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# **Prevalence of anti-neutrophil cytoplasmic antibody-associated vasculitis in the south of France, using the capture-recapture method**

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ANCA-associated vasculitis, epidemiology, prevalence.

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# Abstract

## Objectives:

This study aimed to estimate the prevalence of ANCA-associated vasculitis (AAV). That is, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), in Southern France in 2018, and evaluate differences among Europeans and non-Europeans.

## Methods:

This population-based, cross-sectional study used four sources (hospitals, community-based physicians, laboratories, National Health Insurance) to identify adults  $\geq 15$  years diagnosed with GPA, MPA or EGPA, living in Hérault and Gard in 2018. Cases were defined using the ACR/EULAR classification criteria, and if necessary, the European Medicines Agency algorithm. Prevalence estimates were standardised to the world population and capture-recapture analysis was used to assess the comprehensiveness of the estimation. The influence of geographical origin was evaluated.

## Results:

A total of 202 patients were selected, with 86 cases of GPA (42.6%), 85 cases of MPA (42.1%) and 31 cases of EGPA (15.3%). The standardised prevalence estimates per million inhabitants for 2018 were: 103 (95%CI 84–125) for AAV, 48 (95%CI 35–64) for GPA, 39 (95%CI 28–53) for MPA and 16 (95%CI 9–26) for EGPA, 36 (95%CI 25–50) for anti-PR3 positive AAV, 46 (95%CI 34–61) for anti-MPO positive AAV, and 16 (95%CI 9–26) for ANCA-negative AAV. The global estimation of comprehensiveness by capture-recapture analysis was 80.5%. The number of AAV cases was higher for non-European residents ( $P=0.001$ ), particularly for MPA ( $P<0.0001$ ).

## Conclusion:

We provide a new estimate of AAV prevalence in France and show a higher prevalence of MPA in non-European patients.

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## Introduction

Among the group of primary systemic vasculitides, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) are described as necrotizing vasculitides affecting preferentially small and medium vessels, with a frequent association with antineutrophil cytoplasmic autoantibodies (ANCA) [1], most commonly directed against proteinase 3 (anti-PR3, mostly in GPA) or myeloperoxidase (anti-MPO, mostly in MPA and EGPA). Clinical presentation is often multisystemic, with more prominent symptoms depending on the phenotype of ANCA-associated vasculitis (AAV),

such as involvement of upper airways in GPA, pulmonary-renal syndrome in MPA and asthma in EGPA [2–6]. To categorise AAV subtypes, several tools have been developed, such as the ACR classification criteria first published in 1990 [2, 3], the 2012 revised Chapel Hill Consensus Conference (CHCC) nomenclature of vasculitides [1] and more recently, in 2022, the ACR/EULAR classification criteria [4–6].

Numerous studies have aimed to define the prevalence of AAV, with a large scope of estimations, going from 2 to 261 per million for GPA, 0–184 per million for MPA and 0–37 per million for EGPA [7–10]. They suggest a predominance of GPA in people of Caucasian origin with a declining north-south gradient, while MPA might be predominant in other regions such as Asia [7]. However, these estimates are marked with considerable heterogeneity in methodology, due to the difficulty of accurate case definition and of comprehensive case detection. Over the years, it appears that AAV prevalence has increased, probably because of better case detection, and mortality decrease [8]. However, while several estimations have been conducted over time in the USA, Spain, Germany, Norway, Sweden and the UK [7–10], data are scarcer in France with only two studies using a multisource population based method [11, 12].

The aim of this study was to estimate the prevalence of GPA, MPA and EGPA with a population-based method in two regions of Southern France for the year 2018, and evaluate potential differences among European and non-European subpopulations.

## **Material and methods**

### **Study population and study period**

This cross-sectional study was carried out in two regions of Southern France, Hérault and Gard, covering a territory of 11 953.8km<sup>2</sup> (Supplementary Fig. S1, available at Rheumatology online), with a population of 1 904 618 inhabitants (with 1 583 524 adults  $\geq 15$  years), according to the national census of 2018 [13]. There were respectively 748 798 and 834 726 male and female adults ( $\geq 15$  years), and there were 176 630 inhabitants who were not born in France, of which 113 253 were born in a non-European country [13]. The study period covered the entire calendar year of 2018, and the survey took place between January 2019 and December 2020.

