Changing Incidence and Serotype Trends in ANCA-Associated Vasculitis: A 30-Year Population-Based Study in Norfolk, UK

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Abstract

Objectives

The ANCA associated vasculitides (AAV) are rare diseases with poor outcomes if untreated. Over a 30-year period we have investigated the changing incidence of AAV and its subtypes – Granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA), Proteinase 3 AAV (PR3 AAV), and Myeloperoxidase AAV (MPO AAV).

Methods

The study population included adults in the county of Norfolk, UK between 1991 and 2020. Diagnosis of AAV was made clinically and supported by EMA classification. Classification by ANCA subtype was possible from 2001. The overall incidence of clinical phenotypes GPA, MPA, EGPA, and serological phenotypes PR3 AAV and MPO AAV were analysed for temporal fluctuations and seasonality.

Results

From 1991-2020, the incidence (95% CI) of AAV, GPA, MPA, and EGPA was 25.1 (22.5, 27.9), 13.6 (11.7, 15.8), 8.5 (7.0, 10.2), and 3.0 (2.1, 4.0) per million person-years respectively. From 2001-2020, the incidence (95% CI) of PR3 AAV and MPO AAV was 11.5 (9.4, 13.9) and 11.7 (9.6, 14.1) per million person-years respectively. The temporal fluctuations in the incidence of EGPA and PR3 AAV were not significant. The incidence of GPA has a statistical periodicity of 9 years. The incidence of MPO AAV demonstrated a linear rise from 2001-2020 (R^2=0.66). Our patients are getting older at diagnosis. Seasonality was not observed.

Conclusion

This is the longest incidence study of AAV in the world. The incidence of GPA showed a 9-year periodicity. The incidence of MPO AAV rose steadily. Its relationship to older age at diagnosis needs formal exploration.

Keywords

Incidence

ANCA associated vasculitis

Granulomatosis with polyangiitis

Microscopic polyangiitis

Eosinophilic granulomatosis with polyangiitis

Proteinase 3 ANCA

Myeloperoxidase ANCA

Key Messages

1. The temporal fluctuation in the incidence of GPA demonstrates a 9-year periodicity.
2. The incidence of PR3 AAV is steady, but that of MPO AAV is rising steadily.
3. The age of patients at diagnosis is rising and may contribute to the rise of MPO AAV.

Introduction

Antibodies directed towards specific targets within the cytoplasm of neutrophils – antineutrophil cytoplasmic antibodies (ANCA) were discovered in 1985 (1). This discovery drastically changed the nature of diagnostics for the conditions that became linked with them as ANCA-associated vasculitis (AAV) in 1990 (2). The AAV are Granulomatosis with Polyangiitis (GPA), Microscopic Polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA) (3). They are universally accepted to be rare diseases with poor outcomes (4).

Initially, ANCA were classified as being either 'classical' (cANCA) or 'perinuclear' (pANCA) based on the immunofluorescence appearance (5). Over time, the 'classical' pattern was renamed by common use as 'cytoplasmic' (6). During the 1990s there was recognition that cANCA were directed against the third neutral serine proteinase (PR3 ANCA) and that pANCA were directed against myeloperoxidase (MPO ANCA) (7, 8). International consensus on testing and reporting of ANCA was established in 1999 (9).

The county of Norfolk, UK has demarcated boundaries and clear census data with very little migration out of the country, facilitating epidemiological research. We have previously published that the incidence of AAV may be rising in Norfolk (10). This could have been a true increase in incidence or increased awareness following the widespread introduction of ANCA testing. We have reappraised our data published over 30 years to investigate whether the incidence of AAV is indeed changing (10-13).

Methods

Population

The study period was 1991-2020. The denominator population between 1991 and 2010 was mapped to the Norfolk Health Authority which contained 77 general practices. The adult (>18 years) population numbers were available in 5-year bands. The Norfolk Health Authority was disbanded in 2002. Data were available from the ONS allowing for population to be estimated up to 2010. From 2011 the denominator adult population (>18 years) was estimated from the national census for the post codes NR1 to NR30. The two different methods mapped roughly to the same geographical area of the county of Norfolk. These two different methods have been described in detail in previous papers (10, 11). During the period of the study there has been a gradual increase (0.66%/annum) in the overall population of Norfolk. In the 2021 census, 94.7%

of the population self-identified as 'White', which is higher than the national average (81.0%) (data from https://www.norfolkinsight.org.uk/, accessed on 12/11/2025). In line with the general UK population there has been an increase in the proportion of people aged > 65 years.

