Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

Leveraging a national patient registry to explore relapse in ANCA associated vasculitis

A thesis submitted for the degree of

Doctor of Philosophy

at The School of Medicine, Trinity College Dublin

Volume 2

Jennifer Orna Scott

MB BCh BAO (Hons), MRCPI

2023

Under the supervision of

Professor Mark Little, School of Medicine, Trinity College Dublin (Primary supervisor)

Dr Arthur White, School of Computer Science and Statistics, Trinity College Dublin

Dr James Ng, School of Computer Science and Statistics, Trinity College Dublin

Professor Cathal Walsh, Department of Mathematics and Statistics, University of Limerick

Professor John Kelleher, School of Computer Science, Technological University Dublin

Dr Louis Aslett, Department of Mathematical Sciences, University of Durham

Table of Contents

Volume 2

Table of Contents I

List of Appendices 1

1. COVID-19 registry instrument developed in collaboration with UKIVAS 1
2. SOP for the Rare Kidney Disease Registry: Clinical Data Entry 5
3. SOP for the Rare Kidney Disease Registry: Site Visit 24
4. AVERT Recruitment, Linkage and Engagement: SOP Guide for RKD Nurse 39
5. AVERT: Invitation letter for prior RKD recruits 45
6. SOP: Patient engagement with the AVERT smartphone application 46
7. PatientMpower App Guide for Participants 50
8. Example of a monthly AVERT newsletter to promote engagement 64
9. Detailed search strategy (EMBASE), adapted to each specific database as required 66
10. Supplementary Table 1: Quality Assessment of Case-Control and Cohort Studies using a Modified Newcastle-Ottawa Scale 68
11. Supplementary Table 2: Quality Assessment of Narrative Reviews, Randomised Controlled Trials and Meta-Analyses 83
12. Published Works 85
    - 12.1 Risk Factors for Severe Outcomes in Patients with Systemic Vasculitis and COVID-19: A Binational, Registry-Based Cohort Study 86
    - 12.2 ANCA-associated vasculitis in Ireland: a multi-centre national cohort study 93
    - 12.3 Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review 106
    - 12.4 The association between ambient UVB dose and ANCA associated vasculitis relapse and onset 129

References 143

List of Appendices

1. COVID-19 registry instrument developed in collaboration with UKIVAS

RKD ID	9
Reporter information	
New Encounter Instance	
Name of physician providing care for vasculitis patient	
Name of centre providing care	
Date this form completed * must provide value	15-02-2023 Today D-M-Y
Patient information (Part 1)	
Country of residence	Ireland
County of residence	
Education	
E-cigarette or Vape use	
'Encounters' Data: **Vasculitis/Disease status at time of C-19 diagnosis** **BVAS** **Medication (partial)**	
VDI Score	
Medication	
Angiotensin-converting-enzyme inhibitor at C19 diagnosis (ACE-i)	Yes No Unknown reset
Angiotensin II receptor blocker at C19 diagnosis (ARB)	Yes No Unknown reset
Summary table of entered data in 'Encounters' will be displayed below	

COVID-19 Questions	
Date of C-19 symptom onset (if known)	Today D-M-Y
Date of C-19 diagnosis	Today D-M-Y
Interval (days) between symptom onset and diagnosis	View equation
Age at C-19 diagnosis (years)	View equation
Location at which C-19 diagnosis was made	
Method of C-19 testing (select the most objective option)	

Sars-CoV-2 (COVID-19) IgM	
Sars-CoV-2 (COVID-19) IgG	
Admission to hospital required	○ Yes ○ No ○ Unknown reset
Admission to Intensive Care Unit	○ Yes ○ No ○ Unknown reset
Interval (months) from AAV diagnosis to C-19 diagnosis	View equation
Have patient's symptoms resolved at time of this report?	
Interval (days) between symptom onset and symptom resolution OR current date (if symptoms persist)	View equation
Infection Acquisition	
Clinical features at outset (check all that apply)	☐ Fever - MEDDRA/10016558 ☐ Malaise - MEDDRA/10025482 ☐ Headache - MEDDRA/10019211 ☐ Irritability or confusion - MEDDRA/10010300 ☐ Arthralgia - MEDDRA/10003239 ☐ Myalgia - MEDDRA/10028411 ☐ Conjunctivitis - MEDDRA/10010741 ☐ Rhinorrhea - MEDDRA/10039101 ☐ Anosmia - MEDDRA/10002653 (loss of smell) ☐ Ageusia - MEDDRA/10001480 (loss of taste) ☐ Sore Throat - MEDDRA/10041367 ☐ Cough - MEDDRA/10011224 ☐ Sputum production - MEDDRA/10041805 ☐ Shortness of Breath - MEDDRA/10040604 ☐ Chest pain - MEDDRA/10008479 ☐ RR >24 breaths/min - MEDDRA/10038711 ☐ Abdominal pain - MEDDRA/10000081 ☐ Nausea - MEDDRA/10028813 ☐ Vomiting - MEDDRA/10047700 ☐ Diarrhea - MEDDRA/10012735 ☐ Other (MEDDRA Ontology) ☐ None (asymptomatic) ☐ Unknown
Body temperature (highest recorded, °C)	

Lab values ***(Please enter the highest/peak recorded lab value for each field)***	
CRP (mg/L)	
Creatinine	
Urine PCR / ACR mg/mmol	
Hb	

Total White Cell Count x 10^9/L	
Neutrophil Count x 10^9/L	
Lymphocyte Count x 10^9/L	
Platelet Count x 10^9/L	
AST (U/L)	
Haemoglobin (g/dL)	
ANCA IF	
Anti-PR3 level	
Anti-MPO level	

Creatinine kinase (U/L)	
D-dimer (mg/L)	
Ferritin	
Lactate (mg/dL)	
Prothrombin time (s)	
Lactate dehydrogenase (U/L)	
Troponin	
Troponin Unit	
Findings on chest imaging	
Were antibiotics administered?	○ Yes ○ No ○ Unknown reset

Was treatment administered for C-19 infection (other than best supportive care)?	☐ No treatment except supportive care ☐ Kaletra (Lopinavir/ritonavir) - UATC/J05AR10 ☐ Remdesivir - No ontology code yet as novel ☐ Chloroquine - UATC/P01BA01 ☐ Hydroxychloroquine - UATC/P01BA02 ☐ Neuraminidase inhibitors, direct acting antivirals (e.g. Oseltamivir) - UATC/J05AH ☐ Azithromycin - UATC/S01AA26 ☐ Tocilizumab - UATC/L04AC07 ☐ Bevacizumab - UATC/L01XC07 ☐ Tofacitinib - UATC/L04AA29 ☐ Alfa1 antitrypsin - UATC/B02AB02 ☐ Ciclesonide - UATC/R03BA08 ☐ Plasma (from recovered patients) - UATC/B05AX03 ☐ Monoclonal antibody ☐ Other - ATC backed ontology

Complications / Disease Course (check all that apply)	☐ Acute Respiratory Distress Syndrome - MEDDRA/10001052 ☐ Acute respiratory failure (Type 1/2) - MEDDRA/10001053 ☐ Pneumothorax - MEDDRA/10035759 ☐ Acute liver injury - MEDDRA/10067970 ☐ Acute heart failure - MEDDRA/10000803 ☐ Myocarditis - MEDDRA/10028606 ☐ Cardiac arrhythmia - MEDDRA/10003119 ☐ Cardiac ischaemia - MEDDRA/10007584 ☐ Acute Kidney Injury (AKI) - MEDDRA/10069339 ☐ Sepsis - MEDDRA/10040047 ☐ Vasopressor dependence at any time - MEDDRA/10064148 ☐ Disseminated Intravascular Coagulation - MEDDRA/10013442 ☐ Severe anaemia - MEDDRA/10002082 ☐ Gastrointestinal haemorrhage - MEDDRA/10017956 ☐ Encephalitis - MEDDRA/10014581 ☐ Pregnancy-related complications - MEDDRA/10036569 ☐ Hyperglycaemia - MEDDRA/10020637 ☐ Hypoglycaemia - MEDDRA/10020996 ☐ Rhabdomyolysis - MEDDRA/10039020 ☐ Metabolic acidosis - MEDDRA/10027417 ☐ Secondary infection - MEDDRA/10062158 ☐ Macrophage activation syndrome - MEDDRA/10053867 ☐ Other (MEDDRA ontology) ☐ None
Concomitant respiratory pathogens detected (select all that apply)	☐ Influenza A ☐ Influenza B ☐ NON-COVID-19 Coronavirus ☐ Respiratory syncytial virus (RSV) ☐ Adenovirus
C-19 Outcome (Select the highest level of support the patient received)	
May we contact you to get more information about the outcomes of this case?	○ Yes ○ No reset
Would you like to share any lessons or other aspects from this case? Please include as much information as desired, this will greatly help patients and colleagues.	Expand

2. SOP for the Rare Kidney Disease Registry: Clinical Data Entry

RKD REGISTRY AND BIOBANK

Chief Investigator: Professor Mark Little

STANDARD OPERATING PROCEDURE

SOP:

CLINICAL DATA ENTRY

Author: Jennifer Scott	**Authorised by:** Mark Little **Date: 7/4/20**
Reviewer 1:	**Reviewer 2:**
Distribution: St James's Hospital CRF	
Protocol: VERSION 8_April 2020	

SOP HISTORY - Revision Date:

Version	*Altered (Reason for change)*	*Authorised by*	*Amendment date*	*Next review*
1.0	First issue			Feb 2020
2.0	COVID-19 dataset			April 2021

CONTROLLED DOCUMENT

The user of the SOP must read the following thoroughly before proceeding to undertake the methods described. Under no circumstances are these instructions to be amended or altered in any way other than by the author/authorised personnel.

2.1 Purpose

- This SOP describes the procedure for clinical data entry. This applies to initial data entry for new recruits, and guides data review and updates for site visits.

2.2 Responsibility

- It is the responsibility of the treating physician, research nurse, visiting research fellow and local lead investigator to ensure that all steps are completed competently.

2.3 Procedure

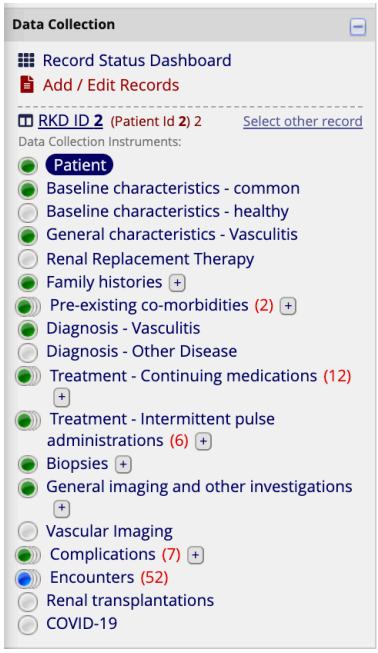
- The researcher (nurse or physician) will follow the guidance below when entering, reviewing or updating clinical data to the registry.
- It may be necessary to consult with the patient's medical doctor in order to accurately complete the registry entry. The Research Nurse may also refer to the pocket guide for Research Nurses on the Rare Kidney Disease Registry and Bio-Resource. If in doubt, don't enter the data, check with the doctor.
- The RKD registry is stored in REDCAP, a database programme, which is hosted on a secure, firewall protected network by TCD High performance computing (HPC) department. In order to access REDCAP, one needs to undergo data protection authorisation by Professor Lucy Hederman. Logins are then provided by a computer scientist in TCD HPC. A TCD VPN is required on a Trinity associated laptop to access REDCAP remotely. Access is available at main hospital sites also.
- Of note, different accounts have different degrees of access and options (e.g. import data, export data, edit data, read-only, full access, pseudonymised). Please clarify with the PI which level of access you are entitled to.

- **Registration Fields are referred to as 'instruments' in REDCAP:**
    - Patient
    - Baseline Characteristics-Common
    - Baseline Characteristics-Vasculitis
    - Renal Replacement Therapy
    - Pre-existing co-morbidities
    - Diagnosis - Vasculitis
    - Treatment: Continuing Medications
    - Treatment-Intermittent Pulse administration
    - Biopsy
    - General imaging and other investigations
    - Vascular imaging
    - Complications
    - Encounters

- Renal transplantations
- COVID-19

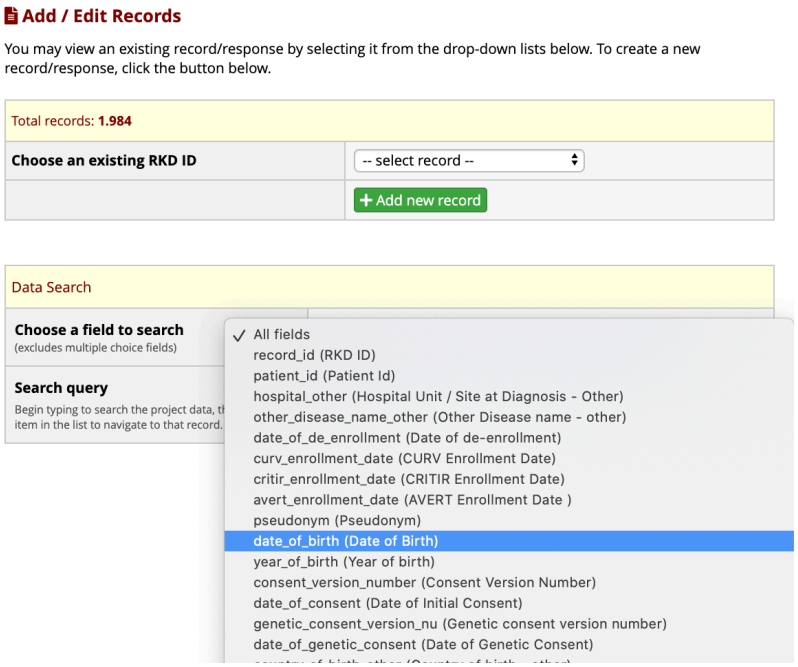
- **Encounter data fields include:**
  - Disease Assessment Common
  - Disease Assessment Vasculitis
  - BVAS (specific training on this can be provided by Prof Little or Dr Clarkson)
  - Investigations Summary
  - Investigations: Common
  - Investigations: Vasculitis
  - EQ5D
  - Biomarkers (only for specific patients)

- **General pointers for using REDCAP**
  - Click on 'Add / Edit Records/ from the left-hand shortlist to add a new patient or to edit any RKD ID record.
  - One can navigate the various instruments from this shortlist, as seen below:



  - Always **save** each page prior to moving to a different instrument. Various options exist including:
    - **'**Save & Stay'
    - 'Save & Exit Form'
    - 'Save & Add new instance' (e.g. to add another drug in treatment instruments)

- When an instrument is fully completed, change 'form status' to 'complete' – this will change the red icon to green on the shortlist.
- To search for a particular RKD ID, use the 'Choose an existing RKD ID' dropdown. One can also search by date of birth, hospital or any other field, by using 'Choose a field to search':



- **Exports** can be customised using the 'Data Export' tool. Seek further guidance in the support videos in REDCAP or from the TCD HPC department. Data can be exported to various programmes including excel and R. Basic statistics and filtering options are also possible.

- **Notes for Registration Data Fields on REDCAP**

<u>Patient</u>

- RKD ID is created for a new recruit via REDCAP by the PI or delegate. This should be communicated to the local site at the time of recruitment for documentation on the local recruitment log:
  - 'Add / Edit records' -> 'Add new record'
- 'RKD ID' should match 'Patient ID'
- 'CURV', 'CRITIR' and 'AVERT' are RKD sub-studies. Indicate whether the patient is enrolled on to these by selecting: yes / no / not known. Of note, CURV and CRITIR are historical, AVERT is ongoing as of April 2020.

<u>Baseline Characteristics- Common</u>

- <u>Ensure key demographics match the local recruitement log (e.g. gender, date of birth and date of initial consent).</u>

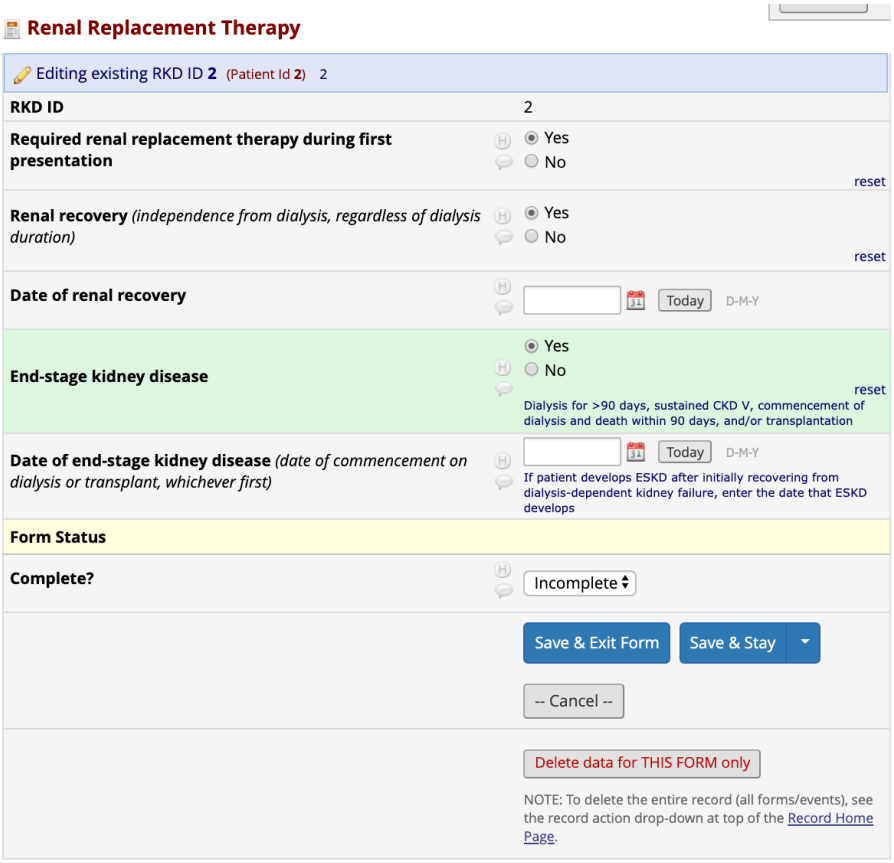
- Key items to chase include ethnicity, height, smoking status (never/ex/current is sufficient)
- Ensure 'patient status' is up to date and the corresponding date of any event:
    - Alive / Dead / Lost to follow-up / Opted-out

General Characteristics-Vasculitis

- Document any previously recorded ANCA IF Result
- Document any previously recorded ANCA ELISA specificity
    - Validation check: typical ANCA patterns include:
        - c (IF) with PR3 (ELISA specificity), typically (but not always) associated with GPA (see appendix VII for full description)
        - p (IF) with MPO (ELISA specificity), typically (but not always) associated with MPA or EGPA (see appendix VII for full description)
- Document Systems involved **at any point**
- Document **summary of treatment** received:
    - It is vital to ensure this section is updated at each review, as this information will change as the patient progresses through their disease course.
    - Ensure this summary correlates with the 'treatment' sections below (practically is it more efficient to complete 'treatment' sections first and then summarise data in this section after).
        - Document induction treatment received, including number of plasma exchange sessions. **ONLY AGENTS USED FOR THE INITIAL INDUCTION AT DIAGNOSIS should be ticked (i.e. do not include additional agents used for subsequent relapse).**
        - Document any previously received maintenance treatment (even if it has since ceased).
- Document any family history in first degree relatives.

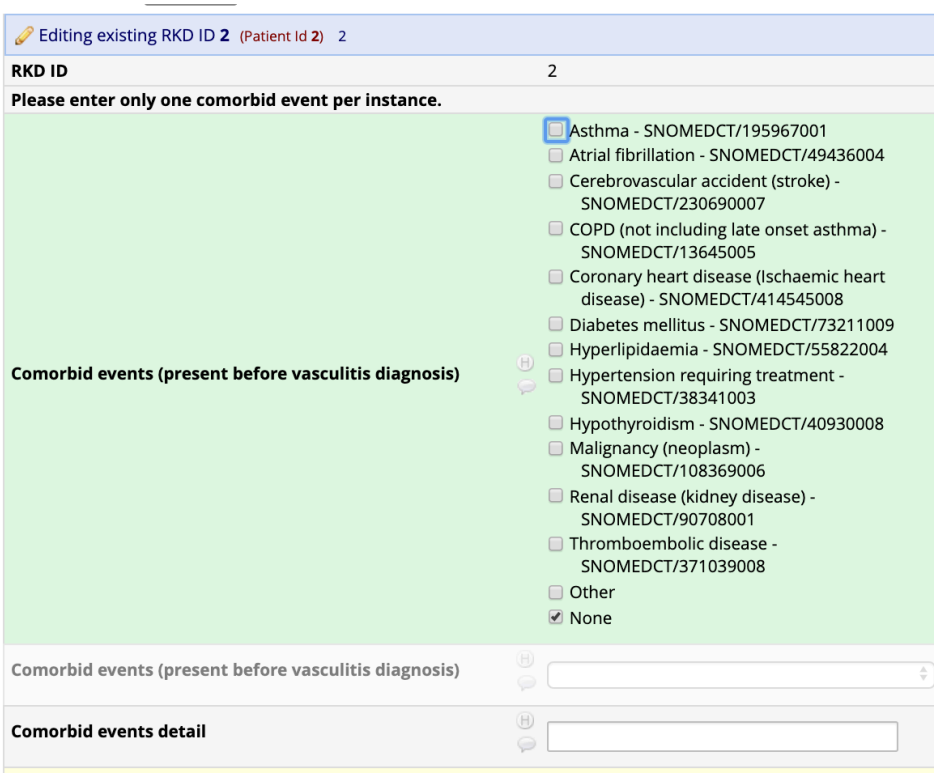
Renal Replacement Therapy

- Complete as appropriate. Field notes define relevant definitions:



Pre-existing co-morbidity

- Document/check on *first* review as this will not change.
- Document past medical history (i.e. comorbidities prior to diagnosis) from the list below. **Enter only one diagnosis per instance**:



- If the diagnosis is not listed, select 'other' and begin typing into the field 'Comorbid events other, snomedCT'. This ontology will suggest terms that match what is typed.

<u>Diagnosis – Vasculitis</u>

- Document date of diagnosis and date of symptom onset (if known). Validate that this date makes chronological sense with other documented dates.
- Record the primary diagnosis from the pre-specified options (Use appendix VII to assist with disease descriptions. If in doubt, check with medical doctor):

Small vessel vasculitis (ANCA associated)	○ **ANCA vasculitis unclassified - ORPHA:156152** ○ **Eosinophilic granulomatosis with polyangiitis (Churg Strauss) - ORPHA:183** ○ **Granulomatosis with polyangiitis (Wegener) - Orpha:900** ○ **Microscopic polyangiitis (including renal limited vasculitis) - ORPHA:727** ○ **reset**
Small vessel vasculitis (Immune complex)	○ **Anti-GBM disease - ORPHA:375** ○ **Cryoglobulinemic vasculitis - ORPHA:91138** ○ **IgA vasculitis (Henoch-Schonlein) - ORPHA:761** ○ **reset**
Medium vessel vasculitis	○ **Classical PAN - ORPHA:439737** ○ **Kawasaki disease - ORPHA:2331** ○ **reset**
Large vessel vasculitis	○ **Takayasu arteritis - ORPHA:3287** ○ **Giant cell arteritis - ORPHA:397** ○ **reset**
Variable vessel vasculitis	○ **Cogan's syndrome - ORPHA:1467** ○ **Behcet's disease - ORPHA:117** ○ **reset**
Single organ vasculitis	○ **Isolated aortitis** ○ **Primary cerebral angitis** ○ **reset**
Secondary vasculitis	○ **No** ○ **Yes** ○ **reset**
Other	○ **Yes** ○ **No** ○ **reset**
Unclassified	○ **Yes** ○ **reset**

- Document whether a biopsy has ever been performed. This information is obtained from the laboratory/pathology system locally. Depending on the age of this system, the researcher may need to liaise with the pathology laboratory directly to ensure accuracy (e.g. diagnosis on biopsy in 1999, but local computer lab system only dates back to 2007).

- It is vital to correlate this 'yes/no' answer with the 'biopsy' section below. If 'biopsy performed' is documented as 'YES', but no biopsy data inputted in 'biopsy'section, it is vital to locate this report and input into the biopsy instrument (assistance can be obtained from Prof Little or the research fellow).
- Document whether the diagnosis is 'histologically confirmed' (i.e. the biopsy reports evidence of this disease).

- Diagnosis Confidence
  - Establish Diagnosis Confidence (Table 1). The Diagnosis Confidence table is accessible on both REDCAP and UKIVAS, and can therefore be entered retrospectively.

Table 1: Diagnosis Confidence Table

Matrix (for ANCA related disease)

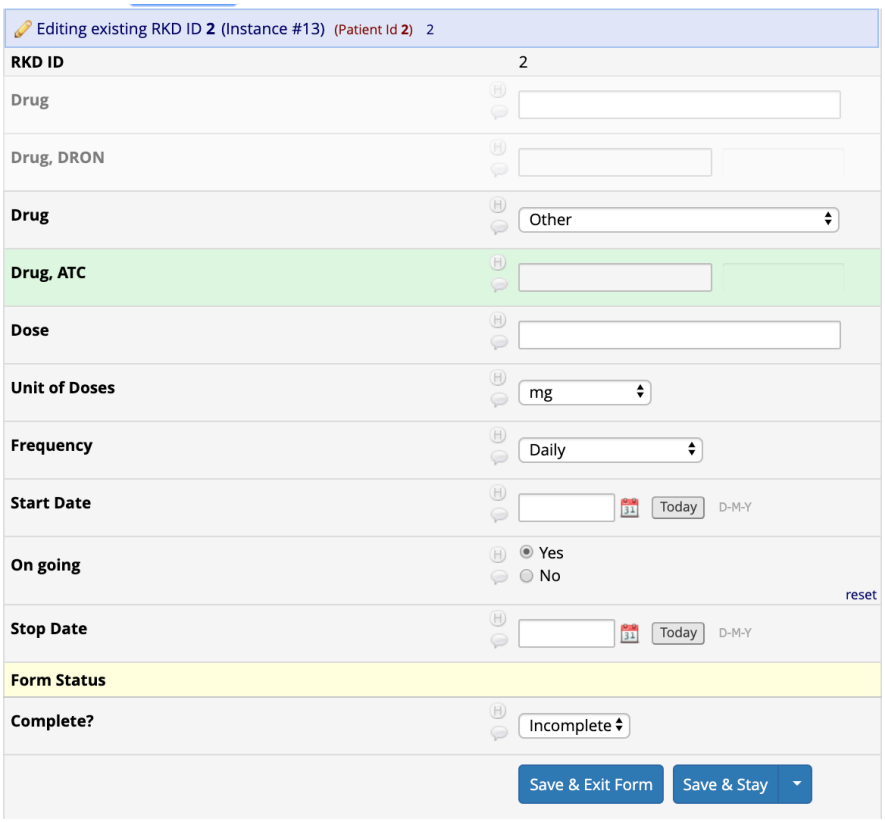
No. of organs with clinical features	Histology or Radiology	ANCA ELISA	Diagnosis confidence
more than one	diagnostic	Positive	Definite
		Negative	Definite
	equivocal	Positive	Definite
		Negative	Probable
	none	Positive	Definite
		Negative	Possible
one	diagnostic	Positive	Definite
		Negative	Definite
	equivocal	Positive	Probable
		Negative	Possible
	none	Positive	Probable
		Negative	Possible

Example 1: A patient who has only one organ involved (i.e. pulmonary haemorrhage), a CT scan which is inconclusive, and a negative ELISA would have a 'possible diagnosis'

No. Of Organs with Clinical Features	Histology or Radiology	ANCA ELISA	Diagnosis Confidence	
One →	Diagnostic	Positive	Definite	
		Negative	Definite	
	Equivocal	Positive	Probable	
		Negative →	Possible	✓
	None	Positive	Probable	
		Negative	Possible	

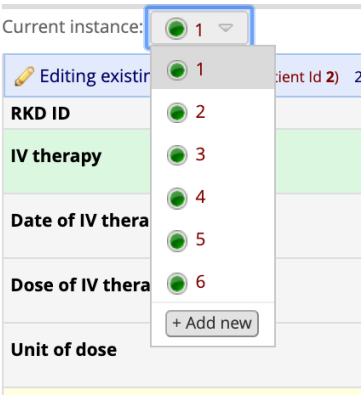
Treatment: Continuing Medications

- This is a critical section and should be updated at each review. Document maintenance immunosuppression (e.g. Azathioprine or Rituximab) and steroid doses, with start and end dates (see appendix VIII for treatment explanation).
- Where possible, aim to document the steroid wean. Practically, one should prioritise the start and end dates for the highest and lowest (this could be 0 mg, i.e. cessation) steroid doses.
- Select the drug from the dropdown list. If it is not listed, select 'other' and proceed to type the drug name in the field 'Drug, ATC', which is backed by the ATC ontology.

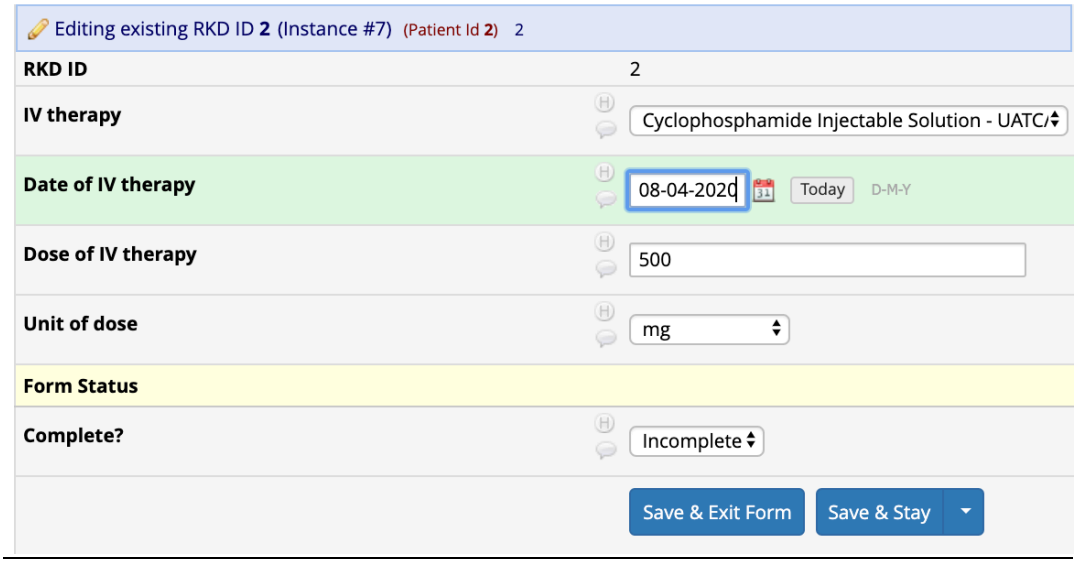


Treatment-Intermittent Pulse administration

- This is a critical section and should be updated at each review.
- Document each dose and date of intravenous therapy, including: methylprednisolone, cyclophosphamide and rituximab.
- To add a new instance, click on the arrow beside 'current instance':



- Select the drug from the dropdown list. Select 'other' if the drug is not listed to enter it into the ATC ontology backed field.



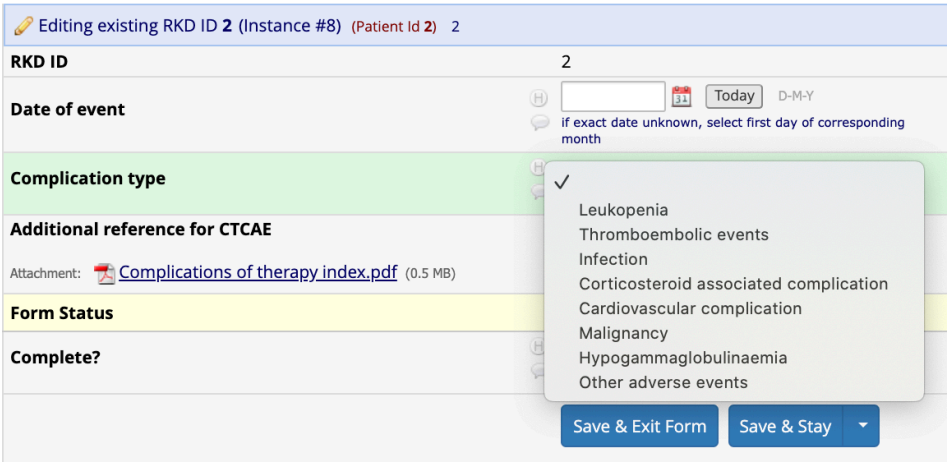
Biopsy

- Document date and site of biopsy.
- Document 'General findings', which will generally be 'definite vasculitis', 'consistent with vasculitis but not definite' or 'non diagnostic'.
- Input details of biopsy (see separate guidance sheet or seek assistance from Prof Little or research fellow).
- Sites of biopsy analysis:
- Galway, Cork, SVUH analyse their biopsies locally (therefore, need to obtain any missing biopsy reports locally). Biopsies performed in TUH prior to 2014 were processed in SJH.
- TUH, SJH, BH, LUH and MMUH all send their biopsies to BH for analysis. If a biopsy has been performed, but is not located on the local pathology system (e.g. the system is newer than the date of the biopsy), the

researcher needs to liaise with the renal pathology secretary in BH to obtain the biopsy result. The patient's name and date of birth is required to locate the result. All BH renal biopsies are stored on a computerised system in the renal pathology department (ask Jennifer Scott, Research Fellow, for details).

Complications

- A complication is defined as an event occurring as an unintended consequence of the disease or therapy.
- Complications are captured under 8 categories, listed below. Select the relevant category – relevant follow-up questions will appear:



- Document if the patient has experienced any complications related to the therapy they have received. The threshold for inclusion is the requirement for the intervention of a medical professional (ie: a self-limiting coryzal illness would not be included). Ensure the date of complication is after the date of diagnosis, otherwise this is a pre-morbid condition.

- ***Leukopenia***
  - If the patient has had an episode of leukopenia (low **total white cell count** obtained from full blood count), document this and grade the event from 1-4 as per table 2. Note that an episode of leukopenia is scored once, even if several white cell count estimations are performed. The nadir white cell count is considered for scoring purposes.

    Table 2: Leukopenia Score

Total white cell count (WCC)	Grade
WCC 3.1-4x10^9/L	1
WCC 2.1-3x10^9/L	2
WCC 1.1-2x10^9/L	3
WCC <1.1x10^9/L	4

- ***Thromboembolic events***

  Document whether the event was a suspected or proven deep venous thrombosis (DVT) or a pulmonary embolism (PE).

- ***Infection***

  If the patient has experienced an infection, document the type of infection (e.g. lung), organism if known using the snomedCT ontology backed field (check microbiology on local laboratory system) and grade it using the Infection Severity Score 1-5 using table 3 or the CTCAE table (viewable on the online clinical data entry system).

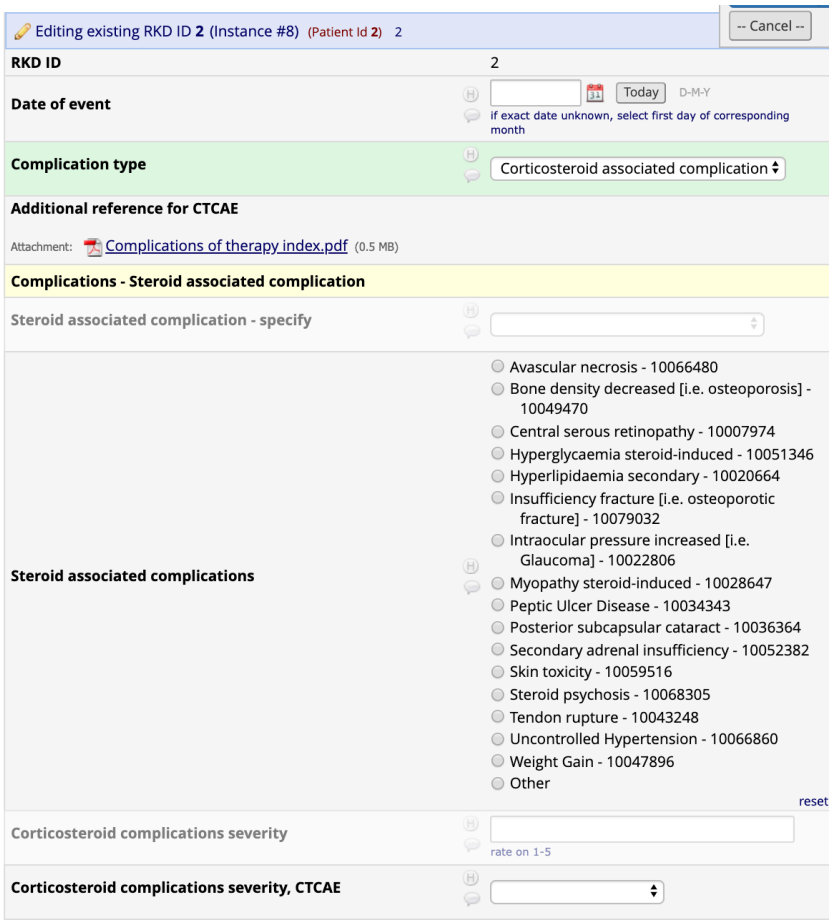
Table 3: Adverse Event Grading

Adverse Event Reporting Guidelines (Grade 1-5 refers to the severity of the AE. Descriptions of severity for each AE are based on the following as a general guideline)	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

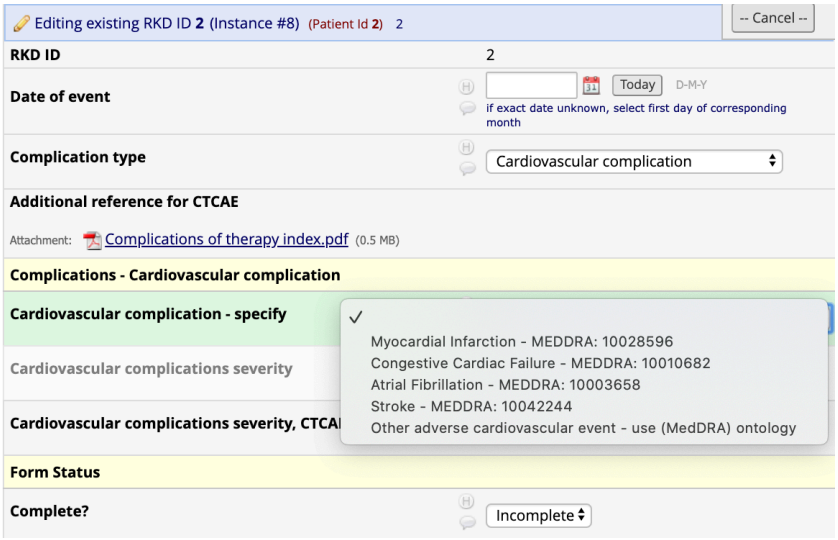
- ***Corticosteroid associated complication***

  Select those that apply from the following list and document the severity of each (using the same CTCAE scale):



- ***Cardiovascular complication***

Document any relevant cardiovascular complication from the list provided and the associated severity score:

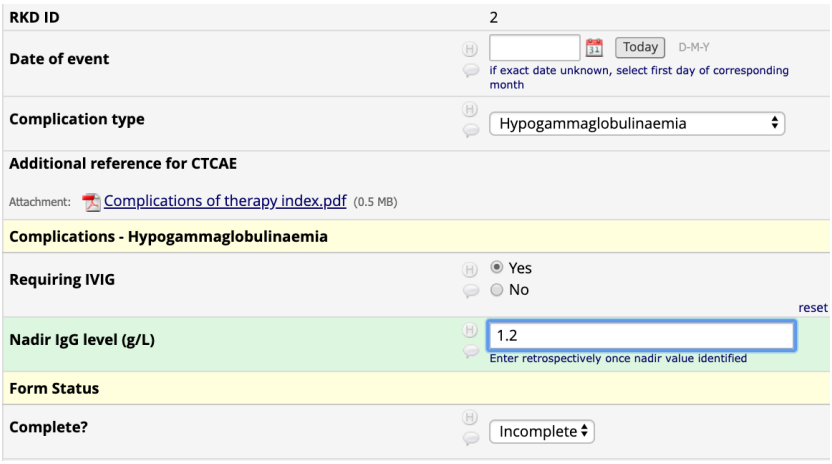


- ***Malignancy***

  Document the type and severity of any malignancy

- **Hypogammaglobulinaemia**

  Document requirement for IVIF: yes/no and the nadir (i.e. lowest) IgG level.



- ***Other Complications***

  Document other complications that have occurred using the MEDDRA ontology backed field and grade it as per Table 3. Please

ensure you only enter diagnoses here that do not fit into the other categories above.

- **Notes for Encounter Data Fields on REDCAP**
  - This is a critical section to update, especially for peripheral sites.
  - **Each patient requires *at least* an annual encounter**, based on the most recent clinic letter. If the patient has had a **'possible flare event'** since last review, this should be inputted as a separate encounter (see appendix VII for flare description) and ideally **an encounter pre- and post-flare** should be inputted (to allow monitoring of the change of patient parameters, such as urinalysis and laboratory results).

<u>Disease assessment – Common</u>

  - Document urinalysis results, whether the patient is dialysis dependent (and relevant dates) and their weight.
    - Of note, **if the patient has started/stopped dialysis since the last encounter, please update the 'Renal Replacement Therapy' module.**
  - Document disease activity since last return. Consult with patient's medical team to clarify this. Note that, for patients with vasculitis, if disease activity is not "remission", there should be at least one active BVAS item recorded, and **if disease activity is "remission" then BVAS will be zero**. It is important to note that a patient may have a persistently active urine sediment (i.e. blood and protein on urinalysis) with a raised creatinine, as a result of the chronic kidney damage, rather than active vasculitis – if this is the case, one should not score for these items in BVAS. BVAS should only score for symptoms related to ACTIVE vasculitis.
  - Document all clinical samples obtained.
  - Complete **BVAS Score** (ask PI for training if required).

<u>Disease assessment – Vasculitis</u>

  - Document whether vasculitis is relapsing at this encounter (this will correlate to disease activity – e.g. 'active disease' will correlate to 'high probability' / 'possibly' relapse if return visit, or 'no' relapse if initial diagnosis).
  - **'Adjudicated probability of relapse'** should be left **blank** as this is determined by an expert group retrospectively.

- **The treatment questions relate to what the patient is taking at <u>that point in time</u> (it does not include the treatment started *as a consequence* of the encounter).**
    - **Immunosuppressive status** – select appropriate description from the dropdown. Treatment naïve means 'no treatment' (this would typically be an acute recruit who was sampled prior to starting treatment).
    - **Corticosteroids** (CCS): yes / no
        - If yes, select the dose range
    - **Immunosuppressive medication**: select from dropdown list.
        - If drug is not included, select 'other' to use the ATC ontology backed field.
        - If the patient is <u>not</u> on any other immunosuppressive agent (other than CCS) select 'no'.
        - Select Rituximab from the list if the patient has received Rituximab in the past 6 months, or if CD19 positive B cell count is <0.005 cells/uL, as these patients are considered to be under the influence of the drug.
        - Immunosuppressive medication in response to this encounter: what happened to the medication in this clinic review – was it increased / no change / reduced / stopped / unknown?
        - Document if the patient is receiving any prophylaxis treatment (including: co-trimoxazole [e.g. Septrin], calcium and vitamin D, pentamidine, bisphosphonate, antifungal [e.g. Fluconazole]) or gastric protection (e.g. PPI or H2RB).

<u>Investigations summary</u>

- This is a summary of pertinent investigations, used to inform the patient's risk of vasculitis flare.
- **ANCA titre**: compared the ANCA (PR3/MPO) titre from this visit to the previous visit. Select the appropriate analysis from the dropdown (e.g. 4 X rise in the preceding ANCA).
- **Suggestive bloods OR urine tests (excluding ANCA)**: these would include anything that suggests a possible relapse event (e.g. rising creatinine/CRP, new haematuria, etc.)
- **Suggestive imaging:** any imaging suggestive of a relapse (e.g. pulmonary nodules).

Investigations

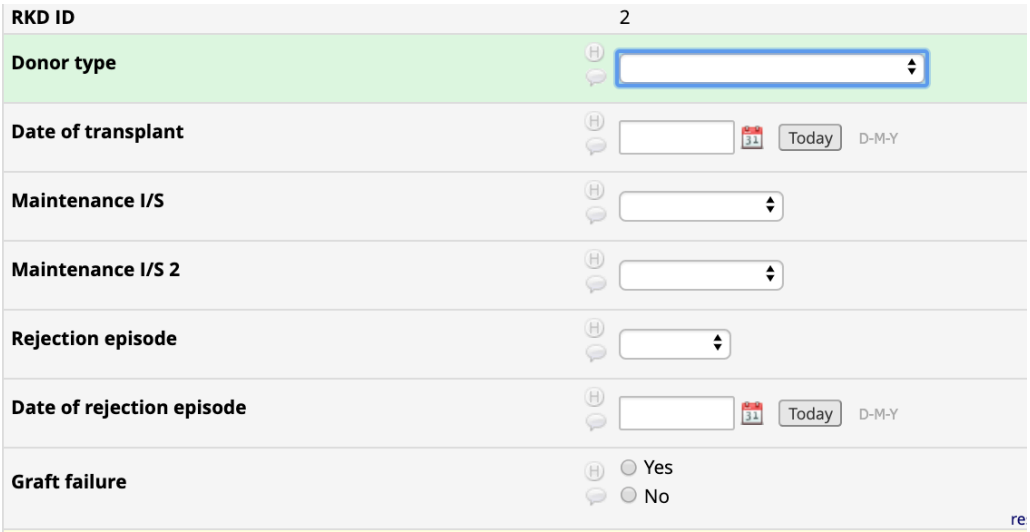
- Blood results are specific to the Research Visit **+/- 7 days**. If clinical bloods have been taken as part of the routine clinical care these should be followed up and documented as part of the clinical data for the research visit.
- Complete **ANCA result** specific to visit **+/- 14 days**.
- Identify whether critical results (e.g. crp, creatinine, ANCA) are **pending or have not been performed**, (e.g. to show that these results have been looked for and just not performed).
- Please note that recording of lab values greatly enhances the research potential of the linked samples, so every effort should be made to complete them, even if they were taken on a different day.
    - A minimum of **CRP, creatinine, urine PCR, ANCA, PR3/MPO** should be completed for each encounter.
    - If time permits, please complete missing laboratory results from prior encounters, especially the first encounter.

EQ5D Results

- EQ5D is a quality of life questionnaire, based on 5 domains each scored 1-5. This cannot be completed retrospectively.

