From the Department of Medicine, Solna
Karolinska Institutet, Stockholm, Sweden

ETIOLOGY AND PROGNOSIS OF SPONDYLOARTHROPATHIES USING FAMILY-BASED EPIDEMIOLOGICAL METHODS

Matilda Morin

Karolinska Institutet

Stockholm 2023

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2023

ISBN 978-91-8017-062-8
Cover illustration: "A sketch of a group of relatives with forest green and gold, minimal composition" generated with Bing Image Creator, 2023.

Etiology and prognosis of spondyloarthropathies using family-based epidemiological methods

Thesis for Doctoral Degree (Ph.D.)

By

Matilda Morin

The thesis will be defended in public at Skandiasalen, Q-building, 1st floor, Karolinska vägen 37A, Karolinska University Hospital, Solna, on October 13, 2023, at 09:00.

Principal Supervisor:
Dr. Thomas Frisell
Karolinska Institutet
Department of Medicine, Solna
Clinical Epidemiology Division

Co-supervisor:
Dr. Karin Hellgren
Karolinska Institutet
Department of Medicine, Solna
Clinical Epidemiology Division

Opponent:
Dr. Anna Moltó
Rheumatology Department, Cochin Hospital and Université Paris Cité
Center for Research in Epidemiology and Statistics (CRESS)
ECAMO team - INSERM (U1153)

Examination Board:
Dr. Therese Andersson
Karolinska Institutet
Department of Medical Epidemiology and Biostatistics

Dr. Johan Karlsson Wallman
Lund University
Department of Clinical Sciences

Professor Cecilia Magnusson
Karolinska Institutet
Department of Global Public Health

Till Astrid och Ture

Popular science summary of the thesis

This doctoral thesis consists of four research studies on different aspects of the rheumatic disease spondyloarthritis (SpA). Actually, SpA is an umbrella term for a whole group of closely related diagnoses with similar symptoms that affect around five out of one thousand people in Sweden. The main symptoms in any arthritis are pain, stiffness, and swelling of joints due to an attack from the body's own immune system. In SpA, the joints typically affected are either those of the spine and where the spine attaches to the pelvis, leading to lower back pain, or joints in hands, knees, and feet. Some patients also experience inflammation in the eyes, skin, and gut. Without adequate treatment, the inflammation can lead to permanent joint damage, to increased risk of for example cardiovascular disease, and even to fusion of the bones in the spine.

One reason why these diagnoses where grouped in the first place was their tendency to run in families. Doctors noted that it was common for patients to have one or more relative with similar symptoms. The questions we wanted to answer in study I was: If I have this disease, what is the risk that my children, or sibling, will get it? And how much depends on genes versus environment? Sweden is an excellent place to study these issues, as Sweden has a long history of keeping registers of its residents. The registers include data on who is related to whom, and what diagnoses people have received at their hospital visits. From these registers we determined how many parents, siblings, and children of patients diagnosed with ankylosing spondylitis (the most studied type of SpA) had received a diagnosis themselves, compared to relatives of individuals without ankylosing spondylitis. We found that there was a 20-times increased risk for relatives of patients. We also calculated the heritability, meaning how much of the vulnerability to develop the disease that is due to genetic factors, as maximum 80%. This is a very high heritability, but still lower than what researchers had calculated before in studies on fewer people. This means that environmental factors also play a role in who develops SpA.

In study II, we focused on a group of very effective, but also expensive, treatments used in SpA called tumor necrosis factor inhibitors (TNFi). Unfortunately, TNFi does not work for all patients. It would save both money and suffering if it was possible to predict which patients who are not likely to respond to treatment, so that they can receive alternative treatment. As having family history of SpA is a strong risk factor for disease development, we wanted to see whether it also affected TNFi treatment response. In study II, we compared SpA patients with and without family history of SpA to see if their disease had improved after 3 and 12 months of treatment, and if there were differences in how long they continued taking the drug. However, we could not find any differences. Our results suggest that the genes that cause disease are not necessarily the same as those determining disease severity, or how you respond to TNFi treatment.

In study III, we assessed the risk of pregnancy complications for women with SpA. It is known that other rheumatic diseases lead to increased risk of for example preterm birth, but previous studies in SpA had been small and showed conflicting results. We conducted the largest study to date on births in women with SpA, comparing the rates of adverse birth outcomes to those of women from the general population. We found that women with SpA more often suffered from pre-eclampsia, delivered preterm, and had a cesarean delivery. In the children, there was an increased risk of infection during the first year of life. However, we also found that these risks had decreased over the study period, while the uptake of TNFi treatment increased in SpA. In the beginning of the study period, TNFi were rarely used during pregnancy owing to lack of safety data, but the uptake slowly increased over time among the women in our study. We cannot conclude from our results that the decrease in adverse outcomes is caused by the increasing use of TNFi, but our study together with studies of women with other diseases exposed to these drugs strengthen the arguments for keeping disease under control during pregnancy, even if it requires pharmacological treatment. Hopefully, this will improve outcomes for both women with SpA and their children.

While we know that environmental risk factors also play a role in SpA development, it has been difficult to identify these factors. Earlier studies of SpA and other chronic diseases have found that circumstances in early development, even before birth, might lead to disease in adulthood. In study IV, we looked at risk factors related to the period around the time of birth, and at childhood infections until age 15. We compared how many had been exposed to these factors among people with ankylosing spondylitis and among healthy controls. We also compared patients and their siblings. Siblings often share an environment growing up, such as having the same living standards, so by comparing them we can rule out that any signal we find is actually a result of for example socio-economy in childhood. We found that people with older siblings were at higher risk of ankylosing spondylitis as adults, and also those that had their tonsils removed in childhood. Children with older siblings are exposed to more infections early in life, and tonsils can be removed because of repeated infections. Therefore, our results suggest that childhood infections are involved in the process leading up to a person developing ankylosing spondylitis.

In summary, we used Swedish national health and population registers to answer questions regarding the risk factors and consequences of SpA. A red thread through all studies was the connection to family members of patients; parents, siblings, and children, that made it possible to study genetic and environmental risks, and the impact of SpA on pregnancy. These results will hopefully be useful in both future research and clinical practice, but also to patients themselves, as they answer at least some questions regarding the risks associated with SpA in families.

Populärvetenskaplig sammanfattning

Denna avhandling består av fyra studier som behandlar olika aspekter av den reumatiska sjukdomen spondylartrit (SpA). SpA är egentligen ett samlingsnamn för en hel grupp av närbesläktade diagnoser som totalt drabbar cirka fem av tusen svenskar. Vanliga symptom vid artritsjukdom är smärta, stelhet och svullnad i leder orsakat av en reaktion från kroppens eget immunförsvar. I SpA är de värst drabbade lederna vanligtvis dem i ryggraden och där ryggraden ansluter till bäckenet, vilket ger ländryggssmärta, eller leder i händer, knän och fötter. En del patienter får också inflammation i ögat, huden eller tarmen. Utan fungerande behandling kan inflammationen leda till permanenta skador på lederna, ökad risk för exempelvis hjärt- och kärlsjukdomar, och i sällsynta fall att ryggkotorna växer ihop.