Cases

A register of all newly diagnosed cases of vasculitis was maintained during the period 1991-2020. Over time, this register has been maintained variably. To begin with it was maintained with patient cards, giving way to a Microsoft Access database. The current form of the database is prospectively maintained as part of our requirement as a centre providing specialized services to allow quarterly data returns to NHS England. The register is stored as a password-protected file and stored on the hospital server with access only to the vasculitis team. A diagnosis of AAV was established based on a clinical presentation of small or medium vessel vasculitis supported by serology and/or histology. The final disease classification was established using the EMA algorithm (14); this provides a standardized method for the application of the ACR 1990 criteria for GPA, EGPA, PAN, combined with the Chapel Hill Consensus Conference (CHCC) definitions for GPA, MPA, EGPA and PAN. No ethics approval was sought. All the patients were under our care. No experimental interventions were performed and no patient identifiable data was needed for this work.

ANCA subtype

For the analysis related to ANCA subtype, reliable ELISA testing was available in a routine laboratory using commercial kits from 2001 for PR3 and MPO. The assays used by the laboratory during the period of the study varied. Positive and negative results have been interpreted as reported at the time, using the threshold titres provided by the manufacturer. Positive ELISA results were not routinely confirmed by indirect immunofluorescence.

Outcomes of interest

The outcomes of interest were – i) the overall and disease specific incidence of AAV and its clinical phenotypes - GPA, MPA, EGPA, as well as serotypes - PR3 AAV and MPO AAV; ii) temporal fluctuations in the incidence in the context of individual years and seasons; iii) whether any fluctuations were linear or periodic.

Seasons

December to February were considered as Winter, March to May as Spring, June to August as Summer, and September to November as Autumn.

Statistics

Incidence was calculated using the formula $i = {}^{n}/_{e}$, where n was the number of events and e was the exposure in person-years. Confidence intervals (CI) were calculated using Byar approximation for a Poisson distribution using the formulae $i_{lower} = n\left(1 - \frac{1}{9(n)} - \frac{z}{3\sqrt{n}}\right)^3$, and $i_{upper} = (n+1)(1 - \frac{1}{9(n+1)} + \frac{z}{3\sqrt{n+1}})^3$, where z was the value at the 97.5 percentile, accepted to be 1.96. The statistical significance of the difference between the observed and expected numbers of patients was tested using the χ^2 test. The expected number of patients for each period (n_p) was calculated using the formula $n_p = \frac{P_p \times n_s}{P_s}$, were P_p was the at-risk population for the period, P_s was the at-risk population for the study, and n_s was the total number of events in the study. If the number of expected events were <5/year, we combined data from consecutive years to get ≥5 expected events. If the χ^2 test was significant for a difference, the incidence was tested for periodicity using the 3-year moving average and linear regression. The R^2 was used to understand the effect of time over diagnosis. If there was suggestion of visual periodicity, this was formally tested using the autocorrelation function with 15 lags. The Kruskal-Wallis test was used to compare the age of the patients by decade of the study, AAV phenotype, and ANCA subtype. The sex distribution over the 3 decades and the seasonality of diagnosis were both tested using the χ^2 test.

Results

338 individuals (175 Male) were diagnosed over a population exposure of 13 489 862 person-years (Table 1). The incidence (95% confidence interval (CI)) of all AAV was 25.1 (22.5, 27.9) per million person-years. 184 had GPA, 114 had MPA, and 40 had EGPA. The incidence (95% CI) of GPA, MPA and EGPA was 13.6 (11.7, 15.8), 8.5 (7.0, 10.2), and 3.0 (2.1 4.0) per million person-years respectively. Reliable ANCA subtype testing was available from 2001 for a population exposure of 9 230 862 person-years. 106 were PR3 ANCA positive, 108 were MPO ANCA positive, and 37 were ANCA negative. Of the 37 ANCA negative individuals, 19 had EGPA, 15 had GPA, and

3 had MPA. The overall incidence (95% CI) of PR3 AAV, MPO AAV, and ANCA negative AAV was 11.5 (9.4, 13.9), 11.7 (9.6, 14.1), and 4.0 (2.8, 5.5) per million person-years respectively.

Chi-squared test

There was a significant difference between the observed and expected numbers of patients diagnosed with all AAV ($p<0.01$), and GPA ($p<0.02$). For MPA, the expected annual numbers were <5, so the analysis was performed in 2-year bands. There was a difference between the observed and expected number of events ($p<0.01$). For EGPA, the expected annual numbers were <5, so the analysis was performed in 5-year bands. There was no difference between observed and expected events ($p=0.60$). There was a significant difference between the observed and expected events for MPO AAV ($p<0.01$), but not for PR3 AAV ($p=0.06$).