Renal transplantations

- Document the occurrence of renal transplantation using the following fields:



COVID-19

- With the emergence of COVID-19, an additional instrument has been designed, in collaboration with UKIVAS. This includes a within-instrument pop-up to a simultaneous encounter for the same date, to ensure relevant data is available in the post-COVID-19 period. Please refer to the separate case report form which details the fields captured in this instrument.

3. SOP for the Rare Kidney Disease Registry: Site Visit

RARE KIDNEY DISEASE

REGISTRY AND BIORESOURCE

Chief Investigator: Professor Mark Little

STANDARD OPERATING PROCEDURE

SOP No:

SITE VISIT

Author: Jennifer Scott, Jack Hartnett	**Authorised by:** **Date:**
Reviewer 1:	**Reviewer 2:**
Distribution: St James's Hospital CRF	
Protocol: VERSION v1.0 October 2018	
SOP HISTORY - Revision Date:	

Version	*Altered (Reason for change)*	*Authorised by*	*Amendment date*	*Next review*
1.0	First issue			Oct 2019

CONTROLLED DOCUMENT

The user of the SOP must read the following thoroughly before proceeding to undertake the methods described. Under no circumstances are these instructions to be amended or altered in any way other than by the author/authorised personnel.

3.1 Goals and Objectives of Site Visit

- As of October 2018, the RKD registry has recruited 704 patients with vasculitis in Ireland. Although the concentration of recruits is centred around Dublin, a number of patients have been recruited from peripheral centres.
    - Tallaght University Hospital (180)
    - St James's Hospital (99)
    - St Vincent's University Hospital (61)
    - Beaumont Hospital (143)
    - Mater Misericordiae University Hospital (14)
    - Cork University Hospital (154)
    - Galway University Hospital (28)
    - Limerick University Hospital (23)
    - Waterford (2) – no longer recruiting

- In order to maintain high quality, accurate, up to date registry information, site visits are necessary. These will be performed by the research nurse and/or research fellow, in conjunction with the local principle investigator (PI).

3.2 Site visit schedule

- Peripheral site visits will occur on a rolling quarterly basis:
    - Month 1: Galway, SVUH
    - Month 2: Cork (2 days)
    - Month 3: Limerick, MMUH

- Given the presence of the PI, research nurses and research fellows at BH, SJH and TUH, the registry is updated on an ongoing basis, typically at weekly clinics.

3.3 Pre-visit organisation

- Research nurse will contact local PI in advance of the planned visit to confirm suitability for same. Usually the local PI will identify a local liaison person, commonly a nephrology registrar, to link in with on the day of visiting.
- In advance of the visit, the research nurse will:
    - Confirm access to data sources, including:
        - Local patient recruitment log to match patient study ID with local medical record number
        - Patient consents
        - Other data systems as needed, see site specific information:
            - eMed
            - Letters
            - Laboratory/Pathology system
            - Discharge letter system

- Identify a dedicated work-space, with computer linked to above hospital systems and internet. Ideally, the research nurse will also bring laptop associated with the study to speed up data entry.
- Identify particular study IDs that require complete medical records (i.e. charts) to be requested, to identify missing data. This is performed by reviewing registry exports (guidance can be sought from the research fellow or Professor Little). Data that may require medical charts include:
  - Number of and dosing of induction treatment
  - Number of plasma exchange treatments
  - Non-nephrology patients, whose primary team do not produce complete electronic records

3.4 Priorities of site visit

1.1.1. Recruitment Log

- The research nurse will validate the local recruitment log with a registry export of the centre. The log should be reviewed in detail to ensure there is a patient name and accurate date of birth corresponding to each study ID.
- Ideally, the research nurse should convert any ongoing paper logs to an excel file. This should be stored securely (behind a university or HSE firewall), in either the local shared folder for nephrology or on the local PI's desktop. The location of the log should be recorded on the master 'Review Log', detailed below (1.4).

1.1.2. Patient consent forms

- The research nurse will review all consent forms to ensure there is a valid consent form corresponding to each study ID on the local recruitment log.

1.1.3. Data priorities

- The aim is to achieve complete registry data for each study ID, to enable a truly granular description of each patient as they move through their disease course.
- Most patients will require only interval updates, as one would envisage that at the time of enrolment a detailed registry entry is made by either the treating physician or via contact by the research nurse, in the case of a peripheral hospital.
- However, to ensure there is no missing data, the first review of each study ID's records will include a detailed review of all prior data (detailed in RKD Sample and Data Collection and Management Protocol V7.4, SOP D2).
- Unless there has been a possible flare event, each study ID should have an **annual** encounter entered into the registry, based on the details of the most time-appropriate clinic visit.
- If a possible flare event has occurred, there should ideally be an encounter pre-flare, at the time of flare and post-flare, in order to be able to assess trend of laboratory findings, urinalysis, system involvement, etc.

3.5 Recording of site visits

- The date of each site visit will be recorded on the master 'National Recruitment Log', stored on the TCD shared folder.
- Key information will also be recorded on this log, including:
    - Biopsy details entered in registry (if biopsy performed): yes/no
    - Death (once registry data is up to date until time of death, there is obviously no reason to review this study ID, and therefore saves time at subsequent visits)
    - Comments column to highlight:
        - Critical missing data (e.g. induction treatment) for follow-up at the next site visit
        - Need to request medical records for the next site visit

3.6 Galway University Hospital (GUH)

- The local PI is Professor Matthew Griffin.
- All nephrology registrars are involved in recruiting. They inform Prof Griffin of any new cases, who then updates the local recruitment log. This is securely stored on his desktop, as there is no shared facility.
- A suggested base for the day is in an office in Merlin Park Hospital, dialysis unit.

1.3.6.1 Medical records (charts) required for:

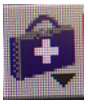
- Induction treatment
- If followed by team other than nephrology

1.3.6.2 Data systems required:

- *eMed*
  - The majority of data, including clinic observations and physician review, is recorded here
  - See below (2.3) for useful tips
- *EDS* (discharge summary) is useful for:
  - Complications (e.g. Admissions – infection, VTE, etc.)
  - Summary of induction treatment from initial admission, at time of diagnosis
  - Dates +/- doses for Cyclophosphamide/Rituximab as they occur as day cases
- *Web lab ward*:
  - Immunology (e.g. ANCA etc.)
    - Cumulative function useful to see ANCA/Anti-GBM trends
  - Biopsy results

1.3.6.3 Useful eMed tips:

- Data viewer:
  - All Drugs – see complete treatment history
  - Drug history – see dates for start/stop & doses
  - Observations
    - Weight
    - Height
    - Urinalysis for a specific date (or can be included in clinic letter)
  - Labs – split into subsection (e.g. FBC)
  - All notes, which can be filtered by 'medical' or 'clinic' to get the most useful information

- 
  - Letter viewer (captures more data) OR
  - All notes (via data viewer [see above icon], but some letters can be missing from here if still pending)
    - Review for possible **flare events** in between encounter dates

- Review for any **complications** (e.g. steroid induced complications such as cataracts, psychosis, diabetes, etc. and other complications such as infections, VTE)
- If no flare/complication, then use letters for up to date annual encounter

3.7 Cork University Hospital (CUH)

- The local PI is Dr Michael Clarkson.
- All nephrology registrars are involved in recruiting. They inform Dr Clarkson of any new cases, who then updates the local recruitment log. This is securely stored on his desktop, as there is no shared facility. Dr Clarkson or an assigned registrar will facilitate access to the required data systems.

1.3.7.1 Medical records (charts) required for:

- If followed by team other than nephrology
- For items not included in the systems below, e.g. sometimes for induction treatment
- Check the master log prior to the site visit, as charts identified as required may be noted from the prior visit. If so, one needs to request these to be pulled in advance of the visit.

1.3.7.2 Data Systems required:

- *Citrix*
    - This is found on an icon on the desktop
    - Useful to obtain letters/discharge summaries and laboratory results

- *iLab*
    - Use to obtain biopsy reports, under pathology
    - This system can also be used to obtain laboratory results if not in ICM-CUH.

- *eMed* may also be useful, but in general is not required given systems above.

3.8 Limerick University Hospital (LUH)

- The local PI is Dr Liam Casserly.
- All nephrology registrars are involved in recruiting. They follow the instructions for recruitment, including updating the local log, which is kept in a red folder in Dr Casserly's office (dialysis unit). There is also an electronic log found in the 'Renal folder (mwrd-proxy), entitled 'ZZZ Rare Kidney Disease (RKD) and Biobank folder' -> 'LUH patient recruitment log'. This is password protected. Ideally the electronic log should be kept up to date, and the paper log as a back-up. All consent forms and corresponding 'Data Sample Collection Sheets' are kept in this red folder also.
- A suggested base for the day is in the conference room, in the dialysis centre.

1.3.8.1 Medical records (charts) required for:

- Specific data missing from all electronic sources. This is unusual for Limerick, given the letters are very detailed.

1.3.8.2 Data systems required:

- *iLab*
    - This stores all the blood results, including off site locations such as St. John's hospital
    - It is found on an icon on the desktop

- *Renal folder*
    - This stores all the letters, biopsy results and external lab results (e.g. CD19 levels), in a folder per patient
    - It is found on an icon on the desktop

3.9 St. Vincent's University Hospital (SVUH)

- The local PI is Dr Eamonn Molloy. Dr John Holian is a consultant Nephrologist who is also actively involved and is the best point of contact for site visits.
- All nephrology registrars are involved in recruiting. They follow the instructions for recruitment, including updating the local log, which is kept on the shared drive: found by the following route 'computer' -> 'Dialysis' folder -> 'Vasculitis Registry' folder -> 'Recruitment Log' (excel file). This should be updated as necessary. All consent forms are kept in a labelled box in this office.
- A suggested base for the day is in the NCHD Nephrology doctor's office on the 4th floor, next to the dialysis unit. The computer facing the window has access to all programmes.

1.3.9.1 Medical records (charts) required for:

- Specific data missing from all electronic sources.

1.3.9.2 Data systems required

- *Clinical Portal*
  - This stores all the patient's episodes (i.e. admissions with corresponding discharge letters, day admissions to IV infusion unit) and blood results.
  - The link is found in 'Favourites' on the intranet

- *TA+*
  - This stores all the patient letters, which are usually quite detailed to determine the clinical course in order to update Encounters in the registry.
  - The link is also found through Favourites on the intranet:

- *Syngo*
  - This is the programme which stores radiology images and reports

3.10 Mater Misericordiae University Hospital (MMUH)

- The local PI is Professor Yvonne O'Meara.
- All nephrology registrars are involved in recruiting. They follow the instructions for recruitment, including updating the local log, which is kept in a folder in the NCHD doctor's office, next to the renal day ward. This should be updated as necessary. All consent forms are kept in the same folder.
- A suggested base for the day is in the NCHD Nephrology doctor's office, next to the renal day ward.

1.3.10.1 Medical records (charts) required for:

- Specific data missing from all electronic sources. This is unusual for MMUH, given the letters are very detailed.

1.3.10.2 Data Systems required:

- *Patient Centre*
    - This programme stores most information you will require including labs, letters and discharge summaries.
    - The icon is found on the desktop

3.11 St. James's Hospital (SJH)

- The local PI is Dr Niall Conlon.
- Nephrology and Immunology are involved in recruiting patients. They inform the research nurse attached to CRF-SJH of any new cases, who then updates the local recruitment log. This is stored on the TCD shared Nephrology folder. Contact the PI to gain access.

1.3.11.1 Getting Setup:

- Contact the CRF Executive Officer or study associated Research Nurse to book a clinic room in advance (*only clinic rooms can be used as only their computers have access to EPR [Electronic Patient Record]*).
- Select patients for whom their physical charts are required and correspond with Executive Officer/Research Nurse to ensure they will be in CRF at selected date and time.

1.3.11.2 Medical Records (charts) required for:

- Clinic letters if not uploaded to the letters programme ('Patient Correspondence Letters' tab on EPR)
  - *Letters are found at the start of physical chart – not all may be uploaded to EPR so chart is worth checking*
  - Clinic letters to GP/Other Consultants provides a broad overview of the OPD review – usually includes main symptoms, signs, impression and plan. This is the key section which will inform: 'complications' (e.g. steroid induced complications such as cataracts, psychosis, diabetes, etc. and other complications such as infections, VTE) and 'Encounters', including potential flare events.
  - If there has been no flare/complication since the last encounter, then use letters for up to date annual encounter.
  - Letters are also particularly useful for medication changes as this is always explained clearly in clinic letters
- OPD clinic notes
  - ***OPD notes are not part of SJH electronic system EPR so the note will only be found in the physical chart***
  - Most OPD information will still be found in the physical chart – including symptoms, examination, urinalysis (usually taped onto note paper), overall impression & plan. Only refer to the physical chart if the letters are incomplete.
- Old biopsy results (*may not be uploaded to EPR if very old or if performed externally*)
  - Usually either found in middle of chart in "Functional Investigations" section or in "Operations and Procedures" section
  - ***Note: Biopsy results often discussed in clinic letters so will point to whether to search through rest of physical chart for histology results or not***
- Old lab results (*may not be uploaded to EPR if very old or if performed externally*)

- Usually found in back of physical chart
- Old discharge summaries (*may not be uploaded to EPR if very old or if performed externally*)
  - Usually found in very front of physical chart in same section as OPD clinic letters
  - Helpful for summarising induction treatment, etc. when patient was initially diagnosed

1.3.11.3 Data Systems required:

- *Electronic Patient Record (EPR):*
  - Radiology and blood test results (*found in 'All Results' tab of EPR home page*)
    - In order to obtain results from many years ago it is **crucial to change the date range** by right clicking on the grey bar -> click 'Change Search Criteria' -> date range is the most useful as you can request 01/01/2000 – today, for example.
    - Radiology results are broken down by investigation type and date
    - Click into individual radiology result to see report
  - Biopsy results (*found in 'All Documents (Chronological)' tab of EPR or in 'All Results'*)
  - Clinic letters (*found in 'All Documents (Chronological)' tab of EPR*)
    - Clinic letters usually titled "srec0" with the date and time
    - Frequently, older clinic letters are not uploaded to EPR. Therefore you must also check the separate letters programme, accessed through the tab: 'Patients Correspondence Letters':
      - Letters are grouped by specialty. To determine which specialties the patient attends click on the tab (on the dark left hand blue bar) 'Patient Information', select 'Visit List'
      - Obtain clinic letters by clicking on appropriate specialty, then search by surname. There is often multiple sections for the one patient.
  - Infusion records
    - All infusions (e.g. Rituximab, IVIG, etc.) are recorded
    - Easier than searching through physical chart notes or clinic letters to see which infusions actually took place
    - The dose of the infusion is not normally included in these EPR records – dose must be found in the actual clinic notes or in the clinic letters
  - **All inpatient admissions from September/October 2018 onwards will only be found in EPR (not in the physical chart)**
    - **This is due to James's trying to move completely electronic (only for inpatients and not for OPD)**

- Always check whether the patient has been admitted by clicking on the top right hand corner where it says “Episode:_____”
- This will provide a list of all inpatient stays, OPD clinic visits, visits to SJH for investigations, etc. that the patient has gone through

- It is worth checking the EPR tabs “Clinical Notes by Speciality”, “Correspondence” , “General Investigations” and “Operation and Consent” because they may – on rare occasions – include documents missed in the previously mentioned tabs
    - For example: If a patient was admitted to SJH after September/October 2018, the patient’s notes for that admission would be in “Clinical Notes by Speciality”

3.12 Tallaght University Hospital (TUH)

- The local PI is Professor Mark Little.
- All nephrology registrars are involved in recruiting. They follow the instructions for recruitment, including updating the local log, which is kept on the shared drive: 'Renal' -> 'Vasculitis'. The corresponding consent forms are kept in folders in the Doctor's office next to dialysis.
- A suggested base for the day is the doctor's office on Osbourne ward or Prof Little's office in the Trinity centre.

1.3.12.1 Data Systems required

- *Key*
  - This is accessed via the desktop.
  - This is the laboratory system for all blood results and histopathology (biopsy)

- *Patient Correspondence*
  - This is accessed via the intranet.
  - This is the letters system and is divided into specialties.

- *Teams*
  - This is accessed via the intranet. It provides discharge summaries.

- *NIMIS (Radiology)*

3.13 Beaumont Hospital (BH)

- The local PI is Professor Peter Conlon.
- All nephrology registrars are involved in recruiting. They follow the instructions for recruitment, including updating the local log, which is kept on the Renal shared folder on the computer. The corresponding consent forms are kept in a folder by the research nurse, who is based in the Smurfit building (ground floor, to the left as you pass security).

- A suggested base for the day is the doctor's office in the Dialysis Therapies Centre (DTC).

1.3.13.1 Data Systems required

- *PIPE*
    - This is accessed via the desktop.
    - This is the system for blood results, histopathology (biopsy), some letters and discharge summaries.

- *eMed*
    - This is accessed via the desktop, via the icon above.
    - See Galway for details
    - The nephrology department largely uses eMed for clinic letters and associated information.
    - Date of first dialysis can be obtained via the clinical summary:
    - Most clinic letters are stored in the 'Clinic' tab
    - Start and stop dates for all medications ever recorded can be obtained via 'Drugs' -> 'All drugs':

- *NIMIS (Radiology)*

4. AVERT Recruitment, Linkage and Engagement: SOP Guide for RKD Nurse

4.1 Location of documents

- All SOPs are stored in: 'Basecamp – AVERT – Docs & Files - Ethics documents' and the appendices are in 'TCD shared folder – AVERT – Ethics Documents – Protocol'
    - SOP1 AVERT: Recruit Identification (& Appendix 1)
        - v2 – updated invitation letter & reference to Appendix 1: SOP1
    - SOP2 AVERT: Informed Consent (v2)
    - SOP3 AVERT: Patient Engagement (& Appendix 2)
        - v2 – reference to Appendix 2: SOP3 Engagement Nurse Dashboard
    - SOP4 AVERT: Data Governance (v2)
    - SOP5 AVERT: Guide for RKD Nurse (v1) (this document)
        - Summary of AVERT Recruitment, Linkage and Engagement, including required documents, programmes and expectations.
    - SOP6 AVERT: Guide for Location Web Application (v1)

- The AVERT Recruitment Log (ARL) is stored in the TCD shared folder:
    - smb://winstor01.college.tcd.ie/Nephrology (the PI needs to grant access for this)
        - AVERT folder
        - Recruitment log
        - 'Master Avert Recruitment log' and
        - 'Appendix 1 AVERT SOP1_link AVERT & RKD ID-confidential'

4.2 Other useful documents

- AVERT Study Phone Script
- PatientMpower App Guide for participants
- Delegation Log for reference

4.3 Required programmes

a. **RKD nurse email** account:
    i. Outlook
    ii. rkdnurse@tcd.ie

b. Link for **REDCAP (RKD) Registry**:
    i. You will need to contact the assigned computer scientist in TCD HPC for login.
    ii. You will also need a **TCD VPN**, obtained through TCD IT services to access this registry, the AVERT Nurse Dashboard and the shared nephrology folder (where the AVERT Recruitment Log is stored) remotely
    iii. This is the detailed entry for each recruit detailing demographics, disease status, treatment, biopsy and laboratory results.

iv. You will use this mainly to link RKD/pMp IDs by the Date of Birth Search function.

c. Link for **AVERT Nurse Dashboard**: *(removed for security)*
   i. You will need to contact the assigned computer scientist at TCD ADAPT for access and login.
   ii. You will also need to be connected to the TCD VPN to login.
   iii. You will use this to get an overview of patient engagement. Search for patient using pMp ID. View summary of location and EQ5D (Quality of Life Survey) data: last logged in, submitted location/EQ5D.

d. The 'avert_pmp_data' tool:
   i. See SOP AVERT 001: Recruit Identification) for details. This provides a list of new pMp app recruits, in order to populate the ARL.
   ii. You will need to contact the assigned computer scientist at TCD ADAPT for access and assistance with set-up or troubleshooting.
   iii. You will use this to update the ARL weekly.

e. **Link for PatientMpower website:**
   https://patientmpower.com/accounts/login/
   i. You will need to contact the PI for access.
   ii. This is a list of the names and details of all AVERT recruits, compiled by pMp.
   iii. You will use this to review step count. Find the patient's name -> click on it -> click on 'Stepcount' tab -> you will be able to see if the app is recording steps or not.

f. **Link for Location Website:**
   https://vma61.scss.tcd.ie/loccapture/
   i. Username and password obtained from the PI
   ii. See SOP 6 for detailed description of use.
   iii. See Appendix 2 (SOP 3) for reference of use.

g. Link for **AVERT portal (OF NOTE – no longer require this as 'avert_pmp_data' tool extracts same data – this is a backup)**: *(removed for security)*
   i. Contains link for **portal login** (contains the patient details of all AVERT recruits)
   ii. And link for **'AVERT Study' Google Sheet** (list of all AVERT IDs, corresponding email address and operating system)
   iii. You will need to contact the pMp representative, through a 'ping' on basecamp to obtain a login

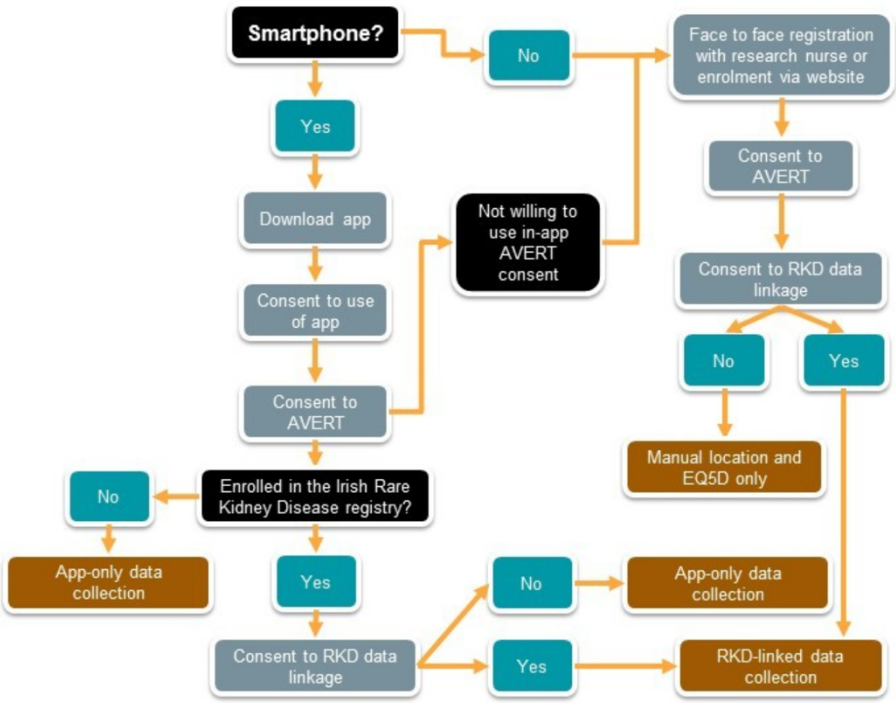
h. **Twitter** account:
   i. @AvertStudy

ii. Password via PI

i. **Monthly newsletter/report** link:
   i. See below

4.4 Recruitment: see SOP1 and Appendix 1 (SOP1)

- Targeted recruitment of RKD recruits at:
  - Initial acute recruitment
  - Study clinics (BH/TUH/SJH)
  - Letter drop from peripheral sites (see instructions below)
- Consent is done primarily via the pMp app. For those without access to a smartphone, website URL or paper formats are available
  - Paper consent form and PIL are on 'Basecamp – AVERT – Docs & Files - Ethics documents'



4.5 Peripheral sites: Letter drop

- In advance of the site visit, print the following and obtain envelopes:
  - Site specific invitation letter
    - The generic template is in Basecamp
      - CDIG -> Docs & Files -> Ethics Documents -> 'Invitation letter_v2_Generic'
    - The site specific letters need to be created by adding the site logo and PI name to this generic version.
  - Patient Information Leaflet

        - Located in basecamp
            - CDIG -> Docs & Files -> Ethics Documents -> 'AVERT Patient info sheet_RKD_v2.1_May2018_UTD contacts'

- Using both the AVERT Recruitment Log and the local RKD recruitment log, identify local RKD recruits who are not enrolled in AVERT
    - For each identified, send a copy of the letter. Enter the recruit's name in the designated area on the letter. Obtain the name and address for the envelope from the local log.
    - For each recruit to whom a letter is sent, add their details to the **AVERT Recruitment Log, in the tab 'Targeted recruitment'**. This will facilitate linkage of AVERT and RKD IDs if and when the patient enrols to AVERT.
    - See point 4 to identify whether a patient has subsequently enrolled to AVERT and for the linkage process of AVERT, pMp and RKD IDs.
    - When it is identified that a patient has enrolled in AVERT, their details should be moved from this 'Targeted recruitment' tab to the main AVERT Recruitment Log.

- If a patient subsequently **does not engage** with the app to **enrol in AVERT**, the letter will be followed by a **phone call** by the research nurse to discuss the study and enrolment process (either via pMP app while on the phone/consent form via mail) 2 weeks later. The outcome of this phone call should be recorded on the AVERT Recruitment Log – 'targeted recruitment' tab.

4.6 Linkage of AVERT study ID to pMp app ID to RKD ID:

- This is explained in detail in SOP1 and Appendix 1 (SOP1 – stored on basecamp).
- AVERT recruitment log and corresponding linkage to RKD ID should be updated **weekly**.

4.7 Engagement of AVERT recruits

- This is explained in detail in SOP3: Maintaining Engagement and accompanying Appendix 1 (SOP3 – stored on basecamp). This process utilises the AVERT Dashboard and PatientMpower website: see 3.c. and 3.e.

- Assessment of participant engagement, using the above documents for guidance, should be updated **weekly –** aim to use a combination of phone, email and text to reach the maximum number of recruits per week. Utilise ideas such as group email (using Bcc to preserve identity) and group text for those participants who respond to these communication methods well. **Aim to engage with 50 recruits per week** (1 x 8 hour day).

- The twitter page should be updated **at least monthly** with interesting facts or summary statistics obtained from the monthly report/newsletter.

- The automated **monthly AVERT report** should be produced on the last day of **each month**. To create the report (for troubleshooting this step contact the assigned computer scientist at TCD ADAPT):
    - Firstly, install php (this step is only required on the first use):
        - On your mac terminal (in utilities), enter the following:
          curl -s http://php-osx.liip.ch/install.sh | bash -s 7.3

        - When that has finished, you need to add php to your OS path. In the terminal again enter:
          export PATH=/usr/local/php5/bin:$PATH

        - Next verify php installed correctly by typing the following in the terminal (You should see something like "PHP 7.3 (cli)..." come up if it is installed correctly):
          php -v

    - Setting up the **avert_engagement tool (Monthly report):**
    - **For WINDOWS computers:**
        - In 'Avert_newsletter' Folder
        - Double click on 'Run (windows)'
        - A window will appear. Enter the number that corresponds to the month which you wish to produce a report for (e.g. March, enter '3').
        - Press any key to continue (past the error message).
        - The report will appear in a new folder, named after the month and year (e.g. 03-2020). Right click on this folder. Click 'PeaZip' -> add to .ZIP
        - Send this new ZIP file (the icon looks like a bin) to Michelle, in the School of Medicine, to host on the THKC website (details below).

    - **For Mac (Apple computers):**
        - Upzip the attachment (avert_engagement.zip) by double clicking on it.
        - Open a terminal in this folder by right-clicking on the folder (avert_engagement) and selecting 'New terminal at folder'
        - Type **./run.sh**
            - Then ENTER
        - Enter the month (1-12) for which you want to produce the report:
        - The generated file should appear in a separate folder, which is named X_XXXX for 'month_year' (e.g. 1_2020).

    - Double click ‘index.html’ to open this file. Right click to copy this link.

- **This link should be:**
    - loaded onto the THKC website (https://www.tcd.ie/medicine/thkc/patient/) by sending the link to the corresponding administrator in the School of Medicine, TCD
    - Notify all researchers using a ‘Basecamp ping’ of the updated report. Include a link to the THKC website page, where the link is hosted.
    - Notify all registered AVERT recruits via email, in a similar fashion to above.

5. AVERT: Invitation letter for prior RKD recruits

rkdnurse@tcd.ie

Mobile number (removed for security)

21/09/2023

Re: AVERT study

Dear

I am writing to you as part of a new study examining the effect of the **environment** on development of **relapse** of vasculitis, called the "**AVERT**" study. You are receiving this as you have previously joined the Irish Rare Kidney Disease registry and biobank, sponsored by Prof Mark Little in Trinity College Dublin. The current study is an extension of this and is managed by the same research group in Trinity.

We would be delighted if you would consider becoming involved in AVERT, which we hope will help us develop a means of identifying and preventing relapses or flares of vasculitis before they happen.

Please find enclosed an information leaflet describing the study in more detail. If you wish to participate, please

- Go to the app store (***iPhone***) or Google Play (***Android***) and
- Download the "**patientMpower**" app onto your phone
- **It is important to enter "AVERT"** into the box at the bottom of the initial 'sign up' page labelled **'Enter signup code (optional)'.**
- After providing your consent for use of the app, you will be asked whether you wish to provide consent for participation in the AVERT study.
- You will be asked if you are already involved in the **Rare Kidney Disease registry and biobank (RKD)**. The answer is **"yes".**

If you have any questions, please do not hesitate to contact me.

Kind regards

Dr. Jennifer Scott

Research Fellow (Wellcome-HRB Irish Clinical Academic Training (ICAT) Fellow)

On Behalf of: Prof. Mark Little

6. SOP: Patient engagement with the AVERT smartphone application

AVERT STUDY

Autoimmunity Relapse Prediction using Multiple Parallel Data Sources

Chief Investigator: Professor Mark Little

STANDARD OPERATING PROCEDURE

SOP No: AVERT-003

MAINTAINING ENGAGEMENT

Author: Mark Little & Jennifer Scott (v2)	**Authorised by:** Lucy Hederman **Date:**
Reviewer 1: Jane Richardson	**Reviewer 2:**
Distribution: St James's Hospital CRF, patientMpower, Chronic Disease Informatics Group	
Protocol: VERSION v1.0 Dec 2017	
SOP HISTORY - Revision Date: v2 March 2020 (Jennifer Scott)	

Version	*Altered (Reason for change)*	*Authorised by*	*Amendment date*	*Next review*
2.0				Dec 2021

CONTROLLED DOCUMENT

The user of the SOP must read the following thoroughly before proceeding to undertake the methods described. Under no circumstances are these instructions to be amended or altered in any way other than by the author/authorised personnel.

6.1 Maintaining engagement: DIRECT

Ensuring that participants remain engaged with the AVERT research processes is critical to its success. Methods to address this include:

a. Regular entering of EQ5D data

i. The research nurse will use the AVERT Nurse dashboard (hosted by TCD, behind a secure firewall) to track participant engagement. Specifically, they will review the frequency of EQ5D submissions for each recruit. Detailed instructions for this are found in Appendix 2 (SOP 3).

ii. The target is a complete EQ5D entry **at least once per month** (but more frequent data entry will be encouraged).

iii. In-app reminders will provide soft encouragement and reminders to complete the EQ5D forms. Detailed instructions on how to set reminders and complete EQ5D surveys are found in 'PatientMpower App Guide for participants'.

iv. If data entry is tailing off or absent the research nurse will contact the participant by phone, text or email to enquire as to whether they can help with recording the data, identify obstacles and provide feedback on the study.

v. In cases of recalcitrant non-entry of EQ5D for >3 months, despite several attempts at direct communication, a direct visit to the participant's home will be proposed.

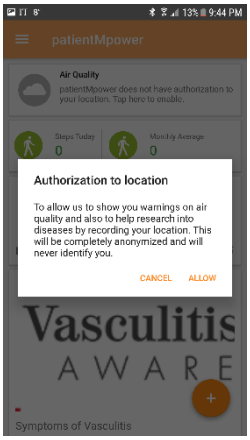
vi. If these measures are not successful in restoring app engagement, several options are available:

i. If RKD-linked and in-phone consent for activity and GPS recording, continue with study monitoring without EQ5D data.

ii. If in-phone consent for activity and GPS recording have been denied and there is no engagement with EQ5D despite direct contact, the participant should be de-enrolled.

b. In-phone permissions to link to GPS and activity data

i. This is critical to AVERT, as it allows linkage of patient location with environmental data



ii. pMp have developed an effective means of obtaining consent that is different from the generic requests (which are easy to dismiss). This separate message reinforces the concept that this linkage is essential to AVERT and that, without it, the participant will not be part of the study (see figure left).

iii. If location and/or activity location linkage are denied (as evidenced by lack of these data points on the dashboard/pMp website), the research nurse will contact the participant by phone, text or email to enquire as to whether there are technical difficulties, identify obstacles and provide feedback on the study. Detailed instructions for troubleshooting are found in 'PatientMpower App Guide for participants'.

iv. In cases of recalcitrant non-linkage of location/activity data for >3 months, despite several attempts at direct communication, a direct visit to the participant's home will be proposed.

v. If these measures are not successful in restoring app engagement, and there is no engagement with EQ5D despite direct contact, the participant should be de-enrolled.

c. General engagement with the app (e.g. medication reminders)

i. Increasing general app usage is an important goal of the AVERT project. If the participant derives benefit from using the app they will be much more likely to engage with the research elements.

ii. Various chronic disease support measures have been incorporated, including a user-friendly medication reminder feature (which includes pictures of the relevant medications), the ability to record measurements (such as weight, blood pressure, blood test results, using blue tooth enabled devices if these are available), a diary feature (that supports clinic visits), educational content and the option to contact research nurse directly. The latter may provide the option for arranging a formal interaction with the patient's physician. Lubricating the bridge between patient and clinician through use of the app is an important means for creating engagement.

6.2 Maintaining engagement: INDIRECT

Various indirect outreach measures will be employed to create a general sense of engagement with the AVERT study, including:

i. **Newsletter**. The research nurse and a nominated AVERT data scientist will draft a newsletter at monthly intervals. This will provide updates on recruitment, study milestones, research outputs and benchmarking summaries (e.g. graphs of EQ5D data recording and activity aggregated across the study cohort), as well as reminding participants about study

contacts. This will be pushed out through the app, via email and posted on the website (via a html link). This link will be sent monthly to a corresponding administrator in the TCD School of Medicine who will update this to the THKC website monthly. A detailed description of how to create and disseminate these automated reports is found in SOP 5 (stored in basecamp).

ii. **Social media**. The research nurse and a nominated AVERT data scientist will maintain a dedicated twitter page to provide updates on study progress and outputs (@AvertStudy). The research nurse will select key pieces of summary information from the monthly newsletter to tweet, including graphs and useful suggestions. For example, "5678 was the average step count per day for all AVERT recruits this month. How do you compare to this? Start slow and build up – try walking 10 minutes each day, add on 2 minutes each day!"

iii. **ResearchGate.** Team members will add periodic posts to provide research updates. Research outputs such as manuscripts and presentations will be posted here.

iv. **Website**. The study group will maintain an up to date web page on the THKC website (hosted by TCD). This will include the twitter feed, a blog, study contact form, data governance documents, information leaflets and newsletters.

v. **Annual AVERT meeting**. The group will hold an annual half-day meeting (linked to another major event such as the Irish Nephrology Society meeting or International Vasculitis Workshop). Participants will be invited and given the opportunity to interact with study personnel, as well as learn directly about study outputs.

7. PatientMpower App Guide for Participants

PatientMpower App – How to get started

Table of Contents

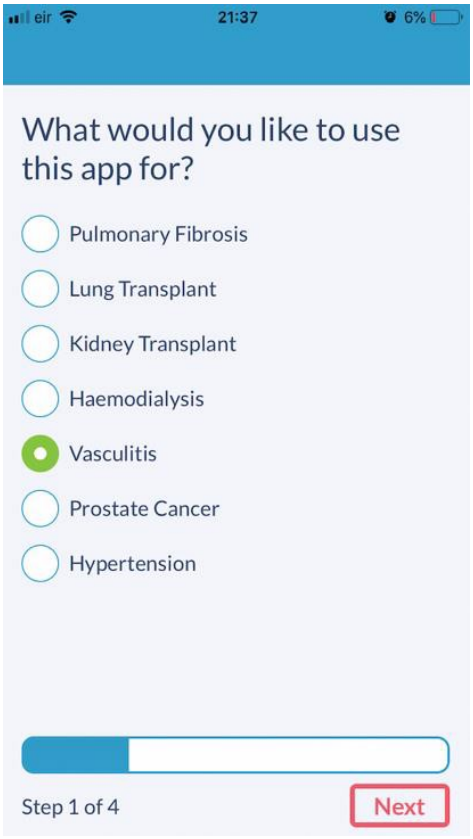
1. Download patientMpower app and sign up: 51
2. Select personalised settings to ensure you are using the correct app format:....51
3. Consent 54
4. Navigating the app....56
4.1. Menu....56
4.2. Home page / Dashboard 58
4.3. Surveys 59
4.4. Settings....59
4.5. Step Count....60
4.6. Calendar....62
4.7. Medication 62
4.8. Activity....62

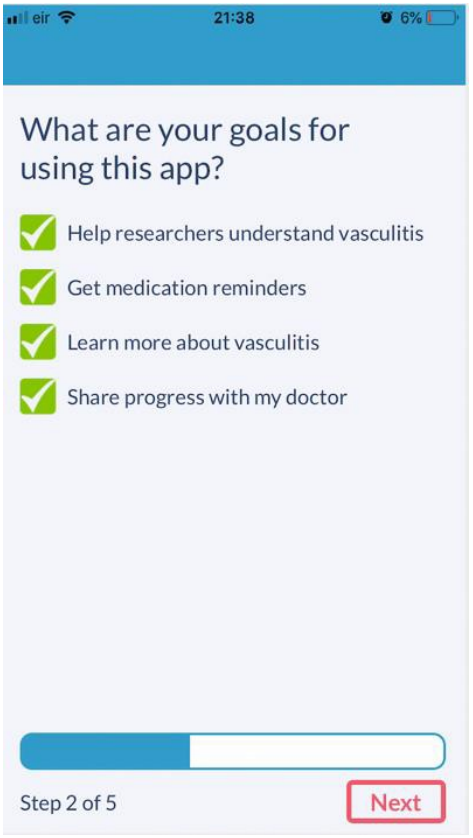
7.1 Download patientMpower app and sign up:

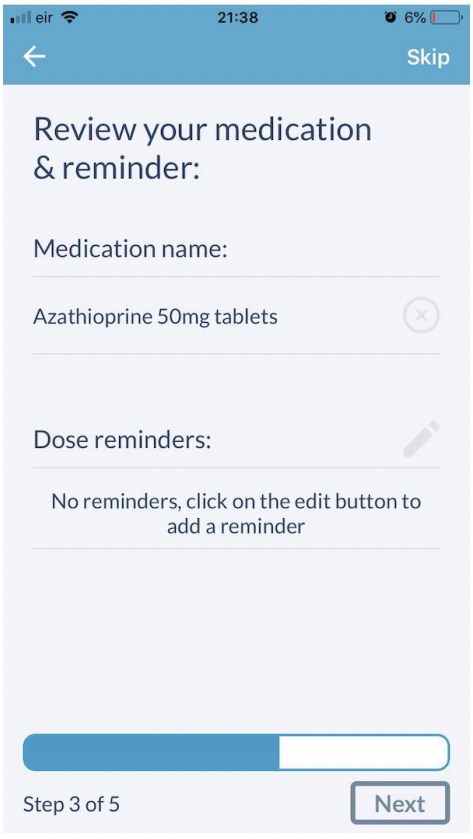
- Go to the app store (***iPhone***) or Google Play (***Android***) and
- Download the "**patientMpower**" app onto your phone
    - Note: select the original 'patientMpower' version, NOT the COVID 19 version
    - **It is important to enter "AVERT"** into the box at the bottom of the initial 'sign up'
      page labelled **'Enter signup code (optional)'.**

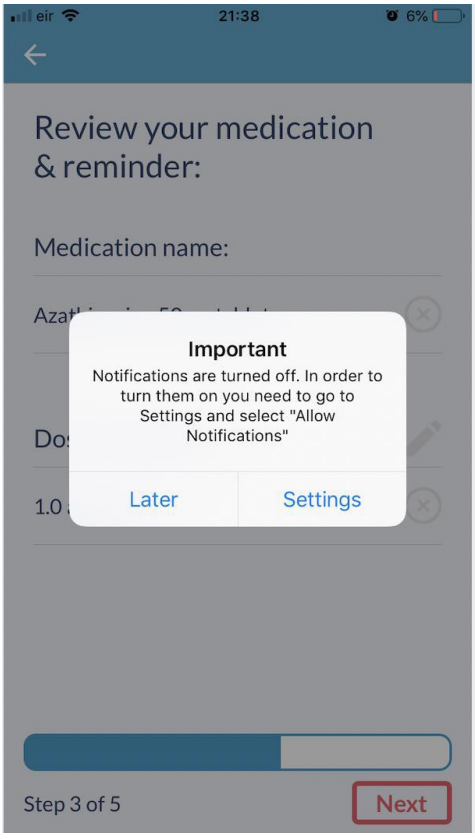
7.2 Select personalised settings to ensure you are using the correct app format:

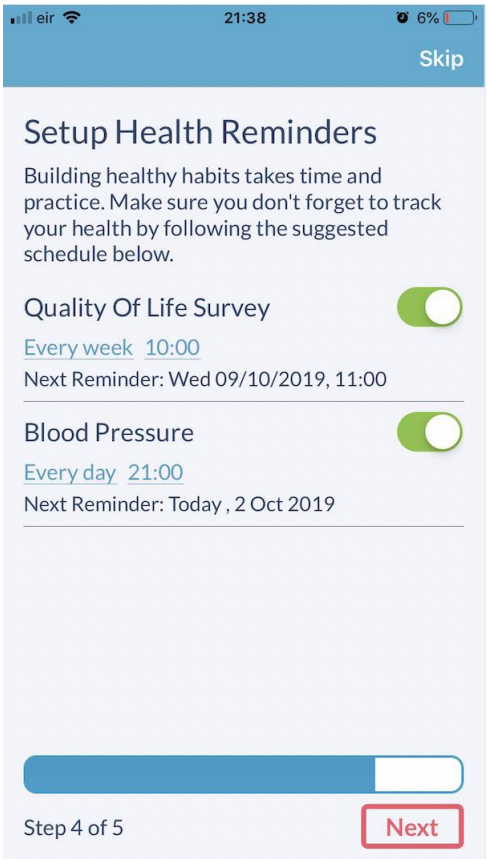
- Progress through the following questions by clicking 'next' once you have selected the
  appropriate boxes (see images below):
    - Select **'Vasculitis'** when asked 'what would you like to use this app for?'
    - Select your **goals**
    - Enter your **medications**. You can decide to set reminders to prompt you. You may be prompted to "Allow Notifications" in "Settings" to enable this option.
    - Choose to set other reminders:
        - We ask you to complete the **'Quality of Life Survey' (EQ5D) every 30 days**. Click 'every week' to change this.
        - You may be prompted to "Allow Notifications" in "Settings"
    - Select **'yes'** when asked 'are you enrolled in the Irish **Rare Kidney Disease registry and biobank (RKD).**

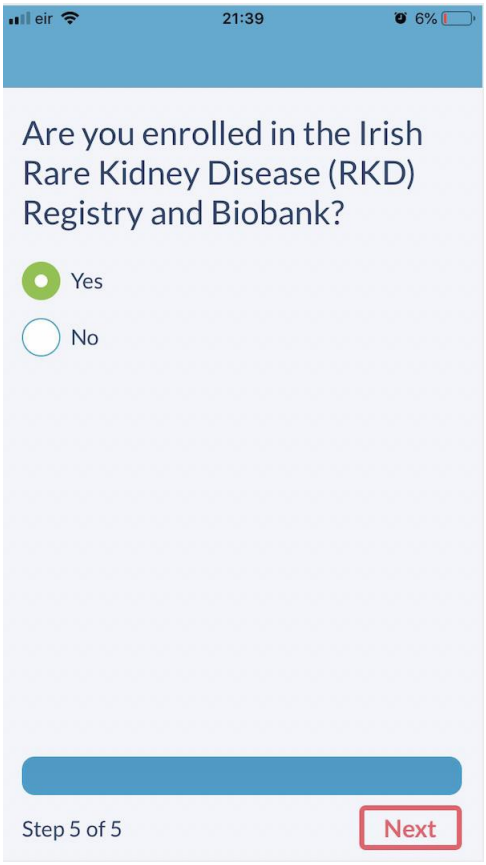

eir
21:37
6%
What would you like to use this app for?
Pulmonary Fibrosis
Lung Transplant
Kidney Transplant
Haemodialysis
Vasculitis
Prostate Cancer
Hypertension
Step 1 of 4
Next


eir
21:38
6%
What are your goals for using this app?
Help researchers understand vasculitis
Get medication reminders
Learn more about vasculitis
Share progress with my doctor
Step 2 of 5
Next


eir
21:38
6%
Skip
Review your medication & reminder:
Medication name:
Azathioprine 50mg tablets
Dose reminders:
No reminders, click on the edit button to add a reminder
Step 3 of 5
Next

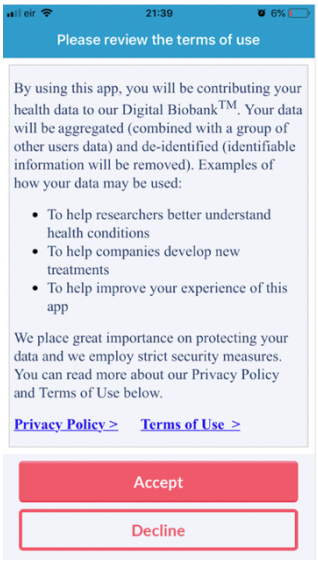

eir
21:38
6%
Review your medication & reminder:
Medication name:
Important
Notifications are turned off. In order to turn them on you need to go to Settings and select "Allow Notifications"
Later
Settings
Step 3 of 5
Next

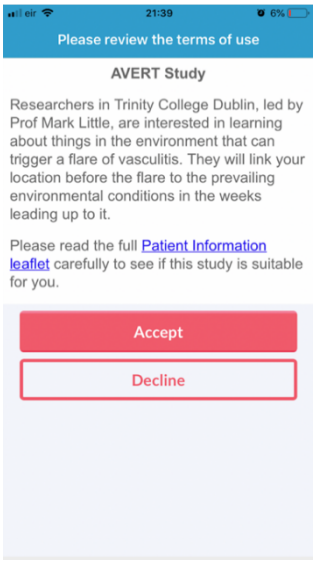

eir
21:38
6%
Skip
Setup Health Reminders
Building healthy habits takes time and practice. Make sure you don't forget to track your health by following the suggested schedule below.
Quality Of Life Survey
Every week 10:00
Next Reminder: Wed 09/10/2019, 11:00
Blood Pressure
Every day 21:00
Next Reminder: Today , 2 Oct 2019
Step 4 of 5
Next