En anledning till att dessa diagnoser grupperades från början var att de ”går i släkten”. Läkare noterade att deras patienter ofta hade en eller fler släktingar med liknande symptom. De frågor vi ville besvara i studie I var följande: Om jag har den här sjukdomen, vad är risken att mina barn eller syskon får den? Och hur mycket beror på arv respektive miljö? Sverige är en utmärkt plats för att studera sådana frågor eftersom vi har en lång historia av att föra register över våra invånare. I registren kan man få svar på bland annat vem som är släkt med vem och vilka diagnoser enskilda personer fått vid besök inom specialistvården. Vi använde dessa register för att fastställa hur många föräldrar, syskon och barn till patienter med ankyloserande spondylit (den mest studerade formen av SpA) som själva fått diagnosen, jämfört med släktingar till personer utan sjukdomen. Vi fann att patienters nära släktingar hade en 20 gångers ökad risk att själva drabbas. Vi skattade också ärftligheten, det vill säga hur mycket av mottagligheten att drabbas av sjukdomen som beror på genetiska faktorer, till max 80 %. Det betyder att ärftligheten är hög, men ändå lägre än vad forskare tidigare beräknat i studier på färre individer. Med andra ord så har även miljöfaktorer betydelse för vem som utvecklar sjukdomen.

I studie II låg fokus på en grupp effektiva, men också dyra, läkemedel mot SpA som heter tumörnekrosfaktorhämmare (TNFi). Dessa läkemedel fungerar tyvärr inte för alla patienter, och det skulle spara både lidande och pengar om man kunde förutspå vilka patienter som inte kommer svara på behandlingen, och erbjuda dem annan behandling. Eftersom familjehistoria av SpA är en stark riskfaktor för att utveckla sjukdomen ville vi se om det också påverkade hur man svarar på TNFi-behandling. I studie II jämförde vi SpA-patienter med och utan familjehistoria av SpA för att se om deras sjukdom hade förbättrats efter 3 och 12 månaders behandling, och om det fanns skillnader i hur länge de fortsatte ta läkemedlet. Vi lyckades dock inte hitta några skillnader. Våra resultat antyder att generna som leder till sjukdom inte nödvändigtvis är samma som de gener som avgör hur allvarlig sjukdomen blir, eller hur du svarar på behandling med TNFi.

I studie III undersökte vi riskerna för graviditetskomplikationer hos kvinnor med SpA. Man vet att andra reumatiska sjukdomar kan innebära en ökad risk för exempelvis förtidig födsel, men tidigare studier i SpA har varit små och visat motstridiga resultat. Vi genomförde den största studien hittills på födslar hos kvinnor med SpA, där vi jämförde andelen komplikationer mot andelen bland födslar från allmänbefolkningen. Vi fann att kvinnor med SpA i större utsträckning drabbades av havandeskapsförgiftning, födde förtidigt, och en större andel förlöstes med kejsarsnitt. Hos barnen fann vi en ökad risk för infektioner under första levnadsåret. Vi såg emellertid att riskerna hade minskat under studieperioden, samtidigt som användningen av TNFi ökade bland SpA-patienter. Under de första åren av vår studieperiod användes inte TNFi under graviditet på grund av bristande säkerhetsdata, men användandet ökade succesivt under perioden. Baserat enbart på vår data kan vi inte dra slutsatsen att minskningen av komplikationer beror på ökad läkemedelsanvändning, men vår studie tillsammans med studier på kvinnor med andra sjukdomar som använt TNFi stärker beläggen för att det är viktigt att hålla sjukdomen under kontroll under graviditeten, även om det innebär läkemedelsbehandling. Förhoppningsvis kommer detta att leda till säkrare graviditeter för både kvinnor med SpA och deras barn.

Även om man vet att miljöfaktorer har viss betydelse för utvecklingen av SpA har dessa faktorer varit svåra att identifiera. Tidigare studier av SpA och andra kroniska sjukdomar har pekat på att händelser tidigt i livet, kanske till och med i fosterstadiet, skulle kunna leda till att man utvecklar sjukdom i vuxen ålder. I studie IV studerade vi riskfaktorer från tiden kring en persons födelse och även infektioner upp till 15 års ålder. Vi jämförde hur många som hade exponerats för sådana faktorer bland personer med ankyloserande spondylit och bland friska kontrollpersoner. Vi jämförde också patienter med deras syskon. Syskon har ofta delat uppväxtmiljö, och genom att jämföra syskon kan vi utesluta att signaler vi hittar egentligen beror på exempelvis socioekonomi i barndomen. Vi fann att personer med äldre syskon hade högre risk att drabbas av ankyloserande spondylit som vuxna, och samma gällde för de som opererat bort sina halsmandlar i barndomen. Barn med äldre syskon utsätts för fler infektioner tidigt i livet, och halsmandlar kan opereras bort på grund av upprepade infektioner. Därför tyder våra resultat på att infektioner i barndomen är involverade i processen som leder till sjukdom.

Sammanfattningsvis använde vi svenska nationella hälso- och befolkningsregister för att svara på frågor rörande riskfaktorer och konsekvenser av SpA. En röd tråd genom alla studier var kopplingen till patienternas familjemedlemmar; föräldrar, syskon och barn, som gjorde det möjligt att studera hur gener och miljöfaktorer påverkar sjukdomsrisk, och hur SpA påverkar graviditeten. Dessa resultat kommer förhoppningsvis att vara användbara både i framtida forskning och i klinisk kontext, men även för patienterna själva, eftersom de besvarar åtminstone några frågor rörande riskerna med SpA ut ett familjeperspektiv.

Abstract

The spondyloarthropathies (SpA) are a group of chronic inflammatory diseases that share several disease characteristics such as inflammation of entheses and extra-musculoskeletal manifestations like uveitis, psoriasis, and inflammatory bowel disease. These diseases, or symptoms thereof, are also known to run in families. The purpose of this thesis was to expand knowledge concerning the etiology and prognosis of SpA, using family-based epidemiological methods on data from Swedish health and population registers.

In study I, we estimated the familial aggregation of a specific SpA subtype, ankylosing spondylitis (AS), in a nested case-control study of AS cases, population controls, and first-degree relatives of both groups. We were able to provide a precise estimate of the familial aggregation, corresponding to a 20-fold increased risk of AS among first-degree relatives of AS cases. We also estimated the heritability of AS to 77%, i.e. the proportion of susceptibility to AS in the population that is due to genetics. Our estimate can be seen as an upper limit for the heritability, as shared environmental effects were not considered. While both estimates are relatively high, they are lower than previous reports for AS, which have been based on small and often selected samples.

In study II, a cohort study, we investigated whether family history of SpA, or its specific subtypes, were predictive of response to treatment with tumor necrosis factor inhibitors (TNFi) in patients with SpA. Despite being such a strong risk factor for disease development, we did not find family history to be associated with prognosis in terms of TNFi drug survival or treatment response at three or twelve months.

In study III, we studied temporal trends in pregnancy outcomes among women with axial SpA. We found that women with axial SpA, compared to women from the general population, were at increased risk of pre-eclampsia, preterm birth, and serious infection in the infant. The proportion of cesarean deliveries was also significantly higher among women with axial SpA. The risks had, however, diminished over the last decade, to reach similar levels as in the general population, while the use of effective treatment in the form of TNFi increased before and during pregnancy over the same period.

