From DEPARTMENT OF MEDICINE
Karolinska Institutet, Stockholm, Sweden

EPIDEMIOLOGIC STUDIES ON RHEUMATIC MUSCLE INFLAMMATION, MYOSITIS

John Svensson

Karolinska Institutet

Stockholm 2017

Published by Karolinska Institutet.
Printed by E-Print AB 2017

ISBN 978-91-7676-895-2

Epidemiologic studies on rheumatic muscle inflammation, myositis

THESIS FOR DOCTORAL DEGREE (Ph.D.)

CMM Lecture hall L8:04, Karolinska University Hospital, Solna
8:00, 15 December 2017

By

John Svensson

Principal Supervisor:
Ingrid E. Lundberg
Karolinska Institutet
Department of Medicine
Rheumatology Unit

Co-supervisor(s):
Anna Tjärnlund
Karolinska Institutet
Department of Medicine
Rheumatology Unit

Marie Holmqvist
Karolinska Institutet
Department of Medicine
Clinical Epidemiology Unit

Elizabeth V. Arkema
Karolinska Institutet
Department of Medicine
Division of Clinical Epidemiology Unit

Opponent:
J. Antonio Aviña-Zubieta
University of British Columbia
Department of Medicine

Examination Board:
Ulf de Faire
Karolinska Institutet
Institute of Environmental Medicine

Aladdin Mohammad
Lunds Universitet
Vasculitis Epidemiology Research Group

Katja Fall
Örebro Universitet
Department of Medical Sciences

ABSTRACT

Observational study designs are often used in medical research. Swedish national registers have successfully been used as data sources for such observational studies in other rheumatic diseases. The Swedish health care system is tax funded and does together with the ability to link multiple national registers, allowing for longitudinal follow-up, make up a great setting for answering many research questions in a real world setting.

We identified 95 patients with idiopathic inflammatory myopathies (IIM) treated with different biologic therapies between 2000 and 2011 in **study 1**. All had previously been treated with prednisolone and at least one Disease modifying anti-rheumatic drug (DMARD). Rituximab was the most commonly used drug and even though large variations were seen in treatment length, no conclusions could be made regarding effectiveness.

Between 2007 and 2011 we found an average incidence rate of 11 per 1 000 000 person-years for IIM in Sweden in **study 2**. We observed a general increase in incidence with age and a peak was observed in the 50-79 year age groups and the highest incidence rate was in the 70-79 year age group. No difference in incidence was observed for different levels of education or population density and even though large variations were seen between Sweden´s 21 counties, no north to south gradient was observed.

In **study 3** we conducted a case-control study with IIM as the outcome and respiratory diseases and infections as the exposure. Previous infections were associated with increased future risk to develop IIM, OR 1.5. The risk was elevated for both infections of the respiratory tract and gastrointestinal tract but not for infections of the skin. Respiratory diseases were less common than infections but the relative risk was higher, odds ratio (OR) 2.3, and was elevated for both upper and lower respiratory tract diseases. A dose-response relationship between number of visits indicating exposure increased the risk of IIM for both respiratory diseases and infections.

In **Study 4** we used a cohort study design to address if the risk of stroke is increased following IIM diagnosis. We identified 663 newly diagnosed IIM patients and 6673 general population comparators without prior stroke or stroke-related events.

We found an increased risk of both ischemic and haemorrhagic stroke (HS), hazard ratio (HR) 1.7 and 2.3 respectively. Because the number of HS were rare we did not further analyse this outcome. For IS, the rate differences were the highest in the oldest age group (≥68) and in men relative risk of IS was highest in the youngest age group (<56 years).

When accounting for the competing risk of death, the HR for IS was decreased by 40% and the cumulative incidence was increased in IIM patients compared to the general population directly following diagnosis but they were similar after 10 years.

LIST OF SCIENTIFIC PAPERS

I. **Svensson, J.**, Holmqvist, M., Tjärnlund, A., Dastmalchi, M., Hanna, B., Magnusson, B.S., Lundberg, I., 2016. Use of biologic agents in idiopathic inflammatory myopathies in Sweden: a descriptive study of real life treatment. Clinical and Experimental Rheumatology. 35, 512-515

II. **Svensson, J.,** Arkema, E.V., Lundberg, I.E., Holmqvist, M., 2017. Incidence and prevalence of idiopathic inflammatory myopathies in Sweden: a nationwide population-based study. Rheumatology 56, 802–810

III. **Svensson, J.,** Holmqvist, M., Lundberg, I.E., Arkema, E.V., 2017. Infections and respiratory tract disease as risk factors for idiopathic inflammatory myopathies: a population-based case–control study. Annals of Rheumatic Diseases. 76, 1803–1808.

IV. **Svensson, J**., Lundberg, I.E., von Euler, M., Holmqvist, M.*, Arkema, E.V.*, The Risk of Ischemic and Haemorrhagic Stroke in Idiopathic Inflammatory Myopathies: a Swedish population-based cohort study. Submitted 2017

* Shared authorship

CONTENTS

LIST OF ABBREVIATIONS

IIM	Idiopathic Inflammatory Myopathies
ICD	International Classification of Diseases
SRQ	Swedish Rheumatology Quality register
NPR	National Patient Register
PDR	Prescribed Drug Register
PPV	Positive Predictive Value
RCT	Randomized Clinical Trial
DMARD	Disease Modifying Anti-Rheumatic Drug
DM	Dermatomyositis
PM	Polymyositis
IBM	Inclusion Body Myositis
JDM	Juvenile dermatomyositis
MSA	Myositis Specific Antibodies
MAA	Myositis Associated Antibodies
ILD	Interstitial Lund Disease
SLE	Systemic Lupus Erythematosus
IVIG	Intravenous Immuno-Globulin
RA	Rheumatoid Arthritis
TNF	Tumour Necrosis-Factor
PIN	Personal Identity Number
IMACS	International Myositis Assessment and Clinical Research Group

1 INTRODUCTION

1.1 WHAT IS EPIDEMIOLOGY?

Epidemiology is a research field with the goal to better understand disease and health conditions, their occurrence, causes and consequences. Common questions include:

- How common is a disease?
    - How many get the disease over a time period (incidence)?
    - How many have the disease at a specific time (prevalence)?
- What is the chance of experiencing a certain event after contracting a specific disease?
- Does a specific factor increase the risk of disease?

Most commonly, epidemiologists seek to investigate the effect of an exposure on an outcome. An example can be smoking´s effect (the exposure) on lung cancer risk (the outcome).

The most obvious way to investigate the effects of an exposure is via an experiment, like a clinical trial. You give one group of individuals packets of cigarettes and tell them to start smoking, while the other group is not allowed to smoke. Of course this type of study will never be conducted, because it is unethical, but we can imagine it could be possible. If you also randomize individual allocation of the groups (smoker/non-smoker) the average difference in outcome (lung cancer) between the two groups, is the average causal effect of the intervention. This type of experiment is called a randomized clinical trial (RCT) and has long been deemed the gold standard when trying to establish the causal effect of an intervention. The problem is that RCTs are not feasible in many situations, are difficult to make inferences from due to a highly selected study populations, might be unethical and finally, are extremely expensive. That is why observational data are used to answer many questions in medical research. Observational data are often collected in a less controlled setting than in RCTs and because individuals are not randomized to a specific intervention, the groups may differ in other factors. Such factors, like age, can affect both the exposure and outcome and therefore cause an association that is not casual. Factors causing such associations are what epidemiologists call confounders and such factors are often the core issue with observational data. Other sources of bias, or systematic errors, include how people have been selected into the population and the analyses and many of the methods used by epidemiologists are performed to reduce and remove these sources of bias. Of course there are other problems with observational data. Often, at least in the setting of this thesis, the data are not collected for the purpose of research and therefore there might be problems with data quality and missing information. Sweden has some incredible data sources for this type of research and is a great setting for conducting observational studies. We have a strong history of collecting

data in a structured way in national registers covering the whole population. Information on when you go to the hospital or when you pick up a prescription at the pharmacy, where you live and what level of education you might have is all listed in different registers. The personal identity number (PIN) (1) enables linking between different register source and makes it possible to follow individuals through time.

In this thesis I have used epidemiological methodology to answer questions on one specific disease, Idiopathic inflammatory myopathies (IIM), collectively called myositis. We have estimated disease occurrence, described treatments, investigated risk factors and looked at prognosis and risk of co-morbid conditions of this disease. In the first two studies, the disease and treatments were described while in the third and fourth study we have answered causal and prognostic questions.

1.2 IDIOPATHIC INFLAMMATORY MYOPATHIES

1.2.1 Clinical description

Idiopathic inflammatory myopathy (IIM) is a rare rheumatic disease mainly affecting skeletal muscle but other organs such as the lung and cardiac system are often involved suggesting it is a systemic inflammatory disease. Patients with IIM present a wide variety in symptoms and is commonly divided into three clinical sub diagnoses based on clinical, pathological, histology and laboratory findings. Some findings are shared, like muscle weakness and inflammatory infiltrates in skeletal muscle, while presence or absence of other help in the diagnostic work up and subgrouping of patients with IIM. Primarily proximal muscles are involved in polymyositis (PM) and dermatomyositis (DM) and respiratory muscles may also be involved in advanced cases (2). Inclusion body myositis (IBM) was acknowledged as a standalone entity in 1978 (3) while diagnostic criteria was introduced as late as 1995 (4). The most commonly used criteria for PM and DM was introduced in 1975 and were suggested both as diagnostic and classification criteria. (5,6). IBM is characterized by both proximal and distal muscle weakness, slower disease progression, over months and years, and generally poorer response to treatment compared to PM and DM (7). Muscle weakness normally progress over weeks to month for PM and DM and commonly affected muscles include neck-flexors, hip-girdle and shoulder muscles. For DM patients, the skin is also involved in form of characteristic rashes including heliotrope rash (affecting the eyelids) and Gottron papules (affecting knuckles and elbows). DM affects adults as well as children and is then called juvenile DM (JDM). For IBM quadriceps, finger flexors and pharyngeal muscles are typically involved affecting the ability to stand up from a chair, grip strength and ability to swallow. Other newer clinical sub diagnoses include immune mediated necrotizing myopathies and overlap myositis but they will not be discussed specifically in this thesis (8).

The cause of IIM is largely unknown but inflammatory infiltrates in muscle tissue of IIM patients are dominated by T-cells and macrophages, This feature of muscle tissue and the

presence of both myositis specific antibodies (MSA) and myositis associated antibodies (MAA), antibodies that can be present in other autoimmune diseases like systemic lupus erythematosus and systemic sclerosis (9), suggest that an autoimmune component is involved in the development of IIM (10). In addition, muscle degenerative features of disease may also play a role, in particular for IBM (11).

The diagnosis of IIM may be difficult to establish, it requires extensive investigation and misclassification is not uncommon. Advances in muscle histopathology, use of magnetic resonance imaging (MRI) and identification of MSA have made diagnosis easier. The classification criteria for PM and DM was for instance updated to include antibody and MRI findings in 1997 (12).

1.2.2 Treatment

1.2.2.1 Traditional pharmacological treatment

Traditionally IIM is treated with high doses of glucocorticoids, such as prednisolone, as first line treatment. The introduction of glucocorticoids has improved the care and prognosis for this patient group but many individuals experience side effects and have limited response to treatment (13). Disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate or azathioprine, are recommended for use in combination with prednisolone to decrease prednisolone side effects and to improve treatment outcome (10,13–17). Other DMARDs, such as cyclosporine as well as high-dose intravenous gammaglobulins (IVIG) are often used as second line therapies (10). Randomized control trials are largely lacking in patients with IIM thus treatment recommendation are mainly based on open studies and case reports. Using currently available therapies still many patients with IIM fail to regain their former muscle strength and there is a strong unmet need for new therapies (7,18).

1.2.2.2 Biologic therapies

The need for new therapeutical options is obvious for all sub groups of IIM and biological agents have, since their introduction in the beginning of the millennia, had a large impact on how other autoimmune diseases like rheumatoid arthritis (RA) are being treated. Biologics agents are, in contrast to tradition small molecular drugs, proteins which generally target specific signal molecules or cells and are therefore said to have a more precise effect compared to traditional pharmacological treatment. These biologic agents have been used to treat IIM but in an off-label setting, meaning they are not formally approved for treatment of IIM and in 2011, many different biologics in addition to mycophenolate mofetil, tacrolimus, cyclophosphamide were included in guidelines as third line therapies (10).

Multiple case reports, case series and few prospective clinical trials have reported on use and effectiveness of biologics in IIM, often with varying results. Early case reports presented positive treatment responses for TNF-inhibitors (19–21) while later reports were more

contradicting. TNF-inhibitors have both been associated with increased number of flares (22) and found to have a favourable response in some patients (23,24). The same is true for anakinra which has shown a favourable response in one study on overall IIM (25) while no effect was seen in a small pilot study of IBM patients (26). Rituximab has been reported to be effective in small pilot studies (27,28) and case reports (29–31) while the largest trial to date, a randomize placebo controlled trial, the Rituximab in Myositis (RIM)-study, including 200 patients, failed to reach the primary end-point, time to improvement (32). Still, 83 % of rituximab-treated patients with refractory adult and juvenile DM and PM met the definition of improvement at the end of the 44-week trial RIM study and a post hoc analysis of the results found that anti-Jo1-antibodies, the most common MSA, was associated with a favourable response (33). Abatacept has been reported as effective in three case reports (34–36) but had not been investigated in any larger trial when planning this thesis. In summary, the use and safety of biologic drugs still remain unknown and further studies are needed to investigate how they are used in IIM.

1.2.3 Epidemiology/Occurrence

In Sweden, incidence of PM and DM has previously been estimated to 7.6 per 1 000 000 person-years between 1984 and 1993 in one county, Gävleborg (37) while incidence for IBM has been estimated to 2.2 per 1 000 000 person-years in Gothenburg between 1983 and 1992 (38). Internationally, the occurrence of IIM has been estimated in many previous studies but with large variation of estimates (Figure 1). The available estimates of incidence rates for IIM range between 1.2 and 66 per 1 000 000 person-years (37,39–48). The prevalence of IIM has also varied greatly in previous studies, between 2.9 to 3.4 per 100 000 (40,43,47–52). Register based studies from the U.S. and Canada have estimated the highest prevalence of IIM, between 17 and 34 per 100,000 (40,47,53).

