Autoimmunity Reviews xxx (xxxx) xxxx

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Environmental risk factors associated with ANCA associated vasculitis: A systematic mapping review

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ARTICLE INFO

Keywords:
ANCA associated vasculitis (AAV)
Environment
Risk factors
Geoepidemiology
Pollution
Infection

ABSTRACT

Background: Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a rare multi-system autoimmune disease, characterised by a pauci-immune necrotising small-vessel vasculitis, with a relapsing and remitting course. Like many autoimmune diseases, the exact aetiology of AAV, and the factors that influence relapse are unknown. Evidence suggests a complex interaction of polygenic genetic susceptibility, epigenetic influences and environmental triggers. This systematic mapping review focuses on the environmental risk factors associated with AAV. The aim was to identify gaps in the literature, thus informing further research.

Methods: Articles that examined any environmental risk factor in AAV disease activity (new onset disease or relapse) were included. Studies had to make explicit reference to AAV, which includes the 3 clinico-pathological phenotypes (GPA, MPA and EGPA), rather than isolated ANCA-positivity. All articles identified were English-language, full manuscripts involving adult humans (> 16 years). There was no restriction on publication date and all study designs, except single case reports, were included. The systematic search was performed on 9th December 2019, using the following databases: EMBASE, Medline (Ovid), Cochrane Library, CINAHL and Web of Science.

Results: The search yielded a total of 2375 articles. 307 duplicates were removed, resulting in the title and abstract of 2068 articles for screening. Of these, 1809 were excluded. Thus, 259 remained for full-text review, of which 181 were excluded. 78 articles were included in this review. The most notable findings support the role of various pollutants - primarily silica and other environmental antigens released during natural disasters and through farming. Assorted geoepidemiological triggers were also identified including seasonality and latitude-dependent factors such as UV radiation. Finally, infection was tightly associated, but the exact microorganism(s) is not clear - *Staphylococcus aureus* is the most presently convincing.

Conclusion: The precise aetiology of AAV has yet to be elucidated. It is likely that different triggers, and the degree to which they influence disease activity, vary by subgroup (e.g. ANCA subtype, geographic region). There is a need for more interoperable disease registries to facilitate international collaboration and hence large-scale epidemiological studies, with novel analytical techniques.

Abbreviations: Anti-neutrophil cytoplasm antibody, ANCA; ANCA associated vasculitis, AAV; Small Vessel Vasculitis, SVV; Autoimmune disease, AID; Microscopic polyangiitis, MPA; Granulomatosis with polyangiitis, GPA; Eosinophilic granulomatosis with polyangiitis, EGPA; renal-limited vasculitis, RLV; American College of Rheumatology, ACR; Chapel Hill Consensus Conference, CHCC; European Medicines Agency, EMEA; Ultraviolet, UV; Tumour necrosis factor-∝, TNF ∝; Mechanism of Action, MOA; Osteoarthritis, OA; Rheumatoid Arthritis, RA; Carbon monoxide, CO; Epstein Barr virus, EBV; Cytomegalovirus, CMV; Immunoglobulin, Ig; Rituximab, RTX; Trimethoprim-sulfamethoxazole, TMP-SMX; Healthy control, HC; Enzyme-linked immunosorbent assay, ELISA; Human Herpesvirus 8, HHV 8; Polymerase chain reaction, PCR; European Medicines Agency (algorithm), EMA; Incidence Rate Ratio, IRR; Not statistically significant, NS; Corticosteroid, CCS; Oral, PO; Glomerulonephritis, GN; Pauci-immune glomerulonephritis, PIGN; Respiratory Tract Infection, RTI; Immunosuppression, IS; Hepatitis B surface antigen, HBsAg; Antibody to hepatitis B core antigen, Anti-HBc; Birmingham Vasculitis Activity Score, BVAS; Five Factor Score, FFS; Chronic Rhinosinusitis, CRS; Sulphur Dioxide, SO_2; Nitrogen Dioxide, NO_2; Carbon Dioxide, CO_2; Adjusted Hazard Ratio, aHR; Relative risk, RR; International Classification of Disease 10th revision, Australian Modification, ICD-10-AM; Randomised Controlled Trial, RCT; European Vasculitis Study Group, EUVAS; Chronic Obstructive Pulmonary Disease, COPD; Glomerular Disease Collaborative Network, (group of 120 nephrologists from 38 public and private institutions in SE USA, GDCN)

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https://doi.org/10.1016/j.autrev.2020.102660
Received 22 March 2020; Accepted 29 March 2020

1. Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a rare multi-system autoimmune disease comprising four clinico-pathological syndromes: Microscopic polyangiitis (MPA), Granulomatosis with polyangiitis (GPA), Eosinophilic granulomatosis with polyangiitis (EGPA) and renal-limited vasculitis (RLV). It is characterised by a pauci-immune necrotising small-vessel vasculitis with a relapsing and remitting course. AAV is associated with the development of characteristic autoantibodies directed against myeloperoxidase (MPO) or proteinase-3 (PR3) molecules (ANCA), which are abundant proteins in neutrophils and monocytes. While outcomes have improved since the advent of immunosuppression in the 1960s, significant treatment related morbidity and mortality remain a problem [1]. Personalised risk assessment and treatment strategies are a priority.

Classification of systemic vasculitis has traditionally been confusing, with little consensus. Initial diagnostic criteria were developed by the American College of Rheumatology (ACR) in 1990 [2]. The Chapel Hill Consensus Conference (CHCC) criteria, focusing on histology, were then published in 1994, and revised in 2012 [3] to include the serological hallmark, ANCA. The European Medicines Agency (EMEA) algorithm incorporates both of these in a pragmatic consensus classification [4], in an effort to standardise their application clinically. It is anticipated that the 'Diagnostic and Classification of the Systemic Vasculitides (DCVAS)' [5] study will aid in uniforming the classification going forward to facilitate large-scale studies and comparisons.

Like many autoimmune diseases (AIDs), the exact aetiology of AAV, and the factors that influence relapse are unknown. Evidence suggests a complex interaction of polygenic genetic susceptibility [6], epigenetic influences [7] and environmental triggers. The aetiological role of the environment has received least attention. Several microbial, occupational and climatic exposures have been implicated, but most studies thus far have been small, underpowered single centre epidemiological studies, primarily due to the rarity of disease. Physicians receive limited training in environmental medicine, while environmental scientists receive scanty medical training, resulting in a collaborative knowledge gap. This, with the lack of validated environmental exposure biomarkers and standardised tools to quantify exposure, has further hampered efforts. The expansion of disease registries and increasing collaboration over the last decade has assisted in more comprehensive case ascertainment, but more concerted and standardised efforts are critical going forward. This review focuses on the environmental risk factors associated with AAV - defined as any non-genetic aetiological factor. Given the diverse nature of both the triggers reported and the study designs utilised, a pragmatic decision to complete a 'systematic mapping review' was made [8], to identify gaps in the literature, thus informing further research.

2. Methods

2.1. Eligibility criteria

Articles that examined any environmental risk factor (defined by any non-genetic aetiological factor) in AAV disease activity (new onset disease or relapse) were included. Studies had to make explicit reference to AAV, which includes the 3 clinico-pathological phenotypes (GPA, MPA and EGPA), rather than isolated ANCA-positivity. All articles identified were English-language, full manuscripts involving adult humans (> 16 years). There was no restriction on publication date and all study designs, except single case reports, were included. Articles which duplicated the findings of other studies were excluded.

2.2. Search strategy

The systematic search was performed on 9th December 2019, using the following databases: EMBASE, Medline (Ovid), Cochrane Library, CINAHL and Web of Science. The search strategy for EMBASE was devised by JS, in consultation with an expert librarian, DM. A comprehensive search strategy can be found in the supplementary material (Supplementary Appendix 1). The search strategy was subsequently adapted for other databases by DM. Duplicates were excluded. Using Covidence [9], JS and JH independently screened titles and abstracts for relevance. Any discrepancies regarding title and abstract eligibility were reviewed by a third independent reviewer, ML. Full texts of articles satisfying eligibility criteria were obtained for full review. Based on expert knowledge and a review of the reference lists of articles, additional relevant articles were identified.

2.3. Data collection, data items and risk of bias

The articles included in this review were evaluated for environmental risk factors associated with AAV disease activity. These risk factors were subsequently grouped into common themes: geoepidemiology, pollution, infection and "other". Each article was assessed for: author, year of publication and country of origin, type of study design and method, environmental risk factor(s) explored and method of determining exposure and outcome of the study (*Tables 1, 2 and 3*). The quality and risk of bias of each study was reviewed using an appropriate tool (Supplementary Tables 1 and 2): the Modified Newcastle-Ottawa Scale for Case-control and cohort studies (> 6/9 is considered good quality) [10], the International Narrative Systematic Assessment (INSA) scoring system for narrative reviews (> 5/7 is considered good) [11], and the respective checklists from the Centre for Evidence-Based Medicine for randomised controlled trials and meta-analyses. In order to produce a complete map of the literature no study was excluded, but the quality of each was considered in the interpretation of results.

2.4. Study selection

The search yielded a total of 2375 articles. 307 duplicates were removed, resulting in the title and abstract of 2068 articles being screened. Of these, 1809 were excluded as the title and/or abstract did not meet the inclusion criteria. Consequently, 259 remained for full-text review, of which 181 were excluded (see Figure 1: PRISMA flow diagram for exclusion details). 78 articles were therefore included in this review.

3. Geoepidemiology

The included studies are summarised in *Table 1*. The introduction of ANCA testing in the 1990s, followed by an increased awareness, improved case definition and enhanced availability of serological testing, resulted in an apparent rising incidence of AAV in recent years [12]. The estimated annual incidence of AAV is currently 13-20 cases/million, with a prevalence of 300 cases/million [13]. However, the distribution of disease phenotypes and serotypes varies worldwide: MPO-ANCA predominates among Asians and Southern Europeans, while PR3-ANCA is more common in Northern Europeans [14]. This aligns with the preponderance of MPA (83%) in Japan [15] and China [16,17], and GPA (66%) in the United Kingdom (UK) [15].

Unusually for an autoimmune disease, AAV is largely a disease of later life, with peak incidence between 65-74 years of age [18]. It predominates in Caucasians [19,20], with a European ethnic bias [21]. Studies mostly report a slightly increased male incidence [22], which contrasts to most AIDs and the female preponderance of AAV reported in China [17], while there is no gender bias noted in Germany [23].

This geographic clustering, in addition to reported temporal clustering, a latitudinal gradient, seasonal variation in disease onset and differences in urban/rural disease prevalence all point towards an environmental trigger(s).

Table 1
Characteristics of the included studies: Geoepidemiology.

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
GEOEPIDEMIOLOGY			
SEASON			
Aries et al. 2008 Hamburg, Germany [32]	Case series. 445 consecutive GPA patients (1966-2002) in the University Hospital Schleswig-Holstein Lubeck	Season. Questionnaire of symptom onset, with cross-check of medical records.	No seasonal variance in symptom onset (p 0.3).
Carruthers et al. 1996 Norfolk, UK [27]	Prospective cohort. All patients attending rheumatology, ENT, respiratory or nephrology departments (Norwich Health Authority) between 1988-1994 with new diagnosis of GPA, OR, those with histopathological diagnosis of GPA were entered into a vasculitis registry (n = 21).	Season. Medical records review.	Symptom onset was most common in winter (Dec-Feb) (43%), and least common in autumn (Sep-Nov) (0%).
Cotch et al. 1996 New York, USA [19]	Population-based cohort study. 571 patients with first hospitalisation with GPA identified from SPARCS (discharge database for all non-federal, nonpsychiatric facilities in New York State) between 1986-1990.	Season. Review of discharge database for season of hospitalisation.	No seasonal variance in hospitalisation of GPA patients (25.6% Spring, 25.2% Summer, 22.1% Autumn and 27.1% Winter). No clear correlation between urban/rural living and GPA.
Draib et al. 2018 Catalonia, Spain [30]	Retrospective cohort. N = 234 AAV patients with renal involvement (2001-2014) in 8 Catalonian hospitals, Spain (75.6% MPO).	Season. Medical records review regarding symptom onset.	There was significantly higher incidence of symptom onset in winter (Jan-Mar) (chi-square = 13.36, p 0.003). Periodic fluctuations of frequencies with peaks every 10-12 months were observed, when Eigen decomposition was applied.
Falk et al. 1990 GDCN, SE USA [24]	Inception cohort study. 70 patients with PIGN and ANCA positivity were included between Sep 1984 – Jan 1989.	Season of symptom onset via medical records.	There was a seasonal variation in symptom onset. The frequency of symptom onset was statistically higher than expected in winter (Dec-Feb, 38% vs. 25% expected, $p < 0.05$) and was lower than expected in summer (June-Aug, 11% vs. 25% expected, $p < 0.05$) in AAV patients with renal involvement.
Koldingsnes et al. 2000 Norway [33]	Retrospective cohort study. 55 GPA patients (ACR criteria) identified from hospital discharge records from all 11 hospitals in the North of Norway and 2 pathology databases (three 5-year periods between 1984-1998).	Season. Medical records review regarding symptom onset.	No seasonal variance in symptom onset of GPA.
Lane et al. 2007 Norfolk, UK [34]	Retrospective cohort study. 51 GPA patients (ACR criteria) diagnosed between 1989-1998 identified from a prospective vasculitis register at the Norfolk and Norwich University Hospital.	Season. Medical records review regarding symptom onset, verified by interview of 47 surviving patients.	There was a non-significant trend towards a higher onset of GPA symptoms onset in autumn (Sep-Nov, 35.3%), and a trough in summer (June-Aug, 15.7%), $p < 0.5$.
Li et al. 2018 China [29]	Retrospective cohort. 299,906 inpatients (split between 2010-12 and 2013-15) from 878 tertiary hospitals across 31 provinces of China, identified by ICD-10 discharge diagnoses in an electronic database (Hospital Quality Monitoring System) with relevant details obtained from corresponding medical records.	Season determined by frequency of AAV per season. Medical record review.	The frequency of AAV was highest in winter (30.2% vs. 21.2 – 25.4% for other seasons).
Mahr et al. 2006, France [31]	Retrospective cohort. 59 consecutive GPA patients (ACR criteria) enrolled by French hospitals to WEGENT and IMPROVE trials between 2001-2004.	Season. Telephone interviews to patients to determine symptom onset. Date subsequently compared to that recorded in medical record – which was on average 2.6 ± 6.6 months later.	There was a significantly higher rate of symptom onset in summer compared to the other 3 seasons combined (chi-square 11.23, 1 df, p 0.001), and particularly in August (chi-square 15.29, 1 df, p 0.001).
Pavone et al. 2006 Italy [28]	Retrospective cohort. 75 AAV (ACR/CHCC criteria) patients (with 2 ≤ organ involvement) identified by the Secondary and Primary Vasculitides study group (1985 – 2003).	Season, identified by retrospective chart review.	Season of onset differed significantly between GPA and MPA (p 0.036). The symptom onset was mainly in autumn and winter for GPA patients (74%), but in spring and summer for MPA patients (69%).
Tidman et al. 1998 Gothenburg, Sweden [25]	Retrospective cohort study. All hospitalised SVV patients in Örebro county between 1975-95 (identified by ICD-8/9 codes), including 127 AAV patients (confirmed with CHCC 1994 criteria). Adjusted population figures obtained from the Statistical Central Bureau of Sweden.	Season, identified by symptom onset via retrospective chart review.	There was significantly increased symptom onset during the 'dark winter months' (Dec-Feb) for patients cANCA positive. There was no significant difference in symptom onset between seasons when analysed by disease phenotype (e.g. GPA), although numbers were small.

