# Health outcomes in people with rare autoimmune rheumatic diseases before and during the COVID-19 pandemic and the effect of corticosteroids: whole population data from England.

Dr Megan Rutter
BMBS, BMedSci, MRCP

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## Declaration/Candidate Statement

This is to certify that the work submitted in this thesis is the result of original research. I substantially conducted the work myself, with assistance as outlined below.

In chapter 3, assistance from Peter Stilwell, an analyst at the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), was received to create reproducible code to extract general population data from the NOMIS website.

The work in this thesis has not previously been submitted as part of a degree. All authors and works to which reference has been made are fully acknowledged.

The study design, data extraction, analysis, writing, and general administration were primarily conducted by myself with support from my supervisors.

Supervision of this thesis was undertaken by Dr Fiona Pearce, Dr Peter Lanyon, Dr Matthew Grainge, and Professor Richard Hubbard.

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# Abstract

**Introduction:**

Rare autoimmune rheumatic diseases (RAIRD) are a heterogenous group of immune-mediated inflammatory diseases. They are chronic and often require immunosuppression.

At the onset of the COVID-19 pandemic, it was unclear whether people with RAIRD were at increased risk of severe COVID-19 outcomes, whether some conditions were associated with greater risk than others and whether immunosuppressive treatments, such as corticosteroids, conferred an increased risk of severe disease.

RAIRD have long been associated with increased morbidity and mortality, with poor outcomes attributable both to the effects of treatment and the underlying disease. Severe infections, including with atypical pathogens, are of concern. Previous studies have found that mortality is approximately 1.2-10-fold higher among people with RAIRD compared with the general population, however there is variability within and between diseases, reflecting lack of statistical power, selection bias and variations in ascertainment of the underlying diseases. There have been few population-based studies and contemporary data regarding cause of death in RAIRD remain scarce.

**Methods:**

I used linked national datasets of routinely collected healthcare data (demographic, death certificate, hospital, PCR testing and prescription data) to describe health outcomes in people with RAIRD.

The specific objectives of the studies were to:

1) Calculate the age-standardised rates of laboratory confirmed COVID-19 infection and death among people with RAIRD in England during the first and second waves of the COVID-19 pandemic (1st March 2020 – 31st July 2020 and 1st August 2020 – 30th April 2021) and compare these rates to those in the

general population. Describe hospital and intensive care admissions related to COVID-19 infection, and all-cause mortality during each wave.

2) Assess the relationship between corticosteroid treatment and COVID-19-related death among people with RAIRD during the second wave of the COVID-19 pandemic.
3) Describe all-cause mortality in people with RAIRD during the years 2013-2020, including the calculation of all-cause and cause-specific age-sex-standardised mortality rates and comparison with the general population in England.

**Results:**

1) Of the 168,680 people with RAIRD alive at the start of the first COVID-19 wave, 1874 (1.11%) had a positive COVID-19 PCR test. The age-standardised infection rate was 1.54 (95% CI 1.50-1.59) times higher than in the general population. 713 (0.42%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.41 (2.30 – 2.53) times higher than in the general population. There was no evidence of an increase in deaths from other causes in the RAIRD population.
2) Of the 168,330 people with RAIRD alive at the start of the second COVID-19 wave, 9,961 (5.92%) had a positive COVID-19 PCR test. The age-standardised infection rate ratio between RAIRD and the general population was 0.99 (95% CI 0.97-1.00). 1,342 (0.80%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.76 (2.63–2.89) times higher than in the general population. There was a dose-dependent relationship between 30-day corticosteroid usage and COVID-19-related death. There was no increase in deaths due to other causes.
3) There were 108,593 people with RAIRD in 2013 and 180,083 in 2020. The majority were female (annual minimum 69.9%, maximum 70.9%). Median age increased from 61.5 to 62.5 years, compared to 39.7 to 40.2 years in the general population. Crude and age-sex-standardised all-cause mortality

gradually reduced between 2013-2019, increasing again in 2020 (during COVID-19). Age-sex-standardised mortality in 2013 was 2,324.5 per 100,000 person/years (95% CI 2,261.5-2,387.6) and in 2020 2,332.8 (2,283.3-2,382.2; rate ratio 2.4 (2.3-2.4) compared to general population). Risk of death due to infection (rate ratio 4.11 (3.82-4.40)), cardiovascular disease (2.51 (2.47–2.56)), COVID-19 (2.77 (2.62–2.92)), and respiratory disease (2.92 (2.84–2.99)) were particularly raised. Intra-disease comparison showed higher all-cause mortality in scleroderma, myositis, microscopic polyangiitis and unspecified arteritis. Only 28/53,166 deaths were secondary to cytomegalovirus, 35 Pneumocystis jirovecii pneumonia and 8 progressive multifocal leukoencephalopathy.

**Conclusions:**

1) During the first wave of COVID-19 in England, people with RAIRD had a 54% increased risk of COVID-19 infection and more than twice the risk of COVID-19-related death compared to the general population. These increases were seen despite shielding policies.
2) During the second wave of COVID-19 in England, people with RAIRD had the same risk of COVID-19 infection but a 2.76-fold increased risk of COVID-19-related death compared to the general population, with corticosteroids associated with increased risk.
3) Adjusting for age and sex, mortality in people with RAIRD was increased across all causes except dementia. Risk of death due to infection, COVID-19 and respiratory disease was particularly raised. Deaths due to infections associated with immunosuppression were rare.

# Abbreviations

| | |
|---|---|
| AAV | ANCA-associated vasculitis |
| ANA | Anti-nuclear antibodies |
| ANCA | Anti-neutrophil cytoplasmic antibodies |
| AOSD | Adult-onset Still's disease |
| APC | Admitted patient care |
| ASMR | Age-standardised mortality rate |
| BSR | British Society for Rheumatology |
| CAG | Comptroller and Auditor General |
| CEV | Clinically extremely vulnerable |
| CI | Confidence interval |
| CMV | Cytomegalovirus |
| COPD | Chronic obstructive pulmonary disease |
| COPI | Control of Patient Information Regulations 2002 |
| COVID-19 | Coronavirus Disease 2019 |
| .csv | Comma separated values |
| CTD | Connective tissue disease |
| DBS | Disclosure and Barring Service |
| DMARDs | Disease modifying anti-rheumatic drugs |
| DOB | Date of birth |
| EGPA | Eosinophilic granulomatosis with polyangiitis |
| ESP | European Standard Population |
| EULAR | European League Against Rheumatism |
| FCE | Finished consultant episode |
| GCA | Giant cell arteritis |
| GPA | Granulomatosis with polyangiitis |
| GPES | General Practice Extraction Service |
| HDR-UK | Health Data Research UK |
| HES | Hospital Episode Statistics |
| HLH | Haemophagocytic lymphohistiocytosis |
| HR | Hazard ratio |
| ICD-10 | International Classification of Diseases 10th Revision |
| ICTV | International Committee on Taxonomy of Viruses |
| ICU | Intensive care unit |

| | |
|---|---|
| IIM | Idiopathic inflammatory myopathy |
| IL-6 | Interleukin-6 |
| IMD | Indices of multiple deprivation |
| IQR | Interquartile range |
| IRAS | Integrated research application system |
| IRR | Incidence rate ratio |
| JC virus | John Cunningham virus |
| JIA | Juvenile idiopathic arthritis |
| LFT | Lateral flow test |
| MBIS | Mortality and births information system |
| MERS-CoV | Middle East respiratory syndrome coronavirus |
| MPA | Microscopic polyangiitis |
| MPO | Myeloperoxidase |
| n | Number |
| NCARDRS | National Congenital Anomaly and Rare Disease Registration Service |
| NDRS | National Disease Registration Service |
| NHS | National Health Service |
| NHSD | NHS Digital |
| NHSE | NHS England |
| NHSI | NHS Improvement |
| OHID | Office for Health Improvement and Disparities |
| ONS | Office for National Statistics |
| OPCS | Operating Procedure Codes Supplement |
| NIMS | National Immunisations Management Service |
| PAN | Polyarteritis nodosa |
| PCR | Polymerase chain reaction |
| PED | Prednisolone equivalent dose |
| PHE | Public Health England |
| PJP | Pneumocystis jirovecii pneumonia |
| PML | Progressive multifocal leukoencephalopathy |
| PMR | Polymyalgia rheumatica |
| PPV | Positive predictive value |
| PR3 | Proteinase 3 |
| RA | Rheumatoid arthritis |
| RAIRD | Rare autoimmune rheumatic diseases |

| | |
|---|---|
| RECORDER | Registration of Complex Rare Diseases – Exemplars in Rheumatology |
| RMD | Rheumatic and musculoskeletal disorders |
| SARS-CoV | Severe acute respiratory syndrome coronavirus |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SCID | Severe combined immunodeficiency |
| SE | Standard error |
| SGSS | Second Generation Surveillance System |
| SLE | Systemic lupus erythematosus |
| SMR | Standardised mortality rate |
| SPL | Shielded Patient List |
| SSc | Systemic sclerosis |
| sJIA | Systemic juvenile idiopathic arthritis |
| TAK | Takayasu arteritis |
| UKHSA | UK Health Security Agency |
| VTE | Venous thromboembolism |

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# Chapter 1: Introduction

This PhD is an exploration of the clinical impact of the COVID-19 pandemic on people living with rare autoimmune rheumatic diseases (RAIRD), focusing on COVID-19 infection, admission, and deaths. It also examines mortality in people living with these conditions in the years preceding the pandemic.

Our understanding of COVID-19 has increased so much in the last three years that it can be difficult now to remember the early stages of the COVID-19 pandemic. Faced with an entirely novel pathogen, with rapid global spread, it was a time of huge uncertainty for all. How severe might the infection prove to be? How transmissible was it? Would health services stand up to the challenge?

For people with immunosuppressive conditions or treatments, or with other co-morbidities likely to confer vulnerability to severe infection, it was a particularly anxious time. Both patients and the clinicians looking after them were desperate for answers.

Within the community of clinicians caring for people with RAIRD, key questions included:

- Were people with autoimmune rheumatic conditions at increased risk of severe COVID-19 outcomes?
- Did this include all autoimmune rheumatic conditions, or were some associated with greater risk than others?
- Did immunosuppressive treatments, such as corticosteroids, confer an increased risk of severe disease or, given the immune activation component of severe COVID-19 might they be protective?

Although there were some early studies of COVID-19 outcomes in people living with RAIRD, they were limited by selected populations or small numbers, and it remained difficult to determine what the true risk might be.

Routinely collected healthcare datasets in England contain whole population data in a patient-identifiable format suitable for linkage and are highly suited to addressing questions about outcomes in rare disease. In this thesis, I use routinely collected healthcare data to conduct whole population studies in England to address questions about COVID-19 outcomes in RAIRD. I then use similar methods to examine all-cause mortality in people with RAIRD in the years preceding the pandemic.

This introductory section provides an overview of the COVID-19 pandemic in England, the background clinical and research context in RAIRD, and a discussion of how the arrival of COVID-19 changed the landscape for people living with these conditions. Due to the rapidly evolving nature of the literature in this area, this introduction focuses on what was known at the time of embarking on my PhD, with updates to the literature found in the introduction and discussion sections of chapters 3, 4 and 5, and in the discussion in chapter 6. It then goes on to describe what was known about causes of mortality in people with these conditions in the years preceding COVID-19. This is followed by the objectives of this thesis, and an outline of the thesis chapters.

## 1.1 The COVID-19 pandemic

### *1.1.1 Timeline of the beginning of the pandemic*

On the 31st December 2019, Wuhan Municipal Health Commission reported a cluster of 27 cases of viral pneumonia in Wuhan, in Hubei Province, China(1, 2). Symptoms and signs included fever, cough, chest discomfort, dyspnoea, and lung infiltrates(3). By 10th January 2020 the first death was reported(1) and on 13th January 2020, the first international case was confirmed in Thailand(2). By 20th January 2020, four international cases had been confirmed in a total of three different countries (Thailand, Japan, and South Korea)(1).

The World Health Organisation (WHO) had set up an incident support management team on 1st January, the day after the announcement of the cluster of infections(2). It went on to publish Disease Outbreak News on 5th January 2020(4), confirming that

contact tracing and follow up was in progress, and issued technical guidance on the virus on 10th January(2).

Human-to-human transmission was suspected early on in the outbreak, with spread to family members noted in a press conference on 14th January 2020(2). There was also evidence of nosocomial infections within hospitals(5). Human-to-human transmission was confirmed in a statement by the WHO Mission to China on 22nd January 2020(2).

On the same day, the WHO convened an Emergency Committee to determine whether the outbreak met the criteria for a public health emergency of international concern (PHEIC)(2, 6). Consensus could not be reached but the committee reconvened eight days later, on 30th January 2020, following the confirmation of human-to-human transmission outside China, and a PHEIC was declared(2, 7).

A pandemic was formally declared by the WHO on 11th March 2020(2). By this time, there had been 118,319 confirmed cases globally and 4,292 deaths across 114 countries(8, 9).

Retrospective analysis showed that symptom onset in the first person known to be infected with the virus started on 8th December 2019(3, 5).

*1.1.2 Identification of the novel coronavirus SARS-CoV-2*

China isolated and identified the virus as a novel coronavirus on 7th January 2020, and this was publicly confirmed two days later, on 9th January 2020(5). The genetic sequence of the virus was published on 12th January 2020(2).

The virus was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11th February 2020(8), according to the International Committee on Taxonomy of Viruses (ICTV). The disease caused by the virus was named coronavirus disease 2019 (COVID-19) on the same date(8).

SARS-CoV-2 is a novel betavirus and genome sequencing has confirmed significant similarities to SARS-CoV and to a lesser extent Middle East respiratory syndrome coronavirus (MERS-CoV)(3). Phylogenetic analysis showed close association with SARS and SARS-related coronaviruses found in bats and pangolins(3). This gave weight to the theory that SARS-CoV-2 had resulted from a spillover event between different animal species and humans(10), with evidence pointing towards a clustering of early cases around the Wuhan wet market. However, there remains significant debate and controversy around the origins of SARS-CoV-2, with many unanswered questions remaining.

*1.1.3 Timeline of the pandemic in England*

The first positive cases of COVID-19 in the UK were confirmed on 29th January 2020, in two individuals who had recently travelled to York, UK, from China(11). Sporadic cases were confirmed and isolated, until on 28th February 2020 the first human-to-human transmission in the UK was confirmed(11). On the same date, the first death of a British national was confirmed, albeit on a cruise ship rather than on British soil(11).

Wide-ranging social restrictions, commonly referred to as lockdown, were commenced on 20th March 2020, with all schools, pubs, restaurants, gyms, and other social venues across the UK instructed to close(11). This was followed up with advice on 23rd March 2020 to only go outside to buy food or to exercise once a day, and not to go into the workplace unless there was no alternative(11). People felt to be at risk of severe COVID-19 outcomes were contacted and advised to shield, as described in section 1.1.4.

On 10th May 2020, there was a limited easing of the lockdown, with individuals allowed to take unlimited exercise and to go back to work if they were unable to work from home(11). A 14-day quarantine period following international travel was also announced(11). On 28th May 2020, Track and Trace was launched, to aid in the contact tracing of exposed individuals(11). The next few months saw a gradual

opening up of society, with schools, places of worship, non-essential retailers, and hospitality reopening.

On 6th July 2020, shielding was eased with the introduction of "support bubbles", which enabled households to mix under limited circumstances(11). Shielding was then formally suspended on 1st August 2020(11) and people felt to be Clinically Extremely Vulnerable (CEV) were advised that they could return to "COVID-secure" workplaces.

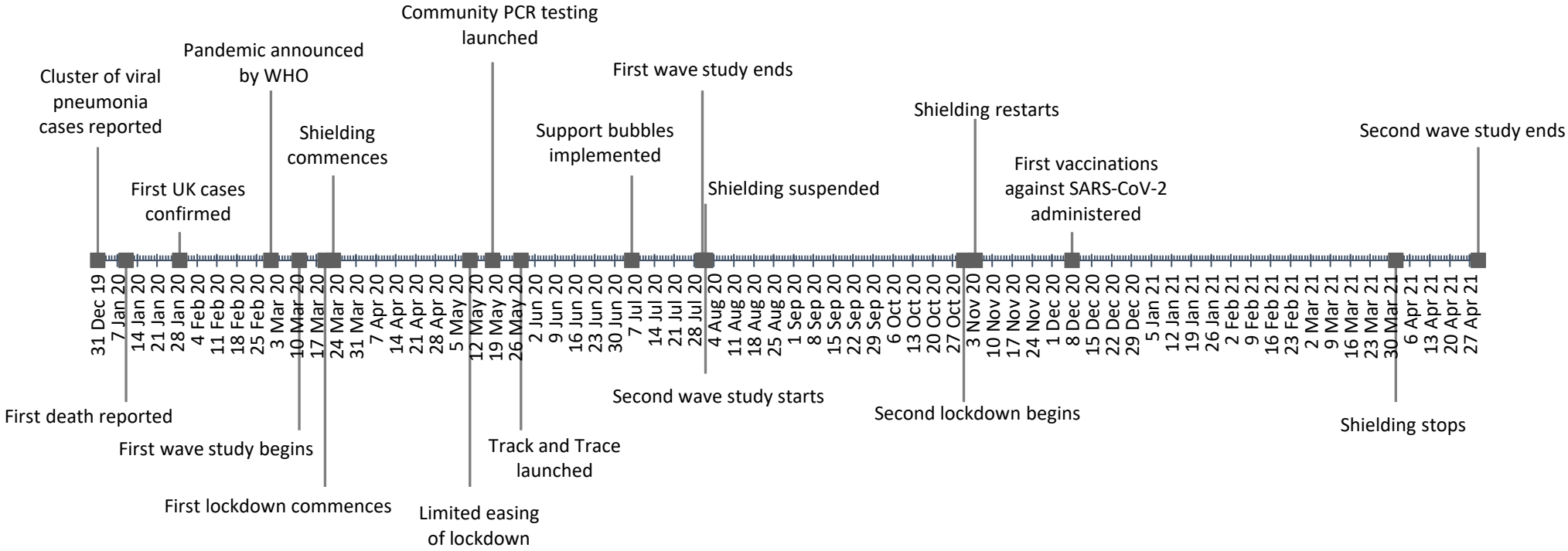
By 9th September 2020, there were fears of an impending second wave of infections and social restrictions were gradually reintroduced, leading up to the formal announcement of a second lockdown on 31st October 2020(11) and the restarting of shielding on 4th November 2020(11).

At the peak of the first wave in England (April 2020), there were 4,812 infections and 1,208 COVID-19-related deaths per day. This reduced to a nadir of 351 infections and 7 deaths in July and August 2020, before rising again to 74,058 infections and 1,328 deaths during the peak of the second wave of the pandemic (December 2020 and January 2021, note difference in testing strategies in the second wave led to higher numbers of detected infections).

In total, shielding was in place in England between 29th March 2020 and 1st August 2020 and 4th November 2020 and 1st April 2021.

A timeline of the pandemic can be found in Figure 1.

Figure 1: Timeline of the COVID-19 pandemic



*1.1.4 Identification of people who were Clinically Extremely Vulnerable to COVID-19*

A rapid process to identify people felt to be at risk of severe COVID-19 outcomes had been undertaken, and on 23rd March 2020 a programme of shielding was announced(12, 13).

This was a targeted public health measure intended to minimise COVID-19 exposure and so infection risk. Based on the risk factors identified from early COVID-19 cases, people felt to be at-risk (CEV(14, 15)) were centrally identified using electronic records, and government letters were issued advising individuals to socially isolate themselves, restricting contact even within their household group, with the help of centralised financial and logistical support(12-14, 16).

There was sparse information available with which to draw up the initial guidelines for who might be at risk of severe COVID-19(14). Early indications were that this was a virus with predominantly respiratory sequelae (although the clinical picture developed as time went on and the haematological, cardiovascular, and systemic inflammatory responses became clearer). Much of the initial guidance therefore took a pragmatic approach, focusing on the cohort of people felt to be at higher risk from influenza infection.

A list of risk factors presumed to predispose to severe COVID-19 infections was drawn up centrally, in work lead by the Chief Medical Officer. Individuals felt to be at particular risk were(14):

- solid organ transplant recipients
- recipients of bone marrow or stem cell transplants in the last 6 months
- individuals with specific cancers (leukaemia, lymphoma, or myeloma) or on active chemotherapy, radical radiotherapy, or targeted immunotherapy
- individuals with severe respiratory conditions including cystic fibrosis, severe asthma, and severe chronic obstructive pulmonary disease (COPD)

- individuals with rare diseases and inborn errors of metabolism that significantly increase the risk of infections (such as severe combined immunodeficiency (SCID), homozygous sickle cell)
- individuals on immunosuppression therapies sufficient to significantly increase the risk of infection
- pregnant women with significant heart disease, congenital or acquired.

Individuals with these conditions were identified using a mixture of national datasets of routinely collected healthcare data, secondary care clinicians (often with the help of guidance issued by medical speciality societies)(17) and latterly primary care clinicians.

Many people with RAIRD were in a category thought to be vulnerable to severe COVID-19 outcomes and this is discussed in section 1.3.1.

**1.2 Rare autoimmune rheumatic diseases**

*1.2.1 Definition and importance of rare diseases*

A rare disease is defined as a disease affecting less than 1 in 2000 people(18). These diseases may be individually rare but together they are common, with 1 in 17 people in the UK predicted to suffer from a rare disease at some point in their lives(18). Rare diseases are a significant resource burden in the NHS and outcomes in these diseases tend to be poorer than in more common diseases. Rare diseases also account for a disproportionate amount of NHS spending: £22.9 billion in 2022-23(19), out of a planned budget of £180.2 billion(17), equating to 12.7% of the total.

In 2013 the Department of Health published the UK Strategy for Rare Diseases(18), which has since been followed up by The UK Rare Diseases Framework(20), published in January 2021. The Framework recognises the progress that has been made in diagnosing and treating rare diseases over the past 7 years, particularly in the field of genomics, but highlights ongoing difficulties including delayed diagnosis, disjointed care and difficulties accessing specialised treatments(18). It reiterates the four nations' commitment to improving the lives and care for those people living

with rare diseases and highlights the power of epidemiological data and patient registries to improve healthcare planning and delivery for people with rare diseases.

*1.2.2 Rare autoimmune rheumatic diseases*

Rare autoimmune rheumatic diseases (RAIRD) are a heterogenous group of diseases which share common underlying mechanisms. All are immune-mediated inflammatory diseases, and all may require immunosuppression, depending on disease severity and subtype.

They are chronic conditions, in some cases with the prospect of remission but not of cure, and treatment focuses on slowing or halting disease progression.

The RAIRD included in this thesis are giant cell arteritis, ANCA-associated vasculitis (comprising eosinophilic granulomatosis with polyangiitis, granulomatosis with polyangiitis and microscopic polyangiitis), polyarteritis nodosa, Takayasu arteritis, Behçet's disease, arteritis unspecified, systemic lupus erythematosus, scleroderma, idiopathic inflammatory myopathy (comprising dermatomyositis, juvenile myositis, and polymyositis), and juvenile idiopathic arthritis. Chapter 2 of this thesis describes the rationale for why these diseases were selected.

A brief description of each disease is given below.

ANCA-associated vasculitis (AAV): AAV comprises three separate conditions; eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). These conditions cause necrotising vasculitis, with little or no immune deposits, of predominantly small vessels. They are associated with antineutrophilic cytoplasmic antibodies (ANCA; myeloperoxidase (MPO) and proteinase 3 (PR3) antibodies)), although in a substantial minority of patients these antibodies are not detectable. As small vessels are ubiquitous, these conditions can affect any organ system, although the upper and lower respiratory tract and kidneys are commonly involved. The disease phenotype often relates disease sub-type, with prominent upper airway involvement

in EPGA for example(21). The combined incidence rate for GPA, MPA and EGPA varies geographically, and in Norway was found to be 24.7 per million person-years(22, 23) compared to 33 per million person-years in the USA(23, 24).

Behçet's disease: Behçet's disease is associated with vasculitis of both the arterial and venous systems and has several different disease phenotypes. It can present as recurrent oral and genital aphthous ulceration, associated with inflammation of the cutaneous, ocular, articular, gastrointestinal, and central nervous systems. Venous thromboembolism and arterial aneurysms may occur(21). There is evidence that Behçet's disease originated along the path of the Silk Road, and global incidence varies significantly depending on migration patterns. Reported incidences vary from 0.05 per 100,000 person-years in Poland(23, 25) to 3.9 per 100,000 person-years in South Korea(23, 26).

Giant cell arteritis (GCA): GCA is a typically granulomatous arteritis affecting the aorta and/or its major branches, particularly the temporal, carotid and vertebral arteries. Onset is typically in the over 50s and the disease usually presents with headache and scalp tenderness. Untreated disease can lead to visual disturbance or loss, and/or stroke, and GCA is both a sight- and potentially life-threatening condition. GCA is associated with another inflammatory condition called polymyalgia rheumatica (PMR) which causes proximal stiffness of the shoulder and hip girdles(21). In a UK study, age adjusted incidence rate of GCA was found to be 2.2 per 10,000 person-years(27).

Idiopathic inflammatory myopathies (IIM): IIM, also known as myositis, are multi-system disorders characterised by inflammation of the muscles(28). Involvement of the skin is common, particularly in the sub-type dermatomyositis, as is interstitial lung disease(28). Incidence varies but is up to 19 per million person-years in adults and 4 per million person-years in children(29).

Juvenile idiopathic arthritis (JIA): JIA is a clinically heterogenous group of arthritides presenting in childhood and ranging from mono- and oligoarthritis to polyarthritis,

axial disease, and systemic inflammatory disease (systemic juvenile idiopathic arthritis, sJIA)(30). sJIA in particular is associated with the development of haemophagocytic lymphohistiocytosis (HLH), a syndrome of immune dysregulation which can be fatal. There is also an association between some subtypes of JIA and uveitis, which can lead to visual loss and blindness and requires careful monitoring(30). Global incidence varies from 1.6 to 23 per 100,000 person-years and the overall pooled incidence rate among Caucasians was found to be around 8 per 100,000 person-years(31).

Polyarteritis nodosa (PAN): PAN is a necrotising vasculitis of medium and small vessels. The disease is often insidious in onset and presents with weight loss, sweats, and fever. Arterial microaneurysms may occur, particularly in the gastrointestinal and renal vasculature. It can be distinguished from AAV as it does not cause glomerulonephritis and is not associated with ANCA(21). PAN is an ultra-rare disease; a population study in Sweden calculated the incidence as 0.9 per million person-years(32).

Scleroderma (or systemic sclerosis, SSc): SSc is an autoimmune condition of unknown aetiology associated with skin fibrosis and involvement of the cardiovascular, respiratory, renal, and gastrointestinal systems. In a UK study, incidence was found to be approximately 19 per million person-years and was 4.7 times higher in females than males(33). It is associated with premature mortality, with 5- and 10-year survival rates of 80.0% and 65.7%(33).

Systemic lupus erythematosus (SLE): SLE is a multisystem autoimmune disease which most commonly presents in women in the reproductive age group, but which can present at any age(34). Disease manifestations include renal, haematological, musculoskeletal, and cutaneous disease. It is associated with a range of antibodies, particularly anti-nuclear antibodies (ANA). The incidence in the UK is approximately 5 per 100,000 person-years(35).

Takayasu arteritis (TAK): TAK causes usually granulomatous inflammation of large vessels, predominantly the aorta and its major branches(21). Its onset is often insidious, with systemic upset, weight loss and fever. More advanced disease can cause claudicant or ischaemic symptoms due to vessel stenosis. TAK is an ultra-rare disease; global incidence is 1.1 per million person-years(36).

### *1.2.4 Similarities between rare autoimmune rheumatic diseases*

Whilst RAIRD have differences in presentation and in underlying disease mechanisms, there are significant similarities, including their basis in immune-mediated inflammation and tendency to cause multi-system disease.

None of the diseases have a definitive clinical test allowing diagnosis, and in all the cases the diagnosis is made on a clinical basis using a combination of the presenting history, examination findings and investigations including blood testing and imaging.

People with RAIRD often develop long-term co-morbidities due to disease- and treatment-related damage. Again, there are commonalities between RAIRD with premature cardiovascular disease, chronic kidney disease and lung disease frequently seen(34, 37, 38). Such co-morbidities have their own negative impacts on COVID-19 outcomes(39).

Due to the similarities between the diseases, they have many treatments in common, which are largely rooted in immunosuppressive therapies and prevention of disease sequelae.

### *1.2.5 Treatment of rare autoimmune rheumatic diseases*

Without treatment, many RAIRD are associated with very high morbidity and mortality. For example, left untreated AAV is rapidly progressive and has a 2-year survival rate of only 20%(40). However, with current treatments the 2-year survival rate in people with AAV is around 85%(41).

Corticosteroids are a mainstay of initial treatment for many RAIRD, particularly GCA, AAV and SLE, helping to bring disease rapidly under control(28, 34, 42). Even in RAIRD where there are concerns about the use of corticosteroids worsening disease (for example in SSc, where steroids have been linked with an increased risk of scleroderma renal crisis), they may still be used sparingly in order to control skin and joint disease. For some conditions, such TAK and GCA, corticosteroids remain the first line treatment throughout the disease course(42, 43). In others they may be used long-term in low doses alongside other disease modifying anti-rheumatic drugs (DMARDs), or at time of flare to bring about remission(28, 34).

DMARDs are commonly used in RAIRD to maintain remission, all of which are associated with immunosuppressive effects. Examples of non-biologic DMARDs include methotrexate, azathioprine, ciclosporin, tacrolimus and cyclophosphamide(28, 30, 34, 44-46). Biologic DMARDs used in RAIRD include infliximab, tocilizumab, and rituximab(28, 30, 34, 44-46).

The effect of immunosuppressive treatments on infection risk is discussed later in section 1.3.2.

### *1.2.6 Identifying rare autoimmune rheumatic diseases in routinely collected healthcare data*

RAIRD are ideal for identification in routinely collected healthcare data as each RAIRD maps to unique ICD-10 codes, not shared with other conditions. Due to the complexity and severity of RAIRD, people with these conditions also frequently require in-patient and day-case treatment, meaning that they are identifiable in secondary care data.

The methodology for identifying RAIRD, including the validation strategies and results, are detailed in chapter 2 of this thesis.

## 1.3 Rare diseases in the context of the COVID-19 pandemic

### *1.3.1 Perception of risk at the beginning of the pandemic*

People with RAIRD were identified as potentially being at heightened risk early in the pandemic. They are often immunosuppressed, and as described section 1.2.2 their underlying disease and/or treatment may cause respiratory, renal, and cardiovascular complications which confer additional risk.

There was early involvement of clinicians caring for people with RAIRD in the identification of those at increased risk of severe COVID-19 outcomes. The government guidance stated that those with "severe respiratory conditions", "individuals with rare diseases… that significantly increase the risk of infections" or "individuals on immunosuppression therapies sufficient to significantly increase the risk of infection" should be contacted and advised to shield(14).

My paper "Estimation of the burden of shielding among a cross section of patients attending rheumatology clinics with SLE – data from the BSR audit of Systemic Lupus Erythematosus" showed that more than a third of patients with SLE were likely to have been identified as CEV and advised to shield(47). This proportion increased to over 50% in those with renal involvement (lupus nephritis).

*1.3.2 Infection and immunosuppression*

People living with RAIRD are vulnerable to infectious diseases as they are frequently on immunosuppressive treatment, as detailed earlier in section 1.2.5. The challenge of balancing the risk of infection conferred by treatment against the risk of morbidity and mortality from active rheumatic disease was particularly pressing during the early phases of the pandemic.

Corticosteroid usage in rheumatic disease has long been thought to increase the risk of infection(48-50), although the confounding factor of immune dysregulation from underlying autoimmune disease is difficult to quantify.

In COVID-19, this was complicated by the emergence of dexamethasone as an effective treatment, significantly lowering mortality in those requiring oxygen (rate ratio 0.82 (95% CI 0.72- 0.94)) or ventilation (rate ratio 0.64 (95% CI 0.51-0.81))(51),

However, concerns remained that corticosteroid treatment preceding infection may predispose to more severe disease(52, 53).

Complicating matters further, interleukin-6 (IL-6) receptor antagonists such as tocilizumab, whilst initially thought to confer additional risk of severe COVID-19 infection(14), were shown to reduce mortality in severe COVID-19 requiring intensive care. In comparison, rituximab, with its mechanism of action of B cell depletion, was thought to impair the antiviral immune response and antibody production, with potentially more severe clinical outcomes(53, 54).

*1.3.3 COVID-19 and all-cause mortality in people with RAIRD*

Given the significant concern that people with RAIRD were at increased risk of adverse outcomes from COVID-19 infection, my research team and I looked at mortality rates in a cohort of people with RAIRD early in the pandemic. Further details of this research, and of my role in it, can be found in chapter 2.

Taking all people in England with these conditions and alive on 01 March 2020, we looked at the age-standardised mortality rate (ASMR) for all-cause mortality over the study period 1st March – 30th April 2020(55). We compared this rate to both the ASMR in the general population and to the mean ASMR for the same months of the previous 5 years. In people with RAIRD, we found that the ratio of the ASMR in March-April 2020 compared with the mean ASMR in March- April 2015–2019 was 1.44 (95% CI: 1.42, 1.45)(55). In the general population, the same ratio was 1.38. In other words, people with RAIRD were more likely to die during the early stages of the COVID-19 pandemic than the general population. However, it was unclear whether this was due to COVID-19 infection itself, or due to the wide-ranging impact of the pandemic on the health service at the time. This study was the catalyst for the research contained in this thesis.

*1.3.4 Review of the published literature on COVID-19 in RAIRD*

Research in RAIRD generally is hampered by the small numbers of people affected by each disease, which makes it difficult to design studies with enough statistical power

to assess outcomes. These limitations made robust studies of COVID-19 outcomes difficult to perform, particularly in the early stages of the pandemic. Most study designs risked biased case selection, as cohorts were derived from disease registries or physician reported cases, which may exclude people with the mildest disease who are never referred.

The COVID-19 Global Rheumatology Alliance registry included physician-reported cases in people with a range of rheumatic diseases, with RAIRD included alongside more common diagnoses such as rheumatoid and psoriatic arthritis(53). The study team reported an association between certain immunosuppressive medications and COVID-19-related mortality(53). They also reported an association with rheumatic disease activity(56), although this may be affected by reporting bias. However, as these studies relied on physician-reported cases they are associated with bias as described above. In addition, the denominator was unknown, so they were unable to describe rates of infection, admission, or COVID-19-related death.

The important OpenSAFELY(39) and QCOVID(57) studies, looking at COVID-19 outcomes in the general population in England using primary care data, were not designed to detect outcomes in rare diseases. They also had less statistical power to do so; OpenSAFELY included 17 million patients registered with GP surgeries(39) and QCOVID used data from 8.26 million adults from 1,205 general practices in England(57) (compared to the whole England population of 56 million used in my research). The QCOVID risk calculator assigned risk to certain rheumatic diseases (rheumatoid arthritis, systemic lupus erythematosus)(57) but was not powered to include other, rarer diseases.

*1.3.5 The effect of age on COVID-19 outcomes*

Reports from early in the pandemic made it clear that advancing age was associated with increased risk of severe COVID-19 outcomes. This was confirmed in larger studies such as OpenSAFELY, which found that those aged over 80 had 20-times the risk of COVID-19 related death compared to those aged 50-60 (hazard ratio (HR) 20.60 (95% CI 18.70-22.68))(39).

This was an important factor to consider when assessing the risk of COVID-19 infection to people with RAIRD. With the exception of JIA, which is by definition a disease starting in childhood, most RAIRD develop in the fourth to sixth decades (e.g., SLE(34, 35), SSc(58)) or later (e.g., AAV, GCA(23)). This means that the RAIRD cohort is older on average than the general population.

*1.3.6 The effect of sex on COVID-19 outcomes*

Male sex also confers an increased risk of adverse COVID-19 outcomes, with a HR of 1.59 (95% CI 1.53-1.65) compared to female sex, as found in the OpenSAFELY study(39).

Again, this was an important factor to account for when considering the risk to people with RAIRD from COVID-19 infection. With the exception of AAV, which is more common in men(23), most RAIRD are more common in women (e.g., SLE(34, 35), SSc(58), TAK(36)), meaning that the RAIRD population has a greater proportion of women than the general population.

*1.3.7 Differences between waves*

As knowledge of the pathophysiology of COVID-19 evolved, so did treatment options and critical care strategies. This resulted in an improved survival rate over time, which was seen even over the course of the first five months of the pandemic in England(59).

There were differing government policies in place at different times, e.g., lockdown, social distancing, access to testing. Testing strategies in particular evolved during the pandemic, with COVID-19 tests largely limited to those admitted into hospital in the first wave, compared to widespread community testing later on as testing capacity increased

The predominant SARS-CoV-2 variant at the time also impacted on clinical outcomes. The dominant variant at any given time was the one which outcompeted the others

due to some sort of survival advantage(60). This meant that as the pandemic progressed, the dominant variant tended to be more transmissible. For example, the wild-type infection seen at the start of the pandemic was largely replaced by the alpha variant, which became dominant on 18th December 2020(61). This was subsequently replaced by the Delta variant, which became dominant on 22nd May 2021 (and latterly this was replaced by Omicron, which become dominant on 19th December 2021)(61). More transmissible infection led to progressively higher peaks in cases, with more people exposed, as well as the possibility of reinfections within the same individual.

*1.3.8 Vaccination against SARS-CoV-2*

Given their increased risk of adverse COVID-19 outcomes, many people with RAIRD were categorised as high priority for vaccination against COVID-19. However, immunosuppression may result in a "suboptimal immune response to the vaccine"(62) and there were fears that vaccination would not provide the same protection in this group that it offered to the general population.

Rituximab in particular was thought likely to cause an inadequate vaccine response, based on data from other immunisations. Early guidance suggested an individualised approach, with delay of immunosuppressive treatment where appropriate(63). The science in this area has moved on considerably over the course of the pandemic and further discussion of vaccination in people with RAIRD, particularly those on rituximab treatment, can be found in chapters 2, 4 and 6.

*1.3.9 Exacerbating inequalities and impact on well-being*

The emerging literature describing the patient experience during the pandemic described a perception of "diversion of resources away from chronic disease care" and fear about increased vulnerability to COVID-19… contributing to health-care-avoidant behaviours" amongst those with systematic autoimmune rheumatic diseases(64).

Discussions with my patient and public involvement group revealed the fears held by those in the RAIRD community, of the potential increased mortality risk from COVID-19 infection, increased barriers to accessing care for their underlying disease and the uncertainty around vaccine efficacy in people with RAIRD on immunosuppression(65). There was a desire within the RAIRD community for research specific to RAIRD, to try to identify modifiable risk factors (for example corticosteroid treatment) and give individuals a clearer idea of their risk.

### 1.4 Mortality in RAIRD before the pandemic

#### *1.4.1 Mortality risk in RAIRD compared to the general population*

How does COVID-19-related mortality relate to mortality more generally in people with RAIRD? RAIRD have long been associated with excess morbidity and premature death. As with COVID-19, poor outcomes are attributable both to the effects of treatment and the underlying disease. Immunosuppression predisposes to other severe infections, including from atypical pathogens.

Previous studies have found that all-cause mortality is approximately 1.2-10-fold higher(66-72) among people with RAIRD compared with the general population. The RAIRD associated with the highest mortality rates include Behçet's disease (with a standardised mortality rate (SMR) up to 10-times that of the general population in certain age categories(70)) and SSc (with an SMR of up to 7.2 in one study(73)). On the other end of the spectrum, a meta-analysis by Hill et al. found that ASMRs in GCA were 1.17 (95% CI 1.02–1.35) times higher than in the general population(72).

There is also variation within diseases, which may reflect selection bias within the study populations. In SSc, for example, a meta-analysis including a total of 1,645 incident cases found an SMR of 1.5-7.2, depending on the cohort(73). There have been few population-based studies.

#### *1.4.2 Mortality trends in RAIRD*

As described in section 1.2.5, the advent of new treatments has dramatically reduced morbidity and mortality in RAIRD. The general trend has therefore been one

of gradually improving survival rates(74, 75), although premature mortality persists(76). As contemporary data regarding cause of death in RAIRD remain scarce, the published literature may no longer reflect the current risk.

In addition, whilst deaths due to underlying RAIRD themselves have reduced, this has come at the expense of an increased risk of infection related to treatment(74, 77).

With a longer life expectancy following diagnosis, complications from both the diseases and their treatments have also become more apparent. For example, one study in SLE found that overall survival gradually improved between the 1950s and the mid-1990s, after which it plateaued(78). However, deaths due to SLE continued to fall throughout the study period (1950-2016), suggesting that the persisting mortality risk was increasingly due to causes other than active autoimmune disease. This highlights the importance of looking at cause-specific, as well as all-cause, mortality.

*1.4.3 Cause-specific mortality in RAIRD*

As well as an increased risk of death due to infection(41, 69), RAIRD are also associated with premature cardiovascular disease, which is a prominent cause of death(41, 79, 80).

Respiratory disease is also described as a significant cause of death in those with IIM(71, 81), SSc(73, 82) and AAV associated with MPO antibodies(75).

In some RAIRD, such as SSc, the majority of deaths remain attributable to the disease itself(83). Notably, the COVID-19 pandemic, and the attendant consequences on healthcare configuration and demand, raised concerns about barriers to accessing care, and the potential for an increase in deaths related to underlying RAIRD disease as a consequence(64).

**1.5 Rationale for thesis**

To summarise the evidence above, at the onset of the COVID-19 pandemic, there were many unanswered questions for people living with RAIRD and the clinicians caring for them. It was unclear whether they were at increased risk of severe COVID-19 outcomes, whether some conditions were associated with greater risk than others and whether immunosuppressive treatments, such as corticosteroids, conferred an increased risk of severe disease or were indeed protective.

The early studies of COVID-19 outcomes in people living with RAIRD were limited by selected populations, small numbers, or included more common conditions which potentially had less severe outcomes such as rheumatoid arthritis or gout. I had access to and the ability to link national datasets, facilitating whole population studies looking at outcomes such as COVID-19 infections, hospital admissions, deaths, and cause of death data, as well as the influence of modifiable risk factors such as corticosteroid treatment.

As described in section 1.1.3, there were significant differences in testing, clinical treatment, and government policies between waves of the pandemic. This thesis therefore describes the first and second waves of the pandemic in England separately. The beginning of the first wave is defined as 1st March 2020, which is the day after human-to-human transmission was confirmed in England (28th February 2020). The end of the first wave is defined as 31st July 2020, which is the day before shielding was formally suspended (1st August 2020). The beginning of the second wave is defined as 1st August 2020, when shielding was formally ended. The end of the second wave is defined as 30th April 2020, which was selected as there was a nadir of deaths related to COVID-19 at this time point.

