younger age-structure of the BME population, and once adjusted for age and sex the effect was reduced and non-significant at the 5% level (IRR 0.81, 95% CI 0.56-1.18, p=0.3)(Table 2).

Prevalence

In 2013, the prevalence the overall prevalence was 134.9 (95% CI 121.3-149.6). The prevalence among adults was 163.8 (95% CI 147.2-181.7) /million and among children (age <16 years) was 4.2 (95% CI 0.5-15.0) (table 3). In analysis mutually adjusted for age, sex and ethnicity, prevalence was lower among women than men (OR 0.79, 95% CI 0.64-0.97, p=0.027), highest in the 70-84 age-group (OR 8.5, 95% CI 5.7-12.5 compared to the 16-39 age-group, p<0.0001), and lower in the BME than white population (OR 0.57, 95% CI 0.39-0.84, p=0.002).

Mortality

120 of 462 patients died in 2049 years of follow up giving a mortality rate of 58.6 /1000 person-years (table 4). Mortality was 4.8% (95%CI 3.2-7.2%) at 30-days, 9.9% (95%CI 7.5-13.0%) at 90-days, and 13.6% (95%CI 10.8-17.2%) at 1-year. Mortality was similar in males and females (Hazard ratio (HR) 0.8, 95% CI 0.6-1.2), higher with increasing age (HR for ≥85-years compared to 16-39 age-group 16.1, 95% CI 3.6-72.8, p-trend<0.0001). Mortality was highest in the group with unknown ethnicity (HR compared to whites 1.8, 95% CI 1.1-3.0), intermediate in whites, and appeared lowest in the BME group (HR 0.5, 95% CI 0.1-2.0) however there were only 2 deaths in this group. Mortality was higher in people identified only in HES-only compared with cases identified in CPRD with or without a HES diagnosis (HR 2.3, 95% CI 1.6-3.4, p<0.0001). This is shown in the Kaplan-Meier survival estimates for people with Granulomatosis with polyangiitis presented separately by source of case ascertainment which are shown in figure 2.

Estimated UK incidence

We estimate that at present each year in the UK there will be 700 new cases of Granulomatosis with polyangiitis, of whom 95 will die within 12 months. We estimate there are 8750 people living with Granulomatosis with polyangiitis in the UK in 2016.

Sensitivity Analysis (Use of data from all CPRD practices)

We identified 574 incident cases of Granulomatosis with polyangiitis during 1995-2014 in the whole CPRD (see online data supplementary figure A). Similar to CPRD-HES, there was a slight male predominance (54.9% male), and a

similar age at diagnosis (mean 58.6(SD 15.8) years. The estimated incidence was lower at 8.1 (95% CI 7.5-8.8) /million person-years. The effect of age and gender were similar (see supplementary data tables B&C). The incidence was stable throughout the period. The mortality rate was also lower: 125 patients of 574 died in 3002.2 years of follow up, giving a mortality rate of 41.6 /1000 person-years with mortality 2.1% at 30-days, 4.0% at 90-days, and 8.5% at 1-year.

DISCUSSION

Main findings

Our estimate of the incidence of Granulomatosis with polyangiitis in the UK is 11.8/million person-years, which is higher than previous estimates. The incidence has been stable from 2000 onwards, and is higher in men than women and is highest in older age-groups. The incidence was lower in the BME than white population in crude analyses, but this was partially explained by the different age and sex distribution of the BME population. The prevalence of Granulomatosis with polyangiitis was 134.9/ million in 2013, higher in men than women, and highest in the 70-85 age-group. Prevalence was lower in BME than white people, and this was again partially explained by confounding by age and sex. Mortality among people with Granulomatosis with polyangiitis was 14% at 1 year, and was significantly worse among those identified in hospital than in GP records.

Strengths:

To our knowledge this is the first study that has combined general-population-based and hospital case ascertainment. Our comparator analysis with case ascertainment from primary care records (CPRD-only) shows that case ascertainment using both primary and secondary care is a more sensitive method, and that it allows identification of an important group of patients with the highest mortality. Compared to case ascertainment only in secondary care, this method is also more sensitive, and identifies a group of patient with lower mortality.