Linear regression and periodicity

Linear regression to test effect of time on diagnosis was done for AAV, GPA, MPA and MPO AAV (Figure 1). The R^2 were 0.30, 0.22, 0.25, and 0.65 respectively.

The moving averages for AAV, GPA, MPA and MPO AAV are as in Figure 1. There was a suggestion of periodicity for GPA during the study period. The peaks were 9-years apart: 16.3 (10.1, 24.9)/million person-years in 1996-98, 16.7 (10.6, 25.7)/million person-years in 2005-07, and of 22.8 (15.6, 32.1)/million person-years in 2014-2016. There was no obvious periodicity noticed for all AAV, MPA and MPO AAV.

Autocorrelation function confirmed a statistical periodicity at 7-9 years with values of 0.40 at year 7 and 0.42 at year 9 (upper confidence interval 0.36) (Figure 2).

Age and sex

The median (IQR) age of the whole cohort was 67.9 (17.5). The median ages of the cohort according to decade of diagnosis, AAV phenotype, and ANCA subtype were as in Table 2. Pairwise comparison showed that patients were older in the decade 2011-2020 compared to 1991-2000 ($p=0.003$) and 2001-2010 ($p=0.025$). There was no difference in age between decades 1991-2010 and 2001-2010 ($p=1.0$). Pairwise comparisons for AAV phenotype showed that patients with MPA were older than GPA ($p=0.036$) and EGPA ($p<0.001$); patients with GPA were older than patients with EGPA ($p=0.005$). Pairwise comparisons for ANCA subtype showed that

patients with MPO AAV were older than PR3 AAV (p=0.005) and ANCA negative patients (p<0.001). There was no difference in age between patients with PR3 AAV and ANCA negative patients (p=0.119). There were 175 male and 163 female individuals in the cohort with no variation in sex distribution across the three decades (p=0.43).

Seasonality

Of the 338 patients, the numbers diagnosed in Spring, Summer, Autumn, and Winter were 81, 79, 74 and 104, respectively (Table 3). This variation was not statistically different (p=0.11).

Discussion

This is the longest epidemiological study of the incidence of AAV in the world (Table 4). Within an at-risk adult population of nearly 13.5 million person-years, the incidence (95% CI) of AAV was 25.1 (22.5, 27.9) per million person-years. The aim of the study was to evaluate temporal trends in the incidence of AAV and its subtypes. We found that the incidence of AAV does fluctuate over time. The fluctuations are a function of changes in the incidence of GPA and MPA, but not EGPA. The serotype of MPO AAV is becoming commoner. An incidence study of AAV from Cantabria, Spain covering the same period did not report a similar finding (15). The incidence of GPA rose during the study. A statistical periodicity of 9 years was demonstrated using autocorrelation function. We have previously reported that the epidemiology of GPA and MPA appeared to be different when studied over 12 years (13). We do not currently have an explanation for this periodicity. It has not been observed in studies from other parts of the world. Rathmann et al from Sweden (16), and Berti et al from the USA (2), both reported the incidence of GPA to be stable over 23 and 20 years respectively. An earlier study from Sweden with the largest at-risk population of >200 million person-years reported that the incidence of GPA steadily rose from 3.3 (2.8, 3.9) per million person-years between 1975 and 1984, to 7.7 (6.9, 8.5) per million person-years between 1985 and 1990, to 11.9 (11.2, 12.6) per million person-years between 1991 and 2001 (17). They did not test for periodicity. This will need further exploration in even longer cohorts. We also found a steady rise in the incidence of MPO AAV between 2001 and 2020. None of the long-term epidemiology studies in Table 4 have described this and so it represents a new finding. The ratio of PR3 AAV : MPO AAV fell from 1.7 in 2001-2010 to 0.8 in 2011-2020, 2010 being the year in which the ratio reversal happened (Supplementary figure 1). Although not formally explored, a potential explanation could be that our population is growing older and MPO AAV is commoner in the older population (Table 2). This remains an area of future research.