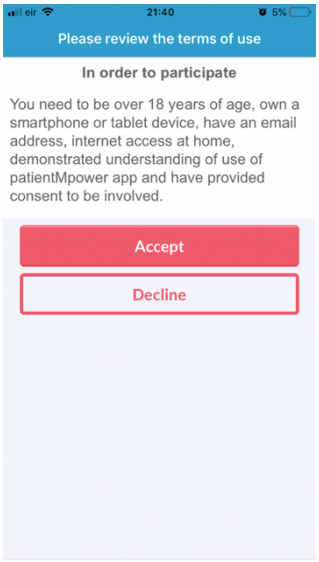

eir
21:39
6%
Are you enrolled in the Irish Rare Kidney Disease (RKD) Registry and Biobank?
Yes
No
Step 5 of 5
Next

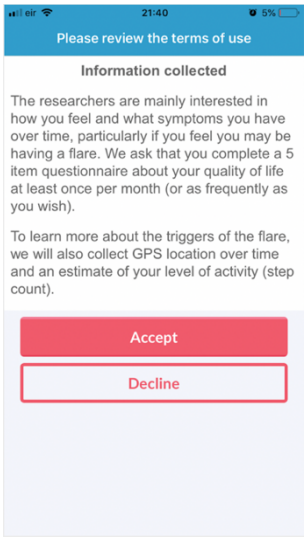
7.3 Consent

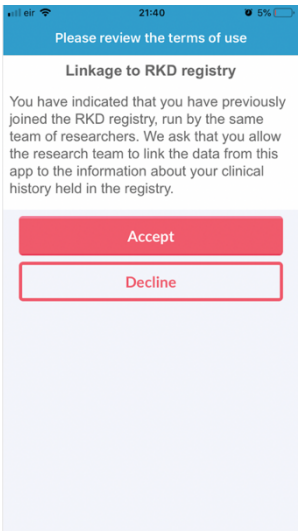
- Progress through the following screens, which all relate to different parts of the consent process. If you agree, click 'Accept' and check the boxes with a tick, where relevant. These following few pages will involve consent for:
    - use of the app
    - participation in the AVERT study.
- Below are images of the consent pages, in the order they appear, from left to right

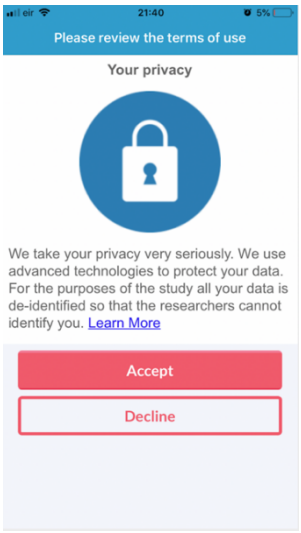


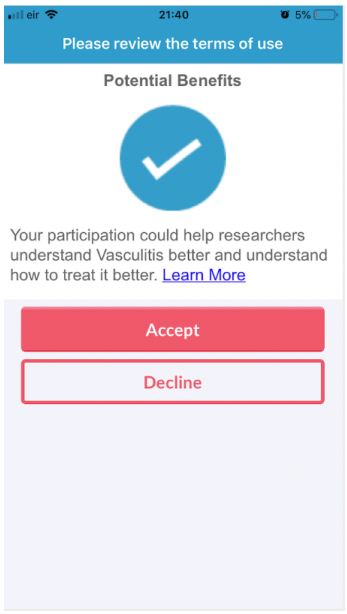


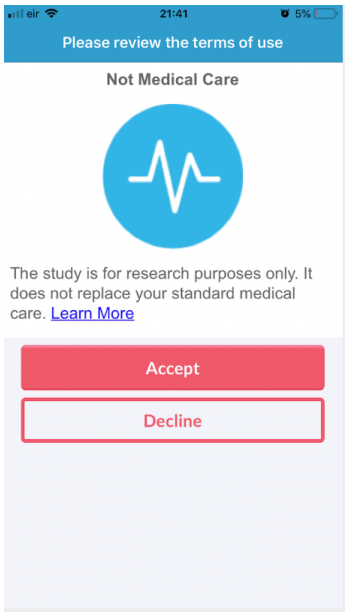


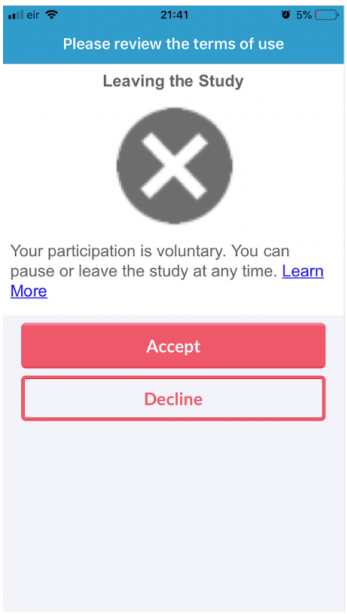


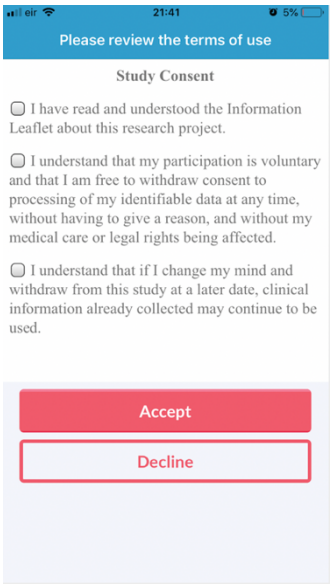


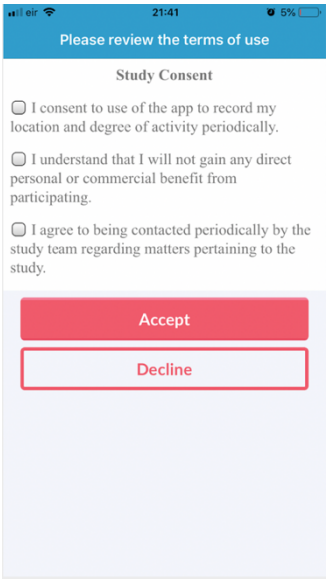


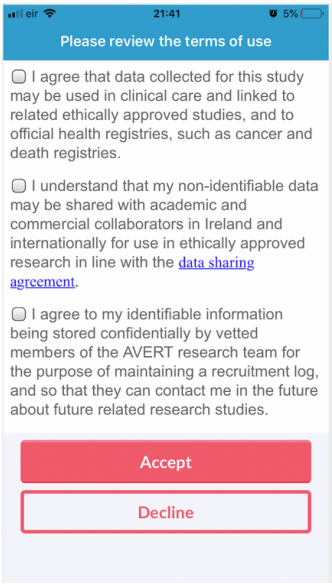

eir 21:40 5%
Please review the terms of use
Potential Benefits
Your participation could help researchers understand Vasculitis better and understand how to treat it better. Learn More
Accept
Decline


eir 21:41 5%
Please review the terms of use
Not Medical Care
The study is for research purposes only. It does not replace your standard medical care. Learn More
Accept
Decline


eir 21:41 5%
Please review the terms of use
Leaving the Study
Your participation is voluntary. You can pause or leave the study at any time. Learn More
Accept
Decline

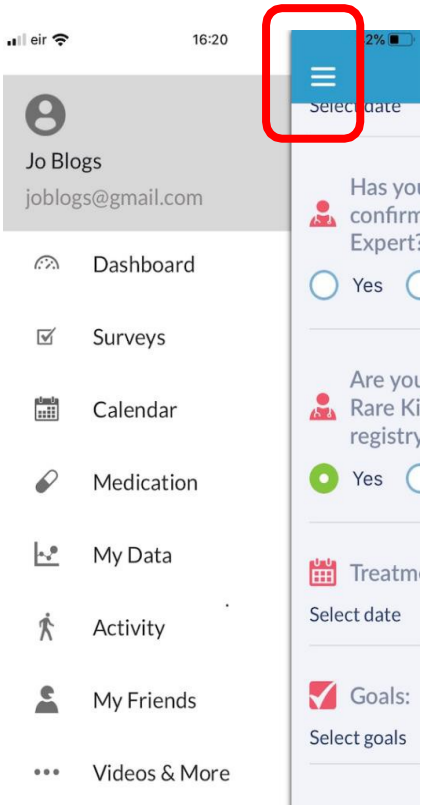

eir 21:41 5%
Please review the terms of use
Study Consent
I have read and understood the Information Leaflet about this research project.
I understand that my participation is voluntary and that I am free to withdraw consent to processing of my identifiable data at any time, without having to give a reason, and without my medical care or legal rights being affected.
I understand that if I change my mind and withdraw from this study at a later date, clinical information already collected may continue to be used.
Accept
Decline


eir 21:41 5%
Please review the terms of use
Study Consent
I consent to use of the app to record my location and degree of activity periodically.
I understand that I will not gain any direct personal or commercial benefit from participating.
I agree to being contacted periodically by the study team regarding matters pertaining to the study.
Accept
Decline


eir 21:41 5%
Please review the terms of use
I agree that data collected for this study may be used in clinical care and linked to related ethically approved studies, and to official health registries, such as cancer and death registries.
I understand that my non-identifiable data may be shared with academic and commercial collaborators in Ireland and internationally for use in ethically approved research in line with the data sharing agreement.
I agree to my identifiable information being stored confidentially by vetted members of the AVERT research team for the purpose of maintaining a recruitment log, and so that they can contact me in the future about future related research studies.
Accept
Decline

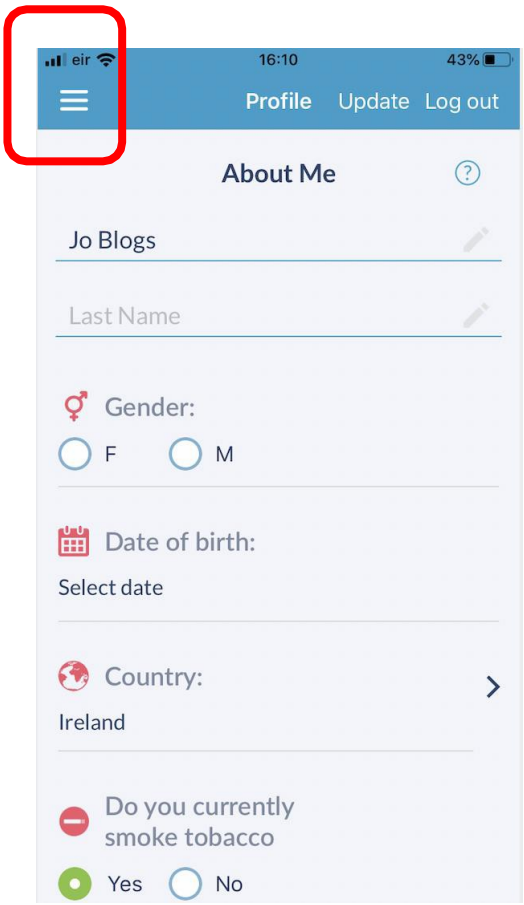
7.4 Navigating the app

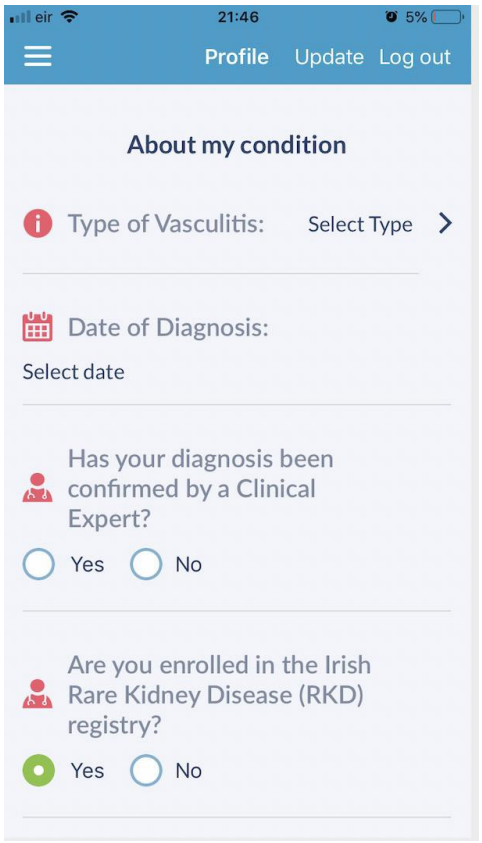
1.7.4.1 Menu



- For iOS: the menu button is 3 horizontal lines (top left of screen, shown in the red circle).
- For Android: the menu button is 3 circles, with 'more' written underneath (your name may not be appear in the android version).

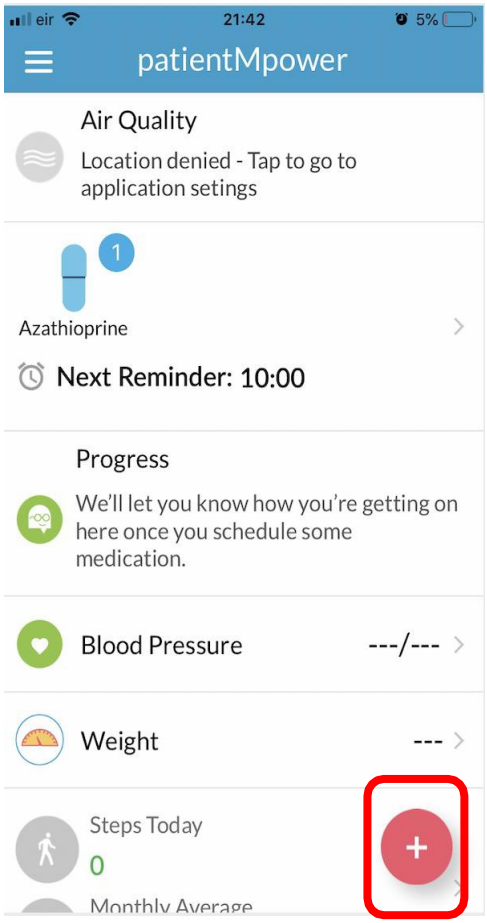
- For iOS: Click this icon, then click on your name/email at the top of the screen. It will bring you to the following screen:
  - Please complete all fields, including your full name, gender and date of birth
  - It important that you select '**Yes'** when asked 'Are you enrolled in the Irish Rare Kidney Disease (RKD) registry?'

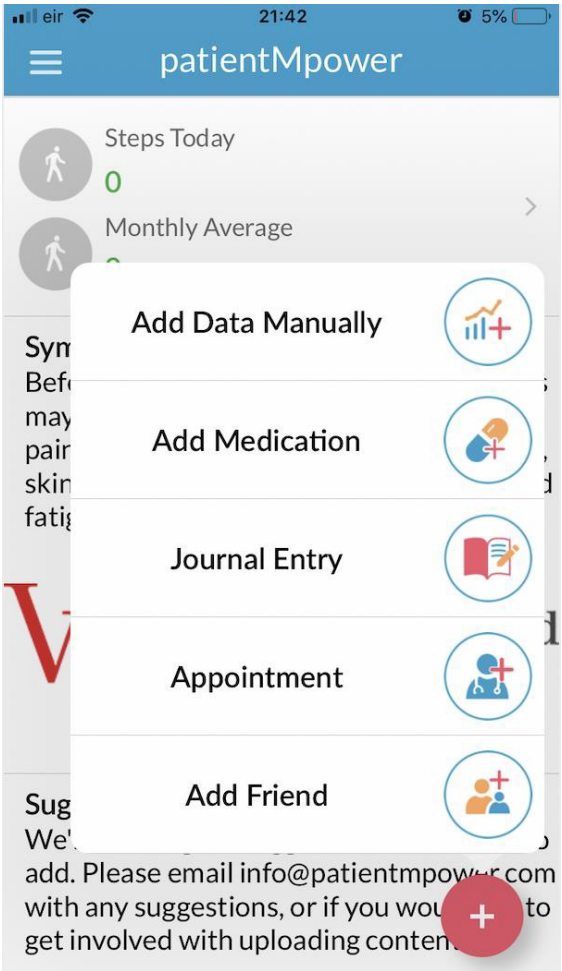

eir
16:10
43%
Profile
Update
Log out
About Me
Jo Blogs
Last Name
Gender:
F
M
Date of birth:
Select date
Country:
Ireland
Do you currently smoke tobacco
Yes
No


eir
21:46
5%
Profile
Update
Log out
About my condition
Type of Vasculitis:
Select Type
Date of Diagnosis:
Select date
Has your diagnosis been confirmed by a Clinical Expert?
Yes
No
Are you enrolled in the Irish Rare Kidney Disease (RKD) registry?
Yes
No

1.7.4.2 Home page / Dashboard

- For iOS: Home page is accessed through the menu icon.
- For Android: Home page is selected when the 'Home' icon on bottom left is in Blue
- This gives a summary of the main information (e.g. air quality, medications, blood pressure, weight, step count).
- There is also a link to the patient group: Vasculitis Ireland Awareness
- Click the 'quick-add' button (the cross inside the red circle) to quickly add:
    - Vital signs (e.g. blood pressure, weight)
    - Medication
    - Journal entry
    - Appointment
    - Add a friend (this allows a family member or friend to help you complete the sections)



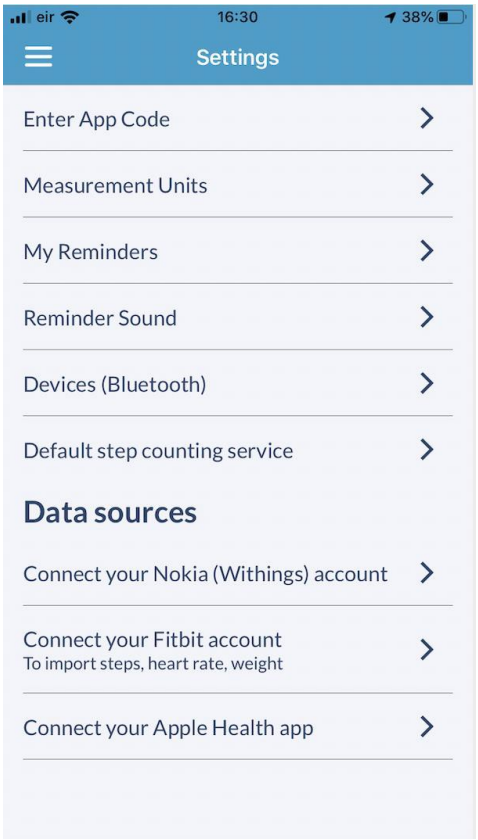


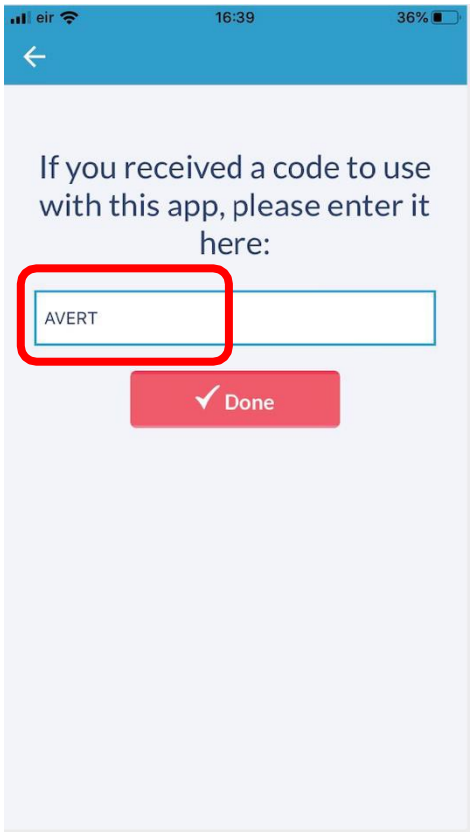
1.7.4.3 Surveys

- Click 'surveys' via the menu icon.
- Click 'Vasculitis Research Survey' to complete. This is a quality of life survey (EQ5D) that lets us know how you are feeling.

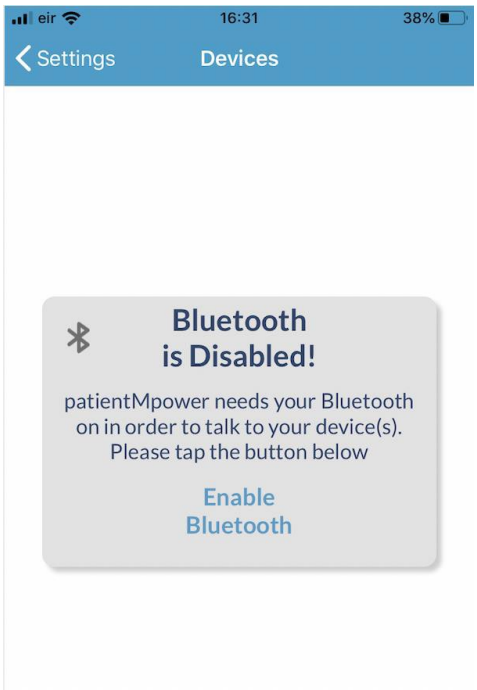
- We encourage you to complete this **once per month**.
- It might be useful to set up a **reminder to prompt you** once per month. To do this
  (see images in 'settings' section):
    - Click menu icon
    - Click 'settings'
    - Click 'my reminders'
    - For 'Quality of Life Survey': change frequency from every week to **every 30 days** and select start today.
    - This will generate an alarm to help remind you the questionnaire needs to be completed.
    - You can other reminders here also, such as to check your blood pressure.

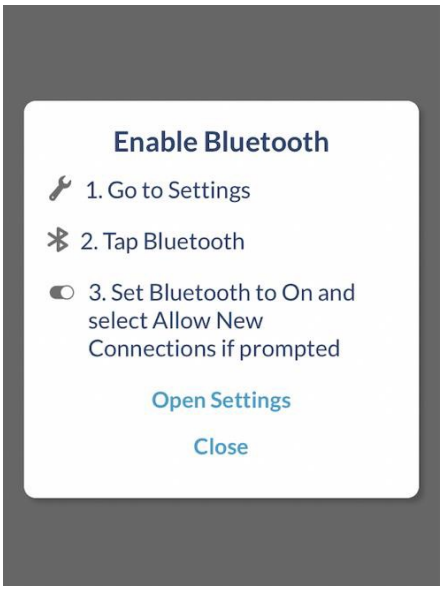
1.7.4.4 Settings





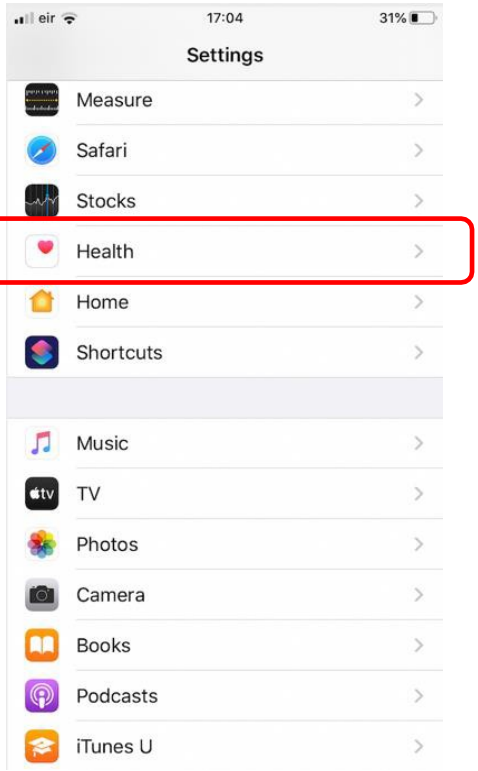
- Select 'Enter App Code': enter **AVERT**
- Select 'My Reminders' to set reminder alarms, as explained above in 'surveys'
- Select 'Devices (Bluetooth)' and follow the prompts to link your devices (e.g. fitbit) to the app, to enable us to track data such as step count.

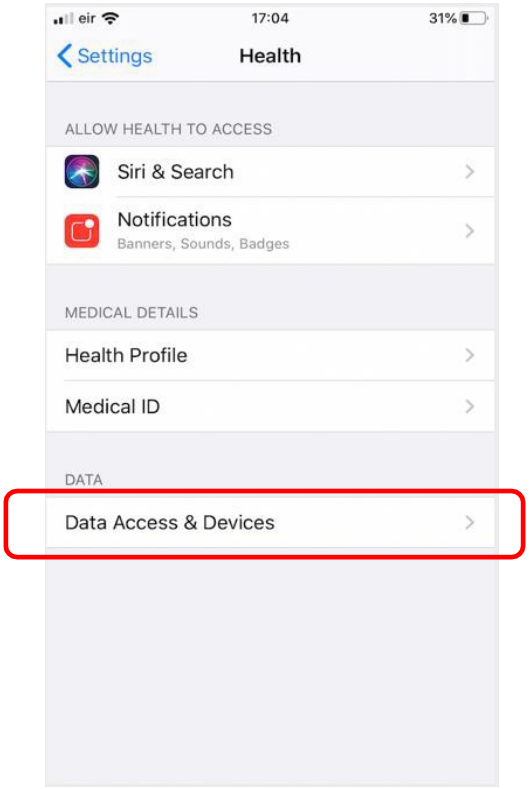


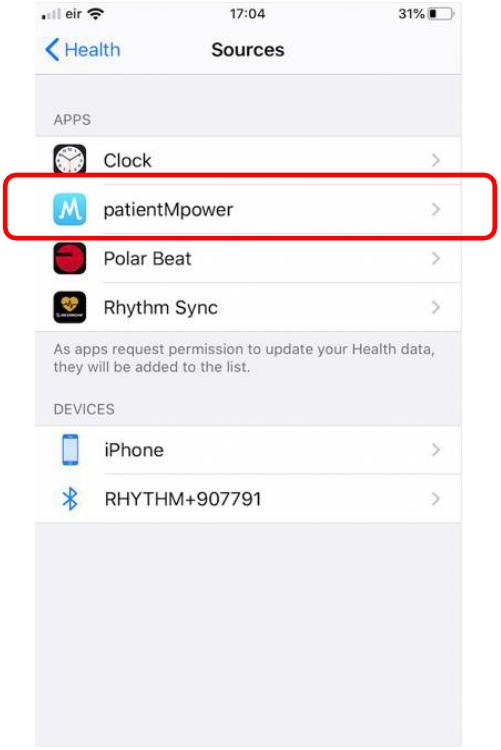


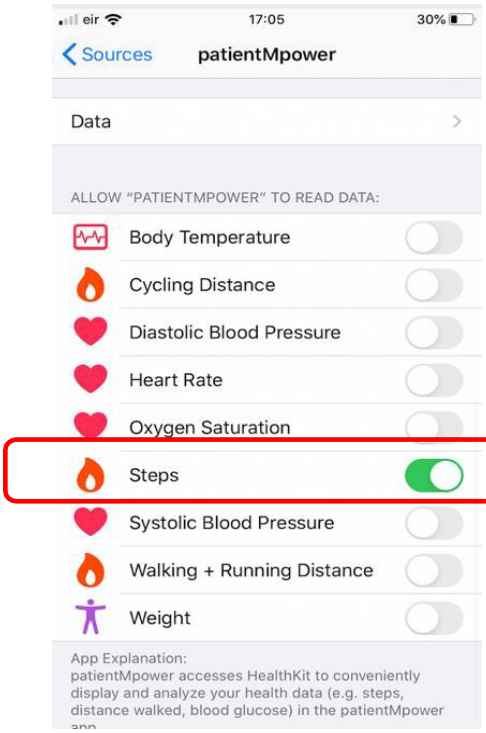
1.7.4.5 Step Count

- Select 'Fitness Data Source' (Android) or 'Default step counting service' (iOS)
- Various options will appear; Google Fit, Fitbit & Apple Health.
- Choose the most appropriate for you: 'fitbit' if you wear one, alternatively 'google fit' for android or 'apple health' for iOS.
- For iOS you also need to 'allow' the patientMpower app access to the fitness data source in the following way:
    - go to settings on your iPhone
    - scroll down and click 'health' (app with love heart as logo)
    - click 'Data access & devices'
    - then click 'patientMpower'
    - scroll down to 'steps', then click the button to the right of it to turn it on (the button goes from being greyed out to green). You can turn on any field that you wish to share in the same way (e.g. Systolic Blood Pressure).


eir
17:04
31%
Settings
Measure
Safari
Stocks
Health
Home
Shortcuts
Music
TV
Photos
Camera
Books
Podcasts
iTunes U

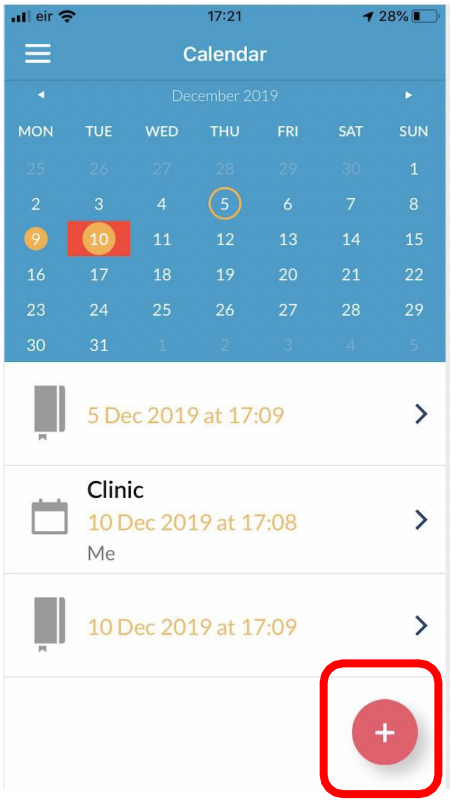

eir
17:04
31%
Settings
Health
ALLOW HEALTH TO ACCESS
Siri & Search
Notifications
Banners, Sounds, Badges
MEDICAL DETAILS
Health Profile
Medical ID
DATA
Data Access & Devices

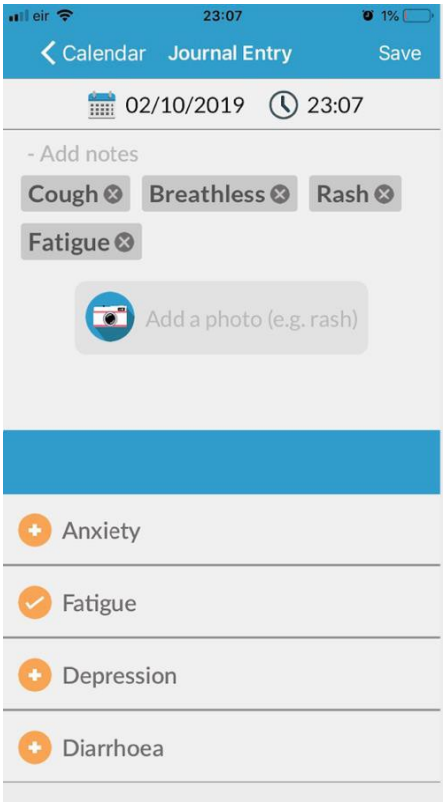

eir
17:04
31%
Health
Sources
APPS
Clock
patientMpower
Polar Beat
Rhythm Sync
As apps request permission to update your Health data, they will be added to the list.
DEVICES
iPhone
RHYTHM+907791


eir
17:05
30%
Sources
patientMpower
Data
ALLOW "PATIENTMPOWER" TO READ DATA:
Body Temperature
Cycling Distance
Diastolic Blood Pressure
Heart Rate
Oxygen Saturation
Steps
Systolic Blood Pressure
Walking + Running Distance
Weight
App Explanation:
patientMpower accesses HealthKit to conveniently display and analyze your health data (e.g. steps, distance walked, blood glucose) in the patientMpower

1.7.4.6 Calendar

- Select the 'quick-add' button (circled in red) to enter an appointment or a journal entry.
- A journal entry enables you to keep track of symptoms you have or to take a picture (e.g. of a rash or swollen joint). You can then use this information to remind yourself of how you have been over the last few weeks – this may be useful for clinic appointments. Dates with journal entries will appear circled in a different colour on the calendar.





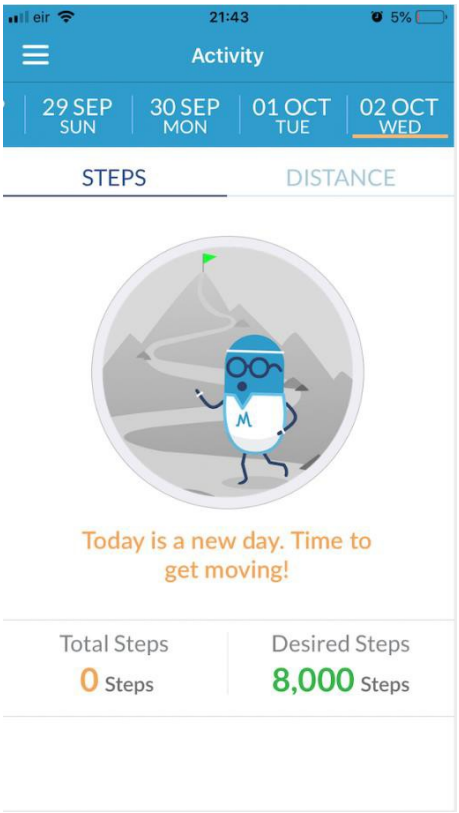
1.7.4.7 Medication

- Add medications here, as described previously using the 'quick-add' button (see image below).

1.7.4.8 Activity

- This tab allows you to review a summary of your step count.
- It is a good idea to check here to make sure the app is capturing your steps. If there is no data here (as in example image below), try following the troubleshooting guide in the 'step count' section above. If this fails, contact our research nurse for further assistance.

eir
17:21
28%
Medication
DEC
SUN
09 DEC
MON
10 DEC
TUE
11 DEC
WED
10:00
Azathioprine
1 tablets
50.00 mg


eir
21:43
5%
Activity
29 SEP
SUN
30 SEP
MON
01 OCT
TUE
02 OCT
WED
STEPS
DISTANCE
Today is a new day. Time to get moving!
Total Steps
0 Steps
Desired Steps
8,000 Steps

8. Example of a monthly AVERT newsletter to promote engagement

TCD Logo AVERT Logo

AVERT Project Patient Engagement Report
August 2020

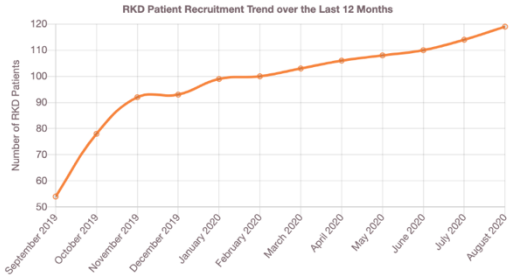
Patient Recruitment

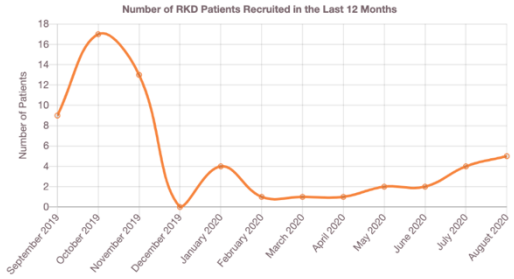
Are there things in your environment that trigger a flare of vasculitis?

Number of patients recruited to date: 223

Of these, 119 are also members of the Rare Kidney Disease (RKD) Registry

Target = 250 RKD Patients





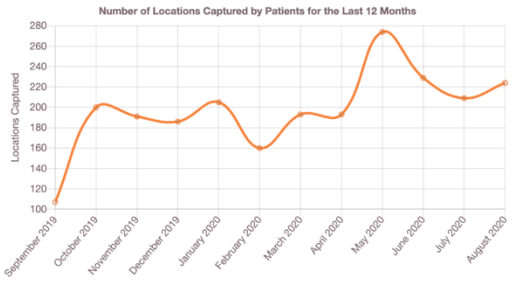
- **Total number of patients recruited month: 5**
- **Of the above number, 5 are in the RKD Registry**

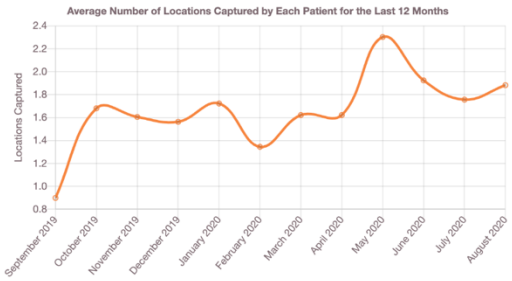
Locations Captured

Why is location important?

It allows us to link vasculitis flare events to the weather and pollution information from that time and place. This data is all anonymised and stored securely

◉ RKD Patients Only ○ All Patients

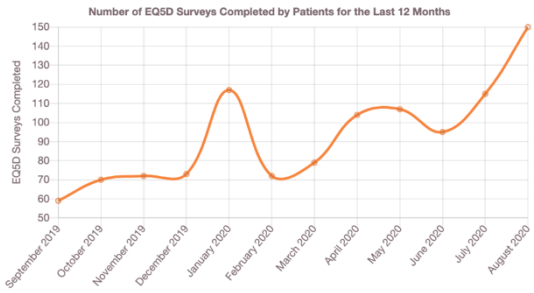


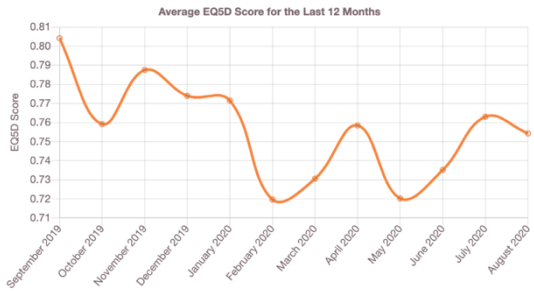


- **Total number of locations captured this month: 224**
- **Average number of locations captured per patient this month: 1.88**
- **How many locations have you submitted this month?**

EQ5D Scores

◉ RKD Patients Only ○ All Patients





- **Total number of EQ5D surveys completed this month: 150**
- **Average EQ5D score this month: 0.754**
- **How have you been feeling?**
- **Let us know by completing EQ5D**

Questions?

- **Contact the Study Coordinator on: 085-150-7587 or email: rkdnurse@tcd.ie**

Report automatically generated as part of the AVERT project. Click here for more details on the project.
Click here for the AVERT Project Patient Information Sheet
Generate on: 07/09/2020.

9. Detailed search strategy (EMBASE), adapted to each specific database as required

1. 'ANCA associated vasculitis'/exp
2. (‘ANCA vasculitis’ OR ‘ANCA-associated vasculitis’ OR ‘anti neutrophil cytoplasmic antibody associated vasculitis’ OR ‘anti-neutrophil cytoplasmic antibody-associated vasculitis’ OR ‘antineutrophil cytoplasmic antibody associated vasculitis’ OR ‘neutrophil cytoplasmic antibody associated vasculitis’ OR ‘neutrophil cytoplasmic antibod*’):ti,ab
3. ‘neutrophil cytoplasmic antibody’/exp
4. 'Churg Strauss syndrome'/exp
5. 'Wegener granulomatosis'/exp
6. 'microscopic polyangiitis'/exp
7. (ang*itis):ti,ab
8. (‘allergic granulomatosis’ OR ‘allergic granulomatous ang*itis’ OR ‘Churg-Strauss’ OR ‘eosinophilic granulomatosis with polyang*itis’):ti,ab
9. (‘granulomatosis with polyang*itis’ OR ’granulomatosis necrotizing respiratory’ OR ‘granulomatosis, wegener’ OR ‘klinger wegener syndrome’ OR ‘morbus wegener’ or ‘necroti*ing respiratory granulomatosis’ OR ‘pneumogenic granulomatosis’ OR ‘Wegener disease’ OR ‘wegener granuloma*’ OR ‘wegener klinger churg syndrome’ OR ‘wegener klinger granulomatosis’ OR ‘wegener syndrome’ OR ‘wegener* granulomatosis’ OR ‘wegner granulomatosis’):ti,ab
10. ('granulomatosis with polyang*itis'):ti,ab
11. (‘Eosinophilic Granulomatosis with Polyang*itis’):ti,ab
12. (‘Microscopic Polyang*itis’):ti,ab
13. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12
14. 'environment’/exp OR 'environmental factor'/exp OR 'environmental exposure'/exp OR ‘environmental, industrial and domestic chemicals’/exp OR ‘latitude’/exp OR ‘vitamin d’/exp OR ‘retinol’/exp OR ‘bacterial infection’/exp OR 'mycetoma'/exp OR ‘mycosis’/exp OR ‘parasitosis’/exp OR ‘virus infection’/exp OR ‘zoonosis’/exp

15. (Environment* OR latitude* OR ‘vitamin d’ OR ‘vitamin a’ OR retinol OR mycetoma* OR mycosis OR parasitosis OR zoonosis OR Zoonoses):ti,ab
16. ((bacteria* OR viral OR virus OR parasit* OR fungal) NEAR/2 (disease* OR infection*))
17. #14 OR #15 OR #16
18. 'clinical study'/de OR 'major clinical study'/de OR 'controlled study'/de OR 'case control study'/de OR 'family study'/de OR 'longitudinal study'/de OR 'retrospective study'/de OR 'prospective study'/exp OR 'randomized controlled trial'/exp OR 'observational study'/exp OR 'cohort analysis'/exp OR ((Cohort OR Case-control OR follow-up OR observational OR epidemiologic* OR cross-sectional OR Controlled) NEAR/1 (study or studies)):ti,ab
19. 'meta analysis'/exp OR ((meta NEXT/1 analy*) or metaanalys*):ti,ab OR (systematic NEXT/1 (review* or overview*)):ti,ab
20. #18 OR #19
21. #13 AND #17 AND #20
22. 'conference abstract':it OR 'conference review':it
23. #21 NOT #22

10. Supplementary *Table 1:* Quality Assessment of Case-Control and Cohort Studies using a Modified Newcastle-Ottawa Scale (NOS, >6/9 is considered good quality)

First author, year of publication, country of origin	Selection (/4)	Comparability (/2)	Outcome, Exposure (/3)	Overall NOS Score (/9)	Comment on quality (Risk of bias)
GEOEPIDEMIOLOGY					
SEASON					
Carruthers et al. 1996 Norfolk, UK (1)	4	0	3	7	• Small number of events • No statistical test performed to compare the frequency of symptom onset across seasons (i.e. no p value).
Cotch et al. 1996 New York, USA (2)	4	0	3	7	• Identification based on ICD-9 diagnoses, therefore not necessarily incident cases (e.g. readmission or elective admission). Potential underdiagnosis and miscoding. • No confirmation of diagnosis using diagnostic criteria (e.g. ACR). • No statistical assessment of differences in seasonal frequencies reported.
Draib et al. 2018 Catalonia, Spain (3)	4	0	3	7	• Inaccuracies with obtaining date of symptom onset from medical records (although Mahr et al (4) found an average difference of 2.6 months between medical record and telephone interview data). • Limited to AAV with renal disease
Falk et al. 1990 GDCN, SE USA (5)	4	0	3	7	• Limited to those with renal involvement (PIGN). • No strict criteria applied as prior to ACR/CHCC, however use of renal biopsy and ANCA serology are quite similar to current classification systems. • Statistical analysis compares symptom onset observed to expected, rather than comparing each season. • Method to obtain date of symptom onset not clearly defined. Therefore, the method may not be homogenous and could create some inaccuracies.

Koldingsnes et al. 2000 Norway (6)	4	0	3	7	• No statistical test reported to compare seasonal variance. • Retrospective and cases identified on discharge diagnoses so possibility some cases missed (e.g. those that died during initial admission). • Small sample, therefore low power (0.45) to detect seasonal variance
Lane et al. 2007 Norfolk, UK (7)	4	0	3	7	• Unblinded interviewer • Recall bias • Selection bias as deceased patients not included • Small numbers exposed • Of note, differing findings from Carruthers et al (1) despite very similar cohort.
Li et al. 2018 China (8)	4	0	3	7	• Incomplete capture of cases as only 54.1% of tertiary hospitals included (however this was constant across study so proportions are still valuable to give indications, but do not allow comparisons with incidence rates in other countries). • ICD-10 diagnosis, which has a relatively low sensitivity (and up to 20% have previously been reported to be incorrect diagnoses) • 77.4% were not classified by 1 of the ACR/CHCC/EMA criteria. • Using first hospitalisation with discharge diagnosis AAV as a proxy for diagnosis. Missing milder non-hospitalised cases. • Winter months not defined. • No statistical tests reported to compare seasonal variations of AAV frequencies.
Mahr et al. 2006, France (4)	4	0	3	7	• Significant recall bias potentially although not SS different from medical records • Small numbers • One country • Non-population based design (recruits in RCTs), although recruitment evenly spread across the year

Pavone et al. 2006 Italy (9)	3	0	3	6	• Selection bias as patients collected by a study group – potentially more severe or complex cases. • Single organ disease excluded. • Time to relapse defined as time from remission, which excludes those who died or never reached remission. • No further data or statistical analysis regarding season of onset provided. • Small numbers and specifically within subgroups.
Tidman et al. 1998 Gothenburg, Sweden (10)	4	1	3	8	• Case ascertainment using ICD-8/9 initially and then confirmed with CHCC 1994, so potential from incorrect labelling and missed diagnoses/coding. • Retrospective, inherent recall bias • Small subgroup size so not powered to detect difference in seasonal symptom onset for subgroups. • Scanty statistics reported for compared seasonal symptom onset rates.
LATITUDE					
Gatenby et al. 2009 Canberra, Australia (11)	4	1	3	8	• Potential impact of differing classification systems used • Ethnic and genetic differences not controlled for (potentially influenced by latitude also).
Kalsch et al. 2009 Groningen, The Netherlands (12)	3	0	3	6	• 25-OH vitamin D as a surrogate for active vitamin D (1, 25-$(OH)_2$ D_3) • Part in vitro study to demonstrate a functional difference in vitamins D and A responsiveness on TNF∝ production in AAV patients – in vivo effect yet to be proven.
Kemna et al. 2017 Maastricht, The Netherlands (13)	4	1	3	8	• Physicians not blinded to ANCA results, therefore could bias them towards increased relapse diagnosis. • 85% PR3 positive, therefore limited generalisability • Low power • Cannot draw conclusions from the trend in 25-OH vitamin D levels as multiple confounders, such as supplementation, for which no information was available.