To our knowledge, it is one of the largest studies of Granulomatosis with polyangiitis ever conducted. The largest studies both report cases identified prior to 2000 and identified cases using hospital discharge registers in Sweden

(n=1938) and Finland (n=492)[6–8], which are difficult to compare to our study as they both report a rising incidence during their study periods, which is at least partially explained by increased recognition of the condition due to the introduction of routinely available ANCA-testing during the 1990s. The largest recent study was the previous CPRD study, which identified 295 incident cases,[3] and our analysis of 462 cases has given the analyses greater power, allowing estimates such as incidence and prevalence in the paediatric (<16 years) population. This study is also the first in the CPRD, and second in the UK, to include ethnicity, and provide predictions for planning health services for the BME population.

Limitations

The main limitation of this study is lack of power, which limits all studies of rare diseases. However we have used the largest existing database of linked primary and secondary care records worldwide. Secondly this study has limitations inherent in research using large databases of routinely collected healthcare information. In particular, the validity and date of each diagnosis could not be verified externally. However, the previous CPRD study examined the anonymised letters from 31 patients coded as G754, and the diagnosis of Granulomatosis with polyangiitis was confirmed in 28 of those giving a positive predictive value (PPV) of 90%[3]. An additional 1 (4%) case had a diagnosis of microscopic polyangiitis, and in 2 (7%) the diagnosis could not be confirmed but it was likely they had some form of vasculitis. Our previous study using multiple sources of case ascertainment to identify incident cases of ANCA-associated vasculitis,[9] found searching inpatient discharges using ICD-10 code M313 identified 119 cases in our local hospital between 2007 and 2013. Of these, review of the medical notes confirmed a diagnosis of Granulomatosis with polyangiitis in 102, giving a PPV of 86%. A further 10 (8%) cases had a diagnosis of microscopic polyangiitis, and only 7 (6%) had no evidence of systemic vasculitis. In both instances, the number of missed cases could not be estimated, however we would expect that some patients were only ever coded as 'vasculitis' and missed by our search. It is most likely that our results are an under-estimate of the true incidence and prevalence.

It is also possible that some prevalent cases may have been wrongly identified as incident, which would falsely increase our estimate of incidence. However, GP

records should record previous significant diagnoses even in new registrations, and most relapses are in first year after diagnosis, meaning that we will have excluded most prevalent cases from our incidence estimate by requiring one year of active follow up prior to diagnosis. This method is the same as used previously,[3] and has been validated in a range of other chronic conditions in the CPRD.[4]

Fits in with other literature:

Overall, our estimate of incidence is higher than in previous studies and we think this was due to the more sensitive strategy of case ascertainment. In the last 10 years in Europe estimates (which are in studies of adults only) have ranged from 4.9/million adult-years in a hospital-based study in Southern Spain to 11.3/million adult-years in a hospital-based study in the UK (Norfolk),[6,10–14] although it is unclear whether differences in methods of case ascertainment or true geographic differences account for the variation. Our incidence in the CPRD-only population of 8.1 (95% CI 7.5-8.8)/ million person-years was very similar to the previous CPRD study conducted 1990-2005 where the incidence was estimated to be 8.3 (95% CI 7.5-9.4),[3] and shows how incidence is under-estimated unless cases are ascertained from secondary as well as primary care. Our findings show a lower incidence in women compared to men (which is in keeping with many,[3,10–13,15] but not all,[6,16,17] previous smaller studies) and confirm the age-group with the highest incidence to be around 60-70 years.[3,13]

The incidence rose rapidly in both CPRD and HES databases in the first 5 years after inception of each database (1987 in the CPRD and 1997 in HES) – which is a finding common to database studies in other conditions and may reflect data collection practices.[18] After these times, each database shows a stable incidence. We did not find evidence of a cyclical pattern of incidence, which has been seen in other studies.[10]

A recent study has shown that CPRD-HES contain the same ethnic mix as the UK in the 2011 census, and that they provide reliable records of self-reported ethnicity.[19] Reliability is much higher for white vs BME differentiation than between BME ethnic groups, so we treated ethnicity as a binary variable (white vs BME) for most analyses. Frequency of ethnicity recording also increased after