Our study has several strengths. We work in a centre that provides secondary care to a stable population with one hospital in our denominator area. While there is a possibility that patients at the periphery of our catchment area may visit other hospitals, all ANCA testing and histopathology for the possible alternative hospitals is performed in our centre, allowing for as near complete as possible capture of cases. Our centre has specialist service provision for immunology, histopathology, renal medicine, chest medicine and rheumatology culminating in a nationally recognised centre for vasculitis specialist care, as evidenced by the multi-disciplinary authorship. All the cases have been verified by a physician, and the diagnosis has been supported by imaging, biopsy or serology. The diagnostic labels have been arrived at using internationally validated criteria and diagnostic algorithms (14). Of all the studies listed in Table 4, our study has the longest duration and the largest study of all the AAV. It is also the only study that has looked at the separate incidence of the two serotypes of AAV. We acknowledge the limitation that we may have missed cases that were diagnosed while they were out of the county on holiday, or if they died acutely prior to diagnosis. We also acknowledge that there is a change in the methodology during the study period. After the Norfolk Health Authority was disbanded, we used national census data to estimate the at-risk population. The at-risk population numbers in Table 1 demonstrate a reassuringly linear growth, rising from 4.26 million (1991-2000) to 4.53 million (2001-2010) to 4.7 million (2011-2020), suggesting that the change in methodology should not have affected our results. Another limitation of this study is our inability to produce age-specific incidence for the entire 30-year period because we no longer have age-specific details of the at-risk population in the first two decades. The change in incidence may therefore be a function of demographic change rather than underlying disease risk.

ANCA testing was in its infancy in the first decade of our study. A formal consensus on the testing and reporting of ANCA was only reached in 1999 (9). Our laboratory techniques incorporated this formally soon after and we have reliable results from 2001. It is interesting to note that this does not seem to have resulted in an immediate change in the incidence of AAV (Table 1). Doubtlessly, although the introduction of an easily performed laboratory test has made the diagnosis easier to achieve, clinical acumen supported by histology appears to have been enough to make a diagnosis of these rare diseases. Over time, improvement in assays, standardisation of ANCA testing, laboratory accreditation processes have meant that ANCA testing is easier, faster and more reliable towards the end of the study than when it was introduced, the diagnostic influence of this gradual change cannot be discounted. It is also possible that in the early part of our study, ANCA were not routinely checked for in elderly patients who were acutely unwell, and this may have resulted in a spuriously lower incidence. MPA was not formally classified as a distinct

disease till 1994 (18). We have used consistent classification criteria/definitions throughout the study. Although the EMA criteria were published in 2007, they built on the existing ACR 1990 criteria and the CHCC 1994 definitions. For patients in the initial years, we reclassified using the EMA algorithm, resulting in eight PAN patients being reclassified as MPA (19).

Our cohort is getting older. The median age of our patients in the third decade of the study was higher than in the previous years. The rural and coastal nature of our county serves as a retirement hotspot attracting migration of older population. Between 2011 and 2020, the proportion of our denominator population that was 65 years or older grew from 26% to 30%. In the coastal postcodes of NR25 and NR26, >40% of the population is now 65 years or older. The peak incidence of AAV between 1988 and 2010 was in the age band 65-74 (13). The peak incidence in the decade 2011-2020 was in the age band 81-90 (10). Better health provision for the elderly, improved diagnostics, and development of specialist services may have contributed to the rise in incidence and median age.

We looked for and did not find a seasonal variation on diagnosis. Rathmann et al found a modest rise in the incidence in spring as compared to winter (16). Our patients presented more in winter than in any other single season. Seasonality can be difficult to establish in AAV if there is a long prodromal phase, as sometimes may be the case.

In conclusion, our study found that GPA has a 9-year periodicity. There has been a change in the serotype of the AAV in Norfolk with a switch from predominant PR3 AAV to MPO AAV. The aging population may have caused a rise in the incidence of AAV, as well as the serotype switch to MPO AAV. This relationship has not been formally tested and may be a function of the aging population. The introduction of ANCA testing did not seem to affect the incidence.

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Conflict of interest

The authors have no direct conflict of interest pertaining to this work. But the details of individual affiliations are as under.

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Data availability

Data can be made available on communicating with the corresponding author for collaborative scientific work.