In study IV, we searched for environmental risk factors for AS, with a focus on perinatal characteristics and infections in childhood. In this nested case-control study, we found that having older siblings and a history of tonsillectomy in childhood were associated with AS in adulthood, even after adjustment for childhood socio-economic status and other family-shared confounders through a sibling comparison.

By using data from national registers, we were able to perform the hitherto largest studies on these topics regarding etiology and prognosis of SpA. While the genetic influence is substantial in AS, there is a larger contribution of environmental risk factors than

previously known. These seem partly related to early life, with a possible influence of childhood infections. We have also added to a growing body of evidence supporting the use of effective treatment in women with axial SpA, before and at least in the beginning of pregnancy, to minimize the risks active that SpA disease pose on pregnancy outcomes.

List of scientific papers

I. Morin M, Hellgren K, Frisell T. Familial aggregation and heritability of ankylosing spondylitis - a Swedish nested case-control study. *Rheumatology (Oxford)* 2020;59:1695-702. doi: 10.1093/rheumatology/kez519.

II. Morin M, Hellgren K, Lindström U, Frisell T. Is family history a predictor of response to tumour necrosis factor inhibitors in spondyloarthritis? A Swedish nationwide cohort study. *Scandinavian Journal of Rheumatology* 2022;51:10-20. doi: 10.1080/03009742.2021.1887928.

III. Morin M, Frisell T, Stephansson O, Hellgren K. Temporal trends in adverse pregnancy outcomes in axial spondyloarthritis in Sweden: a cohort study. *The Lancet Rheumatology* 2023;5:e121-e29. doi: 10.1016/s2665-9913(23)00001-2.

IV. Morin M, Hellgren K, Lindström U, Frisell T. Association of childhood infections and perinatal factors with ankylosing spondylitis: a Swedish nationwide case-control and sibling study. *RMD Open.* [Forthcoming 2023]. doi: 10.1136/rmdopen-2023-003438.

Contents

List of abbreviations

ACR	American College of Rheumatology
AS	Ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis international Society
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score with C-reactive protein
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BMI	Body-mass index
DAPSA	Disease Activity index for PSoriatic Arthritis
CASPAR	Classification Criteria for Psoriatic Arthritis
CI	Confidence interval
CRP	C-reactive protein
DAG	Directed acyclic graph
DMARD	Disease-modifying anti-rheumatic drug
bDMARD	Biologic DMARD
csDMARD	Conventional synthetic DMARD
tsDMARD	Targeted synthetic DMARD
EULAR	European Alliance of Associations for Rheumatology
GWAS	Genome-wide association study
HAQ	Health Assessment Questionnaire-Disability Index
HLA	Human leukocyte antigen
HR	Hazard ratio
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
IL	Interleukin
JAKi	Janus kinase inhibitor
LISA	Longitudinal integrated database for health insurance and labor market studies
MAR	Missing at random
MCAR	Missing completely at random

MHC	Major histocompatibility complex
MNAR	Missing not at random
MRI	Magnetic resonance imaging
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis
ReA	Reactive arthritis
RR	Risk ratio
SGA	Small for gestational age
SNP	Single-nucleotide polymorphism
SpA	Spondyloarthritis
SRQ	Swedish Rheumatology Quality register
TNFi	Tumor necrosis factor inhibitor
uSpA	Undifferentiated spondyloarthritis

1 Introduction

1.1 What is spondyloarthritis?

The spondyloarthropathies, or simply spondyloarthritis (SpA), are a group of chronic inflammatory joint diseases with common disease characteristics, affecting 0.3 to 1.9% of people worldwide.[1 2] "Spondylo–" comes from the Greek *spondylos*, meaning vertebra,[3] and inflammation of the spine and sacroiliac joints causing lower back pain is one of the hallmark symptoms in some, though not all, types of SpA. Other disease characteristics include peripheral arthritis (inflammation of joints in primarily lower limbs), enthesitis (inflammation of the entheses, where tendons and ligaments attach to the bone), and extra-musculoskeletal manifestations such as uveitis (inflammation of the eye), psoriasis (skin), and inflammatory bowel disease (IBD).[2] Without effective treatment, SpA can result in severe pain and increasing disability as the inflammation causes progressive damage to the affected joints.

Already in 1974 when Moll et al. first proposed grouping of the "seronegative spondarthritides", one reason for this was their tendency to aggregate within families.[4] Symptoms from different subtypes of this group are often present in the same patient, but they are also commonly found in relatives of patients. As expected, genetic factors are important risk factors for SpA, with the strongest association found with the Human Leukocyte Antigen (HLA)-B27.[5]

1.2 Classification of SpA

Traditionally, the concept of SpA includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), SpA associated with IBD, and undifferentiated SpA (uSpA).[6] Certain disease characteristics are more common in certain subtypes. Inflammation of the axial skeleton (i.e. spine and sacroiliac joints) and recurrent uveitis are typical for AS,[2] while psoriasis and peripheral arthritis are typical for PsA.[7] Patients with ReA can have a wide range of these symptoms, but with an acute onset following a gastrointestinal or urogenital infection. Both axial and peripheral symptoms of SpA can also occur in patients with IBD. Patients with uSpA have symptoms of SpA, like enthesitis and uveitis, but do not fulfil the criteria for any of the other diagnoses.[8] There is also a considerable overlap between diagnoses, and patients can move between the different diagnoses with time.

Several classification criteria for SpA exist, with the purpose of grouping patients for enrolment in clinical trials and observational research. These criteria are not validated for diagnostic purposes, but their components are used in the collective judgement of the diagnosing rheumatologist.[6] The modified New York criteria for AS that were introduced in 1984 put a lot of emphasis on the presence of structural changes in the sacroiliac joints noticeable on conventional radiography.[9] It has been shown, however, that these changes

often occur late in the disease course. The diagnostic delay in AS has therefore been substantial, in some cases up to 10 years or more.[10 11] Patients with early disease were consequently excluded from clinical trials when using the modified New York criteria for inclusion. Several new criteria have therefore been developed over the years, which do not require radiographic changes for a diagnosis of SpA.[12-14] When the Assessment of SpondyloArthritis international Society (ASAS) proposed new criteria in 2009 and 2011, they aimed to include patients in the early stages of disease, but also to include all types of SpA under two categories (axial or peripheral SpA) based on where the predominant symptoms occurred.[14 15] By reviewing the components of the ASAS classification criteria for axial and peripheral SpA (Table 1.1), it is evident that these are related conditions, but specific features are given different weight in axial and peripheral disease.

