THE SAHLGRENSKA ACADEMY

Impact of COVID-19 on the management of autoimmune disease in Sweden

A registry-based health economic study

Part A
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Abbreviations

CD	Crohn's disease
CoD	Cause of Death Register
HCS	Healthcare system(s)
MS	Multiple sclerosis
NBHW	The Swedish National Board of Health and Welfare
PAR	National Patient Register
QoL	Quality of life
RA	Rheumatoid arthritis
UC	Ulcerative colitis

Part A

Introduction

COVID-19 is the respiratory disease caused by SARS-CoV-2; a positive-sense, single-stranded RNA virus belonging to the Betacoronavirus genus (Lu et al., 2020). The symptoms of the disease include a dry cough, shortness of breath, fever and fatigue (CDC, 2020) as well as more complex clinical developments such as lung infections and pneumonia (Zhang et al., 2020), which can require hospitalisation and assisted ventilation. The first cases of COVID-19 (initially reported as viral pneumonia of unknown cause) were seen in Wuhan, China, in December 2019. The WHO reported that this outbreak of viral pneumonia cases was caused by a novel coronavirus in January 2020 and thereafter instigated global communications between health authorities, governments, and other important stakeholders in order to assess the threat posed by this novel virus (WHO, 2020b). Over the next few months, the number of cases and the spread of the disease steadily increased, and on 4th April 2020, the WHO reported that over 1 million cases of COVID-19 had been confirmed globally (WHO, 2020a).

Following genomic sequencing, it became widely accepted that the SARS-Cov-2 virus likely spread from bats to humans; this is thought to have been made possible by the close proximity of bats (and their faeces) to humans at animal markets. Human-to-human transmission of the virus via respiratory droplets was soon indicated by scientific studies (Chang et al., 2020; Wang et al., 2020) and, as the number of reported cases with no connection to the initial outbreak Wuhan started to grow, this soon became the accepted theory. This transmission route was considered particularly concerning as airborne pathogens have the potential to disperse over great distances with relative ease and be ingested by any number of further individuals whilst potentially remaining undetected. The initial reproduction rate of the virus in China was estimated to be between 2.24 to 3.58 (Zhao et al., 2020); this number is a representation of how many people a single infected person is

expected to infect, where a reproduction rate of more than 1 means that the spread of the virus is increasing. For comparison: the initial reproduction rate for the H1N1 influenza pandemic in 2009 was estimated to be between 1.2 and 2.3 (Boelle, Ansart, Cori, & Valleron, 2011). The drastic rate of spread of COVID-19, and the growing number of patients experiencing serious symptoms, caused worldwide panic as health authorities tried to prepare for what was soon to become a global pandemic.

As of May 16th, 2021, the total number of confirmed cases of COVID-19 in Sweden was reported to be 1,037,126 of which 7,284 have been treated in intensive care and 14,275 have died ("Number of cases of COVID-19 in Sweden," 2021). Figure 1 illustrates how the daily number of cases of COVID-19 in Sweden has changed over time, from the start of the pandemic in early 2020 to the end of April 2021 (the actual number of cases in 2020 is likely to be underreported here due to limited testing at this time). The figure shows the first and second "waves" in Spring/Summer 2020 and Winter 2020, demonstrated by a surge in the number of confirmed cases. Following a sharp increase in cases at the beginning of March 2021, the Swedish Public Health Agency's prediction of a third wave during Spring/Summer 2021 ("Risk för tredje våg av covid-19 enligt nya scenarier," 2021) certainly seems likely.

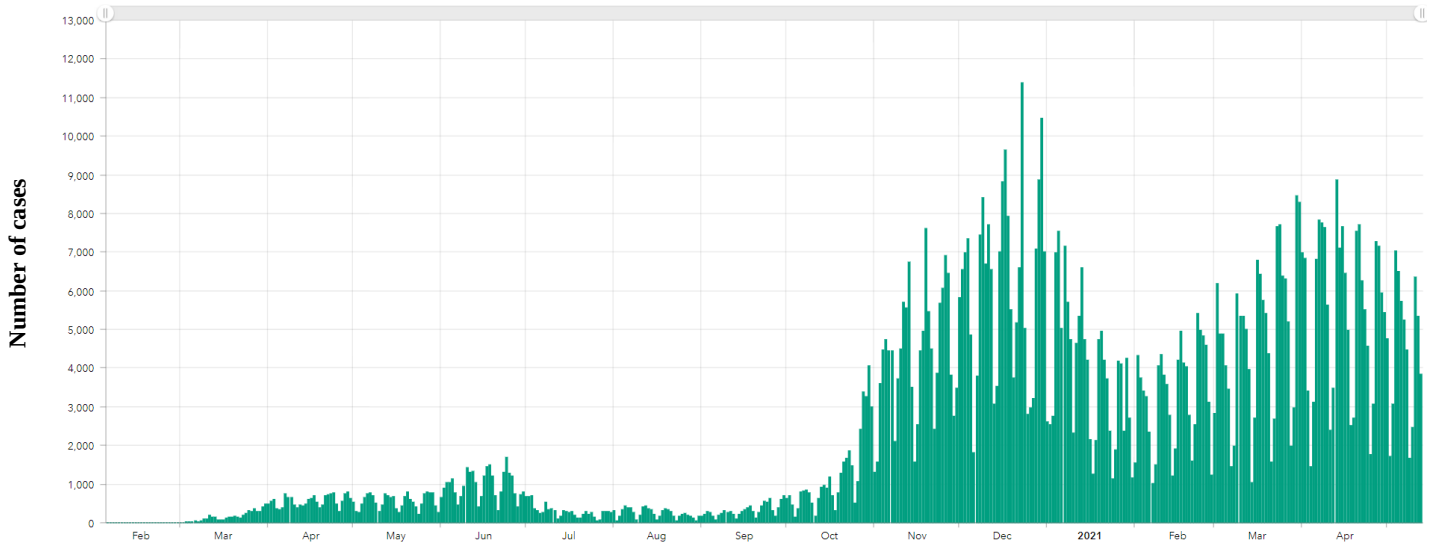

Figure 1. Number of daily confirmed cases of COVID-19 in Sweden ("Number of cases of COVID-19 in Sweden," 2021)

As one of the most significant public health emergencies of the 21st Century so far, COVID-19 has caused disruption to healthcare systems (HCS) around the world, affecting resource allocation, hospital management, and healthcare worker wellness. Healthy individuals have reported increased stress due to COVID-19 (Shevlin et al., 2020), but the burden faced by people living with additional health conditions (e.g. cancer, autoimmune diseases) is expected to be even greater, due to increased uncertainty, health-related stress, and financial hardships caused by the pandemic, which may also delay or disrupt necessary care seeking for their pre-existing conditions.

Response to COVID-19 in Sweden

In Sweden, the Public Health Agency (Folkhälsomyndigheten) is the authority that has been responsible for developing regulations and guidelines to prevent the spread of COVID-19. Unlike many other countries, Sweden has focused on providing recommendations for citizens to control the spread of the virus rather than enforcing strict quarantines or lockdowns. New recommendations were introduced on 14th December 2020, intended to remain in effect until 30th June 2021, with a strong focus on personal responsibility, for example: "Stay at home if you have any symptoms of COVID-19", "Avoid being in close proximity to [other people], especially in confined spaces", and "Ensure that you travel in a way that minimises the risk of infection" (*The Public Health Agency of Sweden's regulations and general guidelines relating to everyone's responsibility to prevent COVID-19 infections*, 2020). These recommendations were introduced with the intention to mitigate the spread of infection without jeopardising social equity, which is typically prioritised in Swedish social systems. Whilst the initial lack of enforcement and reliance on individual responsibility resulted in some criticism against Sweden's "soft measures" strategy, there is a high level of public trust in the Public Health Agency and healthcare professionals in Sweden, and assessment of self-reported adherence surveys has shown that there has been a high degree of compliance to

these measures (Kavaliunas, Ocaya, Mumper, Lindfeldt, & Kyhlstedt, 2020). Even with the introduction of the so-called “pandemilag” in January 2021 ("Lag om särskilda begränsningar för att förhindra spridning av sjukdomen covid-19 (2021:4),") – which gave the Swedish government, state authorities, and municipalities special powers to introduce and enforce rules to limit the spread of COVID-19 – there is potential for individuals to experience uncertainty and doubt as to whether they are safe. One example is the recommendation for members of the public to wear face masks in public places, such as on trains and in shopping centres; even if some individuals follow these recommendations, there is no guarantee that other people will do the same, and if there is no clear enforcement of the recommendation then this can create an environment where doubts and fears around COVID-19 can increase stress and anxiety, thereby affecting people’s wellbeing.

Autoimmune diseases

The term ‘autoimmune disease’ refers to a broad and diverse subpopulation of disorders for which the underlying characteristic is an inappropriate immune response to the body’s own protein antigens that causes a cell-mediated reaction that is in some way detrimental to health (Leuschen, 2008). It is an umbrella term for a wide range and variety of diseases that often affect multiple tissues and organs, and examples include multiple sclerosis (MS), rheumatoid arthritis (RA), Crohn’s disease (CD) and ulcerative colitis (UC). The clinical features, pathogenesis, epidemiology, and common treatments for these autoimmune diseases will be explored in more detail in this section.

MS is a neurological disease in which neuronal axons lose their myelination and progressively deteriorate; this can cause a wide range of clinical symptoms, the most common of which relate to movement e.g. weakness, loss of feeling, and tremors (Leuschen, 2008). Different genetic and environmental risk factors for MS have been identified, including certain risk genes, having a history of mononucleosis, components of the

microbiome, and obesity (Reich, Lucchinetti, & Calabresis, 2018). The Swedish National Board of Health and Welfare (NBHW) reported an incidence of 7.1 per 100,000 population for MS in 2019 (Socialstyrelsen, 2020), with a higher incidence in women (9.4) than men (4.9) (see Appendix, Table A1, for more details on incidence statistics).

CD and UC are often grouped together in clinical and research papers as they are the two main subtypes of chronic inflammatory bowel disease (IBD) and show similar patterns, although they are distinct diseases: UC affects the rectum and colon almost exclusively and is characterised by mucosal inflammation, whereas CD causes transmural inflammation and can affect any part of the gastrointestinal tract (although it is most commonly associated with the lower intestine) (Sarmento, Magro, & Campos, 2017). Previous research suggests that genetics, environment, intestinal microbiota, and the immune system of an individual all contribute in varying ways to the pathogenesis of both CD and UC (Sarmento et al., 2017). The prevalence of IBD – including CD and UC – has steadily increased throughout Europe in the latter half of the 20th Century (Torres, Mehandru, Colombel, & Peyrin-Biroulet, 2017). In Sweden, the nationwide prevalence of physician-diagnosed IBD in 2010 was 0.65%, corresponding to 0.35% for CD, 0.19% for UC and 0.11% for patients with both CD and UC diagnoses (Busch et al., 2013). According to the NBHW, in 2019 the incidence of CD was 14.4 per 100,000 and of UC was 13.6 per 100,000 (Socialstyrelsen, 2020).