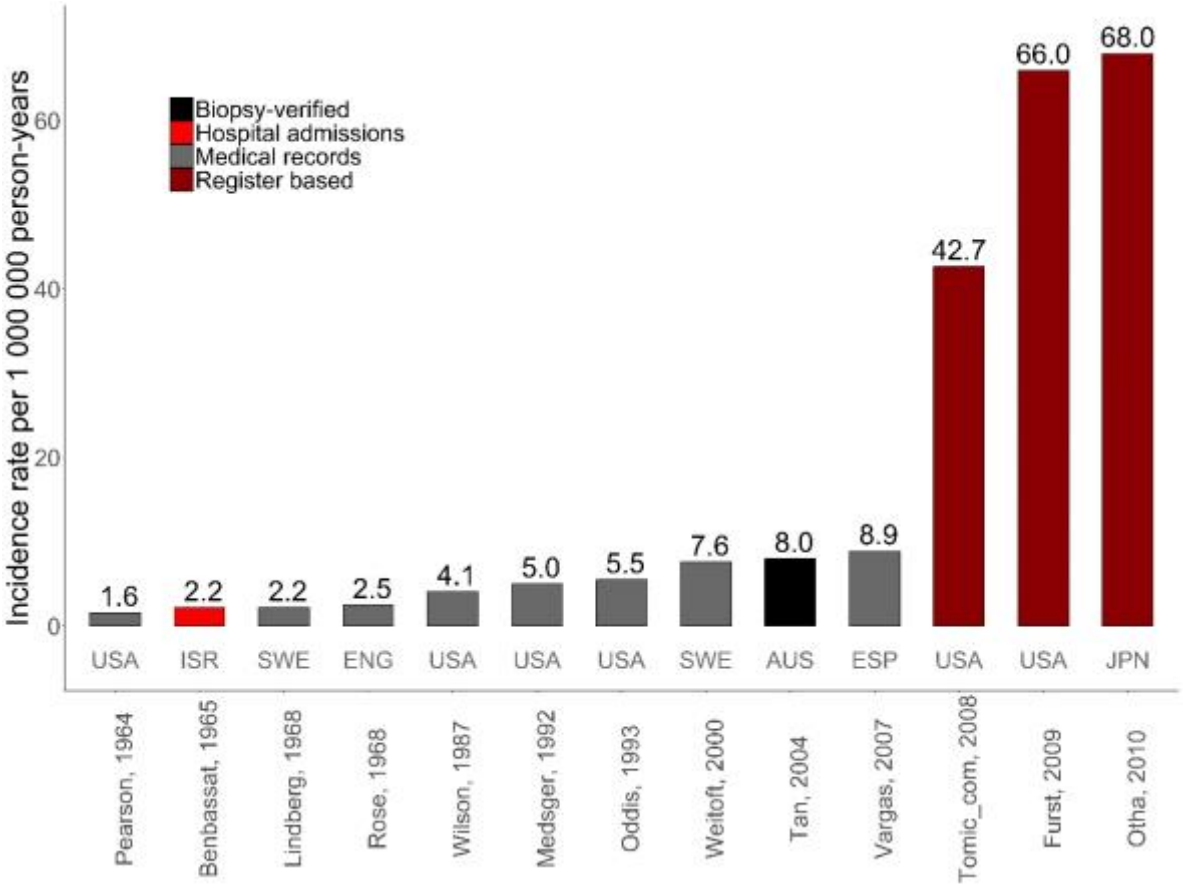

Figure 1. Previously estimated incidence rates of idiopathic inflammatory myopathies.

It is reasonable to believe that the estimates would vary to some degree between different populations due to different genetic and environmental factors but much of these large differences can probably be explained by differences in methodology. The definition of IIM, increased awareness and the introduction of new diagnostic criteria all affect estimates. Some studies are based on investigations of single hospitals or local regions using retrospective chart reviews and diagnostic criteria to ascertain IIM diagnosis. The specificity when using medical charts to ascertain diagnosis is often high but there is a high risk of missing cases due to the stringency of most criteria and the difficulty of collecting information on these criteria retrospectively. Also, estimates from small geographical regions are uncertain, particularly for rare disorders, because of the small source population generating cases. All of the above factors make comparisons between studies difficult and the true occurrence of IIM is still uncertain.

1.2.4 Risk factors

Not much is known about the aetiology of IIM but as with many other autoimmune diseases it is believed to be caused by an interaction of environmental and genetic risk factors. For IIM, both infectious and non-infectious agents have been suggested as potential environmental risk factors but most studies available on IIM risk factors are based on case studies or series, historical cohorts or have used a cross sectional design (54) making it difficult to say anything

about the temporality of the association. Still, evidence of temporal clustering (39,40,42,43,48) found in various regions of the world (USA, Israel, Australia and Japan) and spatial clustering (49,55) could support the hypothesis of involvement of environmental factors and specific factors have been suggested including UV-light (56,57). Additionally, some studies have found seasonal variation in incidence of IIM (58,59) which would further support this hypothesis. On the other hand, others have failed to find evidence of such variations (55).

1.2.4.1 Respiratory risk factors

The lung is the most commonly involved extramuscular organ in IIM and up to 65% of patients have been reported to show signs of interstitial lung disease (ILD) at time of diagnosis (60,61) and 78% of prevalent patients (62). Respiratory exposures have previously been suggested to be triggers of disease or that the immunological events that eventually will target muscles actually start in the lung. No clear evidence for this causal path have been presented but the finding of an interaction between smoking and the allele HLA-DRB1*03 could predict anti-Jo-1 antibody production could support this hypothesis (63). A strong reason for us to include respiratory risk factors in the third study was preliminary data from a retrospective case control study carried out at Karolinska using questionnaires which found that history of pulmonary disease was present in IIM to a higher degree compared to controls (64) but the role of pulmonary inflammatory conditions like infections, ILD, asthma and chronic obstructive pulmonary disease (COPD) in the development of IIM has not been well investigated

In rheumatoid arthritis, smoking is an established risk factor for developing disease and there is a strong gene environment interaction between certain HLA-DR4 genotype and smoking (65,66). Also other airway exposures including silica dust (67) traffic pollution (68) and textile dust (69) and it is hypothesized that inflammatory events in the lungs may play a role in the immune activation leading to anti-citrullinated protein antibodies that later may lead to rheumatoid arthritis.

1.2.4.2 Infectious risk factors

Many types of infections have previously been reported to be associated with IIM and suggested as potential triggers of disease. Both viral, including Epstein Barr virus, hepatitis, retroviruses, enteroviruses (70–74) and bacterial infections such as streptococcus, tuberculosis and borrelia (54,75) have been suggested while one study have presented negative results on enterovirus (76). Reports of infectious risk factors in IIM is primarily presented from case reports or case studies or have been assessed at or after disease diagnosis through questionnaires or antibody tests making results uncertain and population based studies are lacking.

Autoimmune disease can follow infection by multiple different mechanisms. Either through the effect of drugs used to treat infections like antibiotics and antiviral medication, change in the gut microbiome, molecular mimicry or a general activation of the immune system (77,78). In other autoimmune diseases, the same link with infections have been suggested but a recent study on RA reported that a history of gut infection decreased the risk to develop RA (79). Thus the role of infections in autoimmune diseases has not been clarified.

1.2.5 Co-morbidities and prognosis

The care of IIM has certainly improved over time but the disease is still associated with significant increased mortality and morbidity mainly due to cardiovascular disease, pulmonary disease and cancer (80). Quality of life is often affected because of impaired muscle function and up to 80% of patients have a chronic or cyclic disease with frequent repeating flares (81). Reported survival has varied but improved over time (80,82–84).

1.2.5.1 Cardiovascular manifestations

The most common heart manifestations in IIM are conduction abnormalities and arrhythmias. These manifestations are normally sub-clinical and might not have been given much attention in IIM care. An increased risk for more serious CVD, like VTE (85,86), have, however, been shown in some studies but much is still unknown about the risk for other serious CVD like unstable angina, ischemic stroke and myocardial infarction.

1.2.5.2 Stroke

Stroke is the third most common cause of death in Sweden and approximately 20 000 strokes occur yearly in Sweden (87) . Stroke is defined as an event inhibiting the blood flow to a part of the brain either via blockage (ischemic stroke) or the rupture of a blood vessel (haemorrhagic stroke). Stroke is a complicated event to treat acutely because of them being the complete opposite of each other regarding treatment. Stroke often has catastrophic consequences and besides death, often leads to damage of parts of the brain with neurological deficits in survivors with large impact on daily life.

An increased risk have been shown in other inflammatory disease like SLE and RA (88–90) and a few previous cohort studies have identified an increased risk of stroke in PM and DM patients with relative risk ranging between 1.67 and 3.46 (91–93). However, failure to separate IS from HS and differences in study population selection (hospitalized cases), follow-up and comparison groups still make the risk in IIM uncertain and none has taken the competing risk of death into account.

1.2.5.3 Cancer

Case reports first started reporting about the association between PM and DM with solid tumours and it has since then been established in epidemiologic studies and is associated with

worse prognosis (80). Risk of cancer is increased both before and after diagnosis in one meta-analysis (94) while another reported DM being associated with a wide range of cancers while PM only was associated with a few types of cancers (95).

2 OBJECTIVES / AIMS

The overall aim of this thesis was to further the understanding of the rheumatic muscle disease IIM by using observational study designs and multiple Swedish register sources.

The specific aims include:

1. To describe the use of biologic agents in treatment of IIM in Sweden by identifying all patients treated with biologics in Sweden (**study 1**).
2. To develop a robust register based algorithm to identify IIM and to estimate the occurrence of disease, how it varies with age, gender, region and level of education (**study 2)**.
3. To investigate if infections and respiratory diseases affect the risk of developing IIM (**study 3**).
4. To assess the risk of stroke in patients with IIM, to identify specific risk groups and describe how risk varies during disease course (**study 4**).

3 MATERIALS AND METHODS

3.1 SETTING

The Swedish health care system is tax funded and provides public health care and prescription drugs succeeding a threshold of 1100 SEK and 2200 SEK per year respectively since 2012 (900 SEK and 1800 SEK prior 2012). In Sweden, patients with IIM are typically seen by specialist in rheumatology or neurology or in some regions/hospitals, specialist in internal medicine or dermatology are responsible for their care. Individuals under 18 years of age are treated at paediatric clinics. The reporting to administrative register sources are mandatory in a specialist outpatient and inpatient setting which results in almost complete coverage of such health care contacts for all Swedish residents.

The personal identity number (PIN) consists of 10 digits allocated to all Swedish residents since 1947 and administered by the Swedish tax agency (1). The PIN is used to identify patients in different register sources and enables individual information from different register sources and the possibility to combine such individual information.

3.2 DATA SOURCES

Here different register sources used in this thesis are described.

3.2.1 National health registers

3.2.1.1 The Swedish National Patient Register

The most important source used in this thesis is the national patient register (NPR) used to identify the majority of diseases, exposures, outcomes and other variables.

The NPR covers nationwide information on hospitalizations since 1964, nationwide since 1987, and outpatient visits in non-primary care since 2001. The coverage is 100% for inpatient care and somewhat lower for outpatient care mainly due to lower reporting from private and psychiatric care (96). Information on primary and contributory diagnoses and procedures are coded according to International Classification of Disease (ICD) versions 7 through 10 for each visit, and version 10 (ICD10) has been used since 1997.

3.2.1.2 The Prescribed Drug Register

The Prescribed Drug Register (PDR) lists information on all dispensed prescriptions from Swedish Pharmacies since July 2005 while no information on drugs given in ambulatory care is registered. Information on drugs is stored using Anatomical Therapeutic Chemical (ATC) code, amount and route of administration.

3.2.1.3 The Cause of Death Register

The cause of Death Register includes information on historical deaths since 1961. Historical data is available from 1952-1960. From year 2011 the register includes data on all deceased individuals who at the time of death were registered in Sweden. From 2012 it includes all deaths occurring in Sweden. Diagnoses are, in contrast to the NPR, coded using the international ICD version and not the Swedish version (97).

3.2.1.4 The Swedish Cancer register

Registration of all newly detected cancers is mandatory by all care providers in Sweden. The Swedish Cancer register has coverage of 100% of all cancers that have been detected in Sweden since 1958. Information on diagnosis date, cancer type and site is available in the register as well as reporting hospital and department (98).

3.2.1.5 The Swedish Tuberculosis Register

The Swedish Tuberculosis Register includes information on all culture-confirmed cases of tuberculosis in Sweden since 1969, based on the mandatory reporting from treating doctor and tuberculosis laboratories.

3.2.2 The Swedish Rheumatology Quality Register (SRQ)

SRQ is a quality-of-care register used in everyday clinical practice to store information on patient diagnosis, treatment, and disease activity variables longitudinally since 1995 and is

governed by the Swedish Rheumatology Society. The SRQ includes IIM specific variables including the International Myositis Assessment and Clinical Studies (IMACS) core set measures since 2003 (99). The coverage of individuals with early RA was 78% in 2012 depending on the register based definition 83.7% of prevalent cases were included in SRQ in 2016 while the coverage of IIM is not known (100,101). In SRQ, IIM patients are assigned specific sub-diagnoses: PM, DM, IBM, JDM and unspecified myositis.

3.2.3 Demographics databases

3.2.3.1 The Total Population Register

Statistics Sweden has been responsible for the Total Population Register since 1969. The TPR is a subset of the population register at the Swedish Tax agency and includes data on residency, migration, civil status and more and was used to sample matched general population controls for identified IIM individuals (102).

3.2.3.2 Longitudinal integration database for health insurance and labour market studies (LISA)

LISA includes all individuals older than 16 (15 years since 2010) years and registered in Sweden as of December 31 of each year and holds longitudinal information on educational level, health insurance usage and labour market availability (103).

3.3 METHODOLOGICAL CONSIDERATIONS

This section will give a brief overview of epidemiological study designs and other methodological considerations in this thesis.

3.3.1 Sources of bias

Here I present the three sources of bias, or systematic error, that can be present in observation studies and which can lead to incorrect estimates. These biases commonly have other names but structurally they can be classified into three categories.

I will describe the structure of these biases by using directed acyclic graphs (DAGs). DAGs consist of different nodes, representing different variables, connected by arrows, or edges. Arrows indicate a causal relationship between two variables and the variable at the start of the arrow must both proceed and affect the variable at the end of the arrow (Figure 2).

Figure 2. Simple directed acyclic graph where A causes Y.

For there to be an effect of A on Y there must be a direct path going from A to Y (through any other possible mediators). There are only two types of unblocked paths, *direct paths and backdoor paths* through a shared ancestor in DAGs. A marginal (crude) association requires an unblocked path between the two variables but this does however only imply association and not a causal effect. Direct paths imply a casual effect while a backdoor paths only imply an association between the variables (104).

3.3.1.1 Measurement bias

Data are seldom perfect and one must therefore take into consideration the risk of having incorrect information. The register sources that we are using in these studies are great and even though they present a detailed reflection of reality this reflection will always be somewhat distorted. Data can be coded incorrectly or the algorithm used to define a disease state might be incorrect.

This is called misclassification, meaning that the measured value is not equal to the true value and can lead to bias. Misclassification can be differential, meaning that measurement of exposure is affected by the outcome status (Figure 3), or the other way around. Non-differential misclassification normally affect the estimate towards the null while differential measurement error can either increase or decrease an association.

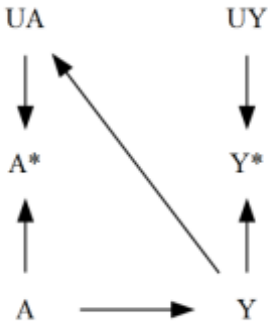

Figure 3. One example of differential misclassification where A = exposure, A = measured value of A, UA = measurement error for A, Y = outcome, Y* = measured value of Y and UY = measurement error of Y.*

In this thesis we estimate the positive predictive value (PPV) and specificity to describe the risk of misclassification of our register based definition of IIM sub diagnoses. *PPV* is the proportion of your positive cases (true positive + false positive) that are actually positive (true positive) from your test while *sensitivity* is the proportion of positives (true positive) that are correctly identified as such.

$$PPV = \frac{True\ positive}{True\ positive + false\ positive}$$

$$Sensitivity = \frac{True\ positive}{True\ positive + false\ negative}$$

3.3.1.2 Confounding

Confounding can arise in the presence of common causes of exposure and outcome. The presence of confounding in a study creates or affects the association between exposure and outcome. The idea of confounding can be described in a DAG. In Figure 4 it is clear that a change in C would affect both A and Y and therefore create a non-causal association between A and Y (105).