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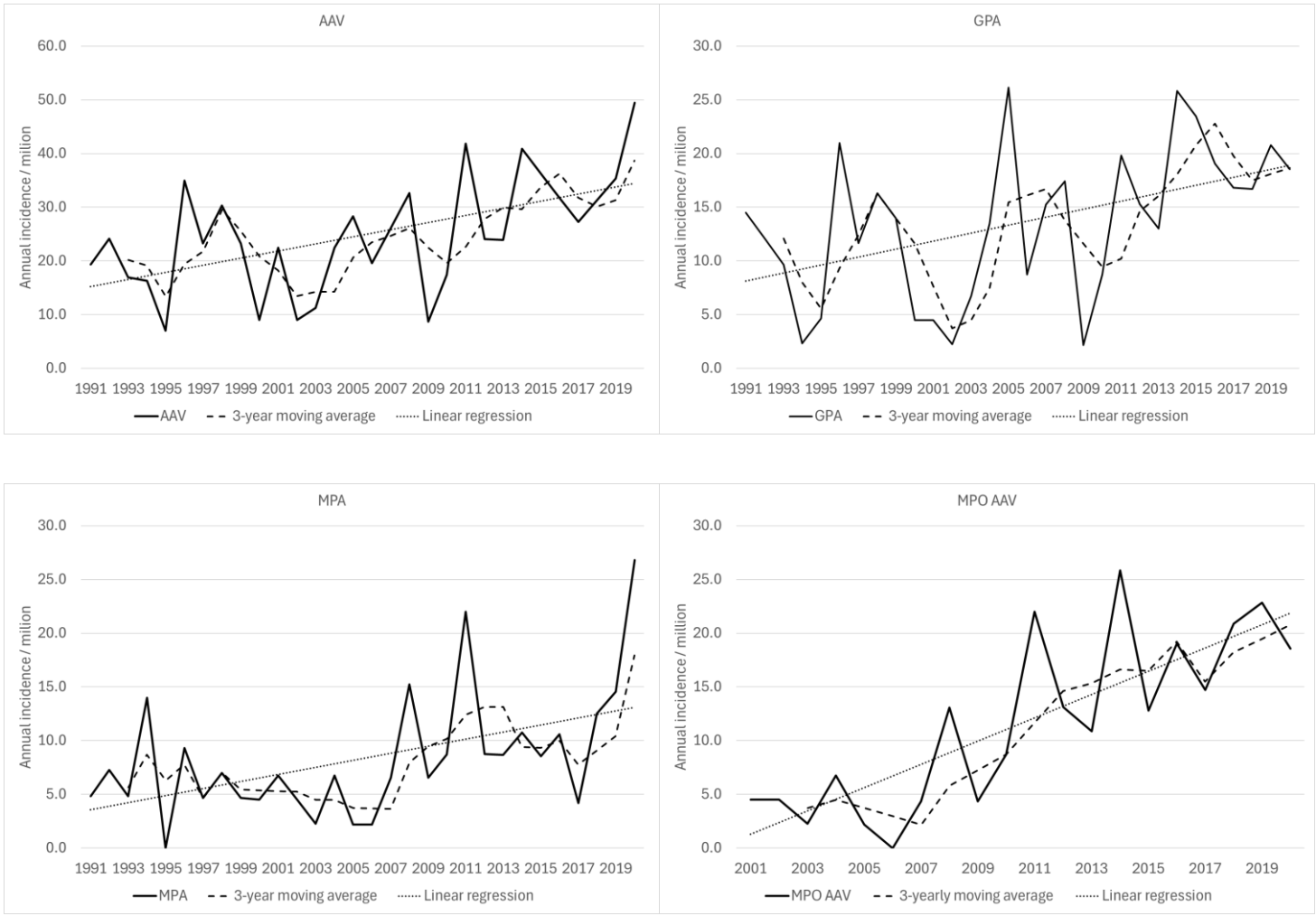

Figure 1 Annual incidence with 3-yearly moving average and linear regression line: Top left- AAV, R^2=0.30; Top right- GPA R^2=0.22; Bottom left- MPA, R^2=0.22; Bottom right- MPO AAV, R^2=0.65

ALT TEXT: 4 graphs in a 2 x 2 configuration of the yearly incidence of AAV, GPA, MPA and MPO AAV. They show a gentle rise for AAV and MPA without an obvious periodicity, but a 9-year periodicity for GPA. The graph for MPO AAV shows a steeper rise as compared to GPA and MPA.