In RA – which is a systemic inflammatory disease – the primary targets of the autoimmune response are the synovial joints, resulting in inflammation and causing symptoms such as stiffness, pain, and reduced motility (Leuschen, 2008). The prevalence of RA in Sweden was estimated to be 0.53% in women and 0.24% in men in 2015, making it the 30th leading cause of years lived with disability in Sweden for that year (Kiadaliri, Kristensen, & Englund, 2018). In 2019, the incidence of RA in Sweden was 8.1 per 100,000 population

(Socialstyrelsen, 2020), and the incidence is generally reported to be higher in women than men.

These autoimmune diseases and their symptoms can significantly affect the quality of life (QoL) of patients living with them, with morbidity and mortality increasing with disease progression and the presence of comorbidities, many of which are relatively common (Marrie et al., 2015; Scalfair et al., 2013). Patients living with autoimmune diseases are also more likely to suffer from mental health disorders: in MS, anxiety and bipolar disorder are more commonly diagnosed than in the general population (Minden et al., 2013), and research has shown an increase in the incidence of psychiatric disorders post-IBD diagnosis, with suggestions that there may even be a shared pathobiology between IBD and psychiatric disease (Bernstein, 2018). For individuals already living with pre-existing conditions who are also facing the effects of a pandemic, there is potential for QoL to be further affected.

Autoimmune diseases and the COVID-19 pandemic

Patients with autoimmune diseases have a heightened risk for both becoming infected with and developing more severe symptoms of viral infections (such as COVID-19) due to a weakened immune system; this can arise as a result of the disease itself or as a side-effect of immunosuppressants used to treat the disease (Fang, Karakiulakis, & Roth, 2020; Grebenciucova & Pruitt, 2017). Immunosuppressants are prescribed based on a harm-benefit principle i.e. the benefit in the treatment of the disease outweighs the risk of harm caused by the drugs. During the COVID-19 pandemic, concern has arisen for patients taking these drugs and, in some cases, doctors may recommend cessation of treatment as the risk of being infected with the virus is too great (for example, in communities where rate of transmission is particularly high). However, these patients may then be at risk of worsening symptoms of their autoimmune disease, or even at a higher risk of mortality.

As a result of the increased risk of infection, poorer expected outcomes, and potentially having to stop their immunosuppressant treatment, COVID-19 is likely to cause a greater burden for patients with autoimmune diseases compared with the general population. They can therefore be considered a 'risk group' for COVID-19. People belonging to risk groups have been encouraged to take additional precautions in order to protect their health during the pandemic; for the aforementioned reasons, and also because they are more likely to require hospitalisation if they do become infected with COVID-19, putting additional pressure on already-overworked HCS. One study showed that patients with rheumatic disease who became infected with COVID-19 were more likely to require intensive care or ventilation than matched COVID-19 positive controls from the general population (D'Silva et al., 2020). Another study associated increasing age, comorbidities and corticosteroids with poorer COVID-19 outcomes in IBD patients (Brenner et al., 2020), highlighting the additive effect of different "risks" (old age is another key "risk group" for COVID-19). As a consequence of the above, autoimmune disease patients might avoid visiting "high-risk" places (such as hospitals and healthcare centres) out of fear of the heightened risk for COVID-19 infection and associated health outcomes, which could result in failure to seek necessary care for their condition. Further, standard of care has been altered to better reflect the crisis situation created by the pandemic, resulting in a shifted focus from healthcare that prioritises individual benefit, to that which benefits the community. This has been achieved through rationing and reallocation of resources in healthcare systems that threaten to become overwhelmed, and low-priority healthcare events such as non-emergency check-ups for autoimmune disease patients have not received the usual standard of care.

Equality in healthcare

The Swedish Commission for Equity in Health (Kommission för Jämlik Hälsa) was founded in 2015, and has been tasked with making suggestions that aim to help reduce social

inequalities in health, with a particular focus on health differences between different socioeconomic subpopulations and differences between women and men ("Kommissionen och dess uppdrag," n.d.). As mentioned previously, autoimmune diseases can be highly sex-specific, in both prevalence and severity (although not necessarily concurrently). For example, MS is more commonly diagnosed in women but a greater proportion of men who are affected have a more aggressive form of the disease than women (Leuschen, 2008). Not only does this highlight the different needs of men and women with autoimmune diseases, but it also begins to generate other questions related to the present study: for example, do the differences in disease severity mean that men with MS will seek care more often than women? Has care seeking been affected by the COVID-19 pandemic? What are the long-term implications, and will the HCS infrastructure meet the needs of the population? It is vital for public health research to factor in health inequalities and inequities and use these to inform future decision-making, so that the individual needs of the population are met sufficiently.

Healthcare registers

Sweden has a strong history of reliable register-based research due to a number of well-maintained, mandatory population-based registers that contain a wide range of personal and societal data, as well as a system of personal identity numbers (PINs). All permanent residents in Sweden are assigned a PIN – consisting of their date of birth and a 4-digit number – by the Swedish Tax Agency (Skatteverket). This PIN is used as a means of identification and can be linked to personal services, such as mobile banking, as well as being used for administrative purposes. The PIN also plays a key role in national registers in Sweden where it can be used as a linkage tool, allowing for data to be linked to a particular individual between different registers, thus opening up possibilities for broader research. In healthcare specifically the PIN can be used to link data collected from registers with data

from medical records, patient charts, and biobanks. This is important for public health research as it increases the breadth of understanding of a health condition or disease, since collected data on e.g. a specific disease, the drug use by patients with this disease, the socioeconomic status of the patients, and the date and cause of death for these patients, can be taken from several distinct registers and used in research.

The Swedish National Patient Register (PAR) is one example of a data register; it contains patient data, geographical data, administrative data (including inpatient and outpatient data), and medical data about specialised care. The International Statistical Classification of Diseases and Related Health Problems (ICD) is a classification system used in most health statistics services – including the PAR – around the world to code and classify patient health data, thereby allowing for clarity, consistency, and ease-of-access for researcher requesting access to such data (CDC, 2020). In Sweden, the NBHW is the government agency responsible for collecting, compiling, analysing, and passing on information about health, medical services, and epidemiology, as well as maintaining data registers and official statistics relating to health (Socialstyrelsen, 2019). Using patient PINs, the NBHW can link data from the PAR to other registers, such as the Prescription Drug Register, or Cause of Death Register, as requested by researchers or private individuals. Due to the nature of the register linking process, the NBHW is the only party that has access to patient PINs, with the researcher only ever receiving data identified by unique serial numbers (see Figure 2). This means that the ethical regulations around accessing register-linked data are reduced, especially when compared to those required when individual-level data are requested, since aggregate data is considered to be non-identifiable (unless the sample includes only a small number of patients, in which case further precautions are taken in order to maintain confidentiality). This makes this type of data much more accessible for research.

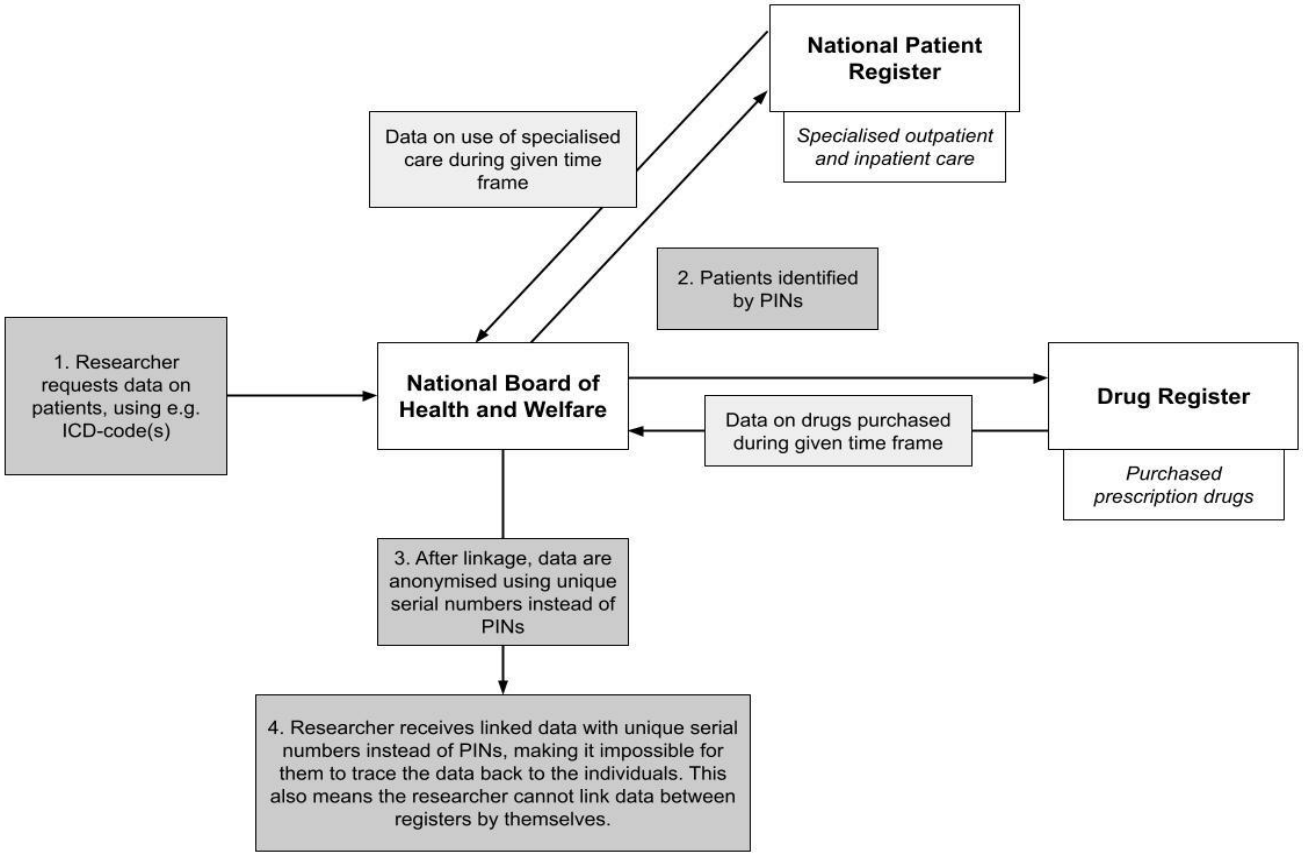

Figure 2. Example of register linking between the National Patient Register and Drug Register, performed by the National Board of Health and Welfare.
Adapted from Ludvigsson, Otterblad-Olausson, Pettersson, and Ekbom (2009)

Ethical considerations

Although the ethical regulations regarding confidentiality are reduced when handling registry data compared to personally identifiable data, there is always a delicate balance between an individual's right to privacy and the need to access and utilise personal information related to health in order to aid policy and healthcare decision making. According to Swedish law, official statistics in the areas of health and medical care must be available to the public for general information, investigation and research ("Official Statistics Act (2001:99)," ; "Official Statistics Ordinance (2001:100),"). However, individual-level data are protected by strict confidentiality, with access restricted to research being carried out in Sweden, and then only once a thorough assessment has been carried out. Encouraging the use of aggregate,

non-identifiable patient data in research studies by making this process quicker and easier allows the register holder to carry out their ethical duty to preserve the confidentiality of personal information (Perrin, 2016).