Table 1.1 SpA classification criteria (adapted from respective publication)

ASAS criteria for axial SpA[15]	**ASAS criteria for peripheral SpA[14]**	**CASPAR criteria for PsA[16]**
Back pain ≥3 months with onset <45 years AND Either sacroiliitis on imaging (radiographs or MRI) and ≥1 SpA feature* Or HLA-B27 and ≥2 SpA features* *SpA features: ▪ Inflammatory back pain ▪ Arthritis ▪ Enthesitis of the heel ▪ Uveitis ▪ Dactylitis ▪ Psoriasis ▪ IBD ▪ Good response to NSAIDs ▪ Family history of SpA ▪ HLA-B27 ▪ Elevated CRP	Arthritis, enthesitis or dactylitis AND Either ≥1 of: ▪ Psoriasis ▪ IBD ▪ Preceding infection ▪ HLA-B27 ▪ Uveitis ▪ Sacroiliitis on imaging (radiographs or MRI) Or ≥2 of the remaining: ▪ Arthritis ▪ Enthesitis ▪ Dactylitis ▪ Inflammatory back pain in the past ▪ Family history of SpA	Arthritis, spondylitis or enthesitis AND ≥3 points: ▪ Current or past psoriasis, or family history of psoriasis (2 points) ▪ Typical psoriatic nail dystrophy ▪ Negative test for rheumatoid factor ▪ Current or past dactylitis ▪ Radiographic evidence of new bone formation in hand or foot

SpA: spondyloarthritis; ASAS: Assessment of SpondyloArthritis international Society; CASPAR: Classification Criteria for Psoriatic Arthritis; PsA: psoriatic arthritis; MRI: magnetic resonance imaging; HLA-B27: human leukocyte antigen B27; IBD: inflammatory bowel disease; NSAIDs: non-steroidal anti-inflammatory drugs; CRP: C-reactive protein.

Axial SpA can be further divided into non-radiographic and radiographic axial SpA, where radiographic axial SpA corresponds to an AS diagnosis. The view today is that both subtypes should be seen as part of the same disease. Some, but not all, patients with non-radiographic axial SpA will eventually progress to radiographic axial SpA.[17] In peripheral SpA, PsA is the largest and by far most studied subtype. There are specific criteria for PsA, namely the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria (Table 1.1), which were published in 2006.[16] Patients with neither axial nor psoriatic involvement, however, have been rather neglected in both clinical trials and observational studies. A significant group of patients also fulfil the criteria for both axial and peripheral SpA.[1] While axial and peripheral SpA is nowadays the preferred nomenclature also for diagnosis, the older disease names, i.e. AS, PsA, and uSpA, are still used in parallel, and these are the diagnoses listed in the International Classification of Diseases 10th Edition (ICD-10), which is currently used to classify diagnoses in for example the Swedish National Patient Register.

1.3 Prevalence and sex distribution

The prevalence of SpA in Europe is around 0.5%, with substantial variation between countries. Such differences could in part can be explained by differences in prevalence of HLA-B27 and other genetic factors, but also by different sampling procedures.[18] Very few studies have reported prevalence based on the ASAS classification criteria (i.e. for axial and peripheral SpA). In southern Sweden, the prevalence of SpA (not including ReA) has been estimated to 0.45%, out of which 0.25% is PsA, 0.12% is AS, 0.1% is uSpA, and 0.015% SpA with IBD.[19] This is in line with a nationwide Swedish study that found a prevalence of AS of 0.18%, with higher prevalence in the north and lower in the south, reflecting an increased prevalence of HLA-B27 in northern Sweden.[20] The prevalence of PsA in Sweden was estimated to 0.35% in 2017,[21] which can be compared to a global prevalence of 0.13%[22] These differences are also partly influenced by the distribution of HLA-B27. The male:female ratio in AS is about 2:1, but closer to 1:1 in non-radiographic axial SpA.[2] Peripheral SpA, including PsA, has an equal (1:1) sex distribution.[1 18 22] The first symptoms of axial SpA typically present during early adulthood,[2] while peripheral SpA is more likely to develop at age 30, or even later for PsA.[17]

1.4 Treatment

The ultimate goal of therapy in SpA is to reduce inflammation to a minimum, as sustained inflammation, beyond pain and other immediate negative effects, is associated with e.g. progression towards structural damage, functional impairment, and increased risk of cardiovascular disease and other comorbidities. The first-line treatment in SpA is non-steroidal anti-inflammatory drugs (NSAIDs), along with recommendations of physical exercise. When joint engagement is not widespread, local injections of corticosteroids can

provide a prompt reduction of pain in peripheral joints.[23 24] For patients with cutaneous psoriasis, topical treatments can also be used to treat skin symptoms.[24]

1.4.1 Disease-modifying anti-rheumatic drugs

The majority of patients with SpA however, require systemic anti-rheumatic treatment. In patients with peripheral disease, conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) like methotrexate or sulfasalazine are used, sometimes already as first-line treatment,[25 26] whereas csDMARDs are not efficacious for axial disease.[23] For a long while, there were few other available treatment options for patients with SpA. During the last two decades however, the introduction of biologic DMARDs (bDMARDs), starting with tumor necrosis factor inhibitors (TNFi), have dramatically improved prognosis for many patients, especially those with axial SpA.

1.4.2 Tumor necrosis factor inhibitors

Biologic DMARDs are recommended for patients who have failed conventional treatment, and among bDMARDs, TNFi are usually the first-hand choice.[23 25] They are monoclonal antibodies against, or in one case a soluble receptor for, tumor necrosis factor alpha, one of the cytokines driving the inflammation in SpA. For many patients, TNFi treatment rapidly reduces inflammation, as seen by lowered CRP levels, leading to reduced pain, increased physical function, and less extra-musculoskeletal manifestations.[27 28] There has been a lack of evidence regarding whether TNFi also halts radiographic progression in axial SpA, meaning new bone formation in the spine, but several recent structured literature reviews on this topic indicate that prolonged TNFi treatment (>2-4 years) might have an effect also on radiographic progression.[29-31] TNFi are administered subcutaneously or by intravenous infusion, depending on the substance.

1.4.3 Other biologic and targeted synthetic DMARDs

While TNFi were the first bDMARDs to be introduced, biologic therapies targeting other immunological pathways have followed and are now possible treatment options in SpA where TNFi treatment has failed or is inappropriate. In PsA, this includes drugs targeting interleukin (IL)-17, IL-12/IL-23, and T-cell activation.[24] Inhibitors of IL-17 have also proven efficacious in AS, while other newer bDMARDs have not.[28] Another class of therapeutics, the targeted synthetic (ts)DMARDs, has also emerged. These are small molecules, taken orally, designed to target specific immunological pathways. Apremilast, a phosphodiesterase 4 inhibitor, has been approved for use in PsA,[32] while Janus kinase inhibitors (JAKi) have been proven effective in both AS and PsA.[24 33] One JAKi is currently approved for use also in non-radiographic axial SpA.[34] The patient group with peripheral SpA, excluding PsA, have however largely been excluded from clinical trials, with the consequence that b/tsDMARDs can only be used off-label in these patients.[1] Despite this, it is common to use of a similar treatment strategy in peripheral SpA as in axial SpA.

1.5 Measures of disease activity and functional status

To allow quantification of a patient's disease activity and functional status in SpA, various composite outcome measures have been developed. These measures are used in clinical practice, but also in clinical trials, to evaluate a patient's disease status and treatment response. Often, they consist of a combination of laboratory parameters and clinician- and/or patient-reported outcomes. A few commonly used measures are described below.