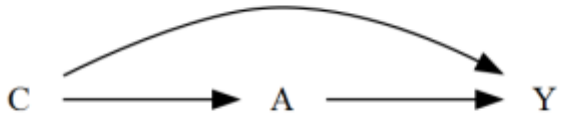

Figure 4. A directed acyclic graph describing confounding. C = confounding variable, A = Exposure, Y = Outcome

3.3.1.3 Selection bias

Selection bias historically has had many different definitions and one common definition, which we will use in this thesis, is conditioning on a common effect of the exposure and the outcome (Figure 5). Common names of different types of selection bias include incorrect selection of controls in case-control studies, informative censoring, volunteer bias (baseline selection) and healthy worker effect which all can be described the same way structurally (106).

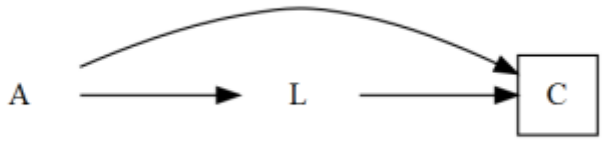

Figure 5. Directed acyclic graph of selection bias. The box around C means we are conditioning on this variable.

If confounding is very intuitive after just thinking about it for a bit, selection bias is the opposite and is often difficult to discover. Selection bias may arise when individuals are selected into the analyses based on certain characteristics. However, one should keep in mind

that selection is not necessarily the same as selection bias. In cohort studies, it is common to select a specific group of individuals to optimize analyses (confounding distribution, number of outcome events etc.). This does not necessarily introduce selection bias but might affect the generalisability (external validity) of your findings. Rather, the selection must be affected by both exposure and outcome for selection bias to occur and result in biased estimates (105,107).

3.3.2 Epidemiological study designs

3.3.2.1 Cohort studies

Cohort studies are the most intuitive study designs for investigating exposure-outcome relationships. Individuals are categorized on exposure status, followed up until the event of interest (outcome) occurs or until censoring and the frequency of the outcome is compared between the exposure groups. In contrast to randomized experiments, when exposure status is assigned through randomization, exposure varies for reasons outside of the investigators control in observational cohort studies. While randomization is the best weapon against confounding RCTs often have short follow-up and often include a highly selected population. Observational cohorts on the other hand have long follow-up and high generalizability by sampling a large representative part of the source population. Still, because randomization is not performed confounding must be handled in other ways, often through conditioning on the confounding variables.

3.3.2.2 Case-Control studies

To study a rare disease in a cohort study one would need a large number of person years, which can be retrieved either through a large number of participants enrolled at baseline or a very long follow-up period. This is often not efficient and instead the case-control design is often preferred. In case-control studies, instead of collecting data on all exposed and unexposed one can instead select all individuals with the outcome of interest (cases) and then sample controls from the same source population as from which the cases arose. The whole study population is then classified based on whether they previously have been exposed and the controls are used to describe the distribution of exposures and confounders in the source population. If the prevalence of the disease is rare and controls are sampled from a dynamic population at the time each case arise, the odds ratio, used to estimate association between exposure and outcome in case-control studies, approximates the incidence rate ratio (108,109).

3.3.2.3 Matching

When controls in a case-control study or comparators in a cohort study are not sampled at random but rather are selected based on specific attributes it is called matching. In the studies included in this thesis individuals are sampled from the general population matched on age,

sex and place of residence at the time of a case´s first IIM diagnosis. This is called density sampling or risk set sampling (109,110). Matching fulfils different purposes in cohort studies and in case-control studies. Matching on certain characteristics in a cohort study that may affect both the exposure and the outcome is one way of dealing with confounding because the distribution of matching variables are the same for the exposed and unexposed group (111). In case-control studies the matching first affects the way the odds ratio is interpreted and by using density sampling, the odds ratio used to estimate the association between exposure and outcome in case-control studies estimates the rate ratio directly but when sampling is carried out from a dynamic population, the analyses have to take matching on time in to account (conditioning on the matching strata) (110). Thus, matching in a case-control study does not, in contrast to cohort studies, remove the potential confounding effect of the matching variables. Instead, matching is used for a more efficient statistical analysis, ensuring an even distribution of cases and controls in the matching strata (108).

3.4 STUDY POPULATIONS

Individuals with IIM were identified using the same methodology for all four studies, namely via the NPR using ICD10 codes (Table 1) and via SRQ. The linkage of multiple registers, described in the section *Data sources* enabled us the get longitudinal information, both before and after IIM diagnosis, on medical conditions requiring healthcare, drug dispensations, cancer, deaths as well as census data, including educational level and place of residence, from Statistics Sweden (Figure 6). The validity of ICD codes used to identify IIM have previous been investigated in Sweden partly including the same study population as in this thesis. The PPV was then estimated to be 88% (64).

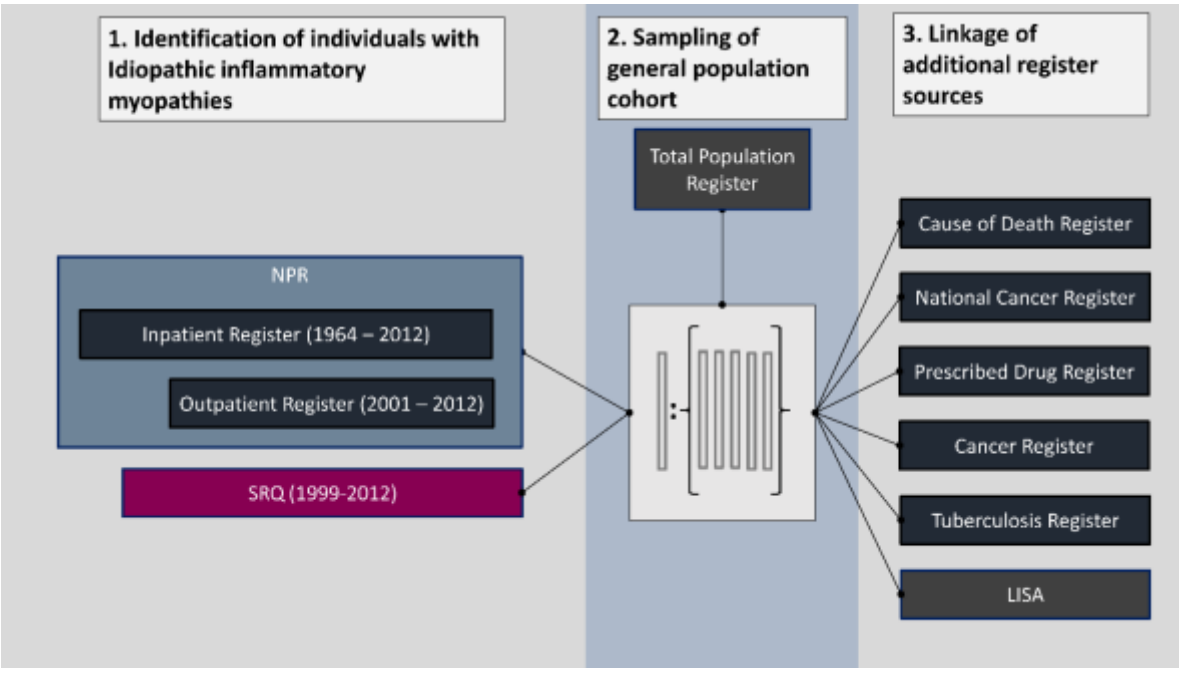

Figure 6. Description of sources used to 1. Identify IIM from the National Patient Register (NPR) and the Swedish Rheumatology Quality register (SRQ), 2. Sample age, sex and place of residence matched general population cohort and 3. Linking of additional data s

Table 1. ICD10 codes used to identify idiopathic inflammatory myopathies from cases from the national patient register.

ICD10 code	Text	Diagnosis
G724	Inflammatory myopathy, not elsewhere classified	Inclusion body myositis
M330	Juvenile dermatomyositis	Juvenile DM
M331	Other dermatomyositis	Dermatomyositis
M332	Polymyositis	Polymyositis
M339	Dermatopolymyositis, unspecified	Dermatomyositis
M608	Other myositis	Unspecified
M609	Myositis, unspecified	Unspecified

ICD10 = International Classification of Disease version 10

3.4.1.1 IIM patients

In **study 1** a wider range of ICD codes were used for identification than for studies 2-4 because the registers were only used to identify individuals suspected of having IIM. The initial identification was then followed by medical chart review which enabled verification of diagnosis. Medical charts were reviewed for individuals with a visit indicating IIM and biologic treatment. Biologic agents were identified from the PDR (Table 2) and SRQ and subjects were included after verifying diagnosis and treatment indication. A physician given IIM diagnosis was sufficient for inclusion but diagnosis was also verified using diagnostic criteria (4–6,12). Also, only had NPR data up until December 31 2011 as it was based on a different and older linkage of the registers only including suspected IIM individuals. Individuals were identified between 2000 and 2011.

Table 2. List of drugs used to identify DMARDs, corticosteroids and biologic agents from the prescribed drug register.

Group	ATC code	Drug
DMARD	L04AA13	leflunomide
	L04AA06	mycophenolate mofetil
	L04AX01	azathioprine
	L04AD01	cyclosporine
	L04AD02	tacrolimus
	L04AX03	methotrexate
	L01BA01	
	L01AA01	cyclophosphamide
Corticosteroids	H02AB06	prednisolone
Biologics	L04AB02	infliximab
	L04AB01	etanercept
	L01XC02	rituximab
	L04AC03	anakinra
	L04AA24	abatacept
	L01XC04	alemtuzumab
	L04AB04	adalimumab

The aims of **study 2** were both to develop a register based algorithm for identification of IIM which were to be used in the following studies. Also, we wanted to estimate the incidence rate and prevalence of IIM in Sweden. Possible IIM individuals were identified as for study 1 but study 2 only included visits at specialist clinics (rheumatology, neurology, internal medicine, dermatology and paediatric clinics) and ICD10 codes M60.8-9 were excluded in the main analyses due to primarily being used in diagnostic work up of IIM patients. Also, as both outpatient visits and hospitalization data were available 2001 through 2012, cases were identified between 2002 and 2011 to allow for a 12 month wash-out period prior study start to exclude prevalent cases, and 12 months following the first visit to allow for sufficient time for a follow-up visit.

Three incidence and three prevalence case definitions were tested to describe robustness of estimates.

Incidence case definitions:

The index date was defined as the first ever IIM visit between 2007 and 2011 identified from the NPR or SRQ. The (**1**) *liberal* case definition was defined as having one or more visits while the (**2**) *base case definition* required one more visit 1-12 months following the index visit to exclude individuals under evaluation and possible miscodings if not registered in SRQ. The (**3**) *strict* case definition additionally required one or more dispensing of prednisolone or DMARDs within 12 months.

Prevalence case definitions:

The prevalence (**2**) *base case* definition required ≥2 specialist visits indicating IIM while the (**1**) *liberal* only required ≥1 visits while the (**3**) *strict* also required dispensation of prednisolone or DMARDs.

The base case definition from **study 2** was then used to define adult (≥18 years) IIM from the registers in **studies 3-4**.

3.4.1.2 Comparators

Studies 1-2, were pure descriptive studies only including individuals with IIM and therefore no comparison group was necessary. For **studies 3-4 however,** we wanted to investigate causality and prognosis so a control cohort sampled from the TPR was matched on age, sex and place or residence 10:1 to each case at time of first IIM visits and were used as controls in **study 3** and comparators in **study 4**.

3.5 STUDY 1 – BIOLOGICS IN IIM

Data on treatment, demographics, disease duration and disease activity variables were collected from medical charts and SRQ and described at start of first biologic therapy. Reason for stopping treatment was assessed within two years from starting biologic treatment.

3.6 STUDY 2 – OCCURRENCE OF IIM

Overall incidence was estimated between 2007 and 2011 and prevalence was estimated on 1 January 2012 and stratified by age, sex, and clinical sub-diagnosis. In addition, age and sex standardized incidence rates were calculated for education level and place of residence.

In addition, a number of alternative case definitions were tested in sensitivity analyses including varying the time allowed between first and second visit and excluding cases that had dispensed immunosuppressive medication within 6 and 12 months prior first IIM visit.

We also estimated the specificity and PPV for included ICD10 codes ability to define clinical IIM sub-diagnosis with SRQ given diagnosis as the gold standard.

3.7 STUDY 3 – RISK FACTORS FOR IIM

In **study 3**, we wanted to investigate risk factors for IIM and therefore a case-control study was conducted with IIM as the outcome and respiratory diseases and infections as the exposure. Adult (≥18 years) newly diagnosed individuals with IIM were identified between 2002 and 2011 using the base case incident definition from study 2 and the first registered visit was used as the index date. Visits indicating exposure were identified from the NPR using ICD codes. Infections included all infections while respiratory diseases excluded respiratory infections. Infections were categorized based on location, including gastrointestinal, respiratory and skin while respiratory diseases were categorized into upper and lower respiratory infections. In addition to the NPR, tuberculosis was identified from the tuberculosis register. To decrease the risk of detection bias and reversed causality (outcome

causing the exposure) we introduced a latency period of 12 months between exposure and outcome.

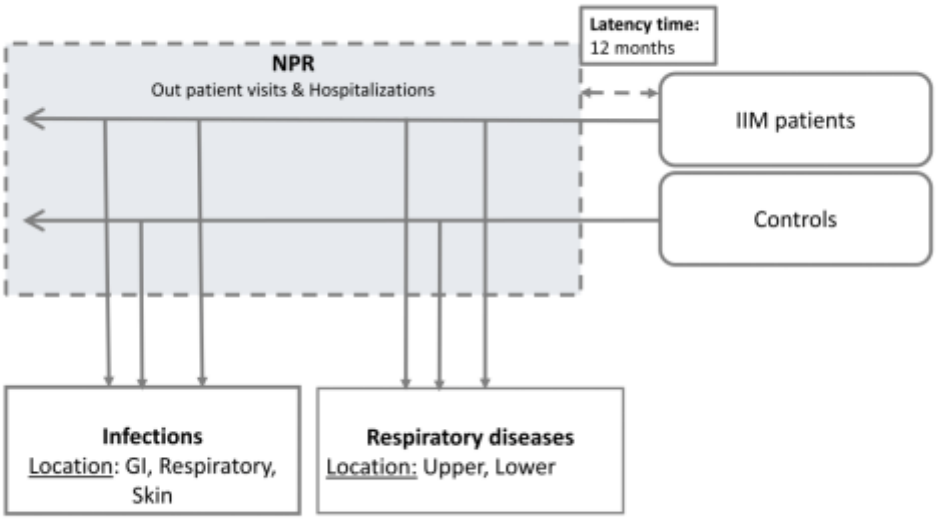

Figure 7. Previous infections and respiratory diseases are identified from the National Patient Register (NPR) for IIM patients and age, sex and place of residence matched general population controls.