It is also important to consider health equity when it comes to public health research. Health equity is defined as "a fair distribution of health determinants, outcomes, and resources within and between segments of the population, regardless of social standing" (Perrin, 2016: p. 35). Health disparities that arise as a result of health inequity limit an individual's capability to reach optimal health. These disparities can often be directly linked to the social determinants of health (SDOH), which are the environmental and social conditions in which people live and work that affect their health and QoL. Examples of SDOH include healthcare access and quality, financial stability, access to education, and safe living conditions ("Healthy People 2030: Social Determinants of Health," n.d.). If any of these determinants disproportionately affect one group within the population, then this group might have poorer health outcomes than the general population, through no fault of their own. Public health authorities and other actors across different sectors can take action to reduce inequity through e.g. the implementation of healthcare interventions, education programmes, or better access. Policies and interventions that aim to improve health outcomes should focus on combatting health inequity by identifying where disparities occur, how these affect health outcomes, and allocating resources in a fair and just way in order to benefit the greatest number of people in the population.

Relevance of the current study

It is inevitable that healthcare resource use will vary from year-to-year as a result of variation in the work of healthcare professionals, as well as in access, outcomes and other indicators produced by a HCS; even the time of day in which a patient is admitted to hospital can have an effect on their health outcomes (Confederation, 2004). However, as the pandemic is

ongoing and large-scale data from 2020 is just becoming available, there is currently a gap in the knowledge as to whether COVID-19 has caused unexpected variation in healthcare resource use. At the start of the pandemic, one study reported that admissions for chemotherapy had already decreased by 45-66% and estimated that 6,270 excess deaths of cancer patients at one year in England and 33,890 in the US could be attributed to the COVID-19 pandemic (Lai et al., 2020).

Healthcare policymakers in Sweden have to decide how and where to allocate resources in order to ensure good public health; the COVID-19 pandemic has not changed this fact, but it has made it more complicated. The Public Health Agency is responsible for monitoring population health and work with other governmental bodies to analyse data and promote good health, with particular focus on reducing health inequities. By understanding how the pandemic has affected, and continues to affect, the healthcare resource use of people living with autoimmune diseases in Sweden, authorities can evaluate the allocation of resources and try to improve this going into the future in order to reduce health inequity and inequality.

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Appendix

Table A1. Data from NBHW statistics database on incidence rates for MS, CD, UC, RA in Sweden in 2019.

Diagnosis	Sex	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85+	Total
MS	Male	0.0	0.0	0.6	5.8	32.8	57.8	95.3	142.3	156.1	161.9	160.7	150.3	145.5	121.0	87.8	58.6	27.0	11.8	84.4
MS	Female	0.0	0.0	3.8	17.1	77.7	134.2	245.8	316.5	372.8	392.3	402.8	400.7	348.8	265.1	193.0	122.9	56.4	11.3	200.4
CD	Male	1.9	9.7	62.3	166.1	201.4	240.0	241.7	213.6	210.6	229.5	213.7	224.0	227.3	243.6	237.6	217.1	145.3	75.0	180.8
CD	Female	3.4	7.6	50.6	126.6	192.0	239.4	228.5	239.5	230.8	235.9	236.8	276.6	280.3	278.2	242.0	227.2	137.7	59.3	188.5
UC	Male	2.6	10.9	44.2	134.3	236.7	309.9	330.6	325.4	338.2	321.8	287.6	315.2	351.3	339.0	344.3	327.1	233.1	136.0	247.8
UC	Female	0.7	12.9	33.2	140.7	197.7	270.0	311.8	312.3	281.0	279.1	281.1	302.5	300.4	310.9	282.0	250.8	206.2	100.3	220.6
RA	Male	0.6	0.9	1.3	3.1	8.3	20	28.8	49.6	90.5	117	162.7	269.8	370.7	540.3	697.4	907.1	876.7	559.9	198.2
RA	Female	1	1.4	2.4	15.2	52.5	113.8	192.9	277.1	364.8	495.5	628.1	905.1	1088.5	1275.8	1619.6	1762.4	1561.5	862.7	559.4

Incidence rates are divided by sex and age and presented as incidence per 100,000 population. Both inpatient and outpatient care are included.

(Socialstyrelsen, 2020)

THE SAHLGRENSKA ACADEMY

Impact of COVID-19 on the management of multiple sclerosis and rheumatoid arthritis in Sweden

A registry-based health economic study

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Impact of COVID-19 on the management of multiple sclerosis and rheumatoid arthritis in Sweden: a registry-based health economic study

Key words: registry data, register linking, healthcare perspective, digital healthcare, autoimmune disease(s).

Abstract (300 words)

Objective: To determine the extent and nature of changes in healthcare resource use and deaths during the COVID-19 pandemic of patients with multiple sclerosis (MS) or rheumatoid arthritis (RA) in Sweden, with a focus on digital events and planned visits. **Methods:** Patients had a main diagnosis of MS or RA between 2014-2020 ("incident") or 1987-2020 ("prevalent"). Retrospective aggregate data were obtained from the National Patient Register on patient characteristics, number of in- and outpatient events in specialised healthcare, planned visits, digital events, inpatient admissions, and length of stay for overnight admissions in each study period. From the Cause of Death Register, the number and top causes of death were obtained for patients in each study period, as well as the number with COVID-19 as an underlying cause of death. Healthcare use during the COVID-19 pandemic was observed for 7 months in 2020, and equivalent annual study periods between 2014-2019 were used to determine normal variation. **Results:** Compared to normal annual variation, specialised healthcare use by MS and RA incident patients did not change during 2020. However, the number of planned inpatient visits decreased, and number of digital outpatient visits significantly increased ($P>0.005$) for both diseases. The number of deaths was not notably different in the COVID-19 study period, although COVID-19 was found to be one of the most common causes of death in RA patients in 2020. **Conclusions:** This study provides evidence of MS and RA patients' healthcare resource use in Sweden during the COVID-19 pandemic, and the results suggest that whilst the use of specialised healthcare has remained fairly unchanged, patients appear to have avoided physical visits and instead migrated towards digital visits. Further research is needed to explore the long-term effects of the pandemic on healthcare resource use in order to strengthen these conclusions.

1. Introduction & Background

In March 2020, a global pandemic was declared by the WHO concerning the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19 (WHO, 2020). The characteristic symptoms of this viral infection include a dry cough, shortness of breath, fever and fatigue (CDC, 2020) as well as more complex clinical developments such as lung infections and pneumonia (Zhang et al., 2020). With a growing fear that the virus would overwhelm the healthcare system (HCS), policymakers implemented measures aiming to prevent spread – including physical distancing guidelines – as well as redirecting resources to meet the changing needs of the population. While this was necessary in mitigating the effects of the sudden health crisis, the management of other, pre-existing diseases may have suffered as a result. The nature of care seeking has also changed during the pandemic, with technologies such as digital visits – that allow patients to "meet" their physician whilst maintaining physical distance – becoming much more desirable to both patients and healthcare providers (Mann, Chen, Chunara, Testa, & Nov, 2020).

Autoimmune disease patients are considered a 'risk group' for COVID-19, due to an increased risk of becoming infected with viral infections (Fang et al., 2020). The Swedish Public Health Agency has issued recommendations for the public to stay home if they experience symptoms of COVID-19, and to avoid close contact with others and crowded places. As a risk group, autoimmune patients may avoid seeking in-person healthcare in order to reduce the likelihood of being infected with COVID-19. Although the risk for serious COVID-19 in MS patients has been reported to be very low in Sweden (only 79 of 17,740 MS patients have reportedly sought hospital care for COVID-19 and of those, only 20 have entered intensive care ("Nyheter Svenska neuroregister," 2021)), register data suggest that immunosuppressant medications for MS that target the CD20 antigen (such as rituximab) can increase the risk of serious COVID-19 infection by 2-3 times (Luna et al., 2020). Rituximab

therapy has also been associated with serious COVID-19 infection and prolonged hospital stay in patients with RA (Avouac et al., 2021).

Against this backdrop, and due to additional strain placed on HCS by the pandemic, monitoring and treatment of these patients may not be adequately performed. Investigating the healthcare resource use of autoimmune disease patients during the pandemic could provide key insight into how their needs have changed, whether these needs have been met, and how they can be met in the future.

2. Aim & Research Questions

The aim of this project is to determine whether the COVID-19 pandemic has affected healthcare resource use of autoimmune patients in Sweden, with a focus on patients with a main diagnosis of multiple sclerosis (MS) or rheumatoid arthritis (RA).

The research questions were:

- For patients with a main diagnosis of MS or RA, compared to normal annual variation:
    - Was there a reduction in overall healthcare resource use in 2020?
    - Was there an increase in the number of digital healthcare events in 2020?
    - Was there a change in the number of planned (vs. unplanned) visits in 2020?
- Did the number of deaths of MS and RA patients change in 2020 compared to normal annual variation, and how many deaths were attributable to COVID-19?

3. Methods

3.1 Register sources.

This register-based study used retrospective data from national healthcare registers in Sweden from 1987-2020[1] and has a healthcare perspective. Register sources were the National Patient Register (PAR) and Cause of Death Register (CoD), which are maintained by the National Board of Health and Welfare (NBHW). These national mandatory registers were used to obtain aggregate data on patient characteristics, healthcare resource use (inpatient and outpatient), date of diagnosis, COVID-19 diagnosis (if applicable), and cause of death (if applicable). Personal identification numbers (PINs) of the study population were used to link data between registers: the linking was performed by the register holders, who provided de-identified data for the study (since only de-identified data were used, ethical approval was not required).