					• 25-OH vitamin D as a surrogate for active 1, 25-$(OH)_2$ D_3).
O'Donnell et al. 2007 New Zealand (NZ) (14)	4	1	3	8	• ICD-10-AM criteria is not recognised diagnostic criteria for accurate AAV diagnoses, nevertheless relative frequencies are still useful for investigating variances between latitude regions. • Very small number of M301 cases, preventing meaningful analysis of this group.
Reinhold et al. 2002 Germany (15)	4	0	3	7	• Small risk that duplication of cases exist due to ascertainment methods that include departments with partial dependence between them. • Short study period (2 years) may be too short to identify residential clusters.
Watts et al. 2001 Europe (16)	4	1	3	8	• No details of how patients were identified (e.g. discharge/admission codes, physician questionnaires, etc.) • Although slim, due to single referral centres in geographically isolated areas, there is a chance that cases were missed. • Numbers of EGPA were very small.
Watts et al. 2001 Europe (17)	4	1	3	8	• Details on case ascertainment were not provided. Potential for selection bias. • Details on background population not provided for Norway. • Small numbers of MPA in Tromsø (n=11) which may affect statistical power.
Weiner et al. 2019 Multi-centre (EU and USA) (18)	4	2	3	9	- Although registry based, selection bias was limited by using consecutively recruited patients from defined regions. - Results limited to biopsy-proven renal involvement, not generalisable. There is also a potential for bias with different centres having different indications for renal biopsy. - Possible that the latitudinal difference are related to genetic variability, which was not considered in analysis.

					- The use of one latitude value and mean UV radiation for each centre may not be representative of all patients.
RESIDENCE					
Herlyn et al. 2013 Northern Germany (19)	3	0	3	6	• Recall bias • Not complete population coverage • Difficult to accurately compare questionnaire response rates between urban/rural areas. • No statistical measures to quantify the difference in prevalence (although stated to be statistically significant).
Kanecki et al. 2017 Warsaw, Poland (20)	4	0	3	7	• Selection bias as OPD diagnoses excluded. • ICD10-coded diagnoses, therefore unable to confirm meets strict ACR/CHCC criteria • Urban, rural areas not stratified for confounders (e.g. age).
Ormerod et al. 2008 Canberra, Australia (21)	4	0	3	7	• Selection bias as used hospitals as source of identifying cases. Cases not referred to those centres or treated as outpatients were missed. • Small numbers (total incidence of MPA very low to begin with) therefore potentially not powered to detect difference in rural/urban incidence.
INFECTION					
STAPHYLOCOCCUS AUREUS & TRIMETHOPRIM-SULFAMETHOXAZOLE					
Besada et al. 2015 Tromso, Norway (22)	3	0	3	6	• Small sample and low event rate (only 28% relapsed) so may not powered to detect differences in subgroups.
Fijolek et al. 2018 Warsaw, Poland (23)	4	1	3	8	• Study controls for gender, ANCA positivity and other antibiotic use in the stepwise logistic regression model.
Lamprecht et al. 2019 Lubeck, Germany (24)	2	0	3	5	• Small numbers • No details on how cases and controls were selected (e.g. consecutive?) • No statistical comparisons provided for baseline characteristics between groups. On examination they are not matched (e.g. healthy controls older

					than GPA patients, while RA patients significantly older).
Laudien et al. 2010 Kiel, Germany (25)	4	0	3	7	• Cases and controls are not matched. • Given some controls were of community origin, we scored for this.
Pavone et al. 2006 Italy (9)	3	1	3	7	• Selection bias as patients collected by a study group – potentially more severe or complex cases. • Single organ disease excluded. • Time to relapse defined as time from remission, which excludes those who died or never reached remission. • No further data or statistical analysis regarding season of onset provided. • Small numbers and specifically within subgroups.
Popa et al. 2007 The Netherlands (26)	4	1	3	8	• Unable to clarify case identification or period study occurred within. Therefore likely selection bias. • Information on prophylactic antibiotic us not provided. • Small numbers of individual SAgs.
Rhee et al. 2018 Philadelphia, USA (27)	3	0	3	6	• While powered to detect differences between GPA and control groups, the study may have been underpowered to detect differences in subgroups. • Cross-sectional so no temporal changes or interindividual differences could be examined. • Some confounders (e.g. inflammation) were not accounted for.
Richter et al. 2009 Birmingham, UK (28)	4	0	3	7	• Potential contamination of BAFL during intubation. • Higher prevalence of LRT SA in GPA patients vs. disease and healthy controls does not confer causality. • Small numbers
Salmela et al. 2017 EUVAS (29)	4	1	3	7	• Selection bias as obtained through RCTs, not representative of entire AAV population. • Add on study to RCTs so not powered to test the effect of CNSAC on relapse rates nor analyse subgroups.
Stegeman et al. 1994	4	1	3	8	• No formal criteria established at the time of the study, instead 'clinical and

Groningen, The Netherlands (30)					histological criteria' were utilised, with all being biopsy-proven cases.
Tan et al. 2019 France (31)	3	0	3	6	• Long mean duration of disease, which pertains a lower relapse risk. Therefore, with a low event rate, the study may not have been powered to detect a difference. • TMP-SMX dose was not uniform, which could affect the effect observed. • Selection bias as single tertiary centre.
VIRAL					
Barzilai et al. 2007 Israel (32)	0	0	3	3	• Inconsistent antibody results for suggesting prior CMV infection • No details on how cases or controls were selected, nor which classification system used, if any.
Cook et al. 1997 Liverpool, UK and Erlangen, Germany (33)	0	0	3	3	• Small sample • No details on how cases or controls were selected, nor which classification system used, if any.
Eden et al. 2003 Paris, France (34)	2	1	3	5	• Small sample • No detail on how cases were selected.
Eriksson et al. 2012 Linkoping, Sweden (35)	1	0	3	4	• Unknown control matching • No details provided regarding how cases or controls were selected. There was also no detail on which classification system was used. • No statistic given to compare frequencies of IgG between groups.
Gerke et al. 2000 Rheumaklinik and Lubeck, Germany (36)	4	0	3	7	
Lee et al. 2018 Seoul, South Korea (37)	3	0	3	6	• Small numbers in subgroups so not powered to detect difference • HBV infection is endemic in Korea, therefore results not generalisable.
OTHER					
Fujita et al. 2009 Osaka, Japan (38)	3	0	3	6	• Small sample size and events.
Iyoda et al. 2007 Tokyo, Japan (39)	1	0	3	4	• Disease definitions (e.g. ACR/CHCC) not defined. • Selection of control group not specified. • Small sample and events.

Lidar et al. 2009 Israel (40)	1	2	3	6	• Small numbers of MPA and EGPA. • No description of how cases or controls were selected. • 'International criteria' were used, but the specific criteria are not reported. • There were no details on duration of disease in patients to assess whether these were newly diagnosed patients or patients who were months or years into treatment. • There were no treatment information provided which is a large confounder, as a potential cause of increased infection. Therefore, the findings could be treatment rather than disease related.
Nielsen et al. 2016 Denmark (41)	4	1	3	8	• ICD criteria used (issues with this noted previously) • Hospitalised for infection therefore representing likely severe end of spectrum and missing milder community treated cases. • Infection within 1 month of AID diagnosis is maximal temporal risk. This could signify that infection is either misdiagnosed (actually initially AID symptoms) or AID increases the risk of infection (e.g. pulmonary in case of GPA lung involvement with haemorrhage). Therefore, is infection causative or just synchronous? • No information of drug treatment available. It is possible that the AID was drug-induced rather than the infection itself. • Some confounders not available for inclusion (e.g. smoking) which increases infectious risk and potentially modulates AID risk.
Stratta et al. 2001 Torino, Italy (42)	2	2	3	7	• Small sample size and event number. • New methods for detecting TB disease had not yet been implemented, so possibly incomplete ascertainment of TB disease. • Selection bias with both cases and controls: limited to those with renal

					involvement, controls also have renal disease.
VACCINATION					
Buhler et al. 2019 Zurich, Switzerland (43)	3	1	3	7	• Small number of AAV patients included • Not age matched
Stassen et al. 2008 Groningen, The Netherlands (44)	4	0	3	7	• Retrospective so recall bias inherent. Vaccination status provided by patient rather than medical records so increased risk of recall issues. • Selection bias as single tertiary-centre. • The groups were not matched - the only significant differences were that the vaccinated group were older (p 0.0006) and had a longer disease duration (p 0.04).
Zycinska et al. 2007 Warsaw, Poland (45)	2	0	3	5	• No details regarding selection of cases or controls. • No reference to diagnostic classification used. • Small numbers and so may not be powered to detect difference.
ALLERGY					
Albert et al. 2004 Philadelphia, USA **(46)**	3	1	1	5	• Control groups not matched by age, sex or race • Disease controls (rather than population controls) may have independent associations with the exposures • Recall bias, • Questionnaire unable to quantify exposure (but included only 'significant' exposure) • Small numbers exposed to each variable => possible some exposures are relevant but lack statistical significance here. • Very wide 95% CIs • Hypothesis generating study • No comment on whether interviewer was blinded or not. There were 2 different interviewers involved which limits consistency.

Cuadrado et al. 1994 London, UK (47)	3	1	2	6	• Recall bias • No comment on whether interviewer was blinded or not. • Patient self-reported allergies therefore may not be fully accurate (no serology). • Selection bias as obtained via vasculitis clinic, potentially attracting the most severe cases. • Heterogeneous disease control group. • Small numbers therefore likely not powered to detect difference adequately.
Lane et al. 2003 UK **(48)**	3	1	2	6	• Unblinded interviewer • Recall bias • Selection bias as deceased patients not included • Small numbers exposed • Exposures self-reported
Stamp et al. 2015 Canterbury, New Zealand (49)	3	1	2	6	• Recall bias as is inherent with any retrospective study • Selection bias potentially as cases obtained from databases (although authors report confidence in almost complete case ascertainment). Bias also could have been introduced by selection of disease controls (e.g. high smoking rates among COPD group). • Interviewer not blinded • Interview heterogeneous method: some face to face, some telephone.
POLLUTION					
SILICA AND OTHER DUSTS					
Beaudreuil et al. 2005 Tours, France (50)	3	1	3	7	• Only 2/3 of the ANCA-positive patients had an associated AAV clinical syndrome. The remainder were of vasculitides. • Selection bias: deceased patients excluded
Rihova et al. 2005 Prague, Czech Republic (51)	3	2	2	7	• Details on case ascertainment lacking. • Small sample and no exposure was reported in controls which affects comparison between groups. • Recall bias as retrospective patient recount of exposure.

					• Single centre
Farquhar et al. 2017 Christchurch, New Zealand (52)	4	0	3	7	• Case finding based on serology rather than clinical syndrome, therefore ANCA negative cases missed (could be up to 10% as reported by the literature). But, only one ANCA referral laboratory in the region so investigators confident they captured all ANCA positive cases. • Small number of cases.
Li et al. 2018 China (8)	4	0	3	7	• Incomplete capture of cases as only 54.1% of tertiary hospitals included (however this was constant across study so proportions are still valuable to give indications, but do not allow comparisons with incidence rates in other countries). • ICD-10 diagnosis, which has a relatively low sensitivity (and up to 20% have previously been reported to be incorrect diagnoses) • 77.4% were not classified by 1 of the ACR/CHCC/EMA criteria. • Using first hospitalisation with discharge diagnosis AAV as a proxy for diagnosis. Missing milder non-hospitalised cases. • Winter months not defined. • No statistical tests reported to compare seasonal variations of AAV frequencies.
Takeuchi et al. 2017 Miyagi, Japan (53)	4	0	3	7	• Retrospective, small sample size, due to rare nature of the disease. • Cases identified based on ICD-10 criteria initially. • Single-centre, presuming complete ascertainment of cases for that region (as only functioning medical centre in the region during the GEJE), but there is a potential cases were treated at other hospitals • Observer bias as knowledge of increased MPO incidence post Kobe earthquake known, and possibly more patients were screened post, with potentially more undiagnosed cases pre-GEJE.

SMOKING					
Haubitz et al. 2005 Germany (54)	4	0	2	6	• Retrospective therefore recall bias may affect accuracy. • Selection bias as patients recruited from 2 renal centres, therefore there may be an imbalance towards renal patients and those with greater severity/complexity of disease. • Sex was not controlled for. • Heterogenous data collection.
Pearce et al. 2018 Nottingham, UK (55)	4	2	3	9	• Strengths: population-based (8% of UK primary care) so more representative of total GPA cohort (limits selection bias a/w hospital/RCT-based studies), prospective limiting recall bias, confounders included (e.g. drug and indication). • Possible misclassification/misdiagnoses: unable to confirm GPA diagnoses meet ACR/CHCC criteria. However, prior studies demonstrate a high (90%) positive predictive value of recording a GPA diagnosis in the CPRD. Cannot validate diagnoses due to data restrictions.
Yamaguchi et al. 2018 Nagoya, Japan (56)	4	0	3	7	• Majority MPA/MPO patients so cannot generalise to GPA subgroup. • Retrospective • Selection bias as largely renal patients via nephrology centres. • No comment of completeness of documentation of smoking history in medical records. • Confounders such as comorbidities (e.g. COPD) were not considered. • Inherent bias of self-reported smoking status and estimation of quantity.
FARMING AND ANIMALS					-
Lane et al. 2003 UK (48)	3	1	2	6	• Unblinded interviewer • Recall bias • Selection bias as deceased patients not included • Small numbers exposed • Exposures self-reported

Stamp et al. 2015 Canterbury, New Zealand (49)	3	1	2	6	• Recall bias as is inherent with any retrospective study • Selection bias potentially as cases obtained from databases (although authors report confidence in almost complete case ascertainment). Bias also could have been introduced by selection of disease controls (e.g. high smoking rates among COPD group). • Interviewer not blinded • Interview heterogeneous method: some face to face, some telephone.
Willeke et al. 2015 Germany (57)	3	1	2	6	• No details regarding selection of participants. • Mixed method of administering questionnaire. • Information for deceased participants (n=3) was obtained by proxy and therefore reducing accuracy of the information. • Inconsistent ascertainment of MRSA status, therefore consistency of method cannot be guaranteed. The status was also not available in 13% of patients and 36% of controls.
OTHER POLLUTANTS					
Albert et al. 2004 Philadelphia, USA **(46)**	3	1	1	5	• Control groups not matched by age, sex or race • Disease controls (rather than population controls) may have independent associations with the exposures • Recall bias, • Questionnaire unable to quantify exposure (but included only 'significant' exposure) • Small numbers exposed to each variable => possible some exposures are relevant but lack statistical significance here. • Very wide 95% CIs • Hypothesis generating study - No comment on whether interviewer was blinded or not. There were 2 different interviewers involved which limits consistency.

Hogan et al. 2001 UNC, USA (58)	2	1	2	5	• Limited to AAV patients with biopsy proven renal disease, which limits generalisability. • Questionnaire was answered by the patient independently. All exposures were self-reported. • Controls were patients with other renal diseases, which may introduce further confounders. • Absolute numbers exposed to some agents (e.g. glues) were very small and therefore the study was likely underpowered to detect these differences.
Knight et al. 2010 Sweden (59)	3	2	3	8	• Cases initially identified using ICD definitions. Cases with occupations demonstrating increased RR were selected for diagnosis validation by reviewing medical records – only 83% of cases were correctly diagnosed when ACR criteria applied. • Possibility the borderline findings were chance findings given the issue of multiple testing. • Possibility that an exposure specific to a certain subcategory of the occupation was not captured.
Nuyts et al. 1995 Antwerp, Belgium (60)	4	1	2	7	• Retrospective, very small sample size and number exposed. • Selection bias as obtained in hospital so may not be representative of entire GPA cohort. • Confounders such as smoking not considered. • No detail on whether the interviewer was blinded.
Pai et al. 1998 Liverpool, UK (61)	2	2	3	7	• Standardised diagnostic criteria (e.g. ACR) not used. 5 patients were ANCA negative, but this was on IF only (no ELISA at that time). • Retrospective and single-centre, so recall and selection bias a potential issue. • Deceased patients excluded which again adds the potential of selection bias.

					• 23/28 had severe renal impairment or were on dialysis, therefore results are not generalisable to non-renal disease.

Published(62)

11. *Supplementary Table 2:* Quality Assessment of Narrative Reviews, Randomised Controlled Trials and Meta-Analyses

First author, year of publication, country of origin	Overall Score & tool used	Quality (Risk of bias?)
GEOEPIDEMIOLOGY		
SEASON		
Aries et al. 2008 Hamburg, Germany (63)	INSA* score: 6/7	• Comparison of absolute numbers rather than incidence rates • Retrospective resulting in recall bias.
INFECTION		
Stegeman et al. 1996 Groningen, The Netherlands (64)	'Therapy study' critical appraisal tool from the CEBM**: other than no details provided on the method of randomisation, the study met the criteria for adequacy using the checklist.	• No details provided on method of randomisation. • Classification of GPA was extended beyond ACR criteria. • CrCl <30ml/min excluded so generalisability limited.
Zycinska et al. 2009 Warsaw, Poland (65)	'Therapy study' critical appraisal tool from the CEBM**: concerning items for quality (see over).	• No details provided on method of randomisation, participant selection, nor whether patients/clinicians were blinded to which treatment arm was received. • No statistical comparison performed between baseline characteristics between groups. The placebo group were slightly older (median age 51.4 years vs. 46.1 years) with marginally worse renal function at baseline (GFR 71 ml/min vs. 81 ml/min). Older patients tend to relapse less so this should would have resulted in underestimation of the effect of TMP-SMX. • Small sample size. • No details provided about how SA chronic nasal carriage was classified nor assessed. • No details provided regarding definition nor classification of relapse.
VIRAL		
Sachetto et al 2006 Brazil (66)	INSA score: 6/7	• No details regarding how cases were selected. • Restricted to MPA cases only. • Descriptive only. Parvovirus B19 DNA was not identified in any sample, however this organism cannot be discounted based on this as prior infection may still be a factor in disease pathogenesis.
OTHER		
Ishiguro et al. 2015 Saitama, Japan (67)	INSA score: 7/7	• Only mildly suggestive, temporal relationship not consistent.
VACCINATION		

Duggal et al. 2013 **Baltimore, USA (68)**	INSA score: 6/7	• Small numbers • Descriptive report suggesting temporal relationship rather than providing any evidence of causality. There is a potential that other triggering factors were at play in this complex multifactorial disease. • No use of diagnostic classification reported. 7 of the 8 patients had definite renal biopsy proven AAV.
POLLUTION		
SILICA AND OTHER DUSTS		
Gomez-Puerta et al. 2013 **Boston, USA (69)**	'Systematic review' critical appraisal tool from the CEBM**: moderate heterogeneity noted, otherwise study was of adequate quality.	• Differing definitions for cases and controls (e.g. some AAV vs. some renal limited disease). • Limited by inherent confounding and bias in observational studies • Possible publication bias identified by asymmetry in funnel plot (unpublished small null studies) • Moderate heterogeneity (I^2 48.4%), although subgroup analysis did not identify a single study influencing the overall pooled OR.
Yashiro et al. 1999 **Kyoto, Japan (70)**	INSA score: 6/7	• All patients were MPO-ANCA positive and had renal involvement (evidenced by PIGN on renal biopsy or requirement for dialysis). No standardised diagnostic criteria used. • Retrospective study involving small numbers, which is descriptive rather than showing any concrete association. • Incomplete case ascertainment possible.
FARMING AND ANIMALS		•
Lee et al. 2007 **Norfolk, UK (71)**	INSA score: 6/7	• Descriptive only. • No statistical analysis as small numbers • No details on measurement of exposure, only yes/no reported.
OTHER POLLUTANTS		•
Albert et al. 2005 Philadelphia, USA **(72)**	INSA score: 6/7	• Recall bias, • Limited exposures included in questionnaire, • Questionnaire unable to quantify exposure • No control group • Descriptive purposes only. Hypothesis generating study

*INSA Score: The International Narrative Systematic Assessment Scoring System (>5/7 is considered good quality)

**CEBM: The Centre for Evidence-Based Medicine, University of Oxford

Published(62)

12. Published Works

All manuscripts included in this thesis were published under the Creative Commons Attribution 4.0 International License, “which permits unrestricted use, distribution, modification, and reproduction in any medium”, and therefore “the author does not need to seek written permission”. Acknowledgment to the original source has been made using a reference where appropriate in each chapter and below, where each manuscript is printed in its full original version.

12.1 Risk Factors for Severe Outcomes in Patients with Systemic Vasculitis and COVID-19: A Binational, Registry-Based Cohort Study (73)

Check for updates

Arthritis & Rheumatology
Vol. 73, No. 9, September 2021, pp 1713–1719
DOI 10.1002/art.41728
© 2021 The Authors. *Arthritis & Rheumatology* published by Wiley Periodicals LLC on behalf of American College of Rheumatology. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

AMERICAN COLLEGE of RHEUMATOLOGY
Empowering Rheumatology Professionals

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Risk Factors for Severe Outcomes in Patients With Systemic Vasculitis and COVID-19: A Binational, Registry-Based Cohort Study

Matthew A. Rutherford,[1] Jennifer Scott,[2] Maira Karabayas,[3] Marilina Antonelou,[4] Seerapani Gopaluni,[5] David Gray,[6] Joe Barrett,[6] Silke R. Brix,[7] Neeraj Dhaun,[8] Stephen P. McAdoo,[9] Rona M. Smith,[5] Colin C. Geddes,[10] David Jayne,[5] Raashid Luqmani,[11] Alan D. Salama,[12] Mark A. Little,[2] and Neil Basu,[13] on behalf of the UK and Ireland Vasculitis Rare Disease Group (UKIVAS)

Objective. COVID-19 is a novel infectious disease with a broad spectrum of clinical severity. Patients with systemic vasculitis have an increased risk of serious infections and may be at risk of severe outcomes following COVID-19. We undertook this study to establish the risk factors for severe COVID-19 outcomes in these patients, including the impact of immunosuppressive therapies.

Methods. A multicenter cohort was developed through the participation of centers affiliated with national UK and Ireland vasculitis registries. Clinical characteristics and outcomes are described. Logistic regression was used to evaluate associations between potential risk factors and a severe COVID-19 outcome, defined as a requirement for advanced oxygen therapy, a requirement for invasive ventilation, or death.

Results. The cohort included 65 patients with systemic vasculitis who developed COVID-19 (median age 70 years, 49% women), of whom 25 patients (38%) experienced a severe outcome. Most patients (55 of 65 [85%]) had antineutrophil cytoplasmic antibody–associated vasculitis (AAV). Almost all patients required hospitalization (59 of 65 [91%]), 7 patients (11%) were admitted to intensive care, and 18 patients (28%) died. Background glucocorticoid therapy was associated with severe outcomes (adjusted odds ratio [OR] 3.7 [95% confidence interval 1.1–14.9]; $P = 0.047$), as was comorbid respiratory disease (adjusted OR 7.5 [95% confidence interval 1.9–38.2]; $P = 0.006$). Vasculitis disease activity and nonglucocorticoid immunosuppressive therapy were not associated with severe outcomes.

Conclusion. In patients with systemic vasculitis, glucocorticoid use at presentation and comorbid respiratory disease were associated with severe outcomes in COVID-19. These data can inform clinical decision-making relating to the risk of severe COVID-19 in this vulnerable patient group.

INTRODUCTION

COVID-19 is a novel, multisystem infectious disease caused by SARS–CoV-2. COVID-19 is associated with a broad spectrum of clinical severity (1), ranging from asymptomatic disease to severe respiratory failure and death. In March 2020, the World Health Organization (WHO) characterized COVID-19 as a global pandemic (2), prompting considerable concerns from health care systems worldwide about their resilience to manage this threat. Critical care service capacity was, and remains, a global priority.

Systemic vasculitis is a rare, multisystem autoimmune disorder. Compared to other rheumatic musculoskeletal diseases, it may result in major organ dysfunction and is therefore typically managed with more potent immunosuppressive therapy and

[1]Matthew A. Rutherford, MBChB, MRCP: University of Glasgow and Queen Elizabeth University Hospital, Glasgow, UK; [2]Jennifer Scott, MRCPI, Mark A. Little, PhD: Trinity College Dublin, Dublin, Ireland; [3]Maira Karabayas, MBChB, MRCP: NHS Grampian, Aberdeen, UK; [4]Marilina Antonelou, MBBS, PhD: University College London, London, UK; [5]Seerapani Gopaluni, MBBS, MRCP, Rona M. Smith, MD, MRCP, David Jayne, MD: University of Cambridge, Cambridge, UK; [6]David Gray, BSc, Joe Barrett, BA: University of Oxford, Oxford, UK; [7]Silke R. Brix, MD, MRCP: Manchester University NHS Foundation Trust and University of Manchester, Manchester, UK; [8]Neeraj Dhaun, MD, PhD: University of Edinburgh, Edinburgh, UK; [9]Stephen P. McAdoo, MBBS, PhD: Hammersmith Hospital and Imperial College London, London, UK; [10]Colin C. Geddes, FRCP: Queen Elizabeth University Hospital, Glasgow, UK; [11]Raashid Luqmani, DM, FRCP, FRCPE: Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [12]Alan D. Salama, PhD, FRCP: University College London and Royal Free Hospital, London, UK; [13]Neil Basu, MD, PhD: University of Glasgow, Glasgow, UK.

Drs. Rutherford and Scott contributed equally to this work.

Dr. Rutherford has received research support from Vifor Pharma. No other disclosures relevant to this article were reported.

Address correspondence to Matthew A. Rutherford, MBChB, MRCP, University of Glasgow, Sir Graeme Davies Building, 120 University Place, Glasgow F12 8TA, UK. Email: matthew.rutherford@glasgow.ac.uk.

Submitted for publication October 29, 2020; accepted in revised form March 4, 2021.

higher doses of glucocorticoids in order to induce and maintain disease remission. While this therapeutic approach successfully manages vasculitis activity, glucocorticoid exposure contributes, in part, to the increased risk of infection in these patients (3,4). Thus, although risk factors associated with poor outcomes from COVID-19 in this population are unknown, there is an assumption that these patients are at a high risk.

The RECOVERY trial has demonstrated a benefit of moderate-dose glucocorticoids in hospitalized general population patients with COVID-19 who require supplemental oxygen or mechanical ventilation, but showed potential harm when used in milder disease (5). Given these paradoxical effects, it is unknown whether chronic background glucocorticoid exposure makes patients more susceptible to severe COVID-19 infection or whether it might be protective.

We report the results of a coordinated binational effort to identify the predictors of a severe outcome in the largest reported cohort of systemic vasculitis patients infected with COVID-19.

PATIENTS AND METHODS

Study design. A registry-based multicenter cohort was designed to facilitate rapid real-world data capture. Centers affiliated with the UK and Ireland Vasculitis Registry (UKIVAS; www.ukivas.org/) and the Irish Rare Kidney Disease Registry (RKD; www.tcd.ie/medicine/thkc/research/rare.php) were invited to contribute. UKIVAS covers 89 sites; RKD covers 8 sites across Ireland. Participating centers represent both secondary and tertiary centers across the UK and Ireland, resulting in a broad population sampling frame. A vasculitis-focused COVID-19 case report form was developed, underpinned by standardized BioPortal ontologies (e.g., SNOMED CT) (6) and interoperable with other emerging data sets, such as the COVID-19 Global Rheumatology Alliance (GRA) (7), thereby facilitating future international data linkage as the COVID-19 pandemic progresses. This enables compatibility of these data with the principles of the global GO-FAIR initiative (8). Additional modules of the UKIVAS and RKD web apps were developed to support data capture.

Study population. Patients were eligible for case submission if they had a diagnosis of systemic vasculitis and COVID-19 (laboratory, radiologic, or clinical). The diagnosis of vasculitis was determined by the local specialist clinician, according to the International Chapel Hill Consensus Conference nomenclature of vasculitides (9). Recruitment commenced on March 28, 2020 and is ongoing. For this analysis, the final case was submitted on July 31, 2020. The population sampling frame consisted of individuals under the clinical care of sites associated with the UKIVAS and RKD registries. At the end of July 2020, there were 795 patients in the RKD registry and ~7,400 patients in the UKIVAS registry, with 4 patients enrolled in both. In the UK, the Health Research Authority decision tool determined that ethics approval was not required, and the local sponsor confirmed the project as a service evaluation (R&D reference no. GN20RH165). RKD registry ethics approval was originally granted by the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (reference no. 2019-08 List 29 [07]). All RKD participants provided informed consent. Additional approvals were not required.

Study variables. Variables included potential predictors of severe outcomes. The selection of predictive variables was informed by emerging risk factors for COVID-19 disease severity in other populations (10,11). These included age, sex, ethnicity, smoking status, comorbid conditions, immunosuppressive treatment for vasculitis, and vasculitis disease activity. Among the comorbid conditions, respiratory disease refers to non–vasculitis-related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis-related respiratory disease. Intravenous immunosuppressive therapy was considered to be "current" if the assessing clinician determined that the therapy was likely to exert a biologic effect at the time of COVID-19 diagnosis; specific definitions were not provided.

Vasculitis disease activity was determined according to global clinician assessment. Outcome data included complications, such as acute kidney injury (AKI), respiratory failure and vasopressor requirement, and death. To enable interoperability, the standardized outcomes (grade range 1–8) from the COVID-19 GRA case reporting form were used (see Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41728/abstract) (10). A severe outcome was defined as a composite of requirement for advanced oxygen therapy (such as noninvasive ventilation or high-flow oxygen device), requirement for invasive ventilation, or death. Dates of hospital and intensive care unit (ICU) admission and discharge were collected in order to derive length of stay. Other variables were collected to characterize the clinical features of COVID-19 in patients with vasculitis. These included symptoms, laboratory tests, and radiology results. Reporting clinicians were asked to indicate which of these variables contributed to diagnosis.

Statistical analysis. Continuous variables are described as the median and interquartile range (IQR). Categorical variables are described as the number and percentage of patients. Associations between various explanatory variables and the odds of severe outcomes were determined. Unadjusted and age/sex-adjusted logistic regression models were individually calculated for each explanatory variable and reported as odds ratios (ORs), *P* values, and 95% confidence intervals (95% CIs). The adjusted ORs for age and sex were derived from a single logistic regression model which included age and sex only. When a potential interaction could account for a positive finding, logistic regression modeling incorporating the explanatory and interacting variables was used. Sensitivity analyses were performed in the event that any effects may have been different in an important subgroup. Missing data were acknowledged in the relevant tables. *P* values less than

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. Baseline characteristics of the study patients (n = 65)*

Characteristic	Value	Characteristic	Value
Age, median (IQR) years	70 (55–76)	Vasculitis, active disease	32 (49.2)
Female sex	32 (49.2)	Vasculitis disease duration, median (IQR) years	2.2 (0.76–6.8)
Ethnicity		Current immunosuppressive therapy	
Asian	7 (10.8)	Any immunosuppressive therapy	56 (86.2)
Black	1 (1.5)	Any immunosuppressive therapy and GCs	43 (66.2)
White	46 (70.8)	Azathioprine	12 (18.5)
Not stated	6 (9.2)	GCs (any dose)	45 (69.2)
Missing data	5 (7.7)	Prednisone 1.0–5.0 mg/day	19 (29.2)
Smoking status		Prednisone ≥5.1 mg/day	26 (40.0)
Current	3 (4.6)	Unknown/missing data	2 (3.1)
Former	15 (23.1)	CYC	10 (15.4)
Never	26 (40.0)	HCQ	4 (6.2)
Unknown/missing data	21 (32.3)	IVIG	1 (1.5)
Comorbidities		MMF	11 (16.9)
Vasculitis†		Rituximab	22 (33.8)
GPA (or PR3 AAV)	24 (36.9)	Tacrolimus	4 (6.2)
MPA (or MPO AAV)	25 (38.5)	Other medications	
EGPA	6 (9.2)	ACE inhibitors	9 (13.8)
LVV	2 (3.1)	ARB	8 (12.3)
Behçet's disease	1 (1.5)	NSAIDs	2 (3.1)
PAN	1 (1.5)	Unknown/missing data	5 (7.7)
Other	5 (7.7)	Laboratory tests, median (IQR)	
Unknown/missing data	1 (1.5)	Creatinine, μmoles/liter¶	127 (69–204)
Diabetes	13 (20.0)	CRP, mg/liter	99 (44–149)
Hypertension	25 (38.5)	Lymphocytes, $\times 10^9$/liter	0.7 (0.4–0.9)
CVD	17 (26.2)	Method used for COVID-19 diagnosis	
Respiratory disease‡	13 (20.0)	PCR	47 (72.3)
Renal disease	30 (46.2)	Radiologic	3 (4.6)
End-stage kidney disease§		Symptoms only	3 (4.6)
Yes	17 (26.2)	Unknown/missing data	12 (18.5)
No	46 (70.8)		
Unknown/missing data	2 (3.1)		
Organ transplant	3 (4.6)		

* Except where indicated otherwise, values are the number (%) of patients. IQR = interquartile range; GPA = granulomatosis with polyangiitis; PR3 = proteinase 3; AAV = antineutrophil cytoplasmic antibody–associated vasculitis; MPA = microscopic polyangiitis; MPO = myeloperoxidase; EGPA = eosinophilic granulomatosis with polyangiitis; LVV = large vessel vasculitis; PAN = polyarteritis nodosa; CVD = cardiovascular disease; GCs = glucocorticoids; CYC = cyclophosphamide; HCQ = hydroxychloroquine; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; NSAIDs = nonsteroidal antiinflammatory drugs; CRP = C-reactive protein; PCR = polymerase chain reaction.
† Other vasculitis diagnoses include IgA vasculitis, leukocytoclastic vasculitis, and unspecified vasculitis.
‡ Refers to non–vasculitis-related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis-related respiratory disease.
§ Includes 13 patients receiving hemodialysis, 3 kidney transplant recipients, and 1 patient with sustained stage 5 chronic kidney disease.
¶ Excludes patients receiving hemodialysis.

0.05 were considered significant. R (version 4.0.2) was used for data analysis with packages including tidyverse and finalfit.

RESULTS

In total, 65 patients with an established diagnosis of systemic vasculitis who developed COVID-19 were registered. Fifty-eight patients were submitted to the UKIVAS registry, and 7 were submitted to the RKD registry, with no duplicate submissions.

Baseline characteristics. The median age was 70 years (IQR 55–76 years) and 49% of the patients were female (Table 1). The majority of patients (55 of 65 [85%]) had antineutrophil cytoplasm antibody–associated vasculitis (AAV): of these, 24 patients (44%) had granulomatosis with polyangiitis, 25 patients (45%) had microscopic polyangiitis, and 6 patients (11%) had eosinophilic granulomatosis with polyangiitis. The characteristics of AAV patients were broadly similar to those of the full cohort (data not shown). Thirty-two patients (49%) were assessed as having concurrent active disease. Fifteen patients (23%) were suspected to have contracted COVID-19 through a health care setting; of these, 9 patients (60%) had some degree of active vasculitis. In one case, COVID-19 was considered to have increased disease activity. For the remaining patients, COVID-19 was not perceived to have altered or induced disease activity.

Forty-seven patients (72%) were diagnosed by polymerase chain reaction (PCR) testing, 3 patients (5%) did not have PCR-confirmed disease but had radiologic evidence of disease, and 3

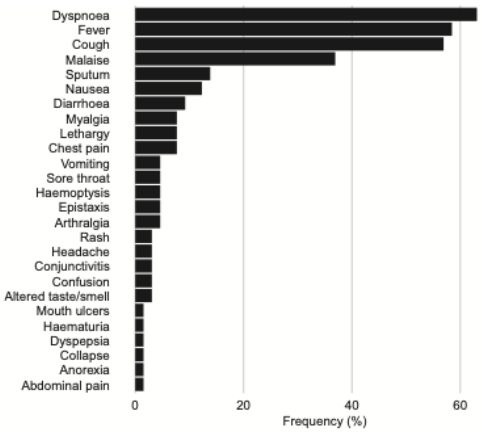


Figure 1. Frequency of patient symptoms at initial presentation.

patients (5%) were diagnosed by clinical presentation only (Table 1). Data on diagnostic testing were unknown/missing for 12 patients (19%). The characteristics of those diagnosed by PCR testing were broadly similar to the full cohort (data not shown).

Most patients were receiving background glucocorticoids (45 of 65 [69%]) at the time of COVID-19 diagnosis. Nineteen patients (29%) were receiving the equivalent of ≤5 mg prednisone, and 26 patients (40%) were receiving >5 mg. For those receiving background glucocorticoids, the median dose was the equivalent of 7.5 mg prednisone daily (IQR 5–25 mg). Twenty-two patients (34%) and 10 patients (15%) had recently been treated with rituximab and cyclophosphamide, respectively (Table 1).

Symptom frequency. The most common symptoms among the included patients were dyspnea (41 of 65 [63%]), fever (38 of 65 [58%]), and cough (37 of 65 [57%]) (Figure 1). Full data on symptoms were missing for 2 patients. Hemoptysis occurred in 3 patients (5%), and epistaxis occurred in 3 individuals (5%); of these, 1 patient had both epistaxis and hemoptysis. Of note, some of these patients had ongoing disease activity prior to COVID-19 diagnosis.

Complication frequency. Respiratory failure was the most commonly reported complication among patients (35 of 65 [54%]), followed by AKI (12 of 65 [18%]) and secondary infection (10 of 65 [15%]) (Figure 2). Full data on complications were missing for 10 patients.

Clinical outcomes. Almost all patients required hospitalization (59 of 65 [91%]); 7 patients (11%) were admitted to an ICU, and 18 patients (28%) died (Table 2). The median length of hospital stay for discharged patients was 11 days (IQR 5–27 days). A severe outcome was experienced by 25 of 65 patients (38%).

Predictors of severe outcomes. Patients with comorbid respiratory disease were more likely to experience a severe outcome than those without (adjusted OR 7.5 [95% CI 1.9–38.2]; $P = 0.006$), as were those who had been receiving glucocorticoids (adjusted OR 3.7 [95% CI 1.1–14.9]; $P = 0.047$) (Table 3). Glucocorticoid exposure remained a poor prognostic indicator even after adjusting for vasculitis disease activity (data not shown). A sensitivity analysis including only patients with a confirmed PCR diagnosis (n = 47) was performed, which demonstrated effect sizes consistent with these findings; this was statistically significant for comorbid respiratory disease but not for glucocorticoid exposure (data not shown). A sensitivity analysis was also performed for individuals with AAV (n = 55) with a similar result. There was insufficient power to assess the association between glucocorticoid dose and poor outcome. Similarly, there was insufficient power to assess for differences between common nonglucocorticoid immunosuppressive agents. Associations were not demonstrated for any demographics, other comorbid conditions, vasculitis diagnosis, vasculitis disease activity, or nonglucocorticoid immunosuppressant medication.

DISCUSSION

This multicenter study includes the largest cohort of patients with systemic vasculitis who have developed COVID-19 to date. It identifies comorbid respiratory disease and background glucocorticoid therapy as significant predictors of a severe outcome, defined as a need for advanced oxygen therapy or invasive ventilation, or death. Routinely used nonglucocorticoid immunosuppressants, such as rituximab and cyclophosphamide, were not associated with a severe outcome, nor was vasculitis disease activity.

Glucocorticoids have pleotropic immunologic effects and are generally considered risk factors for infections (12). Glucocorticoids at high doses have been associated with prolonged viral shedding, with a similar effect being observed in other coronaviruses (13,14). That glucocorticoids are associated with worse COVID-19 disease outcomes is consistent with findings from

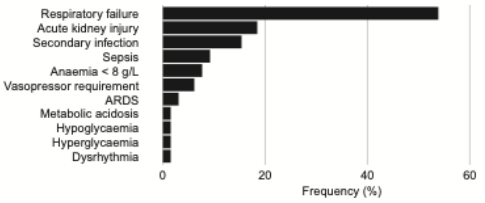


Figure 2. Frequency of patient complications. ARDS = acute respiratory distress syndrome.

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2. COVID-19 disease outcomes in the study patients (n = 65)*

Hospitalization	59 (90.8)
ICU admission	
Yes	7 (10.8)
No	49 (75.4)
Unknown/missing data	9 (13.8)
Graded outcome (grade no.)	
Not hospitalized, no limitations on activities (1)	2 (3.1)
Not hospitalized, limitation on activities (2)	3 (4.6)
Hospitalized, not requiring supplemental oxygen (3)	9 (13.8)
Hospitalized, requiring supplemental oxygen (4)	25 (38.5)
Hospitalized, on noninvasive ventilation or high-flow oxygen devices (5)	4 (6.2)
Hospitalized, on invasive mechanical ventilation or ECMO (6)	3 (4.6)
Death (7)	18 (27.7)
Unknown/missing data (8)	1 (1.5)
Length of hospital stay, median (IQR) days	11 (5–27)
Length of hospital stay, unknown/missing data	40 (61.5)

* Except where indicated otherwise, values are the number (%) of patients. ICU = intensive care unit; ECMO = extracorporeal membrane oxygenation.

across the rheumatic autoimmune spectrum, as demonstrated by the COVID-19 GRA study (10). Our point estimate for the association of any glucocorticoid dose with severe outcomes (OR 3.7 [95% CI 1.09–14.9]) was comparable to that of the COVID-19 GRA evaluation of steroids equivalent to ≥10 mg prednisone per day (OR 2.05 [95% CI 1.06–3.96). The confidence interval for this finding is relatively wide, and thus, it remains to be determined if there is a dose threshold at which risk commences.

The association between glucocorticoids and severe outcomes may appear to conflict with findings from the RECOVERY trial (5). This trial demonstrated that low-dose dexamethasone had a substantial survival benefit in patients hospitalized with COVID-19. However, the groups that benefited in RECOVERY were those requiring supplemental oxygen, with the greatest benefit derived in those requiring mechanical ventilation. In fact, the point estimate for patients not requiring oxygen suggested that glucocorticoids could be associated with increased mortality, though this was not a statistically significant finding (5). Therefore, prior to requiring oxygen, it may be that glucocorticoids are deleterious, as observed in this and other studies of autoimmune disease (15). Our finding that comorbid respiratory disease (most commonly chronic obstructive pulmonary disease, asthma, and interstitial lung disease) was associated with severe disease outcomes was consistent with a recent general population meta-analysis (16). Among some

Table 3. Unadjusted and adjusted ORs for potential risk factors and association with severe outcomes*

	No. of severe outcomes/ no. of cases (%)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Female	13/26 (50)	1.04 (0.51–2.10)	1.05 (0.52–2.13)
Age	–	1.01 (0.98–1.05)	1.01 (0.98–1.05)
Vasculitis diagnosis			
GPA (referent: not GPA)	12/24 (50)	1.71 (0.62–4.81)	2.19 (0.68–7.63)
MPA (referent: not MPA)	7/25 (28)	0.53 (0.17–1.52)	0.43 (0.13–1.36)
Comorbidities (referent: individual comorbidity not present)			
Hypertension	12/25 (48)	1.46 (0.71–3.04)	1.39 (0.64–3.04)
CVD	8/17 (47)	1.32 (0.59–2.93)	1.08 (0.52–2.23)
Respiratory disease	10/13 (77)	7.50 (1.99–36.94)	7.53 (1.93–38.22)†
Diabetes	6/13 (46)	1.25 (0.51–2.99)	1.20 (0.48–2.92)
Renal disease	12/30 (40)	1.00 (0.49–2.03)	1.05 (0.52–2.14)
End-stage kidney disease	6/17 (35)	0.85 (0.25–2.65)	0.77 (0.22–2.48)
Smoking status			
Ever smoker (referent: never)	9/18 (50)	2.25 (0.65–8.05)	2.33 (0.62–9.28)
Immunosuppressive therapy			
Any immunosuppressive therapy (referent: not receiving immunosuppressive therapy)	24/55 (44)	3.10 (0.70–21.79)	3.66 (0.77–27.29)
GCs (referent: no prednisone)			
Prednisone (any dose)	22/45 (49)	3.35 (1.02–13.2)	3.66 (1.09–14.9)‡
Prednisone 1.0–5.0 mg/day	10/19 (53)	3.89 (0.98–17.93)	3.76 (0.91–18.02)
Prednisone ≥5.1 mg/day	12/26 (46)	3.00 (0.82–12.86)	3.32 (0.86–15.35)
Other immunosuppressive therapy			
Azathioprine (referent: not receiving azathioprine)	6/12 (50)	1.65 (0.46–5.97)	1.57 (0.42–5.85)
CYC (referent: not receiving CYC)	5/10 (50)	1.62 (0.41–6.48)	1.83 (0.44–7.76)
Rituximab (referent: not receiving rituximab)	9/22 (41)	1.06 (0.36–3.01)	1.25 (0.40–3.90)

* A severe outcome was defined as a composite of requirement for advanced oxygen therapy (such as noninvasive ventilation or high-flow oxygen device), requirement for invasive ventilation, or death. A separate logistic regression model including sex and age as a continuous variable was calculated for each explanatory variable. The adjusted models for age and sex were derived from a single logistic regression model which included sex and age as a continuous variable. OR = odds ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† $P < 0.00645$. Respiratory disease refers to non–vasculitis-related lower respiratory tract disease, though it is possible that some patients had coexistent vasculitis-related respiratory disease.
‡ $P < 0.047$.

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

patients with chronic lung disease, enhanced respiratory tract angiotensin-converting enzyme 2 expression, the principal binding site for COVID-19 cell entry, is a possible explanation for this association (10). Consistent with findings from the COVID-19 GRA study, we did not find an association of adverse disease outcomes with other immunosuppressive agents (17). This is reassuring, as current guidance emphasizes the importance of maintaining immunosuppressive therapy among uninfected patients due to concerns of destabilizing disease control (18).

This cohort represents a severely affected group, as reflected by the very high proportion of hospitalization (91%). The mortality rate of 28% is similar to that reported in the largest UK study of hospitalized patients carried out by the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) group, in which 26% of patients died (18). Age, sex, and symptom distribution were also broadly similar to the ISARIC WHO CCP-UK study. The most common symptoms, in that cohort and ours, were those that have been the most prominent in the case definition: breathlessness, fever, and cough. Both active pulmonary vasculitis and COVID-19 are recognized causes of hemoptysis (18,19). In the ISARIC WHO CCP-UK group, 3.5% of patients experienced this symptom, compared to 3 patients (4.8%) in our cohort. None were thought to have diffuse alveolar hemorrhage, as assessed by the responding clinician. Differentiating COVID-19 from active pulmonary vasculitis remains a challenge, and indeed these presentations may coexist. Ensuring that these diagnoses are considered when a patient with vasculitis presents with hemoptysis remains of high importance.