- The **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)** is an index solely based on patient-reported answers to six questions regarding level of back pain, fatigue, peripheral joint pain and swelling, localized tenderness, and the duration and severity of morning stiffness.[35] Since first published in 1994, BASDAI has been widely used in clinical trials in AS. The score ranges from 0 to 10 (maximal disease activity) and <4 is commonly used as a cut-off for low disease activity.
- The **Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP)** includes both patient-reported items and objective measures, including a laboratory test for inflammation in the form of CRP. The other four items included are patient-reported level of back pain, peripheral joint pain/swelling, patient-reported global assessment of disease activity, and morning stiffness.[36] It ranges from zero with no upper limit, with a threshold for low disease activity at <2.1. ASDAS-CRP was introduced in 2009 and is currently the preferred measure of disease activity in axial SpA.[23]
- The **Health Assessment Questionnaire-Disability Index** (HAQ) is an instrument to measure physical function in arthritis patients. The self-administered questionnaire consists of 20 questions regarding ability to for example dress, eat, or reach.[37] The HAQ score ranges from 0 to 3, with <0.5 representing normal physical function. A validated and slightly modified version of HAQ is used in Sweden.[38]
- The **Disease Activity index for PSoriatic Arthritis (DAPSA)** is a composite index used in PsA, consisting of an assessment of swelling and tenderness in 66/68 joints (i.e. joint counts, counted by doctor or nurse), patient-reported global assessment of disease activity, patient-reported level of pain, and CRP. Thus, DAPSA is mainly focused on the joint activity of the disease. A DAPSA ≤14 is considered low disease activity.[39]

2 Literature review

This literature review examines and summarizes the literature relevant for the studies in the thesis. As most studies were focused on axial SpA or AS, these SpA subtypes have been given most weight in the review.

2.1 The importance of family history

2.1.1 Familial aggregation

A central reason for grouping the diseases in SpA together in the first place was their tendency to aggregate within families.[4] There are reports suggesting that the risk of developing SpA is 40 times higher among first-degree relatives of SpA patients compared to the general population,[40] but also that the risk of AS is as much as 80 to 90 times higher in first-degree relatives of AS patients.[41-43] Brown et al., when summarizing data from all published studies on this topic until 1999, estimated the recurrence risk ratio of AS in first-degree relatives to 82.[41] The recurrence risk ratio is calculated by dividing the proportion of relatives of cases who develop disease by the prevalence of that disease in the population. This estimate is hence very dependent on what prevalence figure is used, as a change from e.g. 0.1 to 0.2% would result in a 50% reduction in the recurrence risk ratio. It is also common in family-based studies that disease ascertainment in relatives is based on reports from the index patient, or from those relatives who were willing to participate, which might lead to ascertainment bias. To overcome these issues, Icelandic researchers studied the familial relationships among all known AS patients in Iceland. With access to information on relatedness between all Icelanders, their conclusions were still similar to Brown et al.: a relative risk of AS in first-degree relatives between 72 and 94.[42 43] Estimates from all studies mentioned above were, however, based on small numbers of patients. In contrast, a population-based Swedish study of 3500 AS cases, including only hospitalized cases but with sibships ascertained from national registers, reported a sibling risk ratio of merely 17.[44]

2.1.2 Heritability

We might ask ourselves how much of the familial aggregation depends on nature versus nurture, or genes versus environment. Heritability is a measure of the role of genetic factors in the liability to develop a disease. More specifically, the narrow-sense heritability is the proportion of a population's phenotypic variance in a trait that is explained by additive genetic variance, or the genetic component in inheritance from parent to offspring. The additive genetic value for a particular trait is the sum of the effect on that trait from all alleles in an individual. Heritability can be estimated by comparing the observed phenotypic correlation between relatives with their expected genetic correlation.[45]

Based on results from twin studies, the heritability of AS is over 90%.[46 47] Brown et al., in a study of English twins, reported a probandwise concordance rate of AS of 75% in 6 monozygotic twin pairs, and 12.5% in 32 dizygotic twin pairs.[46] On this basis, they estimated a heritability of remarkable 98.8%. A Danish twin study of 27 twin pairs reported probandwise concordance rates of 40% in monozygotic twins and 4% in dizygotic twins, corresponding to a heritability of 90% (95% CI 56-99%).[47] There are reasons to question these estimates however, as they are based on a very small number of subjects, and, as for the studies of familial aggregation above, are relying on the willingness of relatives to participate.

A recent genome-wide association study (GWAS) estimated the heritability of AS to 50-70% based on single-nucleotide polymorphisms (SNPs), with the higher estimates related to AS with uveitis.[48] Such SNP-based methodology tends to result in lower heritability estimates compared to traditional twin studies. The "missing heritability" can have several explanations. Rare genetic variants with large effects might be missed if they are not included on the genotyping array. Alternatively, heritability is overestimated from family data owing to for example shared environmental effects, or gene interactions.[49] Possibly, SNP-based and family-based methods each provide a lower and upper threshold for the heritability. In PsA, heritability has been estimated to 27-43% based on SNPs.[50] For the other SpA disorders, there are no available estimates of heritability.

2.1.3 Family history in diagnosis, classification, and prognosis

Family history of SpA is part of the classification criteria of both axial and peripheral SpA,[14 15] and family history of psoriasis is part of CASPAR.[16] Family history is also included in the clinical evaluation when diagnosing patients with suspected SpA. In the ASAS criteria, family history of SpA is defined as presence of AS, ReA, psoriasis, IBD, or uveitis in a first- or second-degree relative.[14] However, this definition has been questioned, as only a family history of AS and uveitis was actually predictive of axial SpA in a study of over 1000 patients with inflammatory back pain.[51] This suggests that the definition might need to be reevaluated. Whether family history of SpA, in any form, also has an impact on disease prognosis in SpA patients remains to be determined.

2.2 Etiology of SpA

2.2.1 Genetic risk factors

To date, over 100 genetic variants associated with AS have been identified through GWAS studies. The strongest genetic risk factor, explaining ~20% of AS heritability, is HLA-B27.[5] While less than 10% of the general population carry this allele, it is present in around 80-90% of AS patients, with some variation depending on ethnicity.[52 53] Other types of SpA also associate with HLA-B27, but to a lesser extent.[54]

The protein HLA-B27 is a major histocompatibility complex (MHC) class I antigen and it is normally responsible for presenting peptides from within the cell on the cell surface. If these peptides are recognized as foreign (meaning coming from virus or bacteria) by CD8+ T cells, this will result in an inflammatory response. How HLA-B27 can promote SpA is not entirely clear, but there are several theories regarding the pathogenic mechanism including protein misfolding leading to endoplasmic reticulum stress, formation of HLA-B27 homodimers that react with other immune cells on the cell surface, or that the presentation of specific self- or bacteria-derived peptides by HLA-B27 to CD8+ T cells results in cross-reactivity and subsequent joint inflammation.[55]

Outside the MHC, other genetic variants associated with AS include ERAP1, which codes for a protein expressed in the endoplasmic reticulum that processes peptides for MHC class I presentation, and variants of the IL-23 receptor. There is also considerable overlap between the susceptibility loci for AS and other inflammatory diseases, especially IBD.[56] However, the so-far identified genetic variants outside the MHC region only account around 7% of AS heritability.[5]

2.2.2 Environmental risk factors

While the genetic component in the predisposition to develop SpA is strong, especially for axial SpA, the common understanding is that there are environmental factors that trigger the disease in genetically susceptible individuals. Several theories exist regarding what these triggers are, and what mechanisms are involved.