### **Case detection**

*Cases of AAV were detected using multiple sources.*

#### ***Source 1: public and private hospitals***

All departments of internal medicine, rheumatology, nephrology, pulmonology, neurology and ENT in all public and private hospitals of the area of study were contacted through the head of department and medical staff. Requests for participation were sent by email, with a second follow-up email in case of non-response after two months, asking to report cases of patients with AAV who received care in their departments. The detection of cases in hospitals relied on the National Health Data System, a national hospital discharge database, using the international classification of diseases (ICD) (for AAV, codes M30.1, M31.3, M31.7 and M31.8 were searched).

### ***Source 2: community-based physicians***

All community-based general practitioners, and specialists potentially taking care of patients with AAV (rheumatologists, dermatologists, nephrologists, pulmonologists, ENT physicians), were contacted by postal mail to identify cases of interest. A letter with general information and a questionnaire (asking for anonymous information on the case) and a return addressed paid envelope were sent, with a second mailing in case of non-response.

### ***Source 3: laboratories***

Private laboratories researching ANCA levels were contacted via email for cases with ANCA positivity in 2018, with a follow-up email in case of non-response. ANCA positivity was defined as detection of C-ANCA or P-ANCA by indirect immunofluorescence, or anti-PR3 or anti-MPO by enzyme linked immunosorbent assay.

### ***Source 4: National Health Insurance database***

The French Health Insurance system covers health care related expenses for chronic diseases for the majority of French citizens. The medical doctor of the Health Insurance agency of Hérault and Gard was contacted to identify residents recorded in the computerised database in 2018 for exoneration of medical expenses for AAV. The ICD codes used in this database were broader (M30 and M31), including other types of vasculitides, necessitating secondary diagnosis verification. For all sources, each case was transmitted using an anonymised combination of initials of the last name and first name, sex, year of birth, and residential postal code, and the name of the hospital physician responsible for the case was asked.

### **Case definition and inclusion criteria**

The cases of interest were adults  $\geq 15$  years diagnosed with GPA, MPA or EGPA, and living in Hérault or Gard during the year 2018. Duplicate cases were identified by matching the combination of initial letters, sex, year of birth and residential postal code. After contact with the hospital referring doctor, all diagnoses were confirmed with review of the hospital charts by the same investigator (ER). A standardised questionnaire was used to collect demographic data, clinical data, ANCA results and biopsy findings. European or non-European origin was defined on the basis of country of birth, and we also asked for the country of birth of grandparents. This additional information was given by the patient after being contacted by the treating hospital physician. Cases were defined using the ACR/EULAR classification criteria [4–6]. When there was a difficulty for classification, the European Medicines Agency (EMA) algorithm [14] was used in complement, and cases were discussed for consensus (E.R. and A.M.).

### **Statistical analysis**

Quantitative variables were expressed as medians with range and qualitative variables as percentages. Prevalence rates were calculated with the number of cases as the numerator and the adult population as the denominator. The 95% confidence intervals were calculated on the basis of a hypothesis of Poisson distribution. Estimates were standardised for age and sex to the world population by direct standardisation [15], and were stratified according to sex. The capture-recapture method was used to assess the comprehensiveness of the estimation of prevalence for each AAV. This technique relies on the analysis of data extracted from