A large proportion of patients (49%) had concurrent active vasculitis. A considerable proportion of these patients were believed to have contracted COVID-19 from a health care setting. Notably, the onset of vasculitis disease activity preceded COVID-19 infection in almost all cases. However, it is unknown whether COVID-19 may trigger vasculitis activity in the longer term. The emergence of pediatric multisystem inflammatory syndrome temporally associated with SARS–CoV-2, a condition bearing strong similarities to Kawasaki disease, is a potential example of SARS–CoV-2 triggering autoimmune vasculitis, though the pathogenesis is not currently understood (20). We did not find evidence of vasculitis being triggered in the short term. Longitudinal studies will seek to address this question. The prevalence of active disease in this cohort was higher than expected—previous cross-sectional UK studies have shown disease activity prevalence at ~20% (21). Although disease activity was not associated with worse outcomes, it may be that patients with unstable disease are more vulnerable to contracting COVID-19. Physician or patient-led reduction in immunosuppressive treatment, in a bid to limit the impact of COVID-19, is another potential reason accounting for a high proportion of disease activity. Due to the study design, our data are limited in the extent to which they can answer this question.

Ascertainment bias is likely to have affected this study. Given that most patients were hospitalized, it is likely that patients with milder disease were not identified. The number of PCR-diagnosed COVID-19 patients in our study as a proportion of the combined UKIVAS and RKD populations was similar to the proportion of UK cases relative to the UK population for a comparable time period (22). However, due to the study design, it is not possible to derive incidence rates. Patients with vasculitis may have been more likely to contract COVID-19 due to risk factors such as immunosuppressive therapy and the need to attend health care facilities; therefore, ascertainment bias remains possible.

There was a high preponderance of small vessel vasculitis (SVV) in this study compared to giant cell arteritis (GCA). Although it is a more common condition, patients with GCA are typically older and may have adopted stricter self-isolation restrictions (according to national guidance). In addition, SVV may have predominated due to a disproportionate number of renal departments, compared to rheumatology centers, represented in the UKIVAS registry. Due to a large majority of patients in this study having SVV, the extent to which its findings can be generalized to other vasculitides is limited. Other limitations of this study include a relative lack of power. As a result, our analyses may not detect some clinically significant effects, and, conversely, the risk of spurious findings is higher. Similarly, due to the limited number of events, our ability to control for multiple potential confounding factors was limited. Due to the heterogeneous immunobiology, phenotypes, and management approaches of systemic vasculitis, it is possible that individual disorders may incur different risks; due to insufficient power, we were limited in the extent to which this could be examined.

This study is the first to describe a cohort of vasculitis patients with COVID-19. The clinical presentation of COVID-19 was similar to descriptions in large series of patients without autoimmune disease. Glucocorticoids were associated with an increased risk of severe outcomes, but other immunosuppressants were not. Patients with autoimmune disease have been considered vulnerable during the COVID-19 pandemic, and many governments have instructed that they adhere to exceptional social isolation restrictions. While patients with systemic vasculitis remain at a higher risk for severe outcomes, these data indicate that some patients may not need to face similar restrictions in the future if other known risk factors are absent. Conversely, patients who are receiving background glucocorticoids or have comorbid respiratory disease should be closely monitored when presenting with COVID-19, since their risk of progression to a severe state appears to be higher (11). This study primarily describes a cohort of hospitalized patients and is thus more likely to reflect severe COVID-19 disease. Future work should seek to establish risk factors for severe disease in a wider population. Comparisons with controls who did not contract COVID-19 would allow for assessment of incidence and risk factors for contracting COVID-19.

Taken together with findings from other cohorts exposed to immunosuppressant medication, these data could inform future public health guidance for patients with autoimmune disease.

23265205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41728 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

These data were designed to be interoperable with other national data sets. Future work should seek to combine international efforts to allow for greater power to assess the factors that impact this potentially vulnerable group.

ACKNOWLEDGMENTS

The authors thank the following individuals who contributed data for this project: Jocelyn Berdeprado, Nina Brown, Chee Kay Cheung, Denise De Lord, Oliver Flossman, Venkat Gangaram, Sian Griffin, Alex Hamilton, Philip Ind, Vikki Jubb, Maria King, Sarah Logan, Alice Lorenzi, Ann Morgan, Dan Pugh, Ravindra Rajakariar, Saira Risdale, Michael Robson, Bhrigu Sood, Katie Vinen, and Zoe Wellbelove.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Rutherford had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Rutherford, Scott, Gray, Barrett, Brix, Dhaun, McAdoo, Jayne, Luqmani, Salama, Little, Basu.

Acquisition of data. Rutherford, Scott, Karabayas, Antonelou, Gray, Barrett, Brix, Dhaun, McAdoo, Geddes, Luqmani, Salama, Little, Basu.

Analysis and interpretation of data. Rutherford, Scott, Gopaluni, Brix, Dhaun, McAdoo, Smith, Geddes, Jayne, Luqmani, Salama, Little, Basu.

REFERENCES

1. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
2. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19–11 March 2020. URL: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
3. Neumann I. Immunosuppressive and glucocorticoid therapy for the treatment of ANCA-associated vasculitis [review]. Rheumatology (Oxford) 2020;59:iii60–7.
4. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puéchal X, Fujimoto S, et al. Plasma exchange and glucocorticoids in severe ANCA-associated vasculitis. N Engl J Med 2020;382:622–31.
5. Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, et al, for the RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021; 384:693–704.
6. Musen MA, Noy NF, Shah NH, Whetzel PL, Chute CG, Story MA, et al. The National Center for Biomedical Ontology. J Am Med Inform Assoc 2012;19:190–5.
7. COVID-19 Global Rheumatology Alliance. URL: https://rheum-covid.org/.
8. Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, et al. The FAIR Guiding Principles for scientific data management and stewardship. Sci Data 2016;3:160018.
9. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1–11.
10. Gianfrancesco M, Hyrich KL, Al-Adely S, Carmona L, Danila MI, Gossec L, et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis 2020;79:859–66.
11. The OpenSAFELY Collaborative, Williamson E, Walker AJ, Bhaskaran KJ, Bacon S, Bates C, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients [preprint]. medRxiv. May 2020. URL: https://doi.org/10.1101/2020.05.06.20092999.
12. Cain DW, Cidlowski JA. Immune regulation by glucocorticoids [reivew]. Nat Rev Immunol 2017;17:233–47.
13. Johnson RM, Vinetz JM. Dexamethasone in the management of covid-19 [editorial]. BMJ 2020;370:m2648.
14. Li S, Hu Z, Song X. High-dose but not low-dose corticosteroids potentially delay viral shedding of patients with COVID-19. Clin Infect Dis 2020 doi: https://doi.org/10.1093/cid/ciaa829. E-pub ahead of print.
15. Sanchez-Ramirez DC, Mackey D. Underlying respiratory diseases, specifically COPD, and smoking are associated with severe COVID-19 outcomes: a systematic review and meta-analysis. Respir Med 2020;171:106096.
16. Smith JC, Sausville EL, Girish V, Yuan ML, Vasudevan A, John KM, et al. Cigarette smoke exposure and inflammatory signaling increase the expression of the SARS-CoV-2 receptor ACE2 in the respiratory tract. Dev Cell 2020;53:514–29.
17. Landewé RB, Machado PM, Kroon F, Bijlsma HW, Burmester GR, Carmona L, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis 2020;79:851–8.
18. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ 2020;369:m1985.
19. Kitching AR, Anders HJ, Basu N, Brouwer E, Gordon J, Jayne DR, et al. ANCA-associated vasculitis [review]. Nat Rev Dis Primers 2020;6:71.
20. Pouletty M, Borocco C, Ouldali N, Caseris M, Basmaci R, Lachaume N, et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Ann Rheum Dis 2020;79:999–1006.
21. Basu N, McClean A, Harper L, Amft EN, Dhaun N, Luqmani RA, et al. The characterisation and determinants of quality of life in ANCA associated vasculitis. Ann Rheum Dis 2014;73:207–11.
22. Gov.UK Coronavirus (COVID-19) in the UK. URL: https://coronavirus.data.gov.uk/details/cases.

23565205, 2021, 9, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/art.41729 by Health Research Board, Wiley Online Library on [15/02/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

12.2 ANCA-associated vasculitis in Ireland: a multi-centre national cohort study (74, 75)

HRB Open Research

HRB Open Research 2022, 5:80 Last updated: 25 MAY 2023

Check for updates

RESEARCH ARTICLE

ANCA-associated vasculitis in Ireland: a multi-centre national cohort study [version 1; peer review: 2 approved]

Jennifer Scott[1], Eithne Nic an Ríogh[1], Shamma Al Nokhatha[1], Cliona Cowhig[2], Alyssa Verrelli[3], Ted Fitzgerald[1,2], Arthur White[4], Cathal Walsh[5], Louis Aslett[6], Declan DeFreitas[2], Michael R. Clarkson[3], John Holian[7], Matthew D. Griffin[8], Niall Conlon[9], Yvonne O'Meara[10], Liam Casserly[11], Eamonn Molloy[12], Julie Power[13], Sarah M. Moran[1,3*], Mark A. Little[1*]

[1]Trinity Health Kidney Centre, Trinity College Dublin, The University of Dublin, Dublin, D02 PN40, Ireland
[2]Department of Nephrology, Beaumont Hospital, Dublin, D09 V2N0, Ireland
[3]Department of Nephrology, Cork University Hospital, Cork, T12 DC4A, Ireland
[4]Department of Statistics, Trinity College Dublin, The University of Dublin, Dublin, D02 PN40, Ireland
[5]Department of Mathematics and Statistics, University of Limerick, Limerick, V94 T9PX, Ireland
[6]Department of Mathematical Sciences, Durham University, Durham, DH1 3LE, UK
[7]Department of Nephrology, St. Vincent's University Hospital, Dublin, D04 T6F4, Ireland
[8]Department of Nephrology, University Hospital Galway, Galway, H91 YR71, Ireland
[9]Department of Immunology, St. James's Hospital, Dublin, D08 NHY1, Ireland
[10]Department of Nephrology, Mater Misericordiae University Hospital, Dublin, D07 R2WY, Ireland
[11]Department of Nephrology, University Hospital Limerick, Limerick, V94 F858, Ireland
[12]Department of Rheumatology, St. Vincent's University Hospital, Dublin, D04 T6F4, Ireland
[13]Vasculitis Ireland Awareness, Dublin, Ireland

* Equal contributors

v1 **First published:** 01 Dec 2022, **5**:80
https://doi.org/10.12688/hrbopenres.13651.1
Latest published: 01 Dec 2022, **5**:80
https://doi.org/10.12688/hrbopenres.13651.1

Abstract

Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare multisystem autoimmune disease. There is a need for interoperable national registries to enable reporting of real-world long-term outcomes and their predictors in AAV.
Methods: The Irish National Rare Kidney Disease (RKD) registry was founded in 2012. To date, 842 patients with various forms of vasculitis have been recruited across eight nephrology, rheumatology and immunology centres. We focus here on patient- and disease-characteristics, treatment and outcomes of the 397 prospectively recruited patients with AAV.
Results: Median age was 64 years (IQR 55–73), 57.9% were male, 58.9% had microscopic polyangiitis and 85.9% had renal impairment. Cumulative one- and five-year patient survival was 94% and 77% respectively. Median follow-up was 33.5 months (IQR 10.7–52.7). After controlling for age, baseline renal dysfunction (p = 0.04) and the burden of adverse events (p <0.001) were independent predictors of

Open Peer Review

Approval Status ✓ ✓

	1	2
version 1 01 Dec 2022	✓ view	✓ view

1. **Y.K. Onno Teng**, Leiden University Medical Centre, Leiden, The Netherlands

2. **Jessica Ryan**, Monash Health, Melbourne, Australia

Any reports and responses or comments on the article can be found at the end of the article.

death overall. End-stage-kidney-disease (ESKD) occurred in 73 (18.4%) patients; one- and five-year renal survival was 85% and 79% respectively. Baseline severity of renal insufficiency (p = 0.02), urine soluble CD163 (usCD163) (p = 0.002) and "sclerotic" Berden histological class (p = 0.001) were key determinants of ESKD risk.
Conclusions: Long-term outcomes of Irish AAV patients are comparable to other reported series. Our results emphasise the need for personalisation of immunosuppression, to limit treatment toxicity, particularly in those with advanced age and renal insufficiency. Baseline usCD163 is a potential biomarker for ESKD prediction and should be validated in a large independent cohort.

Keywords
ANCA-associated vasculitis, registry, outcomes, death, end-stage-kidney-disease, urine soluble CD163 (usCD163)

Corresponding author: Mark A. Little (mlittle@tcd.ie)

Author roles: Scott J: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing; **Nic an Ríogh E**: Investigation, Writing – Review & Editing; **Al Nokhatha S**: Investigation, Writing – Review & Editing; **Cowhig C**: Investigation, Writing – Review & Editing; **Verrelli A**: Investigation, Writing – Review & Editing; **Fitzgerald T**: Investigation, Writing – Review & Editing; **White A**: Formal Analysis, Supervision, Writing – Review & Editing; **Walsh C**: Methodology, Supervision, Writing – Review & Editing; **Aslett L**: Methodology, Supervision, Writing – Review & Editing; **DeFreitas D**: Conceptualization, Investigation, Methodology, Project Administration, Writing – Review & Editing; **Clarkson MR**: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Holian J**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **Griffin MD**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **Conlon N**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **O'Meara Y**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **Casserly L**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **Molloy E**: Conceptualization, Investigation, Project Administration, Writing – Review & Editing; **Power J**: Conceptualization, Methodology, Project Administration, Writing – Review & Editing; **Moran SM**: Conceptualization, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing; **Little MA**: Conceptualization, Data Curation, Funding Acquisition, Investigation, Methodology, Project Administration, Supervision, Visualization, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: Health Research Board Ireland and Wellcome [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 supports the Irish Clinical Academic Training (ICAT) Programme, of which Dr Jennifer Scott is a Wellcome-HRB Irish Clinical Academic Training (ICAT) Fellow. 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.
The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2022 Scott J *et al*. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Scott J, Nic an Ríogh E, Al Nokhatha S *et al.* **ANCA-associated vasculitis in Ireland: a multi-centre national cohort study [version 1; peer review: awaiting peer review]** HRB Open Research 2022, **5**:80
https://doi.org/10.12688/hrbopenres.13651.1

First published: 01 Dec 2022, **5**:80 https://doi.org/10.12688/hrbopenres.13651.1

Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare multisystem autoimmune disease, characterised by necrotising pauci-immune small-vessel vasculitis. It comprises three clinico-pathological syndromes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The estimated overall annual incidence of AAV is 13–20 cases/million[1] with a prevalence of 300–421 cases per million[2].

Significant treatment advances have occurred over the past 70 years with the advent of corticosteroid use in the 1950s, followed by the addition of cyclophosphamide in the 1960s, resulting in an improvement in two-year survival from 20 to 80%[3]. The introduction of ANCA testing in the 1980s improved detection of AAV and augmented disease awareness. With the achievement of remission in the majority, accompanied by an improvement in immediate survival, focus has now shifted to examining long-term outcomes, influenced by both treatment and the disease itself. AAV still carries a 2.7-fold increased risk of death compared to the general population[4]. Immunosuppression used to induce and maintain remission is a double-edged sword with >80% experiencing adverse events[5]. Given the relapsing and remitting nature of AAV, short randomised controlled trials (RCTs) are unable to provide robust evidence on longer-term outcomes, such as long-term treatment safety and efficacy in the biologic era. Additionally, RCTs do not provide information on diverse populations who may not consent to inclusion in trials, such as those with very severe disease admitted to ICU at presentation, older patients, marginalised populations and pregnant women. This knowledge gap has prompted the development of longitudinal vasculitis registries, including at least eight in Europe[6]. Increasingly, patient registries, linked to biobanks, are being used to facilitate longitudinal cohort studies in rare diseases, with a recent European effort to ensure standardisation and interoperability, via initiatives from FAIRVASC and the European Vasculitis Society (EUVAS) registries group[6]. This will allow collaborative research using aggregated data to analyse critical outcomes at a larger scale with sufficient power.

The Irish Rare Kidney Disease (RKD) registry and biobank was created in collaboration with the Irish national vasculitis patient organisation (https://vasculitis-ia.org/) in 2012 with the aim of collating clinical data and bio-samples from patients with vasculitis, and from disease and healthy controls on a national level. Importantly, this registry included, from inception, input from patient advocates (Vasculitis Ireland Awareness), recruitment during acute hospital admissions (allowing for pre-treatment data and sampling) as well as the involvement of a range of specialists including nephrology, rheumatology and immunology, allowing recruitment of broader clinical phenotypes. The current study arose from a need to appraise current practice and outcomes in the real-world setting. It aims to describe the long-term outcomes and potential prognostic factors at presentation in this large multicentre prospectively recruited cohort of AAV patients in Ireland.

Methods

Study participants

(A) RKD registry. The Irish Rare Kidney Disease (RKD) registry and biobank was established in 2012, recruiting from eight clinical centres (Extended data: Supplementary Table 1)[7]. All patients >16 years of age with prevalent vasculitis were eligible for recruitment and diagnoses were assigned according to the 2012 Chapel Hill Consensus nomenclature[8]. Central ethical approval was granted by the Tallaght University Hospital/St. James's Hospital Joint Research Ethics Committee (reference 2019-08 List 29 (07)) on 30th August 2019, and locally by each study site, and all participants provided written informed consent. Central storage of anonymised registry data is hosted on a secure password-protected web application (REDCap: https://www.project-redcap.org/)[9,10].

(B) Prospective AAV cohort. In this paper we report in detail on participants with definite AAV defined by relevant clinical features of GPA, MPA or EGPA[8], with either positive anti-myeloperoxidase (MPO) or anti-proteinase 3 (PR3) serology[11] and/or diagnostic histopathology. Patients with secondary vasculitis or dual anti-glomerular basement membrane disease were excluded from this analysis[12]. Patients who were positive for both MPO- and PR3-ANCA (n = 5) were classified according to whichever titre was higher[13]. Analysis was restricted to only those diagnosed from 1st January 2012 onwards, to eliminate retrospective recruitment bias (Extended data: Supplementary Figure 1)[7].

Study assessments

The following data were collected prospectively: demographics, date of diagnosis and symptom onset, vasculitis characteristics (diagnostic subtype, organ involvement, ANCA specificity), treatment, histopathology, radiology, complications and follow-up clinical encounters (including disease activity assessed by the Birmingham Vasculitis Activity Score version 3 (BVAS v3)[14]), urinalysis, pertinent laboratory data and exploratory biomarkers. Encounters were usually recorded at three-monthly clinic intervals and at the time of relapse, with a targeted annual minimum. Urine soluble CD163 (usCD163) was measured if clinically indicated in a central clinical laboratory using an accredited ELISA (Euroimmun, GMBH). The observation period was from the date of diagnosis to the occurrence of the event of interest (end-stage kidney disease (ESKD), death or last follow-up). Data collection is in agreement with the core dataset and interoperability principles outlined by EUVAS[6].

Definitions

The degree of certainty in the AAV diagnosis was estimated using a novel pragmatic diagnosis confidence matrix (Extended data: Supplementary Figure 2)[7]; only participants with a "definite" diagnosis were included in the prospective AAV cohort. ESKD was defined by a consensus EUVAS decision as the commencement of renal replacement therapy for at least 90 days (or death within 90 days), sustained estimated glomerular filtration rate <15ml/min and/or renal transplantation. The estimated glomerular filtration rate (eGFR, ml/min/1.73m^2) was calculated using the CKD-EPI formula.

The 'combined burden of events' (CBOE) score is a representative summary variable to describe cumulative adverse events based on the Common Terminology Criteria for Adverse Events (CTCAE) and sub-categorised into "infection", "leucopenia" and "other", each rated on a score of 1–4 based on severity[5].

Statistical analysis

Primary outcomes were time to ESKD and time to death. A composite of time to ESKD or death and factors associated with the occurrence of adverse events were also investigated. Continuous variables are reported as mean (standard deviation, SD) or median (interquartile range, IQR, if not normally distributed), and compared using the independent sample t-test or Mann-Whitney U test, respectively. Categorical variables are summarised by frequency and percentage (%) and compared using the chi-square test. Imputation was performed, using the *mice* R package (Version 3.13.0)[15], to estimate missing (9.1%) eGFR values[16]. Survival probability was determined using Kaplan-Meier survival analysis. Analyses were censored for death or last follow-up and considered, firstly, the events only within the first year and, secondly, the events over the entire period of observation. Between group comparisons were performed using the log-rank test. Uni- and multivariate Cox regression analyses were performed separately to investigate predictors of mortality, ESKD, and the composite of ESKD/death. A backward stepwise method, in conjunction with a priori knowledge of significant confounders, was used to identify the final independent risk factors in the adjusted models. Potential confounders included both patient- and disease- characteristics: age and eGFR at diagnosis, sex, AAV phenotype, ANCA serology, organ involvement and CBOE score (or its components). Diagnosis BVAS was excluded from models due to its degree of missingness (28.5%). "Renal involvement" as a binary variable was also excluded due to strong correlation with diagnosis eGFR. The '*surv_cutpoint*' function of the *survminer* R package (Version 0.4.9)[17] was used to identify the optimal binary cut-point for continuous predictors of importance, based on the maximally selected log-rank statistic[18]. Cox proportional hazard ratios (HR) with 95% confidence intervals (95% CI) are reported, after evaluating the weighted and scaled Schoenfeld residuals to ensure the proportional hazards assumption was met. We performed multivariate logistic regression to identify key predictors of a CBOE score >8. Gender, AAV phenotype and induction treatment were included in this analysis as fixed factors, while diagnosis age and eGFR were continuous covariates. A two-tailed P value <0.05 was considered statistically significant. All statistical analyses were performed using R (Version 4.0.4). All survival analyses were performed using the *survival* R package (Version 3.2-11)[19].

Results

Participant characteristics

(A) RKD registry. As of 31st May 2021, 842 unique patients with vasculitis were recruited (Extended data: Supplementary Table 2)[7]. Most were Caucasian (97.7%) with a median diagnosis age of 59 years (IQR 48–69) and a male: female ratio of 1.2: 1. The commonest diagnosis was AAV (82.3%). A total of 644 (76.5%) underwent diagnostic biopsy, of which 532 (63.2% of all cases) showed definitive vasculitis. According to a diagnosis confidence matrix (Extended data: Supplementary Figure 2)[7], 750 (89.1%), 47 (5.6%) and 45 (5.3%) had a definite, possible and probable diagnosis confidence, respectively.

(B) Prospective AAV cohort. Of the 612 patients with a definite AAV diagnosis, 397 were prospectively recruited from 2012 onwards (Extended data: Supplementary Figure 1)[7]; median age at diagnosis was 64 years (IQR 55–73) and 230 (57.9%) were male. The most observed phenotype was MPA (58.9%) and most (341, 85.9%) had renal involvement. Median baseline eGFR was 28 ml/min/1.73m^2 (IQR 13–62). Median duration from symptom onset to diagnosis was 9.4 weeks (IQR 4.3–25.6) and follow-up continued for a median of 33.5 months (IQR 10.7–52.7). Complete patient- and disease-characteristics, including induction and maintenance treatment, are detailed in Table 1 and Extended data: Supplementary Table 3[7].

Patient survival in the first year from diagnosis (prospective AAV cohort)

In the first-year post diagnosis, twenty-two (5.5%) patients died, and actuarial survival was 93.8% (95% CI 91.3–96.3, Figure 1a). Infection was the leading cause of death (45.5%), followed by active vasculitis (18.2%, Extended data: Supplementary Table 4[7]). Age, degree of renal impairment at diagnosis, weighted infection and leucopenia adverse event scores, and cardiovascular involvement were independent predictors of one-year mortality on multivariate analysis (Table 2). An eGFR cut-off of <20ml/min/1.73m^2 identified those at highest risk of one-year mortality (Figure 1b)[18]. As the CBOE score rose, mortality increased. The optimal CBOE score (Extended data: Supplementary Figure 3)[7] mortality cut-off was >8 (Extended data: Supplementary Figure 4)[7], which was associated with a one-year survival probability of 55.9% (41.0–76.2) compared to 97.5% (95.8–99.2) for those with a score ≤8 (Figure 1c). Renal dysfunction severity was an independent risk factor for a CBOE score >8 (Table 3).

Overall patient survival (prospective AAV cohort)

During the study period 55 patients (13.9%) died. Two- and five-year patient survival was 90.7% (87.7–93.9) and 76.8% (70.8–83.3), respectively (Figure 2a). Figure 2b and Extended data: Supplementary Table 5[7] summarise the factors associated with overall mortality. After controlling for age and other potential confounders, only eGFR at diagnosis and CBOE score were independently significantly associated with mortality. The CBOE mortality association was primarily driven by the cumulative infection score.

Renal survival (prospective AAV cohort)

End-stage kidney disease (ESKD) developed in 73 patients (18.4%). 1-, 2- and 5-year actuarial renal survival was 85.1% (81.5–88.8), 83.3% (79.6–87.3) and 79.2% (74.4–84.4), respectively (Figure 3a). ESKD-free patient survival at 1-, 2-,

Table 1. Baseline characteristics of the AAV cohort. Diagnosed with 'definite' AAV from 1st January 2012 onwards and recruited to the RKD registry before 31st May 2021. 'Other' Induction treatment includes AZA, MMF, MTX or GCC only. 'Other' Maintenance treatment includes: 1 <= of AZA, MMF, MTX, Tacrolimus, Ciclosporin, Cyclophosphamide, Mepolizumab, Ustekinumab, Hydroxychloroquine, Belimumab or unknown maintenance therapy. See Extended data: Supplementary Table 3 for further details on maintenance RTX group. Missing data: Induction treatment N = 6. AAV = ANCA associated vasculitis, eGFR = estimated Glomerular Filtration Rate (CKD-EPI), BVAS = Birmingham Vasculitis Activity Score, CYC = Cyclophosphamide, RTX = Rituximab, AZA = Azathioprine, MMF = Mycophenolate mofetil, GCC = Glucocorticoids. VINE = Vasculitis Ireland Network. IQR = interquartile range; SD = Standard deviation

Variable	Results
n	397
Age at diagnosis (years, median (IQR))	64 [55, 73]
Male (N (%))	230 (57.9)
Ethnicity* (N (%))	
White	392 (98.7)
Asian	5 (1.3)
AAV Phenotype (N (%))	
Granulomatosis with polyangiitis (GPA)	149 (37.5)
Microscopic polyangiitis (MPA)	234 (58.9)
Eosinophilic granulomatosis with polyangiitis (EGPA)	14 (3.5)
ANCA Serotype (N (%))	
Myeloperoxidase	214 (53.9)
Proteinase-3	172 (43.3)
ELISA negative	10 (2.5)
No ELISA performed	1 (0.3)
Organ involvement (N (%))	
Kidney	341 (85.9)
Lung	199 (50.1)
Musculoskeletal	137 (34.5)
Ear, Nose and Throat (ENT)	134 (33.8)
Mucocutaneous	71 (17.9)
Nervous	46 (11.6)
Gastrointestinal	17 (4.3)
Cardiovascular	11 (2.8)
eGFR at diagnosis (ml/min/1.73 m^2, median (IQR))	28.00 [13.00, 62.00]
Induction treatment (N (%))	
Cyclophosphamide	200 (51.2)
Rituximab	104 (26.6)
Cyclophosphamide & rituximab	28 (7.2)
Other	59 (15.1)

Variable	Results
Maintenance treatment (N (%))	
Azathioprine	141 (35.5)
Rituximab +/- 1<= agent(s)	80 (20.2)
MMF	26 (6.5)
Glucocorticoids only	31 (7.8)
Other	78 (19.6)
Non	41 (10.3)
End-stage kidney disease *(N (%))*	73 (18.4)
Major relapse (^{3}1) *(N (%))*	39 (9.8)
Death at any time *(N (%))*	55 (13.9)
Death within the 1st year from diagnosis *(N (%))*	22 (5.5)
Follow-up period (months, median (IQR))	33.5 [10.7, 52.7]
VINE Site *(N (%))*	258 (65.0)

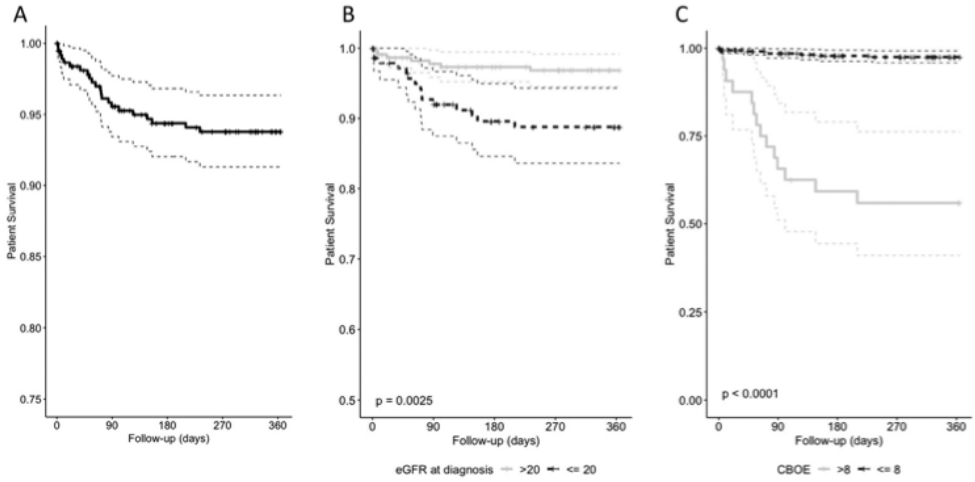


Figure 1. Factors associated with one-year mortality on univariate Kaplan-Meier analysis and compared using the log-rank test. Optimal cut-points were obtained for each factor using the survminer package in R studio. one-year mortality **a**). overall and by **b**). estimated Glomerular Filtration Rate (CKD-EPI, eGFR) <= / >20 ml/min/1.73 m2, and **c**). Combined Burden of Events score (CBOE) <=/>8.

and 5-years was 80.6% (76.6–84.7), 77.7% (73.5–82.1) and 63.9% (57.9–70.5), respectively (Figure 3b). At initial presentation 84 (21.1%) required renal replacement therapy, of whom 37 (44.4%) subsequently became dialysis independent. Of those who had renal involvement (86%), the median eGFR at diagnosis was 22 ml/min (IQR 11–42, Extended data: Supplementary Figure 5)[7]. Factors independently associated with ESKD risk included degree of renal impairment and having >50% globally sclerosed glomeruli on kidney biopsy (Table 4, model 2). usCD163 was measured at diagnosis in a subgroup of 103 patients, in whom usCD163 was tightly associated with ESKD, even after adjustment for eGFR

Table 2. Uni- and Multivariate Cox Proportional Hazards Models to investigate the factors associated with mortality within the first year from diagnosis. Multivariate analysis was performed using backwards elimination. There was no co-linearity (>0.7) observed between the predictive factors. AAV = ANCA associated vasculitis, GPA = granulomatosis with polyangiitis, PR3 = Proteinase-3 ANCA, eGFR = estimated Glomerular Filtration Rate (CKD-EPI), ml/min/1.73 m2, BVAS = Birmingham Vasculitis Activity Score, CYC = Cyclophosphamide, RTX = Rituximab, ENT = Ear, Nose and Throat, 95% CI = 95% Confidence Interval

	Univariate		Multivariate	
Explanatory variable	**Hazard ratio (95% CI)**	**p Value**	**Hazard ratio (95% CI)**	**p Value**
Age at diagnosis, years	1.09 (1.05–1.14)	<0.001	1.07 (1.02–1.12)	**0.009**
Female (Ref: Male)	1.79 (0.77–4.14)	0.174		
AAV Phenotype: Not GPA (Ref: GPA)	1.27 (0.52–3.10)	0.607		
ANCA: Not PR3 (Ref: PR3-ANCA)	1.67 (0.68–4.10)	0.262		
Induction treatment (Ref: CYC)				
RTX	1.42 (0.51–3.99)	0.506		
CYC & RTX	1.56 (0.34–7.20)	0.571		
Other	2.30 (0.77–6.86)	0.136		
eGFR at diagnosis	0.97 (0.95–0.99)	0.013	0.97 (0.94–0.99)	**0.026**
Weighted infection burden score	1.16 (1.11–1.21)	<0.001	1.11 (1.05–1.18)	**<0.001**
Weighted leucopenia burden score	1.37 (1.21–1.54)	<0.001	1.27 (1.11–1.44)	**<0.001**
Weighted adverse event (other) burden score	1.11 (1.07–1.15)	<0.001	1.05 (1.00–1.11)	0.07
Organ Involvement				
Lung	2.16 (0.88–5.31)	0.092		
Nervous	0.85 (0.20–3.65)	0.832		
ENT	0.71 (0.28–1.81)	0.474		
Cardiovascular	3.55 (0.83–15.18)	0.088	20.71 (3.84–111.81)	**<0.001**
Observations	397		395	
Concordance			0.91	

Table 3. Multivariate logistic regression to identify factors associated with a combined burden of adverse events (CBOE) score greater than 8, within the first year from diagnosis. There was no co-linearity (>0.7) observed between the predictive factors. N = 390 as one participant had missing age and six were missing induction treatment data. AAV = ANCA associated vasculitis, GPA = granulomatosis with polyangiitis, eGFR = estimated Glomerular Filtration Rate (CKD-EPI), ml/min/1.73 m2, 95% CI = 95% Confidence Interval

Explanatory variable	**Odds ratio (95% CI)**	**p Value**
Age at diagnosis, years	1.03 (1.00–1.06)	0.065
Female (Ref: Male)	1.10 (0.55–2.21)	0.78
AAV Phenotype: Not GPA (Ref: GPA)	0.95 (0.45–2.15)	0.90
eGFR at diagnosis	0.98 (0.96–0.99)	**0.01**

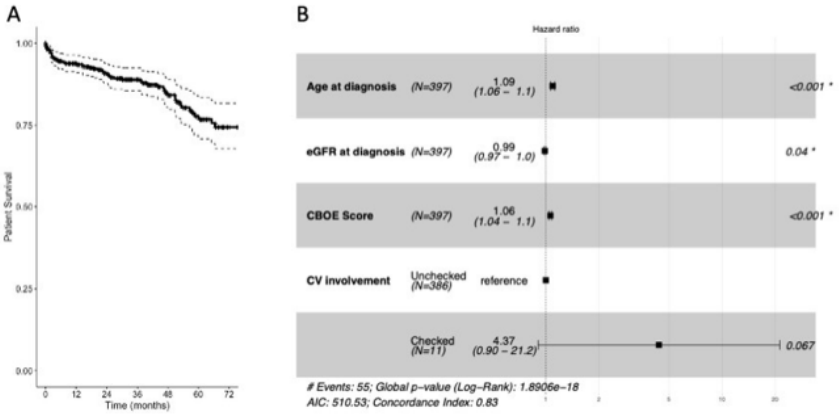


Figure 2. **a**). Kaplan-Meier curve demonstrating overall patient survival (solid line) with 95% CI (dashed lines), **b**). Forrest plot depicting the findings of a multivariate Cox Proportional Hazards Model to investigate the factors associated with overall mortality.

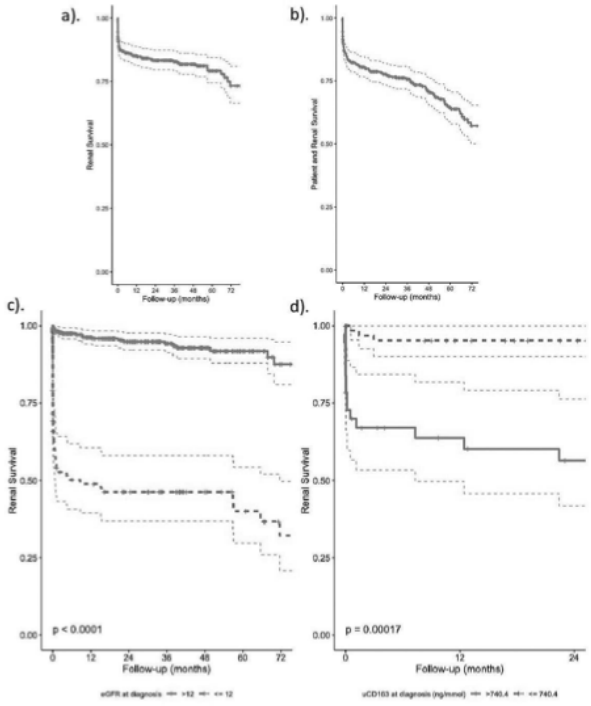


Figure 3. Factors associated with end-stage kidney disease (ESKD) on univariate Kaplan-Meier analysis and compared using the log-rank test. Optimal cut-points were obtained using the survminer package in R. **a**). Overall renal survival, **b**). ESKD-free patient survival, and renal survival stratified by **c**). estimated Glomerular Filtration Rate (CKD-EPI, eGFR) at diagnosis of <= / >12 ml/min/1.73 m2 and **d**). urine soluble CD163 at diagnosis (usCD163) of <= / >740.4 ng/mmol.

Table 4. Uni- and Multivariate Cox Proportional Hazards Models to investigate the factors associated with end-stage kidney disease. [a]Model 1 included baseline eGFR, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and the occurrence of a renal relapse (N = 397). [b]Model 2 included baseline eGFR, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and Berden score on diagnostic renal biopsy (N = 244 as 153 participants did not have biopsy data). [c]Model 3 included baseline uCD163, adjusted for baseline eGFR, age at diagnosis, gender, AAV phenotype and ANCA serotype (N = 103 as 294 participants did not have baseline uCD163 data). There was no co-linearity (>0.7) observed between the predictive factors included in the multivariate models. *Missing data: uCD163 N = 294, Berden score N = 153. AAV = ANCA associated vasculitis, GPA = granulomatosis with polyangiitis, PR3 = Proteinase-3 ANCA, eGFR = estimated Glomerular Filtration Rate (CKD-EPI), ml/min/1.73 m2, BVAS = Birmingham Vasculitis Activity Score, RRT = Renal Replacement Therapy, 95% CI = 95% Confidence Interval.

	Hazard ratio (95% CI, p Value)			
	Univariate		Multivariate	
Explanatory variable		**Model 1[a]**	**Model 2[b]**	**Model 3[c]**
Age at diagnosis, years	1.02 (1.00–1.04, p=0.054)	0.996 (0.98–1.02, p=0.708)	0.996 (0.97–1.02, p=0.709)	1.01 (0.98–1.05, p=0.498)
Female (Ref: Male)	0.68 (0.42–1.11, p=0.126)	0.66 (0.40–1.10, p=0.110)	0.65 (0.37–1.15, p=0.141)	0.17 (0.05–0.62, **p=0.007**)
AAV Phenotype: Not GPA (Ref: GPA)	2.78 (1.55–4.98, p=0.001)	1.34 (0.62–2.91, p=0.456)	0.94 (0.41–2.14, p=0.885)	1.28 (0.30–5.38, p=0.739)
ANCA: Not PR3 (Ref: PR3-ANCA)	1.87 (1.13–3.09, p=0.014)	0.86 (0.45–1.64, p=0.654)	0.69 (0.35–1.35, p=0.275)	2.09 (0.58–7.57, p=0.263)
eGFR at diagnosis	0.92 (0.89–0.94, p<0.001)	0.92 (0.89–0.94, **p<0.001**)	0.93 (0.90–0.96, **p<0.001**)	0.97 (0.94–0.995, **p=0.02**)
Required RRT at initial presentation	13.26 (8.01–21.96, p<0.001)	-	-	-
Renal relapse	0.74 (0.30–1.84, p=0.518)	0.57 (0.23–1.42, P=0.225)	-	-
Berden score on diagnostic renal biopsy (Ref: Focal)				
Crescentic	3.10 (1.16–8.32, p=0.024)	-	0.80 (0.27–2.36, p=0.683)	-
Mixed	3.62 (1.42–9.19, p=0.007)	-	2.13 (0.95–4.79, p=0.275)	-
Sclerotic	12.14 (4.93–29.86, p<0.001)		5.76 (2.61–12.71, **p=0.001**)	-
uCD163 at diagnosis (µg/mmol)	1.37 (1.13–1.68, p=0.002)	-	-	1.76 (1.24–2.50, **p=0.002**)
Observations	397*	397	244	103
Concordance		0.87	0.84	0.80

(Table 4, model 3). The optimal diagnosis eGFR and usCD163 cut-points which maximally split the cohort into low and high-risk groups of ESKD were 12ml/min/1.73m^2 and 740ng/mmol respectively (Figure 3c–d and Extended data: Supplementary Figure 6a–b)[7]. Patients with a 'high' (>740 ng/mmol) baseline usCD163 concentration were over five times more likely to develop ESKD, after adjusting for key confounders (Extended data: Supplementary Figure 7)[7].

Discussion

We describe the Rare Kidney Disease (RKD) national Irish registry at the 10th anniversary of its inception. This multicentre longitudinal cohort study aimed to characterise the Irish AAV cohort, describe their long-term outcomes and identify baseline predictors of these outcomes. The cohort comprises an ethnically homogeneous Caucasian population, with most displaying renal involvement and hence a slight MPA and MPO-ANCA predominance was observed. This contrasts to the GPA preponderance[20–23] in most other European registries, which tend to have lower rates of renal involvement. Our cohort were typically older, in agreement with recent studies showing an older age at diagnosis for those with MPA[21,24,25]. We noted a slight male preponderance, consistent with a prior meta-analysis of EUVAS RCTs[22], which differs

from the equal gender split most commonly reported[2,20,21,23]). Notably, the diagnostic delay (median 9.4 weeks, IQR 4.3–25.6, N = 238) in our cohort was somewhat shorter than other reported series (median range 12–52 weeks[21,26–29]).

Patient survival in our real-world cohort was comparable to the international literature, predominantly based on RCTs, which ranges from 80–97%, 80–85% and 70–80% for one, two and five years respectively[2,5,22,26,30,31]). One may have expected lower rates given our relatively older cohort with frequent renal insufficiency. We too noted a steep decline in survival in the initial 90 days, when maximal concomitant disease activity and immunosuppression occurs. Infection was the primary cause of death, consistent with previous reports[5,22,26,32,33]). Multiple studies have demonstrated an inverse relationship between survival and the number of accrued infections, particularly in the first year[31,34]). In our study, the weighted infection and leucopenia scores, reflecting the accumulation of these adverse events, were the strongest predictors of one-year mortality. This highlights the growing need for personalisation of immunosuppression to simultaneously achieve disease control while avoiding unnecessary excess immunosuppression, in addition to steroid-sparing, borne out by the PEXIVAS trial[35]. It also serves as a key reminder to clinicians to be alert to early infections and to routinely assess the need for infection prophylaxis against *Pneumocystis jirovecii* (PCP), fungi and viruses, as well as timely influenza, pneumococcal, hepatitis B virus and SARS-CoV-2 vaccination, as advised in guidelines[36]. Notably, only one patient died from PCP in our cohort, which may signify the success of trimethoprim/sulfamethoxazole prophylaxis, which is cost-effective in AAV[37].

Our study supports the previously observed association between increasing age, impaired kidney function and early mortality[5,20,21,30,33,38–41]). While most studies have previously attributed this to excess severe infection[21,31,32,42,43], we observed that advanced age and renal dysfunction are independent predictors, *after* adjustment for adverse events. Renal impairment results in immune dysfunction[44] and altered pharmacokinetics, limiting drug clearance and hence increasing the risk of infection and treatment toxicity[45]. Our findings further support the use of dosing nomograms for cyclophosphamide based on age and eGFR to reduce treatment-induced leucopenia, thereby reducing mortality[32,45]. Future prospective research should explore whether a similar approach is necessary for rituximab, rather than the current fixed or weight-based dosing regimens.

Our study validates the use of the combined burden of events (CBOE) score[5], to predict early mortality in an independent real-world cohort. Building on the initial description, we identified 8 as an optimal cut-off score to stratify patients into low/high risk of early death. Like the original description, a score ≤8 was associated with <5% risk of death within the first year. This risk rose 16-fold with a score >8. Analogous to scoring BVAS and Vasculitis Damage Index (VDI) during routine follow-up, clinicians should consider monitoring the cumulative CBOE score. A rising score warrants active assessment and implementation of strategies to reduce further toxicity. We also confirmed that renal dysfunction severity is the strongest independent risk factor of the CBOE score, underpinning the critical importance of accounting for kidney function when prescribing immunosuppression[5]. We found no statistical difference in the risk of a high CBOE score between the cyclophosphamide and rituximab groups, in keeping with the findings of the RAVE trial[46]. Our findings emphasise that no induction regime is 'safe' and future research should focus on developing remission induction strategies that minimise toxicity, while maintaining similar efficacy.

Reported renal survival in AAV is variable, largely related to differing baseline patient and disease characteristics across cohorts. Our one-, two- and five-year renal survival estimates of 85.1%, 83.3% and 79.2% respectively are in line with other series[26,31,47–50]): 20–40% of AAV patients reach ESKD by 5–7 years. Aligned with our relatively short diagnostic delay, the baseline renal function (median eGFR 22 ml/min 1.73m^2) in those with renal involvement was comparable to international benchmarks (median eGFR range 12–25 ml/min/1.73m^2)[51,52]. Our results confirm the importance of baseline renal dysfunction[26,31,32,47,49,53] and of histological evidence of renal scarring[54] in determining ESKD risk. Contrary to prior series, we did not find an association between ANCA serotype[50] or prior relapse[47] and ESKD, in multivariate analysis. Our group has recently demonstrated the benefit of usCD163, a glomerular macrophage marker, as a non-invasive tool for the diagnosis of AAV renal relapse[55]. Another group highlighted its use in the prediction of doubling of serum creatinine in lupus nephritis[56]. We demonstrate, for the first time, the potential use of baseline usCD163 in predicting ESKD at diagnosis, even after adjustment for renal insufficiency. We identified a cut-off of 740ng/mmol to stratify patients into low/high risk groups. The risk of ESKD was five-times higher for participants with a baseline usCD163 of >740.4ng/mmol compared with those below this cut-point. Once validated in independent cohorts, these findings will contribute to the personalisation of immunosuppression to minimise ESKD risk – a costly outcome to patients and society.

The main strengths of our study include the well-characterised national AAV cohort, recruited using uniform classification criteria. Our cohort does not exclude patients with severe disease, EGPA nor older people – commonly excluded in RCTs – and thus serves as a source of real-world data, which is important as outcomes differ to those reported from RCTs[57]. The use of REDCap as the registry infrastructure, with standardised interoperable 'instruments' to enable uniform data collection is another key strength. Our registry formed the basis of the model EUVAS registry which is being applied in nascent vasculitis registries across Europe. This capability is in line with both the EUVAS[6] and European Reference Network initiatives (http://rita.ern-net.eu/about-rita/mission-goals-and-objectives/) to align and integrate European registries, with the aim of improving both care and outcomes in rare disease.

