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Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg–Strauss syndrome within a defined population in southern Sweden

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Objectives. To estimate the point prevalence (p.p.) of Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), polyarteritis nodosa (PAN) and Churg–Strauss syndrome (CSS) within a defined population in southern Sweden.
Method. A cross-sectional p.p. study using multiple sources for case identification. The study area, a healthcare district around the city of Lund in southern Sweden (Mellersta Skånes sjukvårdsdistrikt), had, on 31 December 2002, a total population of 287 479 inhabitants. All the identified cases were verified by medical record review. The patients were classified according to an algorithm based on the American College of Rheumatology classification criteria 1990 and the Chapel Hill Consensus Conference definitions 1994.
Results. Eighty-six patients (49% female) with a median age of 64.8 yrs (range 15–90.5) fulfilled the study criteria. There were 46 patients with WG; 27 with MPA; nine with PAN; and four with CSS. The p.p. per million inhabitants was estimated on 1 January 2003 to be 160 (95% confidence interval 114–206) for WG, 94 (58–129) for MPA, 31 (11–52) for PAN and 14 (0.3–27) for CSS. Capture–recapture analysis estimated the completeness of the case finding to 96%.
Conclusions. The prevalence of WG, MPA, PAN and CSS in our district is the highest figure reported so far. Explanations for this finding may include high incidence, extensive ANCA-testing, good survival as well as sensitive search methods for case identification.

KEY WORDS: Vasculitis, Arteritis, ANCA, Prevalence, Wegener's granulomatosis.

Introduction

Systemic vasculitis constitutes a heterogeneous group of diseases characterized by inflammation and necrosis of the blood vessel walls. According to the Chapel Hill Consensus Conference (CHCC) primary systemic vasculitis has been classified into three main groups: those affecting predominantly large-sized vessels, medium and small-sized vessels, respectively [1]. Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), polyarteritis nodosa (PAN) and Churg–Strauss syndrome (CSS) are primary systemic vasculitis mainly affecting medium- and small vessels. Because of similarities in the clinical and pathological features, including the paucity of the immune deposits among these diseases and the strong association of anti-neutrophil cytoplasmic antibodies (ANCA) with WG, MPA and CSS, many authors regard these diseases as an entity [2], hereafter referred to as PSV (primary pauci-immune systemic medium and small vessel vasculitis).

PSV diseases were considered to be rare but recent data indicate an increasing incidence [3, 4]. The availability of the ANCA test may have led to increased awareness and recognition of these diseases, especially WG and MPA [5]. The prevalence of PSV increased during the last decade [4, 6, 7]. This increment may be explained by improvement in the long-term survival achieved by the use of cyclophosphamide (CYC) and prednisolone as well as the availability of effective maintenance therapy [8]. It is reported from epidemiological studies that there are some variations in incidence and prevalence of PSV among different regions in the world. For example, WG is more common in northern Europe than in Spain while the reverse might be true regarding MPA [9]. Recently published data showed a lower overall risk of PSV among migrants compared with the European background population, a finding that might infer a genetic susceptibility of Caucasians to PSV [6].

The aims of this study were: (i) to estimate the prevalence of WG, MPA, PAN and CSS within a defined population in southern Sweden, (ii) to assess the completeness of case identification using different retrieval sources by application of capture–recapture analysis.

Patients and methods

Study area and population

This point prevalence (p.p.) study was performed in a healthcare district (Mellersta Skånes sjukvårdsdistrikt) situated in the south-west of Skåne, the southernmost county of Sweden (Fig. 1). According to official government statistics [10], the total population of the study area on 31 December 2002 was 287 479, representing 3.2% of the total population in Sweden. Twelve percent were born outside Sweden, most of them being immigrants from other Nordic countries or southern Europe, thus more than 95% of population can be considered as Caucasian. The population of the study area increased by 8191 inhabitants (2.8%) from 1997 to 2002. The study area is 2832 km^2 (about 0.6% of the total area of Sweden) and is divided into 10 municipalities, the largest being the city of Lund with a population of 100 402 inhabitants. There are several suburban communities where a large percentage of the working population commutes to Lund and to Malmö, the third largest city in Sweden. There is a substantial rural population, but 81% live in communities with more than 1000 inhabitants. The distances are short; no community in the area is more than 40 km from Lund, and the distance between Lund and Malmö is only 17 km. Females made up 50.4% of the study population and the age distribution was as follows: 0–14 yrs 18.8%; 15–54 yrs 54.6%; and >55 yrs 26.6% [10]. In the study area, the majority of the employees (78%) work within private and public service sectors, 18% work within

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FIG. 1. Map showing the region of Skåne in southern Sweden and the study area (shaded area).

manufacturing industry and around 2.5% with agriculture. 'Region Skåne' is a regional public body with administrative and financial responsibility for the health of the inhabitants, and for providing medical and dental services. The area is served by two hospitals: Lund University Hospital and Landskrona Hospital, the former being a referral hospital for the 1 575 000 inhabitants in southern Sweden. There are three other hospitals situated nearby the study area; these are Malmö University Hospital, Trelleborg and Helsingborg Hospitals. All hospitals in and around the study area are run by Region Skåne; there are no private hospitals in the district or nearby. Within the area there are only three private out-patient clinics providing services from specialists in Internal Medicine. The National Health Service in Sweden is available to all its population. This covers primary healthcare (general practice) and specialized health services provided by hospitals or private clinics.