multiple sources, and aims to estimate the number of missed cases (cases not detected by any source), based on the number of overlaps (cases detected by several sources), to have the best possible estimation of the total number of cases in the population of study [16]. The criteria enabling the use of this method are: a closed study population, the capacity to match cases, a similar probability of case detection among sources (equal catchability), and source independence [16]. A log-linear analysis was used to obtain capture-recapture estimates and take into account possible bias. Source dependence was considered by comparing different models, including first-degree and second-degree interaction terms between sources [16, 17]. The choice of the best model relied on a stepwise approach, using the results of adequacy tests (model with the lowest Bayesian Information Criterion, BIC, and the lowest Akaike Information Criterion, AIC) and the parsimony principle (choice of the model with the least interaction terms) [16, 17]. To assess the possibility of heterogeneous case capture across sources, we described preselected characteristics of the subjects identified in each source (age, sex, renal involvement, pulmonary involvement, ENT involvement, neurological signs, ANCA positivity), and compared the expected distributions with the distributions observed within each source using  $\chi^2$  test (or Fisher test as appropriate) for categorical variables, and using Student's test for continuous variables. In case of heterogeneous case capture within one source, we introduced in the best-fitted model an interaction term between the source and the corresponding characteristic. To assess differences in terms of geographical origin, prevalences for European and non-European residents were compared using the  $\chi^2$  test. All statistical analyses were two-tailed and P values < 0.05 were considered significant. All statistical analyses were computed using R (version 4.2.1).

## **Ethics**

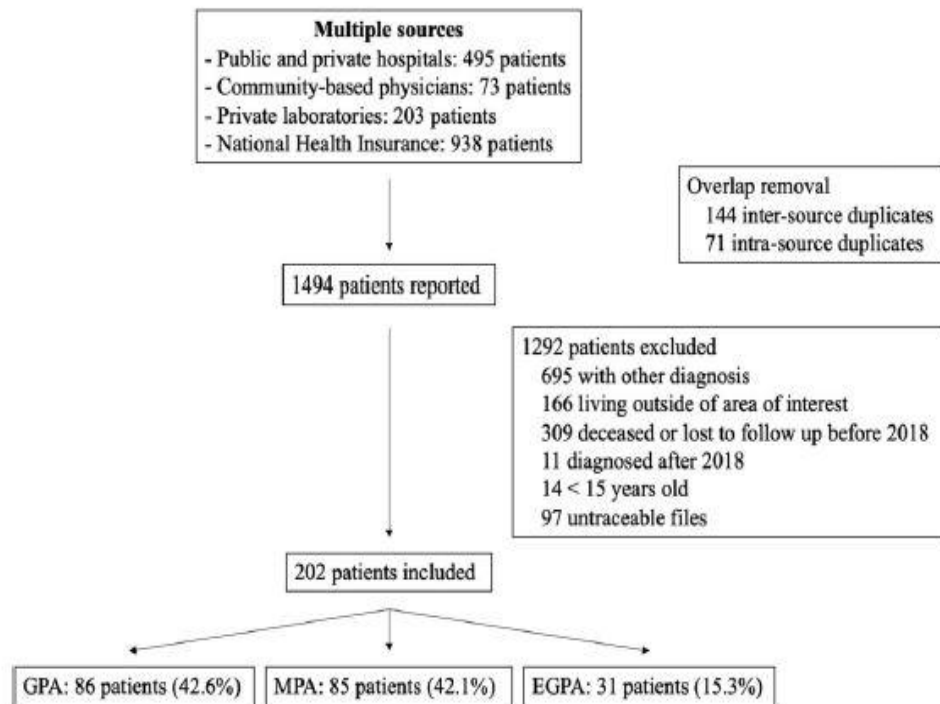
The study was approved by the French ethics administrations (Commission Nationale de l'Informatique et Liberté, Comité de Protection des Personnes, Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé). All patients received an information note and written informed consent was obtained for contact about birth country information.

# **Results**

## **Case detection and selection**

All the public and private hospitals we contacted participated in the study, and they provided 495 potential cases. Among the 2270 community-based physicians, 524 (23%) returned the survey questionnaire. The laboratory reported 203 cases with positive ANCA testing. The National Health Insurance database retrieved 938 patients for the year 2018, with codes M30 and M31 including differential diagnoses. Fig. 1 shows the selection process. After removing 144 inter-source duplicates and 71 intra-source duplicates, 1494 notifications were identified. After verification of cases, 1292 patients were excluded: 695 patients with other diagnoses, 166 living outside the area of interest, 309 deceased or lost to follow-up before 2018, 11 diagnosed after the year 2018, 14 younger than 15 years old and 97 with untraceable files. Other diagnoses included other vasculitides, other auto-immune or inflammatory diseases, drug-induced ANCA, cancer and haematological malignancy. Eventually, 202 patients were included in the analysis, with 86 cases of GPA (42.6%), 85 cases of MPA (42.1%) and 31 cases of EGPA (15.3%).