3.2 Study populations

The study populations comprised patients in the whole of Sweden who had received a main diagnosis of MS or RA. Patients were defined in the PAR as those with International Classification of Diseases, 9th or 10th Revision (ICD-9 or -10) codes for MS or RA, according to Table 1. For each 3-digit ICD code, data were also included for patients classified with all nested codes.

Table 1. ICD-9 and -10 codes for autoimmune diseases of interest

Autoimmune disease	ICD-9 code (1987-1996)	ICD-10 codes (1996 onwards)
Multiple sclerosis	340	G35
Rheumatoid arthritis	714.0	M05 & M06

Patient characteristics included: age at time of first main diagnosis (incident patients only), age at healthcare visit during the study period (prevalent patients only), number of patients,

[1] The National Patient Data includes all outpatient data from 1987 onwards and inpatient data from 2001 onwards; in the present study, prevalent patient characteristic data were obtained from the PAR for the years 1987-2020, and incident patient characteristic data for the years 2014-2020. Data from the Cause of Death Register are available from 1961, and here were obtained for prevalent and incident patients for the years 2014-2020.

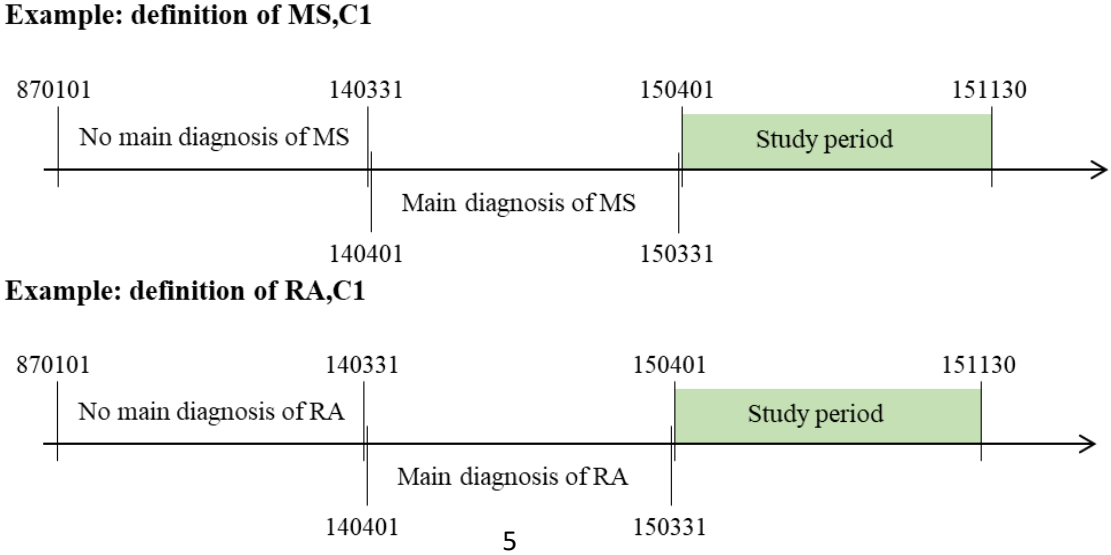
and number of males and females in each subpopulation. Healthcare resource use data included the total number of visits (inpatient and outpatient) with main diagnosis in specialised healthcare, of which: the number of in- and outpatient visits that were planned (i.e. not emergency visits), number of digital outpatient visits, number of inpatient admissions (overnight), and overall length of stay of inpatient admissions.

For each of the COVID-19 subpopulations, the number of unique patients diagnosed with COVID-19 during the study period (200401–201130) was requested. These were classified with ICD-10 codes U07.1 (COVID-19, virus identified), U07.2 (COVID-19, virus not identified), and U08.9 (COVID-19 in medical history). Finally, the frequency data for patients who died during each study period and the number of COVID-19 related deaths (in the COVID-19 subpopulations) were requested, as well as the most common causes of death for each study period.

3.2.1 Incident patients

The incident patient study population included patients with a first main diagnosis of MS or RA between 2014–2020. For MS and RA, patients were divided into one COVID-19 subpopulation and five control subpopulations, resulting in 1+5 subpopulations per diagnosis. Each subpopulation and study period were defined by the period in which the first main diagnosis was made (Figure 1):

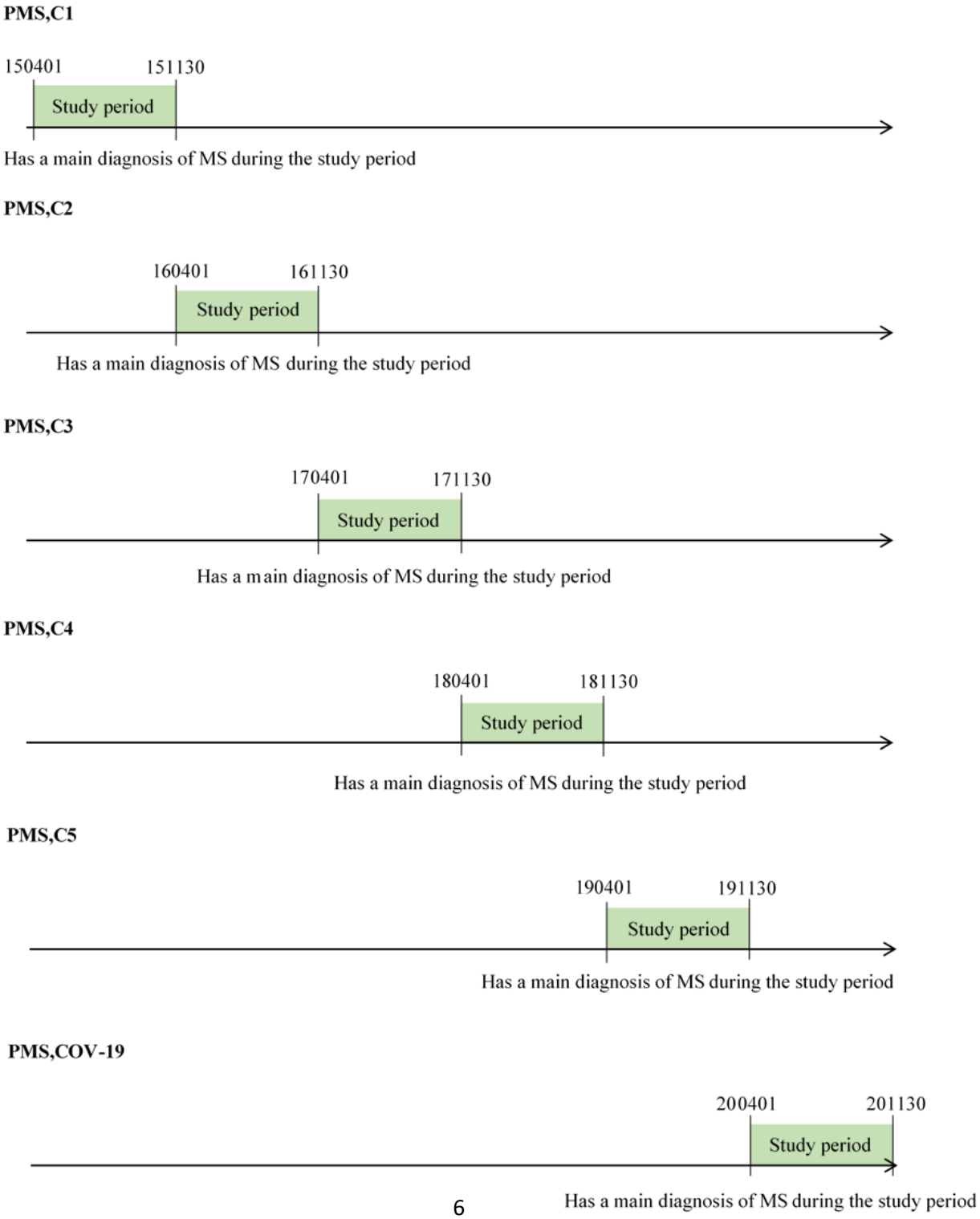
Figure 1. Example patient selection and study period for control 1 (C1) incident subpopulations



3.2.2 Prevalent patients

The prevalent patient study population included *all* patients that had a main diagnosis of MS or RA at any time (i.e. it was not limited to newly diagnosed patients). For these patients, data were obtained from all patients who had a main diagnosis of that disease during each study period, regardless of date of first main diagnosis. The twelve subpopulations were defined by study period, as before (Figure 2):

Figure 2. Patient selection and designated study period for MS prevalent patients



MS, multiple sclerosis; PMS, prevalent MS patients

Table 2. Definitions of patient subpopulations

Subpopulation*	ICD code for main diagnosis	**INCIDENT PATIENTS ONLY**		Study period (YYMMDD)
		Incident diagnosis (first main diagnosis in either inpatient or outpatient setting)		
		Period (YYMMDD)	Definition	
MS Control 1	G35	140401–150331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 140401.	150401–151130
RA Control 1	M05, M06			
MS Control 2	G35	150401–160331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 150401.	160401–161130
RA Control 2	M05, M06			
MS Control 3	G35	160401–170331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 160401.	170401–171130
RA Control 3	M05, M06			
MS Control 4	G35	170401–180331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 170401.	180401–181130
RA Control 4	M05, M06			
MS Control 5	G35	180401–190331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 180401.	190401–191130
RA Control 5	M05, M06			
MS COVID-19	G35	190401–200331	Patients with a main diagnosis of the disease appearing in the Patient Register for the first time during the period indicated in the column to the left. "For the first time" is defined by no main diagnosis between 870101 and 190401.	200401–201130
RA COVID-19	M05, M06			
*Subpopulations were applied to incident and prevalent patient populations separately (i.e. 24 subpopulations in total) but are only shown once each here to be concise.				

3.3 Statistical analysis

The data were analysed using Microsoft Excel (v. 16) and STATA/SE (v. 16) software. For each continuous variable (e.g. number of outpatient visits per patient), the mean, standard deviation (SD), median, minimum, and maximum were calculated by NBHW, as were the frequency and percentage for each categorical variable (e.g. sex distribution of patients). One-way ANOVA from summary statistics (Butt, 2011) was performed by the author to determine significant differences between subpopulations.

4. Results

A selection of results is presented below based on the specific research questions. Full results are presented in tabulated format in the Appendices.

4.1 Description of the study populations

4.1.1 Incident patients

The number, sex distribution and mean age of incident patients in each study period are presented below in Table 3. A sex distribution of approximately 2:1 female to male patients was seen across all MS and RA subpopulations and study periods. The mean age at first main diagnosis was approximately 41 years for MS and 60 years for RA (Appendix 1).