The RAIRD are all associated with increased morbidity and mortality and despite trends towards improvement, premature mortality in these conditions persists. As described in section 1.2.1, The UK Rare Diseases Framework(20) highlights ongoing difficulties with healthcare experienced by those with rare diseases, including delayed diagnosis, disjointed care and difficulties accessing specialised treatments(18), all of which have the potential to negatively impact outcomes

including survival rates. Within the published literature, there is variability within and between diseases, reflecting the relative lack of statistical power in most previous studies. There have been few population-based studies, and contemporary data regarding cause of death in rare autoimmune rheumatic diseases remain scarce. The fourth chapter of this thesis describes contemporaneous all-cause and cause-specific mortality rates in RAIRD, including during the first year of the COVID-19 pandemic, with the aim of informing health policy.

**1.6 Objectives of thesis:**

1) Calculate the age-standardised rates of laboratory confirmed COVID-19 infection and death among people with RAIRD in England during the first and second waves of the COVID-19 pandemic and compare these rates to those in the general population. Describe hospital and intensive care admissions related to COVID-19 infection, and all-cause mortality during each wave.
2) Assess the relationship between corticosteroid treatment and COVID-19-related death among people with RAIRD during the second wave of the COVID-19 pandemic.
3) Describe all-cause mortality in people with RAIRD during the years 2013-2020, including the calculation of all-cause and cause-specific age-sex-standardised mortality rates and comparison with the general population in England.

**1.7 Outline of thesis chapters**

The outline of this thesis is as follows:

**Chapter 1:** As detailed above, this chapter describes the relevant background literature and rationale and objectives for this thesis.

**Chapter 2:** This chapter describes general methodology relevant throughout chapters 3-5 of this thesis, as well as the legal basis and ethical permissions for this research.

**Chapter 3:** This chapter describes COVID-19 outcomes (infection, hospital admission and death) in people with RAIRD during the first wave of the pandemic (March-August 2020) in England.

**Chapter 4:** This chapter describes COVID-19 outcomes (infection, hospital admission and death) in people with RAIRD during the second wave of the pandemic (August 2020-April 2021) in England. It also assesses the relationship between corticosteroid treatment and COVID-19-related death.

**Chapter 5:** This chapter describes all-cause mortality in people with RAIRD during the years 2013-2020 and describes all-cause and cause-specific mortality rates, with comparison to the general population.

**Chapter 6:** This chapter discusses the clinical implications of each of the studies, and the conclusions of this thesis.

**Chapter 7:** This chapter proposes areas for further research.

# Chapter 2: General methodology

This chapter describes the general methodology relevant throughout the work in my thesis, including the data sources used. It also details the preparatory work undertaken before commencing the research.

## 2.1 Background

### *2.1.1 The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)*

The work contained within this thesis utilises the unique data sources available within the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of the National Disease Registration Service (NDRS)(84). Formerly within Public Health England (PHE), NCARDRS moved to NHS Digital (NHSD) following PHE's dissolution.

NCARDRS collects patient-identifiable data for rare diseases without the need for individual informed consent. Under PHE this was performed with permission from the National Information Governance Board under Section 251 of the NHS Health Act 2006 and the authority of the Health Service (Control of Patient Information) Regulations 2002 (CAG ref: CAG 10-02(d)/2015). Following the transition to NHSD, this is performed under Section 254 approval (sections 254(1) and 254(6) of the 2012 Health and Social Care Act).

In effect, this allows unique access to immensely rich linked national datasets of electronic health records of people living with rare diseases, at patient-identifiable level and covering the whole population of England.

For context, the population of England is approximately 56 million people. NHS data is not only acknowledged as some of the most comprehensive health data in the world, but the population of England is larger than any other country with advanced epidemiological infrastructures such as Scotland (5.5 million), Denmark (5.8 million), Sweden (10 million) and Canada (38 million), allowing world-beating research.

*2.1.2 RECORDER project*

The RECORDER (Registration of Complex Rare Diseases – Exemplars in Rheumatology) project(85), based at the University of Nottingham and lead by Dr Fiona Pearce, is a team of clinicians, health data scientists, epidemiologists, and statisticians. RECORDER works in partnership with NCARDRS, focusing on late-onset, non-genetic rare diseases. RECORDER uses novel linkage of existing NCARDRS datasets, including whole population NHS demographics and admissions data, prescriptions data, high-cost drug approval data (Blueteq), and Covid-19 specific data such as testing and vaccination data, to carry out novel research in this space. This whole-population data approach allows every individual to count, and the NDRS provides the largest rare disease data infrastructure in Europe.

The UK Rare Diseases Framework(20) highlights the power of epidemiological data and patient registries to improve healthcare planning and delivery for people with rare diseases. The RECORDER project's unique partnership with NCARDRS(86), which has positioned rare autoimmune rheumatic diseases (RAIRD) at the forefront of national disease registration, is recognised within the Framework as the case study for England(20).

*2.1.3 Transition from Public Health England to NHS Digital*

NCARDRS was launched in July 2015 in response to the UK Strategy for Rare Diseases(18), as part of the NDRS within PHE(87). Its aim is to register people with rare conditions in order to support high quality clinical practice and research, provide epidemiology data and empower patients.

On 29th March 2021 it was announced that PHE would be dissolved, with its functions split between the UK Health Security Agency (UKHSA), the Office for Health Improvement and Disparities (OHID), NHS England/NHS Improvement (NHSE/I) and NHSD(88).

Due to its focus on building disease registries, including the utilisation of routinely collected data to identify people living with rare diseases, NDRS was transitioned to NHSD. This process was completed on 1st October 2020.

The legal permissions to access patient data under both PHE and NHSD are described in section 2.6.

*2.1.4 Transition from NHS Digital to NHS England*

On 1st February 2023, NHSD was merged into NHS England (NHSE)(89). This was a planned merger, which aimed to reduce duplication and improve efficiency(89). As part of NHSD, NDRS made the transition across to NHSE on this date.

The work contained within this thesis was all completed prior to this merger date and so falls under the legal and ethical permissions held by PHE and NHSD and described in section 2.6.

*2.1.5 Health Data Research UK*

The COVID-19 work contained within this thesis is registered with Health Data Research UK (HDR-UK) under their Better Care theme and is integrated into their Innovation Gateway. HDR-UK is the UK's national institute for health data science and aims to improve the utilisation of health data across stakeholders in order to improve health outcomes(90).

**2.2 Data sources**

NCARDRS' legal permissions afford access to NHS national databases of electronic health records including Hospital Episode Statistics, Office for National Statistics Death Registrations (death certificate data), Second Generation Surveillance System COVID-19 PCR testing results and NHS Prescription Services.

Access to the National Immunisations Management Service (NIMS) database and the Shielded Patient List (SPL), both held by NHSD, was applied for, and granted under the Coronavirus (COVID-19) notice under Regulation 3(4) of the National Health

Service (Control of Patient Information Regulations) 2002 (COPI). These data are beyond the scope of the work within this thesis.

### *2.2.1 Hospital Episode Statistics*

Hospital Episode Statistics (HES) contains every episode of admitted patient care (APC) in NHS hospitals in England, including in-patient and day-case admissions(91). For every episode of APC, the dataset includes all prevalent diagnoses, coded according to ICD-10 classification, and details of any procedures performed, including drug infusions, coded according to OPCS (codes used by healthcare providers to classify interventions and procedures).

The RECORDER project has established the methodologies for identification and registration of people with rare autoimmune diseases (RAIRD) within HES data(92). Importantly, each RAIRD maps to unique ICD-10 codes, not shared with other conditions. RAIRD also frequently necessitate in-patient and day-case activity, making them ideal for identification within HES(92-94). The accuracy of coding within HES data has improved over time, increasing the accuracy of case ascertainment(91).

### *2.2.2 Validation of HES data*

As part of the RECORDER project, I have contributed to the validation of methods for ascertainment of the following RAIRD in HES using prevalent ICD-10 codes.

I looked at 12 sets of cases notes with a code for Takayasu arteritis and 36 sets of case notes with a code for polyarteritis nodosa, both at the same hospital trust (Nottingham University Hospitals NHS Trust). As for all the diagnostic ICD-10 codes for RAIRD utilised in this research, additional validation took place at other Trusts, with a total of 3-5 Trusts checked per diagnostic code. This took place either in person (performed by clinicians caring for people with RAIRD) or using remote access to electronic records (performed by NCARDRS' validation staff using their special legal permissions).

The ICD-10 codes for Takayasu arteritis and polyarteritis nodosa were found to have a high positive predictive value (PPV; 79.4% and 90.6% respectively, overall PPV 85.5% (95% CI 82.7-87.9)(55)) and so were amongst the conditions included in my final research.

In addition, I also looked at 37 sets of case notes with a code for Kawasaki disease in the same trust. Overall, ICD-10 codes for Kawasaki disease had a PPV of 97.6% (91.6-99.7%). This validation work contributed to recently published work by my research group and I on the incidence of Kawasaki disease in England(95).

Finally, I looked at five sets of case notes with a code for relapsing polychondritis and 16 sets of case notes with a code for adult-onset Still's disease (AOSD), again in Nottingham University Hospitals NHS Trust. For both conditions, the diagnostic ICD-10 codes were found to have poor reliability (PPV 40.0% (5.3-85.3%) and 42.8% (17.7-71.1%) respectively(92)). More detailed, disease-specific work was therefore required to develop an algorithm to accurately identify them using HES data. Due to the urgent nature of COVID-19 research, these cases were therefore excluded from the work contained in my thesis. Research to develop an algorithm to accurately identify people with AOSD in HES is planned within my research team.

*2.2.3 List of final RAIRD conditions*

The final list of conditions referred to as RAIRD throughout this research is: giant cell arteritis, ANCA-associated vasculitis (AAV; comprising eosinophilic granulomatosis with polyangiitis (EGPA), granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)), polyarteritis nodosa, Takayasu arteritis, Behçet's disease, arteritis unspecified, systemic lupus erythematosus, scleroderma, idiopathic inflammatory myopathy (comprising dermatomyositis, juvenile myositis and polymyositis), and juvenile idiopathic arthritis.

The PPV for the ICD-10 codes for the 14 RAIRD conditions ranged from 65.8% to 100%(55). Overall, when weighted for the actual occurrence of the codes in the study population, the positive predictive value was 84.7%(55). Prevalence estimates

based on our findings for AAV, systemic lupus erythematosus and scleroderma, are similar to reported population estimates(33, 35, 96).

*2.2.4 Arteritis Unspecified (I77.6)*

The ICD-10 code I77.6 represents a diagnosis of "arteritis, unspecified". AAV is often recorded as I77.6, rather than one of the specific AAV diagnostic codes (EGPA = M30.1; GPA = M31.3, MPA = M31.7) and this ICD-10 code is routinely used in AAV research(97, 98). In order to capture as many AAV cases as possible, I77.6 was therefore included in this research. Validation work within the RECORDER team has shown it to have a PPV of 65.8%.

*2.2.5 The NHS Personal Demographics Service*

Where people were identified as having RAIRD in HES APC, data from the NHS Personal Demographics Service were used to confirm whether people were alive or dead and, where dead, to confirm date of death(99).

*2.2.6 Office for National Statistics mortality data*

Mortality and births information system (MBIS) death certificate data were provided by the Office for National Statistics (ONS) in a patient identifiable format, allowing data linkage.

These data contain both free text and ICD-10 coded cause of death, from all parts of the death certificate, as completed by the certifying clinician. Each diagnosis entered by the clinician is subsequently converted to an ICD-10 diagnostic code by the ONS. These data were also included in the dataset.

Using internationally agreed rules, the ONS assigns a further category "underlying cause of death", which contains one ICD-10 code only. This is usually based on the lowest completed line of Part 1 of a death certificate(100).

*2.2.7 COVID-19 PCR testing results*

Positive COVID-19 PCR testing results, held in the Second Generation Surveillance System (SGSS), were provided in patient identifiable format, allowing data linkage.

This dataset contained specimen and lab report dates, allowing me to calculate the time period between a positive COVID-19 PCR test and death. This was relevant to the calculation of 28-day mortality rates.

These data were obtained under COPI legislation, enacted due to the coronavirus pandemic. This allowed the rapid dissemination of relevant data in order to combat the healthcare emergency. Due to the speed at which data sharing was required, only positive testing data were accessible. This was a result of the specifications of the data "view" that was set up, which was limited due to reasons of practicality due to the sheer size of this national dataset. One limitation of this was that I was unable to analyse the negative testing data, such as describing testing behaviour or the proportion of positive tests.

During the first and second wave of the pandemic, the time periods reported within this thesis, the SGSS database only held polymerase chain reaction (PCR) testing data. Later in the pandemic, as lateral flow tests (LFTs) became more widely available and evidence accumulated about their reliability, LFT results were also logged within SGSS. This is not applicable to the interpretation of the results within this thesis.

*2.2.8 NHS Prescription Services*

NHS Prescription Services data is held by the NHS Business Services Authority and analyses all NHS prescriptions issued in England, including those contracted out e.g., to pharmacies and GP practices. These data were provided in patient identifiable format, allowing data linkage.

NHS Prescription Services data do not cover secondary care prescriptions, e.g., those issued in hospitals, and so does not contain some specialist drugs, nor acute prescriptions (which may or may not be subsequently continued by the general

practitioner and therefore included in the data). The former is particularly important when considering prescriptions for disease modifying anti-rheumatic drugs (DMARDS; discussed further in section 4.5.9) and the latter when considering corticosteroid prescriptions. Discussion on the use of HES OPCS codes to identify drug infusions (such as rituximab) can also be found in section 4.5.9.

*2.2.9 General population data*

General population data on deaths with any mention of COVID-19 on the death certificate were provided by the ONS, aggregated by sex and 5-year age bands. The ONS welcomes data requests from researchers and members of the public and these results were made publicly available on their website (see references in the text in sections 3.3.8 and 4.3.7).

General population data on COVID-19 infections and deaths within 28 days of a positive COVID-19 PCR test were provided by PHE, aggregated by sex and 5-year age bands. Whilst they do not have the same public data sharing procedures in place, these data are available on request.

General population data for the all-cause mortality work detailed in chapter 5 was provided by ONS through their NOMIS website, a publicly accessible resource which allows data queries for official census and labour market statistics(101).

**2.3 Initial all-cause mortality findings during the COVID-19 pandemic**

During the early stages of the COVID-19 pandemic, there was significant concern that people with RAIRD might be more likely to have serious adverse outcomes from COVID-19 infection compared to the general population.

Having recently completed validation on methods to identify people with these conditions in HES data, my research team and I were in an ideal position to look at the effects of the pandemic on this cohort. Taking all people in England with these conditions and alive on 01 March 2020, we looked at the age-standardised mortality rate (ASMR) for all-cause mortality over the study period 01 March – 30th April

2020(55). We compared this rate to both the ASMR in the general population and to the mean ASMR for the same months of the previous 5 years. In people with RAIRD, we found that the ratio of the ASMR in March-April 2020 compared with the mean ASMR in March- April 2015–2019 was 1.44 (95% CI: 1.42, 1.45)(55). In the general population, the same ratio was 1.38. In other words, people with RAIRD were more likely to die during the early stages of the COVID-19 pandemic than the general population. However, it was unclear whether this was due to COVID-19 infection itself, or due to the wide-ranging impact of the pandemic on the health service at the time.

I contributed to the above research through my work validating HES ICD-10 codes, by contributing to the design of the research and through edits and revisions of the manuscript.

Following on from this all-cause mortality work, I decided to focus my thesis on COVID-19 outcomes in people living with RAIRD, and in particular to ascertain whether it was COVID-19 infection itself that was driving the increased rate of mortality, or other factors.

**2.4 Data linkage and statistical software**

The data sources within this research contain millions of rows and required statistical software for data cleaning and analysis.

I extracted HES data using SQL queries within the NHSD (formerly PHE) data lake, where it is stored securely in identifiable format, allowing linkage of multiple datasets. The other data sources described were supplied in patient-identifiable formats by NHSD to PHE (prior to the transition) and stored in the NCARDRS secure data network drive. The data were accessed as comma separated values (.csv) or excel files.

Patient-level linkage and data manipulation were performed via a reproducible programming code (R versions 3.6.3 to 4.2.1, updated over the course of the

research). The complete programming code used to clean and transform the data is documented and stored in an accessible text format in order to allow complete replication of the analysis. The R packages used for each section of work are detailed in the respective chapters of this thesis.

## 2.5 Information Governance

These are national datasets and are subject to rigorous data quality control by PHE/NHSD prior to researcher access. They can only be accessed in designated data safe havens following appropriate checks.

In order to conduct this research, I required an honorary contract with PHE (and subsequently NHSD), which I organised through the RECORDER project prior to commencing my PhD. I was then able to access the data via a secure PHE/NHSD laptop in a designated data safe haven. These were largely sited in PHE offices, with one also available on the University of Nottingham City Hospital campus. Due to the pandemic, PHE/NHD switched to homeworking where possible and so I had to ensure that my workspace was suitably secure to be designated a data safe haven.

I completed the necessary checks (including a Disclosure and Barring Service (DBS) check) prior to being offered an honorary contract and undertook rigorous, annual mandatory health data security training in order to continue to access the data.

## 2.6 Legal permissions

### *2.6.1 Legal permissions under Public Health England*

Under PHE, the legal basis to access the data without patient consent was covered by NCARDRS' Section 251 approval (Reference CAG 10-02(d)/2015)(102) and the work contained in chapter 3 of this thesis was predominantly covered on this basis. This included access to HES, personal demographics, and mortality data.

Where the work extended beyond Section 251 approval, it was approved under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (COPI)(103), allowing the processing of confidential patient information for the

purposes of protecting public health and managing the COVID-19 outbreak. This included access to COVID-19 testing data.

*2.6.2 Legal permissions under NHS Digital*

For the remainder of the work in this thesis, the legal basis to access the data is covered by NCARDRS' Section 254 approval (sections 254(1) and 254(6) of the 2012 Health and Social Care Act). This contains specific legal instruction to collect patient data without informed consent(104). NCARDRS have permission to securely store this data for the lifetime of the patient.

**2.7 Ethics**

The COVID-19 focused work in this thesis is covered by ethical approval granted on 18 June 2020 by the London - Camden & Kings Cross Research Ethics Committee, following a successful integrated research application system (IRAS) ethics application.

The all-cause mortality work described in this thesis is covered by NCARDRS' directions and did not require additional ethical approval.

**2.8 Data access and reproducibility**

Due to legal and ethical considerations, supporting data from RECORDER publications containing NCARDRS data cannot be made openly available. A data access statement has been published for each section of this work, giving further details about the data, and describing conditions for access.

The data access statement for the first wave COVID-19 study can be found at this DOI: http://doi.org/10.17639/nott.7131

The data access statement for the second wave COVID-19 study and all-cause mortality study can be found at this DOI: http://doi.org/10.17639/nott.7272

Metadata is included within each R script, explaining each step of the code and the packages required. The version of R used for each stage of the research is described within the relevant thesis chapter.

The code for the all-cause mortality study has been securely uploaded to the PHE gitlab site, allowing this research to be both reproduced and adapted for other rare diseases.

**2.9 Impact of the COVID-19 pandemic**

I started my PhD during the COVID-19 pandemic. Resources and procedures were promptly put in place in order allow me to work from home. My honorary contract with PHE allowed me access to a PHE (later NHSD) computer, with secure access to the necessary data systems. My home office was designated as an approved data safe haven by PHE.

I set up remote access to a university desktop, as well as access to the necessary software, including word-processing software and the statistical package R. Most of my attendance at university training courses has been facilitated remotely, with some in person presentations and assessments.

Team-working was maintained through online meetings and email, both with my academic supervisors and the team at NCARDRS.

# Chapter 3: COVID-19 infection, admission, and death amongst people with Rare Autoimmune Rheumatic Diseases in England: the first wave of the pandemic

This chapter details the first study within my thesis. It is a nationwide cohort study looking at COVID-19 outcomes in people with RAIRD during the first wave of the COVID-19 pandemic in England. The study is published in Rheumatology (Oxford) and a PDF of the manuscript is included within Appendix 3.

## 3.1 Main findings and abstract

### *3.1.1 Main findings*

1. People with RAIRD were at increased risk of COVID-19 infection during the first wave.
2. Compared to the general population, they had over twice the risk of COVID-19-related death.
3. These increased risks were seen despite shielding policies in place in England.

### *3.1.2 Abstract*

**Objectives:**

To calculate the rates of COVID-19 infection and COVID-19-related death among people with rare autoimmune rheumatic diseases (RAIRD) during the first wave of the COVID-19 pandemic in England compared to the general population.

**Methods:**

I used Hospital Episode Statistics to identify all people alive 01 March 2020 with ICD-10 codes for RAIRD from the whole population of England. I used linked national health records (demographic, death certificate, admissions, and PCR testing data) to calculate rates of COVID-19 infection and death up to 31 July 2020. The primary definition of COVID-19-related death was mention of COVID-19 on the death certificate. General population data from Public Health England and the Office for National Statistics were used for comparison. I also describe COVID-19-related hospital admissions and all-cause deaths.

**Results:**

I identified a cohort of 168,680 people with RAIRD, of whom 1874 (1.11%) had a positive COVID-19 PCR test. The age-standardised infection rate was 1.54 (95% CI 1.50-1.59) times higher than in the general population. 713 (0.42%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.41 (2.30 – 2.53) times higher than in the general population. There was no evidence of an increase in deaths from other causes in the RAIRD population.

**Conclusions:**

During the first wave of COVID-19 in England, people with RAIRD had a 54% increased risk of COVID-19 infection and more than twice the risk of COVID-19-related death compared to the general population. These increases were seen despite shielding policies.

## 3.2 Introduction

### *3.2.1 Rare autoimmune rheumatic diseases and COVID-19 infection*

Along with my research team, I have previously shown that people with rare autoimmune rheumatic diseases (RAIRD) were at increased risk of all-cause mortality during the first wave of the COVID-19 pandemic (March-April 2020), when compared to the general population in England(55). However, this study did not examine whether the increased mortality was due to COVID-19 infection itself, or due to indirect effects of the pandemic.

### *3.2.2 Study objectives*

This study uses linked national health records for the whole population of England to calculate the rates of laboratory confirmed COVID-19 infection and COVID-19-related death among people with RAIRD from 01 March to 31 July 2020, the first wave of the COVID-19 pandemic, and compares these rates to that in the general population. I describe COVID-19-related hospital and ICU admission, underlying causes of death by category and COVID-19-related mortality stratified by RAIRD diagnosis.

## 3.3 Methods

### *3.3.1 Background*

The Registration of Complex Rare Diseases Exemplars in Rheumatology (RECORDER) project is a collaboration between the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)(85). NCARDRS, based within Public Health England (PHE), registers people with rare conditions in order to support high quality clinical practice and research, provide epidemiology data and empower patients(105). It has unique access to linked national datasets of electronic health records at patient-identifiable level for the whole population of England.

This study uses Hospital Episode Statistics (HES, which contains every episode of admitted patient care in NHS hospitals in England), COVID-19 polymerase chain reaction (PCR) test results and Office for National Statistics (ONS) death certificate data.

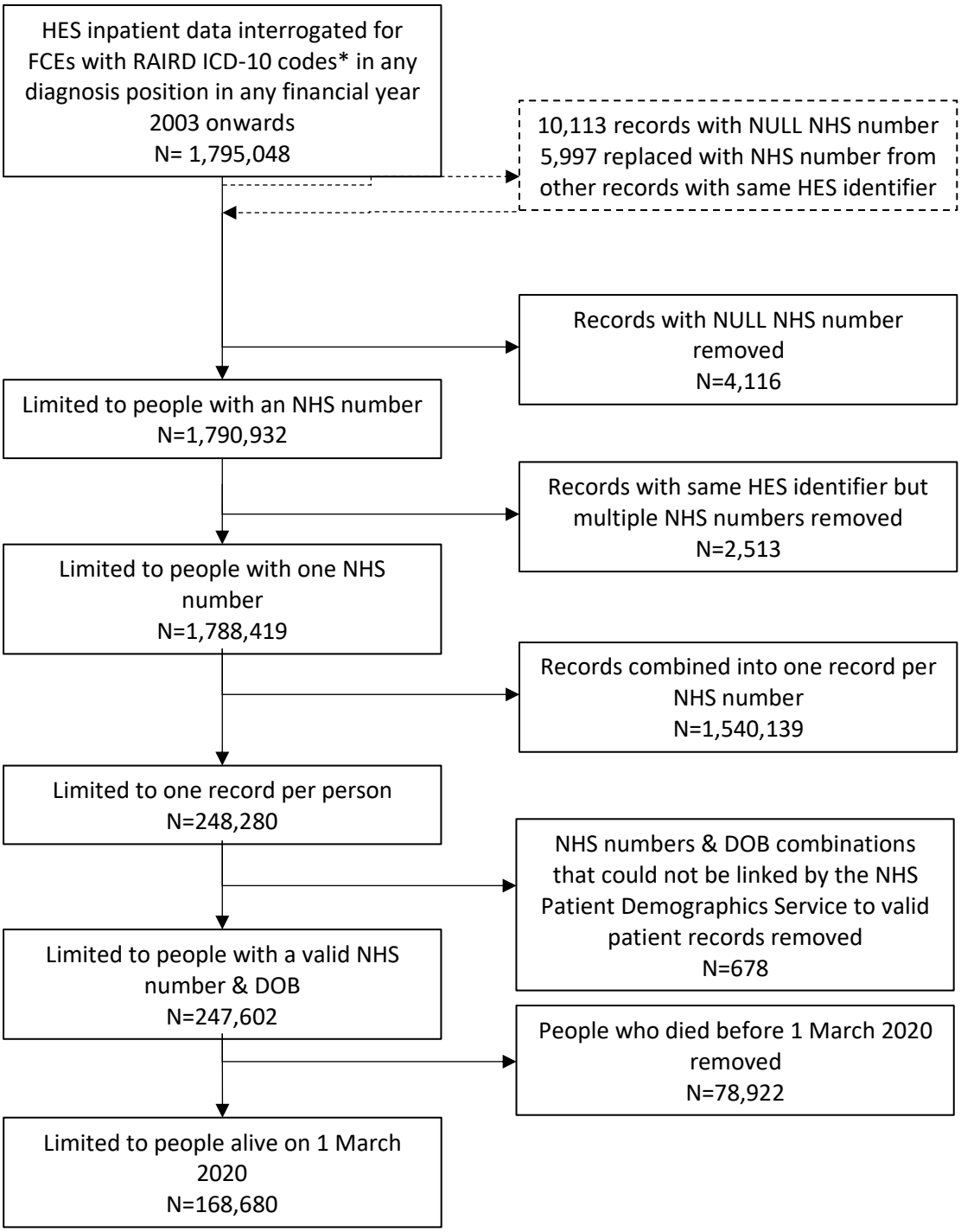
### *3.3.2 Data validation*

My research team and I's previous work validating HES ICD-10 codes for RAIRD has shown high accuracy, with a positive predictive value was 84.7%(55). Prevalence estimates based on our findings for ANCA-associated vasculitis, systemic lupus erythematosus and scleroderma, are similar to reported population estimates(33, 35, 96).

### *3.3.3 Study cohort*

People with a diagnostic code for RAIRD in HES from 2003 onwards, resident in England, and alive 01 March 2020 were included in the study, using the same cohort as the preliminary all-cause mortality study(55). A data flow diagram is shown in Figure 2. Vital status data from the NHS Personal Demographics Service were used to confirm whether people were alive, or to confirm date of death(99).

Figure 2: Data flow diagram showing identification of RAIRD cohort from HES data.
*FCE = finished consultant episode. HES = hospital episode statistics.*

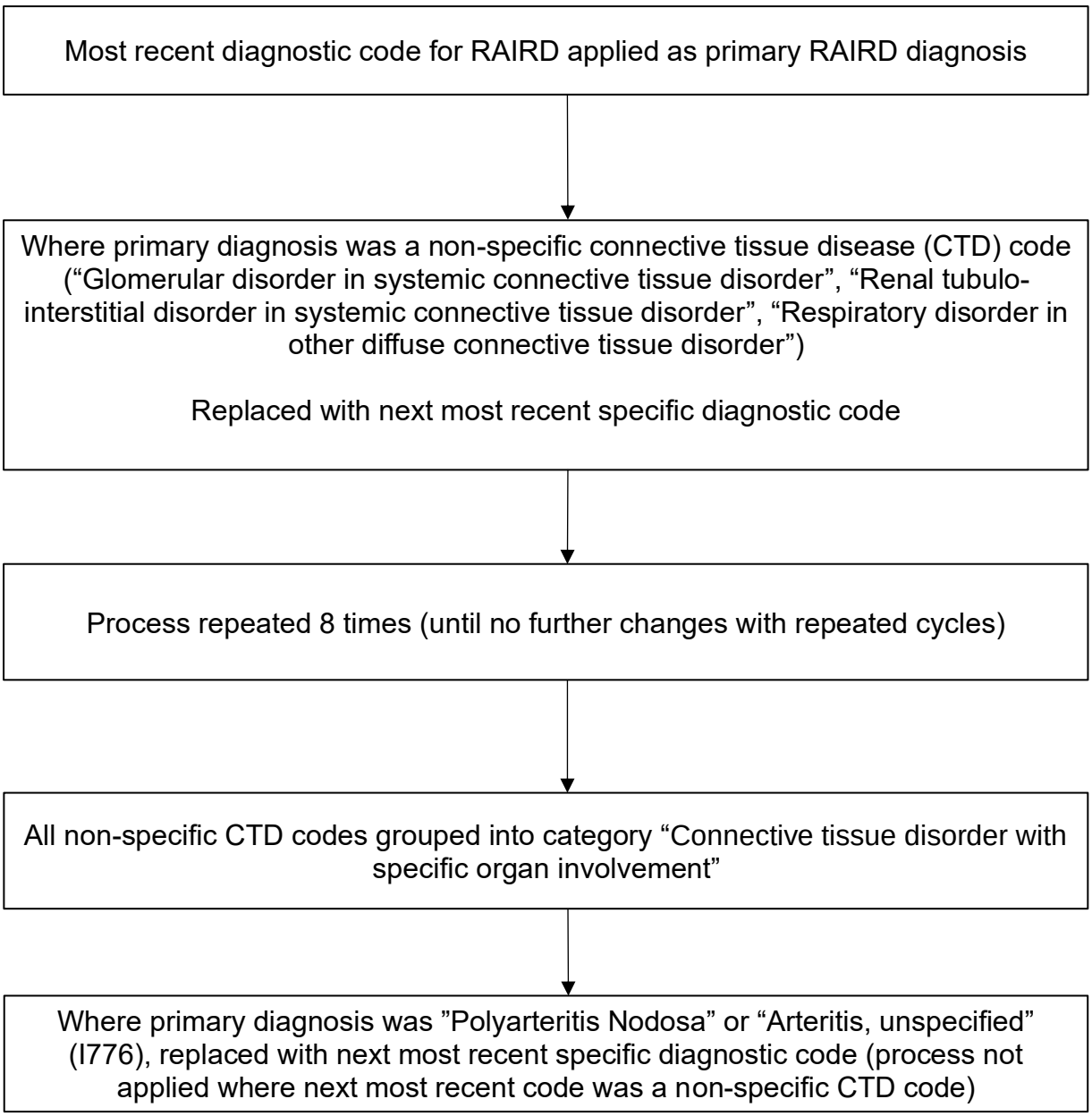



*RAIRD ICD-10 codes comprise: M313, M317, M301, M314, I776, M352, M315, M316, M321, M330, M332, M331, M339, M340, M341, M348, M349, M083, M084, M082, M080, M300, M308, J991, N085, N164, M328, M329, M609, G724, M608, M089

*3.3.4 RAIRD diagnoses*

Participants were grouped by RAIRD diagnosis, based on their most recent diagnostic code. Where the most recent code was non-specific, for example "Renal tubulo-interstitial disorder in systemic connective tissue disorder", earlier, more specific diagnostic codes were used where available, following the algorithm in Figure 3.

Figure 3: Algorithm for assigning main rheumatological diagnosis



*3.3.5 Death certificate data*

Death certificate and underlying cause of death data (both free text and ICD-10 codes) provided by the ONS were utilised. Using internationally agreed rules, ONS assigns underlying cause of death by ICD-10 code, usually based on the lowest completed line of Part 1 of a death certificate(100). The data were examined for ICD-10 codes specific to COVID-19 (U07.1, U07.2). The free text was manually checked for keywords ("*cov"*, "*virus"* or "*19"*) which confirmed that no deaths related to COVID-19 (including misspellings) had been omitted. Whilst COVID-19-specific ICD-10 codes were not introduced until 25 March 2020(106), all deaths with a free text mention of COVID-19 occurring before that date had been captured retrospectively by the ONS coding system.

I categorised underlying cause of death into cardiovascular disease, malignancy, respiratory disease, dementia, underlying RAIRD, COVID-19 infection, non-COVID-19 infection and other. Chi-squared test was used to assess for statistically significant differences between cause of death categories in the 2020 RAIRD cohort, compared to people with a diagnostic code for RAIRD alive 01 March 2019 and who died between 01 March and 31 July 2019.

*3.3.6 COVID-19 status*

A population-level dataset of COVID-19 polymerase chain reaction (PCR) test results, held in the Second Generation Surveillance System in PHE, was used. Positive tests amongst the RAIRD cohort were extracted, along with the date the laboratory reported the result.

During the study period, COVID-19 PCR testing was available as either pillar 1 (in-hospital) or pillar 2 (community) testing. For positive COVID-19 PCR tests, the proportion of tests by pillar were described in the RAIRD cohort and compared to the general population. Demographics, including median age at testing (with interquartile ranges) and, where applicable, age at death where it occurred within 28 days of a positive test, are also described.

*3.3.7 Hospital and intensive care unit admissions*

HES admitted patient care (APC) data on hospital and intensive care unit (ICU) admissions with an ICD-10 diagnostic code for COVID-19 were extracted from the PHE datalake. Duration and number of admissions, and basic and advanced respiratory support days on ICU are described.

*3.3.8 Mortality rate calculation*

I report two measures of COVID-19-related deaths. The primary definition is death with any mention of COVID-19 on the death certificate as used by the ONS(107). This was chosen as the primary measure due to the limited availability of COVID-19 PCR testing in the community during the first wave. The secondary definition is death within 28 days of a positive COVID-19 PCR test, as used by PHE(108).

The crude all-cause mortality rate from 01 March to 31 July 2020 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population, along with the crude mortality rates for the two measures of COVID-19-related death.

Age-sex-standardised mortality rates and sex-specific mortality rates per 100,000 in the population were calculated, standardised to the 2019 mid-year estimate for the England population using 5-year age bands. Age-standardised mortality rates (ASMRs) standardised to the 2013 European Standard Population (ESP) were also calculated. As the ESP is not disaggregated by sex and assumes equal numbers of males and females, and identical age distributions within sexes, this population was not used to calculate age-sex standardised rates.

The ONS provided data for all-cause deaths, and deaths with any mention of COVID-19 on the death certificate, over the same time period in England, split by sex and age band(109, 110). PHE provided comparable data for deaths within 28 days of a positive COVID-19 test (available to the public on request). These data were used to calculate the crude, age-standardised and sex-specific mortality rates as a

comparator. The 2019 mid-year estimate for the population of England was used as the denominator.

Risk ratios with 95% confidence intervals were calculated in order to compare rates between the RAIRD cohort and the general population. Given the size of the general population of England (approximately 56 million), for the purposes of this calculation it was treated as an infinite population (in order to avoid unnecessary complexity, with no meaningful change to the results). Rate ratios were therefore calculated as the general population rate divided by the rate in RAIRD, with confidence intervals.

*3.3.9 COVID-19 infection rate calculation*

Laboratory confirmed COVID-19 infection rate from 01 March to 31 July 2020 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population. Publicly available data from the government Coronavirus dashboard(111) were used to compare infection rates in the general population. Infection rate was age-standardised to the mid-year 2019 England population. It was not possible to standardise by sex as this was poorly recorded in the general population data. Risk ratios were calculated using the same method as for mortality rates.

*3.3.10 Stratification by disease*

Poisson regression methods, with an offset term for follow-up time, were used to analyse rates of COVID-19-related death, adjusted for age, sex and RAIRD diagnosis. Incidence rate ratios for each diagnosis, with 95% confidence intervals, are displayed as a forest plot.

*3.3.11 Ethics*

This study received a favourable opinion from the Camden and Kings Cross Research Ethics Committee, study reference 20/HRA/2076, on 18 June 2020.

This work aligns with NCARDRS's objectives and was approved as a project within the National Disease Registration Service (NDRS) in PHE. The legal basis to access the

data is predominantly covered by NCARDRS' Section 251 approval (Reference CAG 10-02(d)/2015). Where the work extends beyond Section 251 approval, it has been approved under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (COPI), allowing the processing of confidential patient information for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the COVID-19 outbreak.

For quality assurance the data extraction and analysis were re-conducted by an independent analyst from the National Disease Registration Service.

*3.3.12 Patient and public involvement*

This work has been developed with input from people with RAIRD. Following the preliminary finding of increased mortality in this population(55), my research group and I consulted with patients and patient charities to confirm priorities for future research and inform the communication and dissemination of our results. This will continue as an iterative process as results become available. A plain English summary of this study was published as an online supplement and is contained in Appendix 5.

*3.3.13 Data analysis*

I performed cleaning, linkage, and analysis of the data in R version 3.6.3 (packages *tidyverse(112)*, *janitor(113), survival(114), mfx(115), survminer(116), meta(117)*).

**3.4 Results**

*3.4.1 Demographic data*

168,691 people were included in the RAIRD cohort in the all-cause mortality study(55). Updates to personal demographic data revealed that 11 people had died prior to 01 March 2020, leaving 168,680 people included in this study. Descriptive demographic data, including RAIRD diagnoses, are shown in Table 1. The median age of the population was 61.7 years (IQR 41.5 – 75.4) and 118,374 (70.2%) were female.

Table 1: Characteristics of the cohort of people with RAIRD alive 01 March 2020 (n=168,680)

| Characteristic | Value |
|---|---|
| Sex* | |
| Female | 118,374 (70.2%) |
| Male | 50,305 (29.8%) |
| Median age (IQR) | |
| Total cohort | 61.7 (41.5 - 75.4; 33.9) |
| Female | 61.8 (43.0 -75.7; 32.6) |
| Male | 61.3 (36.6 -74.9; 38.3) |
| Most recent diagnosis (n, %) | |
| Systemic lupus erythematosus | 41,261 (24.5%) |
| Giant cell arteritis | 38,014 (22.5%) |
| Juvenile inflammatory arthritis | 21,202 (12.6%) |
| Arteritis, unspecified | 17,632 (10.5%) |
| Polymyositis | 17,447 (10.3%) |
| Scleroderma | 11,578 (6.9%) |
| Granulomatosis with polyangiitis | 6,164 (3.7%) |
| Behçet's disease | 4,880 (2.9%) |
| Dermatomyositis | 2,594 (1.5%) |
| Eosinophilic granulomatosis with polyangiitis | 2,351 (1.4%) |
| Polyarteritis nodosa | 1,597 (0.9%) |
| Microscopic polyangiitis | 1,339 (0.8%) |
| Connective tissue disorder with specific organ involvement | 1,218 (0.7%) |
| Takayasu arteritis | 905 (0.5%) |
| Juvenile myositis | 498 (0.3%) |

ICD-10 codes used: Systemic lupus erythematosus = M321, M328, M329; Giant cell arteritis = M315, M316; Juvenile inflammatory arthritis = M080, M082, M083, M084, M089; Arteritis, unspecified = I776; Polymyositis = G724, M332, M608, M609; Scleroderma = M340, M341, M348, M349; Granulomatosis with polyangiitis = M313; Behçet's disease = M352; Dermatomyositis = M331, M339; Eosinophilic granulomatosis with polyangiitis = M301; Polyarteritis nodosa = M300, M308; Microscopic polyangiitis = M317; Connective tissue disorder with specific organ involvement = J991, N085, N164; Takayasu arteritis = M314; Juvenile myositis = M330. *One person did not have sex recorded

*3.4.2 COVID-19 infection*

Between 01 March and 31 July 2020, 1874 (1.11%) of the RAIRD population had a positive COVID-19 PCR test, compared to 261,348 (0.46%) of the general population. Age-standardised to the England population, the infection rate per 100,000 person-years was 1,720.3 (1670.0-1770.6), compared to 1114.3 (1111.5-1117.0) per 100,000 person-years in the general population (rate ratio 1.54 (1.50-1.59), Table 2).

Characteristics of those with a positive COVID-19 PCR test are shown in Table 2. People with RAIRD with a positive PCR test were more likely to have had a pillar 1 test (86.87% of positive tests) than people with a positive PCR test in the general population (62.31% of positive tests).

Table 2: PCR-proven COVID-19 infections in the RAIRD population compared to the whole population of England

| | RAIRD (n = 168,680) | England (n = 56,286,961) | Rate ratio |
|---|---|---|---|
| Infection rate (n, %) | 1,874 (1.11%) | 261,348 (0.46%) | |
| Death certificate mention of COVID (n, %) | 713 (0.42%) | 56,196 (0.10%) | |
| Death within 28 days of COVID test (n, %) | 574 (0.34%) | 36,658 (0.07%) | |
| Age-standardised COVID-19 infection rate (per 100,000 person-years) | 1,720.3 (1670.0-1770.6) | 1,114.3 (1111.5-1117.0) | 1.54 (1.50-1.59) |
| Positive COVID-19 PCR tests by pillar (n (% total tests)) | RAIRD (n = 168,680) | England (n = 56,286,961) | |
| Pillar 1 | 1,628 (86.87%) | 164,600 (62.31%) | |
| Pillar 2 | 246 (13.13%) | 99,583 (37.69%) | |
| Age of those in RAIRD cohort with a positive PCR test | | | |
| | Mean age | Median age | Interquartile range |
| Pillar 1 | 71.14 | 75.10 | 60.89 – 84.14 (23.25) |
| Pillar 2 | 62.42 | 65.31 | 42.19 – 84.72 (42.53) |
| Deaths in RAIRD cohort within 28 days of a positive PCR test, by pillar (n (% deaths)) | | | |
| Pillar 1 | 560 (97.6%) | | |
| Pillar 2 | 14 (2.4%) | | |
| Age of RAIRD cohort who died within 28 days of a positive PCR test | | | |
| Pillar 1 | 77.03 | 79.21 | 71.26 - 85.94 (14.68) |
| Pillar 2 | 88.13 | 89.47 | 84.84 - 92.55 (7.71) |
| Note: Pillar 1 denotes in-hospital testing and Pillar 2 denotes community testing | | | |

*3.4.3 All-cause mortality*

Between 01 March and 31 July, 3401 (2.02%) people in the RAIRD cohort died of any cause, compared to 257,547 out of 56,286,961 (0.46%) among the general population.