Study period

The study estimated the p.p. of listed diseases on 1 January 2003. Unless stated otherwise, searches of databases were limited to the period from 1 January 1997 to 31 December 2002.

The retrieval sources

Patients were retrieved from three different sources: (i) clinical records, (ii) pathology records and (iii) ANCA serology databases.

Clinical records, including hospital discharge records and databases listing out-patient clinics, were searched using the International Classifications of Diseases ICD-10 codes M300–M319 for the period 1998–2002 and the corresponding ICD-9 codes for 1997. Searches were done at the following departments and hospitals inside the study area: (i) Lund University Hospital: the databases for the Departments of Internal Medicine (including Nephrology, Pulmonology and General Internal Medicine), Rheumatology, ENT, Ophthalmology, Dermatology, Infectious diseases and Paediatrics; (ii) Landskrona Hospital: the databases for the Departments of Medicine; and (iii) the largest private out-patient clinic and two arbitrarily chosen primary healthcare centres. Outside the study area the following databases were utilized: (i) Malmö University Hospital: the databases for the Departments of Internal Medicine (including Rheumatology and Nephrology sections); (ii) Helsingborg Hospital: Department of Internal Medicine; and (iii) Trelleborg Hospital: Department of Medicine. Two laboratories in the area analyse ANCA, the Department of Immunology at Lund University Hospital and the private immunology laboratory Wieslab AB in Lund. The records from both laboratories were searched for positive results in analysis for cANCA, pANCA, PR3-ANCA and MPO-ANCA.

A computerized search was also performed in the database for the Department of Pathology, Lund University Hospital, using the free-text term of 'vasculitis' on the entire text of all pathology reports. The Department of Nephrology at Lund University Hospital operates a separate database for patients who have undergone renal biopsy; this also lists a clinical diagnosis. This database was searched for the period 1980–2002 using the Swedish terms for 'crescentic glomerulonephritis', 'necrotizing glomerulonephritis', 'Wegener's granulomatosis' and 'microscopic polyangiitis'.

Case ascertainment and classification

Matching criteria in this study were the national registration numbers. These are unique identification numbers for each individual living in Sweden. For people born in Sweden, the number is specified at birth, immigrants are given a number if they stay longer than three months. The number is composed of 10 digits—six indicating date of birth plus four, of which one indicates gender. Medical organizations use these numbers to store information about the individual's health status. Each retrieval source generated raw files of national registration numbers with potentially eligible cases, which after removal of duplicates provided 'list 1' for each single retrieval source (Table 1).

Thereafter, we ascertained that the individuals were living within the study area on the day of estimating p.p., using the population register in Sweden; a comprehensive record run by the Swedish Tax Authority providing current information on who is

TABLE 1. Contribution of different retrieval sources for case identification

Retrieval sources	List 1	List 2	Other diagnosis	No diagnosis	PSV
Clinical					
Lund University Hospital					
Internal Medicine 1997	105	46	7	5	34
Internal medicine 1998–2002	184	69	4	9	56
Rheumatology	89	38	4	18	15
ENT	89	46	11	4	31
Dermatology	10	6	3	1	2
Infectious diseases	15	10	1	1	8
Ophthalmology	32	13	4	5	4
Pediatrics 1997	30	16	15	1	0
Pediatrics 1998–2002	43	15	12	2	1
Landskrona Hospital					
Internal medicine	[a]	6	1	0	5
Malmö University Hospital					
Rheumatology	45	3	1	2	0
Nephrology and transplantation	114	9	0	2	7
Trelleborg Hospital					
Internal medicine	10	0	0	0	0
Helsingborg Hospital					
Internal medicine	[a]	0	0	0	0
Private clinics and primary health care facilities	[a]	5	3	0	2
Serology					
Clinical Immunology	1338	228	174	25	29
Wieslab AB	220	77	16	11	50
Pathology					
Pathology	131	54	45	4	5
Renal Biopsy Register	144	16	0	0	16

List 1: the total number of potentially eligible cases generated by each source. List 2: the number of patients who lived in the study area on 1 January 2003. Other diagnosis: other forms of vasculitis and non-vasculitic disease. No diagnosis: available data not sufficient to confirm a diagnosis of vasculitis.
[a]The source provide the step 2 list directly.

living in Sweden and their residential address. Only individuals resident within the study area on the date of p.p. were brought forward to 'list 2'. Finally, we collected relevant individual clinical records to retrospectively verify the diagnosis and only patients fulfilling the classification criteria for a specific form of vasculitis were included in the study.