We also acknowledge the limitations of our study. As with any observational research, missing data is always a challenge. For this reason, we were unable to include BVAS in multivariate models. Although all relevant specialties were represented, most participants were recruited through nephrology centres, reflected in the high degree of renal involvement, which limits the generalisability of our findings to non-renal populations. The strengths and limitations of CBOE score were previously discussed in detail[5]. Additionally, the CBOE score was not adjusted for prophylaxis use. Induction treatment was included as a categorical variable – the variation in intensity of same (denoted by cumulative dosing) was not available. Going forward, we aim to capture the intensity of induction immunosuppression in our registry.

Conclusions

In conclusion, we demonstrated that long-term outcomes from a real-world Irish cohort are similar to international standards. Our results highlight that despite improvement in outcomes over the last number of decades, treatment toxicity is an ongoing concern and individualisation of immunosuppression relative to disease severity and relapse risk remains a key unmet need. Our findings serve to remind clinicians that the accumulation of adverse events, both in the first year and beyond, particularly in older patients and those with renal insufficiency, is strongly associated with premature death and should be accompanied by increased monitoring and adjustment of immunosuppression to further limit treatment-related morbidity. The degree of renal impairment at presentation is also a key determinant in renal survival, hence early identification remains a critical goal. Baseline usCD163 shows promise as a biomarker for ESKD prediction. Future research should further explore this in the context of a multi-modal approach to personalisation of AAV treatment.

Consent

Written informed consent for publication of the patients' details was obtained from the patients.

Data availability

Underlying data

While the underlying patient data is pseudonymised, due to the rarity of ANCA-associated vasculitis, coupled with the identifiable nature of the data included in our analyses, it is not possible in practice to fully anonymise the dataset. Individuals could potentially be re-identified quite easily. Therefore, raw data must remain confidential and cannot be freely shared on an open platform. We would invite any potential research collaborations or data requests through the corresponding author, Professor Mark Little (mlittle@tcd.ie), on reasonable request, as agreed by participants in their written informed consent (detailed on page 3: https://www.tcd.ie/medicine/thkc/assets/pdf/RKD-Vasculitis-Patient-PIL-ICF-Version-5-07AUG19.pdf). Requests will be considered on a case-by-case basis. This approach is endorsed in a recent publication in The Lancet, from another large Irish longitudinal cohort study, TILDA[58].

Extended data

Zenodo: Extended data for 'ANCA-associated vasculitis in Ireland: a multi-centre national cohort study'. https://doi.org/10.5281/zenodo.7342934[7]

This project contains the following extended data:

- Supplementary Table 1: Rare Kidney Disease Registry and Biobank recruitment sites.
- Supplementary Table 2: Baseline characteristics of all vasculitis patients (recruited prior to 31st May 2021).
- Supplementary Table 3: Breakdown of additional agents used for those patients receiving maintenance rituximab (n=80).
- Supplementary Table 4: Causes of death within the first year of observation in the AAV cohort diagnosed since 2012.
- Supplementary Table 5: Uni- and Multivariate Cox Proportional Hazards Models to investigate the factors associated with overall mortality.
- Supplementary Figure 1: Inclusion and exclusion criteria for the AAV patients included in the analysis of long-term outcomes.
- Supplementary Figure 2: Diagnosis confidence matrix.
- Supplementary Figure 3: Frequency and distribution of Combined Burden of Events (CBOE) score within the first year from diagnosis.
- Supplementary figure 4: Impact of the Combined Burden Of adverse Events (CBOE) on mortality.
- Supplementary Figure 5: Distribution of eGFR at diagnosis (ml/min/1.73/m2) in those with renal involvement: overall and stratified by VINE status.
- Supplementary Figure 6: Optimal cut-points of a). 12 ml/min/1.73m2 for eGFR at diagnosis and b). 740.4 ng/mmol for usCD163 at diagnosis were determined, using the *survminer* package in R to categorize patients into low and high risk of ESKD.
- Supplementary Figure 7: Forrest plot depicting the findings of a multivariate Cox Proportional Hazards Model to investigate the factors associated with end-stage kidney disease. usCD163 is included as a binary factor according to the optimal cut-point, leading to slightly different hazard ratios compared to Table 4.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0)

Acknowledgements

The authors would like to thank all participants who are enrolled in the Irish Rare Kidney Disease and Biobank, without whom this research would not be possible. We would also like to acknowledge the support of the clinicians, nurses and

coordinators in the Vasculitis Ireland network (VINE) (https://www.tcd.ie/medicine/thkc/vasculitis/), as well as all consultant and trainee nephrologists in Ireland who are integral to ongoing recruitment to the registry. We also acknowledge the contribution of the scientists in the Trinity Health Research Group Laboratory, including Emma Leacy, Aisling Ui Mhaonaigh and Amrita Dwivedi, who are fundamental to the processing of research samples.

Members of the RKD consortium:

Tallaght Hospital: Mark Little*, Peter Lavin**, Catherine Wall**, George Mellotte**, Ronan Mullan**, Jennifer Scott**, Ted Fitzgerald**, Hannah O'Keefe**, Rachel Dilworth**, Claire Kennedy**, Limy Wong**, Eithne Nic an Ríogh**, Pamela O'Neill#, Vicki Carr#

St James' Hospital: Niall Conlon*, Brenda Griffin*, Donal Sexton*, Caroline Kosgei#

Mater University Hospital: Yvonne O'Meara*, Eoghan White**, Stephen Mahony**

St Vincent's University Hospital: Eamonn Molloy*, John Holian**

Galway University Hospital: Matt Griffin*, David Lappin**, Conor Judge**, Sarah Cormican**, Blathnaid O'Connell**, Michelle Clince**

Limerick University Hospital: Liam Casserly*

Cork University Hospital: Michael Clarkson*, Michelle O'Shaughnessy**, Alyssa Verrelli**, Sinead Stoneman**, Fergus Daly**, Laura Slattery**, Aisling Murphy#

Beaumont Hospital: Mark Little*, Declan De Freitas**, Peter Conlon**, Mark Denton**, Carol Treanor**, Colm Magee**, Conall O Seaghdha**, Paul O'Hara**, Susan McGrath**, Brona Moloney**, Dean Moore**, Dearbhla Kelly**, Mary McCarthy**, Tamara Wanigasekera**, Ayanfeoluwa Obilana** Dervla Connaughton**

*Principal Investigator; **Co-investigator; #Study Coordinator

References

1. Watts RA, Mahr A, Mohammad AJ, *et al.*: **Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.** *Nephrol Dial Transplant.* 2015; **30**(Suppl 1): i14–i22.
PubMed Abstract | Publisher Full Text
2. Kitching AR, Anders HJ, Basu N, *et al.*: **ANCA-associated vasculitis.** *Nat Rev Dis Primers.* 2020; **6**(1): 71.
PubMed Abstract | Publisher Full Text
3. Fauci AS, Haynes BF, Katz P, *et al.*: **Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years.** *Ann Intern Med.* 1983; **98**(1): 76–85.
PubMed Abstract | Publisher Full Text
4. Tan JA, Dehghan N, Chen W, *et al.*: **Mortality in ANCA-associated vasculitis: ameta-analysis of observational studies.** *Ann Rheum Dis.* 2017; **76**(9): 1566–74.
PubMed Abstract | Publisher Full Text
5. Little MA, Nightingale P, Verburgh CA, *et al.*: **Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis.** *Ann Rheum Dis.* 2010; **69**(6): 1036–43.
PubMed Abstract | Publisher Full Text
6. Bajema IM, Bruijn JA, Casian A, *et al.*: **The European Vasculitis Society 2016 Meeting Report.** *Kidney Int Rep.* 2017; **2**(6): 1018–31.
PubMed Abstract | Publisher Full Text | Free Full Text
7. Scott J, Nic an Ríogh E, Al Nokhatha S, *et al.*: **Extended data for 'ANCA-associated vasculitis in Ireland: a multi-centre national cohort study'.** Zenodo. [Dataset]. 2022.
http://www.doi.org/10.5281/zenodo.7342934
8. Jennette JC, Falk RJ, Bacon PA, *et al.*: **2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.** *Arthritis Rheum.* 2012; **65**(1): 1–11.
PubMed Abstract | Publisher Full Text
9. Harris PA, Taylor R, Minor BL, *et al.*: **The REDCap consortium: Building an international community of software platform partners.** *J Biomed Inform.* 2019; **95**: 103208.
PubMed Abstract | Publisher Full Text | Free Full Text
10. Harris PA, Taylor R, Thielke R, *et al.*: **Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support.** *J Biomed Inform.* 2009; **42**(2): 377–81.
PubMed Abstract | Publisher Full Text | Free Full Text
11. Bossuyt X, Cohen Tervaert JW, Arimura Y, *et al.*: **Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis.** *Nat Rev Rheumatol.* 2017; **13**(11): 683–92.
PubMed Abstract | Publisher Full Text
12. Watts R, Lane S, Hanslik T, *et al.*: **Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies.** *Ann Rheum Dis.* 2007; **66**(2): 222–7.
PubMed Abstract | Publisher Full Text | Free Full Text
13. Weiner M, Bjørneklett R, Hrušková Z, *et al.*: **Proteinase-3 and myeloperoxidase serotype in relation to demographic factors and geographic distribution in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis.** *Nephrol Dial Transplant.* 2019; **34**(2): 301–8.
PubMed Abstract | Publisher Full Text | Free Full Text
14. Mukhtyar C, Lee R, Brown D, *et al.*: **Modification and validation of the Birmingham Vasculitis Activity Score (version 3).** *Ann Rheum Dis.* 2009; **68**(12): 1827–32.
PubMed Abstract | Publisher Full Text
15. van Buuren S, Groothuis-Oudshoorn K: **mice: Multivariate Imputation by Chained Equations in R.** 2011; **45**(3): 67.
Publisher Full Text
16. Schemper M, Smith TL: **Efficient evaluation of treatment effects in the presence of missing covariate values.** *Stat Med.* 1990; **9**(7): 777–84.
PubMed Abstract | Publisher Full Text
17. Alboukadel Kassambara MK, Biecek P, Fabian S: **survminer: Drawing Survival Curves using 'ggplot2'.** 2021; [Version 0.4.9].
Reference Source
18. Wright MN, Dankowski T, Ziegler A: **Unbiased split variable selection for random survival forests using maximally selected rank statistics.** *Stat Med.* 2017; **36**(8): 1272–84.
PubMed Abstract | Publisher Full Text
19. Therneau TM: **A Package for Survival Analysis in R.** 2021; [R package version 3.2-11].
Reference Source
20. Wójcik K, Wawrzycka-Adamczyk K, Władarczyk A, *et al.*: **Clinical characteristics of Polish patients with ANCA-associated vasculitides—retrospective analysis of POLVAS registry.** *Clin Rheumatol.* 2019; **38**(9): 2553–63.
PubMed Abstract | Publisher Full Text

21. Solans-Laqué R, Fraile G, Rodriguez-Carballeira M, *et al.*: **Clinical characteristics and outcome of Spanish patients with ANCA-associated vasculitides: Impact of the vasculitis type, ANCA specificity, and treatment on mortality and morbidity.** *Medicine (Baltimore).* 2017; **96**(8): e6083.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Flossmann O, Berden A, de Groot K, *et al.*: **Long-term patient survival in ANCA-associated vasculitis.** *Ann Rheum Dis.* 2011; **70**(3): 488–94.
PubMed Abstract | Publisher Full Text

23. Heijl C, Mohammad AJ, Westman K, *et al.*: **Long-term patient survival in a Swedish population-based cohort of patients with ANCA-associated vasculitis.** *RMD Open.* 2017; **3**(1): e000435.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Mohammad AJ, Jacobsson LT, Westman KW, *et al.*: **Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa.** *Rheumatology (Oxford).* 2009; **48**(12): 1560–5.
PubMed Abstract | Publisher Full Text

25. Sada KE, Yamamura M, Harigai M, *et al.*: **Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study.** *Arthritis Res Ther.* 2014; **16**(2): R101.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Booth AD, Almond MK, Burns A, *et al.*: **Outcome of ANCA-associated renal vasculitis: a 5-year retrospective study.** *Am J Kidney Dis.* 2003; **41**(4): 776–84.
PubMed Abstract | Publisher Full Text

27. Abdou NI, Kullman GJ, Hoffman GS, *et al.*: **Wegener's granulomatosis: survey of 701 patients in North America. Changes in outcome in the 1990s.** *J Rheumatol.* 2002; **29**(2): 309–16.
PubMed Abstract

28. Houben E, Groenland SL, van der Heijden JW, *et al.*: **Relation between duration of the prodromal phase and renal damage in ANCA-associated vasculitis.** *BMC Nephrol.* 2017; **18**(1): 378.
PubMed Abstract | Publisher Full Text | Free Full Text

29. Reinhold-Keller E: **No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register.** *Rheumatology (Oxford).* 2002; **41**(5): 540–9.
PubMed Abstract | Publisher Full Text

30. Mukhtyar C, Flossmann O, Hellmich B, *et al.*: **Outcomes from studies of antineutrophil cytoplasm antibody associated vasculitis: a systematic review by the European League Against Rheumatism systemic vasculitis task force.** *Ann Rheum Dis.* 2008; **67**(7): 1004–10.
PubMed Abstract | Publisher Full Text

31. Titeca-Beauport D, Francois A, Lobbedez T, *et al.*: **Early predictors of one-year mortality in patients over 65 presenting with ANCA-associated renal vasculitis: a retrospective, multicentre study.** *BMC Nephrol.* 2018; **19**(1): 317.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Harper L, Savage CO: **ANCA-associated renal vasculitis at the end of the twentieth century--a disease of older patients.** *Rheumatology (Oxford).* 2005; **44**(4): 495–501.
PubMed Abstract | Publisher Full Text

33. Mahr A, Girard T, Agher R, *et al.*: **Analysis of factors predictive of survival based on 49 patients with systemic Wegener's granulomatosis and prospective follow-up.** *Rheumatology.* 2001; **40**(5): 492–8.
PubMed Abstract | Publisher Full Text

34. McGregor JG, Negrete-Lopez R, Poulton CJ, *et al.*: **Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function.** *Nephrol Dial Transplant.* 2015; **30 Suppl 1**(Suppl 1): i171–i81.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Walsh M, Merkel PA, Peh C-A, *et al.*: **Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis.** *N Engl J Med.* 2020; **382**(7): 622–31.
PubMed Abstract | Publisher Full Text | Free Full Text

36. Geetha D, Jefferson JA: **ANCA-Associated Vasculitis: Core Curriculum 2020.** *Am J Kidney Dis.* 2020; **75**(1): 124–37.
PubMed Abstract | Publisher Full Text

37. Chung JB, Armstrong K, Schwartz JS, *et al.*: **Cost-effectiveness of prophylaxis against Pneumocystis carinii pneumonia in patients with Wegner's granulomatosis undergoing immunosuppressive therapy.** *Arthritis Rheum.* 2000; **43**(8): 1841–8.
PubMed Abstract | Publisher Full Text

38. Reinhold-Keller E, Beuge N, Latza U, *et al.*: **An interdisciplinary approach to the care of patients with Wegener's granulomatosis: Long-term outcome in 155 patients.** *Arthritis Rheum.* 2000; **43**(5): 1021–32.
PubMed Abstract | Publisher Full Text

39. Weidner S, Geuss S, Hafezi-Rachti S, *et al.*: **ANCA-associated vasculitis with renal involvement: an outcome analysis.** *Nephrol Dial Transplant.* 2004; **19**(6): 1403–11.
PubMed Abstract | Publisher Full Text

40. Westman KW, Bygren PG, Olsson H, *et al.*: **Relapse rate, renal survival, and cancer morbidity in patients with Wegener's granulomatosis or microscopic polyangiitis with renal involvement.** *J Am Soc Nephrol.* 1998; **9**(5): 842–52.
PubMed Abstract | Publisher Full Text

41. Slot MC, Tervaert JWC, Franssen CFM, *et al.*: **Renal survival and prognostic factors in patients with PR3-ANCA associated vasculitis with renal involvement.** *Kidney Int.* 2003; **63**(2): 670–7.
PubMed Abstract | Publisher Full Text

42. Mohammad AJ, Segelmark M, Smith R, *et al.*: **Severe Infection in Antineutrophil Cytoplasmic Antibody-associated Vasculitis.** *J Rheumatol.* 2017; **44**(10): 1468–75.
PubMed Abstract | Publisher Full Text

43. Lionaki S, Hogan SL, Jennette CE, *et al.*: **The clinical course of ANCA small-vessel vasculitis on chronic dialysis.** *Kidney Int.* 2009; **76**(6): 644–51.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Dalrymple LS, Go AS: **Epidemiology of acute infections among patients with chronic kidney disease.** *Clin J Am Soc Nephrol.* 2008; **3**(5): 1487–93.
PubMed Abstract | Publisher Full Text | Free Full Text

45. Haubitz M, Bohnenstengel F, Brunkhorst R, *et al.*: **Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency.** *Kidney Int.* 2002; **61**(4): 1495–501.
PubMed Abstract | Publisher Full Text

46. Stone JH, Merkel PA, Spiera R, *et al.*: **Rituximab versus Cyclophosphamide for ANCA-Associated Vasculitis.** *N Engl J Med.* 2010; **363**(3): 221–32.
PubMed Abstract | Publisher Full Text | Free Full Text

47. Trejo MACW, Floßmann O, Westman KW, *et al.*: **Renal relapse in antineutrophil cytoplasmic autoantibody-associated vasculitis: Unpredictable, but predictive of renal outcome.** *Rheumatology (Oxford).* 2019; **58**(1): 103–9.
PubMed Abstract | Publisher Full Text

48. Gopaluni S, Flossmann O, Little MA, *et al.*: **Effect of Disease Activity at Three and Six Months After Diagnosis on Long-Term Outcomes in Antineutrophil Cytoplasmic Antibody-Associated Vasculitis.** *Arthritis Rheumatol.* 2019; **71**(5): 784–91.
PubMed Abstract | Publisher Full Text

49. Westman K, Flossmann O, Gregorini G: **The long-term outcomes of systemic vasculitis.** *Nephrol Dial Transplant.* 2015; **30 Suppl 1**: i60–i6.
PubMed Abstract | Publisher Full Text

50. Mohammad AJ, Segelmark M: **A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis.** *J Rheumatol.* 2014; **41**(7): 1366–73.
PubMed Abstract | Publisher Full Text

51. McAdoo SP, Medjeral-Thomas N, Gopaluni S, *et al.*: **Long-term follow-up of a combined rituximab and cyclophosphamide regimen in renal anti-neutrophil cytoplasm antibody-associated vasculitis.** *Nephrol Dial Transplant.* 2019; **34**(1): 63–73.
PubMed Abstract | Publisher Full Text | Free Full Text

52. Jones RB, Tervaert JW, Hauser T, *et al.*: **Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis.** *N Engl J Med.* 2010; **363**(3): 211–20.
PubMed Abstract | Publisher Full Text

53. Berden A, Casian A, Westman K, *et al.*: **Long-term renal outcome of patients enrolled in the CYCAZAREM trial.** *Clinical and Experimental Immunology.* 2011; **164**: 51.
Reference Source

54. Berden AE, Ferrario F, Hagen EC, *et al.*: **Histopathologic Classification of ANCA-Associated Glomerulonephritis.** *J Am Soc Nephrol.* 2010; **21**(10): 1628–36.
PubMed Abstract | Publisher Full Text

55. Moran SM, Scott J, Clarkson MR, *et al.*: **The Clinical Application of Urine Soluble CD163 in ANCA-Associated Vasculitis.** *J Am Soc Nephrol.* 2021; **32**(11): 2920–32.
PubMed Abstract | Publisher Full Text | Free Full Text

56. Mejia-Vilet JM, Zhang XL, Cruz C, *et al.*: **Urinary Soluble CD163: a Novel Noninvasive Biomarker of Activity for Lupus Nephritis.** *J Am Soc Nephrol.* 2020; **31**(6): 1335–1347.
PubMed Abstract | Publisher Full Text | Free Full Text

57. Pagnoux C, Carette S, Khalidi NA, *et al.*: **Comparability of patients with ANCA-associated vasculitis enrolled in clinical trials or in observational cohorts.** *Clin Exp Rheumatol.* 2015; **33**(2 Suppl 89): S-77–83.
PubMed Abstract | Free Full Text

58. Brayne C, O'Mahoney P, Feeney J, *et al.*: **The challenges of open access data.** *Lancet.* 2022; **399**(10324): 517.
PubMed Abstract | Publisher Full Text

12.3 Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review (62)

Autoimmunity Reviews 19 (2020) 102660

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

Jennifer Scott[a], Jack Hartnett[a], David Mockler[b], Mark A. Little[a,c,*]

[a] Trinity Health Kidney Centre, Trinity Translational Medicine Institute, Trinity College Dublin, Ireland
[b] John Stearne Medical Library, School of Medicine, Trinity College Dublin, Ireland
[c] ADAPT Centre, Trinity College Dublin, Ireland

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)

* Corresponding author at: THKC, Trinity Centre for Health Sciences, St. James's Hospital, St. James's Street, Dublin 8, Ireland.
E-mail address: mlittle@tcd.ie (M.A. Little).

https://doi.org/10.1016/j.autrev.2020.102660
Received 22 March 2020; Accepted 29 March 2020
Available online 15 September 2020
1568-9972/ © 2020 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (http://creativecommons.org/licenses/BY/4.0/).

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.

(*continued on next page*)

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.

(*continued on next page*)

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).

(*continued on next page*)

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

(*continued on next page*)

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

(*continued on next page*)

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).

(*continued on next page*)

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]	Prospective cohort study. 71 consecutive GPA (biopsy-proven) patients attending the outpatient clinic (1988-1991).	Persistent (≥ 75% nasal swabs) SA equating to CNSAC, via culture of bilateral anterior nares swab 4-6 weekly.	CNSAC is associated with a 7-fold increased risk of relapse (aRR 7.16, 95% CI 1.63, 31.5, p 0.009).
Stegeman et al. 1996 Groningen, The Netherlands [88]	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.	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.	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).

(*continued on next page*)

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.

(*continued on next page*)

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).

(*continued on next page*)

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).

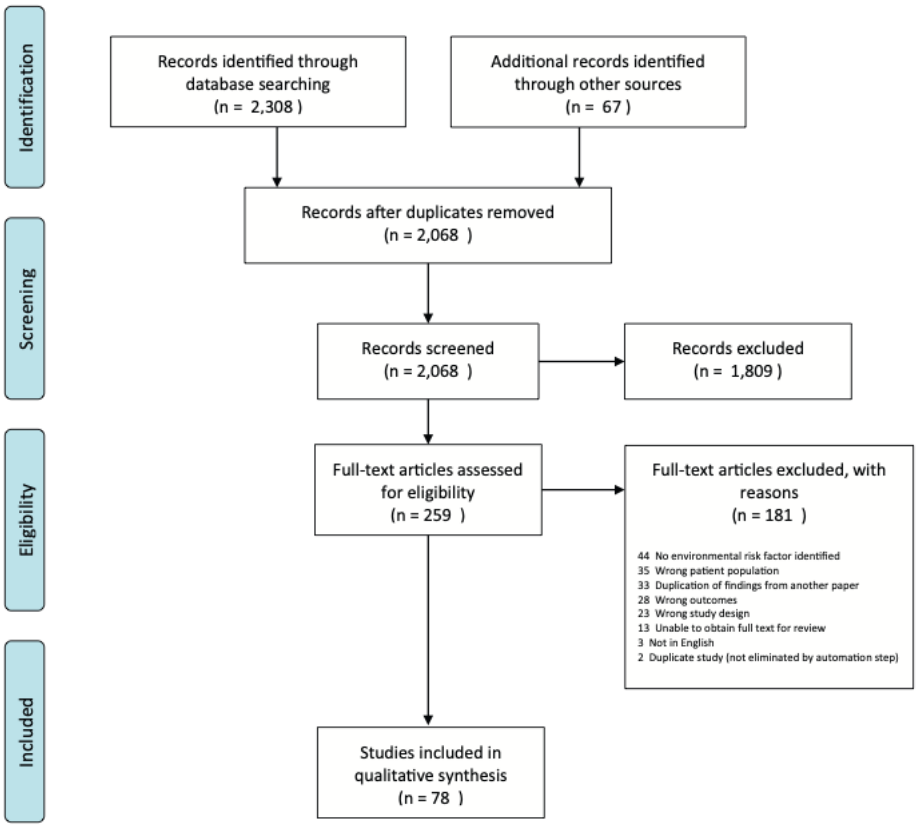


Fig. 1. PRISMA flow diagram depicting study selection process.

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-TNFα 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.

References

[1] Little MA, Nightingale P, Verburgh CA, Hauser T, De Groot K, Savage C, et al. Early mortality in systemic vasculitis: relative contribution of adverse events and active vasculitis. Ann Rheum Dis 2010;69:1036–43.
[2] Fries JF, Hunder GG, Bloch DA, Michel BA, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of vasculitis. Summary. Arthritis Rheum 1990;33:1135–6.
[3] Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis & Rheumatism 2012;65:1–11.
[4] Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Annals of the rheumatic diseases 2007;66:222–7.
[5] Craven A, Robson J, Ponte C, Grayson PC, Suppiah R, Judge A, et al. ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). Clin Exp Nephrol 2013;17:619–21.
[6] Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DRW, et al. Genetically distinct subsets within ANCA-associated vasculitis. N. Engl. J. Med. 2012;367:214–23.
[7] Oates T, Salama AD. Epigenetic Modifications in ANCA-Associated Vasculitis: Potential for Insights into Disease Pathogenesis and Prediction of Outcome? J Am Soc Nephrol 2017;28:1011–3.
[8] Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Info Libr J 2009;26:91–108.
[9] V.H.I. Covidence Systematic Review Software, Melbourne, Australia Available at www.covidence.org. (in: Editor (Ed.)^(Eds.), Book, pp).
[10] Wells SB, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses (Ottawa Hospital Research Institute Web Site). The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. Ottawa Hospital Research Institute Web Site; 2019.
[11] La Torre G, Mannocci A. Rating for narrative reviews:concept and development of the international narrative systematic assessment tool. Senses Sci 2015;2(2):31e5.
[12] Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrology Dialysis Transplantation 2015;30:i14–22.
[13] Mohammad AJ, Jacobsson LTH, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg Strauss syndrome within a defined population in southern Sweden. Rheumatology 2007;46:1329–37.
[14] Pearce FA, Craven A, Merkel PA, Luqmani RA, Watts RA. Global ethnic and geographic differences in the clinical presentations of anti-neutrophil cytoplasm antibody–associated vasculitis. Rheumatology 2017;56:1962–9.
[15] Fujimoto S, Watts RA, Kobayashi S, Suzuki K, Jayne DRW, Scott DGI, et al. Comparison of the epidemiology of anti-neutrophil cytoplasmic antibody-associated vasculitis between Japan and the UK. Rheumatology 2011;50:1916–20.
[16] Chen M, Yu F, Zhang Y, Zou W-Z, Zhao M-H, Wang H-Y. Characteristics of Chinese patients with Wegener's granulomatosis with anti-myeloperoxidase autoantibodies. Kidney International 2005;68:2225–9.
[17] Chen M, Yu F, Zhang Y, Zhao M-H. Antineutrophil Cytoplasmic Autoantibody-Associated Vasculitis in Older Patients. Medicine 2008;87:203–9.
[18] Watts RA, Lane SE, Bentham G, Scott DGI. Epidemiology of systemic vasculitis: A ten-year study in the United Kingdom. Arthritis & Rheumatism 2000;43:414.
[19] Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis Rheum 1996;39:87–92.
[20] Mahr A, Guillevin L, Poissonnet M, Aymé S. Prevalences of Polyarteritis Nodosa, Microscopic Polyangiitis, Wegener's Granulomatosis, and Churg-Strauss Syndrome in a French Urban Multiethnic Population in 2000: A Capture-Recapture Estimate. Arthritis Care and Research 2004;51:92–9.
[21] O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: Evidence for a latitude-dependent incidence gradient. Internal Medicine Journal 2007;37:242–6.
[22] Watts RA. Epidemiology of vasculitis in Europe. Annals of the Rheumatic Diseases 2001;60. (1156a-1157).
[23] Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gutfleisch J, Peter HH, Raspe HH, et al. No difference in the incidences of vasculitides between north and south Germany: First results of the German vasculitis register. Rheumatology 2002;41:540–9.
[24] Falk RJ. Clinical Course of Anti-Neutrophil Cytoplasmic Autoantibody-associated Glomerulonephritis and Systemic Vasculitis. Annals of Internal Medicine 1990;113:656.
[25] Tidman M, Olander R, Svalander C, Danielsson D. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975-95: Organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. Journal of Internal Medicine 1998;244:133–41.
[26] Raynauld JP, Bloch DA, Fries JF. Seasonal variation in the onset of Wegener's granulomatosis, polyarteritis nodosa and giant cell arteritis. Journal of Rheumatology 1993;20:1524–6.
[27] Carruthers DM, Watts RA, Symmons DPM, Scott DGI. Wegener's granulomatosis - Increased incidence or increased recognition? British Journal of Rheumatology 1996;35:142–5.
[28] Pavone L, Grasselli C, Chierici E, Maggiore U, Garini G, Ronda N, et al. Outcome and prognostic factors during the course of primary small-vessel vasculitides. Journal of Rheumatology 2006;33:1299–306.
[29] Li J, Cui Z, Long JY, Huang W, Wang JW, Wang H, et al. The frequency of ANCA-associated vasculitis in a national database of hospitalized patients in China. Arthritis Research and Therapy 2018;20.
[30] Draibe J, Rodó X, Fulladosa X, Martínez-Valenzuela L, Diaz-Encarnación M, Santos L, et al. Seasonal variations in the onset of positive and negative renal ANCA-associated vasculitis in Spain. Clinical Kidney Journal 2018;11:468–73.
[31] Mahr A, Artigues N, Coste J, Aouba A, Pagnoux C, Guillevin L. Seasonal variations in onset of Wegener's granulomatosis: Increased in summer? Journal of Rheumatology 2006;33:1615–22.
[32] Aries PM, Herlyn K, Reinhold-Keller E, Latza U. No seasonal variation in the onset of symptoms of 445 patients with Wegener's granulomatosis. Arthritis Care and Research 2008;59:904.
[33] Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis & Rheumatism 2000;43:2481–7.
[34] Lane SE, Watts RA, Scott DGI. Seasonal variations in onset of Wegener; granulomatosis: increased in summer? The Journal of Rheumatology 2007;34:889.
[35] Duna GF, Cotch MF, Galperin C, Hoffman DB, Hoffman GS. Wegener's granulomatosis: Role of environmental exposures. Clinical and Experimental Rheumatology 1998;16:669–74.
[36] Watts RA, Mooney J, Skinner J, Scott DGI, MacGregor AJ. The contrasting epidemiology of granulomatosis with polyangiitis (Wegener's) and microscopic polyangiitis. Rheumatology 2012;51:926–31.
[37] Mohammad AJ, Jacobsson LTH, Westman KWA, Sturfelt G, Segelmark M. Incidence and survival rates in Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and polyarteritis nodosa, Rheumatology 2009;48:1560–5.
[38] Weiner M, Bjørneklett R, Hrusková Z, Mackinnon B, Poulton CJ, Sindelar L, et al. Proteinase-3 and myeloperoxidase serotype in relation to demographic factors and geographic distribution in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. Nephrology Dialysis Transplantation 2019;34:301–8.
[39] Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases. Current Opinion in Rheumatology 2013;25:184–91.
[40] Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DGI. Geoepidemiology of systemic vasculitis: Comparison of the incidence in two regions of Europe. Annals of the Rheumatic Diseases 2001;60:170–2.
[41] Gatenby PA, Lucas RM, Engelsen O, Ponsonby AL, Clements M. Antineutrophil cytoplasmic antibody-associated vasculitides: Could geographic patterns be explained by ambient ultraviolet radiation? Arthritis Care and Research 2009;61:1417–24.
[42] Kälsch AI, Peters A, Buhl B, Breedijk A, Prem K, Schmitt WH, et al. Retinoid X receptor beta polymorphisms do not explain functional differences in vitamins D and A response in Antineutrophil cytoplasmic antibody associated vasculitis patients. Autoimmunity 2009;42:467–74.
[43] Kemna MJ, Tervaert JWC, Broen K. S.A.M.E.G. Timmermans, P. Van Paassen and J.G.M.C. Damoiseaux, Seasonal influence on the risk of relapse at a rise of anti-neutrophil cytoplasmic antibodies in vasculitis patients with renal involvement. Journal of Rheumatology 2017;44:473–81.
[44] Herlyn K, Buckert F, Gross WL, Reinhold-keller E. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. Rheumatology (United Kingdom) 2014;53:882–9.
[45] Gourley M, Miller FW. Mechanisms of disease: Environmental factors in the pathogenesis of rheumatic disease. Nat Clin Pract Rheumatol 2007;3:172–80.
[46] Albert DA, Albert AN, Vernace M, Sebastian JK, Hsia EC. Analysis of a cluster of cases of Wegener granulomatosis. Journal of Clinical Rheumatology 2005;11:188–93.
[47] Knight A, Sandin S, Askling J. Occupational risk factors for Wegener's granulomatosis: A case-control study. Annals of the Rheumatic Diseases 2010;69:737–40.
[48] Willeke P, Schlüter B, Sauerland C, Becker H, Reuter S, Jacobi A, et al. Farm exposure as a differential risk factor in ANCA-associated vasculitis, PLoS ONE 10. 2015.
[49] Tervaert JW, Stegeman CA, Kallenberg CG. Silicon exposure and vasculitis. Curr Opin Rheumatol 1998;10:12–7.
[50] Gómez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: Systematic review and meta-analysis. Autoimmunity Reviews 2013;12:1129–35.
[51] Beaudreuil S, Lasfargues G, Lauériere L, El Ghoul Z, Fourquet F, Longuet C, et al. Occupational exposure in ANCA-positive patients: A case-control study. Kidney International 2005;67:1961–6.
[52] Lane SE, Watts RA, Bentham G, Innes NJ, Scott DGI. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis and Rheumatism 2003;48:814–23.
[53] Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and Lupus nephritis. Journal of the American Society of Nephrology 2001;12:134–42.
[54] Stamp LK, Chapman PT, Francis J, Beckert L, Frampton C, Watts RA, et al. Association between environmental exposures and granulomatosis with polyangiitis in Canterbury, New Zealand. Arthritis Research and Therapy 2015;17.
[55] Hogan SL, Cooper GS, Savitz DA, Nylander-French LA, Parks CG, Chin H, et al. Association of silica exposure with anti-neutrophil cytoplasmic autoantibody small-vessel vasculitis: a population-based, case-control study. Clinical journal of

the American Society of Nephrology : CJASN 2007;2:290–9.
[56] Leigh J, Wang H, Bonin A, Peters M, Ruan X. Silica-induced apoptosis in alveolar and granulomatous cells in vivo. Environ Health Perspect 1997;105(Suppl. 5):1241–5.
[57] Chen M, Kallenberg CG. ANCA-associated vasculitides–advances in pathogenesis and treatment. Nat Rev Rheumatol 2010;6:653–64.
[58] Yashiro M, Muso E, Itoh T, Oyama A, Ono T, Sasayama S. Significantly high incidence and high morbidity of acute renal failure with respiratory tract involvement of p-ANCA-related angitis revealed in Kobe city and the environs after the Kobe earthquake in 1995 [1]. Clinical Nephrology 1999;51:190–1.
[59] Takeuchi Y, Saito A, Ojima Y, Kagaya S, Fukami H, Sato H, et al. The influence of the Great East Japan earthquake on microscopic polyangiitis: A retrospective observational study. PLoS ONE 2017;12.
[60] Webber MP, Moir W, Zeig-Owens R, Glaser MS, Jaber N, Hall C, et al. Nested case-control study of selected systemic autoimmune diseases in world trade center rescue/recovery workers. Arthritis and Rheumatology 2015;67:1369–76.
[61] Farquhar HJ, McGettigan B, Chapman PT, O'Donnell JL, Frampton C, Stamp LK. Incidence of anti-neutrophil cytoplasmic antibody-associated vasculitis before and after the February 2011 Christchurch Earthquake. Internal Medicine Journal 2017;47:57–61.
[62] Albert D, Clarkin C, Komoroski J, Brensinger CM, Berlin JA. Wegener's granulomatosis: Possible role of environmental agents in its pathogenesis. Arthritis Care and Research 2004;51:656–64.
[63] Nuyts GD, Van Vlem E, De Vos A, Daelemans RA, Rorive G, Elseviers MM, et al. Wegener granulomatosis is associated to exposure to silicon compounds: A case-control study. Nephrology Dialysis Transplantation 1995;10:1162–5.
[64] Pai P, Bone JM, Bell GM. Hydrocarbon exposure and glomerulonephritis due to systemic vasculitis. Nephrol Dial Transplant 1998;13:1321–3.
[65] Lee JHM, Attygalle T, Gaffney K, Scott DGI. Demographics and environmental factors in a Wegener's granulomatosis cluster. Annals of the Rheumatic Diseases 2006;66:278–9.
[66] Pinching AJ, Rees AJ, Pussell BA. Relapses in Wegener's granulomatosis: The role of infection. British Medical Journal 1980;281:836–8.
[67] Nielsen PR, Kragstrup TW, Deleuran BW, Benros ME. Infections as risk factor for autoimmune diseases – A nationwide study. Journal of Autoimmunity 2016;74:176–81.
[68] Pearce FA, Lanyon PC, Watts RA, Grainge MJ, Abhishek A, Hubbard RB. Novel insights into the aetiology of granulomatosis with polyangiitis-a case-control study using the Clinical Practice Research Datalink. Rheumatology (United Kingdom) 2018;57:1002–10.
[69] Lamprecht P, Fischer N, Huang J, Burkhardt L, Lütgehetmann M, Arndt F, et al. Changes in the composition of the upper respiratory tract microbial community in granulomatosis with polyangiitis. Journal of Autoimmunity 2019;97:29–39.
[70] Laudien M, Gadola SD, Podschun R, Hedderich J, Paulsen J, Reinhold-Keller E, et al. Nasal carriage of Staphylococcus aureus and endonasal activity in Wegener's granulomatosis as compared to rheumatoid arthritis and chronic rhinosinusitis with nasal polyps. Clinical and Experimental Rheumatology 2010;28:51–5.
[71] Tan BK, Crabol Y, Tasse J, Laurent F, Nekkab N, Vinter C, et al. No evident association of nasal carriage of Staphylococcus aureus or its small-colony variants with cotrimoxazole use or ANCA-associated vasculitis relapses. Rheumatology 2019;59:77–83.
[72] Richter AG, Stockley RA, Harper L, Thickett DR. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. Thorax 2009;64:692–7.
[73] Rhee RL, Sreih AG, Najem CE, Grayson PC, Zhao C, Bittinger K, et al. Characterisation of the nasal microbiota in granulomatosis with polyangiitis. Annals of the Rheumatic Diseases 2018;77:1448.
[74] Stegeman CA, Cohen Tervaert JW, Sluiter WJ, Manson WL, De Jong PE, Kallenberg CGM. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Annals of Internal Medicine 1994;120:12–7.
[75] Salmela A, Rasmussen N, Tervaert JWC, Jayne DRW, Ekstrand A. Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate. Rheumatology (United Kingdom) 2017;56:965–72.
[76] Popa ER, Stegeman CA, Abdulahad WH, van der Meer B, Arends J, Manson WM, et al. Staphylococcal toxic-shock-syndrome-toxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. Rheumatology 2007;46:1029–33.
[77] Zycinska K, Wardyn KA, Zielonka TM, Krupa R, Lukas W. Co-trimoxazole and prevention of relapses of pr3-anca positive vasculitis with pulmonary involvement. European Journal of Medical Research 2009;14:265–7.
[78] Fijolek J, Wiatr E, Petroniec V, Augustynowicz-Kopec E, Bednarek M, Gawryluk D, et al. The presence of staphylococcal superantigens in nasal swabs and correlation with activity of granulomatosis with polyangiitis in own material. Clinical and Experimental Rheumatology 2018;36:S40–5.
[79] Besada E, Koldingsnes W, Nossent JC. Staphylococcus Aureus carriage and long-term Rituximab treatment for Granulomatosis with polyangiitis. PeerJ 2015;3:e1051.
[80] Salmela A, Rasmussen N, Tervaert JWC, Jayne DRW, Ekstrand A, G. European Vasculitis Study. Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate. Rheumatology 2017;56:965–72.
[81] Pendergraft WF, Preston GA, Shah RR, Tropsha A, Carter CW, Jennette JC, et al. Autoimmunity is triggered by cPR-3(105–201), a protein complementary to human autoantigen proteinase-3. Nature Medicine 2003;10:72–9.
[82] Kain R, Matsui K, Exner M, Binder S, Schaffner G, Sommer EM, et al. A novel class of autoantigens of anti-neutrophil cytoplasmic antibodies in necrotizing and crescentic glomerulonephritis: the lysosomal membrane glycoprotein h-lamp-2 in neutrophil granulocytes and a related membrane protein in glomerular endothelial cells. The Journal of experimental medicine 1995;181:585–97.
[83] Roth AJ, Brown MC, Smith RN, Badhwar AK, Parente O, Chung H, et al. Anti-LAMP-2 antibodies are not prevalent in patients with antineutrophil cytoplasmic autoantibody glomerulonephritis. Journal of the American Society of Nephrology 2012;23:545–55.
[84] Kain R, Tadema H, McKinney EF, Benharkou A, Brandes R, Peschel A, et al. High Prevalence of Autoantibodies to hLAMP-2 in Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis. Journal of the American Society of Nephrology 2012;23:556–66.
[85] Kain R, Exner M, Brandes R, Ziebermayr R, Cunningham D, Alderson CA, et al. Molecular mimicry in pauci-immune focal necrotizing glomerulonephritis. Nature medicine 2008;14:1088–96.
[86] Ooi JD, Jiang JH, Eggenhuizen PJ, Chua LL, van Timmeren M, Loh KL, et al. A plasmid-encoded peptide from Staphylococcus aureus induces anti-myeloperoxidase nephritogenic autoimmunity. Nature Communications 2019;10.
[87] Konstantinov KN, Ulff-Møller CJ, Tzamaloukas AH. Infections and antineutrophil cytoplasmic antibodies: Triggering mechanisms. Autoimmunity Reviews 2015;14:201–3.
[88] Stegeman CA, Cohen Tervaert JW, de Jong PE, Kallenberg CGM. Trimethoprim–Sulfamethoxazole (Co-Trimoxazole) for the Prevention of Relapses of Wegener's Granulomatosis. New England Journal of Medicine 1996;335:16–20.
[89] Hermann J, Demel U, Stünzner D, Daghofer E, Tilz G, Graninger W. Clinical interpretation of antineutrophil cytoplasmic antibodies: Parvovirus B19 infection as a pitfall. Annals of the Rheumatic Diseases 2005;64:641–3.
[90] Eden A, Mahr A, Servant A, Radjef N, Amard S, Mouthon L, et al. Lack of association between B19 or V9 erythrovirus infection and ANCA-positive vasculitides: A case-control study. Rheumatology 2003;42:660–4.
[91] Sachetto Z, Costa SCB, Andrade PD, Conde RA, Amstalden EMI, Samara AM, et al. No evidence of parvovirus B19 in tissue samples from patients with polyarteritis nodosa and microscopic polyangiitis as assessed by the polymerase chain reaction. Annals of the rheumatic diseases 2006;65:418–20.
[92] Barzilai O, Sherer Y, Ram M, Izhaky D, Anaya JM, Shoenfeld Y. Epstein-Barr virus and cytomegalovirus in autoimmune diseases: Are they truly notorious? A preliminary report. Book Epstein-Barr virus and Cytomegalovirus in Autoimmune Diseases: Are They Truly Notorious? A Preliminary Report. 2007. p. 567–77.
[93] Eriksson P, Sandell C, Backteman K, Ernerudh J. Expansions of CD4 + CD28- and CD8 + CD28- T cells in granulomatosis with polyangiitis and microscopic polyangiitis are associated with cytomegalovirus infection but not with disease activity. Journal of Rheumatology 2012;39:1840–3.
[94] Pagnoux C, Seror R, Henegar C, Mahr A, Cohen P, Le Guern V, et al. Clinical features and outcomes in 348 patients with polyarteritis nodosa: A systematic retrospective study of patients diagnosed between 1963 and 2005 and entered into the French vasculitis study group database. Arthritis & Rheumatism 2010;62:616–26.
[95] Lee SW, Kim DY, Ahn SH, Park YB, Han KH, Park JY. HBsAg-negative and anti-HBc-positive in eosinophilic granulomatosis with polyangiitis: a retrospective pilot study. Rheumatology International 2018;38:1531–8.
[96] Cook PM, Schulz TF, Rascu A, Kalden JR, Harrer T. Lack of serologic evidence for involvement of human herpesvirus 8 in autoimmune diseases. Arthritis and Rheumatism 1997;40:1906–7.
[97] Gerke P, Wichmann D, Schonermarck U, Schutt M, Feldmann H, Ksiazek TG, et al. Lack of evidence for an association between hantavirus infections and Wegener's granulomatosis, microscopic polyangiitis. Churg-Strauss syndrome and giant cell arteritis, Rheumatology 2000;39:1424–5.
[98] Iyoda M, Kuroki A, Sugisaki T. Chlamydia pneumoniae infection and MPO-ANCA-associated glomerulonephritis [18]. Nephrology Dialysis Transplantation 2007;22:965–6.
[99] Fujita M, Hatachi S, Yagita M. Acute Chlamydia pneumoniae infection in the pathogenesis of autoimmune diseases. Lupus 2009;18:164–8.
[100] Lidar M, Lipschitz N, Langevitz P, Barzilai O, Ram M, Porat-Katz B-S, et al. Infectious Serologies and Autoantibodies in Wegener's Granulomatosis and Other Vasculitides. Annals of the New York Academy of Sciences 2009;1173:649–57.
[101] Stratta P, Messuerotti A, Canavese C, Coen M, Luccoli L, Bussolati B, et al. The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. The Science of the total environment 2001;270:179–90.
[102] Ishiguro T, Takayanagi N, Takaku Y, Kagiyama N, Kurashima K, Sugita Y. Combined allergic bronchopulmonary aspergillosis and eosinophilic granulomatosis with polyangiitis: Three cases and a review of the literature. Internal Medicine 2016;55:793–7.
[103] Bühler S, Jaeger VK, Adler S, Bannert B, Brümmerhoff C, Ciurea A, et al. Safety and immunogenicity of tetanus/diphtheria vaccination in patients with rheumatic diseases-a prospective multi-centre cohort study. Rheumatology (United Kingdom) 2019;58:1585–96.
[104] Duggal T, Segal P, Shah M, Carter-Monroe N, Manoharan P, Geetha D. Antineutrophil Cytoplasmic Antibody Vasculitis Associated with Influenza Vaccination. American Journal of Nephrology 2013;38:174–8.
[105] Watanabe T. Vasculitis following influenza vaccination: a review of the literature. Current Rheumatology Reviews 2017;13.
[106] Stassen PM, Sanders JSF, Kallenberg CGM, Stegeman CA. Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis. Nephrology Dialysis Transplantation 2008;23:654–8.
[107] Zycinska K, Romanowska M, Nowak I, Rybicka K, Wardyn KA, Brydak LB. Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis. J Physiol Pharmacol 2007;58(Suppl. 5):819–28.