Table 3. Incident patient study populations

(a) MS

Subpopulation	Female (%)	Male (%)	Total patients	Mean age at first main diagnosis (years)
MS,C1	717 (68%)	344 (32%)	1061	41.3
MS,C2	664 (68%)	312 (32%)	976	41.7
MS,C3	642 (67%)	316 (33%)	958	39.9
MS,C4	630 (67%)	305 (33%)	935	40.6
MS,C5	640 (65%)	350 (35%)	990	39.9
MS,COV-19	586 (65%)	317 (35%)	903	39.4

(b) RA

Subpopulation	Female (%)	Male (%)	Total patients	Mean age at first main diagnosis (years)
RA,C1	2504 (67%)	1222 (33%)	3725	59.0
RA,C2	2304 (66%)	1162 (34%)	3466	59.1
RA,C3	2454 (65%)	1304 (35%)	3758	59.4
RA,C4	2393 (66%)	1211 (34%)	3604	59.6
RA,C5	2358 (66%)	1229 (34%)	3587	59.9
RA,COV-19	2388 (68%)	1115 (32%)	3503	59.7

MS, multiple sclerosis; RA, rheumatoid arthritis.

4.1.2 Prevalent patients

The sex distribution for MS and RA prevalent patients was approximately 70% female to 30% male across all subpopulations. There was a sharp decrease in the total number of RA prevalent patients in the COVID-19 study period compared to the apparent annual trend. The mean age at visit was approximately 48 years for MS and 63 years for RA (Appendix 1).

Table 4. Prevalent patient study populations

(a) MS

Subpopulation	Female (%)	Male (%)	Total patients	Mean age at healthcare event* (years)
PMS,C1	7296 (71%)	3017 (29%)	10314	48.2
PMS,C2	7463 (70%)	3128 (30%)	10591	48.3
PMS,C3	7243 (71%)	3015 (29%)	10258	48.4
PMS,C4	7042 (70%)	2985 (30%)	10027	48.7
PMS,C5	7709 (70%)	3227 (30%)	10936	48.6
PMS,COV-19	7025 (70%)	3001 (30%)	10026	48.4

(b) RA

Subpopulation	Female (%)	Male (%)	Total patients	Mean age at healthcare event* (years)
PRA,C1	21551 (74%)	7626 (26%)	29177	63.3
PRA,C2	21752 (74%)	7692 (26%)	29444	63.5
PRA,C3	21965 (74%)	7808 (26%)	29773	63.7
PRA,C4	22210 (74%)	7753 (26%)	29963	63.9
PRA,C5	22219 (74%)	7777 (26%)	29996	64.2

*Mean age at healthcare event for prevalent patients was provided instead of mean age at first main diagnosis due to the nature of the healthcare data available.
MS, multiple sclerosis; RA, rheumatoid arthritis.

The approximate proportion of prevalent patients that were incident patients (i.e. newly diagnosed in each study period) for was estimated to be 9% for MS patients and 13% for RA patients.

4.2 Healthcare resource use

4.2.1 Incident patients

Due to time and budget constraints, data on healthcare resource use were obtained for incident patients but not prevalent patients, as incident patients are presumed to have more frequent contact with healthcare. Seven variables were measured for MS and RA incident patients, and the results are presented in Tables 5 and 6, below:

Table 5. Healthcare resource use for MS incident patients

Subpopulation / Variable	MS,C1		MS,C2		MS,C3		MS,C4		MS,C5		MS,COV-19	
	Total events (mean)	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**
Number of events with main diagnosis of MS (in- and outpatient) in specialised healthcare	1511 (2.08)	727	1317 (1.96)	673	1273 (1.94)	657	1144 (1.91)	599	1371 (2.01)	681	1223 (2.15)	570
Number of outpatient events with main diagnosis of MS in specialised healthcare	1454 (2.01)	723	1281 (1.91)	672	1237 (1.89)	656	1098 (1.85)	592	1327 (1.97)	674	1189 (2.10)	566
Number of planned outpatient events with main diagnosis of MS in specialised healthcare	1412 (1.96)	719	1237 (1.84)	672	1187 (1.81)	654	1045 (1.79)	583	1283 (1.91)	670	1130 (2.05)	552
Number of outpatient digital events with main diagnosis of MS in specialised healthcare	302* (1.90)	157	264* (1.76)	150	301* (1.66)	181	251* (1.68)	149	369* (1.77)	208	546 (1.82)	300
Number of inpatient admissions with main diagnosis of MS in specialised healthcare	57 (1.21)	47	36 (1.33)	27	36 (1.38)	26	46 (1.24)	37	44 (1.42)	31	34 (1.26)	27
Number of planned inpatient events with main diagnosis of MS in specialised healthcare	41 (1.11)	37	21 (1.24)	17	18 (1.20)	15	32 (1.28)	25	28 (1.33)	21	16 (1.60)	10
Length of stay for inpatient admissions with main diagnosis of MS (days)	256 (5.45)	47	328 (12.15)	27	142 (5.46)	26	317 (8.57)	37	230 (7.42)	31	64 (2.37)	27

Mean number of events in each case = total number of events ÷ number of patients with events.
Results for the number of events for control subpopulations C1-5 that were significantly different (P<0.005) to the COVID-19 subpopulation are marked with an asterisk (*).
MS, multiple sclerosis.

Table 6. Healthcare resource use for RA incident patients

Subpopulation / Variable	RA,C1		RA,C2		RA,C3		RA,C4		RA,C5		RA,COV-19	
	Total events (mean)	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**	**Total events (mean)**	**Patients with events**
Number of events with main diagnosis of RA (in- and outpatient) in specialised healthcare	5409 (2.30)	2351	4946 (2.22)	2232	5191 (2.19)	2372	5109 (2.16)	2366	4856 (2.09)	2319	4743 (2.18)	2173
Number of outpatient events with main diagnosis of RA in specialised healthcare	5349 (2.28)	2347	4909 (2.20)	2230	5153 (2.18)	2365	5076 (2.15)	2360	4827 (2.09)	2315	4716 (2.18)	2166
Number of planned outpatient events with main diagnosis of RA in specialised healthcare	5224 (2.24)	2331	4818 (2.17)	2220	5047 (2.15)	2352	5021 (2.13)	2353	4766 (2.07)	2304	4634 (2.16)	2150
Number of outpatient digital events with main diagnosis of RA in specialised healthcare	695* (1.62)	429	767* (1.61)	475	883* (1.71)	512	830* (1.63)	509	982* (1.61)	611	2076 (1.76)	1181
Number of inpatient admissions with main diagnosis of RA in specialised healthcare	60 (1.05)	57	37 (1.16)	32	38 (1.19)	32	33 (1.10)	30	29 (1.12)	26	27 (1.13)	24
Number of planned inpatient events with main diagnosis of RA in specialised healthcare	39 (1.05)	37	17 (1.06)	16	22 (1.22)	18	12 (1.00)	12	15 (1.07)	14	10 (1.11)	9
Length of stay for inpatient admissions with main diagnosis of RA (days)	209 (3.67)	57	148 (4.63)	32	200 (6.25)	32	203 (6.77)	30	150 (5.77)	26	140 (5.83)	24

Mean number of events in each case = total number of events ÷ number of patients with events.
Results for the number of events for control subpopulations C1-5 that were significantly different (P<0.005) to the COVID-19 subpopulation are marked with an asterisk (*).
RA, rheumatoid arthritis.

The total events with main diagnosis of MS (in- and outpatient) in specialised care was between 1144-1511 in the control study periods, with no reduction in the COVID-19 study period (1223). The total patients were also comparable between control subpopulations and the COVID-19 subpopulation. The total events with main diagnosis of RA (in- and outpatient) in specialised care was between 4856-5409 in the control periods; during the COVID-19 study period, the total events were slightly lower at 4743. The total number of patients who had visits was also slightly lower in the COVID-19 study period (2173, compared to 2319-2372).

The number of planned inpatient visits, as well as the number of patients making these visits, was lower for the COVID-19 subpopulation than in the control study periods, for both MS and RA. The length of stay for inpatient visits was also shorter in the COVID-19 subpopulations; this was particularly notable for the MS patients, where the total length of stay during the study period was 64 days (27 patients), compared to 230 days (31 patients) in the previous study period (no significant difference). The number of planned outpatient events remained fairly continuous for both MS and RA and was not observed to change in the COVID-19 subpopulations. In all subpopulations, nearly all outpatient visits and approximately half of all inpatient admissions were planned.

For both MS and RA, there was a significant increase in the number of digital visits between the COVID-19 subpopulation and all control subpopulations ($P<0.005$). The number of patients with digital visits approximately doubled in both the MS and RA COVID-19 subpopulations compared to the controls, and the total number of events more-than-doubled for RA (2076 in the COVID-19 study period, compared to 695-982).

4.3 Number and cause of deaths

4.3.1 Incident patients

There were very few deaths in any of the MS incident patient control study periods; as a result, there were no data available on the most common underlying causes of death in each subpopulation. Only 1 death in the 2020 study period was attributed to COVID-19 (Table 7):

Table 7. Number of deaths for MS incident patients

Subpopulation	Total deaths*	Number of deaths with COVID-19 as an underlying cause
MS,C1	2	N/A
MS,C2	6	N/A
MS,C3	1	N/A
MS,C4	3	N/A
MS,C5	3	N/A
MS,COV-19	4	1

*Total deaths = the total number of deaths during each study period for patients in each of the defined subpopulations with a main diagnosis of MD.
Underlying causes of death were identified using ICD-10 codes (U07.1 or U07.2 for COVID-19).
MS, multiple sclerosis

The total number of deaths of RA incident patients during the study periods ranged from 31-43, and 39 patients died during the 2020 study period; of these, 8 deaths were attributed to COVID-19. Aside from these deaths, the most common underlying causes of death were all related to cancer, heart disease, or pulmonary disease (Table 8):

Table 8. Number and most common causes of death for RA incident patients

Subpopulation	Total deaths*	Most common underlying causes of death (number of deaths)
RA,C1	31	Malignant neoplasm, bronchus & lung (3) Other chronic obs. pulmonary disease (3) Malignant neoplasm of prostate (2) Hypertensive heart disease (2) Atrial fibrillation and flutter (2)
RA,C2	32	Malignant neoplasm, bronchus & lung (5) Malignant neoplasm of breast (2) Malignant neoplasm of ovary (2) Malignant neoplasm of prostate (2) Malignant neoplasm without specification of site (2)
RA,C3	40	Chronic ischemic heart disease (5) Malignant neoplasm, bronchus & lung (2) Acute myocardial infarction (2) Atrial fibrillation and flutter (2) Cerebral infarction (2)
RA,C4	32	Malignant neoplasm, bronchus & lung (4) Malignant neoplasm without specification of site (2) Acute myocardial infarction (2) Chronic ischemic heart disease (2) Other rheumatoid arthritis (2)
RA,C5	43	Acute myocardial infarction (6) Malignant neoplasm, bronchus & lung (4) Other rheumatoid arthritis (4) Chronic ischemic heart disease (3) Heart failure (3)
RA,COV-19	39	COVID-19 (8) Malignant neoplasm of pancreas (3) Chronic ischemic heart disease (3) Other chronic obs. pulmonary disease (2) Other interstitial pulmonary diseases (2)

*Total deaths = the total number of deaths during each study period for patients in each of the defined subpopulations. Underlying causes of death were identified using ICD-10 codes (U07.1 or U07.2 for COVID-19).
RA, rheumatoid arthritis.