*3.4.4 COVID-19 related mortality*

Of the 3401 people who died, death certificate data were available for 3332 (97.97%). 713 (0.42% RAIRD cohort) had COVID-19 mentioned on their death certificate, in any position. This compares to 49,166 (0.09%) of all those who died in the general population.

Of those with a positive COVID-19 PCR test, 574/1874 (30.6%) died within 28 days of a positive test, compared to 36,658/261,348 (14.03%) of the general population. However, the RAIRD cohort were older than the general population of England.

The combined total of people with RAIRD dying with either COVID-19 mentioned on their death certificate, or within 28 days of a positive COVID-19 test, was 743/168,680 (0.44%) and by this measure COVID-19 was implicated in 743/3401 (21.9%) of all deaths during this time-period in this cohort. There is no similar data for the general population of England with which to compare this.

*3.4.5 Age- and age-sex-standardised mortality rates*

The age-sex-standardised mortality rate for all-cause death in RAIRD, standardised to the 2019 mid-year population of England, was 2325.2 (2274.8 – 2375.7), compared to 1098.1 (95% CI 1095.4-1100.9) in the general population (rate ratio 2.12 (2.07 – 2.16)). For deaths mentioning COVID-19 on the death certificate, the age-sex-standardised mortality rate was 505.5 (481.5–529.4), compared to 209.6 (208.4–210.8) in the general population (rate ratio 2.41 (2.30 – 2.53)). For deaths within 28 days of a positive COVID-19 PCR test, the age-sex-standardised mortality rate in RAIRD was 422.0 (399.7–444.3), compared to 156.3 (155.3–157.3) in the general population (rate ratio 2.70 (2.56 – 2.84)). These data are summarised in Table 3. The

ASMR for all-cause death in RAIRD, adjusted to the 2013 European Standard Population is shown in Table 4.

Table 3: Deaths, crude mortality rates, age-sex-standardised mortality rates and sex-specific age-standardised mortality rates during March to July 2020 for the RAIRD cohort compared to the mid-year 2019 population of England

| | Number of deaths | Number of people | Person-years | Crude mortality rate per 100,000 person years | RAIRD age-sex-standardised mortality rate* | England age-sex-standardised mortality rate* | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| All | 3,401 | 168,680 | 70,283 | 4,839.0 (4734.0-4944.0) | 2325.2 (2274.8 – 2375.7) | 1098.1 (1095.4 – 1100.9) | 2.12 (2.07 – 2.16) |
| Female | 2179 | 118,374 | 49,323 | 4417.9 (4298.1-4537.6) | 2131.7 (2073.9 – 2189.4) | 1069.5 (1065.7-1073.3) | 1.99 (1.94 – 2.05) |
| Male | 1222 | 50,305 | 20,960 | 5830.0 (5619.0 - 6041.0) | 2518.8 (2427.7-2610.0) | 1127.5 (1123.5-1131.4) | 2.23 (2.15 – 2.31) |
| Death with any mention of COVID-19 on the death certificate | | | | | | | |
| All | 713 | 168,680 | 70,283 | 1014.4 (966.4-1062.6) | 505.5 (481.5–529.4) | 209.6 (208.4–210.8) | 2.41 (2.30 – 2.53) |
| Female | 427 | 118,374 | 49,323 | 865.7 (812.7 – 918.7) | 417.4 (391.9-443.0) | 186.2 (184.6-187.8) | 2.24 (2.10 – 2.38) |
| Male | 286 | 50,305 | 20,960 | 1164.5 (1262.4 - 1466.6) | 595.5 (551.0-640.1) | 233.6 (231.8-235.4) | 2.55 (2.39 – 2.74) |
| Death within 28 days of a positive COVID-19 test | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| All | 574 | 168,680 | 70,283 | 816.7 (773.6-859.8) | 422.0 (399.7–444.3) | 156.3 (155.3–157.3) | 2.70 (2.56 – 2.84) |
| Female | 332 | 118,374 | 49,323 | 673.1 (626.3 - 719.9) | 327.2 (304.5-349.9) | 131.1 (129.8-132.5) | 2.50 (2.32 – 2.67) |
| Male | 242 | 50,305 | 20,960 | 1154.6 (1060.7 – 1248.5) | 519.0 (476.8-561.2) | 182.1 (180.5-183.6) | 2.85 (2.62 – 3.08) |

*Sex-specific rates are age-standardised only

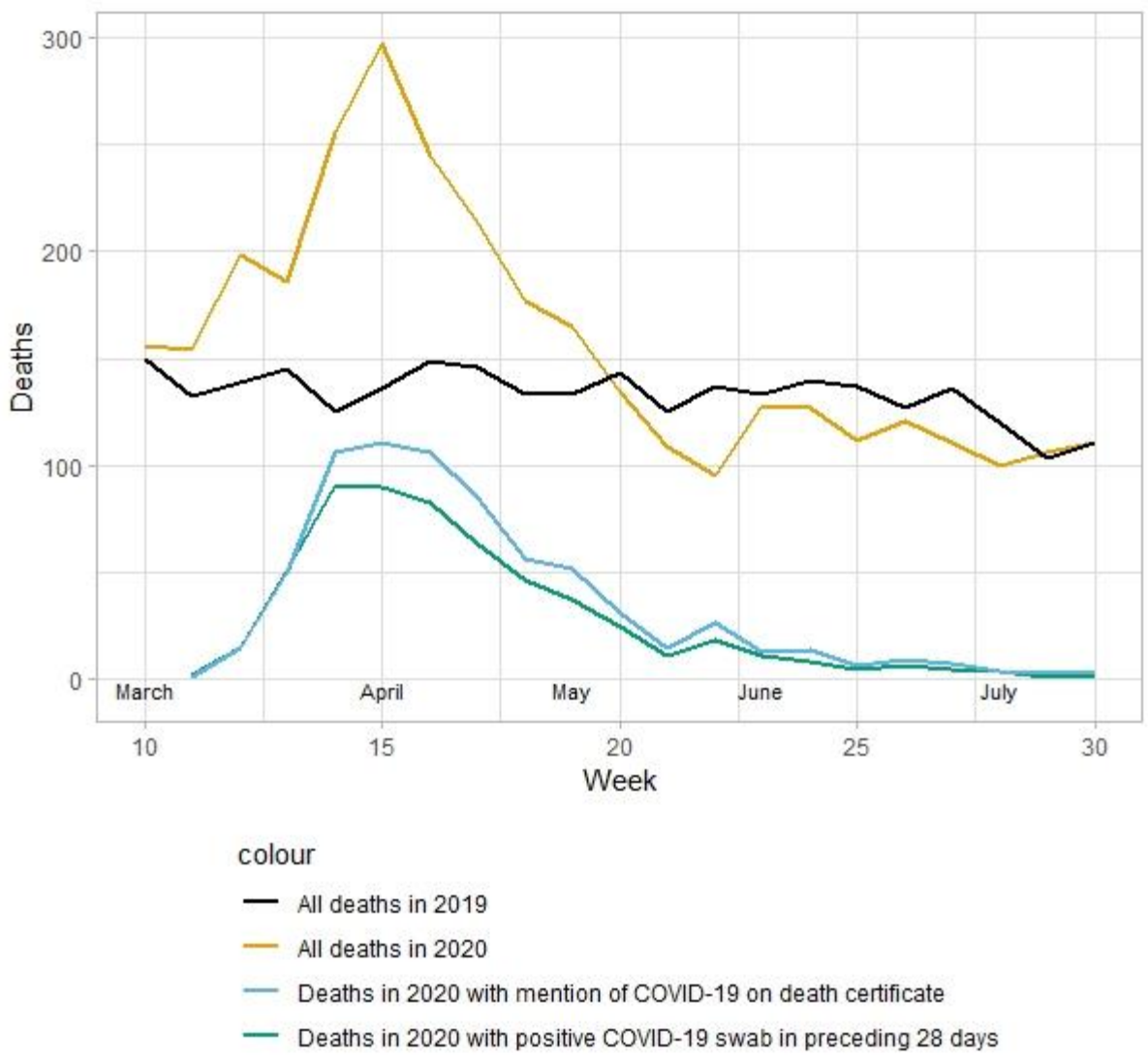
Table 4: Deaths and age-standardised mortality rates during March to July 2020 for the RAIRD cohort compared to the 2013 European Standard Population

| | Number of deaths | Number of people | Person-years | Crude mortality rate per 100,000 person years | RAIRD age-standardised mortality rate | General population age-standardised mortality rate | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| All | 3,401 | 168,680 | 70,283 | 4,775.3 (4614.8-4935.8) | 2,454.4 (2401.1-2507.6) | 1,143.5 (1140.7-1146.4) | 2.15 (2.10 – 2.19) |
| Death with any mention of COVID-19 on the death certificate | | | | | | | |
| All | 713 | 168,680 | 70,283 | 1014.4 (966.4-1062.6) | 478.6 (456.0-501.3) | 218.0 (216.7-219.2) | 2.20 (2.09 – 2.30) |
| Death within 28 days of a positive COVID-19 test | | | | | | | |
| All | 574 | 168,680 | 70,283 | 816.7 (773.6-859.8) | 393.1 (372.3-413.8) | 162.6 (161.5-163.7) | 2.42 (2.29 – 2.54) |

*3.4.6 COVID-19 related deaths over time*

All-cause deaths in 2019 and 2020, deaths with any mention of COVID-19 on the death certificate and deaths within 28-days of a positive COVID-19 PCR test were plotted over time and are shown in Figure 4.

Figure 4: Deaths in RAIRD cohort between 01 March 2020 and 31 July 2020, shown as all deaths, deaths with any mention of COVID-19 on the death certificate and deaths within 28-days of a positive COVID-19 PCR test, with all deaths in RAIRD cohort between 01 March 2019 and 31 July 2019 as a comparator



*3.4.7 Hospital and ICU admissions*

Demographic data for those who were admitted to hospital and/or to ICU with a diagnostic code for COVID-19 are shown in Table 5. The median age of those with a hospital admission was 75.07 years (IQR 62.13-83.64), and for an ICU admission 60.65 years (IQR 48.71-69.79).

For hospital admissions, the median length of stay was 8 days (mean 13.8, range 0-269) and the median number of admissions was 2 (mean 2.3, range 1-20).

For ICU admissions, the median length of stay was 6 days (mean 12.1, range 0-101) and the median number of admissions was 1 (mean 1.2, range 1-3). The median number of basic respiratory support days whilst on ICU was 2 (mean 3.6, range 0-30) and the median number of advanced respiratory support days was 1 (mean 7.9, range 0-93) (Table 5).

Seventy people died within 28 days of a positive COVID-19 PCR test but were not admitted. Within this group, the median age was 84.84 (IQR 78.30-89.62).

Of the 103 people who died with a mention of COVID-19 on their death certificate but who did not have a positive COVID-19 PCR test or a hospital admission, the median age was 84.78 IQR (77.44-89.40).

Table 5: Summary of hospital and intensive care unit (ICU) admissions, including demographics and characteristics of stay

| Demographics | | | | |
|---|---|---|---|---|
| | n | Mean age | Median age | IQR |
| Any admission with COVID-19 code | 1672* | 71.43 | 75.07 | 62.13-83.64 (21.51) |
| Death certificate mention of COVID-19 | 546† | 76.68 | 79.04 | 71.15-85.66 (14.51) |
| Death within 28 days of test | 504 | 76.73 | 78.95 | 71.26-85.65 (14.39) |
| ICU admission with COVID-19 code | 137 | 59.79 | 60.65 | 48.71-69.79 (21.08) |
| Death certificate mention of COVID-19 | 64 | 62.72 | 61.59 | 51.47-74.97 (23.51) |
| Death within 28 days of test | 59 | 64.30 | 65.51 | 53.83-75.91 (22.07) |
| COVID positive, not admitted, all | 595 | 65.30 | 70.72 | 48.83-84.71 (35.88) |
| Death from all causes | 81 | 81.91 | 84.88 | 76.05-90.15 (14.10) |
| Death certificate mention of COVID-19 | 64 | 81.92 | 84.86 | 77.81-89.69 (11.89) |
| Death within 28 days of test | 70§ | 81.46 | 84.82 | 74.70-89.84 (15.14) |
| Mention of COVID-19 on death certificate, without admission or positive PCR | 103 | 82.53 | 84.78 | 77.44-89.40 (11.96) |

*Of whom 1279/1672 had a positive COVID-19 PCR test
† Of whom 502/546 had a positive COVID-19 PCR test
§Of whom 61/70 had mention of COVID-19 on their death certificate

| All hospital admissions‡ (n=1672) | | | |
|---|---|---|---|
| | Median | Mean | Range |
| Duration of admission (days)** | 8.0 | 13.8 | 0-269 |
| Number of admissions per individual | 2.0 | 2.3 | 1-20 |

| ICU admissions‡ (n=137) | | | |
|---|---|---|---|
| | Median | Mean | Range |
| Basic respiratory support days | 2.0 | 3.6 | 0-30 |
| Advanced respiratory support days | 1.0 | 7.9 | 0-93 |
| Duration of admission (days)** | 6.0 | 12.1 | 0-101 |
| Number of ICU admissions per individual | 1.0 | 1.2 | 1-3 |

‡Where an individual had more than one admission, totals are summed
**Reported as 0 where admissions were less than one calendar day

*3.4.8 All-cause death by category*

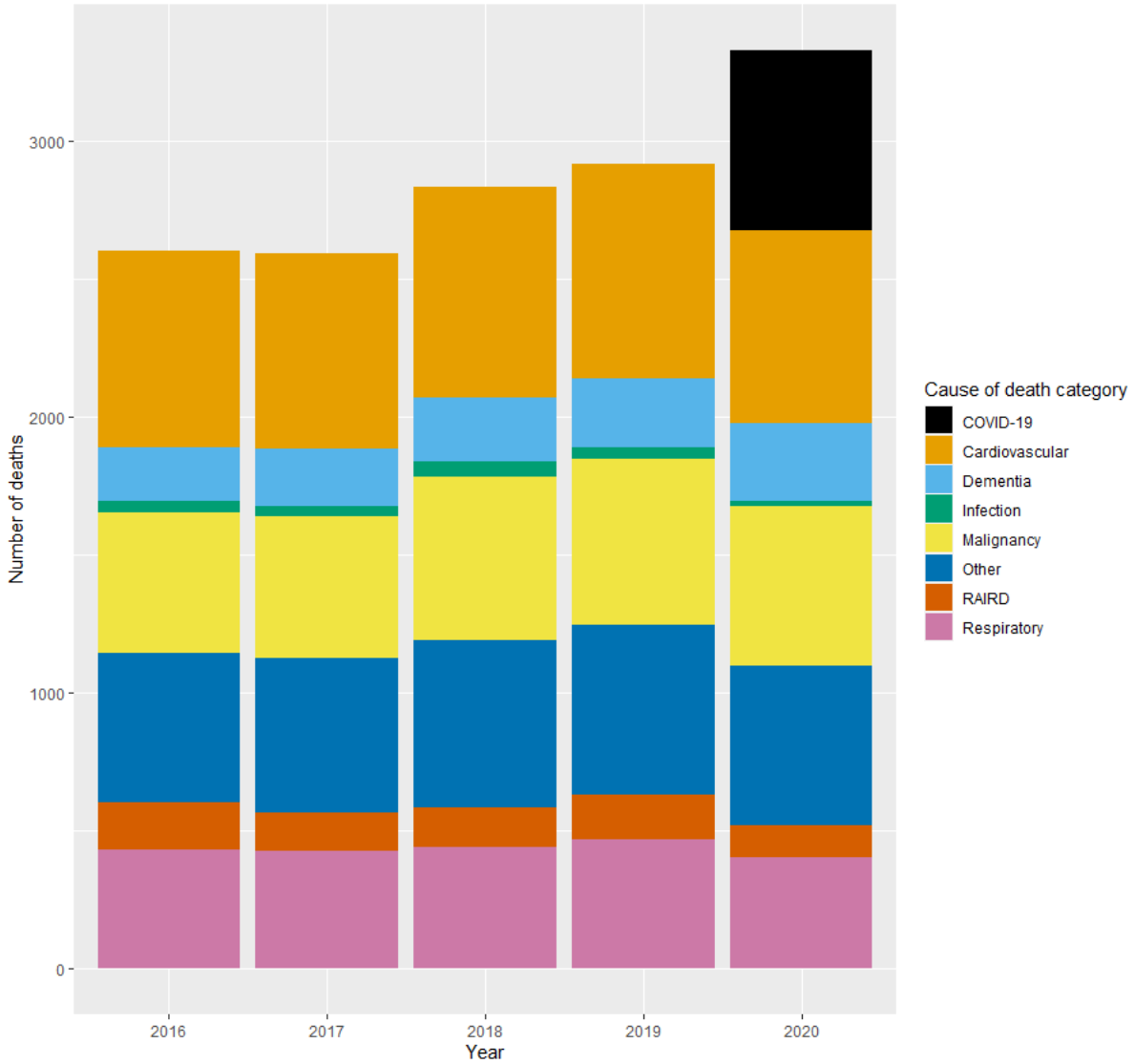
Where death certificate data were available, underlying cause of death by category was extracted and are shown in Table 6. Deaths due to cardiovascular disease were recorded in 703 (21.1%), COVID-19 652 (19.6%), malignancy 581 (17.4%), respiratory 404 (12.1%), dementia 280 (8.4%), underlying RAIRD 113 (3.4%) and non-COVID-19 infection 19 (0.6%), with the remaining 580 (17.4%) ascribed to other causes.

Table 6: ONS ascribed underlying cause of death by category in RAIRD cohort between 1st March and 31st July 2020

| Cause of death | n (%) |
|---|---|
| Category | |
| Cardiovascular | 703 (21.1%) |
| COVID-19 | 652 (19.6%) |
| Malignancy | 581 (17.4%) |
| Other | 580 (17.4%) |
| Respiratory | 404 (12.1%) |
| Dementia | 280 (8.4%) |
| Underlying RAIRD | 113 (3.4%) |
| Non COVID-19 infection | 19 (0.6%) |

For comparison, data were extracted on all-cause death in people with a diagnostic code for RAIRD occurring during March-July 2016-2020 and categorised by underlying cause (Figure 5). There was no evidence of an increase in death from non-COVID-19-related causes during the pandemic.

Figure 5: All cause death by category in people with RAIRD during March-July 2016-2020. Categories align to major ICD-10 code chapters, with the addition of diagnoses pertinent to the cohort (RAIRD, dementia).



*3.4.9 Age at death*

There was no significant change in median age at death between 2016 and 2020 (median age ranged from 79.92-81.50), and this was similar to age at death related to COVID-19 (median 81.31, IQR 72.98-87.34; Table 7).

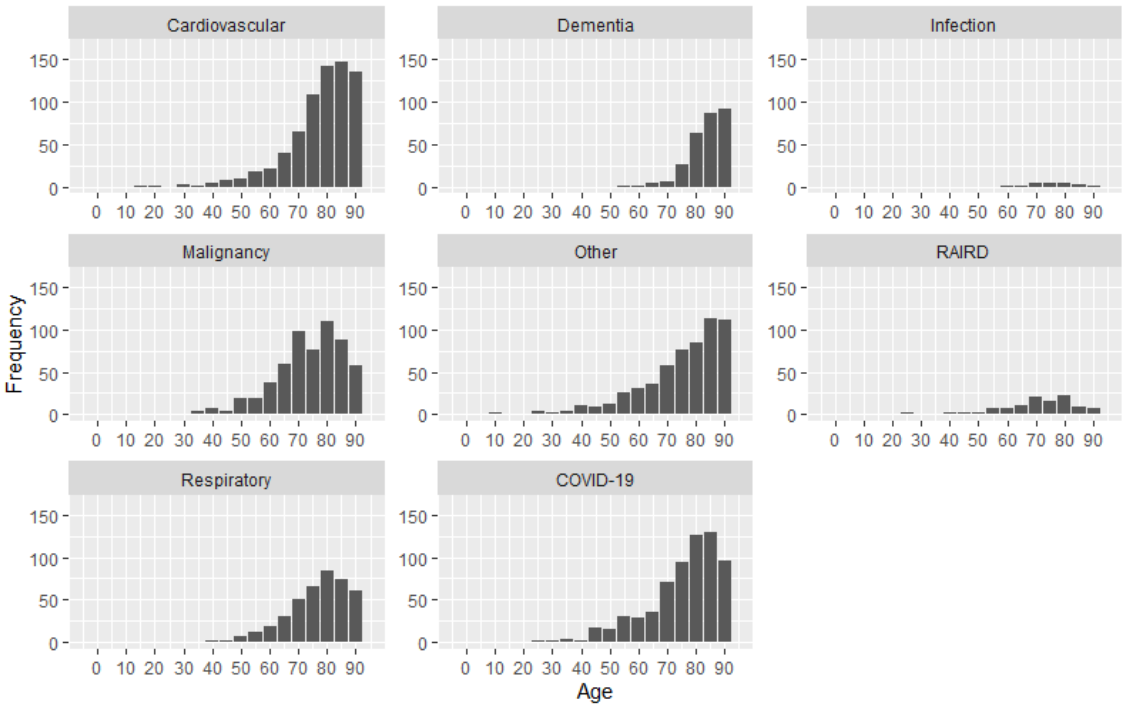
Table 7: Age at death of RAIRD cohort March-July 2016-2020

| Year | Median age | IQR |
|---|---|---|
| 2020 | | |
| All deaths | 81.50 | 72.95-87.82 (14.87) |
| COVID-related | 81.31 | 72.98-87.34 (14.36) |
| Non-COVID-related | 81.59 | 72.92-87.92 (15.01) |
| 2019 | 81.06 | 71.72-87.07 (15.35) |
| 2018 | 79.92 | 71.15-86.99 (15.84) |
| 2017 | 80.77 | 71.05-87.20 (16.15) |
| 2016 | 80.50 | 71.67-86.94 (15.27) |

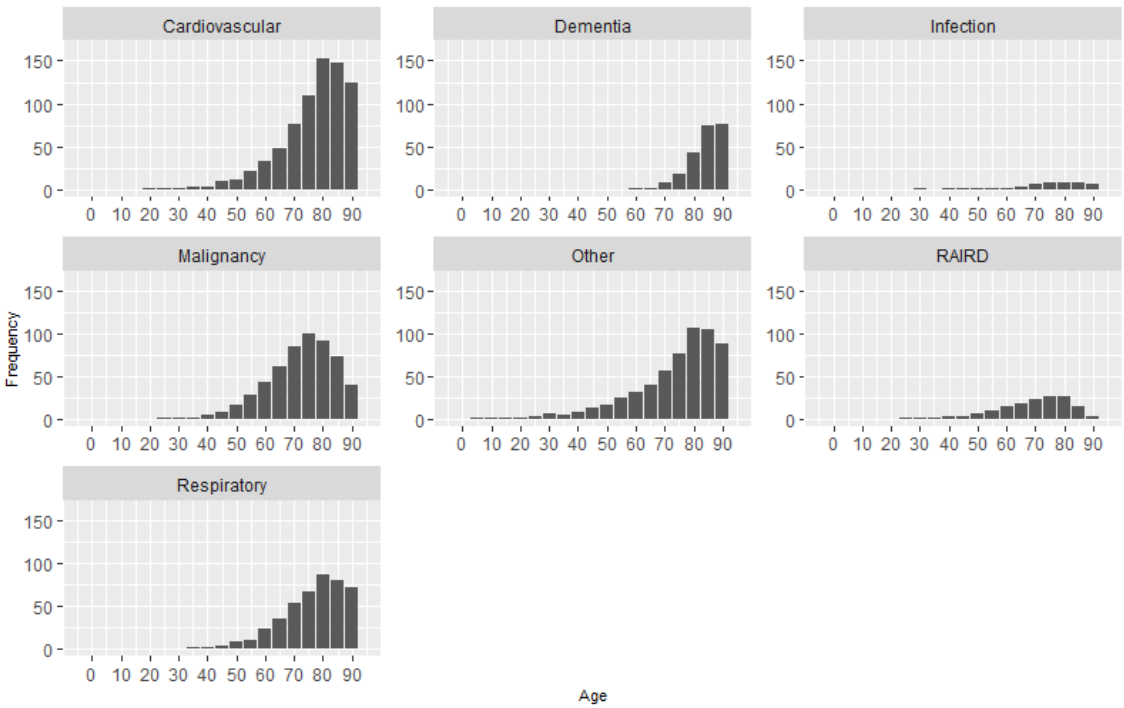
Age at death in people with RAIRD was compared between 2020 and 2019, categorised by underlying cause of death (Figure 6). There was no evidence of earlier age of death occurring in 2020 in certain cause of death categories e.g., in deaths from cardiovascular disease.

Figure 6: Cause of death by category and age in i) between March to July 2020 and ii) mean over March to July 2016-2019

i)



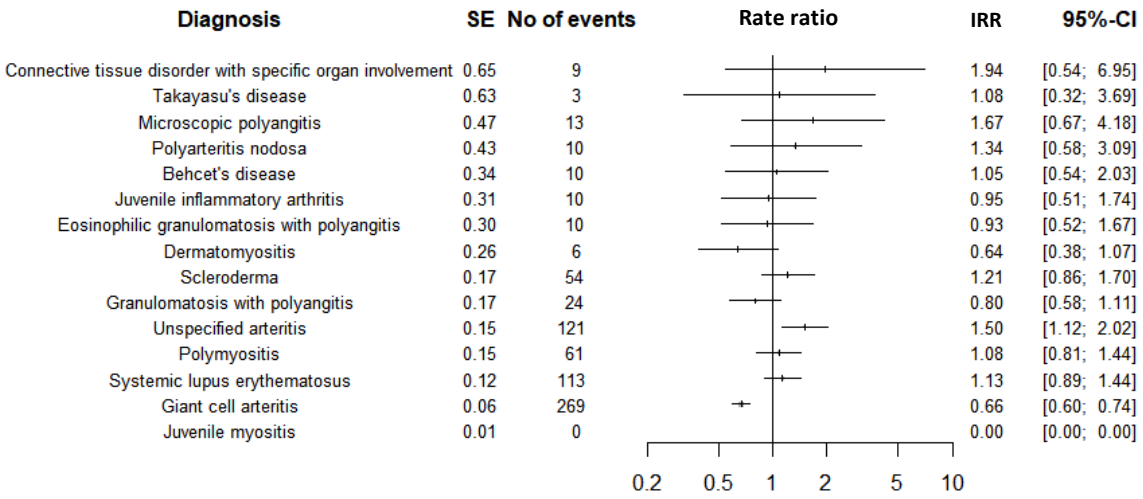

ii)



*3.4.10 Stratification by disease*

Incidence rate ratios for COVID-19-related death stratified by RAIRD diagnosis are displayed in Figure 7. The comparable ratios and overlapping confidence intervals suggest a similar risk across the RAIRD cohort, regardless of diagnosis. People with giant cell arteritis (GCA) were at slightly reduced risk (IRR 0.66, 95% CI 0.60-0.74), which may reflect that GCA is often a self-limiting disease not requiring lifelong immunosuppression. This is discussed further in section 3.5.6. The wide confidence intervals reflect the relatively small number of events in the first wave.

Figure 7: Forest plot showing incidence rate ratios with 95% confidence intervals for COVID-19-related death, stratified by RAIRD diagnosis



## 3.5 Discussion

### *3.5.1 Main findings*

In the first wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD were more than twice that of the general population. This seems to have been contributed to by both higher COVID-19 infection rates, and higher mortality after COVID-19 infection, although further discussion of this continues in section 3.5.5 and in chapter 4.

The age-sex-standardised COVID-19 infection rate was 1.54 (1.50-1.59) times higher among people with RAIRD compared to the general population, despite shielding policies (protection of the clinically extremely vulnerable(15)) in place in England.

### *3.5.2 Strengths*

A major strength is that the denominator population is known, allowing me to describe for the first time both rates of COVID-19 infection and of COVID-19 related death. Previous mortality COVID-19 studies in RAIRD have either included much a smaller group of people or relied on case series and physician reported cases(56) and allowed only internal comparisons within cohorts of people with rheumatic diseases, and not comparison with the general population.

This work uses novel methodology to bring together a number of linked datasets, including HES, COVID-19 PCR testing data and death certificate data for people with rare diseases, through collaboration with NCARDRS.

The patient identifiable nature of the data has allowed validation work to be performed on the methods of case ascertainment from HES. Overall, when weighted for the actual occurrence of the codes in the study population, the positive predictive value was 84.7%(55).

Whilst this RAIRD cohort contains a heterogenous group of diseases they share common underlying mechanisms; all are immune-mediated inflammatory diseases and all may require immunosuppression, depending on disease severity and subtype. My sub-analysis by disease show they all have comparable risks of death due to COVID-19. Pooled analysis of

these diseases increases statistical power to detect outcomes and is clinically justified by their common underlying disease mechanisms and treatments.

*3.5.3 Limitations*

The measures of COVID-19 mortality described were selected to allow comparison with available statistics for the general population. The primary definition, any mention of COVID-19 on the death certificate (used by the ONS), infers that COVID-19 infection contributed to death, even if it was not the main cause and even in the absence of a positive PCR test. This has the theoretical potential to over-estimate deaths due to COVID-19 infection but has been found to be the best measure to explain the excess deaths seen in the national data. In this RAIRD cohort, of the 713 people with a mention of COVID-19 on the death certificate, 661 (93%) had COVID-19 in part 1, meaning that it directly led to death(118). Conversely, I may have underestimated COVID-19-related deaths as death certificate data were unavailable for 2% of the cohort. This proportion is not unexpected and registration delays are common(119), although they may disproportionately reflect certain groups such as deaths in hospital, or due to occupational exposure to disease (including to COVID-19 infection(120)).

The secondary definition was death within 28 days of a positive COVID-19 PCR test, as used by PHE. This measure overlooks deaths where the person never has a positive PCR test, or where the death occurred more than 28 days after diagnosis: important given the prolonged clinical course of COVID-19. In this RAIRD cohort, the median time between a positive test and death was 6 days, and only 22 (4%) of those who had COVID-19 on their death certificate, and had a positive PCR test, had that test more than 28 days prior to death.

I identified this cohort from diagnoses in HES admitted patient care (APC) data and this methodology may not have identified patients with RAIRD who have never had an in-patient or daycase admission for any reason, and who have been treated entirely on an outpatient basis. Due to the nature of RAIRD, I believe this to be the minority of cases, which is supported by disease prevalence in this cohort being similar to previous studies(33, 35, 96). However, the potential impact is to skew this cohort towards those with more severe disease.

This work describes outcomes in the first wave only. Further work is needed to describe the outcomes in the second wave, and assess the influence of immunosuppression, CEV status and shielding policies, and the vaccination programme.

This study does not include data on immunosuppressive medications. The vulnerability to COVID-19 of people living with RAIRD is likely explained in part by the frequent need for immunosuppression in this group. Corticosteroid usage has long been thought to increase the risk of infection(48-50) although in COVID-19, this has been complicated by the emergence of dexamethasone as an effective treatment(51). Concerns remain that corticosteroid treatment preceding infection may predispose to more severe disease(52, 53, 121). Whilst IL-6 receptor antagonists have been shown to reduce mortality in severe COVID-19 requiring intensive care(122), other immunosuppressants, such as rituximab, may impair the antiviral immune response and antibody production, with potentially more severe clinical outcomes(53, 54). This may also impact vaccine effectiveness and recently published data has demonstrated attenuated antibody responses in people with AAV on rituximab(123).

*3.5.4 Comparison to the published literature*

The small numbers of people affected by each RAIRD makes it difficult for studies to have enough statistical power to assess outcomes. Most research has therefore included more common rheumatic diseases such as rheumatoid arthritis (RA).

The COVID-19 Global Rheumatology Alliance describes COVID-19-related mortality in RAIRD and reports an association between immunosuppressive medications and mortality(53). However, this relied on physician-reported cases and could not report rates of COVID-19 infection or deaths. A study looking at the French RMD COVID-19 cohort, a mixture of physician-reported RA and RAIRD patients, found an increased risk of severe COVID-19 in those treated with rituximab(124). There was no increase in mortality in the rituximab group once other risk factors were adjusted for. Data from the same cohort also demonstrated an association between severe infection and treatment with corticosteroids or mycophenolate mofetil(125).

A multi-centre prospective cohort study from Brazil, with a mixed study population of inflammatory arthritis and RAIRD, showed an increased risk of ICU admission and mortality associated with corticosteroids and cyclophosphamide(126).

OpenSAFELY and QCOVID, both of which looked at risk factors for severe COVID-19 outcomes in England, studied smaller populations. At the time of the last published analysis, OpenSAFELY included 24 million patients(39) and QCOVID 8.26 million(56). My research uses the whole England population of 56 million, which has afforded the statistical power to calculate more precise results. The use of whole population data, with a known denominator population, also allows calculation of rates and comparison to the general population.

In addition, of the RAIRD, only systemic lupus erythematosus was included in the QCOVID and OpenSAFELY studies, in both cases combined with RA. Both found a modest increase in the risk of death (HR 1.32 (1.06-1.65) and 1.20 (1.12-1.28) respectively(39, 57)).

Whole population data from Denmark(127) on COVID-19 hospital admissions, including 10,749 people with RAIRD, supports my findings of increased risk in connective tissue disease and vasculitis (age-sex adjusted HR 1.63 (0.78–3.43) and 2.03 (1.02–4.08) respectively). The wide confidence intervals reflect the small number of events, as well as their smaller population of 4.54 million. They do not report on COVID-19 infection rates, nor on mortality in RAIRD specifically.

Whole population data from South Korea(128), including 1,896 people with RAIRD, also found an increased risk of COVID-19 infection and hospitalisation (HR 1.33 (1.02–1.74) and 1.71 (1.06–2.71) respectively). There was also a suggestion of increased COVID-19 mortality, but the small number of events (seven deaths) gave wide confidence intervals, which were not statistically significant (HR 1.87 (0.71–4.85)).

*3.5.5 Infection rate*

There was an increased age-standardised infection rate in the RAIRD cohort, despite the intent of shielding policy to reduce infection exposure. There are several potential reasons for this. They may be more susceptible to symptomatic COVID-19 infection due to their underlying disease and immunosuppression. During the first wave, where testing was predominantly in hospital, their increased contact with healthcare services may have led to increased testing and ascertainment bias. Anecdotally, it is known that some units were performing asymptomatic screening prior to day-case or immunosuppressive treatment. People with RAIRD may also have a worse state of health than the general population, leading to increased hospital admissions, necessitating COVID-19 admission screening tests and the risk of nosocomial infection. Requirements for monitoring bloods and hospital attendances may also have increased the risk of acquiring infection.

*3.5.6 Comparison between RAIRD*

Adjusted for age and sex, the risk of death related to Covid-19 was largely comparable between RAIRD, with overlapping confidence intervals. This suggests a similar risk across the RAIRD cohort, regardless of diagnosis.

The exception was people with GCA, who had a slightly reduced risk (IRR 0.66, 95% CI 0.60-0.74), which may reflect that GCA is often a self-limiting disease not requiring lifelong immunosuppression. This means that people with GCA which has resolved may have a risk more similar to that of the general population of the same age and sex.

Another hypothesis is that people with active GCA are frequently treated with high-dose steroids and/or tocilizumab, both of which have been shown to be effective in reducing mortality in severe Covid-19 infection. This may have served to reduce their risk of death compared to people with other RAIRD, which tend to be treated with more modest doses of steroids and/or alternative immunosuppressants.

Finally, this finding may reflect the relatively large number of events in people with GCA compared to the other conditions included this study. People with GCA make up the majority of the RAIRD cohort and most Covid-19-related deaths occurred within this group, with comparatively few events in the other RAIRD conditions. This served to produce

narrower confidence intervals for GCA compared to the other RAIRD. As described in section 4.4.9, in the second wave the risk for people with GCA was similar to those with other RAIRD, which may reflect the higher number of events across all RAIRD conditions during that time period.

*3.5.7 Clinical and policy implications and future research*

These findings provide clear evidence that during the first wave of the pandemic people with RAIRD were both at higher risk of COVID-19 infection and of COVID-19-related death than people of the same age and sex in the general population. They have important implications for people living with RAIRD, their clinicians and for public health policy.

They confirm at whole population-level that the assumptions at the start of the pandemic, that many people with RAIRD would be clinically extremely vulnerable to the effect of COVID-19(12), were correct. Many people with RAIRD require lifelong immunosuppression, conferring ongoing risk. Protecting the health of people with RAIRD needs specific public health prioritisation, to reduce both their risk of acquiring COVID-19 infection and mortality. Infection prevention measures, including robust alternatives to face-to-face appointments and support to shield during times of heightened infection rates in the community, are paramount, as is vaccine prioritisation in this group.

Within the UK, certain people were classified as “clinically extremely vulnerable” to COVID-19 infection and asked to “shield”(15). Whilst a RAIRD diagnosis alone did not lead to inclusion on the Shielded Patient List (SPL), risk stratification guidance advised that many patients on immunosuppressive therapies, including moderate- to high-dose corticosteroids, and/or with relevant co-morbidities, should shield(14). Given the nature of RAIRD, this included many people living with these conditions(129, 130). My findings suggest that despite this, COVID-19 infection and mortality rates were greater for people with RAIRD than for the general population. This is observational data, and the shielding status of this cohort is not yet known, so it is not possible to determine what the outcomes would have been without shielding policies in place. In addition, shielding policies were instituted on 23 March 2020 and some of my findings may reflect earlier transmission.

Further research in this cohort during later waves of the pandemic, including assessment of the impact of shielding, is ongoing.

I did not find an excess of non-COVID-19-related deaths during this period. This may reflect efforts to prioritise access to urgent care. However, any detrimental effect of the pandemic may have a delayed impact on mortality.

These results highlight the urgent need for analysis of the real-world effectiveness of vaccination among people with RAIRD, given the evidence that they may respond less well to vaccination(123, 131). This will have crucial implications for their ongoing health protection needs, including deciding the optimal vaccination schedule to maximise protection.

**3.6 Conclusions**

My research has shown that in the first wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD were more than twice that of the general population. This seems to have been contributed to by both higher COVID-19 infection rates, and higher mortality after COVID-19 infection.

# Chapter 4: COVID-19 infection, admission and death and the impact of corticosteroids amongst people with Rare Autoimmune Rheumatic Diseases in England: the second wave of the pandemic

This chapter describes the second study within my thesis. It is a nationwide cohort study looking at COVID-19 outcomes in people with RAIRD during the second wave of the COVID-19 pandemic in England. It also describes the association between corticosteroids and COVID-19 outcomes. This study is published in Rheumatology and is currently accessible as an accepted manuscript, with the fully formatted paper due to be published on 30/04/2023. A PDF of the manuscript is included within Appendix 3.

## 4.1 Main findings and abstract

### *4.1.1 Main findings*

1. People with RAIRD had a 2.76-fold increased risk of COVID-19-related death compared to the general population.
2. There was no evidence of increased risk of death from non-COVID-19 related causes.
3. Corticosteroid usage within the 30-days prior to COVID-19 infection was associated with an increased risk of COVID-19-related death, in a dose-dependent fashion.

### *4.1.2 Abstract*

**Objectives:**

To calculate the rates of COVID-19 infection and COVID-19-related death among people with rare autoimmune rheumatic diseases (RAIRD) during the second wave of the COVID-19 pandemic in England and describe the impact of corticosteroids on outcomes.

**Methods:**

Hospital Episode Statistics data were used to identify people alive 01 August 2020 with ICD-10 codes for RAIRD from the whole population of England. Linked national health records were used to calculate rates and rate ratios of COVID-19 infection and death up to 30 April 2021. Primary definition of COVID-19-related death was mention of COVID-19 on the death

certificate. NHS Digital and Office for National Statistics general population data were used for comparison. The association between 30-day corticosteroid usage and COVID-19-related death, COVID-19-related hospital admissions and all-cause deaths were also described.

**Results:**

Of 168,330 people with RAIRD, 9,961 (5.92%) had a positive COVID-19 PCR test. The age-standardised infection rate ratio between RAIRD and the general population was 0.99 (95% CI 0.97-1.00). 1,342 (0.80%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.76 (2.63–2.89) times higher than in the general population. There was a dose-dependent relationship between 30-day corticosteroid usage and COVID-19-related death. There was no increase in deaths due to other causes.

**Conclusions:**

During the second wave of COVID-19 in England, people with RAIRD had the same risk of COVID-19 infection but a 2.76-fold increased risk of COVID-19-related death compared to the general population, with corticosteroids associated with increased risk.

## 4.2 Introduction

### *4.2.1 RAIRD in the first wave of the COVID-19 pandemic*

The research community responded remarkably to the challenge of the COVID-19 pandemic, rapidly describing outcomes in people with rare autoimmune rheumatic diseases (RAIRD) in order to guide clinical practice. However, previous studies have been small and/or relied on case series and physician-reported cases(56, 132-135). This allowed only internal comparisons within cohorts of people with rheumatic diseases and not comparison with the general population.

My previous work has shown that people with rare autoimmune rheumatic diseases (RAIRD) were at increased risk of death related to COVID-19 infection during the first wave of the COVID-19 pandemic (01 March – 31 July 2020), when compared to the general population in England(55, 136).

*4.2.2 Study objectives*

There were concerns that more transmissible SARS-CoV-2 variants (including the Alpha variant) may have further increased the risk to those with RAIRD. This study therefore repeats methods used in my previous work, using linked national health records for the whole population of England, to calculate the rates of laboratory confirmed COVID-19 infection and COVID-19-related death among people with RAIRD during the second wave of the COVID-19 pandemic (01 August 2020 to 30 April 2021) and compares these rates to those in the general population. I also describe COVID-19-related hospital and ICU admission, underlying causes of death by category and COVID-19-related mortality stratified by RAIRD diagnosis.

Finally, as registry studies have highlighted an association between corticosteroids and adverse COVID-19 outcomes(56, 121, 137, 138), I examine the effect of corticosteroids on COVID-19-related death using national community prescriptions data. I also examine the effect of corticosteroid dose, to establish to what extent a relationship between corticosteroid and mortality is influenced by dose.