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Table 1 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
GEOEPIDEMIOLOGY			
LATITUDE			
Gatenby et al. 2009 Canberra, Australia [41]	Ecological study. 13 incidence studies of AAV included (using ACR or CHCC criteria) between 1975-2004.	Latitude, UV radiation. Using the time period and latitude-longitude of the largest city in each study, the mean daily- and winter- ambient UV radiation levels were obtained from satellite data. Ambient UV radiation level weighted to erythemally effective wavelengths and to vitamin D effective wavelengths were then estimated – these various measures were highly correlated.	There was a strong positive correlation between incidence of both GPA (r 0.62, p 0.02) and EGPA (r 0.43, p 0.22) and latitude. For each degree increase in latitude the incidence of GPA and EGPA increased by 3.5% (IRR 1.04, 95% CI 1, 1.07, p 0.03) and 3.4% (IRR 1.04, 95% CI 0.99, 1.08, p 0.11) respectively. There was a strong and modest inverse correlation between ambient UV radiation and GPA and EGPA, respectively. For an increase in UV radiation of 1000 joules/m^2, the incidence decreased by 36% for GPA (IRR 0.64, 95% CI 0.44, 0.94, p 0.02) and by 33% for EGPA (IRR 0.67, 95% CI 0.43, 1.05, p 0.08). These inverse relationships were maximal with measures of winter ambient UV radiation. MPA incidence was not associated with latitude or UV radiation.
Kalsch et al. 2009 Groningen, The Netherlands [42]	Case-control. 51 AAV (CHCC) patients vs. 67 HCs, recruited from outpatient clinic at the University Hospital Mannheim.	Serum 25-hydroxy (25-OH) vitamin D, using the Immunodiagnostic Systems enzyme immunoassay kit (IDS, Germany).	Serum 25-OH vitamin D levels were significantly lower in AAV patients compared to HCs ($p < 0.0001$), despite the majority of patients taking supplements. Active vitamin D (1, 25-$(OH)_2$ D_3, p 0.02), all-*trans* retinoic acid (p 0.001) and 9-*cis* retinoic acid ($p < 0.0001$) (all 1 μmol) all inhibited (LPS stimulated whole blood) TNFα production, which was maximal in AAV patients vs. HCs.
Kemna et al. 2017 Maastricht, The Netherlands [43]	Retrospective cohort study. GPA/MPA (EMA classification) patients with renal involvement and rising ANCA titre during remission (n = 60), attending Maastricht University Medical Centre (2000-2011).	Season, serum 25-hydroxy (25-OH) vitamin D, using the LIAISON 25-OH Vitamin D TOTAL assay (DiaSorin) and antibiotic maintenance therapy.	A rise in ANCA titre during autumn (Sep-Nov) was associated with a 4-fold increased risk of relapse (HR 4.37, 95% CI 1.6, 11.9). 93% had insufficient 25-OH vitamin D levels (< 75 nmol/l) at the time of ANCA rise. These levels fell significantly in those who relapsed (difference -6.3 ± 14.4 nmol/l, p 0.017), but trended upwards (NS) in those who remained in remission (difference 2.7 ± 16.3 nmol/l, p 0.43). Antibiotic maintenance therapy was not protective against relapse (chi-square 0.01, p 0.92), although drug nor dose was specified.
O'Donnell et al. 2007 New Zealand (NZ) [21]	Retrospective cohort. ICD-10-AM M313 (GPA, necrotizing respiratory granulomatosis) and M301 (polyarteritis with lung involvement, including EGPA) first discharge diagnoses identified using the National Minimum Dataset of the Ministry of Health (NZ), between 1999-2003 and standardised by age and ethnicity using the 2001 NZ census.	Latitude using 4 groups regions. Season that the discharge diagnosis identified in. Urban/secondary urban/rural residence defined by Statistics NZ.	There was a positive north-south latitudinal gradient identified for M313 (R^2 0.96, p 0.024), but not for M301 or the 2 codes combined. Incidence peaked in autumn (March-May) (p 0.014). There was no difference in combined disease incidence between urban and rural residence (p 0.142). The incidence among Europeans was twice that of NZ Maoris or Asians (60.2 per million vs. 34.2 per million vs. 33.6 per million, p 0.023 and p 0.014, respectively).
Reinhold et al. 2002 Germany [23]	Registry based prospective cohort study in north and south Germany (1998-1999). 473 incident PSV cases (CHCC) identified from a population of 4,880,543, of which 90 were AAV (56% urban residence).	Latitude.	There was no difference in the incidence of any AAV subtype between north and south Germany. There was no clusters of PSV in urban/rural areas.

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Table 1 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
GEOEPIDEMIOLOGY			
Watts et al. 2001 Europe [40]	Retrospective population-based cohort study. 86 incident SVV cases in Norwich (patients registered with a general practitioner in the Norwich Health Authority and attending a single referral centre, Norfolk and Norwich Hospital) and 41 incident SVV cases in Lugo (attending a single referral centre, Hospital Xeral-Calde) (ACR/CHCC criteria), from a background population of 413,500 and 204,100 respectively, between 1988-1998.	Latitude, by comparing age- and sex-specific incidence rates of SVV between Norwich, UK (latitude 52° N) and Lugo, Spain (43° N).	There was a latitudinal trend in GPA and MPA incidences in Europe, with GPA being more common in the north, while MPA is more common in the south. The incidence of GPA was higher in Norwich (10.6/million, 95% CI 7.8, 14.0) compared to Lugo (4.9/million, 95% CI 2.4, 8.8). The inverse was true for MPA: Norwich 8.4/million (95% CI 5.9, 11.5) vs. Lugo 11.6/million (95% CI 7.6, 17.0). EGPA was more common in northern Europe (Norwich 3.1/million (95% CI 1.7, 5.2) vs. Lugo 0.9/million (95% CI 0.1, 3.2)).
Watts et al. 2001 Europe [22]	Extension of study comparing incidence of SVV in Norwich (UK) and Lugo (Spain) [40]. Utilising the same methodology, incident SVV cases from the University of Tromsø, Norway were compared.	Latitude, as described above [40], by comparing age- and sex-specific incidence rates of SVV between Tromsø, Norway (latitude 70°N), Norwich, UK (52°N) and Lugo, Spain (43°N).	There was a latitudinal trend in GPA and MPA incidences in Europe, with the incidence of MPA decreasing with more northern latitudes (Tromsø 2.7/million (95% CI 1.3, 4.8)), and a trend to GPA increasing (Tromsø 10.5/million (95% CI 7.6, 14.2)).
Weiner et al. 2019 Multi-centre (EU and USA) [38]	Multi-centre (n = 10), multi-national (EU and USA) registry based cohort study. 1408 GPA and MPA patients were included (EMA criteria), who were ANCA (ELISA) positive and had biopsy-proven renal involvement, between 2000-2013. Only registries that recruited consecutive patients from a defined geographic area were included.	Latitude, of the participating centre (EU) or of capital city of each state (USA), was obtained from the World Geodetic System 84 coordinate reference system. Mean monthly erythemally weighted UV radiation level was obtained from the STRANG database (Swedish Meteorological and Hydrological Institute).	Increasing latitude (OR 1.29, 95% CI 1.05, 1.58, p 0.016) and decreasing UV radiation (OR 0.94, 95% CI 0.89, 0.99, p 0.038) were significantly associated with increasing odds of a patient displaying PR3 positivity, when adjusted for age, gender, eGFR and longitude, in separate multivariate analyses. There was a strong inverse correlation between latitude and UV radiation (Spearman's p -0.99).
RESIDENCE			
Herlyn et al. 2013 Northern Germany [44]	Retrospective cohort study. 70 AAV (EMEA/CHCC) patients identified through (postal) questionnaires to all hospital departments, physicians, health insurance providers, pension funds, reference laboratories for AIDs and death registries for Luebeck (urban) and rural Segeberg (Jan-Dec 2006).	Urban/rural residence.	There was a higher prevalence of GPA (114/million vs. 85/million) and MPA (43/million vs. 16/million) in urban areas compared to rural areas, while the inverse was true for EGPA (35/million rural vs. 10/million urban).
Kanecki et al. 2017 Warsaw, Poland [125]	Retrospective, population-based cohort study, to identify new EGPA diagnoses (n = 344) using hospital discharge records (2008-2013), from the Polish National Institute of Public Health survey.	Urban/rural residence.	There was a higher EGPA prevalence in urban compared to rural areas (69% vs. 31% respectively, $p < 0.001$).
Ormerod et al. 2008 Canberra, Australia [126]	Retrospective cohort. 62 AAV cases were identified by ICD-9/10 codes from the inpatient databases of 2 teaching hospitals within the Australian Capital Territory (ACT) Service between 1995-2004. Cases were confirmed by applying ACR/CHCC criteria on medical record review. All ANCA results for these hospitals were also reviewed. Population figures were obtained from census data published by the Australian Bureau of Statistics.	Urban/rural residence.	The incidence of MPA was higher in rural areas (14.4/year per million, 95% CI 7.7, 23.5), compared to urban areas (1.6/year per million, 95% CI 0.2, 7.2), between 2000-2004. A similar trend was noted for GPA (prevalence in rural areas 129/million, 95% CI 108.6, 154.4 vs. 82/million, 95% CI 65.2, 101.8 in urban areas).

3.1. Seasonality and temporal clustering

Reports on seasonality are conflicting, although the majority of hospital- [24–28] and population-based studies [29,30] report a peak onset in winter. These studies report a statistically higher symptom onset in winter (December-February, 30.2% - 43%, expected: 25%), and lower than expected symptom onset in summer (June-August, 11%). Paradoxically, a French study reported a summer peak, particularly in August [31], while an increased incidence during autumn (March-May) was noted in New Zealand [21]. In contrast, five studies were unable to find any consistent seasonal pattern [19,32–35]. Notably, Lane et al [34] re-examined the Norfolk data and found a trend towards higher symptom onset of GPA in autumn, contrasting to the winter peak found by Carruthers et al when analysing a very similar cohort [27]. Interestingly, an Italian group found different seasonal association between GPA and MPA [28]. The symptom onset was mainly in autumn and winter for GPA patients (74%), but in spring and summer for MPA patients (69%). This is consistent with the increased prevalence of MPA and GPA in hot and cold countries, respectively [22].

This argument is further enhanced by studies that display temporal clustering. GPA occurs in a cyclical nature, with non-random peaks, every 4-5 years and 7.6 years in Britain [36] and Norway [33], respectively – this effect was not observed for MPA. A similar 3- to 5-year and 3- year periodicity was noted in Scandinavian SVV patients with renal involvement between 1975-95 [25] and Spanish AAV patients [37], respectively. A shorter periodicity (10-12 months) was noted in