4.3.2 Prevalent patients

For the MS prevalent patients, the total number of deaths was in the range 33-51, with 34 deaths during the 2020 study period (of which 2 were attributed to COVID-19). Although data on underlying causes of death were limited for these patients, it was possible to obtain data on the number of deaths that had MS as an underlying cause (Table 9):

Table 9. Number of deaths for MS incident and prevalent patients

Subpopulation	Total deaths*	Number of deaths with COVID-19 as an underlying cause	Number of deaths with MS as an underlying cause
PMS,C1	41	N/A	23
PMS,C2	33	N/A	21
PMS,C3	34	N/A	19
PMS,C4	39	N/A	26
PMS,C5	51	N/A	34
PMS,COV-19	34	2	19

*Total deaths = the total number of deaths during each study period for patients in each of the defined subpopulations with a main diagnosis of MS.
Underlying causes of death were identified using ICD-10 codes (U07.1 or U07.2 for COVID-19).
MS, multiple sclerosis.

Of the RA prevalent patients, the number of deaths in the control study periods ranged from 181-222. There were 233 deaths in the 2020 study period, of which 19 were attributed to COVID-19. Similarly to RA incident patients, most of the underlying causes of death related to cancer, heart disease, or pulmonary disease. However, in 4 of the 5 control subpopulations, rheumatoid arthritis also featured as one of the most common underlying causes of death (Table 10):

Table 10. Number and most common causes of death for RA prevalent patients

Prevalent patients	Total deaths*	Most common underlying causes of death (number of deaths)
PRA,C1	181	Acute myocardial infarction (10) Chronic ischemic heart disease (10) Malignant neoplasm, pancreas (8) Other chronic obs. pulmonary disease (8) Malignant neoplasm, bronchus & lung (7)
PRA,C2	195	Acute myocardial infarction (15) Other rheumatoid arthritis (13) Chronic ischemic heart disease (10) Nonrheumatic aortic valve disorders (9) Malignant neoplasm, bronchus & lung (8)
PRA,C3	212	Other rheumatoid arthritis (16) Acute myocardial infarction (14) Chronic ischemic heart disease (13) Malignant neoplasm, colon (11) Heart failure (9)
PRA,C4	194	Other rheumatoid arthritis (15) Malignant neoplasm, bronchus & lung (13) Other chronic obs. pulmonary disease (11) Other interstitial pulmonary diseases (11) Acute myocardial infarction (9)
PRA,C5	222	Malignant neoplasm, bronchus & lung (18) Acute myocardial infarction (16) Other rheumatoid arthritis (14) Other interstitial pulmonary diseases (10) Chronic ischemic heart disease (9)
PRA,COV-19	233	Malignant neoplasm, bronchus & lung (25) COVID-19 (19) Chronic ischemic heart disease (12) Acute myocardial infarction (10) Malignant neoplasm, colon (7)

*Total deaths = the total number of deaths during each study period for patients in each of the defined subpopulations. Underlying causes of death were identified using ICD-10 codes (U07.1 or U07.2 for COVID-19).
RA, rheumatoid arthritis.

5. Discussion

Although a number of publications utilising survey data have been released (George et al., 2020; Moss et al., 2020), this is (to the author's knowledge) the first registry-based study investigating how healthcare resource use for patients with a main diagnosis of MS or RA has changed during the COVID-19 pandemic. The sex distribution described in the present study reflects the expected ratio for both MS (Boström, Stawiarz, & Landtblom, 2014) and RA (Eriksson et al., 2013) patients, with a ratio of female-to-male patients of around 2:1, for both

diseases. The mean age of patients reflects previous findings on the age distribution of the two diseases in Swedish patients (Eliasdotter, Hildeman, Longfils, Nerman, & Lycke, 2018; Neovius, Simard, & Askling, 2011), and the higher mean age of prevalent patients compared to incident patients was also expected, given that the prevalent subpopulations included patients who had received their first main diagnosis as far back as 1987, so will by definition be older on average.

Overall, specialised healthcare use did not change in 2020 for MS incident patients, and whilst it slightly decreased for RA, this wasn't found to be significant. There was a reduction in planned inpatient visits for both MS and RA however, and the total inpatient length of stay more-than-halved during the 2020 study period for MS, compared with annual variation. This could suggest an unwillingness to visit the hospital during the pandemic, but it is difficult to say this with certainty as there appear to have been one or a few patients in each subpopulation that stayed in hospital for a longer period of time (considering the median vs. maximum values, Appendices 5 and 6). There was a sharp decrease in the number of RA prevalent patients in the COVID-19 study period compared with normal variation – a much more pronounced change than for MS prevalent patients – which could be due to the differing natures of the diseases i.e. clinical relapses are very common in MS (Kalincik, 2015) and require immediate medical attention, whereas much of the healthcare use for RA is non-urgent and instead aims at reducing chronic symptoms (Neovius et al., 2011), so these non-emergency medical procedures might have been postponed or cancelled as a result of resource reallocation during the pandemic.

One key finding of this study was that the number of digital healthcare visits significantly increased during the COVID-19 study period for MS and RA incident patient populations, compared to annual variation. Although digital visits have not traditionally been considered an adequate replacement for in-person care (Mann et al., 2020), the pressure that the COVID-

19 pandemic has placed on healthcare providers has put a spotlight on these types of services and led to rapid development. The Swedish healthcare provider's guide (Vårdgivareguiden) made the decision in March 2020 to amend care agreements to make it easier for providers to replace physical visits with digital ones ("Digitala vårdtjänster i nuvarande situation med covid-19," 2020), and emerging figures show that whilst many countries have seen a reduction in overall healthcare utilisation during the pandemic (Moynihan et al., 2021), there has been a growing trend of digital health visits in many of these settings (Mann et al., 2020). The results from the present study suggest that although MS and RA patients in Sweden have not reduced their utilisation of specialised healthcare resources during the pandemic, many have in fact migrated from physical to digital visits. Although it may be more convenient and "COVID-friendly", there are, of course, concerns with digital healthcare, with one being that disparities may arise as a result of variable levels of education and technological competency, and this might heighten health inequities. For example, one study in a Swedish setting found that whilst digital health tools were being widely implemented in response to the pandemic, these were not culturally-adapted to migrant communities, despite some of these communities being hit extremely hard by COVID-19 (Valeriani et al., 2020). Socioeconomic data such as education level, country of birth, and income were not included in the present study, but in future research it might be prudent to link this data from additional registers in order to better identify any social disparities and provide a foundation for tailoring future healthcare tools to help the most vulnerable groups within the population access them.

The number of deaths did not drastically change in the 2020 study period compared with normal annual variation; however, the relatively short timeframe of the study may have limited how much can be understood about the effect of the pandemic on this. It was interesting to note that in the 2020 study period, COVID-19 was listed as the second-most common underlying cause of death in RA prevalent patients, and first in RA incident patients.

However, more than one underlying cause of death may be recorded per person in Sweden, so it is impossible to determine from the data whether COVID-19 was directly responsible for these deaths, and whether patients had additional diagnoses that contributed to their death. A recent Swedish study (Bower et al., 2021) found that in March–September, 2020 there was an increase in all-cause mortality for patients with inflammatory joint diseases (such as RA), but that this was largely explained by comorbidities, which the present study did not have the scope to investigate.

One limitation of this study is that the 7-month study periods might not have completely captured the healthcare resource use of MS and RA incident patients. However, this period was selected due to large-scale COVID-19 study data becoming available for research. By including data from the same time period of each study period (i.e. 1st April – 30th November), the study also provided a reasonably comparable snapshot of healthcare resource use for each study period.

6. Conclusions & Implications

The extensive mandatory patient registers that are maintained by the NBHW in Sweden provide a strong foundation for research into healthcare resource use for different patient subpopulations. The ongoing struggle against COVID-19 in Sweden has put pressure on HCS in numerous ways, but as the results of the present study confirm, digital visits have grown in popularity for MS and RA patients in Sweden, and this could well be the beginning of a trend that continues into the future. The research would benefit from a follow-up once the COVID-19 pandemic has released its hold on HCS, in order to identify any lasting trends and effects on, for example, the long-term health and mortality of MS and RA patients in Sweden. It remains unclear whether healthcare resource use will return to ‘normal’ in the coming months

and years, but the pandemic has at least provided a unique opportunity for new technologies to thrive and grow in order to meet the changing needs of the population.

Now that this study has shown how healthcare resource use for MS and RA patients has changed during the pandemic, further research should also be done to explore the effect on healthcare resource use of patients with other autoimmune diseases such as Crohn's disease or ulcerative colitis, in order for public health authorities to identify areas where resources are needed in the event of a similar health crisis in the future. In fact, it has been suggested by some researchers (Valeriani et al., 2020) that the increased use of telemedicine prompted by the pandemic could point towards a more digital future for healthcare, due to improving technologies (propelled by necessity in the case of the pandemic), greater convenience, and increasing technological competence.