1 April 2006 when recording ethnicity was introduced to the UK NHS Quality and outcomes framework (QOF); however this only accounts for 22 of our 462 incident cases. We therefore have incomplete ethnicity data; available for 90.7% of cases, and only 76.8% of the denominator population. We used a "worst case scenario" approach and re-coded the unknown group to white. This approach also reflects the 2011 census results, resulting in 86.2% of the denominator population being white compared to 85.2% in the 2011 census. We found that the incidence was lower in BME compared to whites – but this was not statistically significant at the 5% level. This is similar to our findings in a local hospital cohort of people with all types of ANCA-associated vasculitis (and complete ethnicity data), where the incidence rate ratio adjusted for age and sex for BME compared to white people was 0.7, 95% CI 0.3-1.5, p=0.3).[19] However, we found the prevalence of Granulomatosis with polyangiitis was lower in BME than white populations even after adjustment for age and sex (adjusted OR 0.6, p=0.004). It is possible that a survival bias explains our findings if the disease is more severe in the BME population, or that we only captured the more severe end of the spectrum for this group, however we were unable to analyse the mortality rate difference between the White and BME groups, due to small numbers as there were only two deaths (among 29 patients) in the BME group. If the UK population ages as predicted in the coming years and the age structure of the BME and white populations become more similar, we would expect to see an increase in the number of incident cases of Granulomatosis with polyangiitis, and an increasing proportion from BME ethnic groups.

Our estimate of mortality at 1-year using CPRD-HES is higher than our estimate of mortality in the CPRD-only, and as high as reported estimates from hospital studies. Increased mortality in cases ascertained from HES compared to CPRD has been found in other conditions,[20] which shows the importance of ascertaining cases from secondary care data in addition to GP records, as patients ascertained in hospital are more likely to be sicker. The lowest reported 1-year mortality of 1-7% comes from registry studies, or highly selective (tertiary-referral) centres,[21,22] where patients also have the lowest average age. An intermediate level of 5-11% is found in community studies.[12,23] And the highest mortality of 14-21% is reported from hospitals, [7,9,24,25] and clinical trials of patients with severe disease.[26] The highest mortality is in the

first year after diagnosis, and we did not find a bimodal increase in mortality after 8 years as reported by Luqmani and colleagues.[23] A recent systematic review of mortality confirms ANCA-associated vasculitis has the highest mortality of the autoimmune rheumatic conditions.[27]

Conclusion

Our findings suggest that incidence of Granulomatosis with polyangiitis is stable over time, higher in men than women, and highest in older people. We estimate 700 incident cases in the UK during 2016. Despite improvements in medical care mortality is high, and higher than in other autoimmune rheumatic conditions. We predict 95 people in the UK will die this year within 12 months of their diagnosis. Estimates which do not include hospital data will underestimate both incidence and mortality.

KEY MESSAGES

- We estimate the incidence of Granulomatosis with polyangiitis in the UK is 11.8/million person-years.
- Incidence is similar in Black/Minority Ethnic and White populations, but prevalence remains lower in BME.
- Mortality among people with Granulomatosis with polyangiitis is 14% at 1 year.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest

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Table 1: Annual incidence of Granulomatosis with Polyangiitis 1997-2013 per million person-years

Year	Person- years	Incident cases	Incidence rate (95% CI)
1997	871999	8	9.2 (4.6-18.3)
1998	1269386	6	4.7 (2.1-10.5)
1999	1580708	11	7.0 (3.9-12.6)
2000	1959570	20	10.2 (6.6-15.8)
2001	2152646	18	8.4 (5.3-13.3)
2002	2359964	27	11.4 (7.8-16.7)
2003	2464465	33	13.4 (9.5-18.8)
2004	2548038	23	9.0 (6.0-13.6)
2005	2625711	34	12.9 (9.3-18.1)
2006	2684390	33	12.3 (8.7-17.3)
2007	2747254	38	13.8 (10.1-19.0)
2008	2776129	39	14.0 (10.3-19.2)
2009	2801004	42	15.0 (11.1-20.3)
2010	2760640	38	13.8 (10.0-18.9)
2011	2674883	33	12.3 (8.8-17.4)
2012	2602133	29	11.1 (7.7-16.0)
2013	2408704	30	12.5 (8.7-17.8)

Legend: cases ascertained from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES)

Overall incidence = 462 cases in 39,286,088 person-years of follow up, giving an incidence rate of 11.8 (95% CI 10.7-12.9)

Table 2: Adjusted Incidence of Granulomatosis with Polyangiitis 1997-2013 per million person-years