Table 2
Characteristics of the included studies: Pollution

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
POLLUTION			
SILICA AND OTHER DUSTS			
Beaudreuil et al. 2005 Tours, France [51]	Case-control. All (n = 60) consecutive ANCA-positive patients at CHU Bretonneau (1990-2000) vs. 120 age and sex matched controls, who were inpatients in the hospital (2000-2001). Of note, only 42 of the ANCA-positive cases satisfied the criteria for GPA, MPA or EGPA.	Structured interviewer-administered questionnaire evaluating occupational exposures (silica, silicon, OS, any other toxic agent) and smoking. Results were analysed (blinded) by 5 experts in a qualitative and semi-quantitative manner, creating an exposure score, which was categorised into nil, low, moderate or high.	ANCA-positive patients reported increased occupational dust exposure vs. controls (OR 2.6, 95% CI 1.3, 5.3). Exposure to silica was associated with ANCA-positivity (OR 3.4, 95% CI 1.1, 9.9), in a dose-dependent manner, particularly with regards to intensity of exposure. No difference in ANCA serotype found. The most common occupation associated with silica exposure in the ANCA-positive group was bricklaying. There were no other significant associations identified (smoking, silicon, OS, paint, lead, white spirit, benzene).
Gomez-Puerta et al. 2013 Boston, USA [50]	Systematic review and meta-analysis of 6 observational studies [52,53,55,63,101,127] (1993-2007) examining the association of silica and AAV.	Silica exposure, categorized as ever/never.	Ever being exposed to silica was associated with a more than 2-fold increased risk of AAV (pooled OR 2.57, 95% CI 1.51, 4.36). This risk was significantly elevated in those with renal involvement (OR 3.13, 95% CI 1.68, 5.84), GPA (OR 3.56, 95% CI 1.85, 6.82) and MPA (OR 3.95, 95% CI 1.89, 8.24).
Rihova et al. 2005 Prague, Czech Republic [128]	Case-control study. 31 AAV patients with pulmonary and renal (biopsy proven) involvement (CHCC) diagnosed at Charles University, Prague (1993-2002) vs. 30 age-, sex-, and residence-matched HCs provide by the Occupational Medicine Department.	Silicon-containing chemicals (silica dioxide and asbestos), obtained via a questionnaire designed by an occupational health physician. Extent of exposure was estimated by the intensity x frequency x duration. ANCA serology and smoking status were included as confounders.	Occupational exposure to silica dioxide (12.9%) and asbestos (9.7%) were reported by the AAV group but not (0%) in the control group ($p < 0.05$).
Farquhar et al. 2017 Christchurch, New Zealand [61]	Retrospective cohort. N = 52 AAV cases. Cases were identified by positive ANCA serology (all tests referred to 1 of 2 laboratories) and AAV (EMA) confirmed by review of medical records.	Earthquake related environmental exposures (e.g. dusts). Incidence rates of AAV compared pre- (Feb 2007-2010) and post- (Feb 2011-2014) the 2011 Christchurch earthquake (magnitude 6.1). Denominator obtained from 2013 NZ Census.	No statistically significant difference between the incidence rates of AAV pre- (1.87/100,000/annum) and post- (1.73/100,000/annum) the 2011 Christchurch earthquake. There was also no difference when stratifying by ANCA serotype or restricting to those residing in the urban area.
Li et al. 2018 China [29]	Retrospective cohort. 299,906 inpatients (split between 2010-12 and 2013-15) from 878 tertiary hospitals across 31 provinces of China, identified by ICD-10 discharge diagnoses in an electronic database (Hospital Quality Monitoring System) with relevant details obtained from corresponding medical records.	Air pollutants (average concentrations of SO_2, NO_2, CO_2 and particulate matter such as PM 2.5) (adjusted for annual average temperature, humidity and precipitation) and water pollutants (e.g. ammonia nitrogen) obtained from National Bureau of Statistics of China.	There was a positive correlation between exposure to carbon monoxide and the frequency of AAV (R^2 0.172, p 0.025). The proportion of AAV increased 1.37-fold in Yunnan following the 2014 earthquake (6.5 Richter scale) – from 0.19% in 2013 to 0.26% in 2014, despite no significant increase in PM10 from 2010 to 2015. There was no other significant relationship between the frequency of AAV in China and air (PM 2.5, PM 10, other inhaled particles, SO_2, or NO_2), or water pollutants measured.
Takeuchi et al. 2017 Miyagi, Japan [59]	Retrospective population-based cohort study. 43 newly-diagnosed MPO patients (CHCC 2012) attending the Japanese Red Cross Ishinomaki Hospital between 2007-2015, identified by screening computerised medical records for ICD-10 codes M30, M31, N01 and N05.	Earthquake/tsunami related environmental exposures (e.g. silica-containing sludge). Incidence rates of MPO compared pre- (2008-2010) and post- (2011-2013) the 2011 Great East Japan earthquake (GEJE, magnitude 9.0). Denominator obtained from monthly Government reports of population figures for the Ishinomaki medical district.	The annual incidence of MPO doubled after the GEJE (17.4/million/year (95% CI 7.66, 39.61) before vs. 33.1/million/year (95% CI 17.73, 61.74) after, p 0.044). The patients post-GEJE also displayed a more severe phenotype, with a higher BVAS (16 (IQR 12, 18) pre vs. 18 (IQR 16, 22) post, p 0.02).

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Table 2 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
POLLUTION			
Yashiro et al. 1999 Kyoto, Japan [58]	Case series (n = 29). Group 1 consisted of 14 MPO-AAV patients from Kobe who presented to the Nishi-Kobe Medical Centre between 1995-97 (3-year period). Group 2 consisted of 15 MPO-AAV patients from the Kyoto area (unrelated to the earthquake) and presented between 1990-97 (8-year period).	Earthquake related environmental exposures (e.g. asbestos, silica), following the 1995 Kobe earthquake (magnitude 7.2). The environmental bureau of Kobe city reported a 20-fold increase in asbestos levels in the air following the earthquake, which lasted for 30 months. There is no data on silica.	There was a cluster of MPO-AAV cases observed in the Kobe area within the 3-year period following the 1995 earthquake, equating to a more than doubling in annual frequency (14 cases in Kobe vs. 6 cases in Kyoto between 1995-97). The patients post the Kobe earthquake had higher rates of URT ($p < 0.01$), and displayed a more severe phenotype, with more patients requiring renal replacement therapy at diagnosis ($p < 0.02$) and a high rate of severe pulmonary involvement ($p < 0.01$).
SMOKING			
Haubitz et al. 2005 Germany [110]	Cross-sectional cohort study. 197 patients with GPA/MPA (ACR/CHCC) recruited from 2 German vasculitis referral centres (Hannover Medical School and Franz-Volhard Clinic).	Smoking history obtained from face-to-face or telephone interview with patients. Current smoker defined as a minimum of 1 cigarette per day within 2 years of symptom onset. Smoking prevalence in the general population (denominator) obtained from the 1995 federal randomised micro-census (1% German population).	There was a lower prevalence of smokers in the GPA/MPA group compared with the background population (14% vs. 24.3%, $p < 0.001$).
Pearce et al. 2018 Nottingham, UK [68]	Prospective population-based Case-control. 757 incident GPA patients, identified in the Clinical Practice Research Datalink (CPRD, UK primary care database) (1990-2014) vs. 7546 age-, sex- and general practice-matched controls.	Smoking obtained from GP records and categorized as never, former, current and unknown. Occurrence of infection, preceding diagnosis (> 1 year) including upper and lower RTI, urinary tract (UTI) and cellulitis, captured by CPRD. Use of medications prior to diagnosis: allopurinol, carbimazole, levothyroxine, PTU, sulfasalazine (SSZ), recorded in CPRD.	There was an increased risk of GPA in former smokers compared with never smokers (OR 1.5, 95% CI 1.2, 1.8, $p < 0.001$). Current smoking was marginally protective against GPA compared with never smokers (OR 0.8, 95% CI 0.7, 1.0, p 0.077). Sinus infections (1 to 4 years prior to the index date) were significantly associated with GPA onset. This risk was maximal 1-2 years prior (OR 2.7, 95% CI 1.8, 4.2, o < 0.0001). Upper and lower RTIs were also significantly associated with developing GPA, but only in the 1-2 years prior to diagnosis (OR 1.7, 95% CI 1.3, 2.3, P 0.0004; and OR 1.4, 95% CI 1.0, 2.1, P = 0.05, respectively). There was no association between UTI nor cellulitis and GPA risk (> 1 year prior). All infections were significantly associated with GPA onset in the year prior to the index date.
Yamaguchi et al. 2018 Nagoya, Japan [129]	Multicentre (9 Japanese Nephrology centres) retrospective cohort study. 122 GPA and MPA patients (EMA) included (majority being MPA and MPO-ANCA positive).	Smoking history identified by medical record review. Categorised into never-, ex-, or current-smoker and quantified using number of pack-years (1 PY = 20 cigarettes per day x 1 year) smoked.	Smoking was significantly associated with relapse in MPA (p 0.003), in a dose-dependent manner (p 0.004). Specifically, current smoking was associated with a 7.5-fold increased risk of relapse (aHR 7.48, 95% CI 2.73, 21.0), while ever having smoked (ex/current) was associated with a 3.7-fold increased risk (aHR 3.72, 95% CI 1.57, 9.21, 0.003).
FARMING AND ANIMALS			
Lane et al. 2003 UK [52]	Case-control. 103 AAV cases (1988-2000) at the Norfolk and Norwich University Hospital, identified from prospective vasculitis register. Age and sex matched controls: 220 non-inflammatory musculoskeletal disease (excluded AID), 19 secondary vasculitis and 34 asthma.	Face-to-face structured questionnaire (not-blinded) to elicit - Urban/rural residence - Occupational exposure to silica, organic solvents (OS) and heavy metals, using job exposure matrices (indirect quantitative). Each exposure was graded as any, low, intermediate or high in the index year and at any time during working life. - Farming history - Allergy (self-reported) - Others: domestic pets, blood transfusion, TB history, vaccination or steroid withdrawal within 6 months, smoking history	Farming exposure was associated with risk of GPA (OR 2.7, 95% CI 1.2, 5.8) and MPA (OR 6.3, 95% CI 1.9, 21.6), but not EGPA. High occupational silica exposure in the index year was a risk factor for AAV (OR 3.0, 95% CI 1, 8.4). The risk of MPA also rises with occupations at intermediate or high silica exposure (OR 4.6, 95% CI 1.3, 16.5). No association with duration of silica exposure. Any history of high OS exposure positively associated with AAV (OR 2.7, 95% CI 1.1, 6.6), specifically GPA (OR 3.4, 95% CI 1.3, 8.9) There were no further associations identified including smoking.
Lee et al. 2007 Norfolk, UK [65]	Case series (n = 8) diagnosed with GPA (ACR, 2 localised, 6 generalised) between 2005-06 at the	Environmental exposures including farming, animals, dust, solvents, gardening and	5/8 patients reported high farming activity in the index year – all had generalised GPA. 4/8

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Table 2 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
POLLUTION			
	Norfolk and Norwich University Hospital, Norfolk, UK.	allergy history. Obtained via an interviewer administered questionnaire.	reported close animal contact and frequent gardening activities. All other exposures were reported in < 50%.
Stamp et al. 2015 Canterbury, New Zealand [54]	Case-control study. 49 GPA patients (ACR/CHCC/EMA criteria), identified from Nephrology and Rheumatology databases vs. 4:1 age- and sex-matched controls (2 MSK [OA/fracture], 2 respiratory[asthma/COPD]) identified from the surgical waiting list and a Respiratory database, respectively, at Christchurch hospital.	Environmental exposures (occupation, hobbies, pets, residence, farm, allergy) obtained from a structured interview performed by a single unblinded interviewer (telephone/in-person). Occupational exposure to silica, metal and OSs were defined using job exposure matrices (indirect quantitative: low, intermediate or high). Intensity of exposure = duration (years) x level (e.g. low). 2 timeframes for exposures utilised: in the 1 years prior to index date, or at any time.	There was a significant association between any reported exposure to dust (specifically silica and grain dust) and GPA (OR 3.6, 95 % CI 1.5, 8.3, p 0.003). There was a positive relationship between the intensity of lifetime occupational exposures of silica (p 0.001), OSs (p 0.001) and metals (p 0.003) and GPA. Occupation as a farm worker was associated with an increased GPA risk (OR 3.43, 95% CI 1.5, 7.5, p 0.002). Visiting a farm in the 12 months prior to the index date was also significantly associated with developing GPA (OR 7.2, 95% CI 2.6, 19.4, p < 0.001) vs. working, living or no farm exposure. Specific gardening activities were also associated with GPA including digging (OR 3.2, 95% CI 1.4, 7.0, p 0.003), mowing (OR 2.7, 95% CI 1.3, 5.8, p 0.008) and planting (OR 2.6, 95% CI 1.2, 5.5, p 0.013).
Willeke et al. 2015 Germany [48]	Case-control study. 189 AAV patients (ACR/CHCC/EMA) vs. 190 residence-matched disease controls (119 RA and 71 Large vessel vasculitis), selected from the Rheumatology inpatient and outpatient departments at the University Hospital of Münster, Germany.	Environmental exposures (occupation, pets, farm related parameters, MRSA status [obtained by chart review for patients and nasal/pharyngeal swab culture for MRSA for controls]) obtained from a structured unblinded single- interviewer-administered questionnaire (telephone or face-to-face). Medical records were reviewed to validate disease onset.	Regular farm (OR 3.44, 95% CI 1.43, 8.27, p 0.006), cattle (4.30, 95% CI 1.43, 8.27, p 0.01) and pig (OR 2.75, 95% CI 1.12, 6.75, p 0.025) exposure were strongly associated with AAV. In subgroup analysis, these associations were maximal for GPA, while the associations for MPA and EGPA were not significant. Harvesting was associated with AAV (OR 2.45, 95% CI 0.92, 6.52, p 0.07). There was an association between MRSA carriage and AAV (OR 3.38, 95% CI 1.11, 10.31, p 0.033). For all findings above, on subgroup analysis, these associations were maximal for GPA, while there were no associations with MPA and EGPA. There was no association between pets and AAV (OR 1.15, 95% CI 0.73, 1.91, p 0.54). There were no significant differences in the occupations reported between those with AAV and controls, including no increased number of silica associated occupations among patients.
OTHER POLLUTANTS			
Albert et al. 2005 Philadelphia, USA [46]	Case series (n = 7) of GPA cluster in Dublin, Pennsylvania, in a 3-year period, within a 10-mile radius of an Environmental Protection Agency Superfund toxic waste site.	Exposure questionnaire of 32 environmental variables (e.g. solvents).	This cluster of GPA patients were potentially exposed to high levels of industrially generated contaminants including: - Trichloroethylene (TCE) - Vinyl chloride - Methyl tertiary-butyl ether (MTBE) - Dichloroethene (DCE) - Chromic acid
Albert et al. 2004 Philadelphia, USA [62]	Case-control. 53 GPA in- and outpatients, (initially identified by billing codes and subsequently fulfilled ACR criteria) attending the Hospital of the University of Pennsylvania vs. 53 gout and 50 OA controls.	Telephone administered questionnaire. Occupational, hobbies & chemical exposures, tobacco, allergic history. Analyses were adjusted for age and sex.	Mercury was associated with GPA (OR 10.69, 95% CI 1.1, 533.2, p 0.04). The association between CO and GPA approached statistical significance (OR 3.71, 95% CI 0.9, 17.3, p 0.08) There was no significant association between any other exposure (e.g. farming, coal, lead, welding fumes, other heavy metals or solvents) and GPA.
	Case-control study. 65 AAV patients (renal biopsy proven PIGN) enrolled in the Glomerular Disease	Environmental exposures (smoking, pesticides, cleaning agents, occupational	In a multivariable model, there was a non-significant trend towards an increased risk of