[108] Cuadrado MJ, D'Cruz D, Lloyd M, Mujic F, Khamashta MA, Hughes GRV. Allergic disorders in systemic vasculitis: a case-controlled study. Rheumatology 1994;33:749–53.
[109] Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, et al. Epidemiology of environmental exposures and human autoimmune diseases: Findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. Journal of Autoimmunity 2012;39:259–71.
[110] Haubitz M. Smoking habits in patients diagnosed with ANCA associated small vessel vasculitis. Annals of the Rheumatic Diseases 2005;64:1500–2.
[111] Sopori M. Effects of cigarette smoke on the immune system. Nature Reviews Immunology 2002;2:372–7.
[112] Chen M, Kallenberg CGM. The environment, geoepidemiology and ANCA-associated vasculitides. Autoimmunity Reviews 2010;9:A293–8.
[113] Choi HK, Merkel PA, Walker AM, Niles JL. Drug-associated antineutrophil cytoplasmic antibody–positive vasculitis: Prevalence among patients with high titers of antimyeloperoxidase antibodies. Arthritis & Rheumatism 2000;43:405.
[114] Merkel PA. Drugs associated with vasculitis. Curr Opin Rheumatol 1998;10:45–50.
[115] Pendergraft WF, Niles JL. Trojan horses. Current Opinion in Rheumatology 2014;26:42–9.
[116] Calapai G, Casciaro M, Miroddi M, Calapai F, Navarra M, Gangemi S. Montelukast-induced adverse drug reactions: a review of case reports in the literature. Pharmacology 2014;94:60–70.
[117] Hauser T, Mahr A, Metzler C, Coste J, Sommerstein R, Gross WL, et al. The leucotriene receptor antagonist montelukast and the risk of Churg-Strauss syndrome: A case-crossover study. Thorax 2008;63:677–82.
[118] Harrold LR, Patterson MK, Andrade SE, Dube T, Go AS, Buist AS, et al. Asthma drug use and the development of Churg–Strauss syndrome (CSS). Pharmacoepidemiology and Drug Safety 2007;16:620–6.
[119] Wechsler ME, Pauwels R, Drazen JM. Leukotriene Modifiers and Churg-Strauss Syndrome. Drug Safety 1999;21:241–51.
[120] Chipman HA, George EI, McCulloch RE. BART: Bayesian additive regression trees. The Annals of Applied Statistics 2010;4:266–98.
[121] Csató L, Opper M. Sparse On-Line Gaussian Processes. Neural Computation 2002;14:641–68.
[122] Hinton GE, Osindero S, Teh Y-W. A fast learning algorithm for deep belief nets. Neural Computation 2006;18:1527–54.
[123] Mittleman MA, Mostofsky E. Exchangeability in the case-crossover design. Int J Epidemiol 2014;43:1645–55.
[124] Dixon WG, Beukenhorst AL, Yimer BB, Cook L, Gasparrini A, El-Hay T, et al. How the weather affects the pain of citizen scientists using a smartphone app. NPJ Digit Med 2019;2:105.
[125] Kanecki K, Nitsch-Osuch A, Gorynski P, Tarka P, Tyszko P. Hospital morbidity database for epidemiological studies on Churg-Strauss syndrome. Book Hospital morbidity database for epidemiological studies on Churg-Strauss syndrome. 2017. p. 19–25.
[126] Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Internal Medicine Journal 2008;38:816–23.
[127] Gregorini G, Ferioli A, Donato F, Tira P, Morassi L, Tardanico R, et al. Association between Silica Exposure and Necrotizing Crescentic Glomerulonephritis with p-ANCA and anti-MPO Antibodies: A Hospital-Based Case-Control Study. Book Association between Silica Exposure and Necrotizing Crescentic Glomerulonephritis with p-ANCA and anti-MPO Antibodies: A Hospital-Based Case-Control Study. US: Springer; 1993. p. 435–40.
[128] Rihova Z, Maixnerova D, Jancova E, Pelclova D, Bartunkova J, Fenclova Z, et al. Silica and asbestos exposure in ANCA-associated vasculitis with pulmonary involvement. Renal Failure 2005;27:605–8.
[129] Yamaguchi M, Ando M, Katsuno T, Tsuboi N, Maruyama S. Smoking is a risk factor for relapse of antimyeloperoxidase antibodies-associated vasculitis. Journal of Clinical Rheumatology 2018;24:361–7.
[130] Gerke P, Wichmann D, Schönermarck U, Schütt M, Feldmann H, Ksiazek TG, et al. Lack of evidence for an association between hantavirus infections and Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and giant cell arteritis [2]. Rheumatology 2000;39:1424–5.
[131] Uji M, Matsushita H, Iwata S. Microscopic Polyangiitis after Influenza Vaccination. Internal Medicine 2005;44:892–6.
[132] Spaetgens B, van Paassen P, Tervaert JWC. Influenza vaccination in ANCA-associated vasculitis. Nephrology Dialysis Transplantation 2009;24:3258.
[133] Birck R, Kaelsch I, Schnuelle P, Flores-Suarez LF, Nowack R. ANCA-associated vasculitis following influenza vaccination: causal association or mere coincidence? J Clin Rheumatol 2009;15:289–91.

12.4 The association between ambient UVB dose and ANCA associated vasculitis relapse and onset (76)

Scott *et al. Arthritis Research & Therapy* (2022) 24:147
https://doi.org/10.1186/s13075-022-02834-6

Arthritis Research & Therapy

RESEARCH ARTICLE Open Access

The association between ambient UVB dose and ANCA-associated vasculitis relapse and onset

Jennifer Scott[1], Enock Havyarimana[2], Albert Navarro-Gallinad[3], Arthur White[4], Jason Wyse[4], Jos van Geffen[5], Michiel van Weele[5], Antonia Buettner[1], Tamara Wanigasekera[1], Cathal Walsh[6], Louis Aslett[7], John D. Kelleher[8], Julie Power[9], James Ng[4], Declan O'Sullivan[3], Lucy Hederman[3], Neil Basu[2], Mark A. Little[1,3*†], Lina Zgaga[10†] and on behalf of the RKD and UKIVAS groups

Abstract

Background: The aetiology of ANCA-associated vasculitis (AAV) and triggers of relapse are poorly understood. Vitamin D (vitD) is an important immunomodulator, potentially responsible for the observed latitudinal differences between granulomatous and non-granulomatous AAV phenotypes. A narrow ultraviolet B spectrum induces vitD synthesis (vitD-UVB) via the skin. We hypothesised that prolonged periods of low ambient UVB (and by extension vitD deficiency) are associated with the granulomatous form of the disease and an increased risk of AAV relapse.

Methods: Patients with AAV recruited to the Irish Rare Kidney Disease (RKD) ($n = 439$) and UKIVAS ($n = 1961$) registries were studied. Exposure variables comprised latitude and measures of ambient vitD-UVB, including cumulative weighted UVB dose (CW-D-UVB), a well-validated vitD proxy. An *n*-of-1 study design was used to examine the relapse risk using only the RKD dataset. Multi-level models and logistic regression were used to examine the effect of predictors on AAV relapse risk, phenotype and serotype.

Results: Residential latitude was positively correlated (OR 1.41, 95% CI 1.14–1.74, $p = 0.002$) and average vitD-UVB negatively correlated (0.82, 0.70–0.99, $p = 0.04$) with relapse risk, with a stronger effect when restricting to winter measurements (0.71, 0.57–0.89, $p = 0.002$). However, these associations were not restricted to granulomatous phenotypes. We observed no clear relationship between latitude, vitD-UVB or CW-D-UVB and AAV phenotype or serotype.

Conclusion: Our findings suggest that low winter ambient UVB and prolonged vitD status contribute to AAV relapse risk across all phenotypes. However, the development of a granulomatous phenotype does not appear to be directly vitD-mediated. Further research is needed to determine whether sufficient vitD status would reduce relapse propensity in AAV.

Keywords: ANCA-associated vasculitis, Ultraviolet B (UVB) radiation, Vitamin D, Environment, Geoepidemiology

Introduction

Anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV) is a rare multi-system autoimmune disorder, with an annual incidence of 13–20 cases per million [1].

It manifests as one of three main phenotypes: granulomatosis with polyangiitis (GPA), microscopic polyangiitis

†Mark A. Little and Lina Zgaga contributed equally to this work.

*Correspondence: mlittle@tcd.ie

[1] Trinity Health Kidney Centre, Trinity College Dublin, The University of Dublin, Trinity Translational Medicine Institute, St. James's Street, Dublin 8, Ireland
Full list of author information is available at the end of the article

BMC

© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

(MPA) or eosinophilic granulomatosis with polyangiitis (EGPA). Characteristic autoantibodies directed against myeloperoxidase (MPO) or proteinase-3 (PR3) molecules determine the ANCA serotype. It follows a relapsing and remitting course, resulting in cumulative tissue damage. While the precise triggers of AAV onset and relapse are unknown, evidence supports a complex interaction of genetic susceptibility loci [2], epigenetics [3] and environmental factors [4].

A potential effect of ultraviolet (UV) radiation on disease phenotype and disease activity has been proposed, as marked variations in GPA:MPA incidence ratios occur with latitude [5–8]. Increasing latitude (and hence decreasing UV) [8] is associated with an increased incidence of GPA and EGPA subtypes [5, 8] and of anti-PR3 positivity [9]. The magnitude of association may be strongest for winter UV levels [8], because it is these that particularly limit cutaneous vitamin D (vitD) synthesis [10] and the strongest latitudinal gradient in UV is observed in winter [11]. A similar inverse correlation between UV radiation exposure and incidence is observed in other autoimmune diseases (ADs), for example, multiple sclerosis [12, 13] and type 1 diabetes [12]. In contrast, for the MPA phenotype, an increasing incidence with *decreasing* latitude was observed [5, 6], although Gatenby et al. could not replicate this relationship (nor did they identify an association with UV radiation) [8].

vitD has immunomodulatory effects, including suppression of Th1 and Th17 cells and upregulation of Treg cells, resulting in the reduction of inflammatory cytokines and a more tolerogenic environment [4, 14–16]. Th1, Th17 and Treg cells are crucial to granuloma formation, characteristically seen in GPA and EGPA, but not in MPA, where Th2 cells and antibody-mediated mechanisms predominate [17]. Gatenby et al. postulated that this vitD-mediated UV effect on granulomas was responsible for the strong inverse relationship between GPA (but not MPA) incidence and UV radiation, but this hypothesis has not been tested.

Several small studies demonstrate that serum 25-hydroxyvitamin D (25OHD) levels are lower in AAV patients than in healthy controls [18–20]. Low 25OHD levels have been associated with increased disease activity in other ADs [21–23], with suggestive data in AAV [23]. To our knowledge, there are no large studies examining the influence of UV radiation or vitD on AAV disease activity, as distinct from ANCA phenotype or serotype. Ambient UVB dose at wavelengths that induce cutaneous $vitD_3$ synthesis (vitD-UVB) is the key determinant of an individual's vitD status. Repeated 25OHD assessment is costly and not routinely performed. vitD levels also drop with inflammation limiting the value of 25OHD measurement at relapse. Therefore, we chose to use the cumulative-weighted ambient UVB dose (CW-D-UVB)—a well-validated predictor of an individual's vitD status [24–27]—as a surrogate.

The aim of this study is, firstly, to examine the association between measures of ambient UV radiation, UVB-predicted vitD status (CW-D-UVB) and AAV *relapse*, using a novel *n*-of-1 case-control design. Secondly, we aim to explore the relationship between these variables and ANCA *phenotype and serotype at diagnosis*. We hypothesise that prolonged periods of low ambient UVB (and by extension vitD deficiency) are associated with an increased risk of AAV relapse in GPA/EGPA, but not MPA, and an increased risk of a GPA/EGPA phenotype at diagnosis.

Methods

Study participants

UKIVAS cohort 1 comprised patients from the United Kingdom and Ireland Vasculitis Rare Disease Group (UKIVAS) Registry (https://ukivas.ndorms.ox.ac.uk/), established in 2009. Patients were included in this study if they had a diagnosis of definite AAV with documented diagnosis date and location, defined by relevant clinical features of GPA, MPA or EGPA [28], with either positive anti-MPO or PR3 serology [29] and/or diagnostic histopathology. Patients with secondary vasculitis or dual anti-glomerular basement membrane disease were excluded [30].

RKD cohort 2 comprised non-overlapping patients from the national Irish Rare Kidney Disease (RKD) Registry and Biobank (https://www.tcd.ie/medicine/thkc/research/rare.php), established in 2012. The same inclusion and exclusion criteria were applied. For the AAV relapse component, participants were also required to have > 1 documented period of remission prior to the commencement of the analysis on 18 August 2020. Participant selection is outlined in Additional file 1: Figs. S1 and S2. The AAV diagnosis study included both cohorts, while the AAV relapse study included RKD only, as granular longitudinal follow-up was not recorded in UKIVAS. Ethical approval for the RKD and UKIVAS components was granted by the Tallaght University Research Ethics Committee (ref 2019-08 List 29 (07)) and the NHS National Research Ethics Service (REC 10/H1102/77), respectively. All participants provided written informed consent.

Participant location

Additional file 1: Fig. S3 shows the participant locations at diagnosis. We employed a smartphone application for the RKD cohort (patientMpower) [31] to capture

participants' location by GPS [32]. If unavailable at the time of assessment, the electoral division of the participant's residence or their hospital was used (ranked in preference order). Data linkage was performed using a Resource Description Framework (RDF) semantic web model [33]. Participants' residential postcodes informed the location coordinates for the UKIVAS cohort.

Ultraviolet B (UVB) data source, measures of ambient vitD-UVB and cumulative-weighted UVB dose (CW-D-UVB)

Daily UVB data at wavelengths specific for vitD production (vitD-UVB) were obtained from the Tropospheric Emission Monitoring Internet Service (TEMIS) database [34, 35]. To generate UVB-predicted vitamin D status, a specific cumulative-weighted UVB dose (CW-D-UVB) was calculated for each participant, determined by high-resolution location and date, based on an algorithm proposed by Kelly et al. [24] and later validated [25–27]. Briefly, a daily vitD-UVB dose over 135 days before a given date was used with a decay function assuming a vitD half-life of 35 days (Fig. 1). Further detail is provided in the supplementary materials.

The average (2004–2019) annual, average winter and preceding winter vitD-UVB and CW-D-UVB were derived for each participant. Winter measures were specifically included given the stronger effect sizes previously noted [8].

Study design

The study was split into AAV relapse and diagnosis components, further described in Fig. 2 and supplementary materials. Briefly, relapse was studied using an *n*-of-1 design where each participant acts as their own control, eliminating confounding by time-independent factors such as gender, skin type and occupation and genotype. Case (relapse) and control (remission) windows were defined using an algorithm that considered the effect of residual disease activity and the CW-D-UVB interval (135 days). The diagnosis was studied using the estimated date of symptom onset. Relapse was defined as the return of signs and/or symptoms of active vasculitis (BVAS > 0), with supporting laboratory or histopathological evidence, escalation in immunosuppression and a clinical response to the same. Relapse events were adjudicated by a committee (JS and ML), blinded to the individual's UV data. Remission was defined as the absence of signs, symptoms and laboratory evidence of vasculitis activity. Follow-up continued until the last documented visit or death.

Patient and Public Involvement

Patient and Public Involvement is detailed in supplementary materials.

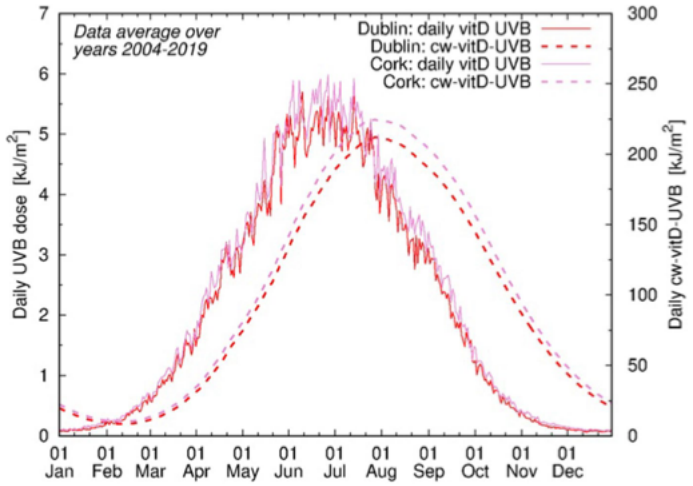


Fig. 1 Annual distribution of average daily CW-D-UVB (dashed line) relative to the average daily vitD-UVB (solid line). Values in Dublin (red) and Cork (pink), averaged over 2004–2019, are displayed. The annual peak and nadir of CW-D-UVB were observed in August and February, respectively, lagging behind those of vitD-UVB by 2 months, thus mimicking 25OHD seasonal fluctuations

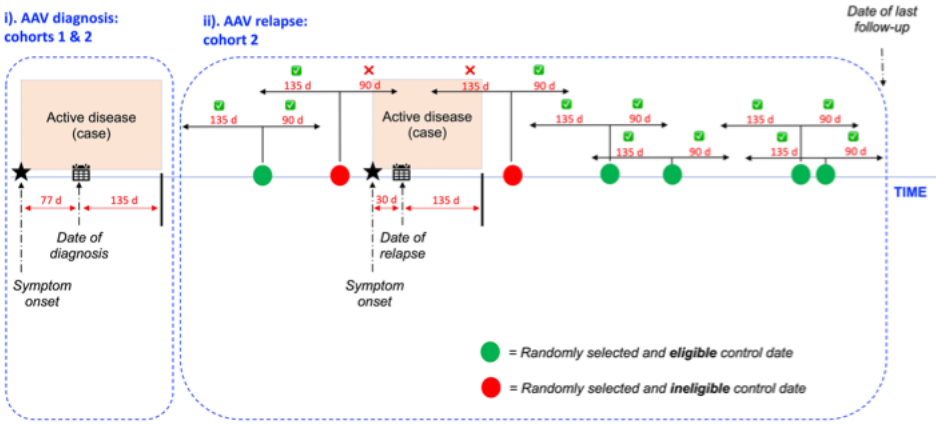


Fig. 2 Study design. **i** *AAV diagnosis* (cohorts 1 and 2). **ii** *AAV relapse* (cohort 2). **i** CW-D-UVB at diagnosis was calculated using the participant's location and date of symptom onset if known, or the date of diagnosis minus 77 days. Seventy-seven days represents the undefined prodromal period [36] informed by the RKD registry analysis (see supplementary material). **ii** In this prospective *n*-of-1 component, each participant was a 'case' during period(s) of disease relapse and a 'control' during period(s) of remission [37]. The case window started at the date of relapse diagnosis minus 30 days (to account for the diagnostic delay) and ended 135 days later (see Additional file 1: Supplementary Methods). To improve the statistical power, 5 control dates were identified per patient, where possible

Statistical analysis

AAV relapse

A multi-level model (*lme4* package, *glmer* function) [38] was applied to investigate the association between latitude/measures of ambient vitD-UVB/CW-D-UVB and AAV relapse. Covariates included age, gender, AAV phenotype, ANCA serotype and treatment. A random effect was included to account for repeated measures and the varying relapse risk between individuals [39]. The disease phenotype was included as an interaction term, to study the (hypothesised) effect of exposure variables on disease subtype relapse risk. Sensitivity analysis restricted to (non-) granulomatous phenotypes was also performed. The power calculation is detailed in supplementary materials.

AAV diagnosis

Logistic regression was used to examine the relationships between AAV phenotype and serotype (outcome variables), latitude, measures of ambient vitD-UVB and CW-D-UVB (examined separately due to collinearity). Covariates included age, gender and ethnicity. We performed a sensitivity analysis restricted to Whites only, given their more substantial vitD synthesis in the skin.

Odds ratios (ORs) and 95% confidence intervals (CIs) were reported. $p < 0.05$ was considered statistically significant. All statistical analyses were performed using R (version 4.0.4).

Results

Participant characteristics

UKIVAS cohort 1 ($N = 1961$, Table 1) and RKD cohort 2 ($N = 439$, Table 2) were similar. An excess of non-White and GPA participants in UKIVAS were the main differences. Induction and maintenance treatment are detailed in Additional file 1: Table S1. The Median follow-up time in RKD was 58.3 months (IQR 32.1–138.1). A total of 343 (78.1%) patients did not relapse; there were 135 relapse events in 96 patients.

UVB patterns

The annual peak and nadir of CW-D-UVB were observed in August and February, respectively, lagging behind those of vitD-UVB by 2 months thus mimicking 25OHD seasonal fluctuations (Fig. 1 and Additional file 1: Fig. S4). The *daily average* vitD-UVB and CW-D-UVB were strongly correlated with latitude (Additional file 1: Fig. S5a-b), as expected. However, latitude alone was weakly correlated with vitD-UVB or CW-vitD-UVB *on a particular day (e.g. diagnosis)*, because the impact of the season is much greater than latitude. This correlation remained weak even when stratified by season due to large variation in daily UVB (Additional file 1: Fig. S5c-g),

Table 1 Baseline characteristics of cohort 1 (UKIVAS)

Characteristics	Total	GPA	MPA	EGPA	*p*
n (%)	1961	1124 (57.3)	600 (30.6)	237 (12.1)	
Age (years, median [IQR])	60 [49, 69]	58 [47, 67]	66 [57, 73]	57 [47, 65]	< 0.001
Male (%)	1017 (51.9)	610 (54.3)	280 (46.7)	127 (53.6)	0.009
Ethnicity (%)					< 0.001
White	1796 (91.6)	1049 (93.3)	534 (89.0)	213 (89.9)	
Asian	85 (4.3)	44 (3.9)	34 (5.7)	7 (3.0)	
Black	29 (1.5)	4 (0.4)	16 (2.7)	9 (3.8)	
Mixed	9 (0.5)	5 (0.4)	3 (0.5)	1 (0.4)	
Others	42 (2.1)	22 (2.0)	13 (2.2)	7 (3.0)	
ANCA subtype (ELISA) (%)					< 0.001
PR3	499 (25.4)	437 (38.9)	53 (8.8)	9 (3.8)	
MPO	340 (17.3)	52 (4.6)	240 (40.0)	48 (20.3)	
ELISA-negative	63 (3.2)	21 (1.9)	15 (2.5)	27 (11.4)	
Others	6 (0.3)	3 (0.3)	2 (0.3)	1 (0.4)	
No ELISA recorded	1053 (53.7)	611 (54.4)	290 (48.3)	152 (64.1)	
Latitude (degrees, median [IQR])	52.24 [51.50, 53.38]	52.40 [51.54, 53.42]	51.82 [51.46, 52.94]	52.24 [51.44, 53.48]	< 0.001
Longitude (degrees, median [IQR])	− 1.20 [− 2.23, − 0.14]	− 1.48 [− 2.36, − 0.20]	− 0.57 [− 2.00, − 0.10]	− 1.38 [− 2.20, − 0.18]	< 0.001
CW-D-UVB at symptom onset (kJ/m^2, median [IQR])	83.82 [25.30, 168.57]	80.72 [25.03, 167.62]	88.40 [26.50, 167.44]	82.51 [24.50, 172.69]	0.914
Season of diagnosis (%)					0.891
Spring	490 (25.0)	285 (25.4)	143 (23.8)	62 (26.2)	
Summer	527 (26.9)	307 (27.3)	161 (26.8)	59 (24.9)	
Autumn	480 (24.5)	274 (24.4)	144 (24.0)	62 (26.2)	
Winter	464 (23.7)	258 (23.0)	152 (25.3)	54 (22.8)	

Continuous variables are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) if not normally distributed and compared using the independent sample *t*-test or the Mann-Whitney *U* test, respectively. Categorical variables are summarised by frequency and percentage (%) and compared using the χ^2 test

Refer to supplementary materials for definitions of 'date of symptom onset' and seasons

ANCA anti-neutrophil cytoplasmic antibodies, *ELISA* enzyme-linked immunoassay, *PR3* proteinase-3, *MPO* myeloperoxidase, *CW-DUVB* cumulative-weighted UVB dose, *SD* standard deviation, *IQR* inter-quartile range

thus strengthening the rationale for using CW-D-UVB as vitD proxy, over latitude or season alone.

Impact of latitude, measures of ambient vitD-UVB and cumulative-weighted UVB (CW-D-UVB) on AAV relapse

Using multi-level logistic regression analysis, latitude was associated with AAV relapse risk (OR 1.41, 95% CI 1.14–1.74, Table 3 and Fig. 3a). There was also a significant inverse relationship between relapse risk and average winter vitD-UVB (0.71, 0.57–0.89, Figs. 3b and 4) and annual vitD-UVB (0.82, 0.70–0.99, Fig. 3d), with a slightly larger effect size in MPA versus not-MPA (Additional file 1: Table S2). However, no relationship was observed with *preceding winter* vitD-UVB (0.90, 0.74–1.10, Table 3 and Additional file 1: Fig. S6b). Similarly, we noted a significant inverse relationship between relapse risk and both average (0.82, 0.70–0.99, Fig. 3c) and preceding (0.81, 0.66–0.99, Additional file 1: Fig. S6c) winter CW-D-UVB. The median CW-D-UVB at symptom onset was not significantly associated with relapse, overall or when stratified by AAV phenotype and ANCA serotype (1.06, 0.88–1.28, Additional file 1: Fig. S6a). The addition of an interaction term between AAV phenotype and any exposure variable did not alter the findings. Additional independent risk factors for relapse included GPA/EGPA subtype (1.78, 1.03–3.05), younger age (0.75, 0.61–0.92) and being off immunosuppression therapy (2.65, 1.70–4.14) or on glucocorticoid monotherapy (1.85, 1.02–3.35, Additional file 1: Table S3).

Impact of latitude, measures of ambient vitD-UVB and cumulative-weighted UVB (CW-D-UVB) on AAV phenotype and serotype at diagnosis

We then investigated the effect of UVB exposure on AAV phenotype and serotype. Approximately half of the cases were diagnosed in winter/spring, with no demonstrable seasonal effect (Tables 1 and 2). UKIVAS and RKD participants reside at a relatively narrow latitudinal range, between 49.4–60.3° and 51.9–55.3°, respectively. Analyses of potential predictors of AAV

Table 2 Baseline characteristics of cohort 2 (RKD)

Characteristics	Total	GPA	MPA	EGPA	*p*
n (%)	439	196 (44.6)	220 (50.1)	23 (5.2)	
Age (years, median [IQR])	59.0 [48.0, 69.0]	54.0 [40.0, 62.3]	65.0 [54.0, 73.0]	57.0 [51.5, 62.5]	< 0.001
Male (%)	253 (57.6)	112 (57.1)	129 (58.6)	12 (52.2)	0.823
Ethnicity (%)					0.353
White	433 (98.6)	194 (99.0)	217 (98.6)	22 (95.7)	
Asian	6 (1.4)	2 (1.0)	3 (1.4)	1 (4.3)	
ANCA subtype (ELISA) (%)					< 0.001
PR3	219 (49.9)	170 (86.7)	45 (20.5)	4 (17.4)	
MPO	207 (47.2)	19 (9.7)	172 (78.2)	16 (69.6)	
ELISA-negative	12 (2.7)	6 (3.1)	3 (1.4)	3 (13.0)	
No ELISA recorded	1 (0.2)	1 (0.5)	0 (0.0)	0 (0.0)	
Organ involvement (%)					
Musculoskeletal	168 (38.3)	103 (52.6)	53 (24.1)	12 (52.2)	< 0.001
Mucocutaneous	115 (26.2)	71 (36.2)	34 (15.5)	10 (43.5)	< 0.001
Eyes	57 (13.0)	37 (18.9)	18 (8.2)	2 (8.7)	0.004
Lung	229 (52.2)	132 (67.3)	78 (35.5)	19 (82.6)	< 0.001
Neurological	60 (13.7)	27 (13.8)	22 (10.0)	11 (47.8)	< 0.001
Ears, nose, throat	193 (44.0)	147 (75.0)	29 (13.2)	17 (73.9)	< 0.001
Cardiovascular	12 (2.7)	6 (3.1)	6 (2.7)	0 (0.0)	1
Kidney	370 (84.3)	146 (74.5)	212 (96.4)	12 (52.2)	< 0.001
Gastrointestinal	25 (5.7)	13 (6.6)	11 (5.0)	1 (4.3)	0.828
Latitude (degrees, median [IQR])	53.30 [52.67, 53.39]	53.29 [52.67, 53.39]	53.32 [52.76, 53.39]	53.29 [52.86, 53.37]	0.350
Longitude (degrees, median [IQR])	−6.39 [−7.77, −6.30]	−6.43 [−8.37, −6.27]	−6.48 [−8.35, −6.22]	−6.39 [−7.77, −6.30]	0.684
CW-D-UVB at symptom onset (kJ/m^2, median [IQR])	75.98 [19.12, 161.06]	78.46 [20.29, 166.07]	74.57 [18.94, 153.51]	60.41 [30.27, 115.27]	0.842
Season of diagnosis (%)					0.502
Spring	129 (29.4)	60 (30.6)	67 (30.5)	2 (8.7)	
Summer	92 (21.0)	41 (20.9)	44 (20.0)	7 (30.4)	
Autumn	112 (25.5)	48 (24.5)	57 (25.9)	7 (30.4)	
Winter	106 (24.1)	47 (24.0)	52 (23.6)	7 (30.4)	
Follow-up (months, median [IQR])	58.3 [32.1, 138.1]	84.7 [39.5, 183.9]	45.4 [26.0, 83.8]	108.4 [49.8, 160.2]	< 0.001
Death (%)	38 (8.7)	11 (5.6)	25 (11.4)	2 (8.7)	0.112
Number of patients experiencing n relapse(s) (%)					
0	343 (78.1)	141 (71.9)	188 (85.5)	14 (60.9)	
1	67 (15.3)	37 (18.9)	26 (11.8)	4 (17.4)	
2	20 (4.6)	12 (6.1)	4 (1.8)	4 (17.4)	
3	8 (1.8)	5 (2.6)	2 (0.9)	1 (4.3)	
4	1 (0.2)	1 (0.5)	0 (0)	0 (0)	

Refer to supplementary materials for the definitions of 'date of symptom onset' and seasons. Refer to Additional file 1: Table S1 for the details on the induction and maintenance treatment. Continuous variables are reported as mean (standard deviation (SD)) or median (interquartile range (IQR)) if not normally distributed and compared using the independent sample *t*-test or the Mann-Whitney *U* test, respectively. Categorical variables are summarised by frequency and percentage (%) and compared using the χ^2 test

ANCA anti-neutrophil cytoplasmic antibodies, *ELISA* enzyme-linked immunoassay, *PR3* proteinase-3, *MPO* myeloperoxidase, *CW-DUVB* cumulative-weighted UVB dose, *SD* standard deviation, *IQR* inter-quartile range

phenotype and serotype are summarised in Tables 4 and Additional file 1: Table S4, respectively, and in Additional file 1: Figs. S7 and S8. We observed no significant associations between latitude (adjusted $p = 0.39$), average annual vitD-UVB ($p = 0.65$), average winter vitD-UVB ($p = 0.46$) or CW-D-UVB at symptom onset ($p = 0.66$) and being diagnosed with MPA or being MPO-ANCA positive. The findings were consistent in the sensitivity analysis when restricted to White participants (Additional file 1: Table S5). While

Table 3 Multi-level models investigating the factors associated with AAV relapse risk

	Latitude	Average winter (2004–2019)		Average annual vitD-UVB	CW-D-UVB at symptom onset	Preceding winter	
		vitD-UVB	CW-D-UVB			vitD-UVB	CW-D-UVB
	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
Random effects (variance (SD))							
Patient ID	0.55 (0.75)	0.56 (0.75)	0.57 (0.76)	0.60 (0.78)	0.64 (0.80)	0.59 (0.77)	0.54 (0.74)
Fixed effects (OR (95% CI, *p*))							
Latitude (degrees)	1.41 (1.14–1.74, **0.002**)	–	–	–	–	–	–
Average winter vitDUVB (kJ/m^2)	–	0.71 (0.57–0.89, **0.002**)	–	–	–	0.90 (0.74–1.10, 0.31)	–
Average winter CWD-UVB (kJ/m^2)	–	–	0.74 (0.60–0.91, **0.005**)	–	–	–	0.81 (0.66–0.99, **0.04**)
Average annual vitDUVB (kJ/m^2)	–	–	–	0.82 (0.70–0.99, **0.04**)	–	–	–
CW-D-UVB at symptom onset (kJ/m^2)	–	–	–	–	1.06 (0.88–1.28, 0.52)	–	–
Not MPA (ref: MPA)	1.78 (1.03–3.05, **0.04**)	1.72 (1.00–2.96, **0.05**)	1.75 (1.01–3.01, **0.05**)	1.74 (1.01–3.02, **0.048**)	1.79 (1.02–3.13, **0.04**)	1.78 (1.03–3.10, **0.04**)	1.78 (1.03–3.07, **0.04**)
Age at diagnosis (years)	0.75 (0.61–0.92, **0.006**)	0.74 (0.60–0.90, **0.004**)	0.74 (0.60–0.91, **0.004**)	0.73 (0.60–0.90, **0.004**)	0.73 (0.59–0.90, **0.003**)	0.74 (0.60–0.90, **0.004**)	0.74 (0.60–0.90, **0.004**)
Gender (male)	0.93 (0.61–1.41, 0.73)	0.92 (0.61–1.39, 0.70)	0.91 (0.60–1.38, 0.67)	0.91 (0.60–0.90, 0.64)	0.90 (0.60–1.38, 0.65)	0.91 (0.60–1.37, 0.65)	0.91 (0.60–1.37, 0.65)
Not MPO-ANCA (ref: MPO-ANCA)	1.10 (0.64–1.86, 0.74)	1.10 (0.65–1.88, 0.72)	1.10 (0.64–1.87, 0.74)	1.10 (0.64–1.89, 0.73)	1.08 (0.63–1.87, 0.77)	1.08 (0.63–1.86, 0.77)	1.08 (0.63–1.83, 0.79)
Off treatment (ref: On treatment)	2.65 (1.70–4.14, **< 0.001**)	2.65 (1.70–4.13, **< 0.001**)	2.66 (1.70–4.16, **< 0.001**)	2.66 (1.70–4.17, **< 0.001**)	2.62 (1.68–4.11, **< 0.001**)	2.65 (1.70–4.14, **< 0.001**)	2.64 (1.70–4.11, **< 0.001**)
Number of individuals	439	439	439	439	439	439	439
Number of observations	2080	2080	2080	2080	2080	2077	2077

N (individuals) differs from *N* (observations) as multiple observations (remission ± relapse) per individual were included, according to each participant's disease course

The odds ratios (OR, 95% CI, *p* value) are reported. The OR refers to the probability of having an AAV relapse (relative to remission)

Model 1 investigates the effect of *latitude*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 2 investigates the effect of *average winter (December to February) vitD-UVB (2004–2019)*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 3 investigates the effect of *average winter (December to February) CW-D-UVB (2004–2019)*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 4 investigates the effect of *average annual vitD-UVB*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 5 investigates the effect of *CW-D-UVB at symptom onset*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 6 investigates the effect of *average vitD-UVB over the preceding winter*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

Model 7 investigates the effect of *average CW-D-UVB over the preceding winter*, adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment

vitD-UVB ambient UVB dose at wavelengths than induce vitD synthesis, *CW-D-UVB* cumulative-weighted UVB dose, *SD* standard deviation, *MPA* microscopic polyangiitis, *MPO* myeloperoxidase, *OR* odds ratio, *95% CI* 95% confidence interval

non-significant, we found that vitD-UVB status at diagnosis (CW-D-UVB) was consistently below the annual average at the participants' location (Additional file 1: Fig. S9).

Discussion

For the first time, we examined the relationships between latitude, measures of ambient vitD-UVB and UVB-predicted vitD status and AAV relapse risk. In keeping

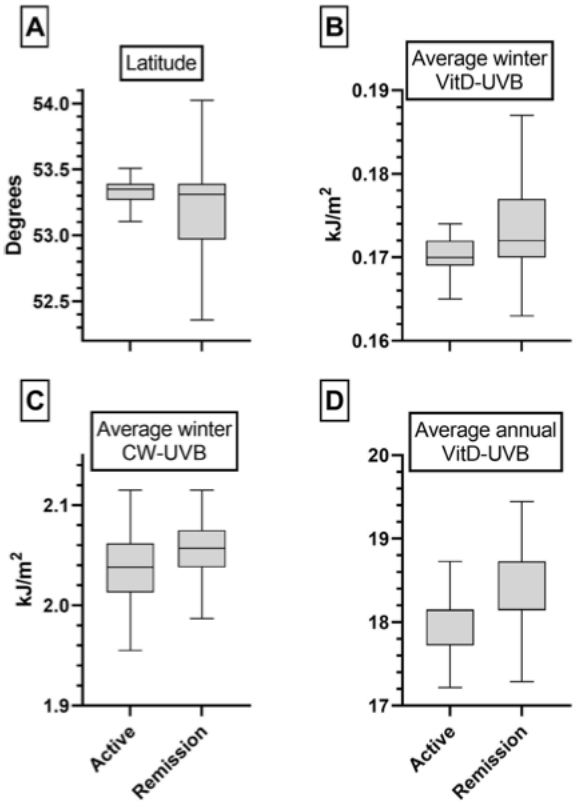


Fig. 3 *AAV relapse.* **a** Latitude (degrees), **b** average winter vitD-UVB (kJ/m^2), **c** average winter CW-D-UVB (kJ/m^2) and **d** average annual vitD-UVB (kJ/m^2) stratified by disease activity (active vs. remission) in the entire cohort 2

with other ADs, we demonstrated that low ambient UVB and, by extension, vitD deficiency are associated with *AAV relapse*, in a genetically homogeneous Irish cohort, after adjustment for key confounders. However, in this large registry-based study that included 2400 AAV patients from an ethnically and latitudinally restricted Irish and British cohort, we found no significant association between latitude, measures of ambient vitD-UVB or UVB-predicted vitD status (CW-D-UVB) and AAV *phenotype* or ANCA *serotype*.

While vitD deficiency has consistently been associated with increased disease activity in other ADs [21, 22], it has not previously been explored in depth in AAV. The risk of AAV relapse was positively associated with residential latitude and negatively with average vitD-UVB. The magnitude of the effect was greatest for average winter vitD-UVB, akin to the findings of Gatenby et al. [8]. This is biologically plausible as low winter exposure to vitD-UVB limits cutaneous vitD synthesis, particularly at more northerly latitudes [10]. We observed a similar negative correlation between average winter CW-D-UVB and relapse risk. For each 1 kJ/m^2 increase in average winter CW-D-UVB, which equates to a 27.2 nmol/L rise in serum 25OHD [24], the odds of relapse decreased by 26%. Clinically, this is similar to moving from vitD 'deficiency' (< 25 nmol/L) to 'sufficiency' (> 50 nmol/L) [42].

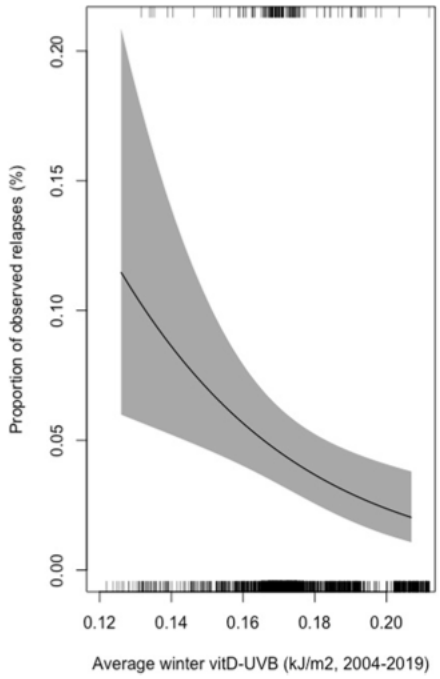


Fig. 4 Effects plot demonstrating the marginal effect of average winter vitD-UVB (kJ/m2) on relapse risk. This is a graphical representation of the multi-level model reported in Table 2 (model 2), controlling for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment status. The average value for continuous covariates and the baseline value for categorical covariates are depicted. Ticks at the top and bottom of the graph refer to the relapse and remission events, respectively. The *predictorEffect* function from the *effects* R package [40, 41] was adapted to create this graphic

We then explored narrower time intervals to pinpoint the at-risk window. While the average CW-D-UVB over the *preceding winter* (to the event) remained independently predictive of AAV relapse, the average vitD-UVB over the same period was not. The vitD-UVB nadir is in December, while CW-D-UVB (and serum 25OHD levels) continues to fall over 'winter', with a nadir 2 months later, so the effect of the latter may thus have been lost by restricting the analysis to winter. Importantly, we found no relationship between UVB-predicted vitD status (CW-D-UVB) at relapse onset and relapse risk. Together, these suggest that, an individual's vitD status over a more prolonged period, particularly during winter, rather than their status peri-relapse, renders them susceptible to relapse and that multiple periods of low UVB and vitD deficiency might be contributing towards disease susceptibility. There was no significant interaction between AAV phenotype and any exploratory variable, suggesting there was no phenotype-specific effect, contrary to our hypothesis.

Drawing on incidence studies from 10 countries, Gatenby et al. [8] observed that GPA (but not MPA) incidence positively and negatively correlated with latitude (35.30° S to 70° N) and ambient UV radiation, respectively [8]. Consistent with this and other series [5–7], we observed a subtle (non-significant) increased odds of MPA (vs. GPA/EGPA) with decreasing latitude and increasing average vitD-UVB. It is possible that this *diagnosis* study component, using standard logistic regression, was underpowered due to the narrow latitudinal range in our cohort. However, contrary to suggestions that phenotype-specific UV effects are mediated by vitD effects on granuloma formation [8], we observed no relationship between UVB-predicted vitD status at symptom onset and AAV phenotype. As with AAV relapse, it may be an individual's vitD status over a longer period, rather than immediately preceding disease onset, that is important. Critically, the outcome was MPA (vs. non-MPA) in this *diagnosis* study component. In our case-only cohorts, we could not directly interrogate whether UV radiation or UVB-predicted vitD status are implicated in *overall* AAV risk (i.e. AAV vs. non-AAV control). It is likely that vitD is important in de novo AAV onset but may not be responsible for defining the (non-) granulomatous phenotype.

The classification of AAV by ANCA serotype is increasingly preferred due to its enhanced predictive value in terms of relapse and renal survival [43, 44]. We found no significant association between latitude, average vitD-UVB or CW-D-UVB and ANCA serotype at diagnosis, although the direction of trends between latitude (negative)/vitD-UVB (positive) and MPO positivity was similar to that of MPA. This diverges from a multi-centre AAV glomerulonephritis registry-based cohort study that found anti-PR3 positivity was positively associated with latitude and negatively with UV radiation [9]. This study was comparable in size ($n = 1408$) to our cohort but covered a wider latitudinal range (Europe and the USA: 35.8° N to 69.6° N) and included a greater ethnic mix. In keeping with our findings, the significant association between ANCA serotype and latitude/UV radiation was lost when the analysis was restricted to centres in North and Central Europe, focusing on a more genetically homogeneous population. The observed variation may therefore be due to genetic or other differences between populations (± their interaction with UVB) as an alternative explanation for reported geographic patterns, for example, the distribution of the frequency of the HLA-DPB*0401 allele [45].