This study was performed in parallel to the development of a proposal for standardized classification of PSV for use in epidemiological studies to which two of the authors had contributed (A.D.M.and M.S.) [11]. A group of experts performing this task was formed after an initiative from EMEA (European Medicines Agency). An algorithm was developed applying the American College of Rheumatology (ACR) criteria [12, 13] and CHCC definitions [1] to classify cases of vasculitis into different categories of PSV. In short, according to this scheme a patient was considered to have PSV if they had symptoms and signs compatible with a diagnosis of vasculitis in combination with a biopsy showing necrotizing vasculitis/granuloma or symptoms and signs typical for vasculitis in combination with a positive ANCA-test, an angiogram showing microaneurysms or an electromyogram (EMG) showing mononeuritis multiplex. Other diagnoses which might account for symptoms and signs such as secondary vasculitis, drug reactions, infections, malignancies, other primary vasculitides and pseudovasculitis had to be ruled out.

Once a clinical diagnosis of vasculitis had been made, patients were classified according to an algorithmic hierarchy set applying classification criteria stepwise (Fig. 2). First, the ACR criteria for CSS were applied. The next step in the algorithm was application of ACR WG. Patients who did not fulfil ACR WG but (i) had histopathological findings compatible with CHCC WG, or (ii) compatible with CHCC MPA and surrogate markers for WG, or (iii) without histopathological findings but with surrogates for WG and a positive test for ANCA, were classified as WG.

Surrogate markers for WG refer to symptoms and signs suggestive of granulomatous disease affecting the upper (bloody nasal discharge and/or crusting for more than 1 month; mastoiditis; retroorbital disease; subglottic stenosis and saddle nose deformity) and lower respiratory tracts (X-ray evidence of pulmonary infiltrates or cavitations present for more than 1 month).

The remaining patients were checked against CHCC definition of MPA. Patients with histological findings compatible with CHCC MPA and who lacked surrogates for WG were classified as MPA. Patients with no histopathological findings but with surrogates for renal vasculitis together with a positive ANCA test where classified as MPA. A surrogate marker for renal vasculitis (necrotizing and crescentic glomerulonephritis) was proteinuria and haematuria with red cell casts. The CHCC definition for PAN was then applied; angiographic evidence of microaneurysms was considered to be highly suggestive for diagnosis in the context of clinical presentation of PAN.

All the charts were reviewed by one physician (A.J.M.), for borderline cases, consensus was sought among three of us (A.J.M., M.S. and G.S.).

Data collection

For each case included in the study, the following data were collected: age, gender, diagnosis delay (the time elapsed in months from the first possible symptoms of vasculitic disease to the date of diagnosis), the presented clinical features, relevant radiological, electromyographical and histopathological findings, serology data including ANCA and hepatitis, laboratory data including blood count, C-reactive protein (CRP), urinary-sediment and serum creatinine level.

Statistical analysis

Point prevalence estimates were calculated using data provided by Statistics Sweden [10]. The normal approximation method was used for calculating the confidence interval (CI) for the prevalence estimates.

Additionally, capture–recapture analysis was applied to the three sources of case ascertainment, i.e. clinical records, pathology records and the ANCA serology databases. As described elsewhere [6], this technique takes advantage from the overlap of cases