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Table 2 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
POLLUTION			
Hogan et al. 2001 UNC, USA [53]	Collaborative Network registry vs. 65 age-, sex-, and race-matched disease controls (nephrology outpatient clinic).	history) obtained from a patient-completed self-reported questionnaire. Of note, influence of silica in this study is included in the meta-analysis elsewhere and so is not considered here [50].	AAV with renal involvement with exposure to pesticides (OR 2.32, 95% CI 0.47, 11.5, p 0.303). There was no association found between AAV and smoking (OR 0.66, 95% CI 0.25, 1.78, p 0.41), fuel exposure (OR 0.43, 95% CI 0.10, 2.01, p 0.28), cleaning agents (OR 1.00, 95% CI 0.25, 3.96, p 0.99), glues (OR 0.49, 95% CI 0.05, 4.65, p 0.54) or paint (OR 0.80, 95% CI 0.25, 6.07, p 0.80).
Knight et al. 2010 Sweden [47]	Population-based case-control study. 2288 GPA patients identified by ICD-discharge diagnosis in Swedish national inpatient registry vs. 10:1 age, sex, county and marital status matched controls from the Swedish Population register.	Occupational exposure (inhaled particles or livestock), via linkage of registries with the Swedish censuses. Exposure assessments were performed by assessing whether the person was in the same occupation in 1, 2 or more censuses.	There was no general association between 32 selected occupations and GPA (pooled OR 1.1, 95% CI 1, 1.3). The RR of individual occupations centred around 1 with ORs ranging from 0.6 to 1.9. Borderline occupations (NS) included: bakers (OR 1.6, 95% CI 1, 2.6) and miners (OR 1.9, 95% CI 1, 3.5). Specifically, there was no association with livestock farming (OR 1.1, 95% CI 0.9, 1.4).
Nuyts et al. 1995 Antwerp, Belgium [63]	Case-control. All consecutive GPA (ACR) patients with renal involvement attending 6 Belgian renal units between 1991-1993 (n = 16) vs. age, sex and region matched HCs (2:1), obtained from voter's lists.	Occupational exposure via interview. Exposure history (degree and frequency) was quantitatively scored by a blinded industrial hygienist (0-4).	There was a non-significant association between lead (OR 3.5, 95% CI 0.3, 30.9) and cadmium (OR 5, 95% CI 0.1, 184.1), and GPA. Exposure to hydrocarbons (OR 1) and welding fumes (OR 0.75, 95% CI 0.4, 1.5) were not risk factors for GPA.
Pai et al. 1998 Liverpool, UK [64]	Case-control study. All surviving (n = 28) GPA/MPA patients diagnosed at the Liverpool Regional renal Unit between 1980-1994 vs. 28 healthy community-based age-, gender-, social class-, and residence-matched controls (randomly selected from blood donors).	Hydrocarbon exposure via structured questionnaire administered by single blinded interviewer. Type, duration and intensity of exposure obtained. Hydrocarbon exposure score calculated from intensity x duration (hours).	The mean hydrocarbon exposure was significantly greater in cases (15,231) vs. controls (4,989), $p < 0.01$.

the Catalan region of Spain, which included mainly MPO-AAV patients with renal involvement [30]. Trends in infection rates has been hypothesized as an explanation of this observed periodicity. However, there was no evidence of cyclic fluctuations in either AAV or infection rates in other studies [23,27,34].

This discrepancy in seasonal variability and periodicity likely reflects the highly variable prodrome, resulting in uncertainty in assigning the date of symptom onset. Furthermore, there is considerable heterogeneity in study methodology, with varying use of disease classifications and definition of disease onset (first symptom or clinical diagnosis). The impact of these variations is evident when one compares two conflicting analyses of essentially the same Norfolk cohort: an autumn peak of GPA diagnoses was described by Lane et al. [34] which differs to a winter predominance in symptom onset reported by Carruthers et al. [27]. It is also plausible that inconsistencies in study findings relate to real differences in triggering factors in diverse geographic regions, such as location-specific infectious trends or UV radiation.

3.2. Latitude

There are marked variations in PR3-ANCA:MPO-ANCA and GPA:MPA incidence ratios with latitude, which further supports the potential effect of an environmental influence on disease phenotype. UV radiation has been postulated as a potential latitude-sensitive factor, due to its strong inverse correlation [38], especially in winter. Lower levels of UV radiation at higher latitudes have been implicated in other AIDs, such as multiple sclerosis and type 1 diabetes [39].

Epidemiological studies suggest a North-South declining gradient in GPA risk in the Northern hemisphere, with the inverse observed for MPA [22,40]. The reciprocal finding is true for GPA, but not for MPA, in the Southern hemisphere [21]. Gatenby et al noted that for each degree increase in latitude the incidence of GPA and EGPA increased by 3.5% (IRR 1.04, 95% CI 1.00, 1.07, p 0.03) and 3.4% (IRR 1.04, 95% CI 0.99, 1.08, p 0.11) respectively [41]. Furthermore, by overlaying models of ambient UV radiation over incidence of vasculitis, this group found a strong and modest inverse correlation between both erythemally and vitamin D effective wavelengths and GPA and EGPA, respectively [41]. Given that PR3-ANCA are highly specific for GPA, it is not unsurprising that a recent multicentre study reported increasing odds of PR3 positivity with increasing latitude and decreasing UV radiation [38]. Nonetheless, this finding is confounded by the known genetic associations of MPO- and PR3-AAV and the genetic variability between Europeans in different regions. In contrast, there was no difference in the incidence of any AAV subtype between north and south Germany [23], but the latitudinal difference here may be too slight.

UVB radiation is a fundamental step in vitamin D synthesis via skin exposure, and hence is one proposed mechanism in which it may trigger immune dysregulation, resulting in AAV. 1, 25-dihydrohydroxyvitamin D3 (1, $25(OH)_2$ D_3), its active form, has immunomodulatory effects, including suppression of Th1 and Th17 cells and upregulation of Treg cells, resulting in decreased production of inflammatory cytokines and a more tolerogenic environment [41]. Th1, Th17 and Treg cells are crucial to granuloma formation. This may explain why the latitudinal and inverse UV radiation gradient is strongest for GPA and EGPA (less so), but not for MPA, where granulomas are not found. It is important to recognise, however, that multiple other factors play a role in vitamin D synthesis and subsequent serum levels: season, skin type, clothing,

Table 3
Characteristics of the included studies: Infection & Other Environmental factors

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
INFECTION			
STAPHYLOCOCCUS AUREUS & TRIMETHOPRIM-SULFAMETHOXAZOLE			
Besada et al. 2015 Tromso, Norway [79]	Retrospective cohort study. 29 GPA patients (ACR, CHCC) receiving RTX maintenance, identified via a vasculitis registry (2001-2014) which follows patients at the University Hospital of North Norway.	Persistent (≥ 75% nasal swabs) SA (*Staphylococcus aureus)*. Biannually swab of 1 anterior naris. Exact identification process not defined, but 'culture' mentioned.	Chronic SA nasal carriage (CNSAC) did not increase the risk of relapse (p 0.24), nor time-adjusted risk of relapse (p 0.84) of GPA.
Fijolek et al. 2018 Warsaw, Poland [78]	Prospective cohort. 150 consecutive GPA (CHCC) patients hospitalised (2009-2016) in the National Research Institute of Tuberculosis and Lung Diseases, Warsaw, comprising of 32.6% active and 67.4% non-active disease.	SA nasal colonisation (n = 115), by swab of anterior nares. Identified by gram stain and culture. Enterotoxicity identified using Oxoid SET-RPLA toxin detection kit.	There was no correlation between the isolation of *Staphylococcus* superantigen (SAg) in nasal swabs (p 0.99), the presence of individual types of SAg (p 0.22 – 0.64) nor the number of positive SAgs in one nasal swab and GPA disease activity. TMP-SMX confers a protective effective on relapse risk in GPA patients (OR 0.52, p < 0.0092). Mupirocin did not offer any reduction in relapse risk.
Lamprecht et al. 2019 Lubeck, Germany [69]	Case-control. 29 GPA (ACR and CHCC criteria) patients vs. 21 RA disease controls and 27 HCs from Departments of ENT, Rheumatology and Immunology at University of Lubeck (Aug 2016 – March 2017).	Composition of nasal microbiome via bilateral nasal swabs, using culture-independent techniques: V3-V4 region 16s rRNA sequencing, unbiased metagenomic RNA sequencing (UMERS) and qPCR.	Significantly higher rates of SA colonisation was identified in GPA patients vs. RA (p 0.005) or HCs (p < 0.0005). Microbial diversity was significantly reduced in GPA patients vs. RA disease controls. There was also a shift in the bacterial composition at a class and family level (but not phylum level): GPA samples had significantly more *Bacilli* vs. controls, and both GPA and RA samples displayed increased Planococcaceae but decreased *Moraxellaceae, Tissierellaceae, Staphylococcaceae,* and *Propionibacteriaceae*. A decreased abundance of *Corynebacteriaceae,* and *Aerococcaceae* was also noted in GPA samples only. There was no significant difference in the relative abundance of bacteria at any level when comparing GPA patients with active disease vs. those in remission.
Laudien et al. 2010 Kiel, Germany [70]	Case-control study. 89 consecutive GPA (ACR/CHCC) patients attending ENT at University of Kiel vs. 35 RA and 40 CRS disease controls and 75 HCs (50 staff members and 25 without regular hospital attendance).	SA nasal colonisation via culture of bilateral swab of anterior nares. Endonasal activity was assessed using direct endoscopy.	There was significantly higher rates of nasal colonisation with SA in GPA patients vs. CRS patients and HCs outside the hospital. The rate was also substantially (but NS) higher vs. RA patients and hospital staff. Nasal carriage of SA was associated with significantly higher endonasal activity (p 0.01) and an over 6-fold increased risk of relapse (OR 6.68, p 0.052) compared to GPA patients who were not colonised with SA. There was no correlation between SA nasal carriage and TMP-SMX.
Pavone et al. 2006 Italy [28]	Retrospective cohort. 75 AAV (ACR/CHCC criteria) patients (with 2 ≤ organ involvement) identified by the Secondary and Primary Vasculitides study group (1985 – 2003).	Nasal SA colonisation utilising the results of retrospective nasal swab cultures (only for patients 1999 onwards).	Nasal SA was associated with a trend towards an increased risk of relapse in EGPA patients (HR 4.45, 95% CI 0.8, 25.12, p 0.087), but a reduced risk in GPA patients (HR 0.12, 95% CI 0.01, 1.15, p 0.066). However, TMP-SMX is likely a confounder, as all GPA patients colonised with nasal SA received antibiotics but EGPA patients did not.
Popa et al. 2007 The Netherlands [76]	Retrospective cohort. 62 consecutive GPA patients (ACR, biopsy proven).	SA nasal colonisation via anterior nares swab, cultured and confirmed with PCR. Detection of Staphylococcal superantigens (SAg) using multiplex PCR. A positive control was used to ensure negative results were not due to technical failure.	Nasal SA isolation (in preceding 3 months) was associated with an increased risk of GPA relapse (RR 3.2, 95% CI 1.2, 8.4). This risk was comparable for SAg-positive and SAg-negative SA. Of those with SAg-positive SA, *tsst-1*-positive SA was associated with the highest relapse risk (RR 13.4, 95% CI 4.2, 42.6, p < 0.001).