An association between mechanical stress and SpA-like disease has been shown in animal models,[57] and corresponds with the notion that SpA mainly affects weight-bearing parts of the body like the spine and large joints of the lower limbs. It is hypothesized that mechanical stress causes micro-damages to entheses, which starts an inflammatory response leading to SpA, but this theory is yet to be proven in humans.[58] Smoking has been reported to increase the risk for incident AS and PsA,[59 60] and smoking has also been associated with more severe disease.[61]

Findings from both animal and clinical studies have indicated a connection between the human microbiome and SpA.[62] An obvious example of how bacteria can trigger SpA is ReA, a type of SpA that debuts 3-4 weeks after an infection, which is often gastrointestinal or urogenital in character.[8] However, other SpA conditions are also suspected to have an association with microbes. Dysbiosis of the gut microflora is one suggested pathway that could lead to inflammatory disease. Several studies have found distinct intestinal microbial profiles in patients with AS compared to healthy controls.[63 64] In additional support of the dysbiosis theory, a French study found that patients with AS had been breastfed less often compared to their healthy siblings as well as general population controls. The mechanism behind their results was not examined, but breastfeeding induces a different gut microflora as compared to bottle-feeding.[65]

Exposures during early life, even before birth, have been shown to be associated with adult onset of disease in several other disorders. This is referred to as "developmental origin of health and disease", thought to be a result of developmental plasticity, i.e. epigenetic changes induced by environmental stimuli in the fetus or newborn leading to permanent changes in gene expression.[66] As an example, low birthweight, as a proxy for fetal growth and nutrition, is associated with cardiovascular disease, hypertension, and type II diabetes.[66] High birthweight has been associated with an increased risk of breast cancer, attributed to the fetal hormonal environment.[67] Early-life environmental exposures, such as maternal stress, infections, pollution, and nutrition, have also been shown to have long-lasting impact on the immune system of the child, which potentially could lead to immune-mediated diseases later in life.[68] Birthweight has been investigated as a risk factor in association with rheumatic diseases, but findings are conflicting. High birthweight was associated with Sjögren's syndrome in one small study,[69] while in rheumatoid arthritis (RA) there are reports both for and against an association.[70-73] A weak association with low birthweight (<3000 g) was found in one study on AS, but not when low birthweight was defined as <2500 g.[74]

Infections in childhood have also been linked to AS development. A Swedish study including 2453 AS cases and population controls found an association with childhood hospitalizations for respiratory tract infections, especially tonsillitis, while appendicitis had a negative association with AS.[75] Additionally, adult tonsillitis has been associated with AS in a Taiwanese study including any in- or outpatient visit with a tonsillitis diagnosis prior to the first AS diagnosis, with stronger effects for longer intervals between diagnoses.[76] The authors hypothesized that respiratory tract infections, or treatment with antibiotics, alters the gut microflora or have an immunological effect that will lead to disease onset in predisposed individuals. Of note, effect sizes were quite low in both studies.

Birth order among siblings is another topic that has been investigated as a risk factor for AS, with conflicting results. While Baudoin et al. found an increased risk of AS in first-borns,[77] this was later contested by Brophy et al. who found no such effect.[78] Lindström and colleagues later found the opposite, that having older siblings was associated with development of AS, with the hypothesis that having older siblings is a proxy for childhood infections.[74]

In summary, the development of SpA, and AS in particular, currently cannot be attributed to any specific environmental exposures.

2.3 Family history and treatment response

Since the first regulatory approvals around year 2000, TNFi (and subsequently other biologic and targeted synthetic drugs) have revolutionized the treatment of SpA. TNFi have been, and are still, strongly recommended for patients with SpA who failed a first-

line treatment with NSAIDs or csDMARDs.[23 24 26] However, not all SpA patients respond to TNFi, and within one year 20-25% of patients discontinue therapy.[79-81] This is unfortunate, as lack of effective treatment might lead to suffering and irreversible disease progression in the patient, and unnecessary costs to society. Much research has therefore been conducted trying to identify patient characteristics associated with treatment response already before treatment start. Factors predictive of a beneficial TNFi treatment response in SpA include young age, male sex, high baseline inflammation, and good functional status at treatment start,[82-92] while smoking and obesity predict poorer outcomes.[93 94] HLA-B27 positivity has also been associated with drug survival and treatment response in axial SpA.[83 95 96] Yet, these factors are not enough to predict response in individual patients, and further advances are required to guide clinicians in treatment choice.

Family history of SpA is a strong risk factor for disease development. Whether it is also a predictor of TNFi response has been investigated along with other factors in two studies of axial SpA. In a single-center study from Toronto, Canada, Alazmi et al. found no association between family history of SpA and lack of response to a first TNFi treatment in 249 axial SpA patients.[96] Similarly, Yahya et al. found no association between family history of SpA and reaching remission or low disease activity under TNFi treatment in 349 axial SpA patients from two specialist centers in the UK.[95] However, the studies had low power to detect clinically meaningful prediction. For PsA, studies of the potential predictive effect of family history on TNFi treatment response are completely lacking.

2.4 SpA and pregnancy

Maternal chronic inflammatory disease can have negative impact on pregnancy outcomes. The bulk of evidence comes from studies in RA and IBD, which have reported increased risks of e.g. preterm birth, infants born small for gestational age (SGA), and a higher proportion of cesarean deliveries in pregnancies among women with these diagnoses.[97-100] Data regarding pregnancy outcomes in SpA are more limited, and the existing literature is heterogeneous, as we shall see in the following sections. In patients with RA, pregnancy can have a beneficial effect on the disease, with at least 50% of women experiencing an improvement of disease activity during pregnancy.[101 102] The same pattern is generally not seen in SpA, where disease activity is unaffected, or according to some studies even aggravated, during pregnancy.[102-106]

2.4.1 Adverse pregnancy outcomes in SpA

Historically, SpA has been grouped with for example RA in the analysis of pregnancy outcomes because of very low numbers of available patients.[107 108] Alternatively, studies have been restricted to patients with AS.[102 105] The first larger study to evaluate pregnancy outcomes in women with AS was a population-based case-control study from Sweden published in 2016, which included 388 deliveries among women with AS and 1082 control deliveries between 2001 and 2009. Increased risks for preterm birth and cesarean

delivery were found in the AS group, and an increased risk for SGA, though the SGA estimate was not significant after adjustment for confounders.[109] Since then, studies from e.g. Denmark, Turkey, South Korea, and North America have both corroborated[110-112] and contradicted[113-116] these results, the majority focusing on women with AS. The increasing interest in this topic over the last couple of years, but also the heterogeneity of findings, was evident when three systematic reviews and meta-analyses were published between 2020 and 2022.[106 117-119] According to these reviews, there is increased risk of preterm birth in women with axial SpA. Two of the three studies also reported increased risks of both elective and emergency cesarean delivery, and SGA. The risk of pre-eclampsia was found to be significantly increased in one review and borderline significant in another, while the third found the underlying studies reporting on pre-eclampsia (and cesarean delivery) too diverse to pool in a meta-analysis. The relative risks for most outcomes in the meta-analyses were between 1.3 and 2.6.