Table 4 Uni- and multivariable logistic regression analysis of factors associated with AAV phenotype at diagnosis, in the combined UKIVAS and RKD cohort

		Not MPA	MPA	Unadjusted	Adjusted			
					Latitude	Average annual vitD-UVB	Average winter vitD-UVB	CW-D-UVB at symptom onset
					Model 1	Model 2	Model 3	Model 4
Age at diagnosis (years)	Mean (SD)	55.6 (15.0)	63.9 (13.7)	1.04 (1.04–1.05, **$p < 0.001$**)	1.04 (1.04–1.05, **$p < 0.001$**)	1.04 (1.04–1.05, **$p < 0.001$**)	1.04 (1.04–1.05, **$p < 0.001$**)	1.04 (1.04–1.05, **$p < 0.001$**)
Gender	Female	685 (63.1)	400 (36.9)	–	–	–	–	–
	Male	831 (67.7)	397 (32.3)	0.82 (0.69–0.97, **$p = 0.022$**)	0.83 (0.69–0.99, **$p = 0.042$**)	0.83 (0.69–0.99, **$p = 0.041$**)	0.83 (0.69–0.99, **$p = 0.042$**)	0.83 (0.69–0.99, **$p = 0.039$**)
Ethnicity	White	1415 (66.0)	728 (34.0)	–	–	–	–	–
	Asian	53 (58.9)	37 (41.1)	1.36 (0.88–2.08, $p = 0.163$)	2.01 (1.26–3.19, **$p = 0.003$**)	2.03 (1.28–3.22, **$p = 0.003$**)	2.03 (1.27–3.21, **$p = 0.003$**)	2.06 (1.29–3.25, **$p = 0.002$**)
	Black	13 (44.8)	16 (55.2)	2.39 (1.15–5.09, **$p = 0.020$**)	3.62 (1.67–8.02, **$p = 0.001$**)	3.67 (1.69–8.13, **$p = 0.001$**)	3.65 (1.68–8.07, **$p = 0.001$**)	3.69 (1.70–8.15, **$p = 0.001$**)
	Mixed	6 (66.7)	3 (33.3)	0.97 (0.20–3.69, $p = 0.968$)	1.27 (0.25–5.30, $p = 0.754$)	1.27 (0.25–5.34, $p = 0.747$)	1.27 (0.25–5.33, $p = 0.750$)	1.27 (0.25–5.33, $p = 0.752$)
	Others	29 (69.0)	13 (31.0)	0.87 (0.44–1.65, $p = 0.683$)	0.93 (0.45–1.82, $p = 0.835$)	0.94 (0.46–1.83, $p = 0.857$)	0.93 (0.45–1.82, $p = 0.837$)	0.95 (0.47–1.85, $p = 0.886$)
Latitude (degrees)	Mean (SD)	52.8 (1.6)	52.6 (1.5)	0.95 (0.90–1.01, $p = 0.078$)	0.98 (0.92–1.03, $p = 0.392$)	–	–	–
Average annual vitD-UVB (kJ/m^2)	Mean (SD)	2.1 (0.2)	2.2 (0.2)	1.29 (0.88–1.91, $p = 0.191$)	–	1.10 (0.74–1.65, $p = 0.645$)	–	–
Average winter vitD-UVB (10 kJ/m^2)	Mean (SD)	1.9 (0.4)	1.9 (0.3)	1.23 (0.96–1.58, $p = 0.102$)	–	–	1.10 (0.85–1.43, $p = 0.458$)	–
CW-D-UVB at symptom onset (J/m^2)	Mean (SD)	0.1 (0.1)	0.1 (0.1)	0.67 (0.21–2.08, $p = 0.487$)	–	–	–	0.77 (0.23–2.51, $p = 0.663$)

The odds ratios (OR, 95% CI, *p* value) are reported. The OR refers to the probability of having MPA-AAV (ref: not MPA) at diagnosis

Model 1 investigates the effect of *latitude*, adjusted for age at diagnosis, gender and ethnicity (observations 2312, 1 missing age, AIC 2798.4)

Model 2 investigates the effect of *average annual vitD-UVB*, adjusted for age at diagnosis, gender and ethnicity (observations 2312, 1 missing age, AIC 2799)

Model 3 investigates the effect of *average winter (December to February) vitD-UVB (2004–2019)*, adjusted for age at diagnosis, gender and ethnicity (observations 2312, 1 missing age, AIC 2798.6)

Model 4 investigates the effect of *CW-D-UVB* at symptom onset, adjusted for age at diagnosis, gender and ethnicity (observations 2312, 1 missing age, AIC 2799)

vitD-UVB ambient UVB dose at wavelengths than induce vitD synthesis, *CW-D-UVB* cumulative-weighted UVB dose, *SD* standard deviation, *MPA* microscopic polyangiitis, *AAV* ANCA-associated vasculitis, *AIC* Akaike Information Criterion, *OR* odds ratio, *95% CI* 95% confidence interval

Our study is the first to investigate the effect of CW-D-UVB, a precise and well-validated vitD proxy, in AAV at an individual level, with high spatial and temporal resolution. This contrasts with the less refined vitD proxies used previously at a population level, such as latitude, sunshine hours or rainfall [8, 9]. The AAV relapse component of our study is the first of its kind to explore the role of ambient measures of vitD-UVB and UVB-predicted vitD on AAV *relapse*. For this, we exploited the benefits of the novel *n*-of-1 study design, primed for use in rare diseases [46], by providing increased power to detect associations by expanding control events. The case-crossover design allowed us to account for many unmeasured determinants of vitD status, such as skin type, lifestyle or SPF use, by comparing UVB measures in active and remission states within the same individual. We were also able to leverage detailed longitudinal immunosuppressive treatment data, enabling us to account for this as a time-varying confounder.

The limitations of our study must also be considered. Our predominantly White cohort originates from a relatively narrow Irish/UK latitudinal gradient. Consequently, restricted latitudinal and genetic variability may contribute to a type II error. Using ambient UVB dose rather than vitD has advantages and disadvantages. While CW-D-UVB as a vitD proxy has been validated in the UK biobank population of almost half a million participants [27], a community-dwelling Irish cohort > 60 years [26] and a RCT of inflammatory bowel disease [25], it has not been validated in AAV patients. Other factors beyond UVB contribute to vitD status: e.g. vitD supplementation might have been high in our cohort (due to its use in renal insufficiency and frequent over-the-counter use following

strong public health campaigns), or disease-associated inflammation might have depleted vitD, potentially weakening the link between UVB and vitD status. We did not have data on vitD supplementation, sun exposure, time spent outside, clothing, SPF use, angle from the sun and many other factors—many of which would be impossible to obtain. However, we assumed each participant's habits were consistent in the application of the multilevel model and the *n*-of-1 study design controls for such within-individual factors. Sporadic measurement of serum 25OHD concentration, the best marker of vitD status is of limited value, because it is strongly affected by season and disease activity [47] (reverse causation) and is not representative of longer-term trajectories. Therefore, a prospective cohort study examining the effect of vitD status on AAV *onset* is impossible (due to disease rarity) and a case-control study would be biassed by reverse causality (inflammation decreases vitD). Therefore, our study design using CW-D-UVB is valuable in the context of these limitations.

Conclusion

In conclusion, we observed a strong inverse relationship between AAV *relapse* risk and individualised measures of vitD-UVB. A maximal effect was observed in winter. Prolonged low ambient UVB likely renders an individual vulnerable to a subsequent 'hit', which ultimately triggers disease activation. We found no evidence limiting this to granulomatous phenotypes. Our large study did not find any significant association between latitude, measures of vitD-UVB nor UVB-predicted vitamin D status and ANCA *phenotype* or *serotype*, albeit in an ethnically restricted cohort, across a narrow latitudinal window. It is plausible that prolonged vitD deficiency predisposes an individual to de novo AAV onset, but it does not appear to be important in the differentiation of AAV phenotype or serotype. Our observations have implications for the design of future vitD studies involving all relapsing-remitting diseases, not just AAV. We recommend a prospective cohort study to measure serial serum (or bloodspot) 25OHD at 3-monthly intervals to examine the trajectory of vitD in AAV *relapse* more accurately, focusing on average or winter vitD status. A RCT of vitD supplementation in AAV, targeting 'sufficient' 25OHD levels (>50nmol/L), with relapse as the primary outcome may then be warranted. vitD supplementation is generally well tolerated, safe and cheap to administer, but routine prescription should be avoided prior to definitive confirmation given the extra pill burden, unnecessary cost and potential for vitD toxicity with resultant hypercalcaemia.

Abbreviations

ANCA: Anti-neutrophil cytoplasm antibody; AAV: ANCA-associated vasculitis; SVV: Small vessel vasculitis; AD: Autoimmune disease; MPA: Microscopic polyangiitis; GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPO: Myeloperoxidase; PR3: Proteinase-3; UV: Ultraviolet; vitD: Vitamin D; 25OHD: 25-Hydroxyvitamin D; vitD-UVB: Ambient UVB dose at wavelengths that induce cutaneous $vitD_3$ synthesis; CW-D-UVB: Cumulative-weighted ambient UVB dose; UKIVAS: United Kingdom and Ireland Vasculitis Rare Disease Group; RKD Registry and Biobank: Rare Kidney Disease Registry and Biobank; RDF: Resource Description Framework; TEMIS: Tropospheric Emission Monitoring Internet Service; ORs: Odds ratios; 95% CI: 95% confidence interval; SD: Standard deviation; IQR: Inter-quartile range; AIC: Akaike Information Criterion; ELISA: Enzyme-linked immunoassay; ns: Not statistically significant; RCT: Randomised controlled trial.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-022-02834-6.

Additional file 1: Fig. S1. Flowchart of participant selection for the UKIVAS cohort (1). **Fig. S2.** Flowchart of participant selection for the RKD cohort (2). **Fig. S3.** Participant locations at diagnosis for i). UKIVAS and ii). RKD cohort. Shading represents the absolute number of participants recruited to the study in that region, at the time of their diagnosis. Tendency to cluster around vasculitis referral centres is observed. **Fig. S4.** Distribution of vitD-UVB (kJ/m2) (a and b) and CW-D-UVB (kJ/m2) (c and d) by month and season: CW-D-UVB peaks in late summer and nadirs in winter. **Fig. S5.** The relationship between latitude (degrees) and a). annual daily average vitD-UVB (kJ/m2, Pearson correlation coefficient (corr) -0.98, p <0.001), b). annual daily average CW-D-UVB (kJ/m2, corr -0.96, p <0.001). CW-D-UVB at diagnosis c). not adjusted for season (kJ/m2, corr -0.12, p <0.001), and d-g). stratified by season (corr winter -0.25, spring -0.15, summer -0.47, autumn -0.22, p <0.001 for all). **Fig. S6.** The relationship between latitude (degrees) and a). annual daily average vitD-UVB (kJ/m2, Pearson correlation coefficient (corr) -0.98, p <0.001), b). annual daily average CW-D-UVB (kJ/m2, corr -0.96, p <0.001). CW-D-UVB at diagnosis c). not adjusted for season (kJ/m2, corr -0.12, p <0.001), and d-g). stratified by season (corr winter -0.25, spring -0.15, summer -0.47, autumn -0.22, p <0.001 for all). **Fig. S7.** AAV diagnosis: a). Latitude (degrees), b). average annual vitD-UVB (kJ/m2), c). average winter vitD-UVB (kJ/m2) and d). CW-D-UVB (kJ/m2) stratified by AAV phenotype (GPA and EGPA ("Not MPA") vs. MPA), at diagnosis. ANCA-associated vasculitis (AAV), Microscopic polyangiitis (MPA), Ambient UVB dose at wavelengths than induce vitD synthesis (vitD-UVB), Cumulative-weighted UVB dose (CW-D-UVB). **Fig. S8.** AAV diagnosis: Latitude (degrees), average annual vitD-UVB (kJ/m2), average winter vitD-UVB (kJ/m2) and CW-D-UVB (kJ/m2) stratified by AAV serotype (a-d: MPO vs. Not MPO), at diagnosis. ANCA-associated vasculitis (AAV), Myeloperoxidase (MPO), Cumulative-weighted UVB dose (CW-D-UVB). **Fig. S9.** Ratio of cumulative-weighted UVB at diagnosis relative to the average value at the participant's location: a). cohort 1 & 2 and stratified by b). AAV phenotype and c). AAV serotype. ANCA-associated vasculitis (AAV), Microscopic polyangiitis (MPA), Myeloperoxidase (MPO), Cumulative-weighted UVB dose (CW-D-UVB), Not statistically significant (ns). If a true association between UVB-predicted vitD status (CW-D-UVB) and AAV phenotype/serotype at diagnosis exists, one would expect that the ratio of CW-D-UVB at diagnosis relative to the average CW-D-UVB at that location would be significantly <1 for non-MPA disease subtypes. A one-sided Wilcoxon rank sum test was used to evaluate if the ratio was significantly different from 1. While the median ratio trended below 1 in the pooled analysis and when stratified by AAV phenotype and serotype, this was not statistically different from 1. **Table S1.** Induction and maintenance treatment of RKD cohort (2). Intravenous (IV). **Table S2.** Multi-level model investigating the factors associated with AAV relapse risk, stratified by AAV phenotype (sensitivity analysis). N (individuals) differs from N (observations) as multiple observations (remission +/- relapse) per individual were included, according to each participant's disease course. The OR refers to the probability of having an AAV relapse (relative to remission). Model 1 investigates the effect of average winter (Dec-Feb) vitD-UVB (2004-2019), adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment, restricted to MPA phenotype. Model 2 investigates the effect of average winter (Dec-Feb) vitD-UVB (2004-2019), adjusted for age at diagnosis, gender, AAV phenotype, ANCA serotype and treatment, restricted to Not MPA phenotype. Cumulative-weighted UVB dose (CW-D-UVB),

Standard deviation (SD), Microscopic polyangiitis (MPA), Myeloperoxidase (MPO), Odds ratio (OR), 95% Confidence interval (95% CI). **Table S3.** Multi-level model investigating the association between CW-D-UVB and the risk of AAV relapse (with treatment breakdown). N (individuals) = 439, N (observations) = 2080 as multiple observations (remission +/- relapse) per individual were included according to each participant's disease course. The OR refers to the probability of having an AAV relapse (relative to remission). Cumulative-weighted UVB dose (CW-D-UVB), Standard deviation (SD), Microscopic polyangiitis (MPA), Myeloperoxidase (MPO), Odds ratio (OR), 95% Confidence interval (95% CI), Azathioprine (AZA), Mycophenolate mofetil (MMF), Methotrexate (MTX). **Table S4.** Uni- and multivariable logistic regression analysis of factors associated with AAV serotype at diagnosis, in the combined UKIVAS and RKD cohort. Note: OR (95% CI, p). The OR refers to the probability of having MPO-positivity (ref: not MPO-ANCA) at diagnosis. Model 1 investigates the effect of latitude, adjusted for age at diagnosis, gender and ethnicity (observations 1260, 1053 missing ANCA serology, AIC 1626.9). Model 2 investigates the effect of average annual vitD-UVB, adjusted for age at diagnosis, gender and ethnicity (observations 1260, 1053 missing ANCA serology, AIC 1626.8). Model 3 investigates the effect of average winter (Dec-Feb) vitD-UVB (2004-2019), adjusted for age at diagnosis, gender and ethnicity (observations 1260, 1053 missing ANCA serology, AIC 1626.5). Model 4 investigates the effect of CW-D-UVB at symptom onset, adjusted for age at diagnosis, gender and ethnicity (observations 1260, 1053 missing ANCA serology, AIC 1627.3). Ambient UVB dose at wavelengths than induce vitD synthesis (vitD-UVB), Cumulative-weighted UVB dose (CW-D-UVB), Standard deviation (SD), Myeloperoxidase (MPO), Akaike information criterion (AIC), Odds ratio (OR), 95% Confidence interval (95% CI). **Table S5.** Uni- and multivariable logistic regression analysis of factors associated with AAV phenotype in the combined UKIVAS and RKD cohort, restricted to White participants (sensitivity analysis). Note: OR (95% CI, p). Observations = 2142 (1 missing age). The OR refers to the probability of having MPA-AAV (ref: not MPA) at diagnosis. Model 1 investigates the effect of latitude, adjusted for age at diagnosis and gender. Model 2 investigates the effect of average annual vitD-UVB, adjusted for age at diagnosis and gender. Model 3 investigates the effect of average winter (Dec-Feb) vitD-UVB (2004-2019), adjusted for age at diagnosis and gender. Model 4 investigates the effect of CW-D-UVB at symptom onset, adjusted for age at diagnosis and gender. Cumulative-weighted UVB dose (CW-D-UVB), Standard deviation (SD), Microscopic polyangiitis (MPA), ANCA-associated vasculitis (AAV), Akaike information criterion (AIC), Odds ratio (OR), 95% Confidence interval (95% CI). **Supplementary Methods**.

Acknowledgements
The authors would like to thank all participants who are enrolled in the UKIVAS and Irish Rare Kidney Disease registries, without whom this research would not be possible. We also extend our sincere gratitude to all clinicians across the UK and Ireland who actively recruit AAV patients to these registries to enable ongoing research.
Members of the RKD consortium:
Tallaght Hospital: Mark Little*, Peter Lavin**, Catherine Wall**, George Mellotte**, Jennifer Scott**, Ted Fitzgerald**, Hannah O'Keefe**, Rachel Dilworth**, Pamela O'Neill[#] and Vicki Carr[#]
St James' Hospital: Niall Conlon*, Brenda Griffin*, Donal Sexton* and Caroline Kosgei[#]
Mater University Hospital: Yvonne O'Meara*, Eoghan White** and Stephen Mahony**
St Vincent's University Hospital: Eamonn Molloy* and John Holian**
Galway University Hospital: Matt Griffin*, David Lappin**, Conor Judge**, Sarah Cormican**, Blathnaid O'Connell** and Michelle Clince**
Limerick University Hospital: Liam Casserly*
Cork University Hospital: Michael Clarkson*, Michelle O'Shaughnessy**, Alyssa Verrelli**, Sinead Stoeman**, Fergus Daly**, Laura Slattery** and Aisling Murphy[#]
Beaumont Hospital: Mark Little*, Declan De Freitas**, Peter Conlon**, Mark Denton**, Carol Treanor**, Colm Magee**, Conall O Seaghdha**, Paul O'Hara**, Susan McGrath**, Brona Moloney**, Dean Moore**, Dearbhla Kelly**, Mary McCarthy**, Tamara Wanigasekera**, Ayanfeoluwa Obilana**, Claire Kennedy**, Dervla Connaughton**, Mark Canney**, Limy Wong** and Sarah Moran**
*Principal investigator; **co-investigator; [#]study coordinator

Authors' contributions
JS, ML, LZ and NB designed the studies, with assistance from JP, our patient representative. JvG and MvW provided the ultraviolet radiation data, specific to each individual's date and location. EH prepared the UKIVAS data for analysis. JS performed all data analysis. AW, JW, CW, LA, JK and JN provided expertise on model development and oversaw all statistical analysis, including data interpretation. AN-G produced the maps of participant locations. AB and TW assisted in the data collection. DO'S and LH oversaw the development of the Resource Description Framework (RDF) triplestore, which facilitated data linkage. All authors read and approved the final submitted manuscript.

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 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 Science Foundation Ireland (13/RC/2106_P2 and 11/YI/B2093). ANG and EH received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No. 813545. The funders were not involved in any part of the study design, analysis or writing of the manuscript.

Availability of data and materials
Due to the rarity of ANCA-associated vasculitis, coupled with the identifiable nature of the data, raw data must remain confidential and cannot be freely shared. We would invite any potential research collaborations or data requests through the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval for the RKD and UKIVAS components was granted by the Tallaght University Research Ethics Committee (ref 2019-08 List 29 (07)) and the NHS National Research Ethics Service (REC 10/H1102/77), respectively. All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Trinity Health Kidney Centre, Trinity College Dublin, The University of Dublin, Trinity Translational Medicine Institute, St. James's Street, Dublin 8, Ireland. [2]Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, UK. [3]ADAPT Centre for Digital Content, Trinity College Dublin, Dublin, Ireland. [4]Department of Statistics, Trinity College Dublin, The University of Dublin, Dublin, Ireland. [5]Royal Netherlands Meteorological Institute (KNMI), De Bilt, The Netherlands. [6]Department of Mathematics and Statistics, University of Limerick, Limerick, Ireland. [7]Department of Mathematical Science, University of Durham, Durham, UK. [8]School of Computer Science, Technological University Dublin, Dublin, Ireland. [9]Vasculitis Ireland Awareness, Galway, Ireland. [10]Department of Public Health and Primary Care, Trinity College Dublin, The University of Dublin, Dublin, Ireland.

Received: 7 September 2021 Accepted: 3 June 2022
Published online: 18 June 2022

References

1. Watts RA, Mahr A, Mohammad AJ, Gatenby P, Basu N, Flores-Suárez LF. Classification, epidemiology and clinical subgrouping of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Nephrol Dial Transplant. 2015;30:i14–22.
2. Lyons PA, Rayner TF, Trivedi S, Holle JU, Watts RA, Jayne DRW, et al. Genetically distinct subsets within ANCA-associated vasculitis. N Engl J Med. 2012;367(3):214–23.
3. Oates T, Salama AD. Epigenetic modifications in ANCA-associated vasculitis: potential for insights into disease pathogenesis and prediction of outcome? J Am Soc Nephrol. 2017;28(4):1011–3.
4. Scott J, Hartnett J, Mockler D, Little MA. Environmental risk factors associated with ANCA associated vasculitis: a systematic mapping review. Autoimmun Rev. 2020;19(11):102660.
5. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. Ann Rheum Dis. 2001;60(2):170–2.
6. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, et al. Epidemiology of vasculitis in Europe. Ann Rheum Dis. 2001;60(12):1156–7.
7. O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient. Intern Med J. 2007;37(4):242–6.
8. Gatenby PA, Lucas RM, Engelsen O, Ponsonby AL, Clements M. Antineutrophil cytoplasmic antibody-associated vasculitides: could geographic patterns be explained by ambient ultraviolet radiation? Arthritis Rheum. 2009;61(10):1417–24.
9. Weiner M, Bjørneklett R, Hrusková Z, Mackinnon B, Poulton CJ, Sindelar L, et al. Proteinase-3 and myeloperoxidase serotype in relation to demographic factors and geographic distribution in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. Nephrol Dial Transplant. 2019;34(2):301–8.
10. Jablonski NG, Chaplin G. The evolution of human skin coloration. J Hum Evol. 2000;39(1):57–106.
11. Frederick JE, Slusser JR, Bigelow DS. Annual and interannual behavior of solar ultraviolet irradiance revealed by broadband measurements. Photochem Photobiol. 2000;72(4):488–96.
12. Gatenby P, Lucas R, Swaminathan A. Vitamin D deficiency and risk for rheumatic diseases: an update. Curr Opin Rheumatol. 2013;25(2):184–91.
13. Ramagopalan SV, Handel AE, Giovannoni G, Rutherford Siegel S, Ebers GC, Chaplin G. Relationship of UV exposure to prevalence of multiple sclerosis in England. Neurology. 2011;76(16):1410–4.
14. O'Connell K, Sulaimani J, Basdeo SA, Kinsella K, Jordan S, Kenny O, et al. Effects of vitamin D(3) in clinically isolated syndrome and healthy control participants: a double-blind randomised controlled trial. Mult Scler J Exp Transl Clin. 2017;3(3):2055217317727296.
15. Fisher SA, Rahimzadeh M, Brierley C, Gration B, Doree C, Kimber CE, et al. The role of vitamin D in increasing circulating T regulatory cell numbers and modulating T regulatory cell phenotypes in patients with inflammatory disease or in healthy volunteers: a systematic review. PLoS One. 2019;14(9):e0222313.
16. Penna G, Amuchastegui S, Giarratana N, Daniel KC, Vulcano M, Sozzani S, et al. 1,25-Dihydroxyvitamin D3 selectively modulates tolerogenic properties in myeloid but not plasmacytoid dendritic cells. J Immunol. 2007;178(1):145–53.
17. Kallenberg CG. Antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. Curr Opin Rheumatol. 2007;19(1):17–24.
18. Zimba O. 338. VITAMIN D DEFICIENCY IN PATIENTS WITH GRANULOMATOSIS WITH POLYANGIITIS. Rheumatology. 2017;56(Issue suppl_2):kex062.340. https://doi.org/10.1093/rheumatology/kex062.340.
19. Korkmaz FN, Ozen G, Unal AU, Can M, Tuglular S, Direskeneli H. AB0530 25-hydroxyvitamin D3 deficiency: prevalance and its impact on disease activity in small-medium vessel vasculitis. Ann Rheum Dis. 2016;75(Suppl 2):1086.
20. Kalsch AI, Peters A, Buhl B, Breedijk A, Prem K, Schmitt WH, et al. Retinoid X receptor beta polymorphisms do not explain functional differences in vitamins D and A response in antineutrophil cytoplasmic antibody associated vasculitis patients. Autoimmunity. 2009;42(5):467–74.
21. Simpson S Jr, Taylor B, Blizzard L, Ponsonby AL, Pittas F, Tremlett H, et al. Higher 25-hydroxyvitamin D is associated with lower relapse risk in multiple sclerosis. Ann Neurol. 2010;68(2):193–203.
22. Laursen JH, Søndergaard HB, Sørensen PS, Sellebjerg F, Oturai AB. Vitamin D supplementation reduces relapse rate in relapsing-remitting multiple sclerosis patients treated with natalizumab. Mult Scler Relat Disord. 2016;10:169–73.
23. Kemna MJ, Tervaert JWC, Broen K. Timmermans SAMEG, Van Paassen P, Damoiseaux JGMC: Seasonal influence on the risk of relapse at a rise of antineutrophil cytoplasmic antibodies in vasculitis patients with renal involvement. J Rheumatol. 2017;44(4):473–81.
24. Kelly D, Theodoratou E, Farrington SM, Fraser R, Campbell H, Dunlop MG, et al. The contributions of adjusted ambient ultraviolet B radiation at place of residence and other determinants to serum 25-hydroxyvitamin D concentrations. Br J Dermatol. 2016;174(5):1068–78.
25. O'Sullivan F, Raftery T, van Weele M, van Geffen J, McNamara D, O'Morain C, et al. Sunshine is an important determinant of vitamin D status even among high-dose supplement users: secondary analysis of a randomized controlled trial in Crohn's disease patients. Photochem Photobiol. 2019;95(4):1060–7.
26. O'Sullivan F, Laird E, Kelly D, van Geffen J, van Weele M, McNulty H, et al. Ambient UVB dose and sun enjoyment are important predictors of vitamin D status in an older population. J Nutr. 2017;147(5):858–68.
27. Li X, et al. Genetically-predicted vitamin D status, ambient UVB during the pandemic and COVID-19 risk in UK Biobank: Mendelian randomisation study. 2020;medRxiv 2020.08.18.20177691. [pre-print]. https://doi.org/10.1101/2020.08.18.20177691.
28. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2012;65(1):1–11.
29. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suarez LF, Guillevin L, et al. Position paper: revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13(11):683–92.
30. Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007;66(2):222–7.
31. patientMpower is a smartphone application. https://apps.apple.com/ie/app/patientmpower/id1077787395. developed in 2019.
32. Trinity Health Kidney Centre: AVERT [https://www.tcd.ie/medicine/thkc/avert/]
33. Reddy BP, Houlding B, Hederman L, et al. Data linkage in medical science using the resource description framework: the AVERT model [version 2; peer review: 2 approved]. HRB Open Res. 2019;1:20. https://doi.org/10.12688/hrbopenres.12851.2.
34. Van Geffen J, Van Weele M, Allaart M, Van der AR. Royal Netherlands Meteorological Institute (KNMI). Dataset. 2017. https://doi.org/10.21944/temis-uv-oper-v2. Accessed August 2021.
35. TEMIS v2 [http://www.temis.nl/uvradiation/UVdose.html; version 2.0]
36. Houben E, Groenland SL, van der Heijden JW, Voskuyl AE, Doodeman HJ, Penne EL. Relation between duration of the prodromal phase and renal damage in ANCA-associated vasculitis. BMC Nephrol. 2017;18(1):378.
37. Shamseer L, Sampson M, Bukutu C, Schmid CH, Nikles J, Tate R, et al. CONSORT extension for reporting N-of-1 trials (CENT) 2015: explanation and elaboration. BMJ. 2015;350:h1793.
38. Bates D, Mächler M, Bolker B, Walker S. Fitting Linear Mixed-Effects Models Using lme4. Journal of Statistical Software. 2015;67(1):1–48. https://doi.org/10.18637/jss.v067.i01.
39. Kirkwood BRSJ. Essential medical statistics. 2nd ed. Oxford: Blackwell Science; 2003.
40. Fox JWS. An R companion to applied regression. 3rd ed. Thousand Oaks: Sage; 2019.
41. Fox J, Weisberg S. Visualizing Fit and Lack of Fit in Complex Regression Models with Predictor Effect Plots and Partial Residuals. Journal of Statistical Software. 2018;87(9):1–27. https://doi.org/10.18637/jss.v087.i09.
42. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab. 2011;96(1):53–8.
43. Lionaki S, Blyth ER, Hogan SL, Hu Y, Senior BA, Jennette CE, et al. Classification of antineutrophil cytoplasmic autoantibody vasculitides: the role of antineutrophil cytoplasmic autoantibody specificity for myeloperoxidase or proteinase 3 in disease recognition and prognosis. Arthritis Rheum. 2012;64(10):3452–62.

44. Mohammad AJ, Segelmark M. A population-based study showing better renal prognosis for proteinase 3 antineutrophil cytoplasmic antibody (ANCA)-associated nephritis versus myeloperoxidase ANCA-associated nephritis. J Rheumatol. 2014;41(7):1366–73.
45. Watts RA, MacGregor AJ, Mackie SL. HLA allele variation as a potential explanation for the geographical distribution of granulomatosis with polyangiitis. Rheumatology. 2014;54(2):359–62.
46. Maclure M. The case-crossover design: a method for studying transient effects on the risk of acute events. Am J Epidemiol. 1991;133(2):144–53.
47. Reid D, Toole BJ, Knox S, Talwar D, Harten J, O'Reilly DS, et al. The relation between acute changes in the systemic inflammatory response and plasma 25-hydroxyvitamin D concentrations after elective knee arthroplasty. Am J Clin Nutr. 2011;93(5):1006–11.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

BMC

References

1. Carruthers DM, Watts RA, Symmons DP, Scott DG. Wegener's granulomatosis--increased incidence or increased recognition? Br J Rheumatol. 1996;35(2):142-5.
2. Cotch MF, Hoffman GS, Yerg DE, Kaufman GI, Targonski P, Kaslow RA. The epidemiology of Wegener's granulomatosis. Estimates of the five-year period prevalence, annual mortality, and geographic disease distribution from population-based data sources. Arthritis & Rheumatism. 1996;39(1):87-92.
3. Draibe J, Rodo X, Fulladosa X, Martinez-Valenzuela L, Diaz-Encarnacion M, Santos L, et al. Seasonal variations in the onset of positive and negative renal ANCA-associated vasculitis in Spain. Clin Kidney J. 2018;11(4):468-73.
4. Mahr A, Artigues N, Coste J, Aouba A, Pagnoux C, Guillevin L. Seasonal variations in onset of Wegener's granulomatosis: increased in summer? J Rheumatol. 2006;33(8):1615-22.
5. Falk RJ, Hogan S, Carey TS, Jennette JC. Clinical course of anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and systemic vasculitis. The Glomerular Disease Collaborative Network. Ann Intern Med. 1990;113(9):656-63.
6. Koldingsnes W, Nossent H. Epidemiology of Wegener's granulomatosis in northern Norway. Arthritis Rheum. 2000;43(11):2481-7.
7. Lane SE, Watts RA, Scott DG. Seasonal variations in onset of Wegener's granulomatosis: increased in summer? J Rheumatol. 2007;34(4):889-90; author reply 90.
8. Li J, Cui Z, Long JY, Huang W, Wang JW, Wang H, et al. The frequency of ANCA-associated vasculitis in a national database of hospitalized patients in China. Arthritis Res Ther. 2018;20(1):226.
9. Pavone L, Grasselli C, Chierici E, Maggiore U, Garini G, Ronda N, et al. Outcome and prognostic factors during the course of primary small-vessel vasculitides. J Rheumatol. 2006;33(7):1299-306.
10. Tidman M, Olander R, Svalander C, Danielsson D. Patients hospitalized because of small vessel vasculitides with renal involvement in the period 1975-95: organ involvement, anti-neutrophil cytoplasmic antibodies patterns, seasonal attack rates and fluctuation of annual frequencies. J Intern Med. 1998;244(2):133-41.
11. Gatenby PA, Lucas RM, Engelsen O, Ponsonby AL, Clements M. Antineutrophil cytoplasmic antibody-associated vasculitides: could geographic patterns be explained by ambient ultraviolet radiation? Arthritis Rheum. 2009;61(10):1417-24.
12. Kalsch AI, Peters A, Buhl B, Breedijk A, Prem K, Schmitt WH, et al. Retinoid X receptor beta polymorphisms do not explain functional differences in vitamins D and A response in Antineutrophil cytoplasmic antibody associated vasculitis patients. Autoimmunity. 2009;42(5):467-74.
13. Kemna MJ, Tervaert JWC, Broen K, Timmermans SAMEG, Van Paassen P, Damoiseaux JGMC. Seasonal influence on the risk of relapse at a rise of antineutrophil cytoplasmic antibodies in vasculitis patients with renal involvement. Journal of Rheumatology. 2017;44(4):473-81.
14. O'Donnell JL, Stevanovic VR, Frampton C, Stamp LK, Chapman PT. Wegener's granulomatosis in New Zealand: evidence for a latitude-dependent incidence gradient. Intern Med J. 2007;37(4):242-6.

15. Reinhold-Keller E. No difference in the incidences of vasculitides between north and south Germany: first results of the German vasculitis register. Rheumatology. 2002;41(5):540-9.
16. Watts RA, Gonzalez-Gay MA, Lane SE, Garcia-Porrua C, Bentham G, Scott DG. Geoepidemiology of systemic vasculitis: comparison of the incidence in two regions of Europe. Annals of the rheumatic diseases. 2001;60(2):170-2.
17. Watts RA, Lane SE, Scott DG, Koldingsnes W, Nossent H, Gonzalez-Gay MA, et al. Epidemiology of vasculitis in Europe. Annals of the rheumatic diseases. 2001;60(12):1156-7.
18. Weiner M, Bjørneklett R, Hrusková Z, Mackinnon B, Poulton CJ, Sindelar L, et al. Proteinase-3 and myeloperoxidase serotype in relation to demographic factors and geographic distribution in anti-neutrophil cytoplasmic antibody-associated glomerulonephritis. Nephrology Dialysis Transplantation. 2019;34(2):301-8.
19. Herlyn K, Buckert F, Gross WL, Reinhold-Keller E. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. Rheumatology (Oxford). 2014;53(5):882-9.
20. Kanecki K, Nitsch-Osuch A, Gorynski P, Tarka P, Tyszko P. Hospital Morbidity Database for Epidemiological Studies on Churg-Strauss Syndrome. Adv Exp Med Biol. 2017;980:19-25.
21. Ormerod AS, Cook MC. Epidemiology of primary systemic vasculitis in the Australian Capital Territory and south-eastern New South Wales. Intern Med J. 2008;38(11):816-23.
22. Besada E, Koldingsnes W, Nossent JC. Staphylococcus Aureus carriage and long-term Rituximab treatment for Granulomatosis with polyangiitis. PeerJ. 2015;3:e1051.
23. Fijołek J, Wiatr E, Petroniec V, Augustynowicz-Kopec E, Bednarek M, Gawryluk D, et al. The presence of staphylococcal superantigens in nasal swabs and correlation with activity of granulomatosis with polyangiitis in own material. Clin Exp Rheumatol. 2018;36 Suppl 111(2):40-5.
24. Lamprecht P, Fischer N, Huang J, Burkhardt L, Lutgehetmann M, Arndt F, et al. Changes in the composition of the upper respiratory tract microbial community in granulomatosis with polyangiitis. J Autoimmun. 2019;97:29-39.
25. Laudien M, Gadola SD, Podschun R, Hedderich J, Paulsen J, Reinhold-Keller E, et al. Nasal carriage of Staphylococcus aureus and endonasal activity in Wegener s granulomatosis as compared to rheumatoid arthritis and chronic Rhinosinusitis with nasal polyps. Clin Exp Rheumatol. 2010;28(1 Suppl 57):51-5.
26. Popa ER, Stegeman CA, Abdulahad WH, van der Meer B, Arends J, Manson WM, et al. Staphylococcal toxic-shock-syndrome-toxin-1 as a risk factor for disease relapse in Wegener's granulomatosis. Rheumatology (Oxford). 2007;46(6):1029-33.
27. Rhee RL, Sreih AG, Najem CE, Grayson PC, Zhao C, Bittinger K, et al. Characterisation of the nasal microbiota in granulomatosis with polyangiitis. Ann Rheum Dis. 2018;77(10):1448-53.
28. Richter AG, Stockley RA, Harper L, Thickett DR. Pulmonary infection in Wegener granulomatosis and idiopathic pulmonary fibrosis. Thorax. 2009;64(8):692-7.
29. Salmela A, Rasmussen N, Tervaert JWC, Jayne DRW, Ekstrand A. Chronic nasal Staphylococcus aureus carriage identifies a subset of newly diagnosed granulomatosis with polyangiitis patients with high relapse rate. Rheumatology (United Kingdom). 2017;56(6):965-72.

30. Stegeman CA, Tervaert JW, Sluiter WJ, Manson WL, de Jong PE, Kallenberg CG. Association of chronic nasal carriage of Staphylococcus aureus and higher relapse rates in Wegener granulomatosis. Ann Intern Med. 1994;120(1):12-7.
31. Tan BK, Crabol Y, Tasse J, Laurent F, Nekkab N, Vinter C, et al. No evident association of nasal carriage of Staphylococcus aureus or its small-colony variants with cotrimoxazole use or ANCA-associated vasculitis relapses. Rheumatology (Oxford). 2020;59(1):77-83.
32. Barzilai O, Sherer Y, Ram M, Izhaky D, Anaya JM, Shoenfeld Y. Epstein-Barr virus and cytomegalovirus in autoimmune diseases: are they truly notorious? A preliminary report. Ann N Y Acad Sci. 2007;1108:567-77.
33. Cook PM, Schulz TF, Rascu A, Kalden JR, Harrer T. Lack of serologic evidence for involvement of human herpesvirus 8 in autoimmune diseases. Arthritis Rheum. 1997;40(10):1906-7.
34. Eden A, Mahr A, Servant A, Radjef N, Amard S, Mouthon L, et al. Lack of association between B19 or V9 erythrovirus infection and ANCA-positive vasculitides: a case-control study. Rheumatology (Oxford). 2003;42(5):660-4.
35. Eriksson P, Sandell C, Backteman K, Ernerudh J. Expansions of CD4+CD28- and CD8+CD28- T cells in granulomatosis with polyangiitis and microscopic polyangiitis are associated with cytomegalovirus infection but not with disease activity. J Rheumatol. 2012;39(9):1840-3.
36. Gerke P, Wichmann D, Schönermarck U, Schütt M, Feldmann H, Ksiazek TG, et al. Lack of evidence for an association between hantavirus infections and Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and giant cell arteritis. Rheumatology (Oxford). 2000;39(12):1424-5.
37. Lee SW, Kim DY, Ahn SH, Park YB, Han KH, Park JY. HBsAg-negative and anti-HBc-positive in eosinophilic granulomatosis with polyangiitis: a retrospective pilot study. Rheumatol Int. 2018;38(8):1531-8.
38. Fujita M, Hatachi S, Yagita M. Acute Chlamydia pneumoniae infection in the pathogenesis of autoimmune diseases. Lupus. 2009;18(2):164-8.
39. Iyoda M, Kuroki A, Sugisaki T. Chlamydia pneumoniae infection and MPO-ANCA-associated glomerulonephritis. Nephrol Dial Transplant. 2007;22(3):965-6.
40. Lidar M, Lipschitz N, Langevitz P, Barzilai O, Ram M, Porat-Katz BS, et al. Infectious serologies and autoantibodies in Wegener's granulomatosis and other vasculitides: novel associations disclosed using the Rad BioPlex 2200. Ann N Y Acad Sci. 2009;1173:649-57.
41. Nielsen PR, Kragstrup TW, Deleuran BW, Benros ME. Infections as risk factor for autoimmune diseases - A nationwide study. J Autoimmun. 2016;74:176-81.
42. Stratta P, Messuerotti A, Canavese C, Coen M, Luccoli L, Bussolati B, et al. The role of metals in autoimmune vasculitis: epidemiological and pathogenic study. Sci Total Environ. 2001;270(1-3):179-90.
43. Buhler S, Jaeger VK, Adler S, Bannert B, Brummerhoff C, Ciurea A, et al. Safety and immunogenicity of tetanus/diphtheria vaccination in patients with rheumatic diseases-a prospective multi-centre cohort study. Rheumatology (Oxford). 2019;58(9):1585-96.
44. Stassen PM, Sanders JS, Kallenberg CG, Stegeman CA. Influenza vaccination does not result in an increase in relapses in patients with ANCA-associated vasculitis. Nephrol Dial Transplant. 2008;23(2):654-8.
45. Zycinska K, Romanowska M, Nowak I, Rybicka K, Wardyn KA, Brydak LB. Antibody response to inactivated subunit influenza vaccine in patients with Wegener's granulomatosis. J Physiol Pharmacol. 2007;58 Suppl 5(Pt 2):819-28.

46. Albert D, Clarkin C, Komoroski J, Brensinger CM, Berlin JA. Wegener's granulomatosis: Possible role of environmental agents in its pathogenesis. Arthritis Rheum. 2004;51(4):656-64.
47. Cuadrado MJ, D'Cruz D, Lloyd M, Mujic F, Khamashta MA, Hughes GR. Allergic disorders in systemic vasculitis: a case-controlled study. Br J Rheumatol. 1994;33(8):749-53.
48. Lane SE, Watts RA, Bentham G, Innes NJ, Scott DG. Are environmental factors important in primary systemic vasculitis? A case-control study. Arthritis Rheum. 2003;48(3):814-23.
49. Stamp LK, Chapman PT, Francis J, Beckert L, Frampton C, Watts RA, et al. Association between environmental exposures and granulomatosis with polyangiitis in Canterbury, New Zealand. Arthritis Res Ther. 2015;17:333.
50. Beaudreuil S, Lasfargues G, Laueriere L, El Ghoul Z, Fourquet F, Longuet C, et al. Occupational exposure in ANCA-positive patients: a case-control study. Kidney Int. 2005;67(5):1961-6.
51. Rihova Z, Maixnerova D, Jancova E, Pelclova D, Bartunkova J, Fenclova Z, et al. Silica and asbestos exposure in ANCA-associated vasculitis with pulmonary involvement. Ren Fail. 2005;27(5):605-8.
52. Farquhar HJ, McGettigan B, Chapman PT, O'Donnell JL, Frampton C, Stamp LK. Incidence of anti-neutrophil cytoplasmic antibody-associated vasculitis before and after the February 2011 Christchurch Earthquake. Intern Med J. 2017;47(1):57-61.
53. Takeuchi Y, Saito A, Ojima Y, Kagaya S, Fukami H, Sato H, et al. The influence of the Great East Japan earthquake on microscopic polyangiitis: A retrospective observational study. PLoS One. 2017;12(5):e0177482.
54. Haubitz M, Woywodt A, de Groot K, Haller H, Goebel U. Smoking habits in patients diagnosed with ANCA associated small vessel vasculitis. Ann Rheum Dis. 2005;64(10):1500-2.
55. Pearce FA, Lanyon PC, Watts RA, Grainge MJ, Abhishek A, Hubbard RB. Novel insights into the aetiology of granulomatosis with polyangiitis-a case-control study using the Clinical Practice Research Datalink. Rheumatology (Oxford). 2018;57(6):1002-10.
56. Yamaguchi M, Ando M, Katsuno T, Tsuboi N, Maruyama S. Smoking Is a Risk Factor for Relapse of Antimyeloperoxidase Antibodies-Associated Vasculitis. J Clin Rheumatol. 2018;24(7):361-7.
57. Willeke P, Schluter B, Sauerland C, Becker H, Reuter S, Jacobi A, et al. Farm Exposure as a Differential Risk Factor in ANCA-Associated Vasculitis. PLoS One. 2015;10(9):e0137196.
58. Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ. Silica Exposure in Anti-Neutrophil Cytoplasmic Autoantibody-Associated Glomerulonephritis and Lupus Nephritis. Journal of the American Society of Nephrology. 2001;12(1):134.
59. Knight A, Sandin S, Askling J. Occupational risk factors for Wegener's granulomatosis: a case-control study. Ann Rheum Dis. 2010;69(4):737-40.
60. Nuyts GD, Van Vlem E, De Vos A, Daelemans RA, Rorive G, Elseviers MM, et al. Wegener granulomatosis is associated to exposure to silicon compounds: a case-control study. Nephrol Dial Transplant. 1995;10(7):1162-5.
61. Pai P, Bone JM, Bell GM. Hydrocarbon exposure and glomerulonephritis due to systemic vasculitis. Nephrology Dialysis Transplantation. 1998;13(5):1321-3.
62. Scott J, Hartnett J, Mockler D, Little MA. Environmental risk factors associated with ANCA associated vasculitis: A systematic mapping review. Autoimmunity Reviews. 2020;19(11):102660.

63. Aries PM, Herlyn K, Reinhold-Keller E, Latza U. No seasonal variation in the onset of symptoms of 445 patients with Wegener's granulomatosis. Arthritis Rheum. 2008;59(6):904.
64. Stegeman CA, Tervaert JW, de Jong PE, Kallenberg CG. Trimethoprim-sulfamethoxazole (co-trimoxazole) for the prevention of relapses of Wegener's granulomatosis. Dutch Co-Trimoxazole Wegener Study Group. N Engl J Med. 1996;335(1):16-20.
65. Zycinska K, Wardyn KA, Zielonka TM, Krupa R, Lukas W. Co-trimoxazole and prevention of relapses of PR3-ANCA positive vasculitis with pulmonary involvement. Eur J Med Res. 2009;14 Suppl 4(Suppl 4):265-7.
66. Sachetto Z, Costa SC, Andrade PD, Conde RA, Amstalden EM, Samara AM, et al. No evidence of parvovirus B19 in tissue samples from patients with polyarteritis nodosa and microscopic polyangiitis as assessed by the polymerase chain reaction. Ann Rheum Dis. 2006;65(3):418-20.
67. Ishiguro T, Takayanagi N, Takaku Y, Kagiyama N, Kurashima K, Sugita Y. Combined Allergic Bronchopulmonary Aspergillosis and Eosinophilic Granulomatosis with Polyangiitis: Three Cases and a Review of the Literature. Intern Med. 2016;55(7):793-7.
68. Duggal T, Segal P, Shah M, Carter-Monroe N, Manoharan P, Geetha D. Antineutrophil cytoplasmic antibody vasculitis associated with influenza vaccination. Am J Nephrol. 2013;38(2):174-8.
69. Gomez-Puerta JA, Gedmintas L, Costenbader KH. The association between silica exposure and development of ANCA-associated vasculitis: systematic review and meta-analysis. Autoimmun Rev. 2013;12(12):1129-35.
70. Yashiro M, Muso E, Itoh T, Oyama A, Ono T, Sasayama S. Significantly high incidence and high morbidity of acute renal failure with respiratory tract involvement of p-ANCA-related angitis revealed in Kobe city and the environs after the Kobe earthquake in 1995. Clin Nephrol. 1999;51(3):190-1.
71. Lee JH, Attygalle T, Gaffney K, Scott DG. Demographics and environmental factors in a Wegener's granulomatosis cluster. Ann Rheum Dis. 2007;66(2):278-9.
72. Albert DA, Albert AN, Vernace M, Sebastian JK, Hsia EC. Analysis of a cluster of cases of Wegener granulomatosis. J Clin Rheumatol. 2005;11(4):188-93.
73. Rutherford MA, Scott J, Karabayas M, Antonelou M, Gopaluni S, Gray D, et al. Risk Factors for Severe Outcomes in Patients With Systemic Vasculitis and COVID-19: A Binational, Registry-Based Cohort Study. Arthritis & Rheumatology. 2021;73(9):1713-9.
74. Scott J, Nic an RÌogh E, Al Nokhatha S, Cowhig C, Verrelli A, Fitzgerald T, et al. ANCA-associated vasculitis in Ireland: a multi-centre national cohort study [version 1; peer review: 2 approved]. HRB Open Research. 2022;5(80).
75. Scott J, Nic an Ríogh E, Al Nokhatha S, Cowhig C VA, Fitzgerald T, White A, Walsh C, Aslett L, DeFreitas D, Clarkson MR, Holian J, Griffin MD, Conlon N, O'Meara Y, Casserly L, Molloy E, Power J, Moran SM, Little MA. Extended data for 'ANCA-associated vasculitis in Ireland: a multi-centre national cohort study'. Zenodo. 2022.
76. Scott J, Havyarimana E, Navarro-Gallinad A, White A, Wyse J, van Geffen J, et al. The association between ambient UVB dose and ANCA-associated vasculitis relapse and onset. Arthritis Research & Therapy. 2022;24(1):147.