**Figure 1.** Flow chart. Process of case detection using multiple sources, and of diagnosis verification

**Table 1.** Characteristics of patients with AAV in 2018 in *Hérault* and *Gard* regions

Characteristics	AAV (n=202)	GPA (n=86)	MPA (n=85)	EGPA (n=31)
Age at diagnosis, years, median (range)	62.0 (15.0–91.0)	56.0 (16.0–91.0)	65.0 (15.0–85.0)	62.0 (16.0–86.0)
Males	121 (59.9)	52 (60.5)	48 (56.5)	21 (67.7)
Country of birth				
France	152 (75.2)	66 (76.7)	58 (68.2)	28 (90.3)
Other European countries	19 (9.4)	9 (10.5)	9 (10.6)	1 (3.2)
North Africa	27 (13.4)	8 (9.3)	17 (20.0)	2 (6.5)
Other	4 (2.0)	3 (3.5)	1 (1.2)	0
Origin <sup>a</sup>				
France	88/135 (65.2)	42/62 (67.7)	30/51 (58.8)	16/22 (72.7)
Other European countries	41/135 (30.4)	21/62 (33.9)	13/51 (25.5)	7/22 (31.8)
North Africa	25/135 (18.5)	7/62 (11.3)	16/51 (31.4)	2/22 (9.1)
Other	5/135 (3.7)	2/62 (3.2)	3/51 (5.9)	0
Time since onset, years, median (range)	5.0 (0–29.0)	6.0 (0–29.0)	4.0 (0–24.0)	5.0 (1.0–23.0)
Clinical signs				
Renal involvement	129 (63.9)	53 (61.6)	72 (84.7)	4 (12.9)
Pulmonary involvement	129 (63.9)	57 (66.3)	42 (49.4)	30 (96.8)
ENT signs	113 (55.9)	68 (79.1)	15 (17.6)	30 (96.8)
Cutaneous signs	69 (34.2)	32 (37.2)	19 (22.4)	18 (58.1)
Ophthalmological signs	32 (15.8)	28 (32.6)	2 (2.4)	2 (6.5)
Gastrointestinal signs	15 (7.4)	12 (14.0)	3 (3.5)	0
Neurological signs	72 (35.6)	24 (27.9)	24 (28.2)	24 (77.4)
Cardiological signs	36 (17.8)	14 (16.3)	11 (12.9)	11 (35.5)
Positive ANCA testing	175 (86.6)	77 (89.5)	84 (98.8)	14 (45.2)
PANCA	107 (53.0)	15 (17.4)	82 (96.5)	10 (32.3)
CANCA	60 (29.7)	59 (68.6)	0	1 (3.2)
Anti-PR3	63 (31.2)	62 (72.1)	0	1 (3.2)
Anti-MPO	101 (50.0)	12 (14.0)	79 (92.9)	10 (32.3)
Positive biopsy	161/171 (94.2)	71/72 (98.6)	64/72 (88.9)	26/27 (96.3)
Glomerulonephritis	92/171 (53.8)	36/72 (50.0)	53/72 (73.6)	3/27 (11.1)
Vasculitis	39/171 (22.8)	20/72 (27.8)	10/72 (13.9)	9/27 (33.3)
Granuloma	32/171 (18.7)	28/72 (38.9)	2/72 (2.8)	2/27 (7.4)
Eosinophilic infiltrate	16/171 (9.4)	0	0	16/27 (59.3)
Inflammatory infiltrate	155/171 (90.6)	69/72 (95.8)	64/72 (88.9)	22/27 (81.5)

Data expressed as number (%) unless indicated otherwise.