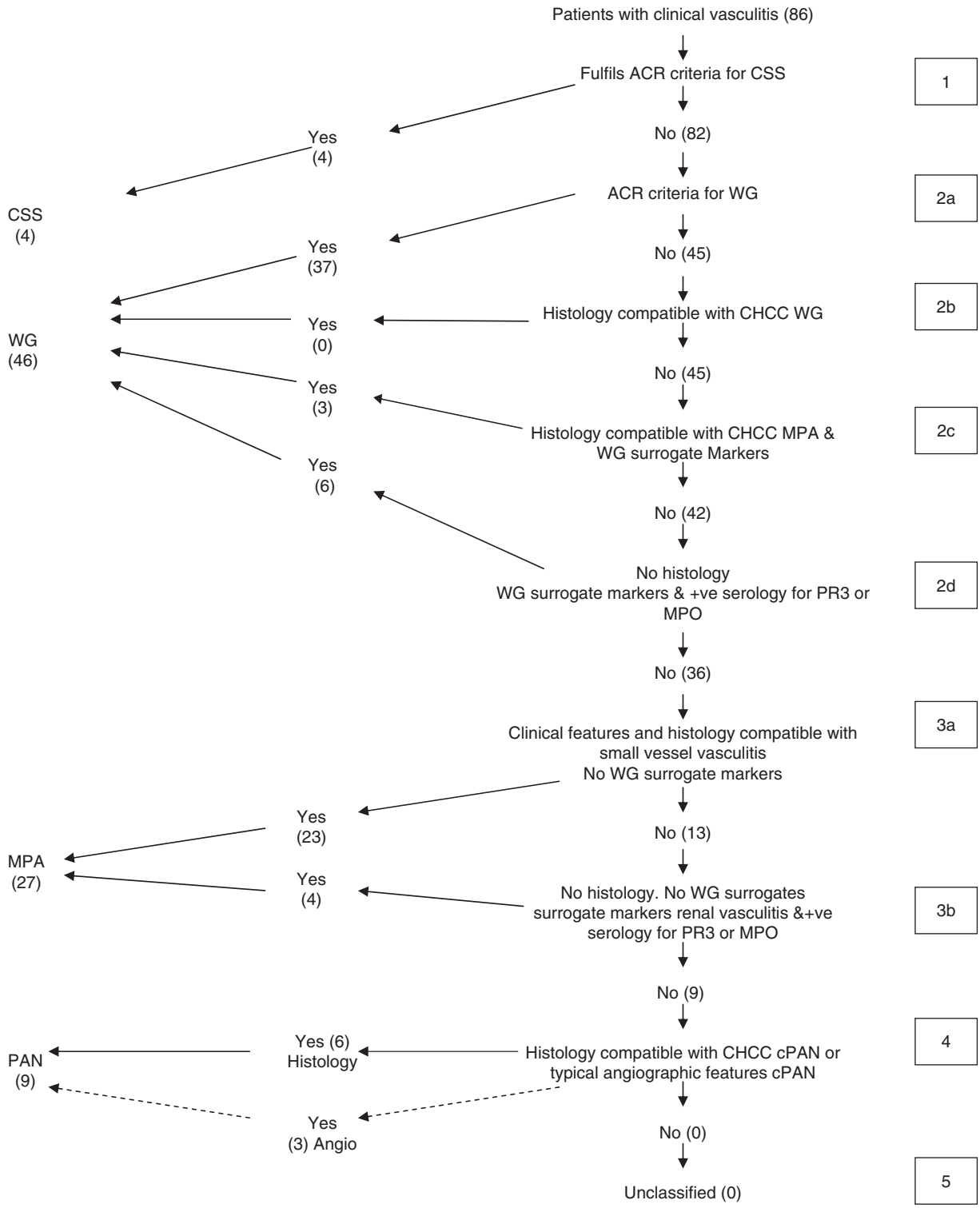

FIG. 2. The flow of the 86 patients with PSV when classified according to the EMEA algorithm, as described by Watts *et al.* [11]. The number between parentheses resembles the number of patients classified in each step on the algorithm.

collected by two or more disaggregated sources of ascertainment to estimate the number of cases missed by any source and, thereby, the completeness of case finding. Using log-linear methods [14, 15], we verified the assumption of 'source independency' by fitting eight models that accounted for all possible two-source interactions. The model that yielded the lowest values for likelihood ratio statistics (deviance G^2, Akaike Information Criterion, Bayesian Information Criterion) and, when ambiguous, the most parsimonious one was selected as the best-fitting model. 'Equal catchability' was evaluated by assessing for each of the three sources, the distributions of ascertained cases for the following categorical covariates: specific diagnoses, histological proof, ANCA-positivity, age (stratified by median value), and period of diagnosis (stratified by median value).

χ^2 tests were used to compare these distributions with those predicted by the best-fitting log-linear model retained in the previous step and, in the case of statistically significant disparities, we corrected the estimates by adding to that log-linear model one (or several) interaction term(s) between the respective source(s) and covariate(s). Variances of the capture–recapture estimates were calculated using goodness-of-fit statistics [16].

Ethics

The study was approved by the local ethical committee at the Faculty of Medicine, Lund University (LU 283-02).

Results

Retrieval sources and case ascertainment

Clinical records proved to be the most important retrieval sources; 79 of the 86 PSV cases (92%) finally included in the study were retrieved from this source (Table 1). Most cases had been recruited from the Department of Nephrology and Department of Rheumatology at Lund University Hospital. A substantial number of patients, who had been assigned ICD codes between M300 and M319, were excluded from our study. As shown in Table 1, some of theses patients have had other connective tissue diseases or other vasculitis ('other diagnosis'), the remaining had symptoms and signs compatible with vasculitis but lacked sufficient data to establish a retrospective diagnosis of PSV according to our criteria ('no diagnosis').

Twenty-three potentially eligible cases living in the study area were identified from the clinical databases of the primary healthcare facilities and four hospitals located in or close to the study area (Table 1). Fourteen patients fulfilled the inclusion criteria; the majority of them ($n = 12$) were identified in the serology registers or clinical registers in Lund. Accordingly, the final net contribution of clinical records outside Lund University Hospital amounted to two patients (2.3% of the total 86 cases included in our study).

The serology sources identified a large number of potentially eligible cases as shown in Table 1. Positive ANCA results were found at the Department of Immunology for 228 individuals living in the study area and 77 cases were retrieved through the Wieslab AB database. Clinical records from the departments that ordered the serology test were reviewed as well as records from the Department of Rheumatology, Department of Nephrology and/or Department of Internal Medicine, when available. In 10 cases (all analysed at the Department of Immunology), we were unable to locate any records and in several other cases there were insufficient data to make a retrospective diagnosis of vasculitis, or a non-vasculitic diagnosis was more likely (Table 1). We find that large number of patients with positive analysis for specially p-ANCA having inflammatory, connective tissue, malignant or infectious diseases other than primary vasculitis. A diagnosis of ANCA-associated vasculitis could be made in only 12.7% (29/228) of the cases with positive p-ANCA or c-ANCA. On the other hand, the corresponding figure for those identified through ANCA screening by enzyme-linked immunosorbent assay (ELISA) at Wieslab AB was 64.9% (50/77). Out of the 27 patients with positive MPO and or PR3 ANCA by ELISA who were not included in the study, 11 patients have had insufficient data to make any specific diagnosis. The remaining 16 patients had other disorders: inflammatory bowel diseases ($n = 3$), infectious diseases ($n = 2$), non-crescentic glomerulonephritis or glomerulosclerosis ($n = 6$), rheumatic diseases ($n = 2$), malignant disease ($n = 1$), amyloidosis ($n = 1$) and bronchial asthma ($n = 1$).