**4.3 Methods**

*4.3.1 Background*

This work is a product of the collaboration between the Registration of Complex Rare Diseases Exemplars in Rheumatology (RECORDER) project at the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)(85). NCARDRS, based within NHS Digital (NHSD), registers people with rare conditions in order to support high quality clinical practice and research, provide whole population epidemiological data and empower patients(105). It has unique access to linked national datasets of electronic health records at patient-identifiable level for the whole population of England.

This study uses Hospital Episode Statistics (HES, which contains every episode of admitted patient care in NHS hospitals in England), COVID-19 polymerase chain reaction (PCR) test results, Office for National Statistics (ONS) death certificate data and NHS prescriptions dispensed in the community.

The RAIRD included in this study comprise of ANCA-associated vasculitis, Behçet's disease, giant cell arteritis, idiopathic inflammatory myopathies, juvenile inflammatory arthritis, scleroderma, systemic lupus erythematosus and Takayasu arteritis (ICD-10 code lists are shown in Figure 8).

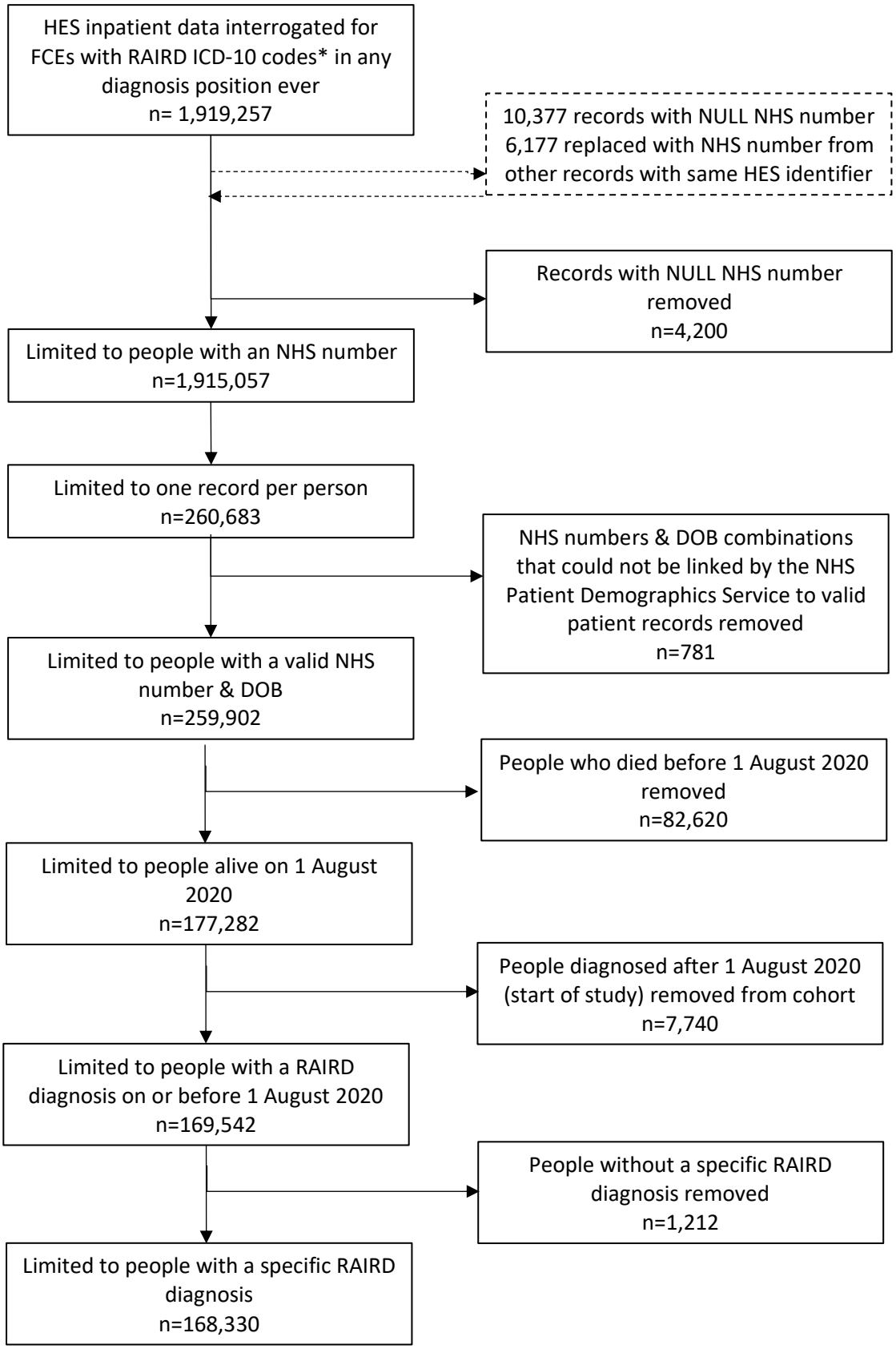
*4.3.2 Data validation*

As described earlier in this thesis, my research team and I's previous work validating HES ICD-10 codes for RAIRD has shown high accuracy, with a positive predictive value of 84.7%(55), and prevalence estimates for individual RAIRD are similar to reported population estimates.

*4.3.3 Study cohort*

People with a diagnostic code ever for RAIRD in HES, resident in England, and alive 01 August 2020 were included in the study. A data flow diagram is shown in Figure 8. Vital status data from the NHS Personal Demographics Service were used to confirm whether people were alive, or where relevant to confirm date of death(99).

Figure 8: Data flow diagram showing identification of second wave RAIRD cohort from HES data.

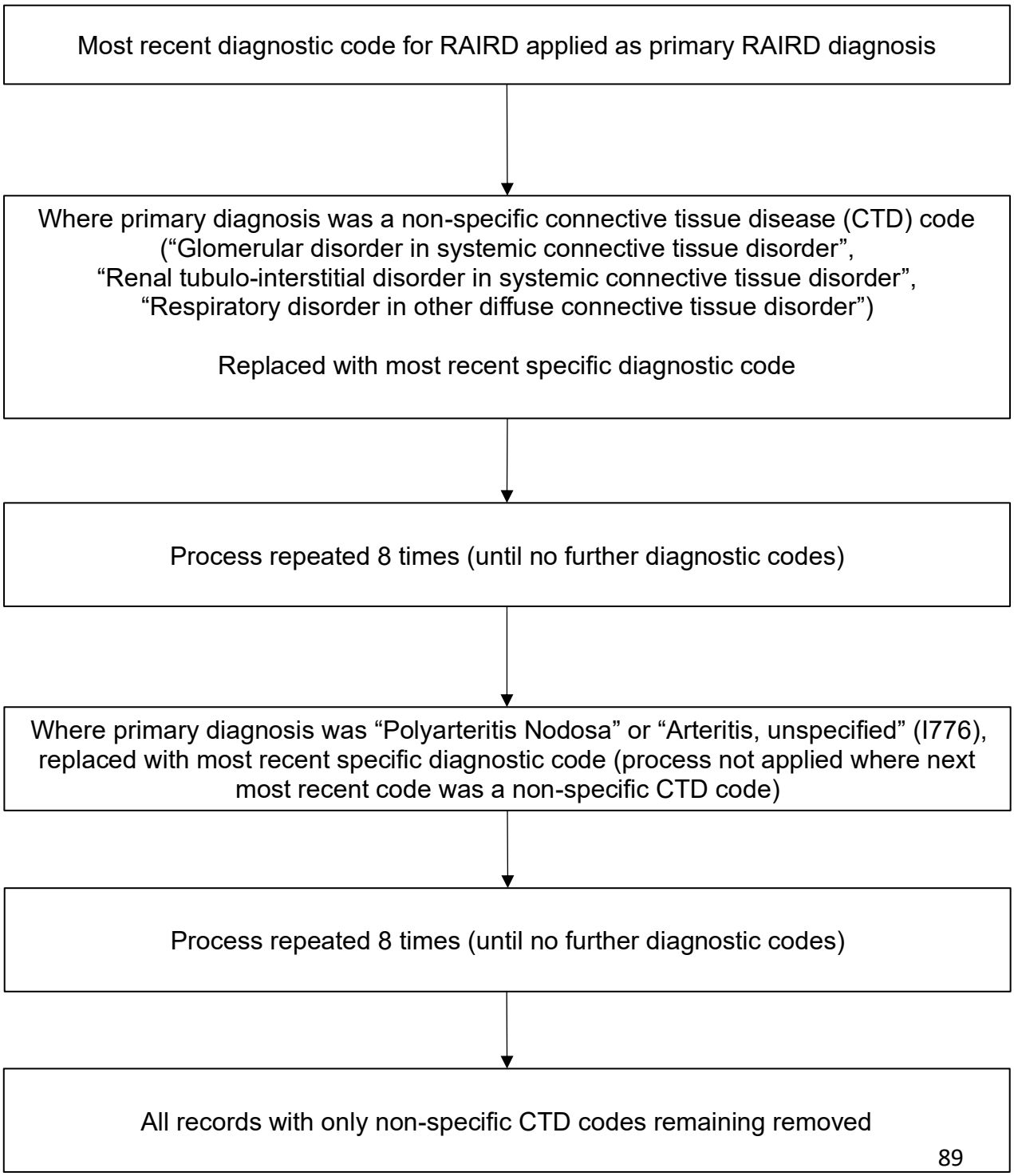



*FCE = finished consultant episode. HES = hospital episode statistics.* *RAIRD ICD-10 codes comprise: M313, M317, M301, M314, I776, M352, M315, M316, M321, M330, M332, M331, M339, M340, M341, M348, M349, M083, M084, M082, M080, M300, M308, J991, N085, N164, M328, M329, M609, G724, M608, M089

*4.3.4 RAIRD diagnoses*

Participants were grouped by RAIRD diagnosis, based on their most recent diagnostic code. Where the most recent code was non-specific, for example "Renal tubulo-interstitial disorder in systemic connective tissue disorder", earlier, more specific diagnostic codes were used. Where only non-specific codes were available, participants were excluded, following the algorithm in Figure 9.

Figure 9: Algorithm for assigning main rheumatological diagnosis



*4.3.5 COVID-19 infection*

A population-level dataset of COVID-19 PCR test results, held in the Second Generation Surveillance System in UK Health Security Agency (UKHSA), was used to determine COVID-19 status. Positive tests amongst the RAIRD cohort were extracted, along with the date the laboratory reported the result. Demographics are described by pillar 1 (in-hospital) or pillar 2 (community) testing.

Laboratory confirmed COVID-19 infection rate from 01 August 2020 to 30 April 2021 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population. Infection rate was age-standardised to the mid-year 2020 England population. Publicly available data from the government Coronavirus dashboard(111) were used to compare infection rates in the general population.

*4.3.6 Death certificate data*

Cause of death data from death certificates (free text and ICD-10 coded) provided by the ONS were utilised. All cause of death fields were examined for ICD-10 codes specific to current COVID-19 infection (U07.1, U07.2). The free text was manually checked for keywords ("*cov*", "*virus*" or "*19*") which found that one death with a mention of COVID-19 was not coded with a relevant code. In order to align with the methodology used for the general population data, this was not included in the final analysis.

For this wave of the pandemic, a sub-analysis was performed to examine the death certificate data for three additional COVID-19 codes, which were issued in November 2020 (U07.3, personal history of COVID-19; U07.4, post-COVID-19 condition; and U07.5, multisystem inflammatory syndrome associated with COVID-19)(139). No death certificates were found to contain these cause of death codes. The ONS general population data included only deaths mentioning codes U07.1 and U07.2 and so the methodology described above was used to describe COVID-19-related deaths and calculate mortality rates.

Underlying all-cause death was classified by ICD-10 category.

*4.3.7 All-cause and COVID-19-related mortality*

The crude all-cause mortality rate from 01 August 2020 to 30 April 2021 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population, along with the crude mortality rates for the two measures of COVID-19-related death.

I report two measures of COVID-19-related deaths. The primary definition is death with any mention of COVID-19 on the death certificate as used by the ONS(107). The secondary definition is death within 28 days of a positive COVID-19 PCR test, as used by UKHSA(108).

Age-sex-standardised mortality rates per 100,000 in the population were calculated, standardised to the 2020 mid-year estimate for the England population using 5-year age bands. Age-standardised mortality rates (ASMRs) standardised to the 2013 European Standard Population (ESP) were also calculated. As the ESP is not disaggregated by sex and assumes equal numbers of males and females, and identical age distributions within sexes, this population was not used to calculate age-sex standardised rates.

The ONS provided general population data for all-cause deaths, and deaths with any mention of COVID-19 on the death certificate, over the same time period in England, split by sex and age band(140). UKHSA provided comparable data for deaths within 28 days of a positive COVID-19 test (available to the public on request). These data were used to calculate the crude, age-standardised and age-specific mortality rates as a comparator. The 2020 mid-year estimate for the population of England was used as the denominator.

All-cause deaths in 2019 and 2020, deaths with any mention of COVID-19 on the death certificate and deaths within 28-days of a positive COVID-19 PCR test were plotted over time in order to allow direct comparison of the different measures, and to assess whether the peak in COVID-19-related deaths corresponded to a peak in all-cause mortality.

Underlying causes of death by ICD-10 category were extracted and categorised e.g., cardiovascular disease, dementia. For comparison, data were extracted on all-cause death occurring during August-April 2016-2021 in people with a diagnostic code for RAIRD, to assess for an increase in deaths due to causes other than COVID-19 infection.

Age at death was calculated and compared to the time period described above, to examine for any impact of the COVID-19 pandemic.

*4.3.8 Stratification by disease*

Poisson regression methods were used to analyse rates of COVID-19-related death, adjusted for age, sex and RAIRD diagnosis. The combined RAIRD cohort was used as the reference category. Incidence rate ratios for each diagnosis, with 95% confidence intervals, are displayed as a forest plot.

*4.3.9 Corticosteroid prescriptions data*

I performed a sub-analysis in those testing positive for Covid-19. A national community prescriptions dataset(141, 142) was used to extract prescriptions for oral corticosteroids in this cohort.

Prednisolone equivalent dose (PED) in mean daily dose bands (0mg, >0-5mg, >5-10mg, >10-15mg, >15mg) was calculated for the 30-day period prior to Covid-19 infection. In those dying related to Covid-19 infection but without a positive PCR test (n = 102), date of infection was taken as date of death minus 10 days. Poisson regression was used to assess the effect of corticosteroid dose on Covid-19-related death, adjusted for age and sex. A p-value for trend was calculated. I ran a sensitivity analysis to check whether there was a linear relationship between steroid dose and Covid-19-related death, dividing steroid dose into quartiles and analysing it as factors, rather than as a continuous variable. Subsequent likelihood ratio testing showed no significant difference and so in the final model steroid dose was included as a continuous variable.

Compared to the first wave of the pandemic, the proportion of COVID-19-related deaths occurring on the same day as the positive PCR test result, and therefore accruing zero person-time and being excluded from the Poisson analysis, increased from 2.9% (21/713) to 3.8% (51/1342). To assess whether excluding these deaths influenced the results, a sensitivity analysis was performed.

*4.3.10 Hospital and intensive care unit admissions*

HES admitted patient care (APC) data on hospital and intensive care unit (ICU) admissions with an ICD-10 diagnostic code for COVID-19 were extracted. Duration and number of admissions, and basic and advanced respiratory support days on ICU are described.

*4.3.11 Ethics*

This study was approved by the Camden and Kings Cross Research Ethics Committee, study reference 20/HRA/2076, on 18 June 2020.

The legal basis to access the data is covered by NCARDRS' Section 254 approval (sections 254(1) and 254(6) of the 2012 Health and Social Care Act), which includes a specific legal instruction to collect patient data without informed consent(143).

For quality assurance the data extraction and analysis were re-conducted by an independent analyst from the National Disease Registration Service.

*4.3.12 Patient and public involvement*

This work has been developed with input from people with RAIRD. Following my initial findings of increased all-cause mortality during COVID-19(55), my research group and I consulted with patients and patient charities to confirm priorities for future research and inform the communication and dissemination of my results. A plain English summary of this study was published as an online supplement and is contained in Appendix 5.

*4.3.13 Data analysis*

Cleaning, linkage, and analysis of the data was performed in R version 4.1.0 (packages *tidyverse(112)*, *janitor(113), survival(114), mfx(115), survminer(116), meta(117)*).

**4.4 Results**

*4.4.1 Cohort demographic data*

168,330 people met the inclusion criteria for this study. Descriptive demographic data, including RAIRD diagnoses, are shown in Table 8. The median age of the population was 61.7 years (IQR 41.5 – 75.5) and 118,199 (70.2%) were female.

Table 8: Characteristics of the cohort of people with RAIRD alive 01 August 2020 (n=168,330)

| Characteristic | **Value** |
|---|---|
| Sex* (n, %) | |
| Female | 118,199 (70.2%) |
| Male | 50,127 (29.8%) |
| Mean age (standard deviation) | |
| Total cohort | 57.5 (22.5) |
| Female | 58.3 (21.8) |
| Male | 55.5 (24.0) |
| Median age (IQR) | |
| Total cohort | 61.7 (41.5 – 75.5; 34.0) |
| Female | 61.8 (43.0 – 75.7; 32.7) |
| Male | 61.2 (36.4 – 74.9; 38.5) |
| Most recent diagnosis (n, %) | |
| Behçet's disease | 4,951 (2.9%) |
| Dermatomyositis | 2,623 (1.6%) |
| Eosinophilic granulomatosis with polyangiitis | 2,328 (1.4%) |
| Giant cell arteritis | 37,970 (22.6%) |
| Granulomatosis with polyangiitis | 6,283 (3.7%) |
| Arteritis, unspecified | 16,502 (9.8%) |
| Juvenile inflammatory arthritis | 21,431 (12.7%) |
| Juvenile myositis | 505 (0.3%) |
| Microscopic polyangiitis | 1,476 (0.9%) |
| Polyarteritis nodosa | 2,517 (1.5%) |
| Polymyositis | 17,584 (10.4%) |
| Scleroderma | 11,530 (6.8%) |
| Systemic lupus erythematosus | 41,719 (24.8%) |
| Takayasu arteritis | 911 (0.5%) |

* 4 patients had no sex recorded

ICD-10 codes used: Systemic lupus erythematosus = M321, M328, M329; Giant cell arteritis = M315, M316; Juvenile inflammatory arthritis = M080, M082, M083, M084, M089; Arteritis, unspecified = I776; Polymyositis = G724, M332, M608, M609; Scleroderma = M340, M341, M348, M349; Granulomatosis with polyangiitis = M313; Behçet's disease = M352; Dermatomyositis = M331, M339; Eosinophilic granulomatosis with polyangiitis = M301; Polyarteritis nodosa = M300, M308; Microscopic polyangiitis = M317; Takayasu arteritis = M314; Juvenile myositis = M330.

*4.4.2 COVID-19 infection*

Between 01 August 2020 and 30 April 2021, 9,961 (5.92%) of the RAIRD population had a positive COVID-19 PCR test, compared to 3,466,193 (6.13%) of the general population. Age-standardised to the England population, the infection rate per 100,000 person-years was 8073.6 (95% CI 7936.3 – 8210.9), similar to 8172.6 (95% CI 8165.1 – 8180.0) per 100,000 person-years in the general population (rate ratio 0.99 (95% CI 0.97 -1.00), Table 9).

Characteristics of those with a positive COVID-19 PCR test are shown in Table 9. A lower proportion of those testing positive had a hospital test (pillar 1; 31.05% of positive tests) than during the first wave (86.87% of positive tests).

Table 9: PCR-proven COVID-19 infections in the RAIRD population compared to the whole population of England

| | RAIRD (n = 168,330) | England (n = 56,550,138) | Rate ratio |
|---|---|---|---|
| Infection rate (n, %) | 9,961 (5.92%) | 3,466,193 (6.13%) | |
| Infection fatality rate - death certificate mention of COVID (n, %) | 1,342 (0.80%) | 82,361 (0.15%) | |
| Infection fatality rate – death within 28 days of COVID test (n, %) | 1,196 (0.71%) | 75,564 (0.13%) | |
| Age-standardised COVID-19 infection rate (per 100,000 person/years) | 8073.6 (7936.3 – 8210.9) | 8172.6 (8165.1 – 8180.0) | 0.99 (0.97 -1.00) |
| Positive COVID-19 PCR tests by pillar (n (% total tests)) | RAIRD (n = 168,330) | England (n = 56,550,138) | |
| Pillar 1 | 3,093 (31.05%) | - | |
| Pillar 2 | 6,868 (68.95%) | - | |
| Total | 9,961 | 3,466,193 | |
| Age of those in RAIRD cohort with a positive PCR test | | | |
| | Mean age | Median age | Interquartile range |
| Pillar 1 | 68.7 | 73.9 | 57.9 – 83.0 (25.1) |
| Pillar 2 | 49.5 | 50.3 | 30.7 – 66.1 (35.4) |
| Combined | 55.5 | 57.0 | 37.0 – 75.2 (38.2) |
| Deaths in RAIRD cohort within 28 days of a positive PCR test, by pillar (n (% deaths))† | | | |
| Pillar 1 | 876 (73.2%) | | |
| Pillar 2 | 320 (26.8%) | | |
| All | 1,196 | | |
| Age of RAIRD cohort who died within 28 days of a positive PCR test | | | |
| Pillar 1 | 77.1 | 78.9 | 71.1 – 85.3 (14.2) |
| Pillar 2 | 78.6 | 82.2 | 71.0 – 88.0 (17.0) |

Note: Pillar 1 denotes in-hospital testing and Pillar 2 denotes community testing
†Data unavailable for general population

*4.4.3 All-cause mortality*

Between 01 August 2020 and 30 April 2021, 5,822 (3.46%) people in the RAIRD cohort died of any cause (Table 10).

*4.4.4 COVID-19 related mortality*

Of the 5,822 people who died, death certificate data were available for 5,651 (97.1%). 1,342 (0.80% RAIRD cohort) had COVID-19 mentioned on their death certificate, in any position. This compares to 82,361 (0.15%) of all those who died in the general population.

Of those with a positive COVID-19 PCR test, 1,196/9,961 (12.0%) died within 28 days of a positive test, compared to 75,564/3,466,193 (2.2%) of the general population. However, the RAIRD cohort were older than the general population of England.

The combined total of people with RAIRD dying with either COVID-19 mentioned on their death certificate, or within 28 days of a positive COVID-19 test, was 1,415/168,330 (0.84%) and by this measure COVID-19 was implicated in 1,415/5,822 (24.3%) of all deaths during this time-period in this cohort. There is no similar data for the general population of England with which to compare this.

*4.4.5 Age- and age-sex-standardised mortality rates*

The age-sex-standardised mortality rate for all-cause death in RAIRD, standardised to the 2020 mid-year population of England, was 2277.9 (95% CI 2227.3 – 2328.6), compared to 1007.2 (95% CI 1004.6 – 1009.8) in the general population (rate ratio 2.26 (95% CI 2.21 – 2.31)). For deaths mentioning COVID-19 on the death certificate, the age-sex-standardised mortality rate was 535.5 (95% CI 510.7 – 560.3), compared to 194.2 (95% CI 193.0 – 195.3) in the general population (rate ratio 2.76 (95% CI 2.63 – 2.89)). For deaths within 28 days of a positive COVID-19 PCR test, the age-sex-standardised mortality rate in RAIRD was 476.6 (95% CI 453.2 – 500.0), compared to 178.2 (95% CI 177.1 – 179.3) in the general population (rate ratio 2.67 (95% CI 2.54 – 2.81)). These data are summarised in Table 10. The ASMR for all-cause death in RAIRD, adjusted to the 2013 European Standard Population is shown in Table 11.

Table 10: Age-sex-standardised mortality rates for RAIRD from 01 August 2020 to 30 April 2021, compared to the general population of England

| | Number of deaths | Number of people | Person/years | Crude mortality rate per 100,000 person years | RAIRD age-sex-standardised mortality rate* | England age-sex-standardised mortality rate* | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| All | 5,822 | 168,330 | 125,902 | 4,611.6 (4509.0 – 4714.2) | 2277.9 (2227.3 – 2328.6) | 1007.2 (1004.6 – 1009.8) | 2.26 (2.21 – 2.31) |
| Female | 3,730 | 118,199 | 88,406 | 4207.6 (4090.7 – 4324.5) | 2000.1 (1944.5 – 2055.7) | 978.7 (975.1 – 982.3) | 2.04 (1.99 – 2.10) |
| Male | 2,092 | 50,127 | 37,492 | 5564.5 (5358.0 – 5771.0) | 2561.6 (2466.5 – 2656.6) | 1036.3 (1032.5 – 1040.0) | 2.47 (2.38 – 2.56) |
| Death with any mention of COVID-19 on the death certificate | | | | | | | |
| All | 1,342 | 168,330 | 125,902 | 1063.0 (1013.7 – 1112.2) | 535.5 (510.7 – 560.3) | 194.2 (193.0 – 195.3) | 2.76 (2.63 – 2.89) |
| Female | 825 | 118,199 | 88,406 | 930.6 (875.6 – 985.6) | 444.7 (418.4 – 471.0) | 177.0 (175.5 – 178.6) | 2.51 (2.36 – 2.66) |
| Male | 517 | 50,127 | 37,492 | 1375.2 (1272.5 – 1477.8) | 628.2 (581.3 – 675.1) | 211.7 (210.0 – 213.4) | 2.97 (2.75 – 3.19) |
| Death within 28 days of a positive COVID-19 test | | | | | | | |
| All | 1,196 | 168,330 | 125,902 | 947.3 (900.8 – 993.8) | 476.6 (453.2 – 500.0) | 178.2 (177.1 – 179.3) | 2.67 (2.54 – 2.81) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Female | 744 | 118,199 | 88,406 | 839.3 (787.0 – 891.5) | 400.9 (376.0 – 425.8) | 162.6 (161.1 – 164.1) | 2.47 (2.31 – 2.62) |
| Male | 452 | 50,127 | 37,492 | 1,202.2 (1106.3 – 1298.3) | 553.8 (509.6 – 598.0) | 194.1 (192.4 – 195.7) | 2.85 (2.63 – 3.08) |

*Sex-specific rates are age-standardised only. Note that 4 people had no sex recorded.

Table 11: Deaths and age-standardised mortality rates 01 August 2020 to 30 April 2021 for the RAIRD cohort, compared to the 2013 European Standard Population

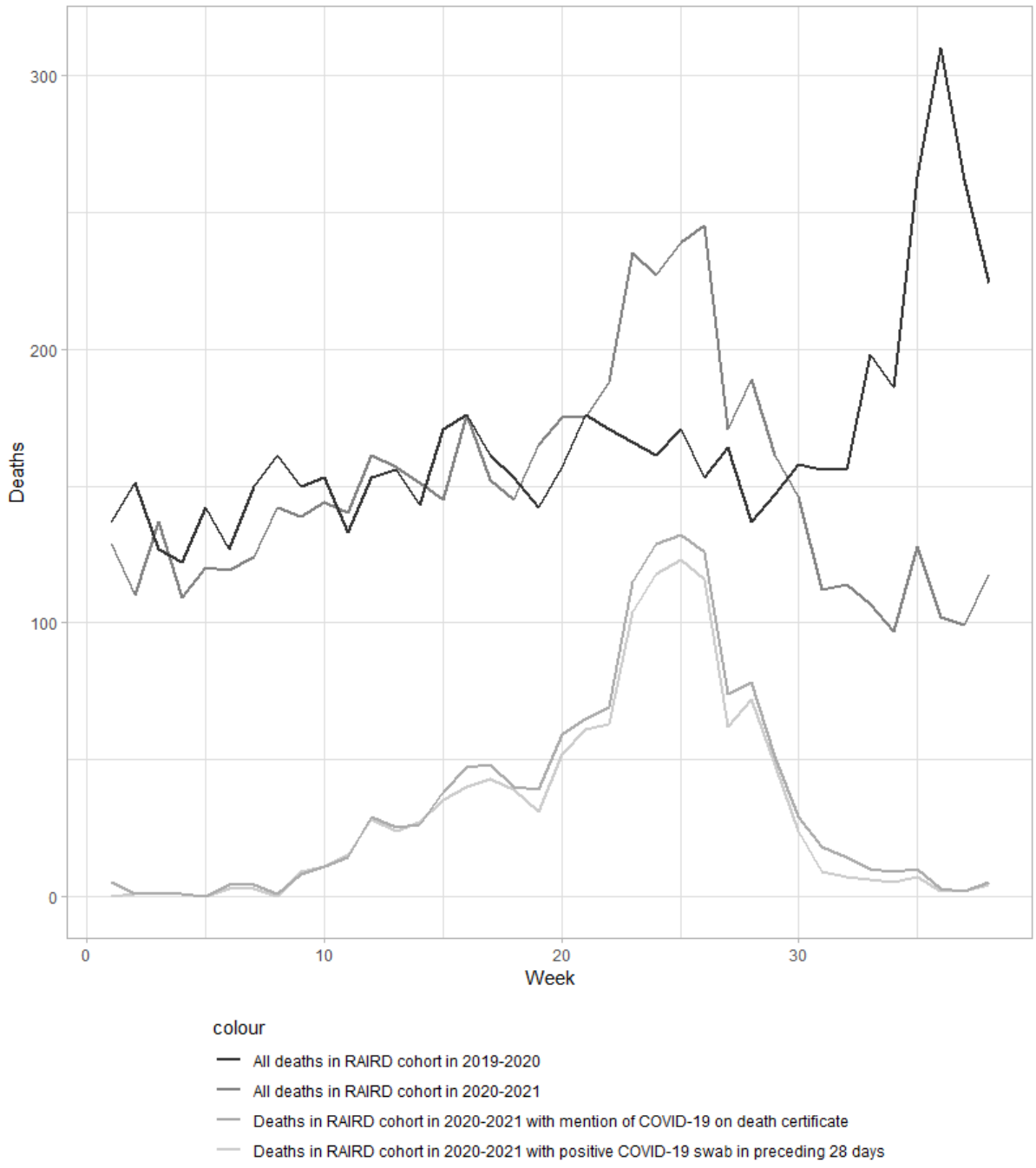
| | Number of deaths | Number of people | Person-years | Crude mortality rate per 100,000 person years | RAIRD age-standardised mortality rate | General population age-standardised mortality rate | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| All | 5,822 | 168,330 | 125,902 | 4,611.6 (4509.0 – 4714.2) | 3064.6 (3006.9 – 3122.3) | 1,042.6 (1039.9 – 1045.3) | 2.94 (2.88 – 2.99) |
| Death with any mention of COVID-19 on the death certificate | | | | | | | |
| All | 1,342 | 168,330 | 125,902 | 1063.0 (1013.7 – 1112.2) | 506.9 (483.4 - 530.4) | 200.9 (199.7 – 202.1) | 2.52 (2.41 – 2.64) |
| Death within 28 days of a positive COVID-19 test | | | | | | | |
| All | 1,196 | 168,330 | 125,902 | 947.3 (900.8 – 993.8) | 451.9 (429.7-474.1) | 184.3 (183.2-185.5) | 2.45 (2.33 – 2.57) |

**Note:** <1 and 1-4 age groups plus 90-94 and 95+ age groups were combined for calculation, to align with format of available general population denominator data.

*4.4.6 COVID-19 related deaths over time*

All-cause deaths in 2019 and 2020, deaths with any mention of COVID-19 on the death certificate and deaths within 28-days of a positive COVID-19 PCR test were plotted over time and are shown in Figure 10.

Figure 10: Deaths in RAIRD cohort between 01 August 2020 and 30 April 2021, shown as all deaths, deaths with any mention of COVID-19 on the death certificate and deaths within 28-days of a positive COVID-19 PCR test, with all deaths in RAIRD cohort between 01 August 2019 and 30 April 2020 as a comparator.



*4.4.7 All-cause death by category*

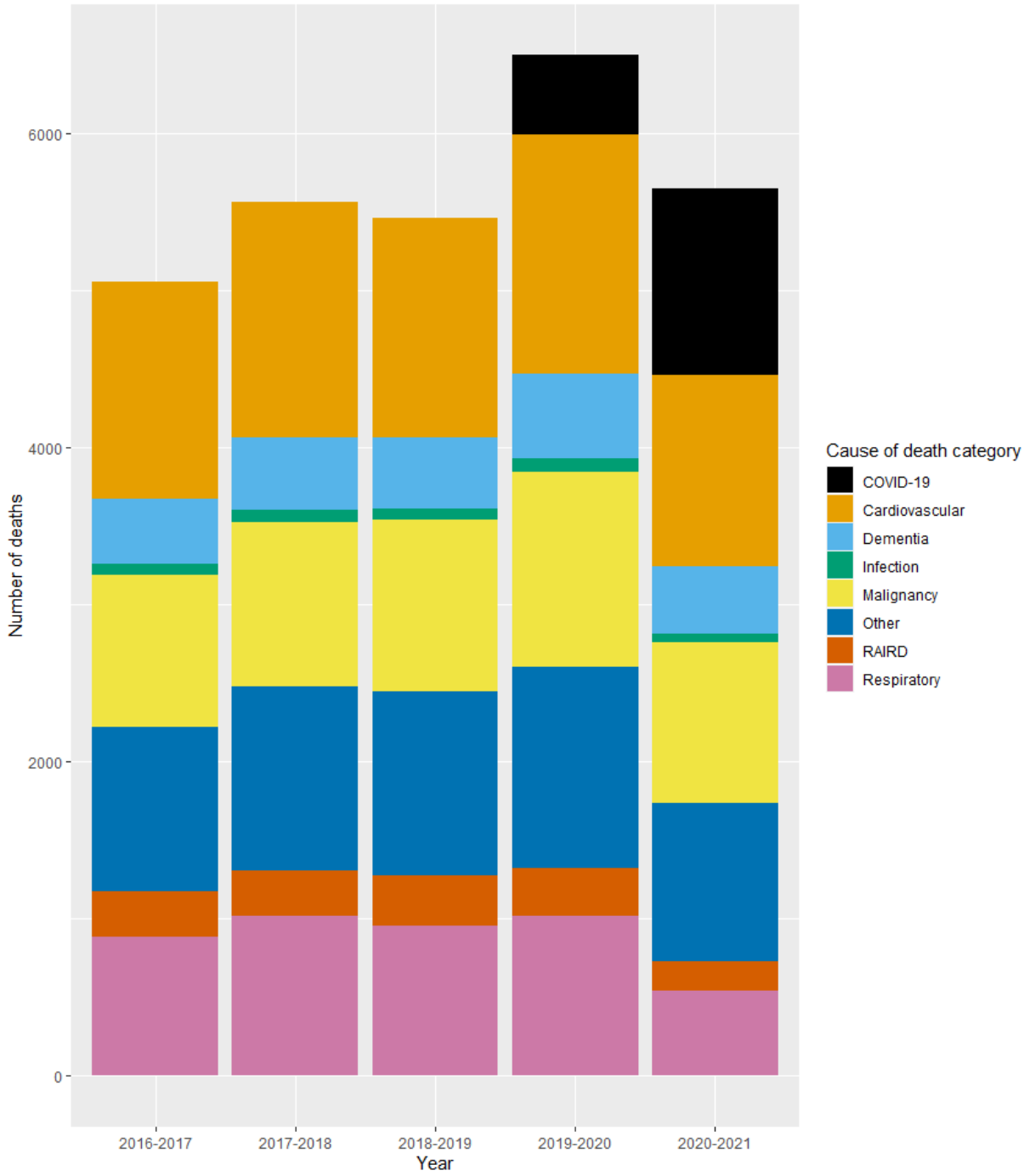
Where death certificate data were available (n=5,651), underlying causes of death by category were extracted and are shown in Table 12. Deaths attributed to cardiovascular disease were recorded in 1,216 (21.6%), COVID-19 1,194 (21.1%), malignancy 1,020 (18.0%), respiratory 539 (9.5%), dementia 430 (7.6%), underlying RAIRD 193 (3.4%) and non-COVID-19 infection 55 (1.0%), with the remaining 1,004 (17.8%) ascribed to other causes.

Table 12: ONS ascribed underlying cause of death by category in RAIRD cohort between 01 August 2020 and 30 April 2021

| Cause of death | n (% total deaths) |
|---|---|
| Category | |
| Cardiovascular | 1,216 (21.5%) |
| COVID-19 | 1,194 (21.1%) |
| Malignancy | 1,020 (18.0%) |
| Other | 1,004 (17.8%) |
| Respiratory | 539 (9.5%) |
| Dementia | 430 (7.6%) |
| Underlying RAIRD | 193 (3.4%) |
| Non COVID-19 infection | 55 (1.0%) |
| Total deaths in RAIRD population with death certificate data available | 5,651 |
| Total RAIRD population | 168,330 |

For comparison, data were extracted on all-cause death in people with a diagnostic code for RAIRD occurring during August-April 2016-2021 and categorised by underlying cause (Figure 11). As in the first wave of the pandemic, there remained no evidence of an increase in death from non-COVID-19-related causes.

Figure 11: All cause death by category in people with RAIRD during months August-April in 2016-2021. Categories align to major ICD-10 code chapters, with the addition of diagnoses pertinent to the cohort (RAIRD, dementia).



*4.4.8 Age at death*

There was no significant change in median age at death between August 2016 and April 2021 (median age ranged from 80.7-81.0), although unlike wave one age at death related to COVID-19 was slightly lower (median 80.2, IQR 70.8-86.6; Table 13).

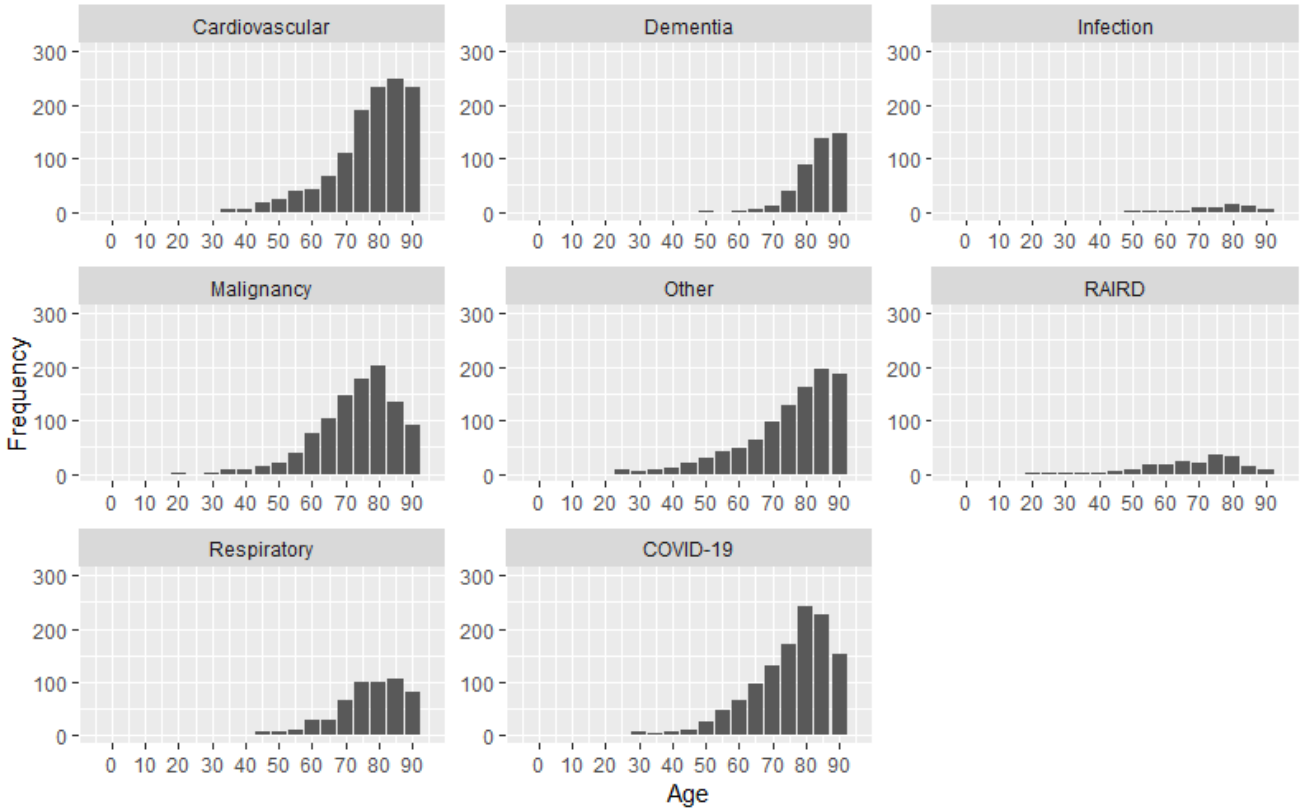
Table 13: Age at death of RAIRD cohort August-April 2016-2021

| Year | Median age | IQR |
|---|---|---|
| 2020-2021 | | |
| All deaths | 80.8 | 72.0-87.2 (15.2) |
| COVID-related | 80.2 | 70.8-86.6 (15.8) |
| Non-COVID-related | 81.0 | 72.2-87.5 (15.3) |
| 2019-2020 | 80.8 | 72.2-87.5 (15.3) |
| 2018-2019 | 80.8 | 71.6-87.3 (15.6) |
| 2017-2018 | 80.9 | 71.9-87.5 (15.6) |
| 2016-2017 | 80.7 | 71.4-87.3 (15.9) |

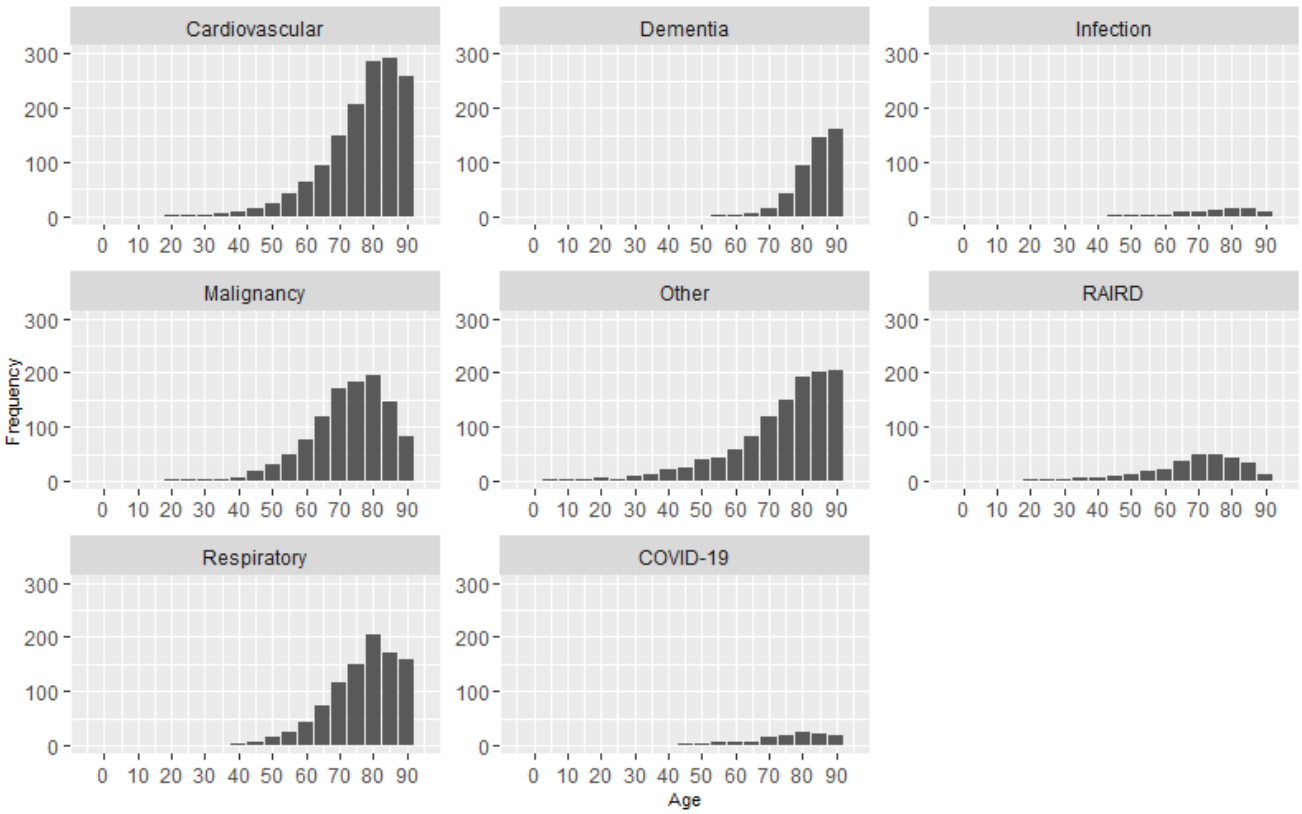
Age at death in people with RAIRD was compared between 2020-2021 and 2019-2020, categorised by underlying cause of death (Figure 12). There was no evidence of earlier age of death occurring in 2020 in certain cause of death categories e.g., in deaths from cardiovascular disease.