	Cases	Person-years	Crude Incidence rate (95% CI)	Crude Rate ratios (95% CI)	Adjusted Rate Ratios[1] (95% CI)	p value[2]
Overall	462	39,286,088	11.8 (10.7-12.9)			
Sex						
Male	262	19,518,443	13.4 (11.9-15.2)	1	1	<0.0001
Female	200	19,767,549	10.1 (8.8-11.6)	0.75 (0.62-0.90)	0.67 (0.56-0.81)	
Age group (years)						
Age 0-15	6	6,812,383	0.9 (0.4-2.0)	0.2 (0.1-0.6)	0.2 (0.1-0.6)	
Age 16-39	42	11,758,023	3.6 (2.6-4.8)	1	1	<0.0001
Age 40-54	100	8,825,359	11.3 (9.3-13.8)	3.2 (2.2-4.6)	3.1 (2.2-4.4)	
Age 55-69	190	6,875,272	27.6 (24.0-31.9)	7.8 (5.6-10.9)	6.8 (4.9-9.6)	
Age 70-84	112	4,113,670	27.2 (22.6-32.8)	7.6 (5.3-10.9)	6.4 (4.5-9.1)	
Age 85+	12	901,382	13.3 (7.6-23.4)	3.7 (2.0-7.1)	3.4 (1.8-6.4)	
Ethnicity						
White	390	24,040,059	16.2 (14.7-17.9)	1	1	<0.0001
BME	29	3,690,640	7.9 (5.5-11.3)	0.48 (0.33-0.70)	0.64 (0.44-0.94)	
Unknown	43	11,555,389	3.7 (2.8-5.0)	0.23 (0.17-0.31)	0.30 (0.22-0.41)	
Sensitivity analysis 1 with all Unknown coded as white						
White	433	35,595,448	12.2 (11.1-13.4)	1	1	0.3
BME	29	3,690,640	7.9 (5.5-11.3)	0.64 (0.44-0.94)	0.81 (0.56-1.18)	

Legend: cases ascertained from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES)

1 Mutually adjusted for other variables in the model (sex, age group and ethnicity)

2 From mutually adjusted analysis using the likelihood ratio test

Table 3: Prevalence of Granulomatosis with Polyangiitis in 2013 per million person-years

	Cases	Denominator	Crude prevalence	Crude Odds Ratios (95% CI)	p value	Adjusted Odds ratios[1] (95% CI)	p value[2]
Overall	359	2,661,668	134.9 (121.3-149.6)				
Male	189	1,311,314	144.1(124.3-166.2)	1		1	0.03
Female	170	1,350,349	125.9 (107.7-146.3)	0.87 (0.71-1.07)	0.201	0.79 (0.64-0.97)	
Age 0-15	2	481,893	4.2 (0.50-15.0)	0.1 (0.02-0.4)	0.002	0.1 (0.02-0.4)	
Age 16-39	33	811,940	40.6 (28.0-57.1)	1		1	
Age 40-54	83	583,600	142.2 (113.3-176.3)	3.5 (2.3-5.2)	<0.001	3.4 (2.3-5.2)	
Age 55-69	121	453,300	266.9 (221.5-318.9)	6.6 (4.5-9.7)	<0.001	6.1 (4.2-9.0)	<0.0001
Age 70-84	106	262,348	404.0 (330.8-488.7)	9.9 (6.7-14.7)	<0.001	8.5 (5.7-12.5)	
Age 85+	14	68,587	204.1 (111.6-342.5)	5.0 (2.7-9.4)	<0.001	4.2 (2.2-7.8)	
White	310	1,681,714	184.3 (164.4-206.0)	1		1	<0.0001
BME	29	457,887	63.3 (42.4-91.0)	0.34 (0.23-0.50)	<0.001	0.46 (0.32-0.68)	
Unknown	20	522,067	38.3 (23.4-59.2)	0.21 (0.13-0.33)	<0.001	0.22 (0.14-0.35)	
If all unknown ethnicity coded as white:							
White	330	2,203,781	149.7 (134.0-166.8)	1		1	
BME	29	457,887	63.3 (42.4-91.0)	0.42 (0.29-0.62)	<0.001	0.57 (0.39-0.84)	0.002

Legend: cases ascertained from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES)

1 Mutually adjusted for other variables in the model (sex, age group and ethnicity)

2 From mutually adjusted analysis using the likelihood ratio test

Table 4: Mortality of Granulomatosis with Polyangiitis 1997-2013 per thousand person-years