Eventually, serology sources identified 57 (66%) of the total cases included in our study, as shown in Fig. 3.

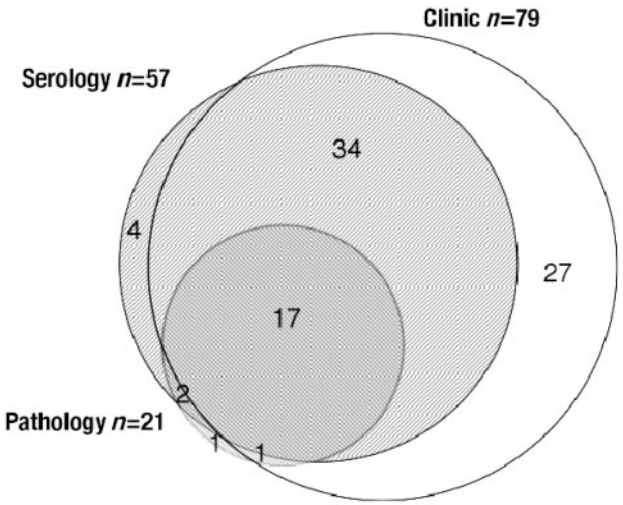

FIG. 3. Overlap between the three major groups of retrieval sources; clinical registers, serology and pathology databases. The number of prevalent cases retrieved uniquely from each source is indicated as well as the numbers retrieved from any combination of sources.

The search using the Swedish free-text term for 'vasculitis' in the databases from the Department of Pathology yielded a substantial number of individuals, of whom 54 were residing in the study area on the day of p.p. (Table 1). We were unable to locate records of four patients. A retrospective diagnosis was established in all the remaining cases, but only five were considered to have diseases within the PSV group. The renal biopsy register, which was searched all the way back to 1980, yielded 16 patients from the study area that were still alive on 1 January 2003. All 16 fulfilled the inclusion criteria. The pathology sources identified only 21 of the total 86 cases (24.4%) with PSV included in our study (Fig. 3).

If we had used only three primary retrieval sources: the Department of Nephrology and Department of Rheumatology in Lund together with Wieslab AB, we would have found 93% of cases ($n = 80$).

P.p. estimates

Eighty-six patients (49% female) living within the catchment area on the date of p.p. fulfilled the inclusion criteria (Table 2). The p.p. per million inhabitants was estimated to be 160 (95% CI 114–206) for WG, 94 (58–129) for MPA, 31 (11–52) for PAN and 14 (0.3–27) for CSS. The overall p.p. of all PSV estimated to 299 per million inhabitants (236–362). The p.p. in the age group above >55 yrs (74.4% of cases) was 837 per million (95% CI 632–1042). The sex distribution was relatively equal with a p.p. per million of 290 (202–378) for women and 309 (217–400) for men.

Capture–recapture analysis

As shown in Fig. 3, 32 (37%) of the PSV cases were identified by a single source, 37 (43%) were identified by two sources and 17 (20%) cases were identified by all three sources; 99% of PSV cases had been collected from either the 'clinical records' and/or the 'ANCA serology databases' sources.

Table 3 summarizes the results of log-linear modelling. The model that best fitted the values (CLIN*PATH SEROL) suggested a positive dependency between the sources 'clinical records' and 'pathology records'. This model estimated the number of cases missed at 3.6 and, consequently, the total number of cases at 89.6 (95% CI 85–95). Furthermore, we identified a deviation from the assumption of 'equal catchability' with respect to the sources 'ANCA serology databases' and 'pathology records' that

contained a significantly higher proportion of ANCA-positive cases than expected (data not shown). However, the log-linear model adjusted to both findings (by inclusion of the appropriate interaction terms in the previously selected model) provided a slightly better fit to the data but an identical estimate of the number of cases missed (3.6). Ultimately, therefore, we retained the more parsimonious model merely accounting for the inter-source dependency (CLIN*PATH SEROL).

Based on this model, we estimated the total number of PSV cases at 89.6 (95% CI 85–95), the completeness of case finding at 96.0% (95% CI 91–100) and the p.p. for all PSV adjusted for incomplete case finding at 312 per million adults (95% CI 247–376).