Figure 12: Cause of death by category and age in people with RAIRD i) between August 2020 to April 2021 and ii) mean over August to April 2016-2020

ii)



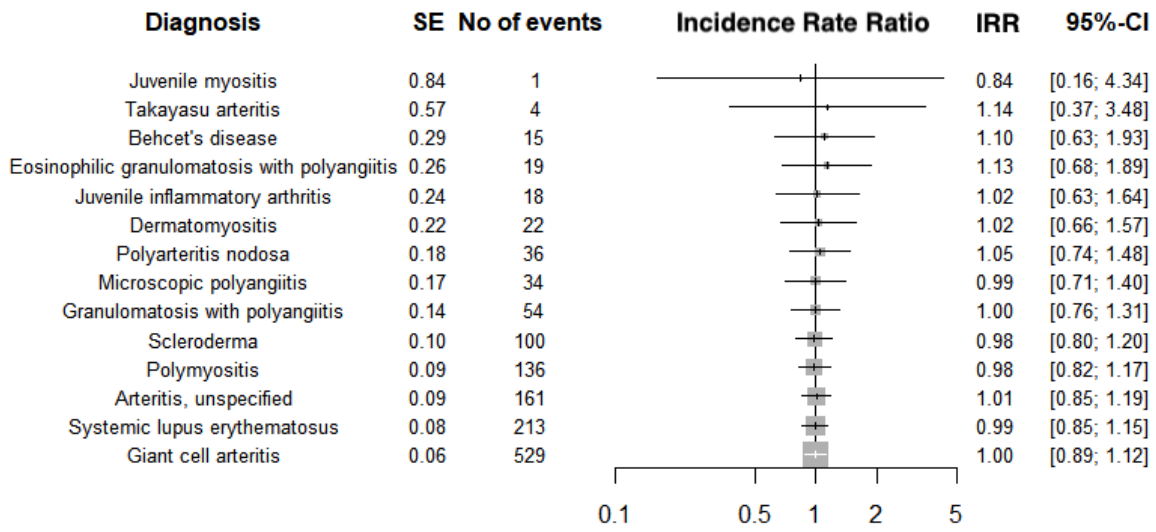

ii)



*4.4.9 Stratification by disease*

Incidence rate ratios for COVID-19-related death stratified by RAIRD diagnosis are displayed in Figure 13. The comparable ratios suggest a similar risk across the RAIRD cohort, regardless of diagnosis.

Figure 13: Forest plot showing incidence rate ratios with 95% confidence intervals for COVID-19-related death stratified by RAIRD diagnosis, with the combined RAIRD cohort used as the reference group




*4.4.10 Corticosteroid prescriptions data*

Risk ratios for COVID-19-related death stratified by prednisolone equivalent dose (PED) are displayed in Table 14. There is a dose response relationship, with a 1.10 (95% CI 1.08–1.13) increase in risk of death for every additional 5mg PED. Those taking >15mg PED/daily at the time of COVID-19 infection had 2.15 times (95% CI 1.80–2.56) higher COVID-19-related mortality than those not taking corticosteroids. The p-value for trend was <0.01.

Table 14: Poisson regression results, with risk ratios for COVID-19-related death in relation to daily corticosteroid dosage†

| Daily corticosteroid dose | Number of people | Number of COVID-19 related deaths | Risk ratio – unadjusted (95% CI) | p-value | Risk ratio – adjusted for age and sex (95% CI) | p-value |
|---|---|---|---|---|---|---|
| 0mg | 8418 | 935 | 1 | | 1 | |
| >0mg-5mg | 232 | 44 | 1.96 (1.43 – 2.61) | <0.01* | 1.21 (0.88 – 1.62) | 0.21 |
| >5mg-10mg | 514 | 116 | 2.30 (1.89 – 2.78) | <0.01* | 1.57 (1.29 – 1.89) | <0.01* |
| >10mg-15mg | 259 | 54 | 2.09 (1.57 – 2.72) | <0.01* | 1.46 (1.09 – 1.89) | <0.01* |
| >15mg | 585 | 142 | 2.49 (2.07 – 2.95) | <0.01* | 2.15 (1.80 – 2.56) | <0.01* |
| Daily corticosteroid dose, increasing in 5mg increments | 10,008 | 1,291 | 1.11 (1.09 – 1.13) | <0.01* | 1.10 (1.08 – 1.13) | <0.01* |

†Participants whose positive COVID-19 PCR test result was received after death due to laboratory delays are included with a person-time of 10 days for this analysis, in keeping with the median time between positive test and death related by COVID-19 described by the WHO.

The results of the sensitivity analysis are shown in Table 15. There was no material difference in the resultant risk ratios.

Table 15: Poisson regression results with risk ratios for COVID-19-related death in relation to daily corticosteroid dosage, including those with zero person-time†

| Daily corticosteroid dose | Number of people | Number of COVID-19 related deaths | Risk ratio – unadjusted (95% CI) | p-value | Risk ratio – adjusted for age and sex (95% CI) | p-value |
|---|---|---|---|---|---|---|
| 0mg | 8,435 | 949 | 1 | | 1 | |
| >0mg-5mg | 235 | 47 | 2.06 (1.52 – 2.73) | <0.01* | 1.28 (0.94 – 1.69) | 0.1 |
| >5mg-10mg | 518 | 120 | 2.35 (1.93 – 2.82) | <0.01* | 1.60 (1.32 – 1.93) | <0.01* |
| >10mg-15mg | 259 | 54 | 2.06 (1.55 – 2.68) | <0.01* | 1.43 (1.08 – 1.87) | 0.01* |
| >15mg | 587 | 144 | 2.48 (2.08 – 2.95) | <0.01* | 2.15 (1.80 – 2.56) | <0.01* |
| Daily corticosteroid dose, increasing in 5mg increments | 10,034 | 1,314 | 1.11 (1.09 – 1.13) | <0.01* | 1.10 (1.08 - 1.13) | <0.01* |

†In this sub-analysis, those with zero person-time are included using 0.5 days person-time. 28 people whose positive PCR tests returned after death due to laboratory delays are excluded.

*4.4.11 Hospital and intensive care admissions*

Demographic data for those who were admitted to hospital and/or to ICU with a diagnostic code for COVID-19 are shown in Table 16. The median age of those with a hospital admission was 73.6 years (IQR 59.6-82.5), and for an ICU admission 60.5 years (IQR 48.2-69.3).

For hospital admissions, the median length of stay was 10 days (mean 15.7, range 0-269) and the median number of admissions was 2 (mean 2.5, range 1-23).

For ICU admissions, the median length of stay was 7 days (mean 12.7, range 0-170) and the median number of admissions was 1 (mean 1.3, range 1-5). The median number of basic respiratory support days whilst on ICU was 3 (mean 4.6, range 0-65) and the median number of advanced respiratory support days was 0 (mean 7.6, range 0-140) (Table 16).

Table 16: Summary of hospital and intensive care unit (ICU) admissions, including demographics and characteristics of stay

| Demographics | n | Mean age | Median age | IQR |
|---|---|---|---|---|
| Any admission with COVID-19 code | 4,433* | 69.6 | 73.6 | 59.6-82.5 (22.9) |
| Death certificate mention of COVID-19 | 1,081† | 76.6 | 78.9 | 69.9-85.2 (15.3) |
| Death within 28 days of positive COVID-19 PCR | 958 | 76.6 | 78.7 | 70.2-85.1 (14.9) |
| ICU admission with COVID-19 code | 387 | 58.6 | 60.5 | 48.2-69.3 (21.1) |
| Death certificate mention of COVID-19 | 128 | 64.7 | 65.2 | 57.8-74.5 (16.7) |
| Death within 28 days of test | 155 | 64.3 | 65.4 | 57.3-75.4 (18.2) |
| COVID positive, not admitted, all | 6,947 | 49.1 | 49.3 | 29.9-65.8 (35.9) |
| Death from all causes | 315 | 81.0 | 84.3 | 76.1-89.6 (13.5) |
| Death certificate mention of COVID-19 | 261 | 81.6 | 84.6 | 76.1-89.9 (13.8) |
| Death within 28 days of test | 240§ | 81.1 | 84.4 | 75.7-89.8 (14.1) |
| Mention of COVID-19 on death certificate, without admission or positive PCR | 36 | 82.6 | 84.6 | 73.8-90.6 (16.8) |

*Of whom 3014/4433 had a positive COVID-19 PCR test
† Of whom 1015/1081 had a positive COVID-19 PCR test
§Of whom 211/240 had mention of COVID-19 on their death certificate

| All hospital admissions with a diagnostic code for COVID-19‡ (n=4432) | Median | Mean | Range | IQR |
|---|---|---|---|---|
| Duration of admission (days) | 10.0 | 15.7 | 0.0-269.0 | 4.0-21.0 |
| Number of admissions per individual | 2.0 | 2.5 | 1.0-23.0 | 1.0-3.0 |

| ICU admissions with a diagnostic code for COVID-19‡ (n=387) | Median | Mean | Range | IQR |
|---|---|---|---|---|
| Basic respiratory support days | 3.0 | 4.6 | 0.0-65.0 | 1.0-6.0 |
| Advanced respiratory support days | 0.0 | 7.6 | 0.0-140.0 | 0.0-8.0 |
| Duration of admission (days) | 7.0 | 12.7 | 0.0-170.0 | 3.0-15.0 |
| Number of ICU admissions per individual | 1.0 | 1.3 | 1.0-5.0 | 1.0-1.0 |

‡Where an individual had more than one admission, totals are summed

## 4.5 Discussion

### *4.5.1 Main findings*

In the second wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD remained more than twice that of the general population.

Unlike in the first wave, the age-standardised COVID-19 infection rate was similar among people with RAIRD compared to the general population, which is likely to reflect testing availability early in the pandemic. It may also reflect earlier vaccination in the RAIRD group compared to the general population due to vaccine prioritisation, although one might expect this to be reflected in the Covid-19 mortality rate too. Further discussion of this can be found in section 4.5.5.

There was no significant difference in the adjusted rates of COVID-19-related death between different RAIRDs.

Corticosteroid usage within the 30-days prior to COVID-19 infection was associated with an increased risk of COVID-19-related death, in a dose-dependent fashion. Patient and clinician education on this risk, and where appropriate steroid minimisation strategies, should be considered.

### *4.5.2 Strengths*

This work adds further support to my findings in the first wave. In addition, it assesses the influence of corticosteroids, a common cause for immunosuppression in people with RAIRD, on COVID-19 outcomes. This is the first time that this has been analysed in whole population data for people with RAIRD.

This study includes the novel use of community prescription data for rare disease analyses within NDRS. Further potential uses for these data are detailed below.

Like my first study, a major strength of this work is that the denominator population is known, allowing me to describe rates of COVID-19 infection and of COVID-19-related death.

The sub-analysis by disease continues to support the grouping together of RAIRD when assessing COVID-19 outcomes, in order to increase statistical power. The diseases have similar underlying disease mechanisms and immunosuppressive treatments and the risk of death related to COVID-19 is shown to be comparable between diseases. Unlike in the first wave, giant cell arteritis (GCA) showed the same risk profile as the other RAIRD, which may be a result of the narrower confidence intervals due to the increased number of events compared to the first wave.

*4.5.3 Limitations*

The two measures of COVID-19 mortality described were selected to allow comparison with available statistics for the general population and with my earlier study(55). I have previously discussed in detail the drawbacks and merits of these measures in Chapter 3 of this thesis and the associated published paper(136).

As I identified this cohort from diagnoses in HES admitted patient care (APC) data, my methodology would not have identified patients treated entirely on an outpatient basis, who have never had an in-patient or day case admission for any reason. Due to the complex nature of RAIRD, I believe this to be the minority of cases, and this is supported by the disease prevalence in this cohort being similar to previous studies(33, 35, 96). However, this could skew this cohort towards those with more severe disease.

This study does not include data on immunosuppressive medications other than corticosteroids. People taking corticosteroids for their RAIRD may be on other immunosuppressants, which may compound their risk from COVID-19.

*4.5.4 Comparison to the published literature*

Rare diseases are notoriously difficult to study as the small numbers of people affected by each condition reduces statistical power, making it harder to assess outcomes.

International studies describing COVID-19 in cohorts with AAV(132), GCA(133), Behçet's disease(134) and systemic sclerosis (SSc)(135) demonstrated higher levels of COVID-19 infection when compared to the general population (in SSc this was only true of those with

interstitial lung disease) but were limited by relatively small numbers(132, 133) and/or methods prone to inclusion bias(134), making it impossible to describe rates. Nationwide cohort studies from Denmark in people living with systemic lupus erythematosus (SLE)(144) and vasculitis(145) showed an increased risk of hospitalisation with COVID-19 but did not look at associated mortality.

Most COVID-19-related research has therefore grouped RAIRD with more common rheumatic diseases such as rheumatoid arthritis (RA).

The COVID-19 Global Rheumatology Alliance described COVID-19-related mortality in rheumatic diseases, including RAIRD, and reported an association with immunosuppressive medication use(53). Studies from the same group looking at individual conditions (Idiopathic inflammatory myopathies (IIM)(138), SLE(146) and vasculitis combined with polymyalgia rheumatica(137)) described associations with steroid use, immunosuppressants including rituximab and COVID-19-related mortality. However, these studies relied on physician-reported cases and could not report rates of COVID-19 infection or deaths.

Whole population data from Denmark(127) found an increased risk of COVID-19 hospital admissions in people with connective tissue disease and vasculitis but did not report on COVID-19 infection rates, nor on mortality in RAIRD specifically. Whole population data from South Korea(128) also found an increased risk of COVID-19 infection and hospitalisation. There was a suggestion of increased COVID-19 mortality, but this was not statistically significant.

OpenSAFELY(39, 147) and QCOVID(57) looked at risk factors for severe COVID-19 outcomes in England, both combining SLE with other rheumatic diseases. Both found a modest increase in the risk of death (HR 1.32 (1.06-1.65) and 1.20 (1.12-1.28) respectively). A pre-print(148) from the QCOVID team looking at outcomes in the Omicron wave suggest a persistently increased risk.

At the time of the last published analyses, OpenSAFELY included 24 million patients(39, 147) and QCOVID 8.26 million(57). My research uses the whole England population of 56 million,

affording us the statistical power to calculate more precise results. The use of whole population data, with a known denominator population, also allows calculation of rates and comparison to the general population.

*4.5.5 Infection rate*

There was no significant difference in the age-standardised COVID-19 infection rate between people with RAIRD and the general population. This differs from the first wave, where the rate in people with RAIRD was around 50% higher.

This is likely to reflect limited testing availability early in the pandemic, where testing was predominantly in hospital with few tests available in the community. It may be that as people with RAIRD have increased contact with healthcare services, they underwent more frequent testing, leading to ascertainment bias.

It could also reflect earlier vaccination in the RAIRD group due to prioritisation of at-risk groups. The first vaccination against SARS-CoV-2 outside of a trial setting was given on 8th December 2020 in England and by the end of this study (30th April 2021) 49.3% of the general population had received at least one vaccine dose and 21.1% two vaccine doses(111). However, given that many people with RAIRD were likely to have been deemed CEV, and so prioritised for vaccination, a larger proportion of the RAIRD population may have received their first and/or second vaccine doses by this date. It is possible that this explains the equalisation of the infection rates between RAIRD and the general population when compared to the first wave. However, vaccination is more effective at preventing Covid-19-related death than Covid-19 infection itself, as is borne out in the whole population figures(111), so if this were the case one might expect a concurrent fall in Covid-19-related mortality rate, which is not seen in this study.

*4.5.6 Comparing mortality rate measures*

There is some evidence that people with RAIRD may have later COVID-19-related mortality than that of the general population, making the death within 28 days measure less suitable for this cohort(149).

I explored using the measure of death within 60 days of a positive COVID-19 PCR test.

Of the RAIRD cohort of 168,330, 164 died between 28 and 60 days after a positive COVID-19 test. Of these 164, 64 (39.0%) died with a mention of COVID-19 on their death certificate. In comparison, 1,196 died within 28 days of a positive COVID-19 test. Of these, 1,034 (86.5%) died with a mention of COVID-19 on their death certificate, making it a more specific measure.

The crude mortality rate for 28-day death in RAIRD was 947.3 (95% CI 900.8 – 993.8) per 100,000 person years, compared to 178.2 (95% CI 177.1 - 179.3) in the general population (rate ratio 5.32 (95% CI 5.06 - 5.58). For 60-day mortality this was 1,077.2 (95% CI 1,027.2 - 1,126.8) per 100,000 person years in RAIRD, compared to 212.7 (95% CI 211.5 - 213.9) in the general population (rate ratio 5.06 (95% CI 4.83 - 5.30).

The 60-day death general population data was not available grouped by sex/age bands and so I was unable to age-sex standardise the mortality rate, as I have done with the 28-day deaths. These crude mortality rates must therefore be interpreted with a caution. However, it is worth noting that whilst the crude rates seem comparatively slightly lower in the 60-day death measure, the confidence intervals for the rate ratios overlap.

As with my study during the first wave of the pandemic, death with any mention of COVID-19 on the death certificate was selected a priori as the primary study outcome.

*4.5.7 Corticosteroids*

COVID-19 registry studies in RAIRD have suggested an association with corticosteroid treatment and severe disease(53, 121, 125). Adverse outcomes were associated with a prednisolone equivalent dose of 7.5-10mg/day(56, 137, 138). However, registry studies tend to include more serious COVID-19 cases due to selection bias, so it was unclear to what extent they reflected the wider risk. Additionally, many of these studies used combined outcomes (varyingly including hospitalisation, oxygen supplementation, ventilation, death). Larger general population studies also showed an association between corticosteroid treatment and severe COVID-19 outcomes(52, 57).

My study is the first specific to the RAIRD cohort to show an association between corticosteroid dose and COVID-19-related death and the first to be able to demonstrate a clear dose-dependent effect. It remains unclear whether this is a causative effect, or whether those on corticosteroid treatment are in poorer health with more active underlying disease, predisposing them to poorer outcomes.

Most corticosteroid prescriptions are issued in the community and so will have been captured in my data. Whilst acute prescriptions issued in secondary care will not have been captured, this would lead me to underestimate total corticosteroid dose and therefore underestimate, rather than overestimate, the effect on COVID-19-related mortality.

Interestingly, glucocorticoids are also implicated in a reduced SARS-Cov-2 vaccine response, including in a cohort of people with SLE(150).

*4.5.8 Use of Poisson or logistic regression*

When deciding on the methodology for calculating the effect of corticosteroids on COVID-19-related death, my PhD supervisors and I considered the use of logistic rather than Poisson regression. This is because the primary focus of the analysis was whether COVID-19-related death occurred (binary outcome), rather than the time until COVID-19-related death (time to event, which would not be accounted for in logistic regression). It was felt that either analysis would be methodologically suitable, but Poisson regression was selected in order to align with the first wave study. This used Poisson regression, with an offset term to account for follow-up time, to compare the outcomes between the different RAIRD diseases. This analysis was also repeated for this second wave study. For consistency and to ease reader interpretation, Poisson regression was therefore also used for the corticosteroid analysis.

*4.5.9 Effect of other immunosuppressants*

The NHS Prescription Services data used in this study contains all NHS prescriptions issued in the community in England. They do not cover secondary care prescriptions, e.g., those

issued in hospitals, and so certain specialist drugs including disease modifying anti-rheumatic drugs (DMARDS) may not be included.

A particular difficulty with analysing the DMARD data contained in this dataset is the geographical variation in the use of shared care protocols. In some regions, the bulk of DMARD prescribing is performed by general practitioners, whereas in others it is predominantly done in secondary care. Therefore, in order to ensure accuracy, it is necessary to determine which geographical areas do not use shared care prescribing (i.e., largely prescribe DMARDs through secondary care), which can be ascertained using publicly available data(151) and exclude them from the analysis. Otherwise, exposed individuals may wrongly be assigned to the non-exposed group, leading to a dilution of any potential effect on COVID-19 outcomes.

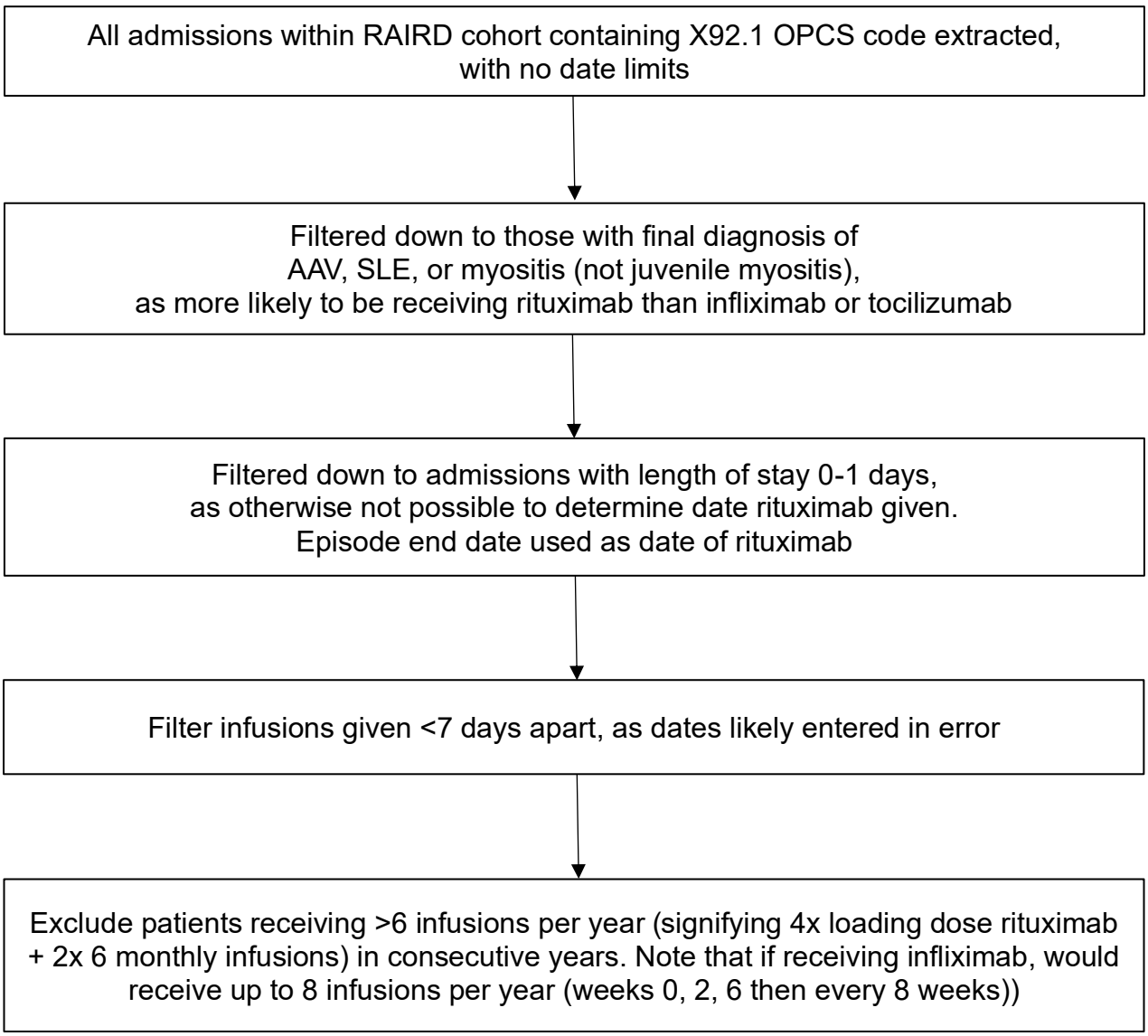
I have developed code to extract relevant DMARD prescriptions from the NHS Prescription Services dataset (azathioprine, ciclosporin, everolimus, hydroxychloroquine, leflunomide, mercaptopurine, methotrexate, mycophenolate, penicillamine, sirolimus, sulfasalazine and tacrolimus) and to quantify the dose of DMARD for each study participant. However, due to the complexities described above, analysis of these data does not form part of the work contained within this thesis. Future research within my research group will look at the association of different DMARDs and outcomes.

I also started to develop methodology to accurately identify rituximab infusions within HES data, as rituximab has been associated with adverse COVID-19 outcomes(138, 146). Rituximab is coded using OPCS code X92.1 (Cytokine inhibitor drugs Band 1). This OPCS code is shared with other drugs, the most relevant of which are infliximab and tocilizumab as they can be delivered intravenously and so may also appear within in-patient or day-case admitted episodes.

All HES APC admissions for the study cohort with a OPCS code X92.1 were extracted, and a clinically informed identification strategy was developed (Figure 14)(152). Unfortunately, on analysing the data, it was not possible to accurately differentiate admissions for rituximab treatment due to the overlapping nature of both the dosing schedules and the total number

of annual infusions of the different drugs. It was therefore decided that further validation was required for these data, with the aim being to use Blueteq data for this purpose.

Figure 14: Algorithm for identifying rituximab infusions within X92.1 OPCS code – remains in development



*4.5.10 Clinical and policy implications and future research*

My findings provide evidence that people with RAIRD remained at increased risk of COVID-19-related death compared to people of the same age and sex in the general population during the second wave of the COVID-19 pandemic. This has important implications for people living with RAIRD, their clinicians and for public health policy; to protect their health and reduce the risk of severe outcomes.

RAIRD may require immunosuppression with corticosteroids. I have demonstrated that corticosteroids are associated with poorer COVID-19 outcomes, and this should form part of the decision-making process when considering a corticosteroid prescription.

As during the first wave, I did not find an excess of non-COVID-19-related deaths. This is likely to reflect efforts across healthcare to prioritise access to emergency care. However, a delayed impact on mortality rates due to delayed or missed diagnoses, particularly from conditions such as cancer, remains possible.

**4.6 Conclusions**

My research has shown that in the second wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD remained more than twice (2.7 times) that of the general population. Whilst COVID-19 infection rates were similar between the RAIRD and general populations, there were higher mortality rates in people living with RAIRD. Corticosteroid usage within the 30-days prior to COVID-19 infection was associated with an increased risk of COVID-19-related death, in a dose-dependent fashion.

# Chapter 5: All-cause and cause-specific mortality in people with Rare Autoimmune Rheumatic Diseases in England using whole population data.

This chapter details the third study within my thesis. It is a nationwide cohort study looking at all-cause and cause-specific mortality in people with RAIRD in England during the years 2013-2020. This work is currently being prepared for publication.

## 5.1 Main findings and abstract

### *5.1.1 Main findings*

1. Adjusted for age and sex, mortality in RAIRD was increased across all causes except for dementia, when compared to the general population.
2. Comparison between RAIRD showed higher all-cause mortality in scleroderma, myositis, microscopic polyangiitis and unspecified arteritis.
3. Risk of death due to infection, COVID-19 and respiratory disease was particularly raised.
4. Deaths due to progressive multifocal leukoencephalopathy (PML), Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV) infection occurred but were rare.

### *5.1.2 Abstract*

**Objectives:**

People with rare autoimmune rheumatic diseases (RAIRD) are more likely to have morbidity and premature death. Poor outcomes are attributable both to underlying disease and treatment. Severe infections, including with atypical pathogens, are of concern.

**Methods:**

All people in England with any ICD-10 code ever for RAIRD were identified from Hospital Episode Statistics. Linked demographic and death certificate data were used to calculate crude and age-sex-standardised all-cause and cause-specific mortality rates. Office for National Statistics general population data were used for comparison.

**Results:**

There were 108,593 people with RAIRD in 2013 and 180,083 in 2020. The majority were female (annual minimum 69.9%, maximum 70.9%). Median age increased from 61.5 to 62.5 years, compared to 39.7 to 40.2 years in the general population. Crude and age-sex-standardised all-cause mortality gradually reduced between 2013-2019, increasing again in 2020 (during COVID-19). Age-sex-standardised mortality in 2013 was 2,324.5 per 100,000 person/years (95% CI 2,261.5-2,387.6) and in 2020 2,332.8 (2,283.3-2,382.2; rate ratio 2.4 (2.3-2.4) compared to general population). Risk of death due to infection (rate ratio 4.11 (3.82-4.40)), cardiovascular disease (2.51 (2.47–2.56)), COVID-19 (2.77 (2.62–2.92)), and respiratory disease (2.92 (2.84–2.99)) were particularly raised. Intra-disease comparison showed higher all-cause mortality in scleroderma, myositis, microscopic polyangiitis and unspecified arteritis. Only 28/53,166 deaths were secondary to cytomegalovirus, 35 Pneumocystis jirovecii pneumonia and 8 progressive multifocal leukoencephalopathy.

**Conclusions:**
Adjusting for age and sex, mortality in people with RAIRD was increased across all causes except dementia. Risk of death due to infection, COVID-19 and respiratory disease was particularly raised. Deaths due to atypical infections were rare.

## 5.2 Introduction

### *5.2.1 Mortality in people with rare autoimmune rheumatic diseases*

People with rare autoimmune rheumatic diseases (RAIRD) are more likely than the general population to have morbidity and premature death. These poor outcomes are attributable both to the effects of treatment and the underlying disease. The frequent use of immunosuppressants in this group is a particular concern for severe infections, including from atypical pathogens.

Previous studies have found that mortality is approximately 1.2-10-fold higher(66-73) among subjects with RAIRD compared with the general population, however there is variability within and between diseases, reflecting the relative lack of statistical power in most previous studies. Within-disease variation may be due to selection of the included population or variations in ascertainment of the underlying diseases, and there have been

few population-based studies. In addition, contemporary data regarding cause of death in RAIRD remain scarce.

*5.2.2 Study objectives*

This study uses linked national health records for the whole population of England in 2013-2020 to describe the rates of all-cause and cause-specific mortality for leading causes of death among people with RAIRD and compares these rates to those in the general population. It also describes deaths due to atypical pathogens of concern in this group, namely progressive multifocal leukoencephalopathy (PML; caused by the JC virus), Pneumocystis jirovecii pneumonia (PJP) and cytomegalovirus (CMV).

## 5.3 Methods

*5.3.1 Background*

This work is a product of the collaboration between the Registration of Complex Rare Diseases Exemplars in Rheumatology (RECORDER) project(85) at the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). NCARDRS, based within NHS Digital (NHSD), registers people with rare conditions in order to support high quality clinical practice and research, provide whole population epidemiological data and empower patients(105). It has unique access to linked national datasets of electronic health records at patient-identifiable level for the whole population of England.

This study uses Hospital Episode Statistics Admitted Patient Care data (HES APC), which contains every episode of in-patient and day-case care in NHS hospitals in England, and Office for National Statistics (ONS) death certificate data.

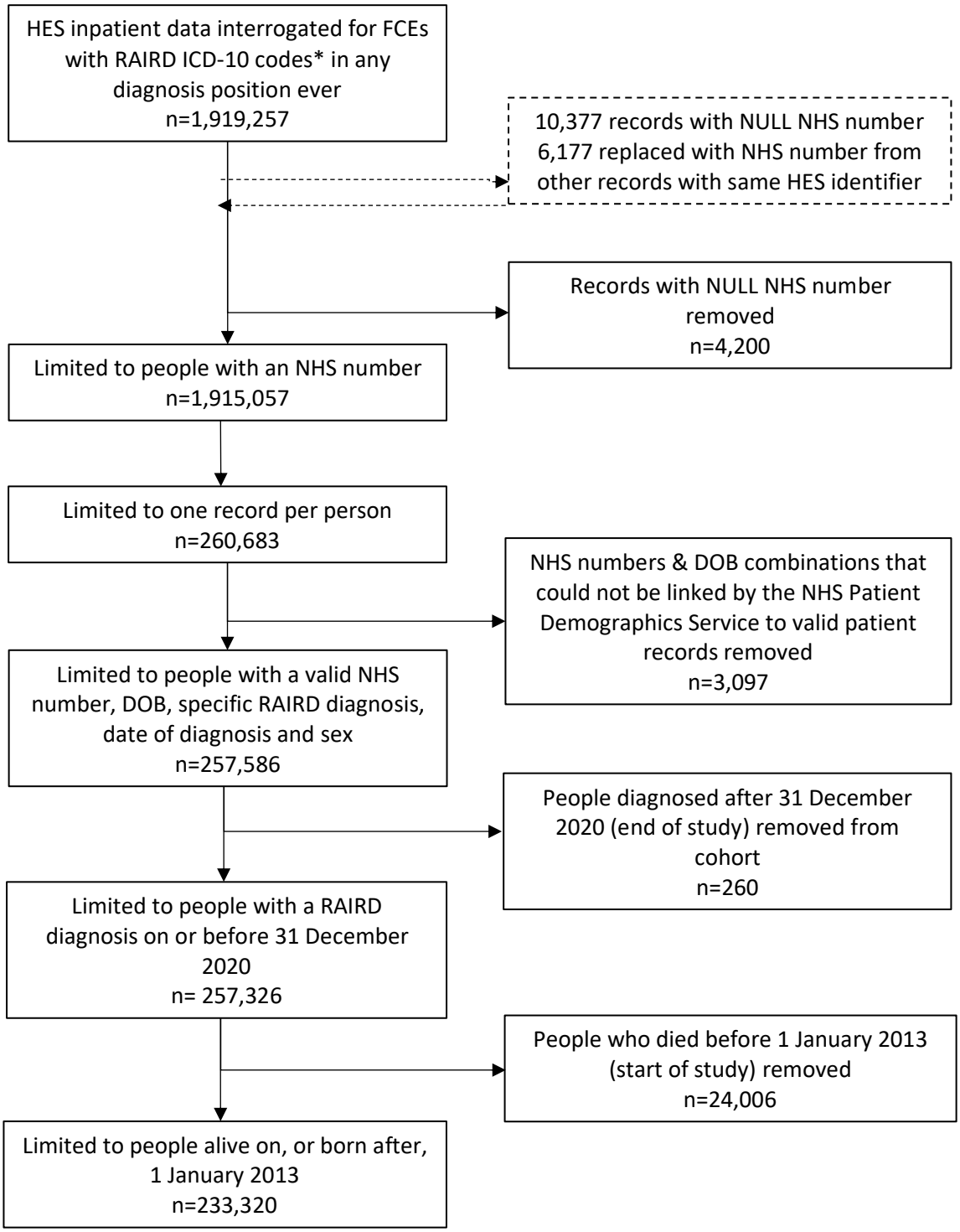
*5.3.2 Data validation*

My research team and I's previous work validating HES ICD-10 codes for RAIRD has shown high accuracy, with a positive predictive value of 84.7%(55). Prevalence estimates for individual RAIRD are similar to reported population estimates(33, 35, 96).

*5.3.3 Study cohort*

People with a diagnostic code ever for RAIRD in HES and resident in England were included in the study. A data flow diagram is shown in Figure 15. Vital status data from the NHS Personal Demographics Service were used to confirm whether people were alive, or where relevant to confirm date of death(99). Demographic data from the cohort were described for each year of the study.

Figure 15: Data flow diagram showing identification of RAIRD cohort from HES data.

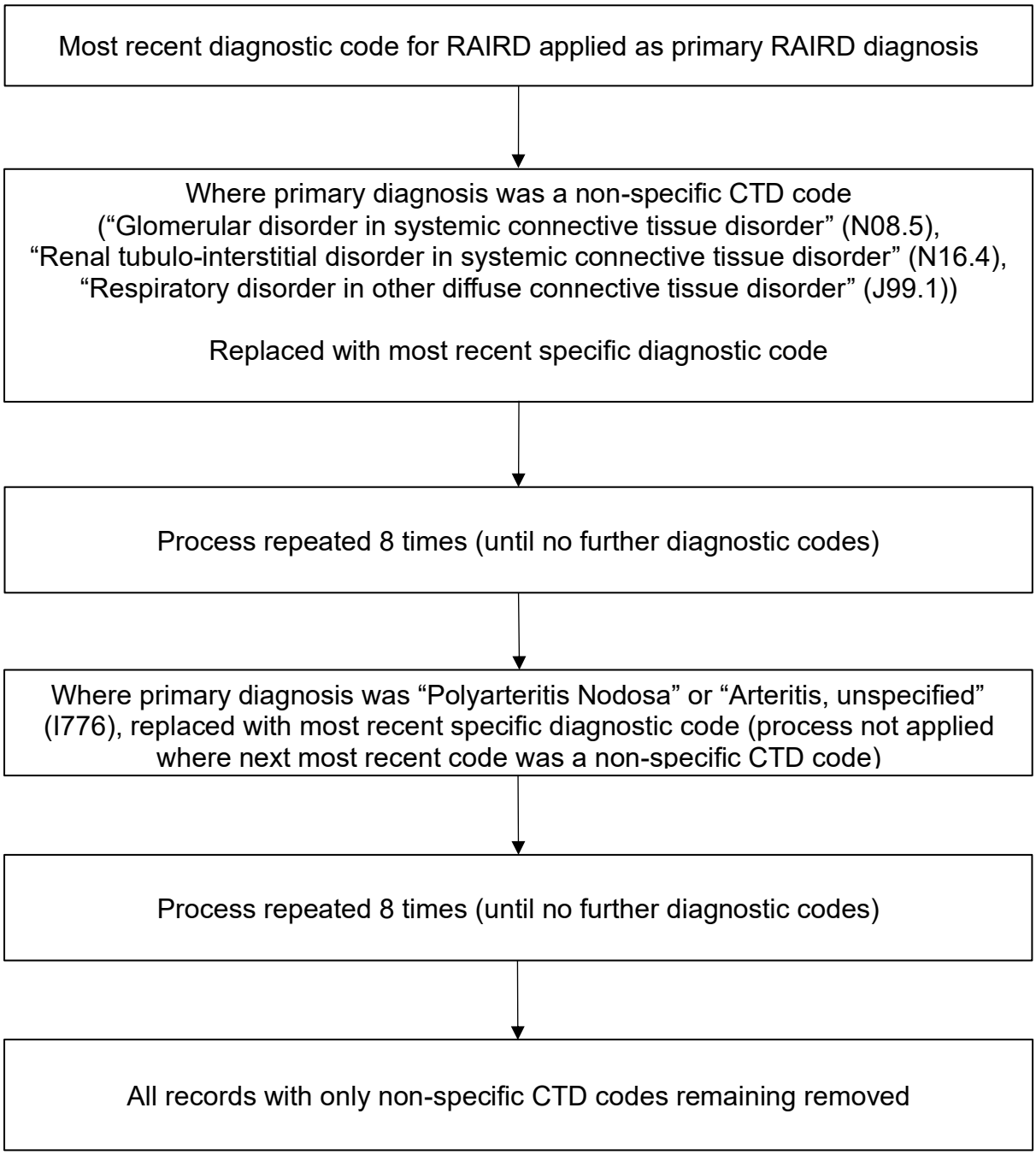



*FCE = finished consultant episode. HES = hospital episode statistics.* *RAIRD ICD-10 codes comprise: M313, M317, M301, M314, I776, M352, M315, M316, M321, M330, M332, M331, M339, M340, M341, M348, M349, M083, M084, M082, M080, M300, M308, J991, N085, N164, M328, M329, M609, G724, M608, M089

*5.3.4 RAIRD diagnoses*

Participants were grouped by RAIRD diagnosis, based on their most recent diagnostic code. Where the most recent code was non-specific, for example "Renal tubulo-interstitial disorder in systemic connective tissue disorder", earlier, more specific diagnostic codes were used. Where only non-specific codes were available, participants were excluded, following the algorithm in Figure 16.

Figure 16: Algorithm for assigning main rheumatological diagnosis



*5.3.5 Death certificate data*

Death certificate data (free text and ICD-10 coded) provided by the ONS were utilised. Using internationally agreed rules, ONS assigns a single underlying cause of death code, usually based on the lowest completed line of Part 1 of a death certificate(100). This underlying cause of death code was used to group deaths by category.

*5.3.6 Cause of death categories*

Causes of death were grouped according to clinical category using their underlying cause of death ICD-10 code. Categories were largely in line with ICD-10 chapters e.g., ICD-10 codes beginning C assigned to “malignancy”, those beginning J to “respiratory” etc.

Where ICD-10 codes for certain groups of conditions are found across ICD-10 chapters, e.g., venous thromboembolic disease, a combination of clinical knowledge and relevant published literature(153) were used to devise complete lists.

A description of the ICD-10 codes used for each cause of death category is available in Table 17.