Measurement bias and residual confounding were of major concern when conducting the study. Individuals with IIM could potentially have poorer health due to an impaired immune system long before the development of IIM. This impaired immune system, which later causes IIM, could increase the risk of both infections and respiratory diseases or the detection thereof due to more frequent contact with healthcare. We therefore assessed the number of healthcare visits before exposure or before the outcome for unexposed individuals and used it as a proxy for general health and adjusted for it in the analyses.

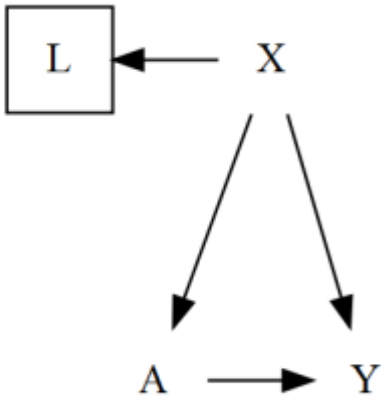

Figure 8. Directed acyclic graph describing how an impaired immune system (X) causes increased health care consumption (L) and measurement or risk of exposure (A) directly as well as development of later idiopathic inflammatory myopathies (Y).

We also conducted multiple sensitivity analyses to investigate the robustness of the estimates. The definition of exposures, latency period and sources used to identify exposures was changed and individuals with IIM associated conditions (connective tissue disorder, lung phenotype and cancer) were excluded in various analyses.

3.8 STUDY 4 – RISK OF STROKE IN IIM

In study 4 we conducted a cohort study with IIM as the exposure and ischemic and haemorrhagic stroke as the outcome (Figure 9). The same algorithm was used, as described in study 2 (but excluding SRQ as a source), to identify individuals with newly diagnosed IIM. The second IIM visit was used as index date and comparators were given the same index date.

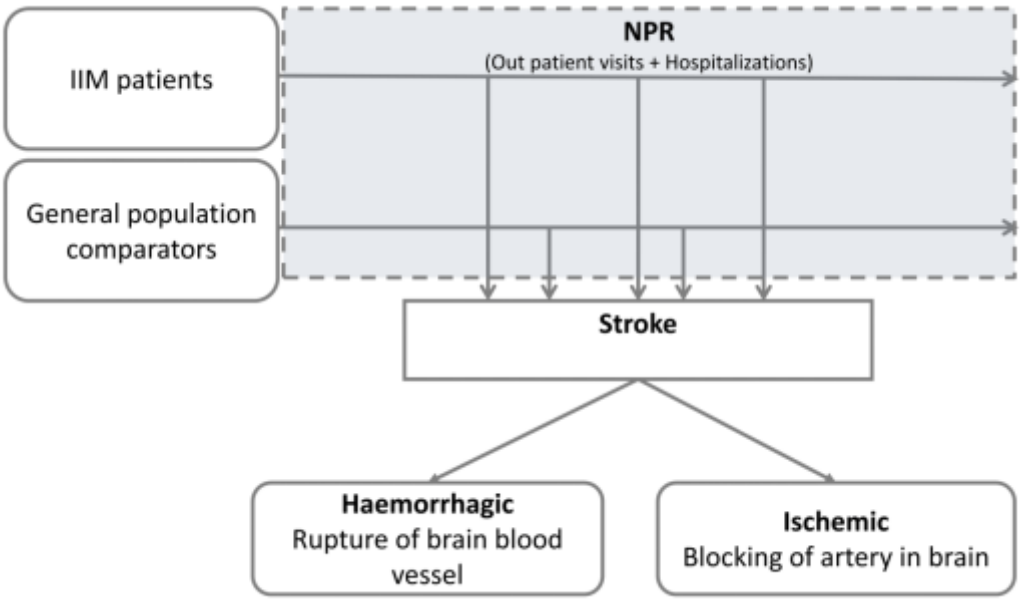

Figure 9. Patients with idiopathic inflammatory myopathies and age, sex and place of residence matched general population comparators were followed prospectively and hospitalizations and outpatient visits indicating haemorrhagic and ischemic stroke were identified from the national patient register (NPR).

Ischemic and haemorrhagic strokes were identified from the NPR using ICD10 codes (Table 3) as well as from the cause of death register. Individuals with prior stroke or stroke related events were excluded from the study. As ischemic and haemorrhagic stroke is caused by different aetiology they were analysed separately. Follow-up was started at index date and ended at first stroke event under evaluation, death, migration or end of study (December 31 2012). Prevalent stroke risk factors at baseline were also identified at baseline because they could be potential confounding factors, possibly increasing the risk of IIM as well as stroke and were adjusted for in sensitivity analysis.

Table 3. International classification of diseases (ICD)
codes used to identify idiopathic inflammatory myopathies, stroke, stroke related events and stroke risk factors.

	ICD9	ICD10
Stroke risk factors		
Diabetes	250	E10, E11
Hypertension	401, 402, 403, 404, 405	I10, I11, I12, I13, I15
Atrial fibrillation	427D	I48
Congestive heart disease	425, 428	I42, I50
Stroke		
Ischaemic stroke	433 -434	I63
Haemorrhagic stroke	431	I61
Unspecified Stroke	436	I64
Stroke related events		
Subarachnoid haemorrhage (SAH)	430	I60
Sequele	438	I69, Z86.6A-B, Z86.7C
Transient ischemic attack (TIA)	435	G45

3.9 STATISTICAL ANALYSES

3.9.1 Logistic regression

Exposure-outcome relationships are commonly analysed using logistic regression models in case-control studies and were used in **study 3** to estimate the association between infections/respiratory diseases and IIM.

Logistic regression is a generalized linear model used when trying to make inference on binary outcomes when the risk in the source population is not known (111). The relationship between predictor variables and the log-odds (logit) transformation of the probability of the outcome (O) given the exposure (X) is linear in the logistic regression model and predictors are estimates using the maximum likelihood function.

$$logit(P(O|X) = \log(odds(O|X)) = \beta_0 + \beta_1 X$$

The likelihood is the probability of obtaining the data that was observed for different predictors and maximum likelihood estimates of the regression coefficients are found by varying the combination of values that maximize the likelihood for the given set of data. In conditional logistic regression analysis is stratified and is often used in observational studies

when cases and controls are matched because it is more efficient and unconditional analyses can lead to biased estimates (112).

3.9.2 Cox regression

Time to event (or survival) analysis is most commonly done by using Cox proportional hazards models (113) (Cox regression) because in logistic regression, time cannot be taken into consideration. Cox regression was used in **study 4** where time from IIM diagnosis to first incident haemorrhagic or ischemic stroke was modelled.

3.9.2.1 General concepts

There are two key concepts in survival analysis: **(1)** the hazard function (*h(t)*) and the **(2)** the survival function (*S(t)*)

1. *The hazard function*

The hazard (or hazard rate) at time *t*, is the incidence rate in a time interval around *t* that approaches zero and is sometimes called the instantaneous rate. The hazard ratio (HR), is the hazard in the exposed group divided by the hazard in the unexposed group and can for all practical reason be interpreted as an incidence rate ratio (IRR).

The Cox model relates the hazards (h) to a set of covariates(X) and associated regression coefficients (β) at time *t* and is used to estimate the relative effect of covariates on the hazard function.

$$h(t) = h_0(\mathrm{t})\ \exp(\beta \mathrm{X})$$

h_o = the baseline hazard, the hazard when X = 0.

The failure function, $\mathrm{F(t)} = \mathrm{Pr(T} \leq \mathrm{t)}$, describes the incidence of the outcome over the duration of the study, where T = time to event of interest.

2. *The survival function*

The survival function is the complement of the failure function:

$$\mathrm{S(t)} = 1 - \mathrm{F(t)} = \mathrm{Pr(T} > \mathrm{t)}$$

and describes the probability of having survived until time *t* and is often estimated using the *Kaplan-Meier estimator*. The relationship between the survival function and regression coefficients (β) from the Cox model can be described as: $S(t) = S_0(t)^{\exp(\beta \mathrm{X})}$, where S_0 denotes the baseline survival function (the survival function for an individual where all covariates equal zero. So, the effect of a specific variable on the relative effect of the hazard (the HR) equals the relative effect of that variable on the logarithm of the survival function (114,115) .

3.9.2.2 Competing risk analyses

Censoring is a distinctive feature of survival analysis data. Examples of censoring events are death or emigration and lead to loss to follow-up for that individual and the possible timing of the outcome is not known. These individuals are commonly excluded from the analyses at censoring and stop contributing person-time. The main assumption made in traditional statistical analyses methods of survival data is that at a given point, individuals that remain in the risk set should have the same future risk of the outcome as individuals who are censored. When the censoring is informative, this is not the case because the censoring is associated with the exposure which leads to selection bias.

A competing event is an event that either hinders or affects the probability of the main event. The cumulative incidence function (CIF) is a proper summary statistics for competing risk data if the question is prognostic rather than casual. The CIF, in contrast to *1 - S(t),* can be used to estimate the incidence of the occurrence of an event while taking competing risks into account. The CIF for the cause k is defined as $CIF_k(t) = \Pr(t \leq T, event = k)$ and is linked to the hazard by: $CIF_k(t) = \int_{t_0}^{t} S(u)h_k(u)du$.

A common question in medical research is often therefore to assess a covariate effect on the CIF. In the absence of competing events, *1 – the Kaplan-Meier estimator* gives a correct estimation of the CIF. However, in the presence of competing risks, estimates are biased upwards even if the competing event and the main event are independent (114,116,117).

One way to analyse competing risk data is to use the sub-distribution hazard function, introduced by Fine and Gray (118). Instead of estimating the hazard in those who have not yet experienced the main event or any competing events, the sub-distribution hazard function estimates the hazard in those who have not yet experienced the main event. Another way to explain it is that individuals who experience a competing risk are not censored but are rather kept in the risk set and given a weight depending on the risk of the main event (Figure 10). The advantage of the sub-distribution hazard is that one can make inference on a variables effect on the cumulative incidence function even in the presence of competing risks.

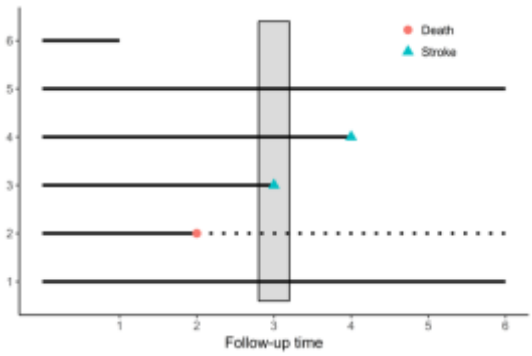

Figure 10. A cohort of 6 individuals followed over time with stroke as the main outcome. In competing risk analysis, individuals are kept in the risk set after censoring events (death) and continue to contribute person-time in contrast to cause-specific survival analysis.

3.10 ETHICAL CONSIDERATIONS

Because we handle sensitive personal information concerning individual´s health, data are stored and managed accordingly. Data are kept at secure servers according to KI guidelines and only processed in relation to our specific research questions. A minimum of new data was collected from medical records of a subset of identified patients to minimize the breach of the individual´s personal integrity. In general, the risks of using register based data are considered small because data stored in available databases are normally sufficient. Furthermore, data is normally pseudo-anonymized (PIN is replaced by key) making identification of research subjects more difficult. IIM is a rare disease making it difficult to perform large studies and epidemiological studies are lacking in the field. Much is still unknown about the disease but with the use of Swedish registers it is possible to further the understanding of this difficult disease.

4 RESULTS

Here, the main results for the included studies are presented.

4.1 STUDY 1

We identified 95 patients with IIM who were treated with biologics off label between 2000 and 2011. Diagnosis and treatment were confirmed via review of clinical charts. Median disease duration was 5.5 years before start of first biologic treatment and all had previously failed multiple previous treatments for their IIM. Rituximab was the most commonly used drug even though the first treated patient was identified in 2003 (Figure 11). Median treatment length varied between 5 to 12.5 months for the different agents but because of different regimens and dose intervals it was difficult conclude if they were really different. More than one biologic was prescribed to 28% of patients.

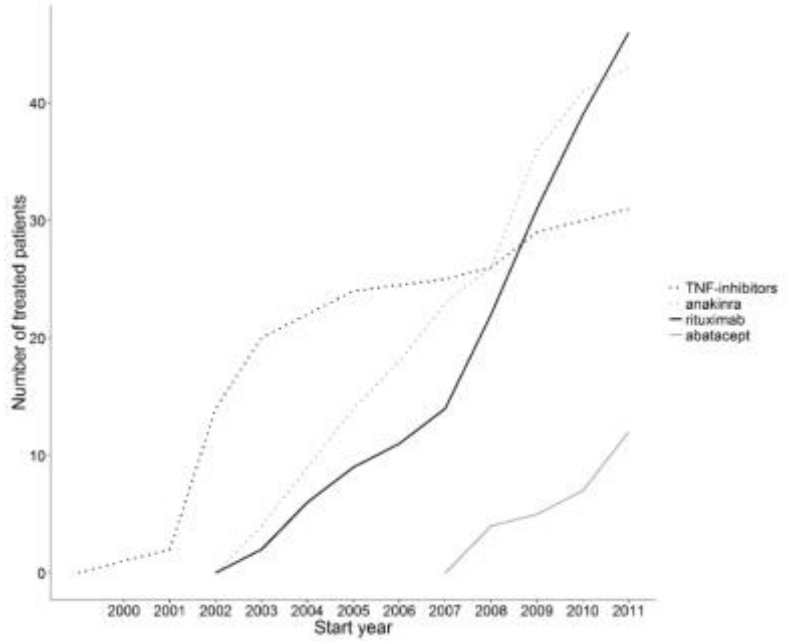

Figure 11. Total number of patients with idiopathic inflammatory myopathies treated with different biologic agents between 2000 and 2011. TNF-inhibitors = etanercept, adalimumab, infliximab.

4.2 STUDY 2

Between 2007 and 2011, 522 individuals were defined as having incident IIM according to the basecase definition corresponding to an average incidence rate of 11 (95%CI 10-12) per 1 000 000 person-years. Rates remained similar when applying more strict and liberal case definitions (Figure 12). The incidence rates generally increased with age but with a peak between 50-79 years and incidence was highest for the 70-79 year age group with higher rates in women for most age groups. Even though large variations were found between Sweden´s 21 counties, no north to south gradient of incidence rates was observed for overall IIM nor for DM (Figure 13). Also, no differences were seen across educational level or population density.