Characteristics of patients

Demographics, age at diagnosis, diagnosis delay and age at p.p. of the 86 patients with PSV are shown in Table 4. The median duration of follow-up from time of diagnosis to last assessment was 9.0 yrs (Interquartile range (IQR) 5–14.75; range 1 month to 37 yrs). The median age at diagnosis for all the patients was 55.5 yrs (range 1–88). There was no statistically significant difference between ages at onset of the studied diseases. The median age at p.p. for all the patients was 64.8 yrs (range 15–90.5). WG was more common in men; conversely, 2/3 of our PAN patients were women, while there was equal sex distribution in the cases of CSS and MPA (Table 4). The median time from the onset of diseases to the diagnosis was 3 months (IQR 1–8, range 0–96). The organ involvement at presentation, organ biopsy and serology data of all PSV patients are shown in Table 5. Positive test for C-ANCA/PR3 or P-ANCA/MPO was found in 86% of patients with ANCA-associated vasculitis [AAV (WG, MPA, CSS)] at diagnosis or any time during the course of their disease. The diagnosis of vasculitis was supported by histopathological findings in 80% of patients. Four patients presented with multiple positive biopsies (all having WG).

TABLE 2. Point prevalence of PSV (WG, MPA, PAN and CSS) in a study area with a total population of 287 479

Disease	*n*	Point prevalence 1 January 2003	95% CI
Wegener's granulomatosis	46	160	114–206
Male	26	182	112–252
Female	20	138	77–198
>55 yrs	34	445	295–594
Microscopic polyangiitis	27	94	58–129
Male	13	91	42–141
Female	14	97	46–146
>55 yrs	20	261	147–377
Polyarteritis nodosa	9	31	11–52
Male	3	21	0–45
Female	6	41	8–74
>55 yrs	7	91	24–159
Churg–Strauss syndrome	4	14	0.3–27
Male	2	14	0–33
Female	2	14	0–33
>55 yrs	3	39	0–84
All PSV	86	299	236–362
Male	44	307	217–400
Female	42	290	202–378
>55 yrs	64	837	632–1042

Wegener's granulomatosis

Forty-six patients with WG (20 women) were included in our study giving a p.p. of 160 (95% CI 114–206). The median age at diagnosis was 55.5 yrs (range 1–76), while at p.p. it was 64.1 yrs (range 15–85). Thirty-seven (80%) patients were classified according to the ACR criteria 1990. Using the ACR criteria 1990, the p.p. will be 129 per million (95% CI 87–170). Three patients were classified as WG because of the presence of biopsy-verified small vessel vasculitis in combination with surrogate markers for granulomatous disease (step 2c, Fig. 2). Additionally, six patients were classified as WG based on the combination of surrogate markers and positive ANCA tests (step 2d, Fig. 2). Thirty-three (72%) patients showed a positive test for either cANCA, PR3 or both. Five patients (11%) had a positive test for pANCA, MPO or both (Table 5).

Microscopic polyangiitis

A total of 27 (13 women) patients were found to fulfil our inclusion criteria for MPA, giving a p.p. of 94 per million inhabitants (95% CI 58–129). The median age at diagnosis was 60 yrs (range 15–88) and at p.p. 70 yrs (range 28–90.5). Twenty-three (85%) patients had histology compatible with CHCC MPA and no surrogate markers for WG (step 3a, Fig. 2). The remaining four patients were included on the basis of surrogate markers for renal vasculitis in combination with positive MPO-ANCA (step 3b, Fig. 2).

Polyarteritis nodosa

Nine patients (six women) with PAN were included in our study giving a p.p. of 31 (95% CI 11–52). The median age at diagnosis was 45 yrs (range 35–79) and at the date of p.p. 66 yrs (range 43.5–80.5). The diagnosis of PAN was confirmed by tissue biopsy in six patients showing evidence of vasculitis affecting small or medium-sized arteries according to the CHCC definition. Angiographic features of multiple micro-aneurysms were documented in three other patients (two mesenteric and one renal vessels). None of the eight PAN patients, tested during active disease, exhibited any positive ANCA test (Table 5).

Churg–Strauss syndrome

Four patients (two women) fulfil the ACR criteria 1990 for diagnosis of CSS giving a p.p. 14 per million inhabitant (95% CI 0.3–27). The median age at diagnosis was 53.5 yrs (range 38–63), while at p.p. 58.5 yrs (range 45.5–76). All the patients had known bronchial asthma prior to the disease onset and peripheral eosinophilia. In all the patients, tissue biopsy obtained for histological diagnosis (lung, muscle, conjunctiva and skin) revealed moderate to heavy infiltration of eosinophiles in the involved tissue.

TABLE 3. Capture–recapture estimates (using log-linear modelling) of the number of cases missed (*x*) by any source of case ascertainment and total number of cases (*n*) in the study area

Log-linear model	df	G^2	*P*	AIC	BIC	*x*	*n*	95% CI
CLIN∗SEROL CLIN∗PATH SEROL∗PATH	0	0	1	0	0.00	27.0	113.0	23–203
CLIN∗PATH SEROL∗PATH	1	1.67	0.20	−0.33	−3.24	3.2	89.2	76–102
CLIN∗SEROL SEROL∗PATH	1	0.00	1	−2	−4.91	27.0	113.0	37–189
CLIN∗SEROL CLIN∗PATH	1	11.24	<0.01	9.24	6.33	2.0	88.0	84–92
CLIN∗PATH SEROL	2	**1.84**	**0.17**	**−2.16**	**−7.97**	**3.6**	**89.6**	**85–95**
CLIN SEROL∗PATH	2	11.25	<0.01	7.25	1.43	2.2	88.2	84–92
CLIN∗SEROL PATH	2	11.56	<0.019	7.56	1.75	3.2	89.2	82–97
CLIN SEROL PATH	3	11.61	<0.01	5.61	−3.11	2.6	88.6	85–93

AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degree of freedom; CLIN, clinical records; PATH, pathology records source; SEROL, ANCA-serology databases source.