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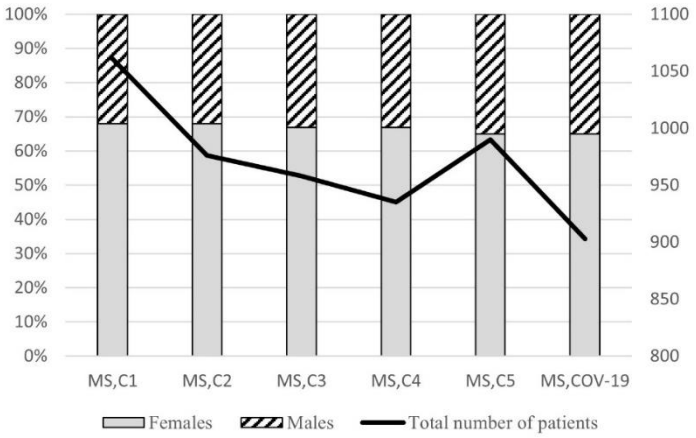
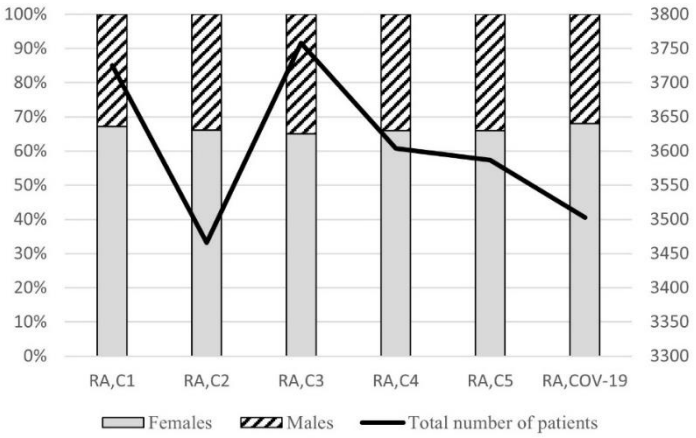
Appendices

Appendix 1. Total number of patients and sex distribution for MS and RA incident and prevalent subpopulations

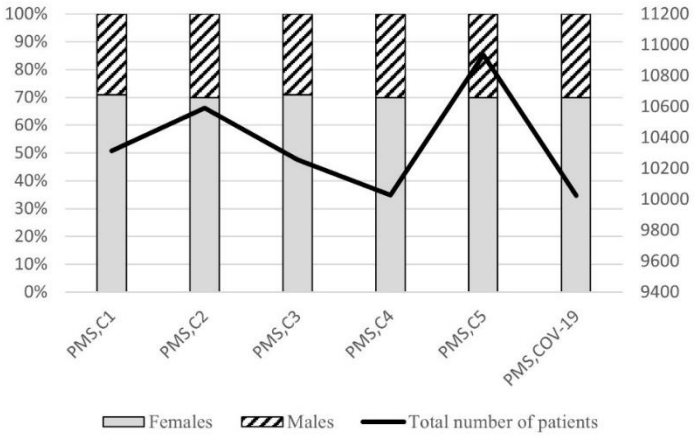
(a) MS incident patients



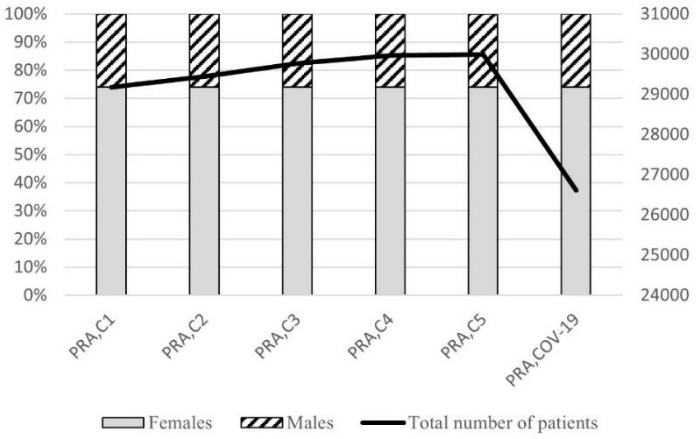
(b) RA incident patients



(c) MS prevalent patients



(d) RA prevalent patients

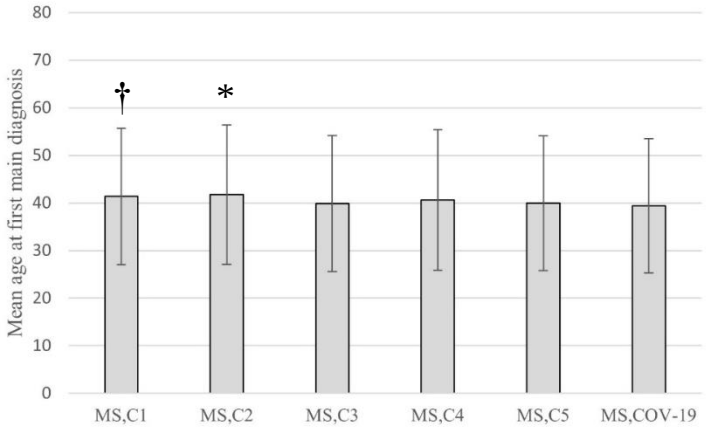


The above figures illustrate the total number and sex distribution of (a) incident MS patients, (b) incident RA patients, (c) prevalent MS patients, and (d) prevalent RA patients, for each of the defined subpopulations.

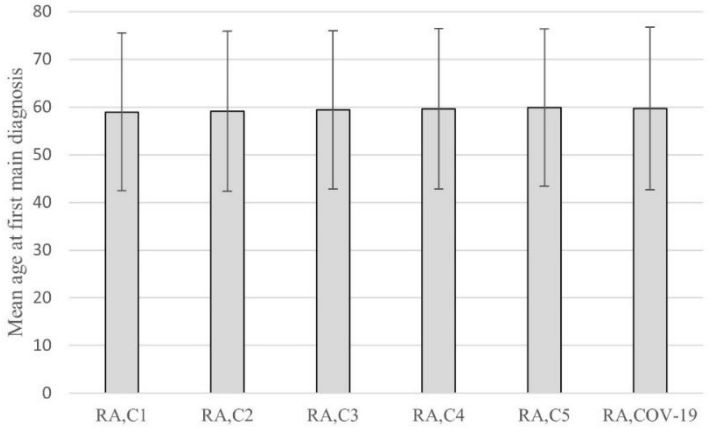
MS, multiple sclerosis; RA, rheumatoid arthritis.

Appendix 2. Mean age of MS and RA incident and prevalent subpopulations

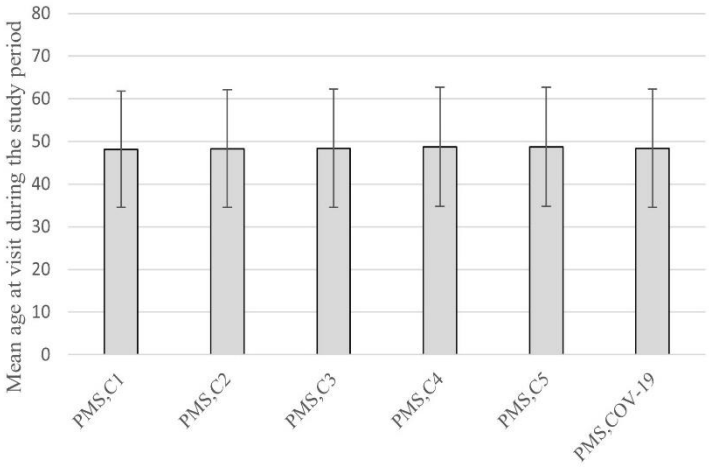
(a) Mean age at first main diagnosis of MS (incident patients)



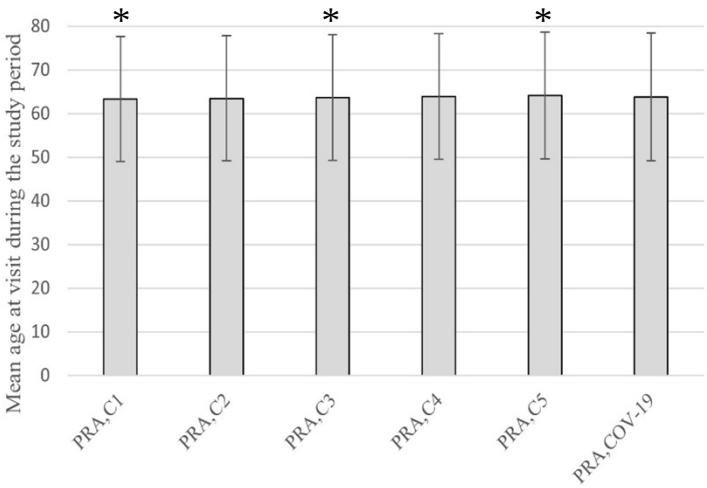
(b) Mean age at first main diagnosis of RA (incident patients)



(c) Mean age at healthcare event (MS prevalent patients)



(d) Mean age at healthcare event (RA prevalent patients)



The above figures illustrate the mean age in years at first main diagnosis for (a) incident MS patients, (b) incident RA patients, and the mean age in years at each healthcare event during the study periods for (c) prevalent MS patients, and (d) prevalent RA patients, for each of the defined subpopulations. Error bars show standard deviation.

Results that were significantly different to the COVID-19 subpopulation in each case are marked with an asterisk * ($P<0.005$) or a dagger † ($P<0.05$).

MS, multiple sclerosis; RA, rheumatoid arthritis.

Appendix 3. Full data – MS incident and prevalent patients, age and sex distribution

Subpopulation	Number of patients	Mean age at diagnosis (years)	Standard deviation	Subpopulation	Number of patients	Mean age at visit (years)	Standard deviation
MS,C1				**PMS,C1**			
Total number	1061	41.344	14.32307	Total number	10314	48.159	13.66837
Females	717	41.428	14.4278	Females	7296	48.206	13.68233
Males	344	41.169	14.12153	Males	3017	48.045	13.63614
MS,C2				**PMS,C2**			
Total number	976	41.749	14.64246	Total number	10591	48.286	13.78748
Females	664	41.633	14.82601	Females	7463	48.275	13.78003
Males	312	41.997	14.26427	Males	3128	48.313	13.8074
MS,C3				**PMS,C3**			
Total number	958	39.876	14.26061	Total number	10258	48.392	13.85305
Females	642	38.977	13.91341	Females	7243	48.236	13.83923
Males	316	41.703	14.79597	Males	3015	48.767	13.88133
MS,C4				**PMS,C4**			
Total number	935	40.629	14.73413	Total number	10027	48.714	13.95575
Females	630	40.159	14.22196	Females	7042	48.660	13.93134
Males	305	41.600	15.71908	Males	2985	48.842	14.01468
MS,C5				**PMS,C5**			
Total number	990	39.933	14.12345	Total number	10936	48.751	13.99452
Females	640	39.125	13.88856	Females	7709	48.795	14.00132
Males	350	41.411	14.4465	Males	3227	48.645	13.97986
MS,COV-19				**PMS,COV-19**			
Total number	903	39.405	14.09068	Total number	10026	48.392	13.8907
Females	586	38.159	13.48822	Females	7025	48.316	13.78635
Males	317	41.710	14.89045	Males	3001	48.571	14.13267

Appendix 4. Full data – RA incident and prevalent patients, age and sex distribution