Table 17: ICD-10 codes used in each cause of death category

| Cause of death category | ICD-10 codes utilised |
|---|---|
| Cardiovascular, exc. stroke and VTE | I00-I99 (except I26, I60-I69, I80.1, I80.2) |
| COVID-19 | U07.1, U07.2 |
| Dementia | F00-F03, G30 |
| Infection | A00-B99 |
| Influenza and pneumonia | J09-J18 |
| Malignancy | C00-C97 |
| Respiratory, exc. influenza and pneumonia | J00-J08, J19-J99 |
| Stroke | I60-I69 |
| VTE | I26, I80.1, I80.2, O22.3, O87.1, O88.2 |
| Other | All other ICD-10 codes |

*5.3.7 Mortality rate calculation*

Crude all-cause and cause-specific mortality rates were calculated overall and per year of the study. The number of people identified as having RAIRD at the mid-point of each year was used as the denominator population, along with the crude mortality rates overall and for each cause of death category.

Age-sex-standardised mortality rates per 100,000 in the population were calculated, standardised to the mid-year estimate for the England population for each year of the study using 5-year age bands.

The ONS provides publicly available general population mortality data through their website NOMIS(101). All-cause and cause-specific deaths in England were extracted for the time period of the study, split by sex and age band. These data were used to calculate the crude,

age-standardised and age-specific general population mortality rates as a comparator. The mid-year estimate for the population of England for each year of the study was used as the denominator.

Rate ratios with 95% confidence intervals were calculated for all-cause and cause-specific mortality rates, comparing the RAIRD and general populations.

*5.3.8 Stratification by disease*

Poisson regression methods were used to analyse rates of all-cause mortality, adjusted for age, sex and RAIRD diagnosis. The combined RAIRD cohort was used as the reference category. Incidence rate ratios for each diagnosis, with 95% confidence intervals, are displayed as a forest plot.

*5.3.9 Deaths from opportunistic infections*

A descriptive analysis of deaths due to PML, PJP or CMV infection was performed separately. These are opportunistic infections, which are defined as infections which affect patients with immunocompromised status and are caused by common microorganisms with more severe presentations, or atypical organisms that do not cause disease in the immunocompetent.

*5.3.10 Ethics*

The legal and ethical basis to access these data is covered by NCARDRS' Section 254 approval (sections 254(1) and 254(6) of the 2012 Health and Social Care Act), which allows for the use of data without specific patient consent.

For quality assurance the data extraction and analysis were re-conducted by an independent analyst from the National Disease Registration Service.

*5.3.11 Patient and public involvement*

Research into causes of death in RAIRD, particularly the risk of cancer and cardiovascular disease, has been identified as a priority area for research by the patient charity Vasculitis

UK. A plain English summary of this study is included in Appendix 5 of this thesis and will be made available as an online supplement.

*5.3.12 Data analysis*

Cleaning, linkage, and analysis of the data was performed in R version 4.1.0 (packages *kableExtra*(154), *lubridate*(155), *nomisr*(156), *tidyverse*(112), *janitor*(113), *readxl*(157), *ggthemes*(158), *gtsummary*(159)).

**5.4 Results**

*5.4.1 Demographic data*

The overall size of the cohort increased from 108,593 in 2013 to 180,083 in 2020. Descriptive demographic data, including RAIRD diagnoses, are shown in Table 18.

The median (IQR) age of the population gradually increased from 61.5 (41.5 - 75.2) years to 62.5 (42.4 - 76.1) years over the course of the study, compared to 39.7 to 40.2 years in the general population of England.

The majority of the cohort were female, with a slight reduction in the proportion over time: 76,973 (70.9%) in 2013 compared to 125,805 (69.9%) in 2020. The median (IQR) age in males was initially slightly higher (61.7 (38.2 - 74.7) years compared to 61.3 (42.3 - 75.4) in females) but this evened out over the course of the study.

Systemic lupus erythematosus (SLE) and giant cell arteritis (GCA) were consistently the most common diagnoses in the cohort (24.3% and 23.4% respectively in 2020) and juvenile myositis (JM) and Takayasu arteritis (TAK) the least common (0.3% and 0.5% respectively in the same year). There was a 1% reduction in the proportion of people with scleroderma (from 8.2% to 6.9%) but over 1% increase in the proportion of people with a diagnosis of arteritis, unspecified (from 8.4% to 10.1%).

Table 18: Characteristics of study cohort on 1st January of each study year

| Characteristic | Study year | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 |
| n | 108,593 | 118,235 | 128,305 | 138,920 | 149,285 | 160,486 | 172,369 | 180,083 |
| Sex (n, %) | | | | | | | | |
| Female | 76,973 (70.9%) | 83,697 (70.8%) | 90,608 (70.6%) | 97,752 (70.4%) | 104,952 (70.3%) | 112,518 (70.1%) | 120,659 (70.0%) | 125,805 (69.9%) |
| Male | 28,678 (29.1%) | 31,620 (29.2%) | 37,697 (29.4%) | 41,168 (29.6%) | 44,333 (29.7%) | 47,968 (29.9%) | 51,710 (30.0%) | 54,278 (30.1%) |
| Mean age | | | | | | | | |
| Total cohort | 56.8 | 57.0 | 57.1 | 57.1 | 57.3 | 57.5 | 57.8 | 58.1 |
| Female | 57.5 | 57.6 | 57.7 | 57.8 | 58.0 | 58.2 | 58.5 | 58.8 |
| Male | 55.3 | 55.5 | 55.6 | 55.3 | 55.6 | 55.8 | 56.1 | 56.4 |
| Median age (IQR) | | | | | | | | |
| Total cohort | 61.5 (41.5 - 75.2) | 61.6 (41.6 - 75.3) | 61.6 (41.7 - 75.4) | 61.7 (41.6 - 75.4) | 61.8 (41.7 - 75.4) | 62.0 (41.9 - 75.5) | 62.2 (42.1 - 75.8) | 62.5 (42.4 - 76.1) |
| Female | 61.3 (42.3 - 75.4) | 61.4 (42.5 - 75.6) | 61.5 (42.7 - 75.6) | 61.6 (42.8 - 75.6) | 61.8 (43.0 - 75.6) | 62.0 (43.2 - 75.7) | 62.2 (43.4 – 76.0) | 62.5 (43.7 - 76.2) |
| Male | 61.7 (38.2 - 74.7) | 62.0 (38.3 - 74.9) | 62.0 (38.2 – 75.0) | 61.8 (37.0 - 74.9) | 61.8 (37.2 - 75.0) | 61.9 (37.6 - 75.2) | 62.2 (38.0 - 75.4) | 62.4 (38.3 - 75.6) |
| Most recent diagnosis (n, %) | | | | | | | | |
| SLE | 26,838 (24.7%) | 29,266 (24.8%) | 31,665 (24.7%) | 34,102 (24.5%) | 36,516 (24.5%) | 39,142 (24.4%) | 41,926 (24.3%) | 43,708 (24.3%) |
| Giant cell arteritis | 25,420 (23.4%) | 27,678 (23.4%) | 29,982 (23.4%) | 32,350 (23.3%) | 34,868 (23.4%) | 37,365 (23.3%) | 40,286 (23.4%) | 42,144 (23.4%) |
| JIA | 13,137 (12.1%) | 14,460 (12.2%) | 15,769 (12.3%) | 17,151 (12.3%) | 18,438 (12.4%) | 19,729 (12.3%) | 21,023 (12.2%) | 21,943 (12.2%) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Polymyositis | 10,154 (9.4%) | 11,168 (9.4%) | 12,398 (9.7%) | 13,962 (10.1%) | 15,163 (10.2%) | 16,523 (10.3%) | 17,853 (10.4%) | 18,765 (10.4%) |
| Arteritis, unspecified | 9,153 (8.4%) | 10,171 (8.6%) | 11,223 (8.7%) | 12,360 (8.9%) | 13,633 (9.1%) | 15,260 (9.5%) | 17,053 (9.9%) | 18,208 (10.1%) |
| Scleroderma | 8,905 (8.2%) | 9,425 (8.0%) | 9,978 (7.8%) | 10,520 (7.6%) | 11,091 (7.4%) | 11,609 (7.2%) | 12,175 (7.1%) | 12,401 (6.9%) |
| GPA | 5,063 (4.7%) | 5,280 (4.5%) | 5,550 (4.3%) | 5,750 (4.1%) | 5,947 (4.0%) | 6,200 (3.9%) | 6,398 (3.7%) | 6,606 (3.7%) |
| Behcet's disease | 2,974 (2.7%) | 3,276 (2.8%) | 3,565 (2.8%) | 3,889 (2.8%) | 4,195 (2.8%) | 4,529 (2.8%) | 4,869 (2.8%) | 5,154 (2.9%) |
| Dermatomyositis | 1,760 (1.6%) | 1,892 (1.6%) | 2,062 (1.6%) | 2,201 (1.6%) | 2,357 (1.6%) | 2,536 (1.6%) | 2,734 (1.6%) | 2,807 (1.6%) |
| PAN | 1,937 (1.8%) | 2,039 (1.7%) | 2,177 (1.7%) | 2,346 (1.7%) | 2,459 (1.6%) | 2,593 (1.6%) | 2,672 (1.6%) | 2,708 (1.5%) |
| EGPA | 1,671 (1.5%) | 1,786 (1.5%) | 1,916 (1.5%) | 2,048 (1.5%) | 2,151 (1.4%) | 2,279 (1.4%) | 2,406 (1.4%) | 2,478 (1.4%) |
| MPA | 738 (0.7%) | 872 (0.7%) | 1,004 (0.8%) | 1,139 (0.8%) | 1,281 (0.9%) | 1,432 (0.9%) | 1,565 (0.9%) | 1,681 (0.9%) |
| Takayasu arteritis | 548 (0.5%) | 605 (0.5%) | 671 (0.5%) | 719 (0.5%) | 775 (0.5%) | 846 (0.5%) | 927 (0.5%) | 958 (0.5%) |
| Juvenile myositis | 295 (0.3%) | 317 (0.3%) | 345 (0.3%) | 383 (0.3%) | 411 (0.3%) | 443 (0.3%) | 482 (0.3%) | 522 (0.3%) |

EGPA = Eosinophilic granulomatosis with polyangiitis; GPA = Granulomatosis with polyangiitis; JIA = Juvenile idiopathic arthritis; MPA = Microscopic polyangiitis; PAN = Polyarteritis nodosa; SLE = Systemic lupus erythematosus

*5.4.2 Crude all-cause mortality*

In 2013, 5,220/108,593 (4.81%) people with RAIRD died of any cause, compared to 7,506/172,369 (4.35%) in 2019. In 2020, the first year of the COVID-19 pandemic, this increased to 8,553/180,083 (4.75%) deaths. Crude all-cause mortality rates gradually reduced from 4,806.9 per 100,00 person-years in 2013 to 4,354.6 in 2019, before increasing again to 4,749.5 in 2020. These data are summarised in Table 19.

*5.4.3 Age- and age-sex-standardised mortality rates*

The age-sex-standardised mortality rate for all-cause death in RAIRD was 2,324.5 (95% CI 2,261.5 – 2,387.6) in 2013, compared to 869.4 (866.9 - 871.9) in the general population (rate ratio 2.7 (2.6 - 2.7)) (Table 19). By 2019, this had reduced to 2,115.9 (95% CI 2,068.0 – 2,163.7) compared to 868.5 (866.1 - 871.0) in the general population, giving a rate ratio of 2.4 (2.4 - 2.5). In 2020, the age-sex-standardised mortality rate increased to 2,332.8 (2,283.3 – 2,382.2) but as there was also an increase in the general population (992.3 (95% CI 989.7 - 994.9)) the rate ratio remained similar (2.4 (2.3 - 2.4)).

Table 19: Age-sex-standardised all-cause mortality rates for RAIRD by year from 2013 to 2020, compared to the general population of England

| | Number of deaths | Number of people | Person/years | Crude mortality rate per 100,000 person years | RAIRD age-sex-standardised mortality rate | England age-sex-standardised mortality rate | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| 2013 | 5,220 | 108,593 | 108,593 | 4,806.9 | 2,324.5 (2,261.5 – 2,387.6) | 869.4 (866.9 - 871.9) | 2.7 (2.6 - 2.7) |
| 2014 | 5,597 | 118,235 | 118,235 | 4,733.8 | 2,280.9 (2,221.1 – 2,340.6) | 852.9 (850.5 - 855.4) | 2.7 (2.6 - 2.7) |
| 2015 | 6,069 | 128,305 | 128,305 | 4,730.1 | 2,257.3 (2,200.5 – 2,314.1) | 893.0 (890.5 - 895.5) | 2.5 (2.5 - 2.6) |
| 2016 | 6,397 | 138,920 | 138,920 | 4,604.8 | 2,215.1 (2,160.9 – 2,269.4) | 876.4 (874.0 - 878.9) | 2.5 (2.5 - 2.6) |
| 2017 | 6,749 | 149,285 | 149,285 | 4,520.9 | 2,158.9 (2,107.4 – 2,210.4) | 884.8 (882.3 - 887.3) | 2.4 (2.4 - 2.5) |
| 2018 | 7,146 | 160,486 | 160,486 | 4,452.7 | 2,218.4 (2,167.0 – 2,269.9) | 890.9 (888.4 - 893.4) | 2.5 (2.4 - 2.5) |
| 2019 | 7,506 | 172,369 | 172,369 | 4,354.6 | 2,115.9 (2,068.0 – 2,163.7) | 868.5 (866.1 - 871.0) | 2.4 (2.4 - 2.5) |
| 2020 | 8,553 | 180,083 | 180,083 | 4,749.5 | 2,332.8 (2,283.3 – 2,382.2) | 992.3 (989.7 - 994.9) | 2.4 (2.3 - 2.4) |

*5.4.4 All-cause deaths over time*

All-cause RAIRD and general population deaths were calculated as a proportion per 5-year age band (to allow comparison over between years) and plotted over time. People with RAIRD died at an earlier age than the general population in each year of the study. This is shown in Figure 17. This pattern was seen in both males and females, as shown in Figure 18.

Figure 17: RAIRD and general population deaths per year 2013-2020, shown as a proportion of deaths per five-year age band

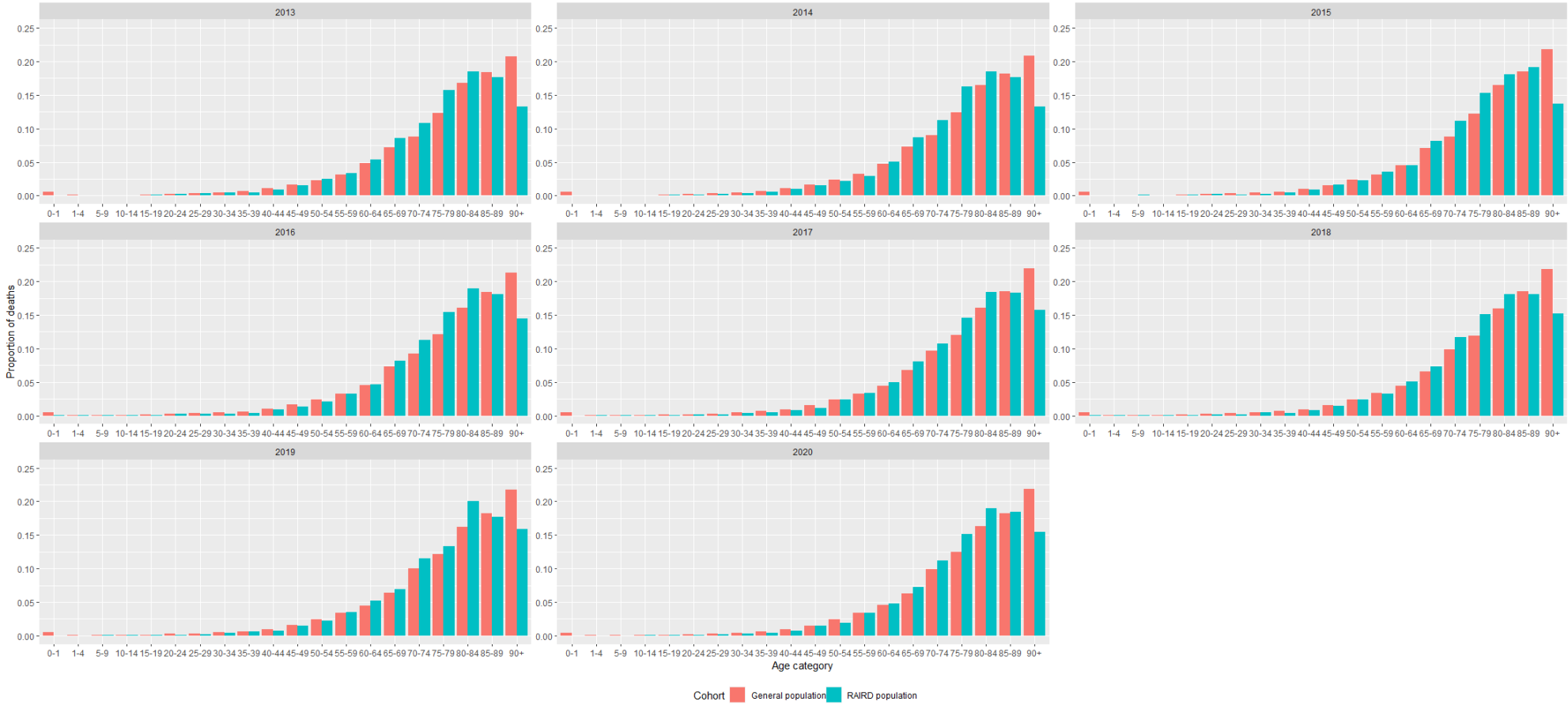


Figure 18: RAIRD deaths per year 2013-2020, shown as a number of deaths per five-year age band and split by sex

*5.4.5 Age at death*

Median age (IQR) at death for each year of the study is shown in Supplementary Table 2. Between 2013 and 2019, there was no significant change (79.9 (70.4 – 86.6) and 80.8 (72.2 - 87.3) respectively). Throughout the study, median age of death was slightly lower for males than for females (in 2020, this was 79.5 (71.3 - 86.2) and 81.5 (72.7 – 88.0) respectively). Median age at death by RAIRD diagnosis, with median age of cohort for comparison, are also shown in Table 20.

Table 20: Age at death (median, IQR) of RAIRD cohort 2013-2020

| Year* | Whole cohort | Females | Males |
|---|---|---|---|
| 2013 | 79.9 (70.4 – 86.6) | 81.0 (71.3 – 87.3) | 78.1 (69.3 – 84.8) |
| 2014 | 79.9 (70.8 - 86.7) | 80.6 (71.6 – 87.4) | 78.5 (69.7 - 85.3) |
| 2015 | 80.3 (71.3 - 87.0) | 81.2 (72.2 – 87.9) | 78.8 (69.7 - 85.4) |
| 2016 | 80.4 (71.6 - 87.0) | 81.0 (72.3 – 87.7) | 79.3 (70.5 – 85.6) |
| 2017 | 80.7 (71.3 - 87.3) | 81.6 (72.4 – 88.2) | 79.3 (70.0 – 85.5) |
| 2018 | 80.5 (71.6 - 87.2) | 81.3 (72.1 – 87.9) | 79.1 (70.6 – 85.8) |
| 2019 | 80.9 (71.8 - 87.3) | 81.8 (72.5 – 88.0) | 79.2 (70.3 - 86.1) |
| 2020 | 80.8 (72.2 - 87.3) | 81.5 (72.7 – 88.0) | 79.5 (71.3 - 86.2) |
| Disease | Median age (IQR)† | Age at death† | |
| Behcet's disease | 44.8 (33.4 – 57.5) | 69.6 (55.8 – 80.4) | |
| Dermatomyositis | 63.7 (49.6 – 74.8) | 73.3 (63.8 – 80.8) | |
| EGPA | 64.5 (51.7 – 73.9) | 76.0 (68.1 – 82.9) | |
| Giant cell arteritis | 78.6 (71.0 – 85.3) | 84.9 (79.2 – 89.7) | |
| GPA | 66.7 (53.6 – 77.1) | 76.6 (68.1 – 82.9) | |
| Arteritis, unspecified | 69.0 (55.0 – 79.2) | 77.9 (69.0 – 84.7) | |
| JIA | 16.4 (10.2 – 29.7) | 62.2 (44.0 – 76.4) | |
| Juvenile Myositis | 12.0 (7.4 – 19.5) | 43.1 (15.6 – 63.6) | |
| MPA | 69.8 (51.5 – 77.4) | 79.4 (73.1 – 84.5) | |
| PAN | 66.3 (51.5 – 77.1) | 77.1 (69.6 – 83.6) | |
| Polymyositis | 57.9 (33.2 – 73.7) | 76.6 (66.9 – 83.7) | |
| Scleroderma | 67.0 (55.4 – 76.6) | 74.8 (66.1 – 81.9) | |
| SLE | 54.1 (40.5 – 67.9) | 72.4 (61.6 – 81.0) | |
| Takayasu arteritis | 56.7 (38.3 – 70.0) | 72.2 (59.5 – 80.5) | |

*Chi-squared test for trend showed no significant difference †On entering the study
EGPA = Eosinophilic granulomatosis with polyangiitis; GPA = Granulomatosis with polyangiitis;
JIA = Juvenile idiopathic arthritis; MPA = Microscopic polyangiitis; PAN = Polyarteritis nodosa;
SLE = Systemic lupus erythematosus

*5.4.6 Cause-specific death*

Underlying causes of death by category are shown in Table 21. In total, there were 53,237 deaths over the course of the study. Deaths attributed to cardiovascular disease were recorded in 10,745 (20.2%), malignancy 10,489 (19.7%), respiratory disease (excluding influenza and pneumonia) 5,649 (10.6%), dementia 3,974 (7.5%), stroke 3,163 (5.9%), influenza and pneumonia 3,036 (5.7%), COVID-19 1,267 (2.4%), infection 784 (1.5%), and VTE 171 (0.3%), with the remaining 13,959 (26.2%) ascribed to other causes.

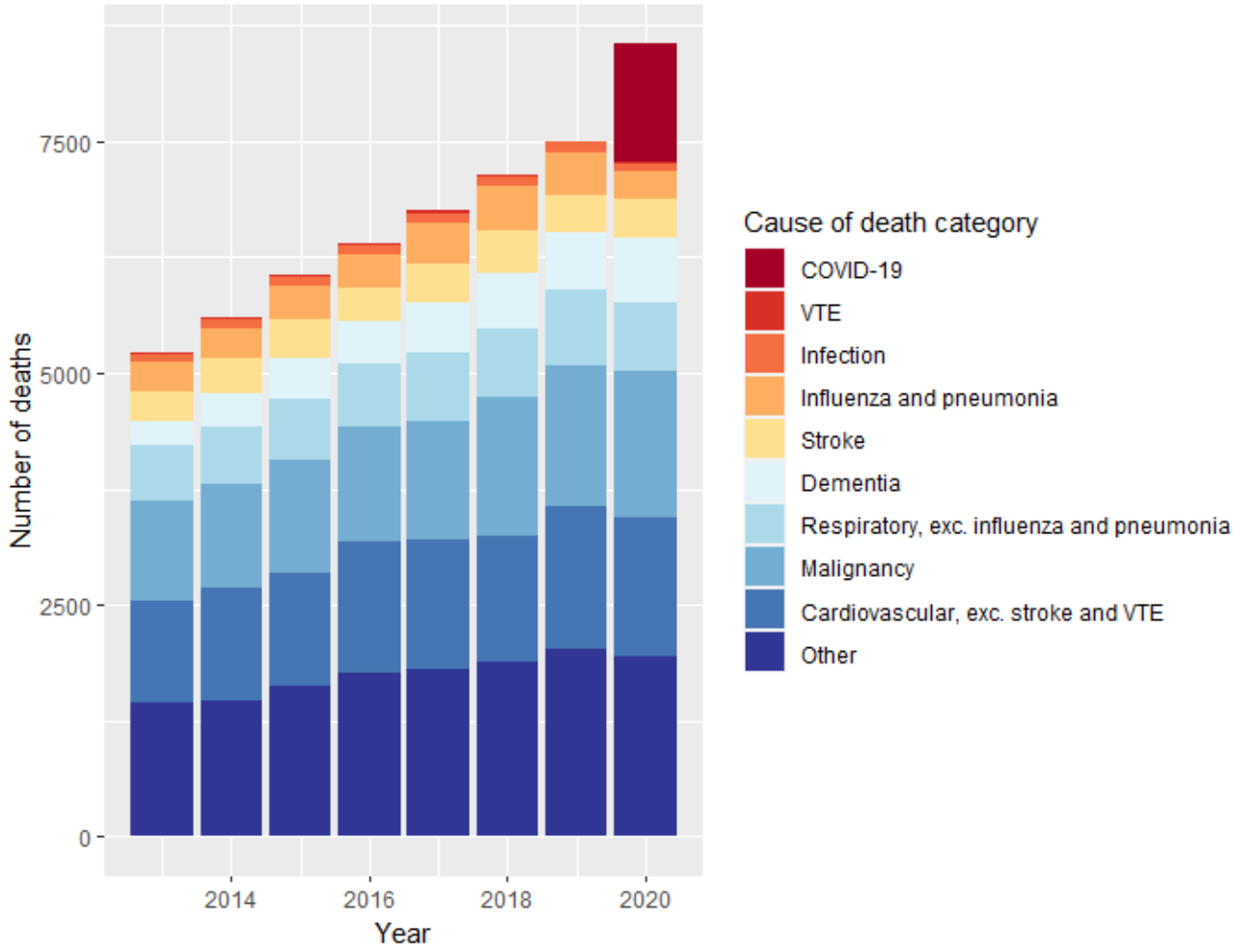
The cause-specific age-sex-standardised mortality rates are also shown in Table 21. For infection the rate was 36.43 (33.88 – 38.98) per 100,000 person-years, compared to 8.86 (8.78 – 8.95) in the general population, giving a of rate ratio 4.11 (3.82 – 4.40). The rate ratio was also significantly higher in cardiovascular disease (2.51 (2.47 – 2.56)), COVID-19 (2.77 (2.62 – 2.92)), respiratory disease (2.92 (2.84 – 2.99)) and other causes (3.96 (3.90 – 4.03)). Only in deaths due to dementia was the rate ratio not raised in RAIRD (0.99 (0.96 – 1.02)).

Table 21: Age-sex-standardised cause-specific mortality rates for RAIRD during 2013 to 2020, compared to the general population of England

| | Number of deaths | Number of people | Person/years | Crude mortality rate per 100,000 person years | RAIRD age-sex-standardised mortality rate | England age-sex-standardised mortality rate | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| Cause of death | | | | | | | |
| All cause | 53,237 | 233,320 | 1,061,969 | 22,817.2 (22,623.3 – 23,011.0) | 2237.49 (2218.48 - 2256.50) | 903.46 (902.57 - 904.34) | 2.48 (2.46 – 2.50) |
| Cardiovascular, exc. stroke and VTE | 10,745 | 233,320 | 1,061,969 | 4,605.3 (4,518.2 – 4,692.3) | 432.63 (424.45 - 440.81) | 172.13 (171.75 - 172.52) | 2.51 (2.47 – 2.56) |
| COVID-19 | 1,267 | 233,320 | 1,061,969 | 543.0 (513.1 - 572.9) | 43.35 (40.96 - 45.74) | 15.65 (15.54 – 15.77) | 2.77 (2.62 – 2.92) |
| Dementia | 3,974 | 233,320 | 1,061,969 | 1,703.2 (1,650.3 – 1,756.2) | 104.54 (101.29 - 107.79) | 105.85 (105.54 - 106.15) | 0.99 (0.96 – 1.02) |
| Infection | 784 | 233,320 | 1,061,969 | 336.0 (312.5 - 359.5) | 36.43 (33.88 - 38.98) | 8.86 (8.78 – 8.95) | 4.11 (3.82 – 4.40) |
| Influenza and pneumonia | 3,036 | 233,320 | 1,061,969 | 1,301.2 (1,254.9 – 1,347.5) | 108.61 (104.75 - 112.47) | 44.46 (44.27 - 44.66) | 2.44 (2.36 – 2.53) |
| Malignancy | 10,489 | 233,320 | 1,061,969 | 4,495.5 (4,409.5 – 4,581.6) | 470.35 (461.34 - 479.35) | 246.05 (245.59 - 246.52) | 1.91 (1.87 – 1.95) |
| Other | 13,959 | 233,320 | 1,061,969 | 5,982.8 (5,883.5 – 6,082.0) | 698.05 (686.47 - 709.63) | 176.07 (175.68 - 176.46) | 3.96 (3.90 – 4.03) |
| Respiratory, exc. influenza and pneumonia | 5,649 | 233,320 | 1,061,969 | 2,421.1 (2,358.0 – 2,484.3) | 221.60 (215.82 - 227.38) | 75.96 (75.70 - 76.21) | 2.92 (2.84 – 2.99) |
| Stroke | 3,163 | 233,320 | 1,061,969 | 1,355.6 (1,308.4 – 1,402.9) | 114.26 (110.27 - 118.24) | 54.59 (54.37 - 54.81) | 2.09 (2.02 – 2.17) |
| Venous thromboembolic disease | 171 | 233,320 | 1,061,969 | 73.3 (62.3 - 84.3) | 7.68 (6.53 - 8.83) | 3.83 (3.77 – 3.89) | 2.01 (1.71 – 2.31) |

Cause specific deaths per year are shown in Figure 19.

Figure 19: Cause-specific deaths, shown as the total number of RAIRD deaths per year of study




The earlier age at death in the RAIRD cohort compared to the general population is demonstrated for all causes of death in Figure 20 and for deaths due to infection in Figure 21.

Figure 20: Deaths from all causes 2013-2020 in RAIRD cohort compared to general population, shown as a proportion of each 5-year age band

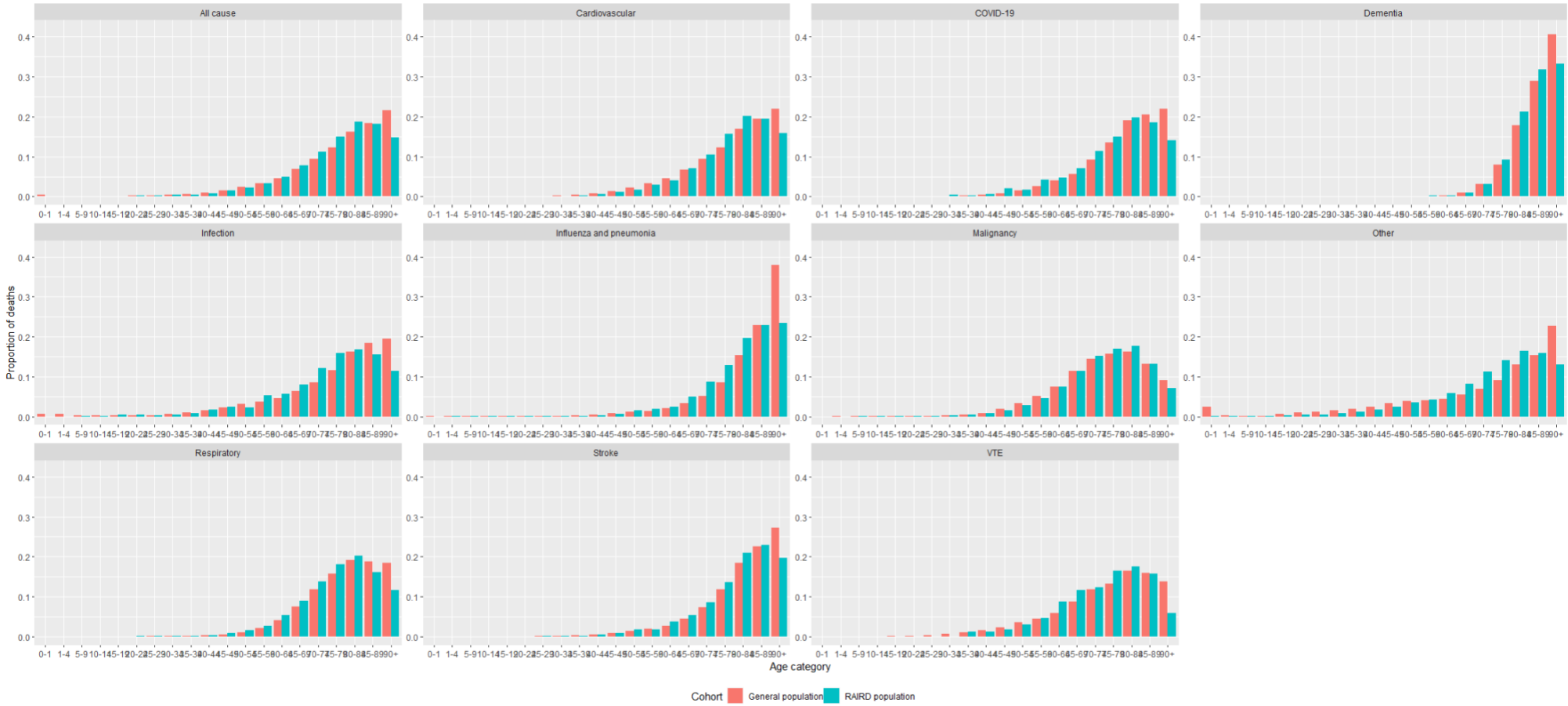
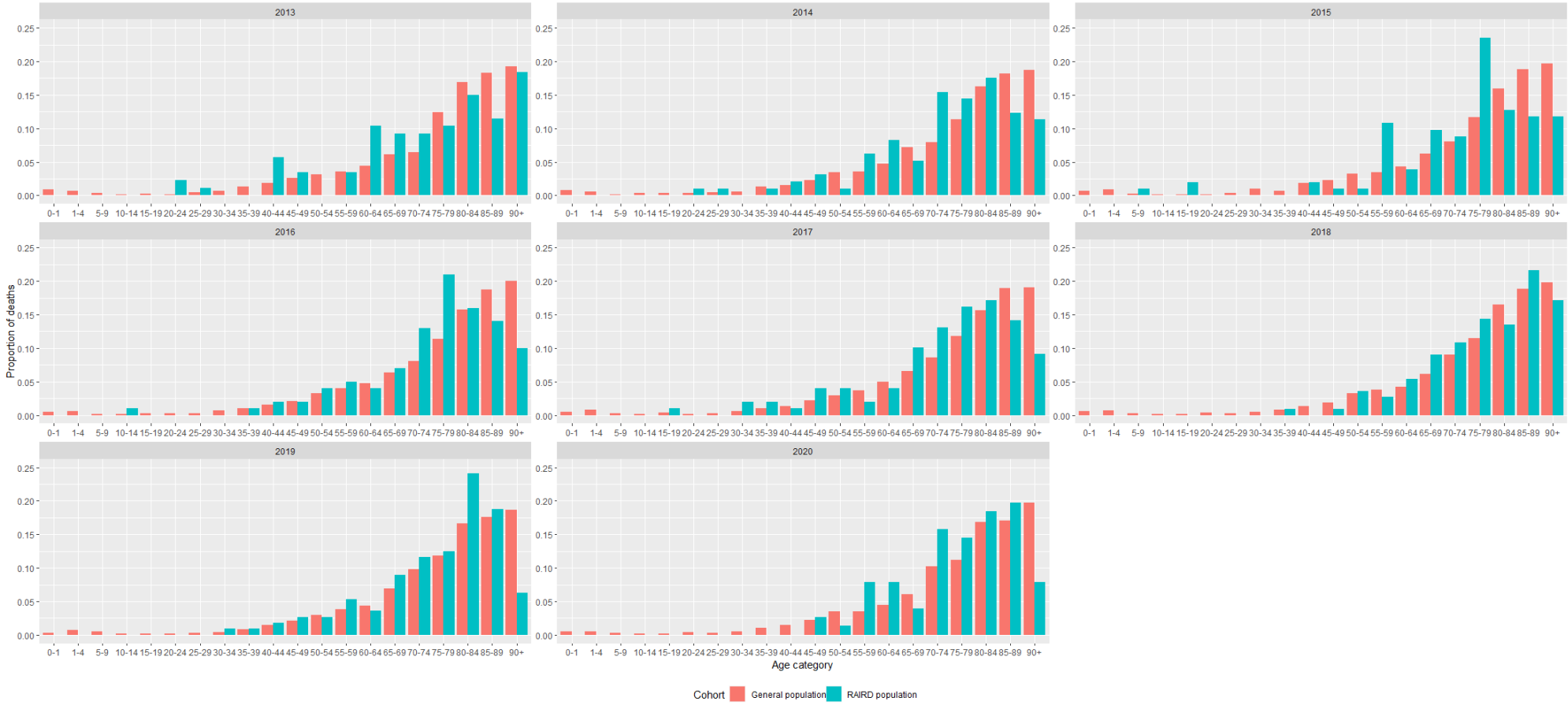


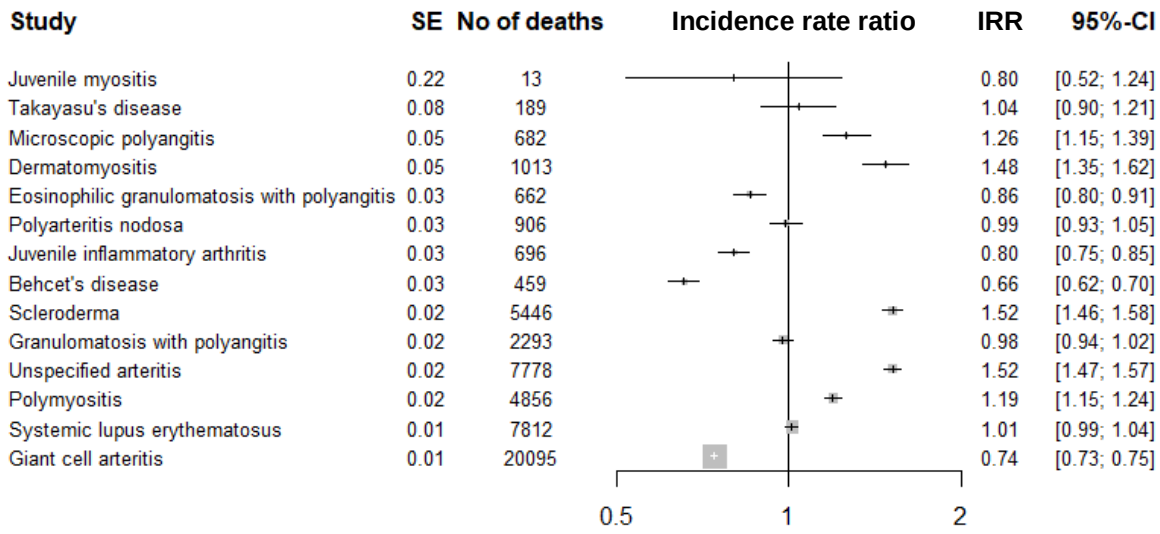
Figure 21: Deaths from infection in RAIRD cohort compared to general population, shown by year and as a proportion of each 5-year age band



*5.4.7 Stratification by disease*

Incidence rate ratios for all-cause death stratified by RAIRD diagnosis are displayed in Figure 22. Scleroderma, dermatomyositis, polymyositis, microscopic polyangiitis and unspecified arteritis are associated with a higher risk of death compared to other RAIRD.

Figure 22: Forest plot showing incidence rate ratios with 95% confidence intervals for all-cause mortality stratified by RAIRD diagnosis, with the combined RAIRD cohort used as the reference group




*5.4.8 Deaths from opportunistic infections*

Over the study period, there were 28 deaths secondary to CMV (0.053%), 35 secondary to PJP (0.066%) and 8 secondary to PML (0.015%). There were 53,166 deaths due to other causes, meaning that deaths from these infections were exceptionally rare.

The median age of death was earlier in these conditions (68, 68 and 70 years respectively) than in deaths from other causes (80, IQR 72-87).

Whilst there is a predominance of women in the cohort (69.9-70.9%), there was a more even split of deaths secondary to these infections, particularly PJP (60% men).
These data are summarised in Table 22.

Table 22: Causes of death due to opportunistic infections in people with RAIRD 2013-2020

| Cause of death | CMV, n = 28† | PJP, n = 35† | PML, n = 8† | Other, n = 53,166† |
|---|---|---|---|---|
| Sex | | | | |
| F | 18 (64%) | 14 (40%) | 5 (62%) | 34,455 (65%) |
| M | 10 (36%) | 21 (60%*) | 3 (38%) | 18,711 (35%) |
| Age at death‡ | 68 (54, 75) | 68 (60, 75) | 70 (64, 74) | 80 (72, 87) |

†n (%); ‡Median (IQR); *statistically significant, p<0.01.
CMV = cytomegalovirus; PJP = pneumocystis jirovecii pneumonia; PML = progressive multifocal leukoencephalopathy

## 5.5 Discussion

### *5.5.1 Main findings*

Adjusted for age and sex, all-cause mortality in RAIRD is increased when compared to the general population.

Comparing all-cause mortality risk between RAIRD, adjusted for age and sex, scleroderma, myositis, microscopic polyangiitis and unspecified arteritis showed the highest risk.

Cause-specific mortality was also increased across all categories except dementia, with the risk of death due to infection, COVID-19, cardiovascular and respiratory disease particularly raised.

Deaths due to the atypical infections PML, PJP and CMV infection occurred but were rare.

### *5.5.2 Strengths*

This is the first time that all-cause and cause-specific mortality data have been described in whole population data for people with RAIRD in England. It is also the first time that all-cause mortality outcomes have been described since the onset of the COVID-19 pandemic. This has been made possible through collaboration with NCARDRS, whose legal permissions allow unique access to patient-identifiable data allowing linkage.

A major strength of this work is that the denominator population is known, allowing me to describe rates and to compare them against the general population. The use of whole

population data also allows me to describe outcomes in a real-world, unselected population cohort, potentially allowing more generalisable results.

*5.5.3 Limitations*

The study cohort was identified from diagnoses in HES admitted patient care (APC) data, meaning that my methodology would not have identified patients treated entirely on an outpatient basis, who have never had an in-patient or daycase admission for any reason. Due to the complex nature of RAIRD, I believe this to be the minority of cases, and this is supported by the disease prevalence in this cohort being similar to previous studies(33, 35, 96). However, this could skew the cohort towards those with more severe disease.

This study uses the single ICD-10 code identified as the "underlying cause of death", as ascribed by the ONS(100), when describing cause-specific deaths. Whilst a standard ONS metric(100), and necessary in order to compare to the general population data, this over-simplifies cause of death, which in many cases is multi-factorial. Using "any mention" of a condition on a death certificate would provide more complete information on the causes contributing to death (although not always their relative importance). However, this information is not available for the general population, making comparisons impossible.