Table 4. Demographics, age at diagnosis, diagnosis delay and age at point prevalence of 86 patients with WG, MPA, PAN and CSS

Disease	Number of patients	Sex F/M	Age at diagnosis [years] median (range)	Diagnosis delay [months] median (range)	Age at p.p. [years] median (range)
All	86	42/44	55.5 (1–88)	3 (0–96)	64.8 (15–90.5)
WG	46	20/26	55.5 (1–76)	6 (0.5–96)	64.1 (15–85)
MPA	27	14/13	60.0 (15–88)	2 (0–18)	70 (28–90.5)
PAN	9	6/3	45.0 (35–79)	4 (0–36)	66.0 (43.5–80.5)
CSS	4	2/2	53.5 (38–63)	1 (0.5–5)	58.5 (45.5–76)

Table 5. Organ involvement at presentation, organ biopsy and serology data in 86 patients with PSV

	All *n* (%)	WG *n* (%)	MPA *n* (%)	PAN *n* (%)	CSS *n* (%)
Clinical features					
General	64 (74)	32 (70)	22 (81)	7 (78)	3 (75)
Cutaneous	14 (16)	4 (9)	3 (11)	4 (44)	3 (75)
Mucous membranes	1 (1)	1 (2)	0 (0)	0 (0)	0 (0)
Eyes	8 (9)	7 (15)	1 (4)	0 (0)	0 (0)
ENT	44 (51)	40 (87)	2 (7)	1 (11)	1 (25)
Chest	38 (44)	27 (59)	9 (33)	0 (0)	2 (50)
Cardiovascular	6 (7)	0 (0)	5 (18)	1 (11)	0 (0)
Abdominal	9 (10)	2 (4)	3 (11)	3 (33)	1 (25)
Renal	39 (45)	18 (39)	20 (74)	1 (11)	0 (0)
Nervous system	9 (10)	2 (4)	1 (4)	5 (55)	1 (25)
Other	8 (9)	2 (4)	5 (18)	1 (11)	0 (0)
Biopsy					
Number of positive biopsies (%)					
Renal	34 (39)	14 (30)	20 (74)	0	0
Nasal	17 (20)	17 (37)	0	0	0
Lung	4 (5)	2 (4)	1 (4)	0	1 (25)
Muscle	4 (5)	0	0	3 (33)	1 (25)
Other	15 (17)	8 (17)	2 (7)	3 (33)	2 (50)
Biopsy not done	5 (6)	2 (4)	1 (4)	2 (22)	0
Negative biopsies	12 (14)	8 (17)	3 (11)	1 (1)	0
Serology					
C-ANCA	35 (40)	33 (71)	2 (7)	0	0
P-ANCA	22 (25)	4 (9)	18 (67)	0	0
PR3	36 (42)	33 (71)	3 (11)	0	0
MPO	25 (29)	5 (11)	20 (74)	0	0
Negative ANCA	19 (22)	6 (13)	3 (11)	8 (89)	2 (50)
ANCA Analysis not done	4 (5)	0	1 (4)	1 (11)	2 (50)

Discussion

This is a population-based cross-sectional study using different epidemiological retrieval sources to estimate the p.p. of PSV and to assess for case completeness by applying capture–recapture analysis. We found a prevalence figure for PSV of 299 per million inhabitants (160 for WG, 94 for MPA, 31 for PAN and 14 for CSS), which is the highest ever recorded. We kept strictly to the inclusion criteria, and several cases were excluded because of lack of histological confirmation that presented symptoms and signs compatible with but not typical of vasculitis. Regarding the classifications of PSV, we applied the ACR classification criteria as well as the CHCC definitions in an algorithmic manner described by Watts *et al*. [11]. Clinical, serology and pathology sources were thoroughly searched to identify cases of vasculitis. There was, as expected, a large degree of overlap between these retrieval sources. This overlap was used to perform capture–recapture estimates of potentially missing cases. These calculations indicated that we probably missed <5% of all cases present in the population. We found ANCA-serology databases screening with ELISA, rewarding for the identification of PSV cases. However, screening with indirect immunofloursence test (IIF) resulted in high numbers of patients with positive tests not having vasculitic disorders. ANCA databases have also been used in recent studies from Germany [17] and New Zealand [7]. A simplified search strategy using the clinical databases at the Department of Nephrology and Department of Rheumatology in Lund University Hospital together with a database from Wieslab AB could identify 93% of the cases in our study. We conclude that the use of these three sources in case identification is a cost effective strategy suitable for future incidence studies of PSV in our area.