<sup>a</sup> Grandparents' country of birth.



## Characteristics of the population

The main demographic and clinical characteristics of the patients are displayed in [Table 1](#). The median age at diagnosis was 62 years (range 15–91), and there were 121 males (59.9%). In 2018, the median time since diagnosis was five years (range 0–29). Most patients were born in Europe (84.7%), the remainder were born in Northern African countries (n=27, 13.4%), in Asia (n=3, 1.5%) or in Sub-Saharan Africa (n=1, 0.5%). When considering origin related to country of birth of grandparents, we counted more people for other European countries than France, and slightly more from Northern Africa. Renal involvement was frequent in GPA (61.6%) and MPA (84.7%) but rare in EGPA (12.9%). Pulmonary involvement was common in all three diseases (63.9%), and predominant in EGPA in relation with asthma (96.8%). ENT symptoms were observed mainly in GPA (79.1%) and EGPA (96.8%). Neurological signs were notably more frequent in EGPA (77.4%) than in GPA (27.9%) and MPA (28.2%). ANCA were detected in 175 patients (86.6%) in immunofluorescence and/or ELISA test. Anti-PR3 were positive in 72.1% of GPA cases, and anti-MPO were positive in 92.9% of MPA cases and in 32.3% of EGPA cases. Biopsies were positive in 94.2% of cases, with findings including: glomerulonephritis (53.8%), vasculitis (22.8%), granuloma (18.7%), eosinophilic infiltrate (9.4%) and inflammatory infiltrate (90.6%).

## Prevalence estimates

The computed prevalence of AAV for the year 2018 was 128 (95%CI 107–152) per million in habitants, 54 (95%CI 41–70) for GPA and for MPA, and 20 (95%CI 12–31) for EGPA. When considering ANCA positivity, the prevalence per million inhabitants was 40 (95%CI 29–54) for anti-PR3 positive AAV, 64 (95%CI 49–82) for anti-MPO positive AAV and 17 (95%CI 10–27) for ANCA-negative AAV ([Table 2](#)). After direct standardisation on age and sex to the world population, the prevalence estimates per million inhabitants for the year 2018 were: 103 (95%CI 84–125) for AAV, 48 (95%CI 35–64) for GPA, 39 (95%CI 28–53) for MPA and 16 (95%CI 9–26) for EGPA. Regarding ANCA positivity, the prevalence per million inhabitants was 36 (95%CI 25–50) for anti-PR3 positive AAV, 46 (95%CI 34–61) for anti-MPO positive AAV and 16 (95%CI 9–26) for ANCA-negative AAV. The female/male ratio was 1:1.5 for AAV and GPA, 1:1.3 for MPA, 1:1.8 for EGPA.

The prevalence of AAV was twice as high for residents of non-European origin compared with those of European origin ( $P=0.001$ ), 1.5 times as high for GPA ( $P=0.03$ ), and three times as high for MPA ( $P<0.0001$ ). For EGPA, the prevalence for residents of European origin did not differ significantly from that of residents of non-European origin ( $P=0.41$ ) ([Table 3](#)).

**Table 2.** Prevalence estimates for ANCA-associated vasculitis (AAV): crude estimates, estimation by capture-recapture analysis and standardised estimates, with stratification according to sex, for AAV, for AAV subtypes, and according to ANCA positivity, for the total adult population of Hérault and Gard