*5.5.4 Comparison to the published literature*

Whilst all-cause mortality has been shown to be raised across all RAIRD, there is some variation between diseases.

One study of 387 people with Behcet's disease in Turkey, with a 20-year follow-up period, found high standardised mortality rates (SMRs) in all ages groups but particularly for those in the cohort aged 14-24 years old, who had a rate 10-times that of the general population(70). The SMR was particularly high in men.

At the other end of the spectrum, a meta-analysis by Hill et al found that age-standardised mortality rates in GCA were only 1.17 (95% CI 1.02–1.35) times higher than the general population(72). This is potentially lower than in the other RAIRD as the highest incidence of GCA is in those aged 70-79(27), and by definition it is rare in people aged over 50, and the

mortality in those in the general population of the same age is also relatively high. There is also the impact of survivor bias to consider, as people need to be in relatively good general health to survive until an age where GCA may develop.

The other RAIRD lie somewhere in-between, with an SMR ranging from 1.75 (95% CI 1.41–2.15) in biopsy-proven idiopathic inflammatory myositis (IIM) in South Australia(71) to 3.7 (95% CI 3.2 to 4.4) in a whole population study of the disease in Sweden(81). In Takayasu arteritis (TAK), a whole population study in South Korea found an SMR of 3.1 (2.4-4.0)(160). In JIA, a UK registry study of 1,556 patients reported the SMR as 2.8 (95% CI 1.4 - 5.2)(69). In a multi-centre, international cohort of SLE (n= 9,547), the SMR was reported as 2.4 (95% CI 2.3–2.5)(67). In scleroderma, a meta-analysis including a total of 1,645 incident cases found an SMR of 1.5-7.2, depending on the cohort(73). In AAV, a meta-analysis including 10 observational studies with a total of 3,338 patients enrolled between 1966-2009 found an SMR of 2.7 (95% CI 2.3 to 3.2))(75). The authors demonstrated a trend towards reducing SMR over time(75). A more recent study, in a US-based cohort of 484 people with AAV diagnosed between 2002 and 2017, the SMR was 2.3 (95% CI 1.9-2.8).

Rare disease research has common challenges, due to the size of the populations involved. Many of the studies described above were limited by relatively small cohorts. compared to my whole population cohort (n=180,083). There were also variations in how diseases were defined (for example, clinical diagnosis vs biopsy-proven disease), which accounts for some of the variation in findings. Changes to treatment protocols, such as the prompt use of corticosteroids or the introduction of rituximab in AAV, have also dramatically changed survival outcomes in RAIRD over the past few decades, so older studies may no longer accurately reflect the current landscape.

With regards to cause-specific mortality, the literature describes common causes but mortality rates are less frequently reported, presumably due the size of the study populations.

Infection has been found to be a leading cause of death across AAV(66, 161), GCA(72), IIM(71), JIA(69) and SLE(67). The SMR in SLE was reported as 5.0 (95% CI 3.7–6.7)(67). This

study found an increased risk ratio of 4.11 (95% CI 3.82 – 4.40) for non- influenza and pneumonia infections among the RAIRD cohort compared to the general population. My previous research has shown an increased risk of death related to COVID-19 in people with RAIRD(162, 163).

Cardiovascular disease is a leading cause of death in AAV(75, 164), Behcet's disease(70), GCA(72), IIM(71, 81), SLE(165), systemic sclerosis (SSc)(83) and TAK(160). The SMR for death due to cardiovascular disease in SLE was reported as 1.7 (95% CI 1.5–1.9)(67). This study found an increased risk ratio of 2.51 (95% CI 2.47 – 2.56) for cardiovascular deaths among the RAIRD cohort compared to the general population.

Respiratory disease is described as a significant cause of death in those with AAV(77), IIM(71, 81) and SSc(73, 82), although some of these studies included influenza and pneumonia within the respiratory category. In AAV, Wallace et al.(77) found a raised SMR for respiratory disease in MPO-antibody disease (2.4 (95% CI 1.1-5.4)) but found no increased risk in those with PR3 antibodies. This study found an increased risk ratio of 2.92 (95% CI 2.84 – 2.99) for respiratory deaths (excluding influenza and pneumonia) among the RAIRD cohort compared to the general population.

Whilst the greatest risk factor for dementia is increasing age(166), it is a recognised complication of many RAIRD(167). Some studies also show an increased incidence of the disease when compared to the general population, for instance in SLE(168). However, I was unable to find studies describing dementia as a cause of death in RAIRD.

*5.5.5 Comparison between RAIRD*

Adjusting for age and sex and comparing between RAIRD, SSc, IIM, microscopic polyangiitis (MPA) and unspecified arteritis showed the highest risk of all-cause mortality. To the best of my knowledge, mortality rates between RAIRD have never been compared in this way, using whole population data, before.

The literature supports high mortality rates in some cohorts of SSc(73) and in MPA(169), and there is some evidence to suggest that MPA may have more severe outcomes than

other forms of AAV(170). Results in IIM are more mixed but this may be due to included populations and case ascertainment, with a whole population study demonstrating a higher SMR(81) than a study including only patients with disease confirmed on muscle biopsy(71).

The interpretation of the finding that "arteritis, unspecified" (I77.6) is associated with higher mortality is more complex. This ICD-10 code is frequently used by clinical coders for cases of AAV, where a more specific diagnosis (such as GPA, EGPA or MPA) is not recorded in the notes. It therefore likely reflects a relatively higher risk of death amongst these diagnoses. However, further research looking at the underlying diagnoses of those with a I77.6 code would aid the interpretation of this finding.

*5.5.6 Opportunistic infections*

Atypical infections such as PJP, PML and CMV are associated with high mortality and their risk is increased both by certain RAIRD themselves(171) but in particular by some treatments e.g., rituximab(172). Treatment guidelines typically recommend vigilance and counselling for, and the in the case of PJP prophylaxis against, these conditions(44, 173) and they remain a source of anxiety for patients and clinicians alike. My findings highlight that these infections do occur in RAIRD but overall are responsible for a reassuringly low proportion of deaths.

Comparing males and females, despite women making up 69.9-70.9% of the cohort, for deaths attributable to PJP men made up the majority (60%), which was statistically significant.

*5.5.9 Temporal trends*

Whilst this was a relatively short study in which to compare temporal trends (2013-2020), there was evidence that mortality risk was gradually reducing with time (although the arrival of the COVID-19 pandemic was associated with an increase in all-cause mortality). This may reflect improved treatments of the diseases themselves, better screening for and treatment of associated co-morbidities, or increased ascertainment of milder cases of disease.

The size of the RAIRD cohort increased by 66% over the course of the study. There are several possible reasons for this, including: increased detection of cases through HES (people had a cumulative chance of admission, and so being added to the cohort, over the course of the study), increased awareness of the diagnosis among physicians, increased availability of testing, true increased incidence. If the increase in the size of the cohort was due to increasing case ascertainment over the study period, it is possible that the detection of milder cases explains some of the reduction in mortality risk. However, there is evidence to suggest that the incidence and prevalence of RAIRD is increasing(22, 35, 174). Whether this is due to a true increase in cases, or increased detection due to improved access to healthcare and evolving diagnostic methods, is unclear. Despite the increasing size of the cohort, the demographics remained fairly stable, suggesting that the cohort was representative throughout the study period.

The impact of the COVID-19 pandemic on all-cause mortality rates, both in RAIRD and the general population, is shown in this study. As yet, there has been no evidence to suggest a significant increase in deaths due to causes other than COVID-19 infection. However, delayed or missed diagnoses during the height of the pandemic, particularly from conditions such as cancer, may further increase all-cause and certain cause-specific mortality rates in future years. It is possible that due to shielding and other COVID-19-related behaviour change, people with RAIRD will be disproportionately affected due to increased health-care avoidance(64).

*5.5.9 Age at death*

There was a lower age at death in both the juvenile myositis (median age at death 43.1 years (IQR 15.6 – 63.6)) and JIA (median age at death 62.2 years (IQR 44.0 – 76.4)) groups. Given that there were few deaths in both groups (juvenile myositis 13/522 (2.5%); JIA 696/21,943 (3.2%)), both as absolute numbers and as a percentage of the cohort, this should be treated with a degree of caution.

In addition, the relatively short duration of this study may have influenced these results. The earliest diagnoses recorded in the study cohort were in 1998, at the start of HES data collection, and so I may not have identified all the people who were diagnosed with juvenile

disease as children but who were adults at the time of the start of the study. Other studies have also found a similar at death in juvenile myositis(175) and JIA(69), despite longer periods of follow up (22 years and 10 years respectively). However, the nature of paediatric onset disease means that their findings were also likely affected by study duration.

Finally, as this study attributed RAIRD diagnosis on the basis of the most recently received RAIRD ICD-10 diagnostic code (as described in figure 15), it may be that people initially diagnosed with juvenile disease later received diagnostic codes for adult equivalent diagnoses. This would mean that in some cases the outcomes of adults with juvenile myositis, for example, would be recorded in a different disease group to their initial diagnosis, such as dermatomyositis.

*5.5.10 Clinical and policy implications and future research*

RAIRD are chronic conditions conferring ongoing risk. Certain causes of death can potentially be mitigated against, for instance with regular screening for and treatment of cardiovascular risk factors. This should be part of routine clinical practice, as described in the recently published EULAR guidance on the management of cardiovascular risk factors in rheumatic disease(176). Early recognition and treatment of infection and delivery of appropriate vaccinations (e.g., influenza, pneumococcal) may help to reduce deaths due to infection.

Further research to determine whether age or time from diagnosis are associated with increased risk of death from specific causes would be of benefit, although due to the sometimes differing disease courses of RAIRD this may be better designed as studies within single or similar groups of diseases.

The increased mortality rate seen in deaths due to malignancy requires further research in order to better understand whether specific types of cancer are driving this or whether it is a more general increase in risk.

**5.6 Conclusions**

My findings provide evidence that people with RAIRD are at increased risk of death compared to people of the same age and sex in the general population. This risk gradually decreased over the course of this study but remained significantly higher (rate ratio 2.4 (95% CI 2.3 - 2.4) in 2020), reflecting an ongoing clinical need in people with these conditions.

An increased mortality rate was seen across all causes except dementia. This may reflect competing risks, with the fact that dementia is typically seen in older age meaning that many people with RAIRD die from other causes before they can develop it. That RAIRD is associated with death at an earlier age across so many different cause of death categories highlights the complexity of these diseases, and the co-morbidities and treatment sequelae with which they are associated. Screening for and treatment of co-morbidities and complications is a key part of clinical care.

# Chapter 6: Overall discussion and conclusions

This chapter discusses the clinical implications of each of the studies contained within this thesis, and the overall conclusions. It describes the implications of the first and second wave studies as they were at the time, taking into account the rapidly changing landscape of COVID-19 research during the period of my thesis.

## 6.1 Outcomes in people with RAIRD during the first wave of the COVID-19 pandemic

### *6.1.1 Summary of main findings*

In the first wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD were more than twice that of the general population when standardised for age and sex (rate ratio 2.41 (95% CI 2.30-2.53)).

The age-standardised COVID-19 infection rate was 1.54 (95% CI 1.50-1.59) times higher among people with RAIRD compared to the general population, despite shielding policies (protection of the clinically extremely vulnerable) in place in England.

Initially, the increased mortality rate seemed to have been contributed to by both higher COVID-19 infection rates and higher mortality after COVID-19 infection. However, in my subsequent study looking at the second wave of the pandemic, the increased mortality rate persisted despite similar age-standardised infection rates between the general population and people with RAIRD. Potential explanations of this are discussed below.

### *6.1.2 Interpretation and clinical and policy implications*

These findings provided clear evidence that during the first wave of the pandemic people with RAIRD were at higher risk of COVID-19-related death than people of the same age and sex in the general population. At the time, there had been conflicting statements issued about risk during the pandemic and so these findings had important implications for people living with RAIRD, their clinicians and for public health policy.

These results confirmed at whole population-level the assumptions at the start of the pandemic: that many people with RAIRD would be clinically extremely vulnerable to the

effect of COVID-19. People with RAIRD may require lifelong immunosuppression, conferring ongoing risk. Protecting the health of people with RAIRD therefore required specific public health prioritisation, to reduce both their risk of acquiring COVID-19 infection and their mortality. Infection prevention measures, including robust alternatives to face-to-face appointments and support to shield during times of heightened infection rates in the community, were paramount.

However, my findings suggest that despite the intent of shielding policy to reduce infection exposure, COVID-19 infection and mortality rates were greater for people with RAIRD than for the general population. This was observational data, and the shielding status of the cohort is not yet known, so it is not possible to determine what the outcomes would have been without shielding policies in place. In addition, shielding policies were instituted on 23 March 2020 and some of my findings may reflect earlier transmission. Further research assessing the impact of shielding on COVID-19 outcomes is necessary to inform future pandemic planning at government level.

There are several potential reasons for the increased infection rate in the RAIRD cohort compared to the general population seen in this study. People with RAIRD may have been more susceptible to symptomatic COVID-19 infection due to their underlying disease and immunosuppression. During the first wave, where testing was predominantly in hospital, their increased contact with healthcare services may have led to increased testing and ascertainment bias. Anecdotally, it is known that some units were performing asymptomatic screening prior to day-case or immunosuppressive treatment. People with RAIRD may also have a worse state of health than the general population, leading to increased hospital admissions, necessitating COVID-19 admission screening tests and increasing the risk of nosocomial infection. Requirements for monitoring bloods and hospital attendances may also have increased the risk of acquiring infection. Notably, this increased infection rate was not seen in the second wave, and this is discussed in more detail below.

These results highlighted the urgent need at the time for vaccine prioritisation in people with RAIRD. They also demonstrated the need to analyse the real-world effectiveness of vaccination among people with RAIRD, given the evidence that they may respond less well

to vaccination(123, 131). Ensuring access to vaccination through government policy, and deciding the optimal vaccination schedule to maximise protection, remains crucial in this group.

This study does not include data on immunosuppressive medications. The vulnerability to COVID-19 of people living with RAIRD is likely explained in part by the frequent need for immunosuppression in this group. Corticosteroid usage has long been thought to increase the risk of infection(48-50) and, despite the emergence of dexamethasone as an effective treatment for COVID-19(51), concerns remained that corticosteroid treatment preceding infection may predispose to more severe disease(52, 53, 121). Other immunosuppressants, such as rituximab, may impair the antiviral immune response and antibody production, with potentially more severe clinical outcomes(53, 54). Rituximab can also impact vaccine effectiveness and at the time of completing this study, data had just been published demonstrating attenuated antibody responses in people with AAV on rituximab(123). It is important to investigate the influence of these potentially modifiable risk factors, in order to inform clinical guidelines, treatment pathways and shared decision making, and to inform health policy.

I did not find an excess of non-COVID-19-related deaths during this period. This goes some way to alleviating concerns that difficulties accessing healthcare could lead to increased mortality due to underlying RAIRD and may reflect efforts to prioritise access to urgent care. However, the pandemic may have a delayed impact on mortality, particularly due to causes such as malignancy, due to delays in diagnosis and screening. Future mortality studies specifically focusing on the years during and following the pandemic would address this question.

This study shows the power of whole population data, accessed through collaboration with NCARDRS, for investigating outcomes in rare diseases. Whole population data bring many benefits; for instance, as the denominator population was known, I was able to describe for the first time both rates of COVID-19 infection and of COVID-19 related death and compare these with the general population. Validation work has shown that my methods of case ascertainment from HES are robust and, as people with RAIRD frequently require in-patient

and day-case, they are an ideal group to identify through HES. However, there is a potential bias towards ascertainment of people with more severe disease and future epidemiological studies would benefit from the inclusion of primary care data, to ensure capture of the whole spectrum of disease. There is potential for this to be made possible with access to General Practice Extraction Service (GPES) data by NCARDRS in the future.

The comparable COVID-19 outcomes seen between RAIRD subtypes strengthens the case for analysing them as one group. Pooled analysis of these diseases increases statistical power to detect outcomes and is clinically justified by their common underlying disease mechanisms and treatments. Given the problems inherent in rare disease research, with the small numbers of people affected by each condition reducing statistical power, grouping together diseases with clinical similarities may offer an appropriate research methodology.

## 6.2 Outcomes in people with RAIRD during the second wave of the COVID-19 pandemic

### *6.2.1 Summary of main findings*

In the second wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD remained more than twice that of the general population when standardised for age and sex (rate ratio 2.76 (95% CI 2.63 – 2.89)). There was no significant difference in the adjusted rates of COVID-19-related death between different RAIRDs.

Unlike in the first wave, the age-standardised COVID-19 infection rate was similar among people with RAIRD compared to the general population, which is likely to reflect testing availability early in the pandemic, although it could also be influenced by earlier vaccination in the RAIRD cohort due to prioritisation of at-risk groups.

Corticosteroid usage within the 30-days prior to COVID-19 infection was associated with an increased risk of COVID-19-related death, in a dose-dependent fashion. People taking more than 15mg prednisolone per day at the time of COVID-19 infection had over twice the risk of COVID-19 related death than those not taking steroids, and even relatively small doses of more than 5mg prednisolone per day were associated with an increase in risk.

### *6.2.2 Interpretation and clinical and policy implications*

This study confirmed ongoing risk of severe COVID-19 outcomes in people with RAIRD. However, whilst the study period encompassed the beginning of the vaccine roll-out (the first UK vaccinations were in December 2020), it is hoped that outcomes will have improved now that full vaccination courses and boosters have been delivered. An up-to-date study looking at current outcomes would be of benefit, in order to guide current health policy. A pre-print(148) from the QCOVID team looking at outcomes in the Omicron wave suggest a persistently increased risk in people with SLE but to my knowledge there is no other published research specific to RAIRD.

There was no significant difference in the age-standardised COVID-19 infection rate between people with RAIRD and the general population. This differs from the first wave, where the rate in people with RAIRD was around 50% higher. This is likely to reflect limited testing availability early in the pandemic, where testing was predominantly in hospital with few tests available in the community. It may be that as people with RAIRD have increased contact with healthcare services, they underwent more frequent testing, leading to ascertainment bias. It could also reflect earlier vaccination in the RAIRD group due to prioritisation of at-risk groups.

My study is the first specific to the RAIRD cohort to show an association between corticosteroid dose and COVID-19-related death, and the first to be able to demonstrate a clear dose-dependent effect. People taking more than 15mg prednisolone per day at the time of COVID-19 infection had over twice the risk of COVID-19 related death than those not taking steroids and even relatively small doses of more than 5mg prednisolone per day were associated with an increase in risk. It remains unclear whether this is a causative effect, or whether treated with corticosteroids are in poorer health with more active underlying disease, predisposing them to poorer outcomes. However, it is important that clinicians take this risk into account when deciding whether to prescribe steroids and consider steroid minimisation strategies where appropriate. Patients should also be made aware, so that they can be vigilant for COVID-19 symptoms and seek early medical advice should they develop.

This study does not include data on immunosuppressive medications other than corticosteroids. The NHS Prescription Services data used in this study contains all NHS prescriptions issued in the community in England but a particular difficulty with analysing the DMARD data contained in this dataset is the geographical variation in the use of shared care protocols. In some regions, the bulk of DMARD prescribing is performed by general practitioners, whereas in others it is predominantly done in secondary care, variation which much be accounted for in study design. However, future studies looking at the effect of DMARDs on COVID-19 outcomes are important so that evidence-based prescribing decisions can be made. It remains vital to bear in mind that certain immunosuppressive drugs may cause an inadequate response to vaccination, potentially leaving people treated with them at ongoing risk of severe COVID-19 outcomes. In particular, B cell depleting agents such as rituximab reduce antibody formation and lead to a lower production of, and poorer quality, T cells in response to COVID-19 vaccination(177). These results may therefore influence health policy, for instance when deciding which patients would be eligible for COVID-19 antibody treatments. As detailed in chapters 2 and 4, I have started to the develop the methodology for these studies and this work is a priority for my research group RECORDER.

As during the first wave, I did not find an excess of non-COVID-19-related deaths, including from underlying RAIRD. However, as discussed above, future epidemiological studies looking for any delayed impact on mortality rates would be of value in order to inform healthcare prioritisation in future pandemics.

The sub-analysis by disease continues to support the grouping together of RAIRD when assessing COVID-19 outcomes, in order to increase statistical power. Unlike in the first wave, giant cell arteritis (GCA) showed the same risk profile as the other RAIRD, which may be a result of the narrower confidence intervals due to the increased number of events compared to the first wave.

## 6.3 All-cause and cause-specific mortality in RAIRD

### *6.3.1 Summary of main findings*

My findings show that people with RAIRD are at increased risk of early death compared to people of the same age and sex in the general population. This risk gradually decreased over the course of the study but remained significantly raised (rate ratio 2.4 (95% CI 2.3 – 2.4) in 2020), reflecting an ongoing clinical need in people with these conditions. Comparing all-cause mortality risk between RAIRD, adjusted for age and sex, scleroderma, myositis, microscopic polyangiitis and unspecified arteritis showed the highest risk.

An increased mortality rate was seen across all causes except dementia. This may reflect competing risks, with the fact that dementia is typically seen in older age meaning that many people with RAIRD die from other causes before they can develop it.

*6.3.2 Interpretation and clinical and policy implications*

That RAIRD is associated with death at an earlier age across so many different cause of death categories highlights the complexity of these diseases, and the co-morbidities and treatment sequelae with which they are associated. Screening for and treatment of co-morbidities and complications is a key part of clinical care, as certain causes of death can potentially be mitigated against. For instance, regular screening for and treatment of cardiovascular risk factors has the potential to improve outcomes, and this should form part of routine clinical practice. There are clinical guidelines available to support this; for instance, the European League Against Rheumatism (EULAR) has recently published guidance on the management of cardiovascular risk factors in rheumatic disease(176).

The high mortality rate due to infection highlights that despite widespread awareness of the susceptibility to infection of people on immunosuppression, associated mortality remains high. Early recognition and treatment of infection by both primary and secondary care clinicians may help to reduce deaths due to infection. The delivery of appropriate vaccinations (e.g., influenza, pneumococcal) is also important, as is patient education on the symptoms of infection, particularly as it may not present typically in the immunosuppressed.

Further research to determine whether age or time from diagnosis are associated with increased risk of death from specific causes may help to develop targeted strategies to

mitigate against any preventable mortality. Due to the sometimes differing disease courses of RAIRD, this may be better designed as studies within single or similar groups of diseases.

The increased mortality rate seen in deaths due to malignancy requires further research, in order to better understand whether this is a general phenomenon or whether specific types of cancer are driving this. This could potentially pave the way for targeted screening or education of patients and clinicians.

Data on socioeconomic status (indices of multiple deprivation (IMD)) and ethnicity were not available at the time of this research. Given the known impact of IMD and ethnicity on mortality rates, future research adjusting for these factors is important in order to be able to stratify risk. I was also unable to adjust for co-morbidities such as renal or cardiovascular disease, as validation of the associated HES codes has not been performed and the PPV of these codes is not known. It is recognised that certain co-morbidities compound the risk of mortality in RAIRD and future whole population research looking at their impact is essential for risk stratification and targeting of resources.

# Chapter 7: Suggestions for further research

The work in this thesis has highlighted the need for further research in a number of areas.

Firstly, it is important to look at the real-world impact of immunosuppressants on COVID-19 outcomes in a whole population cohort. As I have highlighted in my discussion, several studies have shown an association between certain immunosuppressants and poor outcomes, but they are largely limited by small population sizes and/or selection bias. Rituximab is particularly implicated and has also been shown by laboratory studies to both reduce antibody formation and lead to a lower production of, and poorer quality, T cells in response to COVID-19 vaccination. Rituximab has become a lynchpin of treatment of many RAIRD, particularly for those with severe disease, but there are now concerns that individuals prescribed it remain at on-going risk of severe COVID-19 infection, despite vaccination and with fewer societal mitigations in place to protect them. I have developed code to extract community prescriptions for DMARDs from the NHS Prescriptions Service data, and RECORDER is developing techniques to account for regional variation in primary and secondary care prescribing that would enable future research in this area.

Secondly, the impact of shielding on outcomes should be assessed. RECORDER, in collaboration with NCARDRS, has legal permission to access to the Shielded Patient List (SPL) in identifiable format. We intend to identify those living with RAIRD who were deemed to be Clinically Extremely Vulnerable (CEV) and entered onto the SPL and compare their demographics and outcomes against people with RAIRD who were not deemed to be CEV.

Thirdly, a study looking at the COVID-19 outcomes in people living with RAIRD during the delta and omicron waves would give us more up-to-date data on the current risk of COVID-19 to those living with these conditions.

Finally, the association between corticosteroids (and potentially other DMARDs) and cause-specific mortality such as influenza or cardiovascular disease should be investigated, through linkage of the NHS Prescriptions Service and mortality (MBIS) datasets.

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# Appendix 1: PhD Outputs

## A1.1 Published papers arising from this thesis

Rutter M, Lanyon PC, Grainge MJ, Hubbard R, Bythell M, Stilwell P, Aston J, McPhail S, Stevens S, Pearce FA. COVID-19 infection, admission and death and the impact of corticosteroids amongst people with rare autoimmune rheumatic disease during the second wave of covid-19 in England: results from the RECORDER Project, *Rheumatology*, 2023;, kead150, https://doi.org/10.1093/rheumatology/kead150

Rutter M, Lanyon PC, Grainge MJ, Hubbard R, Peach E, Bythell M, Stilwell P, Aston J, Stevens S, Pearce FA. COVID-19 infection, admission and death among people with rare autoimmune rheumatic disease in England: results from the RECORDER project. Rheumatology. 2022 Aug;61(8):3161-71. https://doi.org/10.1093/rheumatology/keab794

Geetha D, Kronbichler A, Rutter M, Bajpai D, Menez S, Weissenbacher A, Anand S, Lin E, Carlson N, Sozio S, Fowler K. Impact of the COVID-19 pandemic on the kidney community: lessons learned and future directions. Nature Reviews Nephrology. 2022 Aug 24:1-4. https://doi.org/10.1038/s41581-022-00618-4

## A1.2 Presentations arising from this thesis

### *A1.2.1 National presentations*

Oral abstract presentation at the British Society for Rheumatology annual conference April 2021: *Risk of death during the 2020 UK COVID-19 epidemic and annual influenza seasons among people with vasculitis compared to the general population.*

Oral presentation at the Public Health England Public Health Research and Science Conference May 2021: *Mortality from COVID-19 Amongst People with Rare Autoimmune Rheumatic Disease in England. Results from the RECORDER Project.*

Oral presentation at the Royal Society of Medicine/UKIVAS: Vasculitis: Registries, pathways and therapeutics conference November 2020: *RECORDER results: Risk of death during the 2020 UK COVID-19 epidemic and annual influenza seasons among people with vasculitis.*

Oral presentation at the Royal Society of Medicine/UKIVAS – Vasculitis: From Cell to Service conference November 2021. *Using whole population data to describe COVID-19 outcomes in rare autoimmune rheumatic disease: The RECORDER project collaboration with National Congenital Anomaly and Rare Disease Registration Service (NCARDRS).*

### *A1.2.2 Local Presentations*

Oral presentation at the University of Nottingham Research Impact Forum 2022. Winner of third prize and students' choice prize.

Oral presentation at the University of Nottingham Sue Watson Presentation Event 2023. Winner of third prize.

*A1.2.3 Patient charity presentations*

Lupus UK Virtual Events. *Covid-19 in people with lupus.* October 2020

Lupus UK Virtual Events. *An update on Covid-19 in people with lupus.* November 2021

*A1.2.4 Podcasts*

Rheumatology podcast. Bukhari, M., Rutter, M. COVID-19 infection and related death amongst people with RAIRD. November 2021

Rheumatology podcast. Galloway, J., Rutter, M. Dr Megan Rutter on shielding patterns among patients with lupus. January 2021

**A1.3 Abstracts arising from this thesis**

Groves DJ, Rutter M, Lanyon PC, Odingo M, Grainge MJ, Bythell M, Aston J, Stevens S, Hannah JR, Mason J, Pearce FA. P300 Comparison of birth rates, gestational diabetes and non-standard maternal deliveries between Takayasu arteritis patients and the England and Wales population. Rheumatology. 2022 May;61(Supplement_1):keac133-299.

Godsave, C., Chakravorty, M., Rutter, M., Lanyon, P., Aston, J., Bythell, M., Stevens, S., Pearce, F. Identifying high-cost drugs for rare rheumatic diseases in routinely collected NHS data. Results from a pilot study of rituximab use in vasculitis using data from the National Congenital Anomaly and Rare Disease Registration Service and the Registration of Complex Rare Diseases - exemplars in Rheumatology (RECORDER) project. Presented as a poster at European League Against Rheumatism (EULAR) conference 2021.

Chakravorty, M., Pearce, F., Rutter, M., Lanyon, P., Aston, J., Bythell, M., Stevens, S. Can patient-level data for high cost drugs in Rheumatology be obtained using clinical coding? Results and national implications from a pilot study in Nottingham. Presented as a poster at the British Society of Rheumatology conference 2021.

Rutter, M., Lanyon, P.C., Peach, E., Grainge, M.J., Hubbard, R.B., Aston, J., Bythell, M., Stevens, S., Pearce, F.A. Risk of death during the 2020 UK COVID-19 epidemic among people with rare diseases compared to the general population. Presented as a poster at the British Society of Rheumatology conference 2021.

**A1.4 Prizes**

Midlands Rheumatology Society spring meeting 2022 - best poster prize

University of Nottingham Research Impact Forum 2022 - Students' Choice Prize

University of Nottingham Research Impact Forum 2022 - Third Prize

University of Nottingham Sue Watson Presentation Event 2023 – Third Prize

**A1.5 Grants awarded**

**Versus Arthritis** Clinical Research Fellowship
(Co-applicants Prof R Hubbard/Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£154,695.00
01/08/2021 – 31/07/2023

**Lupus UK Grant** to Dr M Rutter
(Co-applicants Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£16,428.40

**Scleroderma and Raynauds UK** to Dr M Rutter
(Co-applicants Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£16,428.40

**British Society of Rheumatology** Grant to Dr M Rutter
(Co-applicants Prof R Hubbard/Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£32,857
01/02/2021 - 31/07/2021

**Vasculitis UK** Grant to Dr M Rutter (grant reference CV01)
(Co-applicants Prof R Hubbard/Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£32,856.71
01/08/2020 - 31/01/2020

**Vasculitis UK** Grant to Dr M Rutter (grant reference V2009)
(Co-applicants Prof R Hubbard/Dr F Pearce/Dr P Lanyon/Dr M Grainge)
£49,766

# Appendix 2: ICD-10 and OPCS Codes

| ICD-10 code | Description | Rare Autoimmune Rheumatic Disease |
|---|---|---|
| I77.6 | Arteritis, unspecified | Arteritis, unspecified |
| M35.2 | Behçet disease | Behcet's disease |
| M33.1 | Other dermatomyositis | Dermatomyositis |
| M33.9 | Dermatopolymyositis, unspecified | Dermatomyositis |
| M30.1 | Polyarteritis with lung involvement [Churg-Strauss] | Eosinophilic granulomatosis with polyangiitis |
| M31.5 | Giant cell arteritis with polymyalgia rheumatica | Giant cell arteritis |
| M31.6 | Other giant cell arteritis | Giant cell arteritis |
| M31.3 | Wegener granulomatosis | Granulomatosis with polyangiitis |
| M08.0 | Juvenile rheumatoid arthritis | Juvenile inflammatory arthritis |
| M08.2 | Juvenile arthritis with systemic onset | Juvenile inflammatory arthritis |
| M08.3 | Juvenile polyarthritis (seronegative) | Juvenile inflammatory arthritis |
| M08.4 | Pauciarticular juvenile arthritis | Juvenile inflammatory arthritis |
| M08.9 | Juvenile arthritis, unspecified | Juvenile inflammatory arthritis |
| M33.0 | Juvenile dermatomyositis | Juvenile myositis |
| M31.7 | Microscopic polyangiitis | Microscopic polyangiitis |
| M30.0 | Polyarteritis nodosa | Polyarteritis nodosa |
| M30.8 | Other conditions related to polyarteritis nodosa | Polyarteritis nodosa |
| G72.4 | Inflammatory myopathy, not elsewhere classified | Polymyositis |
| M33.2 | Polymyositis | Polymyositis |
| M60.8 | Other myositis | Polymyositis |
| M60.9 | Myositis, unspecified | Polymyositis |
| M34.0 | Progressive systemic sclerosis | Scleroderma |
| M34.1 | CR(E)ST syndrome | Scleroderma |
| M34.8 | Other forms of systemic sclerosis | Scleroderma |
| M34.9 | Systemic sclerosis, unspecified | Scleroderma |
| M32.1 | Systemic lupus erythematosus with organ or system involvement | Systemic lupus erythematosus |
| M32.8 | Other forms of systemic lupus erythematosus | Systemic lupus erythematosus |
| M32.9 | Systemic lupus erythematosus, unspecified | Systemic lupus erythematosus |
| M31.4 | Aortic arch syndrome [Takayasu] | Takayasu arteritis |

| | | |
|---|---|---|
| U07.1 | COVID-19, virus identified | COVID-19 |
| U07.2 | COVID-19, virus not identified | COVID-19 |
| U07.3 | Personal history of COVID-19 | COVID-19 |
| U07.4 | Post-COVID-19 condition | COVID-19 |
| U07.5 | Multisystem inflammatory syndrome associated with COVID-19 | COVID-19 |

| **OPCS code** | **Description** | **Contains** |
|---|---|---|
| X92.1 | Cytokine inhibitor drugs Band 1 | Biologic drug treatments including rituximab |

# Appendix 3: Published papers arising from this thesis

RHEUMATOLOGY

Rheumatology 2022;61:3161–3171
https://doi.org/10.1093/rheumatology/keab794
Advance Access publication 26 October 2021

Original article

## COVID-19 infection, admission and death among people with rare autoimmune rheumatic disease in England: results from the RECORDER project

**Megan Rutter [1,2], Peter C. Lanyon[1,2,3,4], Matthew J. Grainge [1], Richard Hubbard[1,4], Emily Peach[1], Mary Bythell[3], Peter Stilwell[3], Jeanette Aston[3], Sarah Stevens[3] and Fiona A. Pearce [1,2,3,4]**

### Abstract

**Objectives.** To calculate the rates of COVID-19 infection and COVID-19-related death among people with rare autoimmune rheumatic diseases (RAIRD) during the first wave of the COVID-19 pandemic in England compared with the general population.

**Methods.** We used Hospital Episode Statistics to identify all people alive on 1 March 2020 with ICD-10 codes for RAIRD from the whole population of England. We used linked national health records (demographic, death certificate, admissions and PCR testing data) to calculate rates of COVID-19 infection and death up to 31 July 2020. Our primary definition of COVID-19-related death was mention of COVID-19 on the death certificate. General population data from Public Health England and the Office for National Statistics were used for comparison. We also describe COVID-19-related hospital admissions and all-cause deaths.

**Results.** We identified a cohort of 168 680 people with RAIRD, of whom 1874 (1.11%) had a positive COVID-19 PCR test. The age-standardized infection rate was 1.54 (95% CI: 1.50, 1.59) times higher than in the general population. A total of 713 (0.42%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardized mortality rate for COVID-19-related death was 2.41 (2.30–2.53) times higher than in the general population. There was no evidence of an increase in deaths from other causes in the RAIRD population.

**Conclusions.** During the first wave of COVID-19 in England, people with RAIRD had a 54% increased risk of COVID-19 infection and more than twice the risk of COVID-19-related death compared with the general population. These increases were seen despite shielding policies.

**Key words:** COVID-19, coronavirus, mortality, rare autoimmune rheumatic diseases, epidemiology, shielding, infection

**Rheumatology key messages**

- People with rare autoimmune rheumatic diseases were at increased risk of COVID-19 infection during the first wave.
- Compared to the general population, they had over twice the risk of COVID-19-related death.
- These increased risks were seen despite shielding policies in place in England.

### Introduction

Our previous work has shown that people with rare autoimmune rheumatic diseases (RAIRD) were at increased risk of all-cause mortality during the first wave of the COVID-19 pandemic (March–April 2020), when compared with the general population in England [1]. However, this study did not examine whether the increased mortality was due to COVID-19 infection itself, or due to indirect effects of the pandemic.

This study uses linked national health records for the whole population of England to calculate the rates of laboratory confirmed COVID-19 infection and COVID-19-related death among people with RAIRD from 1 March to 31 July 2020, the first wave of the COVID-19 pandemic, and compares these rates to that in the general population. We describe COVID-19-related hospital and and intensive care unit (ICU) admission, underlying

[1]Department of Population and Lifespan Sciences, School of Medicine, University of Nottingham, [2]Department of Rheumatology, Nottingham University Hospitals NHS Trust, Nottingham, [3]National Congenital Anomaly and Rare Disease Registration Service, National Disease Registration Service, Public Health England, London and [4]National Institute for Health Research (NIHR), Nottingham Biomedical Research Centre, Nottingham, UK

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Correspondence to: Megan Rutter, Clinical Sciences Building, City Hospital Campus, University of Nottingham, Nottingham NG5 1PB, UK. E-mail: megan.rutter@nottingham.ac.uk





CLINICAL SCIENCE

causes of death by category and COVID-19-related mortality stratified by RAIRD diagnosis.

## Methods

### Background

The Registration of Complex Rare Diseases Exemplars in Rheumatology (RECORDER) project is a collaboration between the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS). NCARDRS, based within Public Health England (PHE), registers people with rare conditions in order to support high quality clinical practice and research, provide epidemiology data and empower patients [2]. It has unique access to linked national datasets of electronic health records at patient-identifiable level for the whole population of England.

This study uses Hospital Episode Statistics (HES, which contains every episode of admitted patient care in NHS hospitals in England), COVID-19 polymerase chain reaction (PCR) test results and Office for National Statistics (ONS) death certificate data.

### Data validation

Our previous work validating HES ICD-10 codes for RAIRD has shown high accuracy, with a positive predictive value of 84.7% [1]. Prevalence estimates based on our findings for ANCA-associated vasculitis, SLE and scleroderma are similar to reported population estimates [3–5].

### Study cohort

People with a diagnostic code for RAIRD in HES from 2003 onwards, resident in England, and alive on 1 March 2020 were included in the study, using the same cohort as our preliminary all-cause mortality study [1]. A data flow diagram is shown in Supplementary Fig. S1, available at *Rheumatology* online. Vital status data from the NHS Personal Demographics Service were used to confirm whether people were alive, or to confirm date of death [6].

### RAIRD diagnoses

Participants were grouped by RAIRD diagnosis, based on their most recent diagnostic code. Where the most recent code was non-specific, for example 'Renal tubulo-interstitial disorder in systemic connective tissue disorder', earlier, more specific diagnostic codes were used where available, following the algorithm in Supplementary Data S1, available at *Rheumatology* online.

### Death certificate data

Death certificate and underlying cause of death data (free text and ICD-10 coded) provided by the ONS were utilized. Using internationally agreed rules, ONS assigns underlying cause of death, usually based on the lowest completed line of Part 1 of a death certificate [7]. Our data were examined for ICD-10 codes specific to COVID-19 (U07.1, U07.2). The free text was manually checked for keywords ('*cov*', '*virus*' or '*19*') which confirmed that no deaths related to COVID-19 (including misspellings) had been omitted. While COVID-19-specific ICD-10 codes were not introduced until 25 March 2020 [8], all deaths with a free text mention of COVID-19 occurring before that date had been captured retrospectively by the ONS coding system. We classified underlying all-cause death by category.

### COVID-19 status

A population-level dataset of COVID-19 PCR test results, held in the Second Generation Surveillance System in PHE, was used. Positive tests among the RAIRD cohort were extracted, along with the date the laboratory reported the result. Demographics are described by pillar 1 (in-hospital) or pillar 2 (community) testing.

### Hospital and intensive care unit admissions

HES admitted patient care (APC) data on hospital and ICU admissions with an ICD-10 diagnostic code for COVID-19 were extracted. Duration and number of admissions, and basic and advanced respiratory support days on ICU are described.

### Mortality rate calculation

We report two measures of COVID-19-related deaths. Our primary definition is death with any mention of COVID-19 on the death certificate as used by the ONS [9]. This was chosen due to the limited availability of COVID-19 PCR testing in the community during the first wave. Our secondary definition is death within 28 days of a positive COVID-19 PCR test, as used by PHE [10].

The crude all-cause mortality rate from 1 March to 31 July 2020 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population, along with the crude mortality rates for the two measures of COVID-19-related death.

Age-sex-standardized mortality rates per 100 000 in the population were calculated, standardized to the 2019 mid-year estimate for the England population using 5-year age bands. Age-standardized mortality rates (ASMRs) standardized to the 2013 European Standard Population (ESP) were also calculated. As the ESP is not disaggregated by sex and assumes equal numbers of males and females, and identical age distributions within sexes, this population was not used to calculate age-sex standardized rates.

The ONS provided data for all-cause deaths, and deaths with any mention of COVID-19 on the death certificate, over the same time period in England, split by sex and age band [11, 12]. PHE provided comparable data for deaths within 28 days of a positive COVID-19

test (available to the public on request). These data were used to calculate the crude, age-standardized and age-specific mortality rates as a comparator. Publicly available data from the government Coronavirus dashboard [13] were used to compare infection rates in the general population. The 2019 mid-year estimate for the population of England was used as the denominator.

### COVID-19 infection rate calculation

Laboratory confirmed COVID-19 infection rate from 1 March to 31 July 2020 was calculated, with the cohort of patients identified as having RAIRD used as the denominator population. Infection rate was age-standardized to the mid-year 2019 England population.

### Stratification by disease

Poisson regression methods were used to analyse rates of COVID-19-related death, adjusted for age, sex and RAIRD diagnosis. Incidence rate ratios for each diagnosis, with 95% CIs, were displayed as a forest plot.

### Ethics

This study was approved by the Camden and Kings Cross Research Ethics Committee, study reference 20/HRA/2076, on 18 June 2020.

The legal basis to access the data is predominantly covered by NCARDRS' Section 251 approval (Reference CAG 10–02(d)/2015). Where the work extends beyond Section 251 approval, it has been approved under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (COPI), allowing the processing of confidential patient information for the purposes of protecting public health and managing the COVID-19 outbreak.

For quality assurance, the data extraction and analysis were re-conducted by an independent analyst from the National Disease Registration Service.

### Patient and public involvement

This work has been developed with input from people with RAIRD. Following our findings of increased mortality in this population [1], we consulted with patients and patient charities to confirm priorities for future research and inform the communication and dissemination of our results. This will continue as an iterative process as results become available. A plain English summary of this study is available in the Supplementary Material, available at *Rheumatology* online.