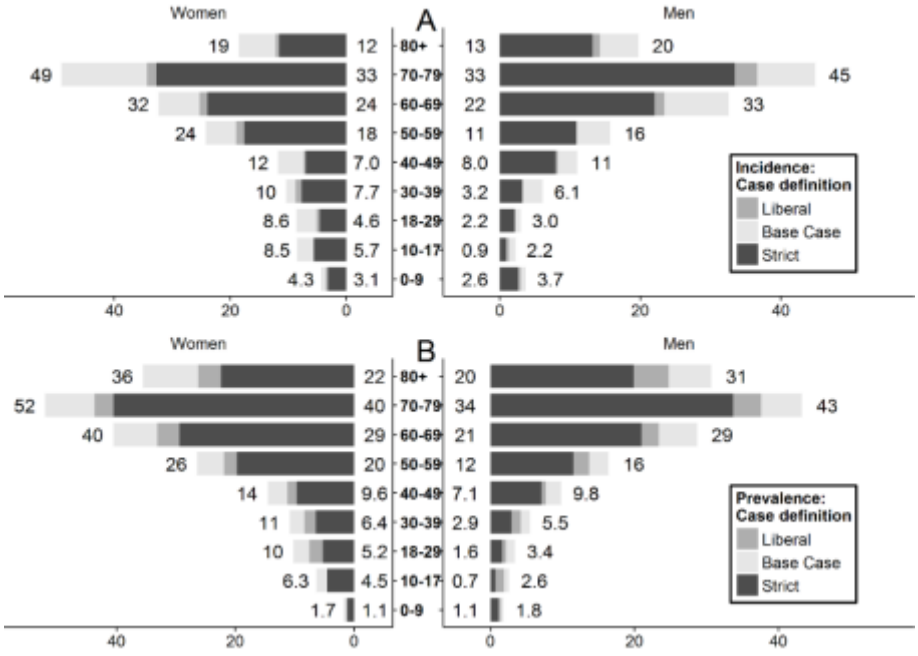

Figure 12. (A) Mean annual incidence rates per 1 000 000 person years and (B) prevalence per 100 000 of idiopathic inflammatory myositis (IIM) stratified by age and sex for three case definitions.

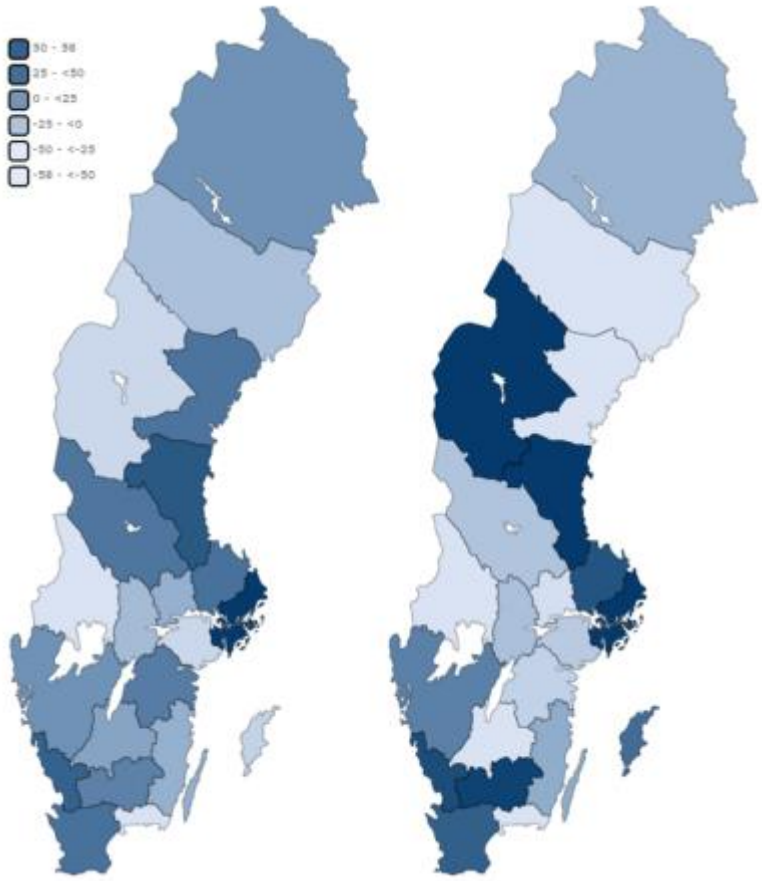

Figure 13. Heat map of incidence rates by Sweden's 21 counties Difference (%) in age and sex standardized incidence rates compared with overall incidence rate for idiopathic inflammatory myositis (left) and DM (right) for Sweden's 21 counties.

Prevalence was estimated to 14 (95%CI 13-14) per 100 000 on 1 January 2012 when using the base case definition. Estimates were highest for women in all age groups and the overall prevalence were 17 and 11 per 100 000 for women and men respectively.

We also found that sensitivity and PPV for most included ICD codes were high when using SRQ given diagnosis as the gold standard. However, it was difficult to separate IBM from PM because of low specificity for ICD code used to define IBM and low PPV for ICD code used to specify IBM.

4.3 STUDY 3

We identified 957 IIM cases and 9576 controls from the NPR and SRQ that fulfilled the inclusion criteria between 2002 and 2011. Previous infections were identified in 125 (13%) of IIM cases and 877 (9%) of controls. Previous infections were associated with increased future risk to develop IIM, OR 1.5 (95%CI 1.2 - 1.9). The association was true for both infections of the gastrointestinal and respiratory tract but not for infections of the skin (Figure 14).

We also observed a dose response relationship for both exposures in that the ORs increased with number of previous visits (Figure 15).

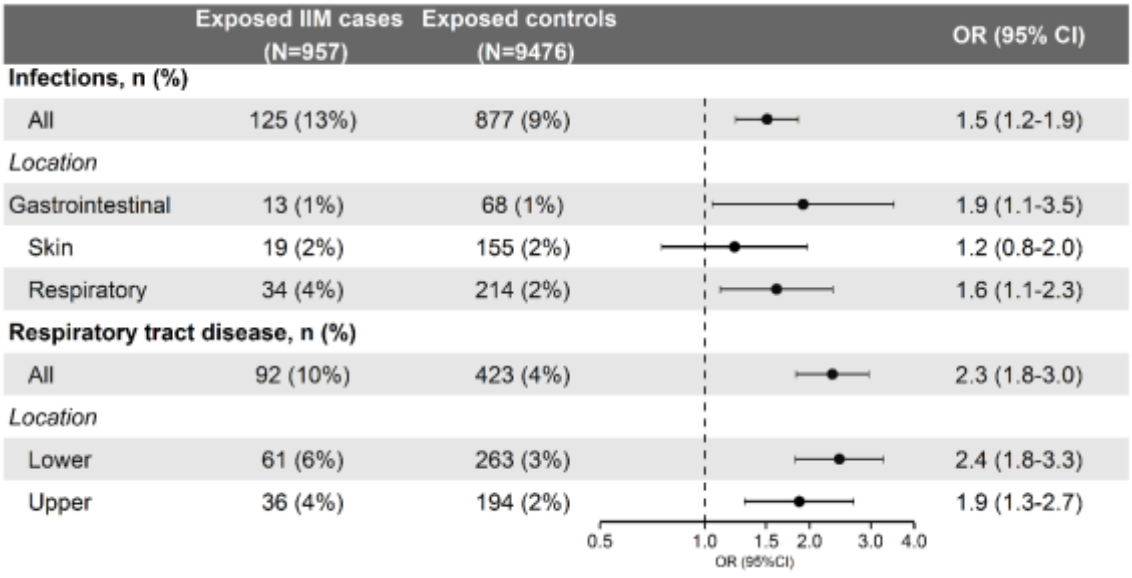

Figure 14. Number of exposed IIM cases and controls and corresponding odds ratio (OR) for infections and respiratory tract diseases.

	IIM cases, n	Controls, n	OR (95%CI)
Infections			
0 visits	832	8599	ref
1 visit	70	528	1.4 (1.1-1.8)
2-4 visits	41	273	1.6 (1.1-2.2)
≥5 visits	14	76	2.0 (1.1-3.5)
Respiratory			
0 visits	865	9053	ref
1 visit	42	212	2.1 (1.5-3)
2-4 visits	33	149	2.3 (1.6-3.4)
≥5 visits	17	62	3.0 (1.7-5.2)

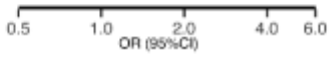

Figure 15. Number of visits indicating exposure and corresponding odds ratio (OR) for infections and respiratory tract diseases.

We conducted multiple sensitivity analyses to investigate the robustness and to find alternative explanations to our findings. We varied the latency period between exposure and outcome, changed the exposure definition and data sources used to identify exposures, excluded other IIM associated conditions which potentially could be driving the associations and finally we adjusted for previous health care consumption as a proxy for general health. None, did however change the overall interpretation of our results.

4.4 STUDY 4

Between 2002 and 2011 we identified a total of 716 new cases of IIM from the NPR that fulfilled our case definition. After exclusion for prior stroke or stroke related events 663 and 6673 were included in the IIM and general comparator cohorts.

We observed a younger age at first incident stroke and shorter median follow-up time for IIM patients indicating that they either experience their stroke at an earlier age than their comparators. We also observe a higher degree of censoring due to death in the IIM (24%) cohort compared to the comparator cohort (8%).

Association between IIM and stroke

For haemorrhagic stroke, the age and sex adjusted HR was 2.4 (95%CI 0.8-7.1) and the rate difference 0.5 (95%CI -0.6-1.6). Because the number of events was low, 4 in IIM and 22 in comparators, only overall estimates were calculated for HS.

For ischemic stroke, 22 events were identified in IIM and 174 in the comparators. The overall HR was 1.7 (95%CI 1.1-2.7) and the rate difference 2.6 (95%CI 0.0-5.3).

The absolute rates of IS were the highest in the oldest age group (≥68) and in men relative risk of IS was highest in the youngest age group (<56 years) while the rate difference was highest in the youngest and oldest age group (Figure 16).

	IIM patients			General population				
	n	Follow-up	Rate (95%CI)	n	Follow-up	Rate (95%CI)	RD (95%CI)	HR (95%CI)
Ischemic stroke								
Overall	22	2993	7.4 (4.6-11.1)	174	35487	4.9 (4.2- 5.7)	2.6 (0.0-5.3)	1.7 (1.1-2.7)
Gender								
Female	9	1711	5.3 (2.4-10.0)	94	20365	4.6 (3.7- 5.6)	1.7 (-1.3-4.6)	1.4 (0.7-2.7)
Male	13	1282	10.1 (5.4-17.3)	80	15122	5.3 (4.2- 6.6)	4.5 (-0.5-9.4)	2.1 (1.2-3.8)
Age group								
<56	5	1214	4.1 (1.3-9.6)	14	13157	1.1 (0.6-1.8)	3.0 (-0.6-6.6)	3.9 (1.4-10.7)
56-≤68	5	1003	5.0 (1.6-11.6)	36	11667	3.1 (2.2- 4.3)	1.8 (-2.6-6.1)	1.7 (0.6-4.2)
68-≤90	12	777	15.4 (8.0-27.0)	124	10662	11.6 (9.7-13.9)	3.7 (-5.3-12.6)	1.4 (0.8-2.5)
Diagnosis								
Dermatomyositis	5	904	5.5 (1.8-12.9)	49	11312	4.3 (3.2- 5.7)	1.0 (-3.9-5.9)	1.3 (0.5-3.3)
Other IIM	17	2089	8.1 (4.7-13.0)	125	24175	5.2 (4.3- 6.2)	2.9 (-1.1-6.8)	1.6 (1.0-2.6)

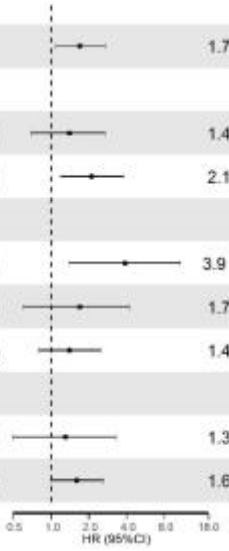

Figure 16. Absolute risk, risk difference and hazard ratios for ischemic stroke in idiopathic inflammatory myopathies (IIM) patients compared to general population comparators.

Competing risk of death

When taking the competing risk of death into account using Fine and Gray´s competing risk models, the sub-distribution HR (sd-HR) was lower, 1.3 (95%CI 0.8-2.0), compared to the HR from the cause specific model. The cumulative incidence was increased in IIM compared to comparators directly following diagnosis but was similar at 10 years the risk of death is significantly higher for IIM than in comparators (Figure 17).

Stroke risk in relation to time since IIM diagnosis

The relative risk of ischemic stroke was the highest the year following diagnosis (Figure 18). The increased risk persisted for up to five years but was then similar between IIM and comparators 5-11 years after diagnosis.

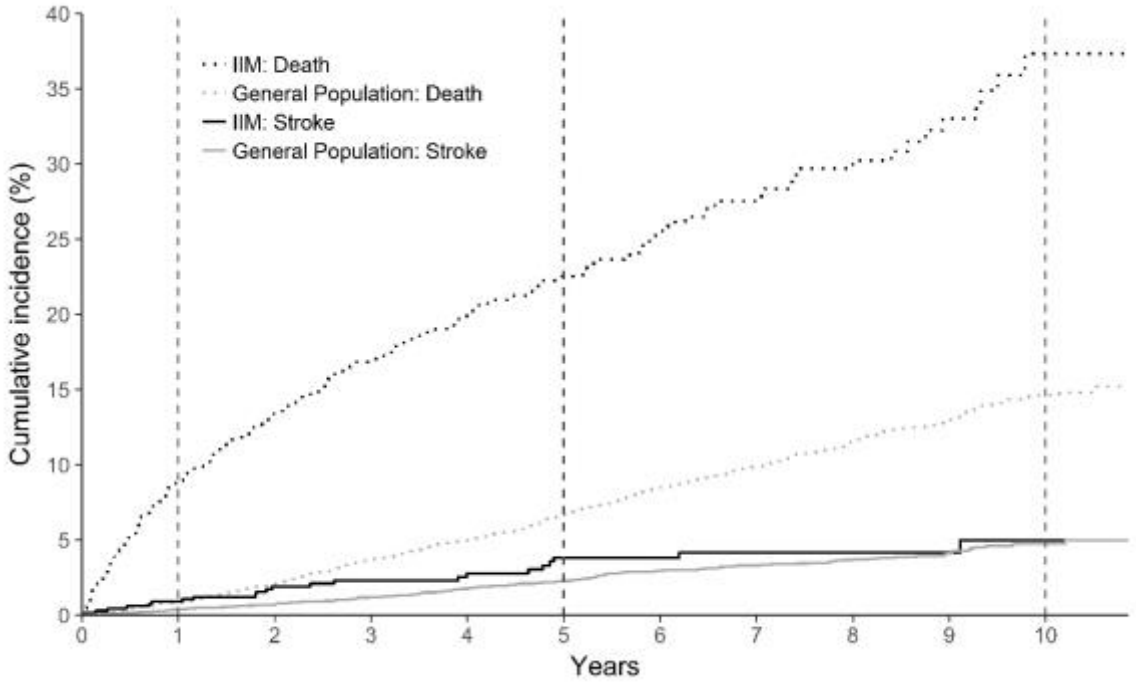

Figure 17. Cumulative incidence of stroke and death for idiopathic inflammatory myopathies (IIM) patients and general population.

	IIM patients		General population		
	n	Follow-up	n	Follow-up	HR (95%CI)
Time since diagnosis					
<1 year	6	622	25	6587	2.6 (1.1-6.3)
1-5 years	17	2189	101	25342	2.2 (1.3-3.7)
5-11 years	2	2131	57	27121	0.6 (0.1-2.4)

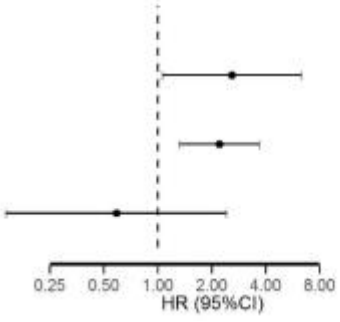

Figure 18. The risk of ischemic stroke in relation to diagnosis of idiopathic inflammatory myopathies (IIM).