Subpopulation	Number of patients	Mean age at diagnosis (years)	Standard deviation	Subpopulation	Number of patients	Mean age at visit (years)	Standard deviation
RA,C1				**PRA,C1**			
Total number	3725	58.951	16.54804	Total number	29177	63.291	14.30311
Females	2503	57.441	17.05592	Females	21551	62.534	14.60776
Males	1222	62.042	14.99525	Males	7626	65.431	13.17253
RA,C2				**PRA,C2**			
Total number	3466	59.126	16.77485	Total number	29444	63.467	14.36136
Females	2304	57.965	17.21752	Females	21752	62.759	14.6492
Males	1162	61.429	15.61434	Males	7692	65.469	13.31288
RA,C3				**PRA,C3**			
Total number	3758	59.379	16.56483	Total number	29773	63.670	14.36125
Females	2454	57.914	16.98388	Females	21965	62.899	14.67191
Males	1304	62.137	15.37798	Males	7808	65.841	13.21018
RA,C4				**PRA,C4**			
Total number	3604	59.620	16.79362	Total number	29963	63.931	14.38864
Females	2393	57.898	17.39302	Females	22210	63.136	14.74052
Males	1211	63.024	14.9763	Males	7753	66.210	13.06475
RA,C5				**PRA,C5**			
Total number	3587	59.856	16.4867	Total number	29996	64.189	14.51193
Females	2358	58.092	17.00637	Females	22219	63.296	14.87188
Males	1229	63.238	14.87289	Males	7777	66.740	13.10023
RA,COV-19				**PRA,COV-19**			
Total number	3503	59.686	17.03132	Total number	26607	63.756	14.65791
Females	2388	58.282	17.45691	Females	19618	62.825	14.94086
Males	1115	62.692	15.67172	Males	6989	66.369	13.49492

Appendix 5. Full data – Healthcare resource use for MS incident patients

Subpopulation	Nr. of patients	Total events	Mean (all)*	SD (all)*	Mean (events)†	SD (events)†	Median	Min	Max
MS,C1									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	727	1511	1.424128	1.754547	2.078404	1.770018	1	1	15
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	723	1454	1.370405	1.669208	2.011065	1.673449	1	1	15
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	719	1412	1.33082	1.590325	1.963839	1.577638	1	1	13
Nr of digital visits with main diagnosis G35 in specialised healthcare	157	302	0.284637	0.890219	1.923567	1.487303	1	1	9
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	47	57	0.053723	0.274614	1.212766	0.549156	1	1	4
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	37	41	0.038643	0.211499	1.108108	0.3148	1	1	2
Length of stay for inpatient admissions with main diagnosis G35	47	256	0.241282	2.223424	5.446809	9.216735	1	0	45
MS,C2									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	673	1317	1.349385	1.594818	1.956909	1.581021	1	1	14
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	672	1281	1.3125	1.509521	1.90625	1.475631	1	1	13
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	672	1237	1.267418	1.435521	1.840774	1.391888	1	1	13
Nr of digital visits with main diagnosis G35 in specialised healthcare	150	264	0.270492	0.813092	1.76	1.298838	1	1	9
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	27	36	0.036885	0.249455	1.333333	0.733799	1	1	4
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	17	21	0.021516	0.188239	1.235294	0.752447	1	1	4
Length of stay for inpatient admissions with main diagnosis G35	27	328	0.336066	3.216906	12.14815	15.46138	4	0	60
MS,C3									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	657	1273	1.32881	1.595915	1.937595	1.59192	1	1	20
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	656	1237	1.291232	1.526412	1.885671	1.510485	1	1	20
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	654	1187	1.23904	1.480722	1.814985	1.471846	1	1	20
Nr of digital visits with main diagnosis G35 in specialised healthcare	181	301	0.314196	0.819324	1.662983	1.146109	1	1	9
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	26	36	0.037578	0.247553	1.384615	0.637302	1	1	3
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	15	18	0.018789	0.157242	1.2	0.414039	1	1	2
Length of stay for inpatient admissions with main diagnosis G35	26	142	0.148225	1.792517	5.461538	9.634234	1	0	39
MS,C4									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	599	1144	1.223529	1.55012	1.90985	1.562056	1	1	14
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	592	1098	1.174332	1.467194	1.85473	1.46216	1	1	14
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	583	1045	1.117647	1.404741	1.792453	1.39826	1	1	14

Nr of digital visits with main diagnosis G35 in specialised healthcare	149	251	0.268449	0.755862	1.684564	1.097215	1	1	6
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	37	46	0.049198	0.261229	1.243243	0.494717	1	1	3
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	25	32	0.034225	0.224097	1.28	0.541603	1	1	3
Length of stay for inpatient admissions with main diagnosis G35	37	317	0.339037	2.79291	8.567568	11.3982	3	0	38
MS,C5									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	681	1371	1.384848	1.765978	2.013216	1.808022	1	1	24
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	674	1327	1.340404	1.719537	1.968843	1.762388	1	1	24
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	670	1283	1.29596	1.68028	1.914925	1.728228	1	1	24
Nr of digital visits with main diagnosis G35 in specialised healthcare	208	369	0.372727	0.927865	1.774038	1.270969	1	1	8
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	31	44	0.044444	0.27362	1.419355	0.672022	1	1	4
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	21	28	0.028283	0.218479	1.333333	0.730297	1	1	4
Length of stay for inpatient admissions with main diagnosis G35	31	230	0.232323	2.181493	7.419355	10.08885	2	0	32
MS,COV-19									
Nr of visits with main diagnosis G35 (in- and outpatient) in specialised healthcare	570	1223	1.354374	1.763953	2.145614	1.79773	1	1	15
Nr of outpatient visits with main diagnosis G35 in specialised healthcare	566	1189	1.316722	1.709312	2.100707	1.736266	1	1	15
Nr of planned outpatient visits with main diagnosis G35 in specialised healthcare	552	1130	1.251384	1.668123	2.047101	1.709786	1	1	15
Nr of digital visits with main diagnosis G35 in specialised healthcare	300	546	0.604651	1.182776	1.82	1.414545	1	1	9
Nr of inpatient admissions with main diagnosis G35 in specialised healthcare	27	34	0.037652	0.24176	1.259259	0.655896	1	1	4
Nr of planned inpatient visits with main diagnosis G35 in specialised healthcare	10	16	0.017719	0.193338	1.6	0.966092	1	1	4
Length of stay for inpatient admissions with main diagnosis G35	27	64	0.070875	1.190066	2.37037	6.593401	0	0	26

* Mean and SD calculated from number of events compared to total number of patients in the subpopulation.
† Mean and SD calculated from number of events compared to number of patients with events only.

Appendix 6. Full data – Healthcare resource use for RA incident patients

Subpopulation	Nr. of patients	Total events	Mean (all)*	SD (all)*	Mean (events)†	SD (events)†	Median	Min	Max
RA,C1									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2351	5409	1.452080	1.886885	2.300723	1.920592	2	1	20
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2347	5349	1.435973	1.861618	2.279079	1.891809	2	1	19
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2331	5224	1.402416	1.815745	2.241098	1.840939	2	1	19
Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	429	695	0.186577	0.623847	1.620046	1.028867	1	1	9
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	57	60	0.016107	0.132149	1.052631	0.225281	1	1	2
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	37	39	0.010469	0.106944	1.054054	0.229243	1	1	2
Length of stay for inpatient admissions with main diagnosis M05 or M06	57	209	0.056107	0.601482	3.666666	3.253203	3	0	18
RA,C2									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2232	4946	1.427005	1.806037	2.215949	1.821224	2	1	21
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2230	4909	1.416330	1.785967	2.201345	1.797086	2	1	20
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2220	4818	1.390075	1.754369	2.170270	1.764100	2	1	20
Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	475	767	0.221292	0.694498	1.614736	1.127426	1	1	9
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	32	37	0.010675	0.115975	1.15625	0.368902	1	1	2
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	16	17	0.004904	0.073887	1.0625	0.25	1	1	2
Length of stay for inpatient admissions with main diagnosis M05 or M06	32	148	0.042700	0.681582	4.625	5.481640	3	0	27
RA,C3									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2372	5191	1.381319	1.786037	2.188448	1.813158	2	1	19
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2365	5153	1.371208	1.768259	2.178858	1.791281	2	1	19
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2352	5047	1.343001	1.731887	2.145833	1.752069	2	1	19
Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	512	883	0.234965	0.753931	1.724609	1.266897	1	1	10
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	32	38	0.010111	0.117211	1.1875	0.470929	1	1	3
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	18	22	0.005854	0.089167	1.222222	0.427792	1	1	2
Length of stay for inpatient admissions with main diagnosis M05 or M06	32	200	0.053219	0.903863	6.25	7.683245	3	0	27
RA,C4									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2366	5109	1.417591	1.748598	2.159340	1.748080	2	1	18
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2360	5076	1.408435	1.737153	2.150847	1.735388	2	1	18
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2353	5021	1.393174	1.721351	2.133871	1.719836	2	1	18

Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	509	830	0.230299	0.725196	1.630648	1.200854	1	1	11
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	30	33	0.009156	0.103636	1.1	0.305128	1	1	2
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	12	12	0.003329	0.057614	1	0	1	1	1
Length of stay for inpatient admissions with main diagnosis M05 or M06	30	203	0.056326	0.849738	6.766666	6.537337	4.5	1	31
RA,C5									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2319	4856	1.353777	1.586162	2.094006	1.530183	2	1	13
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2315	4827	1.345692	1.575161	2.085097	1.517434	2	1	11
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2304	4766	1.328686	1.560588	2.068576	1.503674	2	1	11
Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	611	982	0.273766	0.744408	1.607201	1.054054	1	1	8
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	26	29	0.008084	0.098462	1.115384	0.325812	1	1	2
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	14	15	0.004181	0.068725	1.071428	0.267261	1	1	2
Length of stay for inpatient admissions with main diagnosis M05 or M06	26	150	0.041817	0.747505	5.769230	6.766432	3	1	27
RA,COV-19									
Nr of visits with main diagnosis M05 or M06 (in- and outpatient) in specialised healthcare	2173	4743	1.353982	1.714408	2.182696	1.711523	2	1	27
Nr of outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2166	4716	1.346274	1.707056	2.177285	1.703944	2	1	27
Nr of planned outpatient visits with main diagnosis M05 or M06 in specialised healthcare	2150	4634	1.322866	1.677260	2.155348	1.670106	2	1	23
Nr of digital visits with main diagnosis M05 or M06 in specialised healthcare	1181	2076	0.592634	1.107537	1.757832	1.261133	1	1	13
Nr of inpatient admissions with main diagnosis M05 or M06 in specialised healthcare	24	27	0.007707	0.096766	1.125	0.337831	1	1	2
Nr of planned inpatient visits with main diagnosis M05 or M06 in specialised healthcare	9	10	0.002854	0.058467	1.111111	0.333333	1	1	2
Length of stay for inpatient admissions with main diagnosis M05 or M06	24	140	0.039965	0.568144	5.833333	3.726131	5	0	14

* Mean and SD calculated from number of events compared to total number of patients in the subpopulation.
† Mean and SD calculated from number of events compared to number of patients with events only.