Disease	Prevalence per 1 000 000 adults (95% CI)	
	Crude estimates	
AAV	128 (107–152)	
GPA	54 (41–70)	
MPA	54 (41–70)	
EGPA	20 (12–31)	
Anti-PR3 AAV	40 (29–54)	
Anti-MPO AAV	64 (49–82)	
ANCA-negative AAV	17 (10–27)	
	Standardised estimates <sup>a</sup>	
AAV	103 (84–125)	
GPA	48 (35–64)	
MPA	39 (28–53)	
EGPA	16 (9–26)	
Anti-PR3 AAV	36 (25–50)	
Anti-MPO AAV	46 (34–61)	
ANCA-negative AAV	16 (9–26)	
	Standardised estimates, stratified by sex <sup>b</sup>	
	Male	Female
AAV	123 (102–147)	84 (67–104)
GPA	58 (44–75)	38 (27–52)
MPA	44 (32–59)	33 (23–46)
EGPA	21 (13–32)	12 (6–21)
Anti-PR3 AAV	46 (34–61)	25 (16–37)
Anti-MPO AAV	53 (40–69)	39 (28–53)
ANCA-negative AAV	17 (10–27)	15 (8–25)
	Estimates with capture-recapture analysis	
AAV	159 (141–188)	
GPA	66 (57–89)	
MPA	71 (58–101)	
EGPA	21 (20–28)	
Anti-PR3 AAV	47 (40–65)	
Anti-MPO AAV	82 (69–110)	
ANCA-negative AAV	19 (17–29)	

<sup>a</sup> Standardised to the world population for age and sex by direct standardisation.

<sup>b</sup> Standardised to the world population for age by direct standardisation, with stratification by sex.

AAV: ANCA-associated vasculitides; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

**Table 3.** Prevalence estimates for ANCA-associated vasculitis (AAV) according to geographic origin: prevalence estimates for AAV, for AAV subtypes, and according to ANCA positivity for the total adult population of Hérault and Gard, stratified according to geographic origin (European or non-European)

	Prevalence per 1 000 000 adults (95% CI)	Prevalence per 1 000 000 adults (95% CI)	P
Stratification by origin	European	Non-European	
AAV	119 (99–142)	238 (209–270)	0.001
GPA	52 (39–68)	79 (63–98)	0.3
MPA	47 (35–63)	141 (119–166)	<0.0001
EGPA	20 (12–31)	18 (11–28)	1
Anti-PR3 AAV	39 (28–53)	44 (32–59)	0.8
Anti-MPO AAV	58 (44–75)	141 (119–166)	0.001
ANCA-negative AAV	16 (9–26)	26 (17–38)	0.4

AAV: ANCA-associated vasculitides; EGPA: eosinophilic granulomatosis with polyangiitis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis.

## Capture-recapture analysis

Among the 202 cases included, 96 (47.5%) were obtained from one source, 89 (44.1%) from two sources, 17 (8.4%) from three sources and none from the four sources (Fig. 2). The results of the capture-recapture analysis are expressed in Table 2. Supplementary Table S1 (available at Rheumatology online) shows the ten best-fitted models among all possible log-linear models. Following the parsimony principle and favouring the lowest combination of AIC and BIC, we selected the model with an interaction between the sources ‘hospitals’, ‘laboratories’ and ‘Health Insurance’. Regarding the preselected characteristics (age, sex, renal involvement, pulmonary involvement, ENT involvement, neurological signs, ANCA positivity), there was no between-source heterogeneity, so no additional interaction term was included in the model. Thus, the estimate obtained by log-linear modelling was 251 cases, the estimated number of missed cases was 49, the comprehensiveness of the estimation was 80.5%. Finally, the total prevalence of AAV was 159 (95%CI 141–188) per million inhabitants. For each subtype of AAV (GPA, MPA and EGPA), the capture-recapture analysis estimated 105, 112 and 33 cases, with a comprehensiveness of 81.9%, 75.9% and 93.9%, respectively. Thus, the total prevalence per million inhabitants was 66 for GPA (95%CI 57–89), 71 (95%CI 58–101) for MPA and 21 (95%CI 20–28) for EGPA. Regarding ANCA positivity, the capture-recapture analysis estimated 74 cases for anti-PR3 positive AAV, 130 cases for anti-MPO positive AAV and 30 cases for ANCA-negative AAV, with a comprehensiveness of 85.1%, 77.7% and 90.0%, respectively, and an estimated prevalence per million inhabitants of 47 (95% CI 40–65), 82 (95%CI 69–110) and 19 (95%CI 17–29), respectively.