5 DISCUSSION

5.1 SUMMARY

By using Swedish registers we have, first, described how biologics have been used in an off-label real world setting. Second, estimated the incidence rates and prevalence of IIM in Sweden with high level of detail (stratified by age, sex, population density and educational level) while also addressing the possible limitations of using register based algorithms for case identification. Third, we have shown that both infections and, more so, respiratory diseases increase the future risk of developing IIM. Last, we have demonstrated an increased risk of stroke in patients with IIM and that the risk was elevated directly following disease diagnosis.

We have been able to demonstrate the advantages of using population based registers for investigating both descriptive, causal and predictive epidemiological questions regarding a rare disease and have been able to contribute with new knowledge as well as establishing prior believes. Strong observational population based study design with long term follow-up and the possibility to look both forwards and backwards in time in relation to IIM diagnosis enables investigation of many outcomes and risk factors. This method includes real world patients and data with good coverage, enabling identification of all IIM patients in Sweden. Because IIM is such a rare disease it is challenging to study because of problems recruiting study subjects, thus using these comprehensive register sources should be of great importance moving IIM research forward.

5.2 PREVIOUS RESEARCH AND IMPLICATIONS

5.2.1 Study 1

Since the initiation of this study, a few clinical trials have investigated the effectiveness of biologics in IIM. Rituximab seem to be effective in a subset of patients, especially patients with anti-Jo1-antibodies (25,32,33,119). Abatacept treatment was recently shown to decrease disease activity in almost half of the included patients in one study (119). A similar effect was observed in 15 patients treated with anakinra (25).

Our results from **study 1** indicate that biologics is commonly used to treat IIM and that the use has increased over time and that a shift in type of drug has occurred. This real world description of use is important as it demonstrates that even though so little effectiveness data is available, the use is still common. This overall increased use of biologic therapies during the last years of the study could be explained by an increased number of agents being available or the added availability of the PDR from 2005 as well as the increased number of published reports in IIM but it may also suggest an unmet need for new therapies in IIM. Therefore, greater efforts should be made upon trying to collect effectiveness data on all treated patients in a structured way, preferably in national or international registers such as SRQ and

Euromyositis, enabling studies which determine which treatments work for different patient groups.

While conducting the first study I scrutinized the medical charts of many patients with IIM. This process enabled me to get to know this disease better and made me understand what a heterogeneous group of patients it includes. I was also able to understand how difficult the diagnosis of IIM really is and how difficult it is to verify diagnosis retrospectively using diagnostic criteria.

5.2.2 Study 2

With this study, using a population-based design including Sweden´s almost 10 million citizens, it is one of the largest studies to date on juvenile and adult IIM. The occurrence of IIM has been estimated previously but with large variations making the actual estimates uncertain. In Sweden incidence has previously been estimated to 2.2 and 7.6 per 1 000 000 person-years for IBM and PM-DM respectively(37,38) while internationally, incidence has been estimated as low as 1.2 and as high as 66 per 1,000,000 person-years (40,44) while prevalence has varied between 0.49 and 32 per 100,000 (47,120).

We were able to produce stable estimates in line with previous regional diagnosis verified studies on IIM prevalence from Norway (50,51) and a recently published meta-analysis (121). The same meta-analysis estimated incidence to be somewhat lower, 8 per 1,000,000 person-years, compared to ours.

In contrast to what is commonly reported, we did not find incidence by age to be bimodal but rather, a steady increase in incidence was observed up to the 80+ years for both men and women and a clear peak in the 50-59 age groups, which is higher than previously reported in Taiwan (46) but similar to studies from the USA and Australia (40,47,48).

Previous studies have demonstrated both a difference in incidence comparing rural to urban (49) as well as a north to south gradient (56,57,121) while we found no evidence of this. This could be explained by Sweden being one of Europe´s most northern countries.

To our knowledge, incidence rates of IIM has not previously been estimated based on educational level. In contrast to what has been found in RA (122,123) we found no difference between different levels of education.

Results from **study 2** indicate that neither incidence nor prevalence is as high as recently reported in register based studies in US and Canada. Neither did we find any time trend indicating IIM becoming more common like what some recent studies have implicated. This study also demonstrated the importance of clear and transparent case definitions when identifying disease and demonstrates the effects they can have on estimates.

5.2.3 Study 3

Our results indicate that both respiratory diseases and infections increase the risk of developing IIM. Previous studies have suggested similar connections for infections but evidence has been limited due to studies only including prevalent cases, using a cross sectional design, or case reports making it difficult to infer anything about the temporality of the association (70,76,124–126). Concerning respiratory diseases it has long been known that many individuals with IIM suffer from respiratory diseases to a high degree already at disease diagnosis (60) but no causal relationship has been established. A recent case control study including hospitalised IIM found increased levels of exposure of sarcoidosis, pneumonia and tuberculosis compared to controls (64). This study does however rely on questionnaires, which could introduce measurement bias, and only hospitalised individuals were included, which could cause problems both with selection bias and with generalizability. Furthermore, our results are based on a wider definition of respiratory diseases.

Only including exposures occurring more than one year before IIM diagnosis enabled us to investigate factors having larger impact on disease development than triggering factors occurring in close proximity to disease. Furthermore, this design decreases the risk of detection bias and reversed causality. Also, using national registers with long follow-up it is possible to identify exposures occurring in an early stage in disease development. We believe this time window is of greater importance for causes of disease as the mechanisms leading to IIM may occur many years before disease onset as immunomodulation later leading to disease may be triggered by exposures many years before disease onset.

In this study, much focus was put into sensitivity analyses, especially adjusting for previous health care consumption. As cases might have poorer health, leading to more contact with health care and later IIM. We therefore adjusted for previous health care consumption in the statistical analysis to remove the effect of this possible confounder. The associations were slightly decreased but our conclusions were not affected.

Our results suggest that inflammatory events that may follow infections and respiratory disease may play a role in disease pathogenesis and that the location of exposure may play a role and further studies should be carried out finding the biologic mechanisms related to this relationship. Previously suggested mechanisms of infections causing autoimmune diseases included molecular mimicry, where a foreign antigen shares structural similarities with self-antigens (77) and change in gut microbiota, affecting immunoregulatory mechanisms (127). Also, just like infections, many respiratory diseases like asthma and chronic obstructive pulmonary disease (COPD) lead to an increased inflammatory load and an activation of the immune system, which could cause autoimmunity through priming of self-reactive lymphocytes and autoantibody production (78,128).

5.2.4 Study 4

The risk of both ischemic and haemorrhagic stroke seems to be elevated in individuals with IIM compared to the general population and the risks are especially high in older individuals and in men. Our estimate of IS is similar to what was recently reported in a meta-analysis (129) where the pooled risk ratio was estimated to 1.6 but somewhat lower compared to a recent Canadian study, HR 2.5 (130). Most previous studies have failed to separate HS from IS which might be problematic as they have different aetiologies and should be analysed separately (91,92,130).

Because it has previously been shown that IIM has an increased risk of death (80) and death is a competing event for stroke as it hinders the event of interest (stroke), the cause specific hazard is not describing the risk of stroke from a prognostic perspective as it estimates the effect on the rate of occurrence of the outcome in subjects who are currently event free (both main event and competing events). Because censoring due to death is informative, the individuals remaining in the risk set in cause specific Cox models are not representative of the censored individuals. We therefore used sub-distribution hazard models to better describe the risk in the context of prognosis. The sd-HR was decreased by 40% compared to the HR from the cause specific models and the cumulative incidence of ischemic stroke was elevated early in disease but then reached levels in line with the general population after 10 years.

We were not able to investigate the biological mechanism and of the increased risk of stroke in these IIM patients. Inflammatory markers like C-reactive protein have been associated with an increased risk of stroke but as these markers seldom are elevated in IIM, other mechanisms must be involved. Further efforts should therefore be made into combining epidemiological methods with laboratory and clinical data to better describe exposures and outcome and to find possible causal and biologic pathways for suggested associations.

Even if the risk of both IS and HS is increased in patients with IIM, it should be kept in mind that these are rare events and focus on prevention should therefore be made in the groups with the highest absolute risk, especially older individuals and men.

5.3 STRENGTHS

The data sources used to identify both individuals with IIM, outcomes, exposures, confounders, comorbidities and other important information were strengths of this thesis. Using population based registers with good coverage we were able to identify an unselected population, and we were able to describe a rare condition in a real world setting with high generalizability to other populations. The main strength is that we managed to identify all individuals followed for IIM in Sweden. The possibility to compare IIM to the general population and look both forward and backward in time enables addressing a wide range of research question in this rare disease. Also, this register linkage can later be reproduced to investigate time trends of specific research questions. Finally, all data in included registers is

prospectively collected minimizing the risk of recall and detection bias as well as non-response.

5.4 LIMITATIONS

Register based case definition

We did not review medical records of all identified patients to ascertain diagnosis. Instead we chose to use an algorithm which tries to mimic the patient´s flow through the healthcare system to identify patients. As shown in **study 1**, diagnosis ascertainment using diagnostic criteria retrospectively can prove difficult due criteria requiring several investigations, especially EMG and muscle biopsies, that might not always be necessary in a clinical context. Defining patients based on classification criteria using retrospective chart review would therefore have a high risk to exclude many true cases as not all patients with IIM present a typical biopsy finding or EMG and muscle biopsy may not even have been performed. The introduction of new classification criteria will surely help in this context (131)

There is always a limitation using register based case definition / identification of cases. Considering this limitation and the future studies planned we concluded that it was more important with a stricter case definition in contrast to a more liberal. This because the effect of including false positive cases would potentially have large effects on planned studies 3 and 4 where IIM would be the outcome and exposure in respective study. Such misclassification of the outcome and exposure would in most cases move the estimates towards the null.

Misclassification of exposure and outcome

Like with IIM diagnosis, there is a risk of misclassifying other variables, such as exposures and outcomes. We have not ascertained the exposure and outcome status in **study 3** and **study 4** but rather relied on the identification from the registers. As previously addressed, this has led to some misclassification as we cannot identify, for instance, the common cold and other exposures only requiring primary care or no care at all.

Separating sub-diagnosis

When investigating sensitivity and positive predictive value of included ICD10 we came to realize that it was difficult to separate PM from IBM because of overlapping use of ICD codes. Also, the estimates of incident IBM was less than half of what has previous been reported in Sweden (38) and when comparing to the proportion registered in SRQ, 15% had IBM compared to 7% when using ICD codes. This is because there is no specific ICD code for IBM and therefore the code for PM is commonly used in clinical practice. We were therefore unable to correctly separate these two sub-diagnosis and therefore, these clinical sub-diagnoses were analysed together in study 3 and 4. A more recently identified subgroup, the immune mediated necrotizing myopathy, has no separate ICD code and does not yet have an

own code in SRQ so we assume that these patients are also included among the PM cases. This demonstrates the need for specific ICD codes for all sub-types of IIM.

Missing variables

Residual and unmeasured confounding is a major concern in all observational studies as it can cause associations that are not casual. For us, smoking status and other life-style factors were missing making it impossible for us to investigate their effects. Furthermore, we did not have detailed clinical and laboratory data available on study subjects, making it difficult to identify clinical subsets and to identify biologic mechanisms explaining observed associations.

5.5 CONCLUSIONS

By using population based registers and observation study designs it is possible to overcome many problems caused by IIM being a rare disease. Finding a sufficiently large study population can be cumbersome in such diseases and therefore this methodology is of a great resource for moving research on this serious disease forward and can help answer both descriptive, prognostic and causal questions. We found that:

- Biologic agents are frequently being used to treat IIM off-label and an overall increased use over time was observed. Treated patients had all previously failed at least one DMARD and prednisolone.
- Using our register-based case defintion we were able to produce robust estimates of the occurrence of IIM, describe how it varies over sub-groups and to investigate spatial trends. Incidence increased with age for both men and women while no difference were seen based on educational level and place of residence.
- Both respiratory diseases and infections increase the future risk to develop IIM. Infections of the respiratory and gastrointestinal tract are associated with an increased future risk while infections of the skin are not indicating that site of increased inflammatory load might play a role in disease pathogenesis.
- There is an increased risk of both ischemic and haemorrhagic stroke following an IIM diagnosis and the risk is the highest up to 5 years after disease debut. Stroke is however a rare event in these individuals and in the context of prognosis, the cumulative incidence is similar compared to the general population over 10 years. Efforts of prevention should be made in the groups with the highest absolute risk, newly diagnosed, the oldest age group and men.

5.6 FUTURE RESEARCH

I believe, that with this thesis, we have illustrated the power of these methods, but also some of its flaws. We might be able to draw conclusions based on large amounts of data but we are at the same time limited in making conclusions richer in detail. As previously discussed, efforts should be made on including all IIM patients in national or international registers like SRQ or

Euromyositis, where diagnosis and clinical subtype is ascertained. Also, all patients treated with biologics should be carefully monitored and effectiveness measures should be done routinely.

Linking of other sources, such as biobank data, could help produce better and more detailed estimates enabling a further understanding of the pathophysiology of IIM. In the meantime, basic research should try to answer mechanisms involved in identified risk factors as well as the increased risk of stroke found directly after IIM diagnosis.

6 ACKNOWLEDGEMENTS

Slowly but surely I start to realise that I am reaching the end of this important period of my life and if not before, I understand that I have many people to be thankful to. Without the guidance from my awesome team of supervisors I would definitely not have been here but I am also grateful to all of my colleagues, friends and family who have supported me along the way.

Ingrid Lundberg - My main supervisor. The big boss! Thank you for convincing me to embark on this journey. I had not been here if it was not for you. For all the support, quick feedback, answers to stupid question and general guidance of an occasionally lost soul. Thank you for all your trust and for the freedom it includes. I have never doubted your support. Not even for one second.

Anna Tjärnlund – My co-supervisor. The one that was on board from the beginning to the end. Thank you for always offering to help. With all your patience and thorough explanations when I had not yet realised that I did not know what I was doing.

Marie Holmqvist – When Marie go in to the picture as my supervisor, my epidemiology knowledge finally started accelerating. With patient hands-on and clear advice you were able to decrease my anxiety levels significantly. Thank you for understanding my frustrations and for always pushing me in the right direction.

Elizabeth Arkema – The last co-supervisor to join the team. But what a recruitment. One of the most skilful epidemiologist I have ever talked to. Thank you for all of our long chats regarding research, and not regarding research. For always keeping your door open and for your support. I also appreciate all the time you have spent trying to sort out my English and I am sorry about all the hyphens.

Kristian Neovius - *Double Rainbow Rider Nr. 1* – Thank you for being the best mentor anyone can ever dream of having. For seriously being one of the most interesting persons in my life. For showing me that there are alternatives in life and that you do not always have to follow the path of least resistance. I think, asking you to become my mentor is one of the best decisions I have ever made. With clear guidance and advice, both from an academic perspective, but also on a personal and professional level you have made my life both easier but also, a lot more interesting. Tack för mitt liv!