The EMEA classification algorithm may have had a major impact on the designation to the specific disease categories, but only to a smaller extent on the total number of patients included. All the 86 patients with PSV had a clinical diagnosis of vasculitis supported either by histology and or by other findings typical of vasculitis (serology, angiography, etc.). The organ involvement and the pattern of clinical presentation of the WG patients in our study, are comparable with findings in previous studies with respect to lung and kidney involvement [18] and ENT involvement [4]. The impact of the algorithm is evident for the nine patients with WG who did not fulfil the ACR criteria. Theses patients, especially those with histopathology findings compatible with CHCC MPA, would be classified as MPA or PAN if allowing only ACR criteria for a classification as WG. There is no doubt that the EMEA algorithm (which is a consequence of the relative priority to CHCC definitions) has an impact on whether a patient is considered to have PAN or MPA. All patients classified as PAN did fulfil ACR criteria for this disease, however, many patients in the MPA also fulfilled such criteria. The only situation for which the EMEA algorithm really influences the total number of PSV cases concerns renal limited vasculitis, which all gets classified as MPA. The size of this effect is in comparison with other studies is difficult to discern since there is no consensus, that we are aware, of how the distinction between MPA and 'idiopathic'

ANCA-positive pauci-immune crescentic glomerulonephritis should be made.

There are few studies addressing the epidemiology of PSV; most of them focus on incidence rates. To our knowledge, there are only three studies giving prevalence figures for all the diseases included in our PSV definition. These were performed in England, France and Germany, the prevalences per million were 144.5 [19], 90.3 [6] and 46–83 [20], respectively.

For WG, the most studied disease in this group, we found a p.p. of 160 per million according to EMEA classification, and 129 per million when using ACR criteria 1990. Previous studies performed in Europe, using ACR WG, have reported figures ranging between 23.7 per million [6] and 95.1 per million [4], whereas the estimated prevalence of WG in the United States was reported to be 30 per million [21]. However, a recently published study from New Zealand showed the prevalence of WG to be 112 per million, but when using only ACR criteria the prevalence was 93.5 per million [7]. Also for MPA, we find high figures. Mahr *et al*. [6] have reported a prevalence of 25.1 per million in Paris, and similar figures have recently been reported from the State of Montana in USA [22] and from New Zealand 30 per million and 37 per million, respectively [7], which is considerably less than our figure of 94 per million. The difference can only to a minor degree be explained by cases with renal limited vasculitis or other effects directly related to the EMEA algorithm. For PAN, our figure of 31 per million is in the same range as that reported from Paris, 30.7 per million [6], but substantially higher than the prevalence reported from two German regions [20]. The estimated prevalence of CSS at 14 per million is higher than those reported from France [6], and Germany [20] but similar to that reported from Norway [23].

The possible explanations for these differences can be divided into three broad categories: differences in incidence, in survival and methodological differences.

Incidence studies performed in Norway, England and Spain indicate that there are geographical variations, that WG is more common in northern Europe and that the incidence of MPA is higher in the south. These differences may arise from variations in the distribution of environmental factors important for the development of these diseases. The so-called 'north–south hypothesis' might very well be a partial explanation for our high figures for the WG prevalence. However, this hypothesis cannot explain the high figures for MPA. On the contrary, our findings clearly challenge this hypothesis that MPA might be more common in southern Europe [9]. Many studies show that incidence increases with age, so prevalence rates could be affected by differences in age distribution. However, in our study, the percentage of individuals $\geq$55 yrs old is comparable with the studies from France [6] and Germany [20]. The high prevalence figures in our study could not be explained by the age distribution in our population.

Incidence is also affected by the awareness of the specific disease by all physicians and the availability of diagnostic tests (i.e. ANCA testing) in a study area. ANCA testing has been used extensively at the Lund University Hospital since 1986, especially at the Department of Nephrology [24]. This might have had a major impact on the results of this study.

Prevalence is by definition a direct consequence of patient survival. In our area, the vast majority of patients is treated and followed at university clinics with highly specialized care. Many patients have participated in clinical trials. However, we do not believe that better care is a major contributor to our results. Better survival would eventually lead to a higher age for prevalent vasculitis cases, however, if the median age of 65 yrs in our study is elevated or not is difficult to discern since age at p.p. is seldom reported.

Finally, methodological issues may have a major influence on results. Sweden is well suited for a study like this because of the structure of the healthcare system and the circumstances that all registers use the Swedish national registration numbers to list patients. Most probably, the thorough search and the use of multiple sources to identify cases have had a major impact on our prevalence figures.

In conclusion, we find a prevalence of PSV to be close to 300 per million adults in our southern Swedish study area. Possible explanations for these high estimates are a genuinely high incidence in the area, good survival and effective search strategy to find eligible cases. Future studies focused on incidence might help to elucidate the importance of these factors.

Rheumatology key messages

- The overall point prevalence of WG, MPA, PAN and CSS in our area is close to 300 case per million inhabitants, which is the highest figure ever reported.
- Using different retrieval sources in case identification give a case completeness to be as high as 96%.
- Explanation to these high estimates could be truly high incidence in the area, good survival and effective search strategy.

The authors have declared no conflicts of interest.

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