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Table 3 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
INFECTION			
Rhee et al. 2018 Philadelphia, USA [73]	Cross-sectional case-control study. 60 GPA (ACR) patients recruited from the Penn Vasculitis Centre vs. 41 HCs (from centre, without SVV or other inflammatory disorder).	Composition of nasal microbiome via swab of middle meatus, using culture-independent techniques: V1-V2 region 16s rRNA (bacterial) and internal transcribed spacer gene sequencing (fungal).	There was a significant difference in the nasal microbiome between GPA patients and controls (p 0.04). These differences were maximal in those off non-CCS IS and with active disease. GPA patients displayed nasal dysbiosis with significantly less *Propionibacterium acnes* and *Staphylococcus epidermidis* than controls (p 0.02 for both). They also displayed a significantly reduced abundance of *Malasseziales* vs. controls (p 0.04), which was maximal in those with active disease (vs. those in remission, p 0.04). There was no significant difference in the abundance of nasal SA between GPA and controls (p 0.49).
Richter et al. 2009 Birmingham, UK [72]	Case-control. 33 consecutive GPA patients (ACR) attending the University of Birmingham (2003-2008) vs. 22 patients with Idiopathic pulmonary fibrosis (IPF, American Thoracic Society (ATS) criteria) as disease controls and 8 HCs.	Pathogens from bronchoalveolar lavage fluid (BALF) via mouth intubation with matched nasal swab. Quantitative culture of BALF was performed.	SA growth in BAFL was more common in GPA patients (40%) vs. IPF patients (0%, p 0.001) or controls (0%). SA was more common in BAFL of GPA patients relapsing or in remission vs. those presenting acutely (p 0.031). Most but not all GPA patients with SA in BAFL had concurrent nasal SA colonisation.
Salmela et al. 2017 EUVAS [80]	Prospective multi-centre cohort study based on the NORAM and CYCAZAREM RCTs conducted by EUVAS. 200 newly diagnosed GPA and MPA patients (2012 CHCC) included.	Chronic (≥ 75% of ≥ 4 swabs) SA nasal carriage (CNSAC) via culture of anterior nares swab at diagnosis, monthly and at relapse.	CNSAC was not associated with an increased risk of relapse for all AAV patients (OR 1.57, 95% CI 0.66, 3.76, p 0.31). 23/24 chronic SA carriers had GPA – in this group, the relapse risk was elevated in both those with generalised GPA (n = 73, HR 4.10, 95% CI 1.37, 12.25, p 0.01) and early systemic GPA (n = 78, HR 2.73, 95% CI 0.95, 7.87, p 0.06) with CNSAC, although the latter did not meet statistical significance. Prophylactic TMP-SMX (960mg 3 times weekly) reduced CNSAC by 81% (OR 0.19, 95% CI 0.04, 0.91, p 0.04), but this was not associated with a reduced relapse risk (OR 0.71, 95% CI 0.36, 1.41, p 0.33).
Stegeman et al. 1994 Groningen, The Netherlands [74] Stegeman et al. 1996 Groningen, The Netherlands [88]	Prospective cohort study. 71 consecutive GPA (biopsy-proven) patients attending the outpatient clinic (1988-1991). Prospective, randomised, placebo-controlled, double-blinded trial. 81 GPA (extended ACR) patients, in remission, identified by all physicians treating GPA in The Netherlands between September 1990 and June 1993.	Persistent (≥ 75% nasal swabs) SA equating to CNSAC, via culture of bilateral anterior nares swab 4-6 weekly. Trimethoprim-sulfamethoxazole (TMP-SMX) 960mg twice daily (BD) PO (n = 41) vs. placebo (n = 40) for 24 months. Patients evaluated at least every 3 months for signs of relapse, compliance (tablet counts), side effects and infections.	CNSAC is associated with a 7-fold increased risk of relapse (aRR 7.16, 95% CI 1.63, 31.5, p 0.009). TMP-SMX is protective against GPA relapse with a 68% relative risk reduction in relapse compared to those who received placebo (HR 0.32, 95%CI 0.13, 0.79, p 0.02), when adjusted for ANCA-positivity at the outset of the study. There were less infections, both respiratory (p 0.005) and non-respiratory (p0.05), in the treatment group.
Tan et al. 2019 France [71]	Prospective, monocentric, case-control study. 119 consecutive AAV patients in remission (CHCC) followed at the French National Vasculitis Referral Centre vs. 88 hospitalised (in department of medicine) non-AAV controls (without risk factors for SA carriage) (Sep 2012 – May 2013).	Nasal SA and the intracellular small-colony variant phenotype of SA (SCV) carriage, via culture of bilateral anterior nares swabs and sub-cultured for SCV phenotype. Patients were followed for ≥ 4 years to assess frequency of relapse (BVAs > 0).	The rate of nasal SA carriage was higher in GPA patients not taking TMP-SMX vs. controls (39.5% vs. 20.5%, p 0.04). The rate of nasal SCV carriage was higher in AAV patients vs. controls (11.9% vs. 1.1%, p 0.02). While TMP-SMX reduced the rates of nasal SA carriage (8.7% vs. 36.2%, p 0.02), this did not confer a reduced relapse risk. There was no association between nasal SA carriage and early (prior to inclusion, p 0.97) or late AAV relapses (p 0.55).

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Table 3 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
INFECTION			
Zycinska et al. 2009 Warsaw, Poland [77]	Prospective, randomised, placebo-controlled trial. 31 GPA (ACR/CHCC criteria, biopsy-proven) patients, attending the Primary Systemic Vasculitis outpatients clinic of the Czerniakowski Hospital, Poland.	Trimethoprim-sulfamethoxazole (TMP-SMX) 960mg 3 times weekly PO (n = 16) vs. placebo (n = 15). Patients evaluated 3-4 monthly for signs of relapse.	TMP-SMX is protective against relapse, with a 60% relative risk reduction in relapse compared to placebo (HR 0.4, 95% CI 0.12, 0.69, p 0.003). Chronic nasal carriage of SA, both MRSA (HR 6.15, 95% CI 2.15, 33.2, p 0.002) and MSSA (HR 4.56, 95% CI 2.45, 7.65, p 0.001), were associated with an increased risk of relapse in GPA. There was no association between the number nor type of infection and GPA relapse.
VIRAL			
Barzilai et al. 2007 Israel [92]	Case-control. Sera collected from 10 GPA, 9 MPA, 6 EGPA from a cohort of AID patients vs. 140 Columbian autoimmune and 100 Italian controls.	EBV and CMV exposure via IgG and IgM antibody panels using Bio-Rad's BioPlex 2200.	There was a significant increase EBV viral capsid antigen IgG seropositivity (signifying prior infection) in GPA patients compared to healthy controls. Increased titres of CMV IgM antibodies, but not IgG antibodies, were found in many AIDs, including GPA and EGPA.
Cook et al. 1997 Liverpool, UK and Erlangen, Germany [96]	Case-control. Sera from 6 GPA and 3 EGPA patients from a AID cohort (n = 47) vs. sera from HIV +/- Kaposi sarcoma patients were used as positive controls.	HHV 8 exposure via antibodies to the capsid-related protein encoded by open reading frame (orf) 65 of HHV 8, by ELISA.	No evidence of prior HHV 8 exposure in the AIDs studied (all 47 patients antibody negative).
Eden et al. 2003 Paris, France [90]	Case-control. Sera from 13 newly diagnosed AAV patients (CHCC, ACR). Age and sex matched HCs (3:1, blood donors or healthy hospital staff).	Parvovirus B19- and V9-specific IgG and IgM antibodies, using 3rd generation ELISA, and erythrovirus DNA using PCR.	Equal IgG B19 seropositivity among cases and controls (OR 0.84, p 0.84). All cases negative for IgM and DNA for B19.
Eriksson et al. 2012 Linkoping, Sweden [93]	Case-control. Sera from 34 AAV patients vs. 20 HCs.	CMV exposure via IgG antibodies, analysed with a chemiluminescent microparticle immunoassay (Abbott, USA).	No significant difference in frequency of CMV IgG between cases and controls.
Gerke et al. 2000 Rheumaklinik and Lubeck, Germany [130]	Case-control. Sera from 161 AAV patients (CHCC, ACR) attending 2 Rheumatology departments in N. Germany (1994-1998). 69 RA and 238 healthy volunteers served as controls.	Hantavirus exposure via IgG antibodies, using ELISA (Nalge Nunc International). Seropositivity was considered with titres ≥ 1:400.	There was no hantavirus seropositivity detected in any sample (positive controls were used to validate the assay), suggesting low overall prevalence of the virus in N. Germany and no serological evidence of its association with AAV.
Lee et al. 2018 Seoul, South Korea [95]	Retrospective cohort. 91 AAV (ACR/EMA/CHCC) HBsAg-negative patients attending Rheumatology department at Severance hospital (2000-2017).	Resolved HBV infection, characterised by Anti-HBc positive and HBsAg negative, measured with ELISA (Abbott Diagnostics) with retrospective medical record review for disease activity scores (BVAS and FFS).	EGPA patients with resolved HBV infection had more severe initial disease (BVAS p 0.03, FFS p < 0.001) and higher relapse rates (RR 16, p 0.016) compared to those without. A trend towards increased severity of initial disease was also noted in AAV in general, but did not reach statistical significance (BVAS 0.09, FFS 0.07).
Sachetto et al 2006 Brazil [91]	Case series (n = 7) of MPA (CHCC) patients.	Parvovirus B19 DNA in biopsy samples using a nested PCR approach (DNeasy tissue kit, Quiagen). Positive and negative controls were included in each PCR run.	Parvovirus B19 DNA was not identified in any tissue sample from MPA patients.
OTHER			
Fujita et al. 2009 Osaka, Japan [99]	Case-control. 82 patients with AIDs, of which 6 were AAV (ACR), diagnosed within 9 weeks and treatment naïve. 70 controls comprising pre-operative, osteoarthritis and healthy volunteers (AID excluded).	*Chlamydia pneumoniae* (CP) acute infection via IgM titres, using Hitazyme ELISA kit.	CP IgM seropositivity was more common in AAV than in controls (33% vs. 10%), although this wasn't statistically significant, likely due to small sample size.
Ishiguro et al. 2015 Saitama, Japan [102]	Case series (n = 9) of combined EGPA and Allergic bronchopulmonary mycosis (ABPM).	Causative fungi of ABPM identified by sputum culture or *Aspergillus*-specific IgG and IgE antibodies, by complement fixation method.	5/9 cases ABPM preceded EGPA diagnosis, 3/9 cases EGPA diagnosed before/simultaneous to ABPM, although findings suggestive of ABPM (e.g. mucus plugs) were noted prior to EGPA diagnosis. Causative fungi identified included: *Aspergillus* spp. (6), *Candida* spp. (3) and *Fusarium vasinfectum (1)*.
Iyoda et al. 2007 Tokyo, Japan [98]	Case-control. Sera from 15 MPO-ANCA GN (active) patients and 10 ANCA (remission) patients vs. 50 HCs.	*Chlamydia pneumoniae* (CP) active, chronic persistent and inactive infection via IgM, IgA and IgG titres, respectively, using ELISA.	CP IgM seropositivity was higher in the active MPO-ANCA GN group when compared to controls (OR 4.27, 95% CI 1.27, 14.33, p 0.01) and the remission group (OR 3.5, 95% CI 0.64, 19.2, p 0.22), although the latter did not reach statistical significance. There was no difference in IgA or IgG seropositivity among the 3 groups.

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Table 3 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
INFECTION			
Lidar et al. 2009 Israel [100]	Case-control study. Sera of 80 vasculitis patients (including 54 GPA, 8 MPA, 6 EGPA) vs. 99 age-, sex- and ethnicity-matched HCs.	Prior infection with *Toxoplasma gondii, Treponema pallidum, Saccharomyces cerevisiae,* CMV, EBV using BioPlex 2200 Multiplexed immunoassay method (BioRad) and HBV, HCV and *Helicobacter pylori* using commercial ELISA kits.	The prevalence of IgG antibodies to anti-HCV (p < 0.0001), *H. pylori* (p 0.002), *T. gondii (p < 0.0001), EBV VCA (p 0.02) and EBV early antigen (p 0.0065)* and IgM antibodies to CMV (p 0.0158) were significantly higher among patients with GPA vs. controls. There were no significant differences in the prevalence of antibodies to *T. pallidum* between patients and controls.
Nielsen et al. 2016 Denmark [67]	Retrospective nation-wide cohort study. 4.5 million persons identified by the Danish Civil Registration System included. 166,090 cases of AID identified (using the Danish Hospital Register), of which 613 were GPA (ICD-8/10) between 1977-2010.	Hospitalisation for infection, including number of infections, identified using the Danish Hospital Register. Temporal proximity of infection to AID grouped into 5 time periods.	Hospitalisation for infection was associated with increased risk of developing GPA (IRR/RR 2.31 95% CI 1.96, 2.72). There was a dose-response effect: risk rose with an increasing number of infections (IRR/RR 6.04 95% CI 4.33, 8.21 with 5 ≤ infections). The risk of GPA was maximal for those hospitalised in close proximity (< 1 month) to their diagnosis (IRR/RR 73.80 95% CI 50.36, 104.27). The risk was similar for all types of infection (bacterial, viral and other).
Stratta et al. 2001 Torino, Italy [101]	Case-control study. 45 AAV patients with renal involvement attending the Department of Nephrology, of the University of Turin between 1976-1998 (CHCC 1994 criteria, renal biopsy proven) vs. 45 age-, sex- and residence-matched disease controls (renal disease).	Prior Tuberculosis (TB) infection as defined by i). overt clinical diagnosis (medical records) and ii). radiological diagnosis.	Prior TB infection was more common in AAV patients with renal involvement compared to controls (27% vs. 9%, p < 0.05).
VACCINATION			
Buhler et al. 2019 Zurich, Switzerland [103]	Multi-centre prospective cohort study (2014-2015). N = 284 patients with rheumatic disease (including 17 AAV patients) vs. 253 HCs (sex but not age matched).	Diphtheria/tetanus booster vaccination.	No relapses occurred in AAV patients who received the diphtheria/tetanus vaccine. Functional status and median BVAS scores did not change significantly.
Duggal et al. 2013 Baltimore, USA [104]	Case series (n = 8) describing new (6)/ relapsing (2) GPA/MPA following influenza vaccination [131–133].	Influenza vaccination.	8 adults (20-83 years) developed GPA (n = 6) and MPA (n = 2), with an equal distribution of ANCA serotypes (50% PR3- and 50% MPO- positivity), between 12-28 days post influenza vaccination. Renal involvement occurred in 100% while 50% had pulmonary involvement.
Stassen et al. 2008 Groningen, The Netherlands [106]	Retrospective cohort study. 230 consecutive AAV (CHCC) patients (mainly GPA) attending the Department of Nephrology at the University Medical Centre Groningen (1999-2003).	Influenza vaccination history, as assessed by patient interview. Uncertainties were validated by the patient's general practitioner. Relapse attributed to vaccination if within 1 year of vaccine.	The relapse rate was lower in patients vaccinated against influenza compared to those not vaccinated (3.4 vs. 6.3 per 100 patients at risk). The findings were similar regardless of the time-window used for vaccination-related relapse.
Zycinska et al. 2007 Warsaw, Poland [107]	Case-control study. 35 GPA patients in remission (group 1) vs. 28 GPA patients with active disease on IS (group 2) vs. 35 HCs (group 3).	Influenza vaccination (inactivated subunit vaccine, *Influvac*) prior to 2006/07 epidemic season. Group 1 and 3 were vaccinated.	There were no cases of disease relapse in group 1 following the influenza vaccine. There was similar immunogenicity noted in both group 1 and 3 in response to the vaccine, suggesting it is effective in GPA patients in remission.
ALLERGY			
Albert et al. 2004 Philadelphia, USA [62]	Case-control. 53 GPA in- and outpatients (initially identified by billing codes and subsequently fulfilled ACR criteria) attending the Hospital of the University of Pennsylvania vs. 53 gout and 50 OA controls.	Telephone administered structured questionnaire. Occupational, hobbies & chemical exposures, tobacco, allergic history. Analyses were adjusted for age and sex.	Allergic history reduces risk of GPA (OR 0.25, 95% CI 0.1, 0.6, p 0.001). A history of sinusitis > 3 times/1 year is associated with a trend towards increased risk of GPA (OR 2.43, 95% CI 0.97, 6.2, p 0.06).
Cuadrado et al. 1994 London, UK [108]	Case-control study. 60 consecutive SVV patients (of which 20 GPA and 8 EGPA patients, ACR criteria) attending the Vasculitis clinic in the Rheumatology department of St Thomas' Hospital, London between March and May 1993 vs. 2:! Age- and sex-matched controls (60 healthy [from staff] and 60 disease controls from Rheumatology department).	Atopic history, obtained using a structured interviewer-administered questionnaire.	GPA and EGPA patients reported a significantly higher rate of atopy when compared to healthy (p 0.0003 and p 0.002, respectively) and disease controls (p 0.0008 and p 0.004, respectively).