Johan – Big boss Nr 2. Thank you for letting me join your group and KEP and for creating such a great environment for research. This environment have had a large impact on my development.

Martin Neovius – Thank you for both academic and professional advice.

The Myositis group – Big thanks to everyone in the myositis group. Past and present. For your patience in explaining the most basic clinical or laboratory thing to a simple farmer from Skåne. **Inka, Jayesh, Valérie, Eva, Lara, Helene, Malin, Joan, Angeles, Cátia, Cecilia, Fabricio, Li, Mei, Paulius, Quan, Louise, Antonella, Karina, Marina, Angeles, Ingela** and **Maryam**. Special thanks to **Inka**, **Joan**, **Cátia**, **Jayesh** and **Angeles** for the great company at all of our retreats and all the support before nervous conference presentations.

The Askling group –For all the great feedback when I needed it the most and for broadening my research horizon. **Hjalmar Wadström, Thomas Frisell, Thomas Bergman Carl-Martin Pethrus, Peter Alping, Viktor Wintzell, Marios Rosides, Bénédict Delcoigne, Ängla Mantel, Ola Olén, Martin Neovius, Gustaf Bruze, Peter Ueda, Björn Pasternack, Matila Morin, Helga Westerlind, Mattias Norrbäck, Pauline Raaschou, Karin Hellgren, Kristin Waldenlind** and **Andrei Barbulescu.**

Special thanks to:
Carl-Martin for our long talks about everything and nothing. For all the great times traveling and for generally for being an inspiration. For your extraordinary imagination and enthusiasm when it comes to finding interesting research questions and new ways to answer them.
Thomas Frisell, for entertaining, passionate and strong opinioned stories at the *fika*. For hosting an awesome methods club and for your willingness to share your knowledge.
Henrik Benoni and **Hjalmar Wadström** for making it feel like Skåne is never far away when Stockholm feels extra cold.
Jonas Söderling – SAS and data management king. For letting me steal your code and for always keeping your door open.

Also, special thanks to **Nora Döring**, **Bénédict**, **Carl-Martin** and **Peter Alping** for help with proofreading.

Stina Nordman – Thanks for keeping all administration in check. You have made my life so much easier.

Lingjing Chen – For sharing this final process of the PhD with me. Great team work.

Parents and family – For trying to understand what I do. For supporting me and being patient with me even though you do not fully understand what I am still doing in school at my age.

All friends who have shown their support and enthusiasm of my work. Special thanks to **Anton**, **Henrik** and **Sanaz** who help me with that extra push whenever I need it.

Aila – Where should I start? The most important person of all. The person that makes me want to get up in the morning and perform to my fullest potential. The one that supports me when I am down and cheers me on no matter what. *Dosett daram yek donia*!

7 REFERENCES

1. Ludvigsson J, Otterblad-Olausson P, Pettersson B, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009 Nov 1;24(11):659–67.

2. Dalakas MC. Polymyositis, Dermatomyositis, and Inclusion-Body Myositis. N Engl J Med. 1991;325(21):1487–98.

3. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis A distinct variety of idiopathic inflammatory myopathy. Neurology. 1978;28(1):8–8.

4. Griggs RC, Askanas V, Dimauro S, Engel A, Karpati G, Mendell JR, et al. Inclusion-Body Myositis and Myopathies. Ann Neurol. 1995 Nov;38(5):705–13.

5. Bohan A, Peter JB. Polymyositis and dermatomyositis .1. N Engl J Med. 1975;292(7):344–7.

6. Bohan A, Peter JB. Polymyositis and dermatomyositis .2. N Engl J Med. 1975;292(8):403–7.

7. Benveniste O, Guiguet M, Freebody J, Dubourg O, Squier W, Maisonobe T, et al. Long-term observational study of sporadic inclusion body myositis. Brain. 2011 Nov;134(Pt 11):3176–84.

8. Dalakas MC. Inflammatory Muscle Diseases. N Engl J Med. 2015;372(18):1734–47.

9. Lega J-C, Fabien N, Reynaud Q, Durieu I, Durupt S, Dutertre M, et al. The clinical phenotype associated with myositis-specific and associated autoantibodies: a meta-analysis revisiting the so-called antisynthetase syndrome. Autoimmun Rev. 2014;13(9):883–91.

10. Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. Jama. 2011;305(2):183–90.

11. Needham M, Mastaglia FL. Inclusion body myositis: current pathogenetic concepts and diagnostic and therapeutic approaches. Lancet Neurol. 2007;6(7):620–31.

12. Targoff IN, Miller FW, Medsger Jr TA, Oddis CV. Classification criteria for the idiopathic inflammatory myopathies. Curr Opin Rheumatol. 1997;9(6):527–35.

13. Choy EH, Isenberg DA. Treatment of dermatomyositis and polymyositis. Rheumatol Oxf. 2002 Jan;41(1):7–13.

14. Bunch TW. Azathioprine with Prednisone for Polymyositis. Ann Intern Med. 1980;92(3):365.

15. Joffe MM, Love LA, Leff RL, Fraser DD, Targoff IN, Hicks JE, et al. Drug-Therapy of the Idiopathic Inflammatory Myopathies - Predictors of Response to Prednisone, Azathioprine, and Methotrexate and a Comparison of Their Efficacy. Am J Med. 1993 Apr;94(4):379–87.

16. Malaviya AN, Many A, Schwartz RS. Treatment of dermatomyositis with methotrexate. Lancet. 1968 Aug 31;2(7566):485–8.

17. Metzger AL, Bohan A, Goldberg LS, Bluestone R, Pearson CM. Polymyositis and dermatomyositis: combined methotrexate and corticosteroid therapy. Ann Intern Med. 1974 Aug;81(2):182–9.

18. Henriksson KG, Sandstedt P. Polymyositis--treatment and prognosis. A study of 107 patients. Acta Neurol Scand. 1982 Apr;65(4):280–300.

19. Hengstman GJD, van den Hoogen FHJ, Barrera P, Netea MG, Pieterse A, van de Putte LBA, et al. Successful treatment of dermatomyositis and polymyositis with anti-tumor-necrosis-factor-alpha: preliminary observations. Eur Neurol. 2003;50(1):10–5.

20. Hengstman GJD, van den Hoogen FHJ, van Engelen BGM. Treatment of dermatomyositis and polymyositis with anti-tumor necrosis factor-alpha: long-term follow-up. Eur Neurol. 2004;52(1):61–3.

21. Sprott H, Glatzel M, Michel BA. Treatment of myositis with etanercept (Enbrel), a recombinant human soluble fusion protein of TNF-alpha type II receptor and IgG1. Rheumatol Oxf. 2004;43(4):524–6.

22. Dastmalchi M, Grundtman C, Alexanderson H, Mavragani CP, Einarsdottir H, Helmers SB, et al. A high incidence of disease flares in an open pilot study of infliximab in patients with refractory inflammatory myopathies. Ann Rheum Dis. 2008 Dec;67(12):1670–7.

23. Efthimiou P, Schwartzman S, Kagen LJ. Possible role for tumour necrosis factor inhibitors in the treatment of resistant dermatomyositis and polymyositis: a retrospective study of eight patients. Ann Rheum Dis. 2006 Sep;65(9):1233–6.

24. Muscle Study Group. A randomized, pilot trial of etanercept in dermatomyositis. Ann Neurol. 2011;70(3):427.

25. Zong M, Dorph C, Dastmalchi M, Alexanderson H, Pieper J, Amoudruz P, et al. Anakinra treatment in patients with refractory inflammatory myopathies and possible predictive response biomarkers: a mechanistic study with 12 months follow-up. Ann Rheum Dis. 2014 May;73(5):913–20.

26. Kosmidis ML, Alexopoulos H, Tzioufas AG, Dalakas MC. The effect of anakinra, an IL1 receptor antagonist, in patients with sporadic inclusion body myositis (sIBM): a small pilot study. J Neurol Sci. 2013 Nov 15;334(1–2):123–5.

27. Chung L, Genovese MC, Fiorentino DF. A pilot trial of rituximab in the treatment of patients with dermatomyositis. Arch Dermatol. 2007;143(6):763–7.

28. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. Arthritis Rheum. 2005 Feb;52(2):601–7.

29. Chiappetta N, Steier J, Gruber B. Rituximab in the Treatment of Refractory Dermatomyositis. JCR J Clin Rheumatol. 2005;11(5):264–6.

30. Lambotte O, Kotb R, Maigne G, Blanc F-X, Goujard C, Delfraissy JF. Efficacy of rituximab in refractory polymyositis. J Rheumatol. 2005 Jul 1;32(7):1369–70.

31. Noss EH, Hausner-Sypek DL, Weinblatt ME. Rituximab as therapy for refractory polymyositis and dermatomyositis. J Rheumatol. 2006 May 1;33(5):1021–6.

32. Oddis CV, Reed AM, Aggarwal R, Rider LG, Ascherman DP, Levesque MC, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. Arthritis Rheum. 2013 Feb;65(2):314–24.

33. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, et al. Predictors of Clinical Improvement in Rituximab-Treated Refractory Adult and Juvenile Dermatomyositis and Adult Polymyositis. Arthritis Rheumatol. 2014 Mar;66(3):740–9.

34. Arabshahi B, Silverman RA, Jones OY, Rider LG. Abatacept and Sodium Thiosulfate for Treatment of Recalcitrant Juvenile Dermatomyositis Complicated by Ulceration and Calcinosis. J Pediatr. 2012 Mar 1;160(3):520–2.

35. Kerola A, Kauppi M. Abatacept as a successful therapy for myositis—a case-based review. Clin Rheumatol. 2014 Feb 4;1–4.

36. Musuruana JL, Cavallasca JA. Abatacept for treatment of refractory polymyositis. Joint Bone Spine. 2011 Jul;78(4):431–2.

37. Weitoft T. Occurrence of Polymyositis in the County of Gavleborg, Sweden. Scand J Rheumatol. 1997;26(2):104–6.

38. Lindberg C, Persson L, Björkander J, Oldfors A. Inclusion body myositis: clinical, morphological, physiological and laboratory findings in 18 cases. Acta Neurol Scand. 1994;89(2):123–31.

39. Benbassat J, Geffel D, Zlotnick A. Epidemiology of polymyositis-dermatomyositis in israel, 1960-76. Isr J Med Sci. 1980;16(3):197–200.

40. Furst DE, Amato AA, Iorga SR, Gajria K, Fernandes AW. Epidemiology of adult idiopathic inflammatory myopathies in a U.S. managed care plan. Muscle Nerve. 2012 May;45(5):676–83.

41. Medsger Jr TA, Dawson Jr WN, Masi AT. The epidemiology of polymyositis. Am J Med. 1970;48(6):715–23.

42. Oddis CV, Conte CG, Steen VD, Medsger TA. Incidence of polymyositis-dermatomyositis: a 20-year study of hospital diagnosed cases in Allegheny County, PA 1963-1982. J Rheumatol. 1990 Oct;17(10):1329–34.

43. Ohta A, Nagai M, Nishina M, Tomimitsu H, Kohsaka H. Prevalence and incidence of polymyositis and dermatomyositis in Japan. Mod Rheumatol. 2014 May;24(3):477–80.

44. Pearson CM. Polymyositis. Annu Rev Med. 1966;17:63-.

45. Rose AL, Walton JN. Polymyositis - A survey of 89 cases with particular reference to treatment and prognosis. Brain. 1966;89:747-.

46. See L-C, Kuo C-F, Chou IJ, Chiou M-J, Yu K-H. Sex- and age-specific incidence of autoimmune rheumatic diseases in the Chinese population: A Taiwan population-based study. Semin Arthritis Rheum. 2013;43(3):381–6.

47. Smoyer-Tomic KE, Amato AA, Fernandes AW. Incidence and prevalence of idiopathic inflammatory myopathies among commercially insured, Medicare supplemental insured, and Medicaid enrolled populations: an administrative claims analysis. Bmc Musculoskelet Disord. 2012 Jun 15;13(1):103.

48. Tan JA, Roberts-thomson PJ, Blumbergs P, Hakendorf P, Cox SR, Limaye V. Incidence and prevalence of idiopathic inflammatory myopathies in South Australia: a 30-year epidemiologic study of histology- proven cases. Int J Rheum Dis. 2013 Jun;16(3):331–8.

49. Bernatsky S, Joseph L, Pineau CA, Belisle P, Boivin JF, Banerjee D, et al. Estimating the prevalence of polymyositis and dermatomyositis from administrative data: age, sex and regional differences. Ann Rheum Dis. 2009 Jul;68(7):1192–6.

50. Dobloug C, Garen T, Bitter H, Stjärne J, Stenseth G, Grøvle L, et al. Prevalence and clinical characteristics of adult polymyositis and dermatomyositis; data from a large and unselected Norwegian cohort. Ann Rheum Dis [Internet]. 2014 Apr 2; Available from: http://ard.bmj.com/content/early/2014/04/02/annrheumdis-2013-205127.abstract

51. Dobloug GC, Antal EA, Sveberg L, Garen T, Bitter H, Stjärne J, et al. High prevalence of inclusion body myositis in Norway; a population-based clinical epidemiology study. Eur J Neurol. 2015;22(4):672-e41.

52. Wilson FC, Ytterberg SR, St Sauver JL, Reed AM. Epidemiology of sporadic inclusion body myositis and polymyositis in Olmsted County, Minnesota. J Rheumatol. 2008 Mar;35(3):445–7.

53. Barnabe C, Joseph L, Bélisle P, Labrecque J, Barr SG, Fritzler MJ, et al. Prevalence of autoimmune inflammatory myopathy in the first nations population of Alberta, Canada. Arthritis Care Res. 2012;64(11):1715–9.

54. Gan L, Miller FW. State of the art: what we know about infectious agents and myositis. Curr Opin Rheumatol. 2011;23(6):585–94.

55. Patrick M, Buchbinder R, Jolley D, Dennett X, Buchanan R. Incidence of inflammatory myopathies in Victoria, Australia, and evidence of spatial clustering. J Rheumatol. 1999;26(5):1094–100.

56. Hengstman G, Van Venrooij W, Vencovsky J, Moutsopoulos H, Van Engelen B. The relative prevalence of dermatomyositis and polymyositis in Europe exhibits a latitudinal gradient. Ann Rheum Dis. 2000;59(2):141–2.

57. Love LA, Weinberg CR, McConnaughey DR, Oddis CV, Medsger TA, Reveille JD, et al. Ultraviolet radiation intensity predicts the relative distribution of dermatomyositis and anti–Mi-2 autoantibodies in women. Arthritis Rheum. 2009;60(8):2499–504.

58. Leff RL, Burgess SH, Miller FW, Love LA, Targoff IN, Dalakas MC, et al. Distinct seasonal patterns in the onset of adult idiopathic inflammatory myopathy in patients with anti-jo-1 and anti-signal recognition particle autoantibodies. Arthritis Rheumatol. 1991;34(11):1391–6.

59. Symmons DP, Sills JA, Davis SM. The incidence of juvenile dermatomyositis: results from a nation-wide study. Br J Rheumatol. 1995 Aug;34(8):732–6.