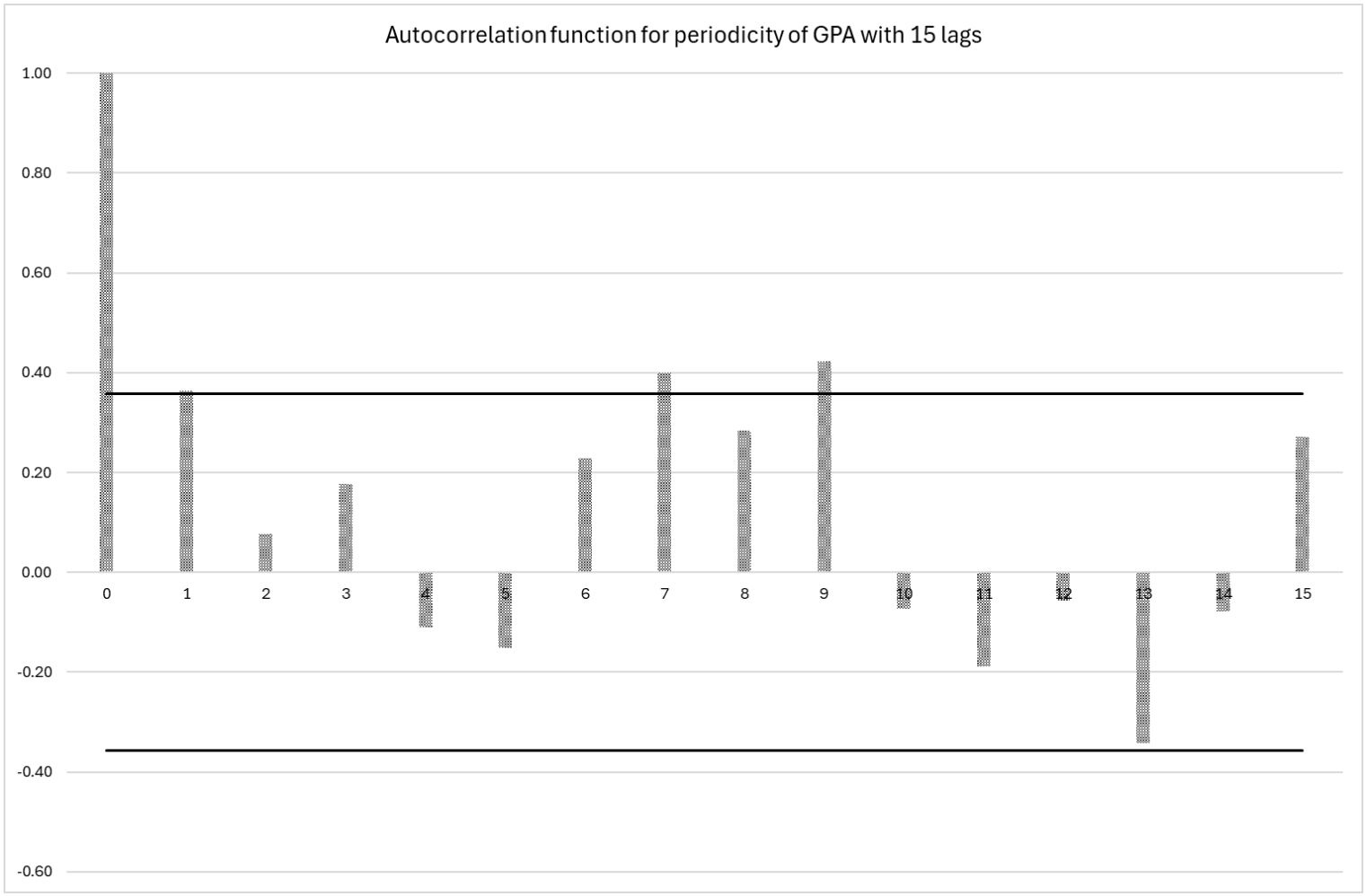

Figure 2 Autocorrelation function for periodicity of GPA. The autocorrelation values on the Y-axis are computed for the number of lags on the X-axis. The horizontal bands are the upper and lower confidence bands

ALT TEXT: A graph showing the autocorrelation function as a column on the X-axis with 95% confidence intervals.