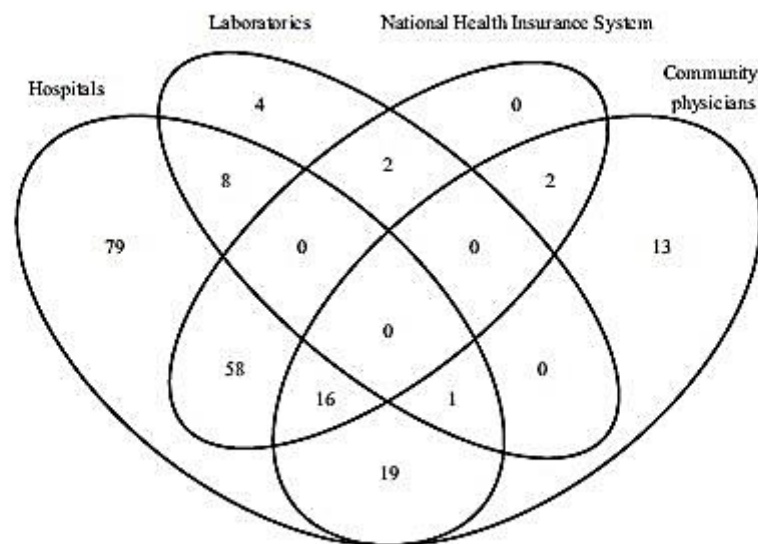


Figure 2. Venn diagram. Representation of the four sources and of case overlaps.

## Discussion

In this population-based study carried out in Southern France, we estimated the global prevalence of AAV at 103 per million inhabitants, and at 48 per million for GPA, 39 per million for MPA and 16 per million for EGPA. Considering ANCA positivity, estimates were 36 per million inhabitants for PR3-AAV, 46 per million inhabitants for MPO-AAV and 16 per million inhabitants for ANCA-negative vasculitis. In each AAV subtype, there was a predominance of male patients, which is in line with previous reports for GPA [11, 12, 18, 19], but is unexpected for MPA, where the majority of patients are typically female [9, 11, 12, 19–21]. A difference was observed between people of European and non-European origin, with mainly a higher prevalence of MPA in non- Europeans.

Our study provides prevalence estimates for France that are almost twice as high as the numbers previously reported in 2000 for a population in the Greater Paris area [11]. Keeping in mind that these estimations are not directly comparable, these differences are in line with the trend of increasing prevalence over time that has been observed in several countries for which serial estimations have been reported [8–10, 22]. This evolution can be explained by the progress made in case detection and diagnosis with the development of pertinent classification criteria and the use of ANCA testing [7, 8]. Also, improvement of treatment strategies resulting in better survival can account for a higher prevalence of AAV [7, 8]. Another estimation, which also used the capture-recapture methodology, has recently been published for the Alsace region in Eastern France in 2016 [12]. There, the prevalence per million inhabitants was 66 for GPA and 19 for MPA. While our estimations for GPA are in the same order of magnitude, the prevalence estimation for MPA in Alsace is almost half of ours. These contrasting results may be due to differences regarding disease definition, as implied by the authors of the study, where a distinction was made between renal-limited AAV (RLV) and other AAV (GPA and MPA) [12]. As RLV were mostly associated with MPO-ANCA (in 67% of cases), they would probably have been classified as MPA in our study, as well as in the study by Mahr et al. [11].

The prevalence of AAV in our study is substantially lower than other estimations recently reported from Norway [9], Sweden [10], UK [18], Germany [20] or the USA [21]. Especially for GPA, these studies reported much higher prevalence estimations of 164–261 per million inhabitants [9, 10, 18, 20, 21]. The possibility of a decreasing north-south gradient in the northern hemisphere has been hypothesised for GPA, as estimations have been consistently higher in northern European countries or among residents of Minnesota, USA, which has a large proportion of descendants from northern Europe [7–10, 21]. For MPA, it has been formerly hypothesised that it might follow a latitudinal gradient that is inverse to that of GPA [7]. This hypothesis has been recently questioned by the high prevalence estimations for MPA in Sweden (94–150 per million inhabitants) [10, 19] and in Minnesota, USA (184 per million inhabitants) [21]. However, the much lower prevalence for MPA reported for Norway (58 per million inhabitants) [9] and Germany (28 and 46 per million inhabitants) [20, 22], which are close to our estimation for southern France, highlight that no clear geographic distribution pattern may exist for MPA in Europe.