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Table 3 (*continued*)

First author, year of publication, country of origin	Study design & method (including population & control group, study timeline)	Environmental risk factor (assessment of exposure, method to obtain information, terms of the exposure estimate)	Outcome (OR/RR, 95% CI, if applicable)
INFECTION			
Lane et al. 2003 UK [52]	Case-control. 103 AAV cases (1988-2000) at the Norfolk and Norwich University Hospital, identified from prospective vasculitis register. Age and sex matched controls: 220 non-inflammatory musculoskeletal disease (excluded AID), 19 secondary vasculitis and 34 asthma.	Face-to-face structured questionnaire (not-blinded) to elicit multiple exposures detailed in 'pollution' table, including allergic and vaccination history.	History of allergy was associated with AAV overall (OR 2.2, 95% CI 1.2, 3.9), specifically GPA (OR 2.7, 95% CI 1.4, 5.7). Subgroup analysis identified drug allergy as most significant (mainly antibiotics). There was no association between AAV and vaccination within 6 months of the index date (OR 1.7, 95% CI 0.8, 3.4).
Stamp et al. 2015 Canterbury, New Zealand [54]	Case-control study. 49 GPA patients (ACR/CHCC/EMA criteria), identified from Nephrology and Rheumatology databases vs. 4:1 age- and sex-matched controls (2 MSK [OA/fracture], 2 respiratory[asthma/COPD]) identified from the surgical waiting list and a Respiratory database, respectively, at Christchurch hospital.	Environmental exposures (occupation, hobbies, pets, residence, farm, allergy) obtained from a structured interview performed by a single unblinded interviewer (telephone/in-person).	There was no association between GPA and any of the following: personal/family atopic history (OR 1.58, 95% CI 0.65, 3.85), smoking (OR 0.59, 95% CI 0.28, 1.25, p 0.17), pet ownership nor home heating method. Vaccination in the 6 months prior to the index date was found to have a protective effect on GPA risk (OR 0.4, 95% CI 0.2, 0.9, p 0.03).

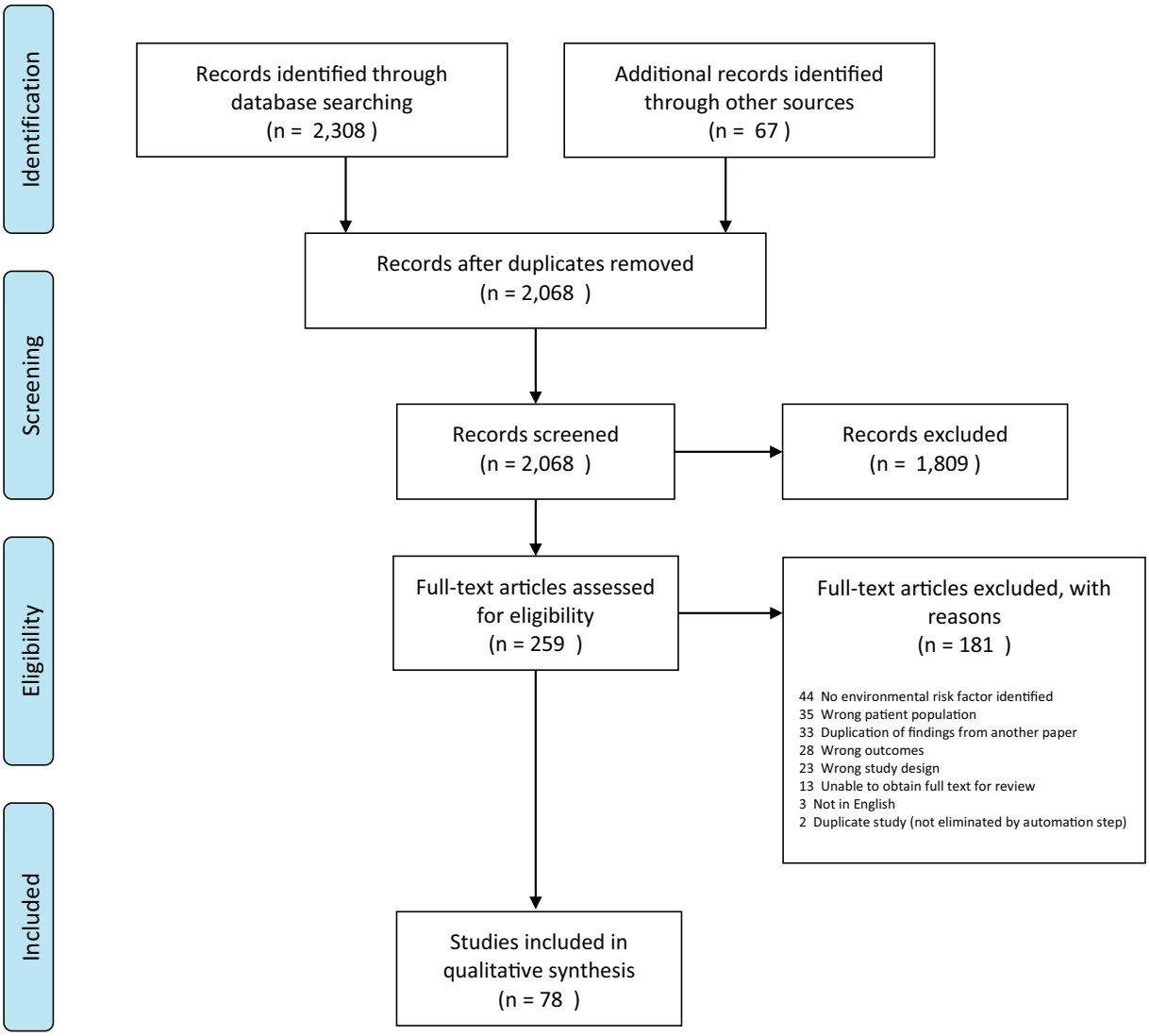

Fig. 1. PRISMA flow diagram depicting study selection process.

lifestyle, diet, supplementation (available over-the-counter in many countries) and comorbidities – these should be, but to date have not been, considered as confounders. It is also plausible that UV radiation may exert other effects beyond its indirect vitamin D effects. $1,25(OH)_2 D_3$ is notoriously difficult to measure, given its short half-life, hence its inactive metabolite 25-hydroxy vitamin D (25(OH)D) is used as a proxy. Kalsch et al showed that serum 25(OH)D levels were significantly lower in AAV patients compared to healthy controls ($p < 0.0001$), despite the majority taking supplements [42]. Low levels of 25(OH)D have been associated with increased disease activity in other AIDs, such as multiple sclerosis and systemic lupus erythematous (SLE) [43]. Kemna et al found that a rise in ANCA titre during autumn (Sep-Nov) was associated with a 4-fold increased risk of relapse (HR 4.37, 95% CI 1.6, 11.9) for those with renal involvement. In keeping with the findings of Kalsch et al, 93% had insufficient 25(OH)D levels (< 75 nmol/l) at the time of ANCA rise [43]. Unsurprisingly, given the seasonal trend in 25(OH)D levels, serum titres fell significantly in those who relapsed, which occurred more often in autumn (difference -6.3 ± CI 14.4 nmol/l, p 0.017), but trended upwards in those who remained in remission (difference 2.7 ± 16.3 nmol/l, p 0.43) [43]. It remains to be seen whether these changes in 25(OH)D levels are biologically significant. An *in vitro* study revealed that $1,25(OH)_2 D_3$ (p 0.02), all-*trans* retinoic acid (p 0.001) and 9-*cis* retinoic acid ($p < 0.0001$) (1 μmol) all inhibited lipopolysaccharide stimulated TNFα production in AAV [42]. TNFα is important in AAV pathogenesis via its neutrophil priming effect. Vitamin D supplementation may therefore be useful in down-regulating TNFα production, in AAV. Population data on vitamin D levels from inception cohorts is required to further explore this hypothesis.

3.3. Residence

Many studies have explored the impact of urban versus rural living on AAV with divergent findings. There were no significant differences in the frequency of AAV between rural and urban areas of New York state, Germany and New Zealand [19,21,23]. A separate North German study, found that there was a higher prevalence of GPA (114/million vs. 85/million) and MPA (43/million vs. 16/million) in urban compared to rural areas, while the inverse was true for EGPA (35/million rural vs. 10/million urban) [44]. This is the opposite to what was reported by Kanecki's group in Poland, where the prevalence of EGPA was higher in urban areas (69% vs. 31% respectively, $p < 0.001$). It also contrasts to the findings from Australia where the incidence of MPA was higher in rural compared to urban areas (14.4/year per million vs. 1.6/year per million), with a similar trend noted for GPA (prevalence in rural areas 129/million vs. 82/million in urban areas). Given the rarity of AAV and the variation in defining urban/rural status between studies, there is currently no clear consensus. As with other geoepidemiological factors, the influence of urban/rural living may vary in different regions.

4. Pollution

There is evidence for the role of silica, pesticides and organic solvents in AIDs such as rheumatoid arthritis, SLE and systemic sclerosis [45]. Many occupational and industrially generated exposures [46] have been implicated in the pathogenesis of AAV, often thought to cause effect through inhalation, as high levels of upper respiratory tract involvement are observed. Conflictingly, a large Swedish case-control study found no association between 32 selected occupations and GPA, with odds ratios ranging from 0.6 to 1.9 [47]. Borderline occupations included bakers (OR 1.6, 95% CI 1, 2.6) and miners (OR 1.9, 95% CI 1, 3.5), although these were not statistically significant [47]. Similarly, there were no differences in the occupations reported between AAV cases and controls in a large German study [48]. However, of particular note are exposure to silica, other environmental dusts and farming, which have the most convincing evidence to date (*Table 2*).

4.1. Environmental dusts, including silica

Of all potential environmental risk factors, the evidence for silica is most consistent. Since 1951, researchers have reported several cases of pulmonary silicosis associated with proliferative glomerulonephritis. When immunofluorescence became used to analyse renal biopsies in the 1980s, it was noted that these cases were largely pauci-immune (few immune deposits). Later, they were also found to be ANCA positive [49]. These findings are consistent with case-control studies that report 22-46% of AAV patients have previously been exposed to silica. These studies culminated in a meta-analysis that found that 'ever being exposed' to silica was associated with a 2.5-fold increased risk of AAV – this risk was even higher for patients with renal involvement, GPA or MPA [50]. It is important to note that there was moderate heterogeneity among the included studies (I^2 48.4%), although subgroup analysis did not identify a single study influencing the overall pooled odds ratio. There was also a possible publication bias identified by asymmetry of the funnel plot. Some studies also reported a dose-response relationship, particularly with regards to intensity, rather than duration, of exposure [51–54].

Silica is abundant on earth, occurring in both crystalline and non-crystalline forms. Sand, soil and rock are composed of the crystalline form and consequently workers involved in 'dusty trades' may be exposed when handling raw materials [53]. The most common occupation associated with silica exposure in an ANCA-positive French group was bricklaying [52]. Others include farming, mill and textile work, and dusty construction labour [55]. The mechanism by which silica triggers AAV has yet to be fully elucidated. It stimulates an inflammatory reaction through accelerated apoptosis of neutrophils and alveolar macrophages in a dose-dependent manner [56]. MPO released by neutrophils can be taken up by activated alveolar macrophages and may be presented to T- and B-lymphocytes resulting in the development of anti-MPO antibodies and a dysregulated immune response in a genetically predisposed individual, culminating in AAV [57].

The role of silica and other environmental dusts is further supported by the outbreaks of AAV, mainly MPO-ANCA positive, observed following 3 large earthquakes in Asia [29,58,59]. A cluster of MPO-AAV cases was observed in the Kobe area in the 3-year period following the 1995 earthquake, equating to a more than doubling in annual frequency [58]. The patients diagnosed post the Kobe earthquake had higher rates of upper respiratory tract involvement and displayed a more severe phenotype, with more requiring renal replacement therapy and exhibiting severe pulmonary involvement. The environmental bureau of Kobe city reported a 20-fold increase in asbestos levels in the air following the earthquake, which lasted for 30 months. There was no measured data regarding silica but it was postulated that large amounts were released into the atmosphere as a result of large-scale building destruction [58]. Similarly, the annual incidence of MPO-AAV doubled after the Great East Japan Earthquake of 2011, with a more severe phenotype noted by higher BVAS scores and higher silica concentrations in the bronchoalveolar lavage compared to pre-earthquake [59]. In addition to silica, the deposited marine sludge contained sand and soil, microorganisms, hydrocarbons, heavy metals and other industrial pollutants. Analogously, a 1.37-fold increase in AAV frequency (from 0.19% in 2013 to 0.26% in 2014) was noted following the 2014 Yunnan earthquake in China, despite no significant increase in PM10 from 2010 to 2015 [29]. Most recently, Webber et al. performed a nested case-control study among world-trade centre (WTC) rescue workers following the 9/11 terrorist attacks – prolonged work at the WTC site was an independent predictor of subsequent AIDs [60]. GPA and EGPA were included in the analysis but very small numbers precluded subgroup analysis. In contrast, no increase in AAV was detected following the 2011 Christchurch earthquake, despite increased particulate matter and overall reduced air quality noted [61]. The earthquake in NZ was less severe than those in Asia, with a magnitude of 6.1 on the Richter scale, compared to 6.5 to 9.0. Furthermore, the population studied differed

from the Asian disasters, in that the population density in Christchurch is less than a quarter of that of Kobe and the Asian MPO-ANCA predominance is not seen. To our knowledge, the psychosocial impact of these natural disasters has not been studied in detail – it has been proposed that psychological stress may also trigger neutrophil activation and the subsequent inflammatory cascade responsible for AAV.