Table 1 Incidence by year, decade and whole cohort for AAV by subtypes

Year	Population (n)	GPA (/million (95% CI))	MPA(/million (95% CI)	EGPA(/million (95% CI))	PR3 AAV (/million (95% CI))	MPO AAV(/million (95% CI))	All AAV(/million (95% CI))
1991	413 500	14.5 (5.3, 31.6)	4.8 (0.5, 17.5)	0.0			19.3 (8.3, 38.1)
1992	413 500	12.1 (3.9, 28.2)	7.3 (1.5, 21.2)	4.8 (0.5, 17.5)			24.2 (11.6, 44.5)
1993	413 500	9.7 (2.6, 24.8)	4.8 (0.5, 17.5)	2.4 (0.0, 13.5)			16.9 (6.8, 34.9)
1994	429 000	2.3 (0.0, 13.0)	14.0 (5.1, 30.4)	0.0			16.3 (6.5, 33.6)
1995	429 000	4.7 (0.5, 16.8)	0.0	2.3 (0.0, 13.0)			7.0 (1.4, 20.4)
1996	429 000	21.0 (9.6, 39.8)	9.3 (2.5, 23.9)	4.7 (0.5, 16.8)			35.0 (19.6, 57.7)
1997	429 000	11.7 (3.8, 27.2)	4.7 (0.5, 16.8)	7.0 (1.4, 20.4)			23.3 (11.2, 42.9)
1998	429 000	16.3 (6.5, 33.6)	7.0 (1.4, 20.4)	7.0 (1.4, 20.4)			30.3 (16.1, 51.8)
1999	429 000	14.0 (5.1, 30.4)	4.7 (0.5, 16.8)	4.7 (0.5, 16.8)			23.3 (11.2, 42.9)
2000	444 500	4.5 (0.5, 16.2)	4.5 (0.5, 16.2)	0.0			9.0 (2.4, 23.0)
1991-2000	**4 259 000**	**11.0 (8.1, 14.7)**	**6.1 (4.0, 8.9)**	**3.3 (1.8, 5.5)**			**20.4 (16.4, 25.2)**
2001	444 500	4.5 (0.5, 16.2)	6.7 (1.4,19.7)	11.2 (3.6, 26.3)	6.7 (1.4, 19.7)	6.7 (1.4, 19.7)	22.5 (10.8, 41.4)
2002	444 500	2.2 (0.0, 12.5)	4.5 (0.5, 16.2)	2.2 (0.0, 12.5)	2.2 (0.0, 12.5)	4.5 (0.5, 16.2)	9.0 (2.4, 23.0)
2003	444 500	6.7 (1.4, 19.7)	2.2 (0.0, 12.5)	2.2 (0.0, 12.5)	2.2 (0.0, 12.5)	2.2 (0.0, 12.5)	11.2 (3.6, 26.3)
2004	444 500	13.5 (4.9, 29.4)	6.7 (1.4, 19.7)	2.2(0.0, 12.5)	11.2 (3.6, 26.3)	6.7 (1.4, 19.7)	22.5 (10.8, 41.4)
2005	459 000	26.1 (13.5, 45.7)	2.2 (0.0, 12.1)	0.0	19.6 (8.9, 37.2)	2.2 (0.0, 12.1)	28.3 (15.1, 48.4)
2006	459 000	8.7 (2.3, 22.3)	2.2 (0.0, 12.1)	8.7 (2.3, 22.3)	6.5 (1.3, 19.1)	0.0	19.6 (8.9, 37.2)
2007	459 000	15.3 (6.1, 31.4)	6.5 (1.3, 19.1)	4.4 0.5, 15.7)	15.3 (6.1, 31.4)	4.4 (0.5, 15.7)	26.1 (13.5, 45.7)
2008	459 000	17.4 (7.5, 34.3)	15.3 (6.1, 31.4)	0.0	15.3 (6.1, 31.4)	13.1 (4.8, 28.5)	32.7 (18.3, 53.9)
2009	459 000	2.2 (0.0, 12.1)	6.5 (1.3, 19.1)	0.0	2.2 (0.0, 12.1)	4.4 (0.5, 15.7)	8.7 (2.3, 22.3)
2010	459 000	8.7 (2.3, 22.3)	8.7 (2.3, 22.3)	0.0	8.7 (2.3, 22.3)	8.7 (2.3, 22.3)	17.4 (7.5, 34.3)
2001-2010	**4 532 000**	**10.6 (7.8, 14.0)**	**6.2 (4.1, 8.9)**	**3.1 (1.7, 5.2)**	**9.0 (6.5, 12.3)**	**5.3 (3.4, 7.9)**	**19.9 (16.0, 24.4)**
2011	454 315	19.8 (9.0, 37.6)	22.0 (10.5, 40.5)	0.0	17.6 (7.6, 34.7)	22.0 (10.5, 40.5)	41.8 (25.2, 65.3)
2012	457 327	15.3 (6.1, 31.5)	8.7 (2.4, 22.4)	0.0	10.9 (3.5, 25.5)	13.1 (4.8, 28.6)	24.1 (12.0, 43.0)
2013	460 417	13.0 (4.8, 28.4)	8.7 (2.3, 22.2)	2.2 (0.0, 12.1)	10.9 (3.5, 25.3)	10.9 (3.5, 25.3)	23.9 (11.9, 42.8)