60. Fathi M, Dastmalchi M, Rasmussen E, Lundberg I, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis. 2004;63(3):297–301.

61. Mimori T, Nakashima R, Hosono Y. Interstitial lung disease in myositis: clinical subsets, biomarkers, and treatment. Curr Rheumatol Rep. 2012;14(3):264–74.

62. Fathi M, Lundberg IE. Interstitial lung disease in polymyositis and dermatomyositis. Curr Opin Rheumatol. 2005;17(6):701–6.

63. Chinoy H, Adimulam S, Marriage F, New P, Vincze M, Zilahi E, et al. Interaction of HLA-DRB1*03 and smoking for the development of anti-Jo-1 antibodies in adult idiopathic inflammatory myopathies: a European-wide case study. Ann Rheum Dis. 2012;71(6):961–5.

64. Helmers SB, Jiang X, Pettersson D, Wikman A-L, Axelman P, Lundberg Å, et al. Inflammatory lung disease a potential risk factor for onset of idiopathic inflammatory myopathies: results from a pilot study. RMD Open. 2016;2(2):e000342.

65. Bergström U, Jacobsson LTH, Nilsson J-Å, Berglund G, Turesson C. Pulmonary dysfunction, smoking, socioeconomic status and the risk of developing rheumatoid arthritis. Rheumatology. 2011 Nov 1;50(11):2005–13.

66. Klareskog L, Stolt P, Lundberg K, Källberg H, Bengtsson C, Grunewald J, et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA–DR (shared epitope)–restricted immune reactions to autoantigens modified by citrullination. Arthritis Rheum. 2006;54(1):38–46.

67. Stolt P, Yahya A, Bengtsson C, Källberg H, Rönnelid J, Lundberg I, et al. Silica exposure among male current smokers is associated with a high risk of developing ACPA positive rheumatoid arthritis. Ann Rheum Dis. 2009;ard. 2009.114694.

68. Hart JE, Laden F, Puett RC, Costenbader KH, Karlson EW. Exposure to traffic pollution and increased risk of rheumatoid arthritis. Environ Health Perspect. 2009;117(7):1065.

69. Too CL, Muhamad NA, Ilar A, Padyukov L, Alfredsson L, Klareskog L, et al. Occupational exposure to textile dust increases the risk of rheumatoid arthritis:

results from a Malaysian population-based case–control study. Ann Rheum Dis. 2016 Jun 1;75(6):997–1002.

70. Chen D-Y, Chen Y-M, Lan J-L, Chen H-H, Hsieh C-W, Wey S-J, et al. Polymyositis/dermatomyositis and nasopharyngeal carcinoma: the Epstein–Barr virus connection? J Clin Virol. 2010;49(4):290–5.

71. Douche-Aourik F, Berlier W, Féasson L, Bourlet T, Harrath R, Omar S, et al. Detection of enterovirus in human skeletal muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects. J Med Virol. 2003;71(4):540–7.

72. Johnson RW, Williams FM, Kazi S, Dimachkie MM, Reveille JD. Human immunodeficiency virus–associated polymyositis: A longitudinal study of outcome. Arthritis Care Res. 2003 Apr 15;49(2):172–8.

73. Posnett DN. Herpesviruses and autoimmunity. Curr Opin Investig Drugs Lond Engl 2000. 2008;9(5):505–14.

74. Sherman MP, Amin RM, Rodgers-Johnson PEB, Morgan OSC, Char G, Mora CA, et al. Identification of human t cell leukemia/lymphoma virus type i antibodies, dna, and protein in patients with polymyositis. Arthritis Rheum. 1995 May 1;38(5):690–8.

75. Koch MJ, Brody JA, Gillespie MM. Childhood polymyositis: a case-control study. Am J Epidemiol. 1976;104(6):627–31.

76. Pachman LM, Lipton R, Ramsey-Goldman R, Shamiyeh E, Abbott K, Mendez EP, et al. History of infection before the onset of juvenile dermatomyositis: results from the National Institute of Arthritis and Musculoskeletal and Skin Diseases Research Registry. Arthritis Care Res. 2005;53(2):166–72.

77. Cusick MF, Libbey JE, Fujinami RS. Molecular mimicry as a mechanism of autoimmune disease. Clin Rev Allergy Immunol. 2012;42(1):102–11.

78. Vanderlugt CL, Miller SD. Epitope spreading in immune-mediated diseases: implications for immunotherapy. Nat Rev Immunol. 2002;2(2):85–95.

79. Sandberg ME, Bengtsson C, Klareskog L, Alfredsson L, Saevarsdottir S. Recent infections are associated with decreased risk of rheumatoid arthritis: a population-based case-control study. Ann Rheum Dis. 2015;annrheumdis-2014-206493.

80. Dobloug GC, Svensson J, Lundberg IE, Holmqvist M. Mortality in idiopathic inflammatory myopathy: results from a Swedish nationwide population-based cohort study. Ann Rheum Dis. 2017;

81. Bronner IM, Meulen MFG van der, Visser M de, Kalmijn S, Venrooij WJ van, Voskuyl AE, et al. Long-term outcome in polymyositis and dermatomyositis. Ann Rheum Dis. 2006 Nov 1;65(11):1456–61.

82. Hochberg MC, Feldman D, Stevens MB. Adult onset polymyositis/dermatomyositis: An analysis of clinical and laboratory features and survival in 76 patients with a review of the literature. Semin Arthritis Rheum. 1986 Feb 1;15(3):168–78.

83. Medsger TA, Robinson H, Masi AT. Factors Affecting Survivorship in Polymyositis. A Life-Table Study of 124 Patients. Arthritis Rheum. 1971 Mar 1;14(2):249–58.

84. Schiopu E, Phillips K, MacDonald PM, Crofford LJ, Somers EC. Predictors of survival in a cohort of patients with polymyositis and dermatomyositis: effect of corticosteroids, methotrexate and azathioprine. Arthritis Res Ther. 2012 Jan 27;14:R22.

85. Carruthers EC, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of deep venous thrombosis and pulmonary embolism in individuals with polymyositis and dermatomyositis: a general population-based study. Ann Rheum Dis [Internet]. 2014 Sep 5; Available from: http://ard.bmj.com/content/early/2014/09/05/annrheumdis-2014-205800.abstract

86. Zöller B, Li X, Sundquist J, Sundquist K. Risk of pulmonary embolism in patients with autoimmune disorders: a nationwide follow-up study from Sweden. The Lancet. 2012 Jan 21;379(9812):244–9.

87. Riksstroke. Stroke och TIA - Slutlig årsrapport från riksstroke [Internet]. 2017 Oct [cited 2017 Nov 1]. Available from: http://www.riksstroke.org/wp-content/uploads/2017/07/Riksstroke%C3%85rsrapport2016_slutversion.pdf

88. Arkema EV, Svenungsson E, Euler MV, Sjöwall C, Simard JF. Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. Ann Rheum Dis. 2017 Sep 1;76(9):1544–9.

89. Aviña-Zubieta JA, To F, Vostretsova K, De Vera M, Sayre EC, Esdaile JM. Risk of Myocardial Infarction and Stroke in Newly Diagnosed Systemic Lupus Erythematosus: A General Population-Based Study. Arthritis Care Res. 2017;69(6):849–56.

90. Holmqvist M, Gränsmark E, Mantel Ä, Alfredsson L, Jacobsson LT, Wallberg-Jonsson S, et al. Occurrence and relative risk of stroke in incident and prevalent contemporary rheumatoid arthritis. Ann Rheum Dis. 2013;72(4):541–6.

91. Lai Y, Dai Y, Yen M, Chen L, Chen H, Cooper R, et al. Dermatomyositis is associated with an increased risk of cardiovascular and cerebrovascular events: a Taiwanese population-based longitudinal follow-up study. Br J Dermatol. 2013;168(5):1054–9.

92. Tisseverasinghe A, Bernatsky S, Pineau CA. Arterial events in persons with dermatomyositis and polymyositis. J Rheumatol. 2009;36(9):1943–6.

93. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol. 2012;12(1):1.

94. Zantos D, Zhang Y, Felson D. The overall and temporal association of cancer with polymyositis and dermatomyositis. J Rheumatol. 1994 Oct;21(10):1855–9.

95. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, et al. Frequency of specific cancer types in dermatomyositis and polymyositis: a population-based study. The Lancet. 2001 Jan 13;357(9250):96–100.

96. Ludvigsson J, Andersson E, Ekbom A, Feychting M, Kim J, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.

97. National Board of Health and Welfare. Dödsorsaksregistret [Internet]. 2016. Available from: http://www.socialstyrelsen.se/register/dodsorsaksregistret

98. National Board of Health and Welfare. Swedish Cancer Registry [Internet]. 2013 [cited 2017 Oct 23]. Available from: http://www.socialstyrelsen.se/register/halsodataregister/cancerregistret/inenglish

99. Miller FW, Rider LG, Chung YL, Cooper R, Danko K, Farewell V, et al. Proposed preliminary core set measures for disease outcome assessment in adult and juvenile idiopathic inflammatory myopathies. Rheumatol Oxf. 2001;40(11):1262–73.

100. National Board of Health and Welfare. Rapporteringen till nationella kvalitetsregister och hälsodataregistren - Jämförelser av täckningsgrader [Internet]. 2013 [cited 2017 Oct 23]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/19285/2013-12-12.pdf

101. National Board of Health and Welfare. Täckningsgrader 2016 - Jämförelser mellan nationella kvalitetsregister och hälsodataregistren [Internet]. 2017 [cited 2017 Oct 23]. Available from: http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/20473/2017-1-23.pdf

102. Statistics Sweden. Registret över Totalbefolkningen [Internet]. 2017. Available from: https://www.scb.se/sv_/Vara-tjanster/Bestalla-mikrodata/Vilka-mikrodata-finns/Registret-over-totalbefolkningen-RTB/

103. Statistics Sweden. Longitudinell integrationsdatabas för sjukförsäkrings- och arbetsmarknadsstudier (LISA) [Internet]. Statistiska Centralbyrån. 2017 [cited 2017 Oct 24]. Available from: http://www.scb.se/sv_/vara-tjanster/bestalla-mikrodata/vilka-mikrodata-finns/longitudinell-integrationsdatabas-for-sjukforsakrings--och-arbetsmarknadsstudier-lisa/

104. Greenland S, Pearl J, Robins JM. Causal Diagrams for Epidemiologic Research. Epidemiology. 1999;10(1):37–48.

105. Savitz DA, Wellenius GA. Interpreting Epidemiologic Evidence: Connecting Research to Applications. Oxford University Press; 2016. 241 p.

106. Hernán MA, Hernández-Díaz S, Robins JM. A Structural Approach to Selection Bias: Epidemiology. 2004 Sep;15(5):615–25.

107. Hernan M, Robins J. Causal Inference [Internet]. forthcoming. Boca Raton: Chapman & Hall /CRC; 2012 [cited 2017 Oct 23]. Available from: https://www.hsph.harvard.edu/miguel-hernan/causal-inference-book/

108. Rothman KJ. Epidemiology: An Introduction. OUP USA; 2012. 281 p.

109. Vandenbroucke JP, Pearce N. Case–control studies: basic concepts. Int J Epidemiol. 2012 Oct 1;41(5):1480–9.

110. Knol MJ, Vandenbroucke JP, Scott P, Egger M. What Do Case-Control Studies Estimate? Survey of Methods and Assumptions in Published Case-Control Research. Am J Epidemiol. 2008 Nov 1;168(9):1073–81.

111. Rothman KJ, Greenland S, Lash TL. Modern Epidemiology. Lippincott Williams & Wilkins; 2008. 776 p.

112. Pearce N. Analysis of matched case-control studies. BMJ. 2016 Feb 25;352:i969.

113. Cox DR. Regression Models and Life-Tables. J R Stat Soc Ser B Methodol. 1972;34(2):187–220.

114. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017 Nov 30;36(27):4391–400.

115. Collett D. Modelling Survival Data in Medical Research, Second Edition. CRC Press; 2003. 413 p.

116. Austin PC, Lee DS, Fine JP. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. Circulation. 2016 Feb 9;133(6):601–9.

117. Lau B, Cole SR, Gange SJ. Competing Risk Regression Models for Epidemiologic Data. Am J Epidemiol. 2009 Jul 15;170(2):244–56.

118. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496–509.

119. Tjärnlund A, Tang Q, Wick C, Dastmalchi M, Mann H, Studýnková JT, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: a randomised, phase IIb treatment delayed-start trial. Ann Rheum Dis. 2017;annrheumdis-2017-211751.

120. Badrising UA, Maat-Schieman M, van Duinen SG, Breedveld F, van Doorn P, van Engelen B, et al. Epidemiology of inclusion body myositis in the Netherlands: a nationwide study. Neurology. 2000 Nov;55(9):1385–7.

121. Meyer A, Meyer N, Schaeffer M, Gottenberg J-E, Geny B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatology [Internet]. 2014 Jul 26; Available from: http://rheumatology.oxfordjournals.org/content/early/2014/07/26/rheumatology.keu289.abstract

122. Bengtsson C, Nordmark B, Klareskog L, Lundberg I, Alfredsson L. Socioeconomic status and the risk of developing rheumatoid arthritis: results from the Swedish EIRA study. Ann Rheum Dis. 2005 Nov 1;64(11):1588–94.

123. Eriksson JK, Neovius M, Ernestam S, Lindblad S, Simard JF, Askling J. Incidence of Rheumatoid Arthritis in Sweden: A Nationwide Population-Based Assessment of Incidence, Its Determinants, and Treatment Penetration. Arthritis Care Res. 2013 Jun;65(6):870–8.

124. Douche-Aourik F, Berlier W, Féasson L, Bourlet T, Harrath R, Omar S, et al. Detection of enterovirus in human skeletal muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects. J Med Virol. 2003;71(4):540–7.

125. Gilbert D, St C Morgan O, Smikle M, Simeon D, Barton E. HTLV-1 associated polymyositis in Jamaica. Acta Neurol Scand. 2001;104(2):101–4.

126. Rider LG, Wu L, Mamyrova G, Targoff IN, Miller FW. Environmental factors preceding illness onset differ in phenotypes of the juvenile idiopathic inflammatory myopathies. Rheumatology. 2010;49(12):2381–90.

127. Rook GA. Hygiene hypothesis and autoimmune diseases. Clin Rev Allergy Immunol. 2012;42(1):5–15.

128. Mikuls TR, Payne JB, Deane KD, Thiele GM. Autoimmunity of the lung and oral mucosa in a multisystem inflammatory disease: The spark that lights the fire in rheumatoid arthritis? J Allergy Clin Immunol. 2016;137(1):28–34.

129. Ungprasert P, Cheungpasitporn W, Wijarnpreecha K, Ahuja W, Ratanasrimetha P, Thongprayoon C. Risk of ischemic stroke in patients with polymyositis and dermatomyositis: a systematic review and meta-analysis. Rheumatol Int. 2015;35(5):905–9.

130. Rai SK, Choi HK, Sayre EC, Aviña-Zubieta JA. Risk of myocardial infarction and ischaemic stroke in adults with polymyositis and dermatomyositis: a general population-based study. Rheumatology. 2016;55(3):461–9.

131. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M de, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Ann Rheum Dis. 2017 Oct 26;annrheumdis-2017-211468.