Evidence regarding pregnancy outcomes in PsA specifically is even scarcer, with most studies gathering less than 150 pregnancies.[111 116 120 121] Once again, the most influential reports rely on Swedish or Nordic data. Bröms et al., in a population-based study including 964 births in Swedish and Danish women between 2007 and 2012, found an increased risk of gestational hypertension, pre-eclampsia, and cesarean delivery.[122] Another Swedish nationwide cohort study of 541 births between 1997 and 2014 found women with PsA to be at increased risk of preterm birth and cesarean delivery, but not pre-eclampsia or SGA compared to general population controls.[123]

One reason for the heterogeneity of previous studies could be their inability to take patient characteristics such as disease activity and treatment into account. Disease activity has been shown to correlate with adverse pregnancy outcomes in RA.[124-126] Disease activity and inflammation is most likely an important driver of adverse events also in SpA, but not much data is available to support this. One study found active disease to be associated with preterm labor and cesarean delivery in AS and with preterm birth in PsA.[120] Another study found elevated CRP in the second trimester, but not elevated ASDAS, to be associated with preterm birth in axial SpA.[110]

2.4.2 Anti-rheumatic treatment during pregnancy

It is not only the inflammation that may affect pregnancies in women with rheumatic diseases, but also the treatments used. The csDMARD methotrexate used in PsA, is a known teratogenic substance and should be discontinued three months before pregnancy.[127] NSAIDs are contraindicated in the second half of pregnancy owing to an increased risk of premature closure of the ductus arteriosus and fetal renal dysfunction.[128]

When TNFi were introduced, it was not known if they would affect a growing fetus. Pregnant women were excluded from clinical trials, and with this lack of evidence, TNFi treatment during pregnancy was discouraged. Over time, a growing body of evidence

from observational studies, mainly in women with IBD, have shown that there are no indications of increased risks of pregnancy loss or congenital malformations associated with TNFi exposure during pregnancy.[127 129] TNFi use during pregnancy has been associated with other adverse outcomes, such as preterm birth and cesarean delivery in RA, but this association is vulnerable to confounding by indication, i.e. that women with high disease activity are more likely to continue treatment throughout pregnancy.[130] Attempts to separate the effects of disease activity and treatment have been made for RA, but studies in SpA have not yet been sufficiently well-powered.[110 126 131]

A lingering concern regarding TNFi use during pregnancy is the risk of infection in both mother and child. Due to placental transfer of antibodies in the last months of pregnancy, the fetus may receive high doses of these immune-modulatory drugs that remain up to six months after birth. Children exposed to TNFi in late pregnancy are not recommended to be given live vaccines during this time. Certolizumab pegol has the lowest placental transfer among the TNFi, and is recommended over the other TNFi if anti-rheumatic treatment throughout pregnancy is necessary.[127 129]

3 Research aims

The overarching aim of this thesis was to contribute to the knowledge on etiology and prognosis of spondyloarthritis (SpA), focusing on the information contained in a family history of disease and other family-based approaches, in order to inform both future etiological research and clinical practice.

More specifically, the individual studies had the following aims:

- To provide precise estimates of the familial aggregation and heritability of ankylosing spondylitis
- To evaluate if a family history of SpA is predictive of prognosis and treatment response in patients with SpA starting a first treatment with biologic disease-modifying anti-rheumatic drugs
- To assess the risks of adverse pregnancy outcomes in women with axial SpA and their offspring, and to investigate how adverse outcomes vary over time and in relation to anti-rheumatic treatment
- To identify perinatal and early-life risk factors for ankylosing spondylitis, while controlling for family-shared confounding with a sibling comparison design

4 Methods

The studies in this thesis are based on "real-world evidence", or in other words, data generated from hospital visits, disease registers, and civil registration systems etcetera. While randomized controlled trials are often regarded the gold standard of epidemiological study designs, they are simply not useful to answer most of the questions in this thesis, as you cannot randomize your family history or your birth circumstances. The major strength of randomized controlled trials is that all possible causes of the outcome, except the exposure under investigation, should be equally distributed in the study groups. As this is not the case using real-world, observational data, these differences must be addressed in the design or statistical analysis stage of register-based studies such as those included in this thesis. Moreover, using this type of secondary data, not primarily recorded for research purposes, comes with additional challenges to study validity. In section 4.1, we first explore the real-world data sources used in this thesis, and in the following sections, we will concentrate on the study designs used and methodological considerations that comes with them.

4.1 Setting and data sources

Healthcare in Sweden is tax-funded and provides equal access to healthcare services, with hospital referral mainly based on geography. Patients with SpA are generally cared for within the public healthcare system by hospital-based rheumatologists. Sweden has a long history of recording health and demographic data on its residents, captured in a series of registers with a high degree of completeness thanks to mandatory and semi-automated registration. The most important registers are held and curated by governmental agencies, from which de-identified data can be requested for research purposes. What makes the Swedish registers an even more powerful source of research data is the ability to link them together, using the unique personal identification number given to all Swedish residents at birth or immigration.[132] The registers used in this thesis are described below.

The Swedish **National Patient Register**, maintained by the National Board of Health and Welfare (Socialstyrelsen in Swedish), contains information on hospitalizations and visits in non-primary outpatient care. Healthcare providers are bound by law to provide data to this register. Data on in-patient hospitalizations are included since in 1964 with complete national coverage from 1987, and non-primary outpatient care was added in 2001.[133] The information in the National Patient Register includes e.g. visit or discharge date, primary and secondary diagnoses as assigned by the discharging physician, treating hospital and medical specialty. Diagnoses are coded according to the Swedish version of the International Classification of Diseases (ICD) system.

The **National Prescribed Drug Register** was established in July 2005.[134] It contains data on all dispensations of prescription drugs at Swedish pharmacies, including date of prescription and dispensation, the personal identification number of the patient, the brand and amount of the substance dispensed, and information about the prescriber. Data reporting is mandatory and directly linked to the software used in pharmacies, resulting in almost complete coverage. The register does not, however, capture over-the-counter drugs, or drugs dispensed in a hospital-based setting.

The Swedish **Medical Birth Register** was established in 1973, and includes >98% of births in Sweden since its establishment.[135] The register contains data on antenatal, obstetric, and neonatal care, starting from the mother's first antenatal visit in early pregnancy and ending when mother and child are discharged from the hospital after birth. This information is prospectively recorded in standardized records by the healthcare providers, which are obliged by law to forward it to the National Board of Health and Welfare who compiles the register.

The **Total Population Register** is the core for the entire system of national registers and is fundamental for epidemiological research in Sweden. It is maintained by Statistics Sweden based on census data from the Swedish Tax Agency. The register contains data on residency for all Swedish residents, including dates of birth, death, immigration, and emigration. It also contains e.g. country of birth, region of residence, and civil status.[136] In epidemiological research, it is used to identify general population controls, and to censor subjects lost to follow-up due to death or emigration.