4.2. Other environmental pollutants

Several other small studies report conflicting relationships with other environmental pollutants.

Solvents are chemical compounds that are routinely used in industry. They include aromatic hydrocarbons, alcohols, paint thinners, glues and many other toxic products. Lane et al observed that any history of high organic solvent exposure was positively associated with AAV, specifically GPA. This was not substantiated in three other studies [52,53,62] which also reported no association between AAV and fuels, lead, welding fumes or other heavy metals. This is also in keeping with the findings of Nuyts et al, who found that exposure to hydrocarbons or welding fumes were not risk factors for GPA. However, they did identify non-significant associations between GPA and lead and cadmium [63]. In contrast, Pai et al. found a significantly higher mean hydrocarbon exposure in GPA and MPA cases compared to controls [64] and mercury exposure was associated with a 10-fold increased risk of GPA in Philadelphia [62].

Li et al identified a positive correlation between carbon monoxide (CO) exposure and the frequency of AAV in China [29]. Interestingly, they found no significant relationship with any other air (e.g. PM 2.5, PM 10, other particulate matter, sulphur dioxide or nitric dioxide) or water (e.g. ammonia nitrogen) pollutant measured, adjusted for annual average temperature, humidity and precipitation. Likewise, Albert et al uncovered a positive association between CO and GPA, which approached statistical significance [62]. Given the availability of granular location specific CO data, its influence on AAV disease activity should be investigated in a larger cohort.

4.3. Farming and animals

Farming and various associated aspects have been postulated as a trigger for AAV disease activity, via the exposure to innumerable inhaled antigens from soil, dusts, animals and pesticides. Lane et al. first reported the association between farming and AAV – specifically in those with GPA and less so MPA (but not EGPA), who visited a farm in the 12 months prior to the index date, or had significant livestock exposure [52]. This association was not observed for those living on a farm, possibly due to their immune tolerance from prolonged and early exposure. A similar observation was reported in a case series [65]. The findings were also replicated by two other groups [48,54], although specific animal types varied: cows and chickens in the UK [52], cattle and pigs in Germany [48], while sheep conferred the highest risk in New Zealand [54]. These variations likely reflect differences in local farming practices. There was no association identified between AAV and pet ownership [52,54]. The increased risk of GPA associated with gardening, specifically digging, mowing and planting [54,65], also supports the hypothesis that inhaled antigens from the soil are a potential culprit. It is possible that other specific triggers within the farming environment are responsible, but have not been sufficiently studied. One such example is the non-significant trend towards an increased risk of AAV with renal involvement following pesticide exposure (OR 2.32, 95% CI 0.47, 11.5, p 0.303) [53].

The relationship between farming and AAV is not a universal finding – several studies found no association [35,47,62]. A large high-quality Swedish registry study involving 2288 GPA cases and a 10-fold larger control group found no association with livestock farming [47]. They used linked occupation registry data capturing a less detailed exposure history compared to a structured questionnaire and excluded exposures outside of the workplace (e.g. leisure farming or gardening). In the remainder of studies, numbers were often small, and participants were exposed to multiple factors, making it difficult to draw conclusions. While the notably large Swedish study essentially eliminates livestock farming as a significant player, it is possible that a subtle relationship exists between exposure to a farm in the year before diagnosis and GPA occurrence.

5. Infection

There is broad agreement that infection plays a role in triggering AAV disease activity, but the exact microorganism(s) has yet to be determined. Pinching et al. first described the potential role of infection, primarily respiratory, in triggering disease relapse in 1980 [66] in a case series of 18 patients with GPA. There are many case reports proposing various organisms (e.g. Rickettsiae, Enterococcus, etc. [12]) that are temporally related to the occurrence of ANCA positivity and less so to the associated clinical syndrome, AAV. However, these findings often conflict with the negative results of larger observational studies [31]. Here, we will focus only on studies that report overt clinical ANCA-associated vasculitis, and exclude single case reports (*Table 3*).

Supporting the idea of an underlying infectious agent, several studies have demonstrated the spatial and temporal clustering in AAV onset, in addition to seasonality, with incidence peaking in the winter when upper respiratory tract infections are most common (see 3.1. *seasonality and temporal clustering)*. Anecdotally, the disease prodrome often includes flu-like symptoms and disease relapses not infrequently coincide with infection. A large Danish registry study demonstrated a dose-response effect between increasing number of hospitalisations for infection and increased GPA risk, which was maximal for those hospitalised in close proximity to their diagnosis [67]. Similarly, Pearse et al found that respiratory tract and sinus infections were associated with increased odds of developing GPA in the 1-2 and 1-4 years prior to the index date, respectively [68], but they were unable to find evidence of infection as a long-term triggering factor [68]. It is possible that these infectious episodes act as stochastic triggering events, however, it is more likely that the overlapping symptoms are an undiagnosed grumbling prodrome.

5.1. Staphylococcus aureus

The role of *Staphylococcus aureus* (SA) in the pathogenesis of AAV has been extensively explored by many research groups in both clinical and mechanistic studies. Multiple studies have illustrated higher rates of chronic nasal SA colonisation in GPA patients compared to healthy and disease controls [69–71], as well as higher rates of the small-colony variant phenotype of SA [71] and SA in bronchoalveolar fluid [72]. This finding is possibly due to underlying damage of the nasal mucosa observed in GPA, or as a consequence of the significantly deranged nasal microbiome [73]. In contrast, a study by Rhee et al did not detect a significant difference in the abundance of nasal SA between GPA patients and controls [73]. This may be due to more sensitive culture-independent identification techniques, which do not differentiate between viable and non-viable SA. Furthermore, samples in the latter study by Rhee et al were obtained from the middle meatus, in contrast to the anterior nares in prior studies.

It is widely accepted that chronic nasal SA carriage (CNSAC) is associated with an increased risk of relapse in GPA (aRR 7.16, 95% CI 1.63, 31.5, p 0.009), since the seminal trial by Stegeman et al [74]. This has been replicated in multiple subsequent studies [70,75–77]. In addition to confirming a 6-fold increased risk of relapse for GPA patients with CNSAC, Laudien et al also demonstrated its association with significantly higher levels of endonasal activity compared to non-colonised GPA patients [70]. Zycinska et al found a slightly higher risk of relapse for those colonised with Methicillin-resistant SA (MRSA) compared to

Methicillin-sensitive SA (MSSA) [77]. While the risk appears comparable for those with superantigen (SAg) positive and negative SA [76], of those with SAg-positive SA, SAg *toxic-shock-syndrome-toxin-1* was associated with the highest risk for relapse [76]. On the contrary, Tan et al found no association between CNSAC and AAV relapse [71], although this study included all AAV patients, not just those with GPA. The low relapse rate observed in this study (11.8% relapsed over 4 years) may also have prevented the detection of any association [71]. Similarly, a small Norwegian study of GPA patients receiving rituximab maintenance therapy did not find any association between CNSAC and relapse risk [79], likely due to methodological differences: concomitant antibiotics were allowed in this study and the overall frequency of SA carriers was significantly lower(20-28% vs. 63%). Interestingly, an Italian group reported a reduced relapse risk associated with nasal SA colonisation in GPA patients – these results are largely confounded by all patients with nasal SA receiving trimethoprim-sulfamethoxazole (TMP-SMX) and topical mupirocin until culture negative [28], further supporting the protective effect of TMP-SMX.

The elevated relapse risk does not extend to MPA patients [80], but there is some evidence in EGPA patients not receiving antimicrobials [28]. Interestingly, Salmela et al found an unexpectantly low rate of CNSAC in MPA patients (2%), who typically avoid destructive nasal disease [80]. This suggests that those with CNSAC may reflect a subgroup of GPA, which in itself is associated with an increased relapse risk, rather than SA itself being responsible.

With the advent of more sophisticated culture-independent techniques, there is increasing evidence for disruption of the nasal microbiome in GPA patients, known as dysbiosis [69,73], particularly in those with active disease and those off non-glucocorticoid immunosuppression. These novel studies suggest that SA is not the only player in the altered microbial composition of the nasal cavity in GPA patients – there are significant differences in the relative abundance of multiple bacteria at a class and family level, including a reduction in negative competitors of SA [69,73]. Further research is required to assess the clinical implication of this.

There has been much mechanistic work performed into how SA may cause its effect. The concept of autoantigen complementarity has been well documented, whereby a pathogenic microbe (e.g. SA) introduces a peptide, which is a mimic of the reverse-transcribed PR3 peptide (cPR3, the peptide translated from the anti-sense DNA strand of the PR3 gene). Antibodies to both the sense and anti-sense peptide are produced, resulting in PR3 autoantibodies, which trigger an inflammatory cascade in a primed individual, although this finding has not yet been replicated [81].

There has been more debate surrounding the role for infection and molecular mimicry. Kain et al originally demonstrated that 90% of patients with active focal PIGN have intermittent autoantibodies to lysosomal membrane protein-2 (anti-LAMP-2) [82]. This was not reproduced by Roth et using cohorts from Boston and North Carolina [83], although they did not stratify patients by disease activity, which appears to be important for this autoantibody. Kain et al later confirmed the high frequency of Anti-LAMP-2 in acute AAV patients, in three independent European cohorts [84] – they become rapidly undetectable on initiation of induction treatment and often reappear during relapse. Anti-LAMP-2 antibodies cross-react with the bacterial adhesin, FimH, which is derived from many gram negative fimbriated organisms, due to the strong sequence homology between it and a LAMP-2 epitope. Rats immunised with FimH were found to develop AAV-GN due to anti-LAMP-2 antibodies [85]. This provides evidence for the role of infection with fimbriated bacteria in the aetiopathogenesis of AAV, via the production of Anti-LAMP-2 autoantibodies, through molecular mimicry. Recently, Kitching's group demonstrated molecular mimicry mediated by a peptide, $6PGD_{391-410}$, which is part of an immunogenic plasmid found in certain SA strains. Bacterial plasmids may act as a vehicle to transfer the propensity for autoimmunity. Ooi et al. demonstrated that by injecting mice with either $6PGD_{391-410}$ or genetically engineered SA containing $6PGD_{391-410}$, this cross-reactive peptide can precipitate loss of tolerance to MPO and subsequent development of anti-MPO glomerulonephritis in an experimental model [86]. Other potentials mechanisms have been postulated and summarised in a review by Konstantinov et al [87]: enhanced autoantigen expression via epigenetic modulations, NETosis and the involvement of Toll-like receptors. Further mechanistic work is required to refine these mechanisms.

5.2. Trimethoprim-sulfamethoxazole

Two randomised controlled trials demonstrate the protective effect of trimethoprim-sulfamethoxazole (TMP-SMX) in reducing the rate of relapse in GPA. Stegeman et al initially reported a 68% relative risk reduction in relapse in those taking TMP-SMX (960mg twice daily) compared to those who received placebo (HR 0.32, 95% CI 0.13, 0.79, p 0.02), when adjusted for ANCA-positivity at the outset [88]. Subsequently, a Polish group reported a 60% relative risk reduction in relapse when treated with TMP-SMX (960mg three times weekly) compared to placebo (HR 0.4, 95% CI 0.12, 0.69, p 0.003) [77]. Another Polish cohort study confirmed this protective effect (OR 0.52, $p < 0.0092$). A re-analysis of two EUVAS trials (NORAM and CYCAZAREM trials) showed a non-significant trend towards a reduced relapse risk with TMP-SMX (960mg 3 times weekly). In contrast to the other trials, this study included both GPA and MPA patients. Similarly, a French study including all AAV subgroups found that while TMP-SMX reduced rates of nasal SA carriage, this did not translate to a reduce relapse risk [71]. The TMP-SMX dose in this study was not uniform, however, and the effect of TMP-SMX was a secondary endpoint, with a low event rate, resulting in the study being potentially underpowered to detect a difference. The benefit of TMP-SMX is multi-faceted: firstly its anti-microbial effect, but also its immunosuppressive effect through its anti-folate metabolism.

5.3. Viral infections

The evidence to support the role of a viral pathogen in AAV is scanty, with the quality of studies being suboptimal. With regards to other autoimmune diseases, there is a strong association between Epstein-Barr virus (EBV) and both rheumatoid arthritis (RA) and SLE, and between parvovirus and RA [45].

Parvovirus B19 has received the most attention in the context of AAV, with no significant association found. It is recognised that acute parvovirus infection is often accompanied by transient ANCA seropositivity, which falls spontaneously with resolution of infection [89]. However, a group from France reported equal IgG parvovirus B19 seropositivity between cases and controls, with all cases being negative for IgM and DNA [90], suggesting that neither acute nor chronic parvovirus infection is a risk factor for AAV. Molecular studies support this finding in a small case series of MPA patients [91].

The only positive association identified between AAV and any virus is with EBV and cytomegalovirus (CMV), albeit the evidence is weak. Barzilai et al demonstrated a significant increase EBV viral capsid antigen Immunoglobulin G (IgG) seropositivity (signifying prior infection) in GPA patients compared to healthy controls [92]. They also found increased titres of CMV IgM, but not IgG, antibodies in GPA and EGPA patients compared to controls, suggesting recent CMV infection may play a role. However, the selection of cases and controls were not well defined in this study. No significant differences in CMV IgG positivity between cases and controls was later confirmed by a Swedish group [93].

The relationships between hepatitis B virus (HBV) and hepatitis C virus (HCV), and polyarteritis nodosa (PAN) and cryoglobulinaemia, respectively, are well recognised. Patients with PAN who have HBV-associated disease have been shown to display a more severe initial phenotype [96]. Similarly, EGPA patients with resolved HBV infection

had more severe initial disease (BVAS p 0.03, FFS $p < 0.001$) and higher relapse rates (RR 16, p 0.016) compared to those without [95]. A trend towards increased severity of initial disease was also noted for AAV in general, but did not reach statistical significance [95]. There was no serological evidence for the involvement of prior human herpes virus (HHV) 8 [96] or hantavirus [95]. Overall, as yet, there is no convincing evidence that any viral agent plays a significant role in AAV aetiopathogenesis.