2014	464 507	25.8 (13.3, 45.1)	10.8 (3.5, 25.1)	4.3 (0.5, 15.5)	10.8 (3.5, 25.1)	25.8 (13.3, 45.1)	40.9 (24.6, 63.9)
2015	468 653	23.5 (11.7, 42.0)	8.5 (2.3, 21.9)	4.3 (0.5, 15.4)	17.1 (7.4, 33.6)	12.8 (4.7, 27.9)	36.3 (21.1, 58.1)
2016	472 412	19.1 (8.7, 36.2)	10.6 (3.4, 24.7)	2.1 (0.0, 11.8)	12.7 (4.6, 27.6)	19.1 (8.7, 36.2)	31.8 (17.8, 52.4)
2017	476 130	16.8 (7.2, 33.1)	4.2 (0.5, 15.2)	6.3 (1.3, 18.4)	8.4 (2.3, 21.5)	14.7 (5.9, 30.3)	27.3 (14.5, 46.7)
2018	479 078	16.7 (7.2, 32.9)	12.5 (4.6, 27.3)	2.1 (0.0, 11.6)	10.4 (3.4, 24.4)	20.9 (10.0, 38.4)	31.3 (17.5, 51.6)
2019	481 128	20.8 (10.0 38.2)	14.5 (5.8, 30.0)	0.0	12.5 (4.6, 27.1)	22.9 (11.4, 40.9)	35.3 (20.6, 56.6)
2020	484 895	18.6 (8.5. 35.2)	26.8 (14.3, 45.8)	4.1 (0.5, 14.9)	26.8 (14.3, 45.8)	18.6 (8.5, 35.2)	49.5 (31.7, 73.6)
2011-2020	**4 698 862**	**18.9 (15.2, 23.3)**	**12.8 (9.7, 16.4)**	**2.6 (1.3, 4.5)**	**13.8 (10.7, 17.6)**	**18.1 (14.4, 22.4)**	**34.3 (29.2, 40.0)**
1991-2020*	**13 489 862**	**13.6 (11.7, 15.8)**	**8.5 (7.0, 10.2)**	**3.0 (2.1, 4.0)**	**11.5 (9.4, 13.9)***	**11.7 (9.6, 14.1)***	**25.1 (22.5, 27.9)**

*The data for PR3 and MPO AAV were calculated for 2001-2020 over 9 230 862 person-years

Table 2 Median age by decade of diagnosis

	Number of cases (n)	Median (IQR) age at diagnosis (years)	Kruskal-Wallis test
Decade			χ^2=13.4 (df=2); p<0.001
1991-2000	87	65.4 (15.8)	
2001-2010	90	64.1 (20.3)	
2011-2020	161	71.4 (19.2)	
AAV phenotype			χ^2=21.7 (df=2); p<0.001
GPA	184	67.6 (17.4)	
MPA	114	71.4 (15.7)	
EGPA	40	58.6 (21.2)	
ANCA subtype			χ^2=21.5 (df=2); p<0.001
PR3 positive	106	64.9 (21.8)	
MPO positive	108	73.4 (14.3)	
Negative	37	59.4 (20.4)	

Table 3 Diagnosis by season

Diagnosis	Spring	Summer	Autumn	Winter	Total	χ^2 test
GPA	45	45	37	57	184	p=0.55
MPA	27	27	30	30	114	
EGPA	9	7	7	17	40	
Total	81	79	74	104	338	

Table 4 Epidemiological studies of AAV over 20 years or more (All incidence are numbers/million)

Study	Method	At-risk population	Region (Time)	GPA N Incidence (95% CI)	MPA N Incidence (95% CI)	EGPA N Incidence (95% CI)	All AAV N Incidence (95% CI)
Knight 2006 (17)	National inpatient register	209.7*	Sweden (1975-2001)	1636 7.8 (7.4, 8.2)			
Berti 2017(20)	Linked medical records	1.8*	Olmsted county, Minnesota, USA (1996-2015)	23 13.0 (8.0, 18.0)	28 16.0 (10.0, 22.0)	7 4.0 (1.0, 6.0)	58 33.0 (24.0, 41.0)
Rathmann 2023(16)	Health register	12.4*	Southern Sweden (1997-2019)	192 15.4 (13.3, 17.6)	159 12.8 (10.8, 14.8)	23 1.8 (1.1, 2.6)	374 30.1 (27.0, 33.1)
Benavides-Villanueva 2025(15)	Patient database	11.4*	Cantabria, Spain (2000-2023)	64 5.6 (3.9, 7.3)	67 5.9 (4.0, 7.8)		
This study	Cohort study	13.5	Norfolk county, UK (1991-2020)	184 13.6 (11.7, 15.8)	114 8.5 (7.0, 10.2)	40 3.0 (2.1, 4.0)	338 25.1 (22.5, 27.9)

* **At risk population estimated from the numbers and reported incidence. All numbers are in million person-years**

Supplementary figure 1 Incidence of PR3 AAV and MPO AAV with the linear regression lines for both.