### Data analysis

Cleaning, linkage and analysis of the data was performed in R version 3.6.3 (packages *tidyverse [14], janitor [15], survival [16], mfx [17], survminer [18], meta [19]*).

## Results

### Demographic data

A total of 168 691 people were included in the RAIRD cohort in our all-cause mortality study [1]. Updates to personal demographic data revealed that 11 people had died prior to 1 March 2020, leaving 168 680 people included in this study. Descriptive demographic data, including RAIRD diagnoses, are shown in Table 1. The median age of the population was 61.7 years (IQR 41.5–75.4) and 118 374 (70.2%) were female.

### COVID-19 infection

Between 1 March and 31 July 2020, 1874 (1.11%) of the RAIRD population had a positive COVID-19 PCR test, compared with 261 348 (0.46%) of the general population. Age-standardized to the England population, the infection rate per 100 000 person-years was 1720.3 (1670.0–1770.6), compared with 1114.3 (1111.5–1117.0) per 100 000 person-years in the general population [rate ratio 1.54 (1.50–1.59), Table 2].

Characteristics of those with a positive COVID-19 PCR test are shown in Table 2. People with RAIRD with a positive PCR test were more likely to have had a pillar 1 test (86.87% of positive tests) than people with a positive PCR test in the general population (62.31% of positive tests).

### All-cause mortality

Between 1 March and 31 July, 3401 (2.02%) people in the RAIRD cohort died of any cause, compared with 257 547 out of 56 286 961 (0.46%) among the general population.

### COVID-19 related mortality

Of the 3401 people who died, death certificate data were available for 3332 (97.97%). In total, 713 (0.42% RAIRD cohort) had COVID-19 mentioned on their death certificate, in any position. This compares to 49 166 (0.09%) of all those who died in the general population.

Of those with a positive COVID-19 PCR test, 574/1874 (30.6%) died within 28 days of a positive test, compared with 36 658/261 348 (14.03%) of the general population. However, the RAIRD cohort were older than the general population of England.

The combined total of people with RAIRD dying with either COVID-19 mentioned on their death certificate, or within 28 days of a positive COVID-19 test, is reported in Supplementary Data S1, available at *Rheumatology* online.

### Age- and age-sex-standardized mortality rates

The age-sex-standardized mortality rate for all-cause death in RAIRD, standardized to the 2019 mid-year population of England, was 2325.2 (2274.8–2375.7), compared with 1098.1 (95% CI: 1095.4, 1100.9) in the general population [rate ratio 2.12 (2.07–2.16)]. For

**Table 1** Characteristics of the cohort of people with RAIRD alive 1 March 2020 ($n = 168\,680$)

| Characteristic | Value |
|---|---|
| Sex* | |
| Female | 118 374 (70.2%) |
| Male | 50 305 (29.8%) |
| Median age (IQR) | |
| Total cohort | 61.7 (41.5–75.4; 33.9) |
| Female | 61.8 (43.0–75.7; 32.6) |
| Male | 61.3 (36.6–74.9; 38.3) |
| Most recent diagnosis (*n*, %) | |
| SLE | 41 261 (24.5%) |
| GCA | 38 014 (22.5%) |
| Juvenile inflammatory arthritis | 21 202 (12.6%) |
| Arteritis, unspecified | 17 632 (10.5%) |
| Polymyositis | 17 447 (10.3%) |
| Scleroderma | 11 578 (6.9%) |
| Granulomatosis with polyangiitis | 6164 (3.7%) |
| Behcet's disease | 4880 (2.9%) |
| DM | 2594 (1.5%) |
| Eosinophilic granulomatosis with polyangiitis | 2351 (1.4%) |
| Polyarteritis nodosa | 1597 (0.9%) |
| Microscopic polyangiitis | 1339 (0.8%) |
| Connective tissue disorder with specific organ involvement | 1218 (0.7%) |
| Takayasu arteritis | 905 (0.5%) |
| Juvenile myositis | 498 (0.3%) |

ICD-10 codes used: SLE = M321, M328, M329; GCA = M315, M316; juvenile inflammatory arthritis = M080, M082, M083, M084, M089; arteritis, unspecified = I776; polymyositis = G724, M332, M608, M609; scleroderma = M340, M341, M348, M349; granulomatosis with polyangiitis = M313; Behcet's disease = M352; DM = M331, M339; eosinophilic granulomatosis with polyangiitis = M301; polyarteritis nodosa = M300, M308; microscopic polyangiitis = M317; connective tissue disorder with specific organ involvement = J991, N085, N164; Takayasu arteritis = M314; juvenile myositis = M330. *One person did not have sex recorded.

**Table 2** PCR-proven COVID-19 infections in the RAIRD population compared with the whole population of England

| | RAIRD ($n = 168\,680$) | England ($n = 56\,286\,961$) | Rate ratio |
|---|---|---|---|
| Infection rate (*n*, %) | 1874 (1.11%) | 261 348 (0.46%) | |
| Death certificate mention of COVID (*n*, %) | 713 (0.42%) | 56 196 (0.10%) | |
| Death within 28 days of COVID test (*n*, %) | 574 (0.34%) | 36 658 (0.07%) | |
| Age-standardized COVID-19 infection rate (per 100 000 person-years) | 1720.3 (1670.0–1770.6) | 1114.3 (1111.5–1117.0) | 1.54 (1.50–1.59) |
| Positive COVID-19 PCR tests by pillar [*n* (% total tests)] | RAIRD ($n = 168\,680$) | England ($n = 56\,286\,961$) | |
| Pillar 1 | 1628 (86.87%) | 164 600 (62.31%) | |
| Pillar 2 | 246 (13.13%) | 99 583 (37.69%) | |
| Age of those in RAIRD cohort with a positive PCR test | | | |
| | Mean age | Median age | Interquartile range |
| Pillar 1 | 71.14 | 75.10 | 60.89–84.14 (23.25) |
| Pillar 2 | 62.42 | 65.31 | 42.19–84.72 (42.53) |
| Deaths in RAIRD cohort within 28 days of a positive PCR test, by pillar [*n* (% deaths)] | | | |
| Pillar 1 | 560 (97.6%) | | |
| Pillar 2 | 14 (2.4%) | | |
| Age of RAIRD cohort who died within 28 days of a positive PCR test | | | |
| Pillar 1 | 77.03 | 79.21 | 71.26–85.94 (14.68) |
| Pillar 2 | 88.13 | 89.47 | 84.84–92.55 (7.71) |

Note: Pillar 1 denotes in-hospital testing and Pillar 2 denotes community testing.

deaths mentioning COVID-19 on the death certificate, the age-sex-standardized mortality rate was 505.5 (481.5–529.4), compared with 209.6 (208.4–210.8) in the general population [rate ratio 2.41 (2.30–2.53)]. For deaths within 28 days of a positive COVID-19 PCR test, the age-sex-standardized mortality rate in RAIRD was 422.0 (399.7–444.3), compared with 156.3 (155.3–157.3) in the general population [rate ratio 2.70 (2.56–2.84)]. These data are summarized in Table 3. The ASMR for all-cause death in RAIRD, adjusted to the 2013 European Standard Population is available in Supplementary Table S1, available at *Rheumatology* online.

### COVID-19 related deaths over time

All-cause deaths in 2019 and 2020, deaths with any mention of COVID-19 on the death certificate and deaths within 28 days of a positive COVID-19 PCR test were plotted over time and are shown in Supplementary Fig. S2, available at *Rheumatology* online.

### Admissions

Demographic data for those who were admitted to hospital and/or to ICU with a diagnostic code for COVID-19 are shown in Table 4. The median age of those with a hospital admission was 75.07 years (IQR 62.13–83.64), and for an ICU admission 60.65 years (IQR 48.71–69.79).

For hospital admissions, the median length of stay was 8 days (mean 13.8, range 0–269) and the median number of admissions was 2 (mean 2.3, range 1–20).

For ICU admissions, the median length of stay was 6 days (mean 12.1, range 0–101) and the median number of admissions was 1 (mean 1.2, range 1–3). The median number of basic respiratory support days while on ICU was 2 (mean 3.6, range 0–30) and the median number of advanced respiratory support days was 1 (mean 7.9, range 0–93) (Table 4).

### All-cause death by category

Where death certificate data were available, underlying cause of death by category was extracted and are shown in Supplementary Table S2, available at *Rheumatology* online. Deaths due to cardiovascular disease were recorded in 703 (21.1%), COVID-19 652 (19.6%), malignancy 581 (17.4%), respiratory 404 (12.1%), dementia 280 (8.4%), underlying RAIRD 113 (3.4%) and non-COVID-19 infection 19 (0.6%), with the remaining 580 (17.4%) ascribed to other causes.

For comparison, data were extracted on all-cause death in people with a diagnostic code for RAIRD occurring during March–July 2016–2020 and categorized by underlying cause (Fig. 1). There was no evidence of an increase in death from non-COVID-19-related causes during the pandemic.

### Age at death

There was no significant change in median age at death between 2016 and 2020 (median age ranged from 79.92–81.50), and this was similar to age at death related to COVID-19 (median 81.31, IQR 72.98–87.34; Supplementary Table S3, available at *Rheumatology* online).

Age at death in people with RAIRD was compared between 2020 and 2019, categorized by underlying cause of death (Supplementary Fig. S3, available at *Rheumatology* online). There was no evidence of earlier age of death occurring in 2020 in certain cause of death categories, e.g. in deaths from cardiovascular disease.

### Stratification by disease

Incidence rate ratios for COVID-19-related death stratified by RAIRD diagnosis are displayed in Fig. 2. The comparable ratios and overlapping CIs suggest a similar risk across the RAIRD cohort, regardless of diagnosis. People with GCA were at slightly reduced risk (RR 0.66, 95% CI: 0.60, 0.74), which may reflect that GCA is often a self-limiting disease not requiring lifelong immunosuppression. The wide CIs reflect the relatively small number of events in the first wave.

## Discussion

### Main findings

In the first wave of the COVID-19 pandemic, COVID-19-related death rates among people with RAIRD were more than twice that of the general population. This was contributed to by both higher COVID-19 infection rates, and higher mortality after COVID-19 infection.

The age-sex-standardized COVID-19 infection rate was 1.54 (1.50–1.59) times higher among people with RAIRD compared with the general population, despite shielding policies (protection of the clinically extremely vulnerable [20]) in place in England.

### Strengths

A major strength is that the denominator population is known, allowing us to describe for the first time both rates of COVID-19 infection and of COVID-19-related death. Previous mortality COVID-19 studies in RAIRD have either included a much smaller group of people, or relied on case series and physician-reported cases [21] and allowed only internal comparisons within cohorts of people with rheumatic diseases, and not comparison with the general population.

This work uses novel linkages of HES, COVID-19 PCR testing data and death certificate data for people with rare diseases, through collaboration with NCARDRS.

While our RAIRD cohort contains a heterogeneous group of diseases, our sub-analysis by disease show they have comparable risks of death due to COVID-19. Pooled analysis of these diseases increases statistical power to detect outcomes and is clinically justified by their common underlying disease mechanisms and treatments.

TABLE 3 Mortality rates for the RAIRD cohort compared with the general population of England

| | Number of deaths | Number of people | Person-years | Crude mortality rate per 100 000 person years | RAIRD age-sex-standardized mortality rate[a] | England age-sex-standardized mortality rate[a] | Risk ratio for mortality rates |
|---|---|---|---|---|---|---|---|
| All-cause mortality | | | | | | | |
| All | 3401 | 168 680 | 70 283 | 4839.0 (4734.0–4944.0) | 2325.2 (2274.8–2375.7) | 1098.1 (1095.4–1100.9) | 2.12 (2.07–2.16) |
| Female | 2179 | 118 374 | 49 323 | 4417.9 (4298.1–4537.6) | 2131.7 (2073.9–2189.4) | 1069.5 (1065.7–1073.3) | 1.99 (1.94–2.05) |
| Male | 1222 | 50 305 | 20 960 | 5830.0 (5619.0–6041.0) | 2518.8 (2427.7–2610.0) | 1127.5 (1123.5–1131.4) | 2.23 (2.15–2.31) |
| Death with any mention of COVID-19 on the death certificate | | | | | | | |
| All | 713 | 168 680 | 70 283 | 1014.4 (966.4–1062.6) | 505.5 (481.5–529.4) | 209.6 (208.4–210.8) | 2.41 (2.30–2.53) |
| Female | 427 | 118 374 | 49 323 | 865.7 (812.7–918.7) | 417.4 (391.9–443.0) | 186.2 (184.6–187.8) | 2.24 (2.10–2.38) |
| Male | 286 | 50 305 | 20 960 | 1164.5 (1262.4–1466.6) | 595.5 (551.0–640.1) | 233.6 (231.8–235.4) | 2.55 (2.39–2.74) |
| Death within 28 days of a positive COVID-19 test | | | | | | | |
| All | 574 | 168 680 | 70 283 | 816.7 (773.6–859.8) | 422.0 (399.7–444.3) | 156.3 (155.3–157.3) | 2.70 (2.56–2.84) |
| Female | 332 | 118 374 | 49 323 | 673.1 (626.3–719.9) | 327.2 (304.5–349.9) | 131.1 (129.8–132.5) | 2.50 (2.32–2.67) |
| Male | 242 | 50 305 | 20 960 | 1154.6 (1060.7–1248.5) | 519.0 (476.8–561.2) | 182.1 (180.5–183.6) | 2.85 (2.62–3.08) |

Deaths, crude mortality rates, age-sex-standardized mortality rates and sex-specific age-standardized mortality rates during March to July 2020 for the RAIRD cohort compared with the mid-year 2019 population of England. [a]Sex-specific rates are age-standardized only.

### Limitations

The measures of COVID-19 mortality described were selected to allow comparison with available statistics for the general population. Our primary definition, any mention of COVID-19 on the death certificate (used by the ONS), infers that COVID-19 infection contributed to death, even if it was not the main cause and even in the absence of a positive PCR test. This has the theoretical potential to over-estimate deaths due to COVID-19 infection but has been found to be the best measure to explain the excess deaths seen in the national data. In our RAIRD cohort, of the 713 people with a mention of COVID-19 on the death certificate, 661 (93%) had COVID-19 in part 1, meaning that it directly lead to death [22]. Conversely, we may have underestimated COVID-19-related deaths as death certificate data were unavailable for 2% of our cohort. This proportion is not unexpected and registration delays are common [23], although they may disproportionately reflect certain groups such as deaths in hospital, or due to occupational exposure to disease (including COVID-19 [24]).

Our secondary definition was death within 28 days of a positive COVID-19 PCR test, as used by PHE. This measure overlooks deaths where the person never has a positive PCR test, or where the death occurred >28 days after diagnosis: important given the prolonged clinical course of COVID-19. In our RAIRD cohort, the median time between a positive test and death was 6 days, and only 22 (4%) of those who had COVID-19 on their death certificate, and had a positive PCR test, had that test >28 days prior to death.

We identified our cohort from diagnoses in HES admitted patient care (APC) data and our methodology may not have identified patients with RAIRD who have never had an in-patient or daycase admission for any reason, and who have been treated entirely on an outpatient basis. Due to the nature of RAIRD, we believe this to be the minority of cases, which is supported by disease prevalence in our cohort being similar to previous studies [3, 5, 25]. However, the potential impact is to skew our cohort towards those with more severe disease.

This work describes outcomes in the first wave only. Further work is needed to describe the outcomes in the second wave, and assess the influence of immunosuppression, shielding policies and the vaccination programme.

This study does not include data on immunosuppressive medications. The vulnerability to COVID-19 of people living with RAIRD is likely explained in part by the frequent need for immunosuppression in this group. Corticosteroid usage has long been thought to increase the risk of infection [26–28] although in COVID-19, this has been complicated by the emergence of dexamethasone as an effective treatment [29]. Concerns remain that corticosteroid treatment preceding infection may predispose to more severe disease [30–32]. While IL-6 receptor antagonists have been shown to reduce mortality in severe COVID-19 requiring intensive care [33],

TABLE 4 Summary of hospital and intensive care unit (ICU) admissions, including demographics and characteristics of stay

| Demographics | | | | |
|---|---|---|---|---|
| | *n* | Mean age | Median age | IQR |
| Any admission with COVID code | 1672[a] | 71.43 | 75.07 | 62.13–83.64 (21.51) |
| Death certificate mention of COVID-19 | 546[b] | 76.68 | 79.04 | 71.15–85.66 (14.51) |
| Death within 28 days of test | 504 | 76.73 | 78.95 | 71.26–85.65 (14.39) |
| ICU admission with COVID code | 137 | 59.79 | 60.65 | 48.71–69.79 (21.08) |
| Death certificate mention of COVID-19 | 64 | 62.72 | 61.59 | 51.47–74.97 (23.51) |
| Death within 28 days of test | 59 | 64.30 | 65.51 | 53.83–75.91 (22.07) |
| COVID positive, not admitted, all | 595 | 65.30 | 70.72 | 48.83–84.71 (35.88) |
| Death from all causes | 81 | 81.91 | 84.88 | 76.05–90.15 (14.10) |
| Death certificate mention of COVID-19 | 64 | 81.92 | 84.86 | 77.81–89.69 (11.89) |
| Death within 28 days of test | 70[c] | 81.46 | 84.82 | 74.70–89.84 (15.14) |
| Mention of COVID-19 on death certificate, without admission or positive PCR | 103 | 82.53 | 84.78 | 77.44–89.40 (11.96) |
| All hospital admissions[d] ($n = 1672$) | | | | |
| | Median | Mean | Range | |
| Duration of admission (days) | 8.0 | 13.8 | 0–269 | |
| Number of admissions per individual | 2.0 | 2.3 | 1–20 | |
| ICU admissions[d] ($n = 137$) | | | | |
| | Median | Mean | Range | |
| Basic respiratory support days | 2.0 | 3.6 | 0–30 | |
| Advanced respiratory support days | 1.0 | 7.9 | 0–93 | |
| Duration of admission (days) | 6.0 | 12.1 | 0–101 | |
| Number of ICU admissions per individual | 1.0 | 1.2 | 1–3 | |

[a]Of whom 1279/1672 had a positive COVID-19 PCR test. [b]Of whom 502/546 had a positive COVID-19 PCR test. [c]Of whom 61/70 had mention of COVID-19 on their death certificate. [d]Where an individual had more than one admission, totals are summed.

other immunosuppressants, such as rituximab, may impair the antiviral immune response and antibody production, with potentially more severe clinical outcomes [31, 34]. This may also impact vaccine effectiveness and recently published data has demonstrated attenuated antibody responses in people with AAV on rituximab [35].

### Comparison to the published literature

The small numbers of people affected by each RAIRD makes it difficult for studies to have enough statistical power to assess outcomes. Most research has therefore included more common rheumatic diseases such as RA.

The COVID-19 Global Rheumatology Alliance describes COVID-19-related mortality in RAIRD and reports an association between immunosuppressive medications and mortality [31]. However, this relied on physician-reported cases and could not report rates of COVID-19 infection or deaths. A study looking at the French RMD COVID-19 cohort, a mixture of physician-reported RA and RAIRD patients, found an increased risk of severe COVID-19 in those treated with rituximab [36]. There was no increase in mortality in the rituximab group once other risk factors were adjusted for. Data from the same cohort also demonstrated an association between severe infection and treatment with corticosteroids or MMF [37].

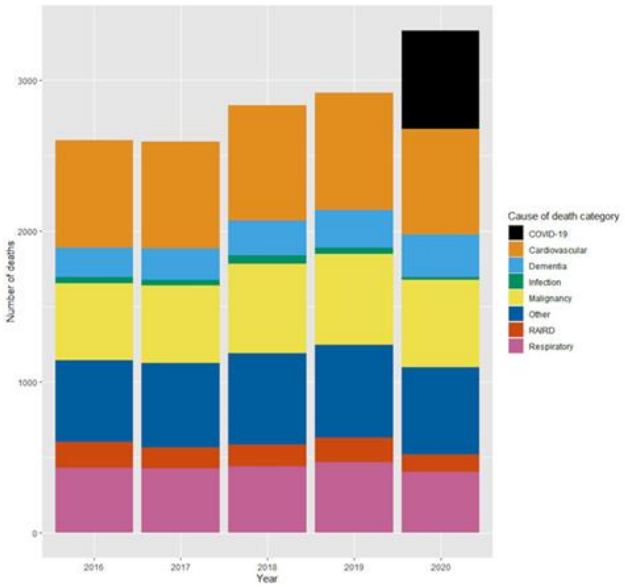
A multicentre prospective cohort study from Brazil, with a mixed study population of inflammatory arthritis and RAIRD, showed an increased risk of ICU admission and mortality associated with corticosteroids and CYC [38].

OpenSAFELY and QCOVID, both of which looked at risk factors for severe COVID-19 outcomes in England, studied smaller populations. At the time of the last published analysis, OpenSAFELY included 24 million patients [39] and QCOVID 8.26 million [21]. Our research uses the whole England population of 56 million, which has afforded us the statistical power to calculate more precise results. The use of whole population data, with a known denominator population, also allows calculation of rates and comparison to the general population.

In addition, of the RAIRD, only SLE was included in the QCOVID and OpenSAFELY studies, in both cases combined with RA. Both found a modest increase in the risk of death [HR 1.32 (1.06–1.65) and 1.20 (1.12–1.28), respectively [39, 40]].

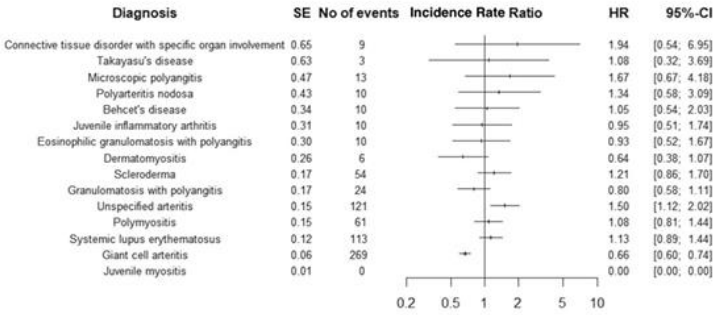
Whole population data from Denmark [41] on COVID-19 hospital admissions, including 10 749 people with

FIG. 1 All cause death by category in people with RAIRD during March–July 2016–2020




Categories align to major ICD-10 code chapters, with the addition of diagnoses pertinent to the cohort (RAIRD, dementia).

FIG. 2 Forest plot showing incidence rate ratios with 95% CIs for COVID-19-related death, stratified by RAIRD diagnosis




RAIRD, supports our findings of increased risk in connective tissue disease and vasculitis [age-sex adjusted HR 1.63 (0.78–3.43) and 2.03 (1.02–4.08), respectively]. The wide CIs reflect the small number of events, as well as their smaller population of 4.54 million. They do not report on COVID-19 infection rates, nor on mortality in RAIRD specifically.

Whole population data from South Korea [42], including 1896 people with RAIRD, also found an increased risk of COVID-19 infection and hospitalization [HR 1.33 (1.02–1.74) and 1.71 (1.06–2.71), respectively]. There was also a suggestion of increased COVID-19 mortality but the small number of events (seven deaths) gave wide CIs, which were not statistically significant [HR 1.87 (0.71–4.85)].

### Infection rate

There was an increased age-standardized infection rate in the RAIRD cohort, despite the intent of shielding policy to reduce infection exposure. There are several potential reasons for this. They may be more susceptible to symptomatic COVID-19 infection due to their underlying disease and immunosuppression. During the first wave, where testing was predominantly in hospital, their increased contact with healthcare services may have led to increased testing and ascertainment bias. People with RAIRD may have a worse state of health than the general population, leading to increased hospital admissions, necessitating COVID-19 admission screening tests and the risk of nosocomial infection. Requirements for hospital attendances may also have increased the risk of acquiring infection.

### Clinical and policy implications and future research

Our findings provide clear evidence that during the first wave of the pandemic people with RAIRD were both at higher risk of COVID-19 infection and of COVID-19-related death than people of the same age and sex in the general population. These findings have important implications for people living with RAIRD, their clinicians and for public health policy.

They confirm at whole population-level that the assumptions at the start of the pandemic, that many people with RAIRD would be clinically extremely vulnerable to the effect of COVID-19 [43], were correct. Many people with RAIRD require lifelong immunosuppression, conferring ongoing risk. Protecting the health of people with RAIRD needs specific public health prioritization, to reduce both their risk of acquiring COVID-19 infection and mortality.

Within the UK, certain people were classified as 'clinically extremely vulnerable' to COVID-19 infection and asked to 'shield' [20]. While a RAIRD diagnosis alone did not lead to inclusion on the Shielded Patient List (SPL), risk stratification guidance advised that many patients on immunosuppressive therapies, including moderate- to high-dose corticosteroids, and/or with relevant co-morbidities, should shield [44]. Given the nature of RAIRD, this included many people living with these conditions [45, 46]. Our findings suggest that despite this, COVID-19 infection and mortality rates were greater for people with RAIRD than for the general population. This is observational data, and the shielding status of this cohort is not yet known, so it is not possible to determine what the outcomes would have been without shielding policies in place. In addition, shielding policies were instituted on 23 March 2020 and some of our findings may reflect earlier transmission. Further research in this cohort during later waves of the pandemic, including assessment of the impact of shielding, is ongoing.

We did not find an excess of non-COVID-19-related deaths during this period. This may reflect efforts to prioritize access to urgent care. However, any detrimental effect of the pandemic may have a delayed impact on mortality.

Our results highlight the urgent need for analysis of the real-world effectiveness of vaccination among people with RAIRD, given the evidence that they may respond less well to vaccination [35, 47]. This will have crucial implications for their ongoing health protection needs, including deciding the optimal vaccination schedule to maximize protection.

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At the time of her contribution to this study, E.P. was employed by the University of Nottingham. She has gone on to work for Astra Zeneca, who had no influence on the design, conduct or interpretation of this study.

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## Data availability statement

Due to legal and ethical considerations, supporting data cannot be made openly available. However, NCARDRS data are available to all who have a legal basis to access them. Further details about the data and conditions for access are available by application to the National Disease Registration Service (https://www.gov.uk/guidance/the-national-congenital-anomaly-and-rare-disease-registration-service-ncardrs). Information on how to access this data can also be

obtained from the University of Nottingham data repository: DOI: 10.17639/nott.7131.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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JOURNAL ARTICLE ACCEPTED MANUSCRIPT

# COVID-19 infection, admission and death and the impact of corticosteroids amongst people with rare autoimmune rheumatic disease during the second wave of covid-19 in England: results from the RECORDER Project

Megan Rutter ✉, Peter C Lanyon, Matthew J Grainge, Richard Hubbard, Mary Bythell, Peter Stilwell, Jeanette Aston, Sean McPhail, Sarah Stevens, Fiona A Pearce

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## Abstract

### Objectives

To calculate the rates of COVID-19 infection and COVID-19-related death among people with rare autoimmune rheumatic diseases (RAIRD) during the second wave of the COVID-19 pandemic in England, and describe the impact of corticosteroids on outcomes.

### Methods

Hospital Episode Statistics data were used to identify people alive 01 August 2020 with ICD-10 codes for RAIRD from the whole population of England. Linked national health records were used to calculate rates and rate ratios of COVID-19 infection and death up to 30 April 2021. Primary definition of COVID-19-related death was mention of COVID-19 on the death certificate. NHS Digital and Office for National Statistics general population data were used for comparison. The association between 30-day corticosteroid usage and COVID-19-related death, COVID-19-related hospital admissions and all-cause deaths were also described.

### Results

Of 168 330 people with RAIRD, 9,961 (5.92%) had a positive COVID-19 PCR test. The age-standardised infection rate ratio between RAIRD and the general population was 0.99 (95% CI 0.97–1.00). 1,342 (0.80%) people with RAIRD died with COVID-19 on their death certificate and the age-sex-standardised mortality rate for COVID-19-related death was 2.76 (2.63–2.89) times higher than in the general population. There was a dose-dependent relationship between 30-day corticosteroid usage and COVID-19-related death. There was no increase in deaths due to other causes.

### Conclusions

During the second wave of COVID-19 in England, people with RAIRD had the same risk of COVID-19 infection but a 2.76-fold increased risk of COVID-19-related death compared with the general population, with corticosteroids associated with increased risk.

**Keywords:** COVID-19, coronavirus, mortality, rare autoimmune rheumatic diseases, epidemiology, shielding, infection

**Issue Section:** Original Article

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# Appendix 4: Ethical Approval

Health Research Authority
**London - Camden & Kings Cross Research Ethics Committee**
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

18 June 2020

Dr Fiona Pearce
Clinical Sciences Building
City Hospital
Nottingham
NG5 1PB

Dear Dr Pearce,

| | |
|---|---|
| **Study title:** | **Studying the risks of COVID-19 to people with rare autoimmune rheumatic disease, and assessing potential health inequalities resulting from disruption to healthcare during COVID-19.** |
| **REC reference:** | **20/HRA/2076** |
| **IRAS project ID:** | **282765** |

The Research Ethics Committee reviewed the above application at the meeting held on 15 June 2020. Thank you for attending to discuss the application.

**Ethical opinion**

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

**Conditions of the favourable opinion**

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

**Membership of the Committee**

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Learning**

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

| **IRAS project ID: 282765** | **Please quote this number on all correspondence** |
|---|---|

With the Committee's best wishes for the success of this project.

Yours sincerely,

**Katie Arnold**
**Approvals Officer**
**P.P**
**Mrs Rosie Glazebrook**
**Chair**

E-mail: CamdenandKingsCross.REC@hra.nhs.uk

| | |
|---|---|
| Enclosures: | List of names and professions of members who were present at the meeting and those who submitted written comments |
| | "After ethical review – guidance for researchers" [SL-AR2 for other studies] |
| Copy to: | Dr Emily Peach, University of Nottingham |
| | Lead Nation England: approvals@hra.nhs.uk |

Department of Health and Social Care
39 Victoria Street
London SW1H 0EU

Department of Health & Social Care

Sarah Wilkinson
Chief Executive
NHS Digital
1 Trevelyan Square
Boar Lane
Leeds
LS1 6AE

17 March 2020

Dear Sarah,

**Covid-19 – Notice under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002**

The health and social care system is taking action to manage and mitigate the spread and impact of the current outbreak of Covid-19. Action to be taken will require the sharing of confidential patient information amongst health organisations and other appropriate bodies for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the outbreak.

I am therefore writing to you to serve notice on the Health and Social Care Information Centre, known as NHS Digital, under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002 (**COPI**) to require NHS Digital to process confidential patient information in the manner set out below for purposes set out in Regulation 3(1) of COPI (insofar as those purposes relate to the current outbreak of Covid-19).

1. **Purpose of this Notice**

   The purpose of this Notice is to provide NHS Digital with the necessary statutory power to disseminate confidential patient information to organisations permitted to process confidential patient information under Regulation 3(3) of COPI for the purposes set out in Regulation 3(1) of COPI to support the Secretary of State's response to Covid-19 (**Covid-19 Purpose**).

I consider this Notice is necessary so that NHS Digital can lawfully and efficiently disseminate confidential patient information to those organisations set out in Regulation 3(3) of COPI being persons employed or engaged for the purposes of the health service or other persons employed or engaged by a Government Department or other public authority in communicable disease surveillance in connection with the health and social care system's management of the response to Covid-19.

**2. Requirement to Disseminate Confidential Patient Information**

2.1. I hereby provide NHS Digital with notice under Regulation 3(4) that, for the purposes set out above, I require NHS Digital to disseminate confidential patient information in respect of which it is a controller[1], including that which it has obtained by complying with a direction made under section 254 or a request made under section 255 of the Health and Social Care Act 2012 (**2012 Act**), to a person or organisation permitted to process confidential information under Regulation 3(3) of COPI.

2.2. NHS Digital is only required to disseminate such confidential patient information where it is:

2.2.1. requested to do so by an authorised officer of the Department of Health and Social Care acting on my behalf or requested to do so by another organisation permitted to process confidential information under Regulation 3(3) of COPI (the **Requestor),** and

2.2.2. reasonably satisfied that the confidential patient information to be disclosed pursuant to the request is required by the Requestor for a Covid-19 Purpose and will be processed by the Requestor or by a processor[2] on behalf of the Requestor, solely for that Covid-19 Purpose and in accordance with the restrictions set out in Regulation 7 of COPI; and

2.2.3. from the date of this notice for the period up to 30 September 2020.

**3. Notification to Requesters**

NHS Digital is requested when sharing confidential patient information under this Notice:

3.1. to remind recipients of confidential patient information of their responsibilities under COPI when processing the confidential patient information, including

[1] As defined in Article 4(7) of the General Data Protection Regulation 2016
[2] As defined in Article 4(8) of the General Data Protection Regulation 2016

the restrictions which apply to their processing of it under Regulation 7 of COPI; and

3.2. to publish details of the organisations with whom it has shared confidential patient information under this Notice and the purposes for which it was shared in the NHS Digital Data Release Register[3].

**4. Review and Expiry of this Notice**

This Notice will be reviewed on or before 30 September 2020 and may be extended by me by further notice in writing for the period specified in that notice. If no further notice is sent to you by me, this Notice will expire on 30 September 2020.

I am grateful for your continued support at this critical time for the nation.

Yours sincerely

On behalf of
Secretary of State for Health and Social Care

[3] https://digital.nhs.uk/services/data-access-request-service-dars/register-of-approved-data-releases

Department of Health and Social Care
39 Victoria Street
London
SW1H 0EU

Department of Health & Social Care

Sarah Wilkinson
Chief Executive
NHS Digital
1 Trevelyan Square
Boar Lane
Leeds
LS1 6AE

29 July 2020

Dear Sarah,

**Covid-19 – Notice under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002**

The health and social care system is taking action to manage and mitigate the spread and impact of the current outbreak of Covid-19. Action to be taken will require the sharing of confidential patient information amongst health organisations and other appropriate bodies for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the outbreak.

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2.2.2. reasonably satisfied that the confidential patient information to be disclosed pursuant to the request is required by the Requestor for a Covid-19 Purpose and will be processed by the Requestor or by a processor[2] on behalf of the Requestor, solely for that Covid-19 Purpose and in accordance with the restrictions set out in Regulation 7 of COPI; and

2.2.3. from the date of this notice for the period up to 31 March 2021.

**3. Notification to Requesters**

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I am grateful for your continued support at this critical time for the nation.

Yours sincerely

**On behalf of**
**Secretary of State for Health and Social Care**

[3] https://digital.nhs.uk/services/data-access-request-service-dars/register-of-approved-data-releases

Department of Health & Social Care

Sarah Wilkinson
Chief Executive
NHS Digital
1 Trevelyan Square
Boar Lane
Leeds LS1 6AE

27 January 2021

Dear Sarah,

**Covid-19 – Notice under Regulation 3(4) of the Health Service Control of Patient Information Regulations 2002**

The health and social care system is taking action to manage and mitigate the spread and impact of the current outbreak of Covid-19. Action to be taken will require the sharing of confidential patient information amongst health organisations and other appropriate bodies for the purposes of protecting public health, providing healthcare services to the public and monitoring and managing the outbreak.

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NHS Digital is only required to disseminate such confidential patient information where it is:

- requested to do so by an authorised officer of the Department of Health and Social Care acting on my behalf or requested to do so by another organisation permitted to process confidential information under Regulation 3(3) of COPI (the **Requestor),** and
- reasonably satisfied that the confidential patient information to be disclosed pursuant to the request is required by the Requestor for a Covid-19 Purpose and will be processed by the Requestor or by a processor[22] on behalf of the Requestor, solely for that Covid-19 Purpose and in accordance with the restrictions set out in Regulation 7 of COPI; and
- from the date of this notice for the period up to 30 September 2021.

**3. Notification to Requesters**

NHS Digital is requested when sharing confidential patient information under this Notice:

- to remind recipients of confidential patient information of their responsibilities under

1As defined in Art 4(7) of the UK GDPR. The UK GDPR means Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, as it forms part of the law of England and Wales, Scotland and Northern Ireland by virtue of section 3 of the European Union (Withdrawal) Act 2018 (and see section 205(4)).

2 As defined in Article 4(8) of the UK GDPR

COPI when processing the confidential patient information, including

- the restrictions which apply to their processing of it under Regulation 7 of COPI; and
- to publish details of the organisations with whom it has shared confidential patient information under this Notice and the purposes for which it was shared in the NHS Digital Data Release Register[3].

**4. Review and Expiry of this Notice**

If no further notice is sent to you by me, this Notice will expire on 30 September 2021.

I am grateful for your continued support at this critical time.

Yours sincerely,

**On behalf of the Secretary of State for Health and Social Care**

3 https://digital.nhs.uk/services/data-access-request-service-dars/register-of-approved-data-releases

# Appendix 5: Plain English Summaries

## Plain English summary: Infection rates and outcomes from COVID-19 Amongst People with Rare Autoimmune Rheumatic Disease in England. Results from the RECORDER Project.

### Background

We are a team of doctors and researchers from the RECORDER project (Registration of Complex Rare Diseases Exemplars in Rheumatology), working with the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Disease Registration Service at Public Health England. We used electronic health records that cover the whole of England for this research.

Our earlier research had shown that people with rare autoimmune rheumatic diseases such as vasculitis, lupus, scleroderma, juvenile idiopathic arthritis, myositis and Behcet's disease were more likely to die, from any cause, during the first two months of the pandemic. However, we weren't sure why this was happening.

We looked at whether people with rare autoimmune rheumatic diseases were more likely to have COVID-19 infection and whether they were more likely to die of COVID-19 compared to people from the general population during the first wave of the COVID-19 pandemic.

### Our findings

We studied nearly 170,000 people in England with rare autoimmune rheumatic diseases. Between March and July 2020, during the first wave of the COVID-19 pandemic in England, we found that:

- 1874 (1.11%) had COVID-19 infection (PCR test positive)
- Taking age into account, people with rare autoimmune rheumatic diseases were 54% more likely to have a COVID-19 infection than the general population
- 713 (0.42%) people living with rare autoimmune rheumatic disease died following COVID-19 infection
- Taking age and sex into account, death following COVID-19 was 2.4x more common in people with rare autoimmune rheumatic disease compared to the general population
- During this time period, there was no evidence of an increase in deaths from other causes, such as heart attacks. However, it may have been too soon to detect any change.

### Implications for health policy

Our results show that people with rare autoimmune rheumatic diseases are at increased risk of COVID-19 infection and COVID-19-related death. Many people with these conditions are immunosuppressed and protecting their health needs to have a higher prioritisation in public health policy. The impact of immunosuppression, and of shielding, is a focus of our ongoing research. Our results also highlight the urgent need to study the effectiveness of vaccination among people with rare autoimmune rheumatic diseases.

**Plain English summary: Findings from the Second Wave of Covid-19 In England: Infections, deaths and the impact of steroids amongst people with Rare Autoimmune Rheumatic Diseases. Results from the RECORDER Project.**

**Background**
We are a team of doctors and researchers from the RECORDER project (Registration of Complex Rare Diseases Exemplars in Rheumatology), working with the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Disease Registration Service at NHS Digital. We used electronic health records that cover the whole of England for this research.

Our earlier research had shown that people with rare autoimmune rheumatic diseases such as vasculitis, lupus, scleroderma, juvenile idiopathic arthritis, myositis and Behcet's disease were more likely to die from COVID-19 infection during the first wave of the pandemic in England.

In this study, we looked at whether people with rare autoimmune rheumatic diseases remained more likely to die of COVID-19 compared to people from the general population during the second wave of the COVID-19 pandemic. We also looked at whether taking steroids affected the risk of death.

**Our findings**
We studied nearly 170,000 people in England with rare autoimmune rheumatic diseases. Between August 2020 and April 2021, during the second wave of the COVID-19 pandemic in England, we found that:

- 9,961 (5.92%) had COVID-19 infection (PCR test positive)
- Taking age into account, people with rare autoimmune rheumatic diseases had a similar risk of COVID-19 infection to that of the general population
- 1,342 (0.80%) of people living with rare autoimmune rheumatic disease died following COVID-19 infection
- Taking age and sex into account, death following COVID-19 was 2.7x more common in people with rare autoimmune rheumatic disease compared to the general population
- During this time period, there was no evidence of an increase in deaths from other causes, such as heart attacks.

**Implications for health policy**
Our results show that people with rare autoimmune rheumatic diseases remained at increased risk of COVID-19-related death during the second wave of the pandemic. The risk was higher in those taking steroids, and the risk got higher as the steroid dose increased. This should form part of the decision-making process when considering starting steroid treatment.

We did not find an increase in deaths from non-COVID-19 causes such as heart attacks. However, a delayed impact due to later or missed diagnoses remains possible.

**Plain English summary: Risk of death and underlying cause of death in people with Rare Autoimmune Rheumatic Diseases in England.**

**Background**
We are a team of doctors and researchers from the RECORDER project (Registration of Complex Rare Diseases Exemplars in Rheumatology), working with the University of Nottingham, Nottingham University Hospitals NHS Trust and the National Disease Registration Service at NHS England. We used electronic health records that cover the whole of England for this research.

It is recognised that people with rare autoimmune rheumatic diseases such as vasculitis, lupus, scleroderma, juvenile idiopathic arthritis, myositis and Behcet's disease have a higher risk of death than the general population. However, the absolute risk for people with these conditions in England was not clear. We also did not know what they were dying from.

In this study, which looked at health records between 2013 and 2020, we looked at everyone with a rare autoimmune rheumatic disease to see whether they had died and, if so, what the cause was. We calculated rates of death, taking into account age and sex.

**Our findings**
We studied 233,320 people in England with rare autoimmune rheumatic diseases. During the 2013-2020, we found that:

- 53,237 (22.8%) people with rare autoimmune rheumatic diseases died in total.
- Taking age and sex into account, in 2020 people with rare autoimmune rheumatic diseases were 2.4x more likely to die than people in the general population.
- Comparing between the diseases, people with scleroderma (or systemic sclerosis), myositis and microscopic polyangiitis were at the highest risk of death.
- Risk of death due to infection (4.1x higher), respiratory disease (2.9x), COVID-19 (2.8x) and cardiovascular disease (2.5x) was particularly raised.

**Implications for health policy**
Rare autoimmune rheumatic diseases are chronic conditions, with ongoing risk. Certain causes of death can potentially be delayed, for instance the development of heart disease can be slowed down by treating risk factors such as high blood pressure. We would like to see screening for these risk factors becoming part of usual care for people with rare autoimmune rheumatic diseases. Early recognition and treatment of infection, and regular vaccinations (e.g., against flu), may help to reduce deaths due to infection.

Further research to determine whether age or time from diagnosis are associated with increased risk of death from specific causes would be of benefit, as would further research looking at deaths from cancer, to better understand which types of cancer are driving this.