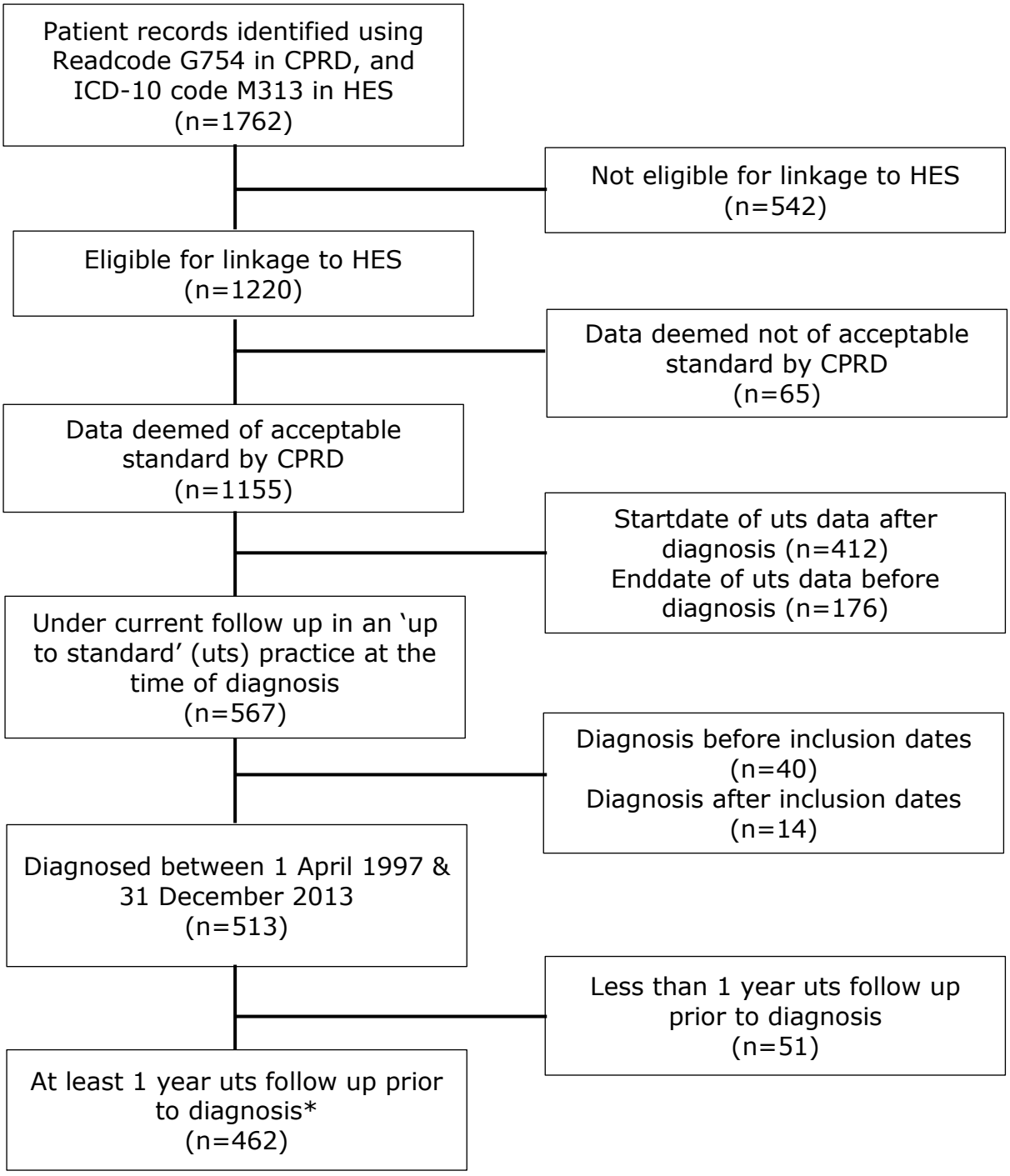
	Cases	Deaths	Years at risk	Crude mortality	Crude Odds Ratios (95% CI)	p value	Adjusted Odds ratios[1] (95% CI)	p value[2]
Overall	462	120	2049	58.6				
Male	262	76	1137	66.9	1		1	
Female	200	44	912	48.2	0.7 (0.5-1.1)	0.12	0.8 (0.6-1.2)	0.7
Age 0-15	6	0	16	0	-		-	
Age 16-39	45	2	156	12.8	1	<0.0001	1	<0.0001
Age 40-54	114	7	428	16.3	1.3 (0.3-6.5)		1.2 (0.3-5.9)	
Age 55-69	224	36	837	43.0	3.6 (0.9-15.1)		3.3 (0.8-13.8)	
Age 70-84	174	60	551	108.8	9.8 (2.4-40.1)		7.2 (1.7-29.7)	
Age 85+	30	15	60	249.0	24.4 (5.5-107)		16.1 (3.6-72.8)	
White	390	95	1794	53.0	1	<0.0001	1	0.03
BME	29	2	115	17.4	0.3 (0.08-1.3)		0.5 (0.1-2.0)	
Unknown	43	23	141	163.2	2.9 (1.8-4.5)		1.8 (1.1-3.0)	
CPRD	319	62	1621	38.2	1		1	<0.0001
HES-only	143	58	428	135.5	3.1 (2.2-4.5)	<0.0001	2.3 (1.6-3.4)	