5.4. Other infections

There is sparse epidemiological data pertaining to other organisms. As for viral infections, the studies are small and the evidence is generally weak. Two studies demonstrate a trend towards higher levels of Chlamydia pneumoniae IgM seropositivity in AAV than controls [98`,99]. There was no difference in IgA or IgG seropositivity, suggesting that active Chlamydia pneumoniae infection may play a role. Furthermore, there is weak serological data to suggest a variety of other organisms are more commonly observed in GPA patients vs. controls: the prevalence of IgG antibodies to *Helicobacter pylori* and *Toxoplasma gondii* were significantly higher in GPA patients vs. age-, sex-, and ethnicity-matched healthy controls [100]. No difference in serology between GPA patients and controls was noted for *Treponema pallidum* [100]. An Italian group noted that prior TB infection, defined by an overt clinical or radiological diagnosis was more common in AAV patients with renal involvement compared to disease controls [101]. The robustness of clinical diagnosis is questionable however, as culture was not confirmed in all cases and this study preceded the use of Quantiferon testing. Finally, a Japanese case series by Ishiguro et al highlights the potential of various causative fungi including *Aspergillus* species, *Candida* species and *Fusarium* vasinfectum in the pathogenesis of EGPA due to the temporal relationship of onset noted with the disease [102]. At present, all of these microorganisms are speculative at best. Further large scale longitudinal studies are required to further investigate these organisms.

6. Other environmental risk factors

6.1. Vaccination

The onset of autoimmunity post vaccination is not infrequently recorded as an adverse event. Few studies concentrate on AAV specifically (*Table 3*). Two case-control studies exploring multiple potential risk factors did not find any positive association between vaccination within 6 months of symptom onset and the occurrence of AAV – they may have been underpowered to detect this, however [52,54]. In a multi-centre Swiss study, no relapses of AAV occurred in patients who received the diphtheria/tetanus vaccine [103].

There are many case reports and series reporting the onset or relapse of AAV between 12-28 days post influenza vaccination [104,105]. This has not been substantiated by any large scale observational study [106,107]. In fact, Stassen et al performed a retrospective cohort study demonstrating its safety and protective effect: the relapse rate was lower in patients vaccinated against influenza compared to those not (3.4 vs. 6.3 per 100 patients at risk) [106].

6.2. Atopy

Atopy has been postulated as a potential risk factor due to the higher rate of symptom onset observed during summer months in France [31]. Furthermore, O'Donnell's group hypothesized that the 'hygiene hypothesis' of allergic and autoimmune disease was responsible for the significantly lower incidence of AAV among socially deprived groups compared to all others [21]. It is important to note, from the outset, that the quality of evidence was low for all studies exploring the role of atopy. Half of the studies found that patients with GPA [52,108] and EGPA [108] reported a significantly higher rate of atopy when compared to controls. Subgroup analysis identified drug allergies (particularly antibiotics) as most significant. These findings were not replicated by other studies [54]: on the contrary, one reported a reduced GPA risk associated with an allergic history (OR 0.25, 95% CI 0.1, 0.6, p 0.001) [62]. There is thus insufficient evidence to accurately conclude the role of atopy (*Table 3*).

6.3. Smoking

Despite the toxic nature and recognised detrimental health consequences of smoking, the association between it and various AIDs is not strong. While there is a positive correlation between smoking and SLE, multiple sclerosis, Crohn's disease, Hasimotos thyroiditis and Graves' disease [109], smoking appears protective against ulcerative colitis [110]. A cross-sectional study involving two German vasculitis referral centres found that there was a lower prevalence of smokers among newly diagnosed AAV patients compared with the background population [110] (*Table 2*). It is important to note that confounders, such as gender, were not considered in this study. Similarly, Pearse et al reported a slightly protective effect of current smoking on GPA risk, but an increased risk in former smokers, in the UK [68]. Nicotine's immunosuppressive effect has been proposed as a potential explanation for these findings [111]. A Japanese study, primarily including MPO-ANCA MPA patients with renal involvement, reported conflicting findings: smoking increased the risk of relapse (p 0.003) in a dose-dependent manner (p 0.004). Specifically, current smoking was associated with a 7.5-fold increased risk of relapse (aHR 7.48, 95% CI 2.73, 21.0). On the contrary, four case-control studies found no relationship between smoking and AAV [52–54]. Biological biomarkers to qualify smoking status were not used, thus the inherent bias in self-reported smoking status must be considered when interpreting these findings.

6.4. Drugs

Drug-induced AAV is often regarded as a separate entity to primary AAV. It usually exhibits a milder phenotype that reverses with cessation of the drug, with simultaneous fall of ANCA titres, negating the risk for prolonged immunosuppression and resulting in relatively good long-term outcomes. There are multiple recent reviews that explore implicated drugs: propylthiouracil (PTU), hydralazine, anti-TNF∝ agents, sulfasalazine, D-penicillamine, minocycline [112,113], other anti-thyroid drugs including carbimazole and methimazole [114], and levamisole-adulterated cocaine [115]. Most of these agents have potent epigenetic effects (e.g. hypomethylation), resulting in altered gene expression – this is likely the mechanism by which they induce autoimmunity. Furthermore, there are multiple case reports describing the occurrence of EGPA following the use of anti-leukotriene agents (e.g. montelukast). However, there is broad agreement that this phenomenon is attributed to the simultaneous withdrawal of corticosteroids in severe asthma cases, which unmasks undiagnosed EGPA [116–119]. Multiple other studies report increased ANCA positivity in the context of certain drugs, without overt clinical vasculitis. A recent review attempted to separate the risk of developing GPA from that conferred by its indication - allopurinol was the only drug that conferred a greater risk for developing GPA (OR 1.8, 95% CI 1.2, 2.8, p 0.01) than its indication, gout (OR 1.2, 95% CI 0.9, 1.8, p 0.3) [68]. Interestingly, the risk associated with sulfasalazine and anti-thyroid drugs (levothyroxine, carbimazole, PTU) were similar to those of rheumatoid arthritis and thyroid disease, respectively, suggesting no additional risk conferred by the drug itself [68].

7. Conclusion

The precise aetiology of AAV has yet to be elucidated. The current consensus is that there is a complex interplay between various

Table 4
Summary of environmental risk factors in ANCA-associated vasculitis disease activity.

Risk factor	Study design (n=)	Summary of outcome (if applicable)	Considered a risk factor (based on available evidence)	Level of evidence (based on quality assessment)
GEOEPIDEMIOLOGY				
Season	Cohort (11) Case series (1)	6/12 report winter predominance, while 4/12 report no seasonal association. Autumn and summer peaks are reported in 1 study each.	Yes	High
Latitude, UV Radiation	Cohort (6)	Increasing latitude and decreasing ambient UV radiation are associated with increasing incidence of GPA and PR3 positivity and a trend towards the same for EGPA (NS). Evidence for MPA is more conflicting but it tends to be more common with decreasing latitude, in southern Europe.	Yes	High
Vitamin D	Cohort (1) Case-control (1)	Serum 25-OH vitamin D levels are significantly lower in AAV patients compared to HCs. Levels fall significantly during relapse.	Yes	High
Urban/rural residence	Cohort (6)	Findings are conflicting across studies, with no association found in 50%.	Unclear (but unlikely)	High
INFECTION				
Staphylococcus aureus (SA)	RCT (1) Cohort (6) Case-control (5)	Nasal dysbiosis in GPA is reported in 2 studies. The rate of chronic nasal SA carriage (CNSAC) is higher in GPA patients vs. healthy and disease controls in the majority. 5/9 studies demonstrate CNSAC is associated with a 2.7 – 7 fold increased risk of relapse in GPA, with associated increased endonasal activity reported in 1 study.	Yes	High
Trimethoprim-sulfamethoxazole (TMP-SMX)	RCT (2) Cohort (3)	TMP-SMX confers a protective effect on relapse risk for GPA patients in 4/5 studies (relative risk reduction 29-60%). 1 further study could not prove this, despite showing a reduction in CNSAC with TMP-SMX.	Yes	High
Viral infections (including Ebstein-barr virus, Cytomegalovirus, Human herpes virus, Parvovirus B19, Hantavirus and Hepatitis B virus)	Cohort (1) Case-control (5) Case series (1)	There was no convincing evidence for any association with viral infections, although the quality of evidence was suboptimal.	No	Low
Other infections (including *Chlamydia pneumoniae*, Allergic bronchopulmonary mycosis, Tuberculosis, *Helicobacter pylori, Toxoplasma gondii, Treponema pallidum)*	Case-control (3) Case series (1)	2 poor quality studies demonstrate *Chlamydia pneumoniae* IgM seropositivity is more common in AAV than controls. There is weak serological data to suggest a variety of other organisms are more commonly observed in GPA patients vs. controls.	Unclear	Low
POLLUTION				
Silica	Meta-analysis (1) Case-control (4)	22-46% of AAV patients have a history of silica exposure, largely through occupational exposures (dusty manual labour). A meta-analysis of 6 observational studies reported a 2.5-fold increased risk of AAV with 'ever being exposed' to silica. A dose-dependent response is noted, particularly in relation to intensity of exposure, rather than duration of same.	Yes	High
Natural disasters	Cohort (3) Case series (1)	Clusters of AAV, mainly MPO-ANCA positive, were noted after 3 large earthquakes in Asia, postulated to be due to increases in silica, asbestos and carbon monoxide. In contrast, no increased incidence of AAV was noted following the 2011 Christchurch earthquake.	Yes	High
Other industrial contaminants (e.g. organic solvents, OS)	Case-control (5) Case series (1)	Any history of high OS exposure was positively associated with AAV in 1 study, specifically GPA. Similarly, a significantly higher mean hydrocarbon exposure was found in GPA and MPA patients vs. controls. These findings were not reproduced in 3 other studies.	Unclear	High
Mercury	Case-control (1)	Mercury was associated with a 10-fold increased risk of GPA in 1 study.	Yes	Low
Carbon Monoxide (CO)	Cohort (1) Case-control (1)	There is a trend towards an association between CO and AAV, specifically GPA.	Unclear	Variable (1 high, 1 low)
Farming, Animals	Case-control (5) Case series (1)	4/6 studies report an increased risk of AAV with farming. The risk is maximal for those with GPA who were exposed in the year prior to diagnosis, particularly to livestock.	Yes	Low

(*continued on next page*)

Table 4 (*continued*)

Risk factor	Study design (n =)	Summary of outcome (if applicable)	Considered a risk factor (based on available evidence)	Level of evidence (based on quality assessment)
OTHER				
Influenza vaccination	Cohort (1) Case-control (1) Case series (1)	Although case reports of AAV following influenza vaccination exist, the majority of studies demonstrate a protective effect on relapse risk.	No	High
Atopy	Case-control (4)	2 studies reported increased atopy in AAV patients compared to healthy and disease controls. 1 study reported a protective effect on GPA risk, while 1 found no association.	Unclear	Low
Smoking	Cohort (2) Case-control (5)	No association was found in > 50% of studies. 2 studies demonstrated a protective effect of current smoking, but an increased risk associated with former smoking. 1 study found a dose-dependent increased risk of MPA relapse associated with smoking, which was maximal for current smokers compared to 'ever having smoked'.	Unclear	High

environmental and epigenetic factors, in a genetically susceptible individual. It is likely that different triggers and the degree to which they influence disease activity vary by subgroup (e.g. ANCA subtype, geographic region). The most notable findings support the role of various pollutants - primarily silica and other environmental antigens released during natural disasters and through farming. Assorted geoepidemiological triggers are also implicated including seasonality and latitude-dependent factors such as UV radiation. Finally, infection is a likely culprit, yet the exact microorganism(s) are debated - *Staphylococcus aureus* is the most presently convincing. *Table 4* synthesises the evidence and overall perceived risk for each identified factor.

Given the lack of uniformity in disease identification and classification, as well as the challenge of obtaining adequate power in epidemiological studies, due to the rarity of disease, the overall quantity of evidence is small and the study quality is generally poor. The anticipated Diagnostic and Classification Criteria in Vasculitis (DCVAS) [5] may aid in categorising disease subgroups to allow uniformity in case ascertainment. There is a need for validated exposure biomarkers and more interoperable disease registries that can be integrated with other data streams (e.g. genetic, epigenetic and environmental) to facilitate international collaboration and large-scale epidemiological studies, with novel statistical and machine learning analytical techniques. Possible approaches include Bayesian Additive Regression Trees (BART) [120], Gaussian Processes [121], Artificial Neural Networks [122] and various case-crossover study designs [123], such as those recently utilised by Dixon et al. to explore the impact of weather on chronic pain [124].

AAV is one of over 100 AIDs, which when considered together affect approximately 10% of the population. Accordingly, the degree of individual- and population-level burden of AID makes the exploration and understanding of potential initiating factors critical. Discovering further insights into aetiopathogenesis is crucial to allow personalisation of risk stratification and treatment regimens, thereby optimising the risk-benefit balance associated with toxic immunosuppression. By identifying triggers of AAV relapse, we can learn to predict disease flares and hence develop a precision medicine approach in this cohort – a critically unmet need. Strides made in AAV have the potential to create a new paradigm for how AIDs are studied going forward.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2020.102660.

Funding

Dr Jennifer Scott is a Wellcome-HRB Irish Clinical Academic Training (ICAT) Fellow, and this work was performed within the Irish Clinical Academic Training (ICAT) Programme, supported by the Wellcome Wellcome Trust and the Health Research Board (Grant Number 203930/B/16/Z), the Health Service Executive, National Doctors Training and Planning and the Health and Social Care, Research and Development Division, Northern Ireland. MAL received funding from Health Research Board/Irish Nephrology Society (MRCG-2016-12) and from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 813545.

Declaration of Competing Interest

JS, JH, DM, ML none declared.

Acknowledgements

Thank you to Professor John Browne who leads the 'Systematic Reviews for the Health Sciences' module (PG7016, University College Cork) for sharing the necessary skills to complete this review.

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