In our population, we saw a significantly higher prevalence of AAV in non-European residents compared with those of European origin, which was mainly due to a higher prevalence of MPA in non-European residents. Previous studies that looked at multiethnic populations mainly suggested that GPA is less common in people of non-European than European ancestry [11] or in black and minority ethnic groups than in white residents [18]. The positive association of MPA with non-European origins found in our study is in line with the observation that MPA is the predominant AAV phenotype in China and Japan [7]. In our study, almost all cases of non-European origin came from Northern Africa, probably because of the proximity with Hérault and Gard, which are Mediterranean regions, while there was a larger proportion of patients from Sub-Saharan Africa in other studies [11]. Further research would be helpful to understand to what extent the development of AAV relies on genetic predisposition, as described in genome-wide association studies with major-histocompatibility-complex (MHC) and non-MHC associations [23], on ethnicity which may also influence disease severity [24], and on environmental factors.

Our work has the advantage of using the most recent ACR/EULAR classification criteria for AAV [4–6]. For the majority of our cases, these criteria allowed classification with a result consistent with the diagnosis retained by the treating hospital physician. However, we found that some rare cases could be defined as both GPA and MPA using these criteria, as they were not mutually exclusive. Precisely, these cases usually had clinical characteristics suggesting the presence of granuloma associated with GPA (i.e. destructive ENT signs, retro-orbital pseudo-tumours or subglottic stenoses) with positive MPOANCA. In such situations, we additionally used the EMA algorithm, which includes the use of surrogate markers for granuloma in upper and lower airways when there is no histologic proof, to distinguish GPA from MPA classification [14]. It is noteworthy that many recent epidemiological studies have used the EMA algorithm [9, 10, 12, 19, 21, 22], before the 2022 ACR/EULAR criteria were available.

The present study has methodological strengths. It aimed for a comprehensive estimation of prevalence, with the use of a population-based method relying on multiple sources, and the capture-recapture method to assess the comprehensiveness of our case-finding. To ensure case veracity, a methodical and standardised verification of cases was conducted, using clinical, biological and histological information, and validated classification criteria [4–6]. To align with recent studies [10, 12, 21], we expressed prevalence estimations in terms of both clinical (GPA, MPA or EGPA) and serological AAV subtypes (anti-PR3 AAV or anti-MPO AAV), as differences of outcome have been described depending on ANCA type [21, 25]. Limitations can be seen in the relatively low percentage of responses from the community-based physicians (23%), even though we believe that physicians who had knowledge of cases were more likely to answer. Another issue concerns the 97 residents recorded in the Health Insurance database, with less specific ICD, who could not be traced. With the hypothesis that the proportion of AAV cases is the same in this subgroup than in the identified patients of the database, we would not expect more than nine cases, i.e. <5% variation of the estimation. The potential bias related to incomplete case detection of single sources should have been compensated by our use of multiple sources of case-finding combined with the capture-recapture method. Also, we think the considerable response we got from hospitals probably limited the number of missed cases. Lastly, it should be noted that our study is geographically limited to a specific region in southern France, which may not be representative of the entire country, notably in terms of potential environmental risk factors.



In conclusion, while there is evidence that the prevalence of AAV is rising in multiple countries, the geographical distribution of AAV and its phenotypes is not well elucidated yet. Further studies, using homogeneous criteria and methodology, are needed to increase our knowledge about the geo-epidemiology of AAV, and to have a better understanding of the roles of ethnic or genetic predisposition vs environmental risk factors in the aetiology of AAV.

### **Data availability**

The data that support the findings of this study are not publicly available due to confidentiality issues but are available from the corresponding author (E.R.) upon reasonable request.

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### **Disclosure statement:**

The authors declare no conflict of interest for this work.

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