Legend: cases ascertained from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES)

1 Mutually adjusted for other variables in the model (sex, age group and ethnicity and source of case ascertainment)

2 From mutually adjusted analysis, using the likelihood ratio test

Figure 1: Flow diagram of ascertainment of incident cases of granulomatosis with polyangiitis

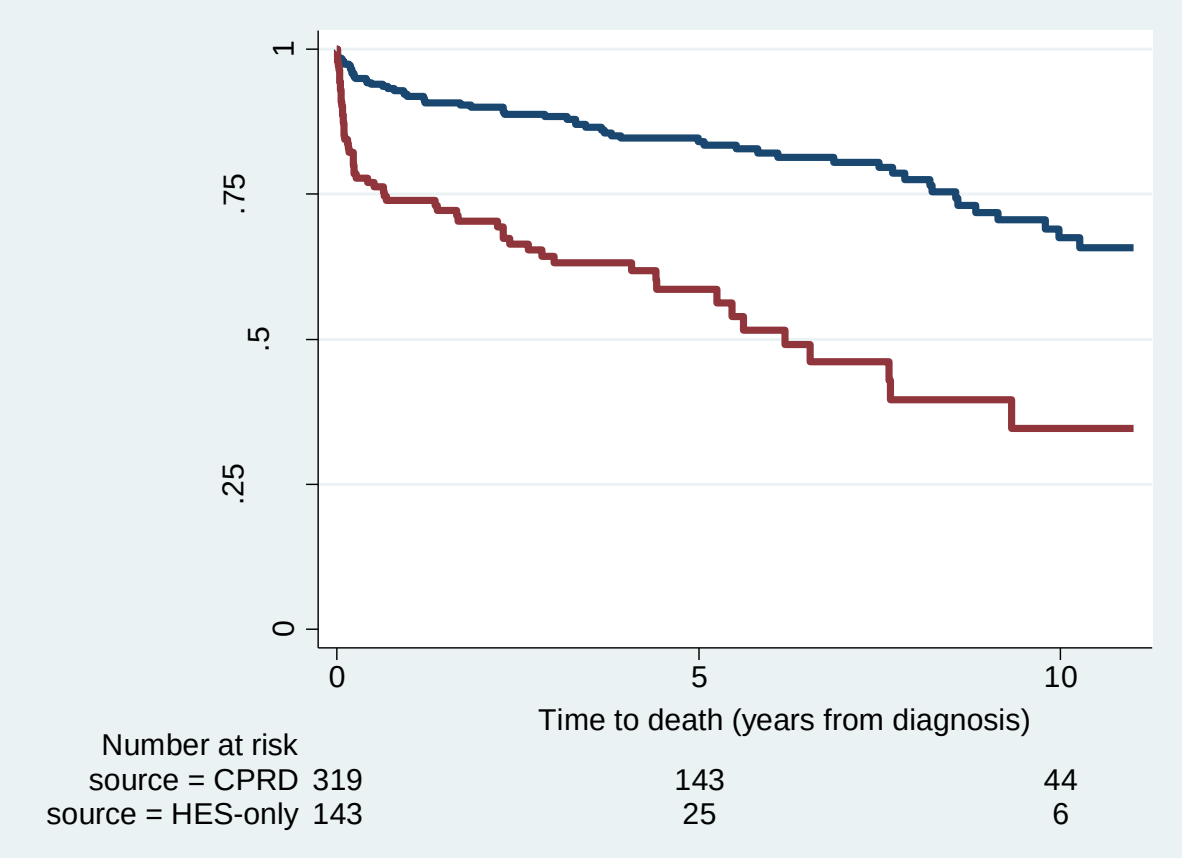


*in order to exclude prevalent cases

'acceptable' patient records and 'up to standard' practices are quality standards for research devised by the CPRD

legend: cases ascertained from the Clinical Practice Research Datalink and Hospital Episode Statistics (CPRD-HES)

Figure 2: Kaplan-Meier survival curve for Granulomatosis with Polyangiitis in the Clinical Practice Research Datalink (CPRD)



legend: Hazard ratio 3.21 (95% CI 2.23-4.64), p<0.001 (Schoenfeld's test to detect departure from non-proportional hazards; p=0.32)