The Swedish **Multi-Generation Register** is part of the register system for the Total Population Register (above) and contains data on biological and adoptive parents for all individuals born in Sweden from 1932 onwards, and registered as living in Sweden at any point in time since 1961.[137] Apart from the personal identification numbers of index persons and their parents, data on country of birth for index patients and parents are included. From the information in the register, it is also possible to identify for example full siblings, half-siblings, and other relatives of interest. The coverage for index persons is virtually complete, but only parents registered as living in Sweden from 1947, when the personal identification number was introduced, are recorded in the register.

The **Longitudinal integrated database for health insurance and labor market studies (LISA)**, held by Statistics Sweden, contains annual data for people 15 years of age or older who are registered as living in Sweden on 31 December each year. It gathers information from several official agencies regarding for example sick leave and disability pension, unemployment, education level, and disposable income.[138]

The **Swedish Rheumatology Quality register (SRQ)**, as other Swedish national quality registers, was implemented to allow for evaluation and improvement of care both for the individual patient and for the healthcare system as a whole. The SRQ, initiated in 1995, is

integrated into the clinical workflow and collects information on diagnoses, treatments, and disease-related measurements for Swedish patients with rheumatic diseases.[139] Coverage is best for patients on biologic treatments, and at least 86% of SpA patients with a filled prescription for a biologic in the Prescribed Drug Register are also found in the SRQ.[140]

4.2 General study designs

There are two main study designs employed within this thesis: cohort studies and nested case-control studies.

In a **cohort study**, a group of individuals is identified based on an exposure, and followed over time in order to study the incidence of an event or disease of interest. It is also common to include a reference group from the same source population who are unexposed in order to quantify the risk associated with being exposed. In cohort studies, person-time at risk is often measured, and the risk of the outcome is calculated in relation to the accrued person-time. The outcome measures obtained include incidence rates ratios and hazard ratios. By instead comparing incidence proportions between groups, cohort studies can also be used to produce risk ratios.

A **case-control study** instead starts by identifying the individuals who had the event or disease of interest. Control individuals are randomly selected from the source population from which the cases originated. The exposure history is then ascertained for both groups. A case-control design might be the only feasible option when the outcome is rare, and when it is not possible, financially or otherwise, to collect exposure data for everyone in the population. Because of the sampling of controls, we cannot directly estimate the risk of the outcome in the source population. Instead, we obtain the odds of being a case rather than a control if exposed, and likewise for unexposed, resulting in an odds ratio.[141] However, under certain circumstances, the odds ratio is an estimate of the incidence rate ratio in the source population.

In a **nested case-control study**, the source population from which the cases and controls originated is fully enumerated from the beginning. This can be an ongoing cohort study in which some or all individuals with the outcome and a sample of those without the outcome are selected, or for example the entire Swedish population.[142] Sampling of the controls is performed with risk-set sampling, meaning that controls are selected from individuals at risk of becoming a case at the time (for example the same day) a case occurred. Risk-set sampling, or density sampling, allows us to estimate an incidence rate ratio from case-control data.[143]

4.3 Bias, and how to deal with it

Bias, or systematic error, is a major threat to the validity of results in epidemiological studies, and it requires considerable attention in study design and analysis. Bias is often divided into three main categories: confounding, selection bias, and information bias, which will be discussed further below.

A useful tool when thinking about bias is the directed acyclic graph (DAG) approach. A DAG is a causal diagram where the exposure, outcome, and measured and unmeasured covariates are depicted as "nodes", and our assumptions about causal effects between these variables are drawn with single-headed arrows, called "edges". An example of a DAG is given in Figure 4.1, where node E is an exposure and node O an outcome of interest. A "path" is a route between nodes connected by arrows. If the path follows the direction of the arrows it is said to be a causal path, while if we can trace a path through arrows pointing in opposite directions, the path is non-causal. If we follow the edges from E to O we see that there is an open, causal path between E and O that goes through the variable B. Node B is then a mediator of the effect of E on O. There is also a so-called backdoor path between E and O through node A, which is non-causal because it contains arrows in opposite directions. It will introduce a statistical association between E and O unless we find a way to block it, as associations only flow through open paths. A path can be blocked by e.g. conditioning on a variable on the path, or by the presence of a "collider", which is a variable with two arrows pointing towards it.[144] Node C, which is a common effect of E and O, is a collider on the backdoor path from E to O via C. This path is therefore blocked and will not introduce a statistical association between E and O unless we open the path by conditioning on the collider.

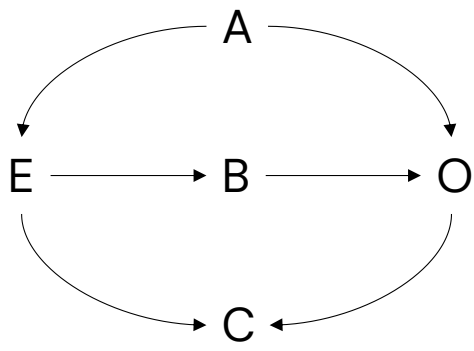

Figure 4.1 Example of a directed acyclic graph (DAG), where E is the exposure, O the outcome, B a mediator of the effect of E on O, A a common cause and C a common effect of E and O.

4.3.1 Confounding

Compared to randomized studies, observational studies are at higher risk of confounding, with the extent depending on the study design. Confounding occurs when there are common causes of exposure and outcome, such as node A in the DAG in Figure 4.1. When there is an open backdoor path between exposure and outcome, these will be statistically associated even if there is no causal effect of E on O. To remove the confounding, we need to block the path from E to O via A, which can be done by conditioning on A.[144] Different methods used in this thesis to control for confounding are mentioned below.

Stratification means studying the association between E and O within levels of A. Stratification was used in study IV to study potential risk factors for AS by sex, i.e. in males and females separately. If the confounding variable has many levels, stratification can be difficult, and often we need to use other methods.

Matching means that we deliberately select comparator subjects based on certain characteristics, such as age and sex, to ensure these characteristics are evenly distributed among cases and comparators. Matching was used in study I and IV to select controls of the same sex and birth year as cases. In study III, births in women with axial SpA were matched to comparator births by year of delivery, maternal age, and parity.

In regression analysis, it is possible to **adjust** for covariates by including them in the regression model. It is important that the variables adjusted for are actually confounders, otherwise we risk increasing instead of decreasing bias, as discussed in section 4.3.2. Adjustment was used in all four studies in this thesis, to account for differences in region of residence, socio-economic status, and comorbidities for example. For a variable to be included in the regression model, we need to be able to measure it. While it is sometimes possible to use a proxy variable (e.g. income, to capture socio-economic status), there is risk for residual confounding if our adjustment does not control for all of the confounding effect, or if there are additional, unmeasured confounders.

A **sibling comparison** is a special type of matching. When studying early-life events as exposures for adult disease, there is a large risk of confounding from other early-life factors, which are difficult or impossible to measure. By using the cases' unaffected siblings as controls, we automatically match on all factors the siblings share, measured or unmeasured, such as maternal factors and childhood socio-economic status. A sibling comparison was used in study IV to study perinatal and early-life events as risk factors for AS.

4.3.2 Selection bias

Selection bias can occur through many different processes, but they are all a result of what we in DAG terminology call collider-stratification bias. In the DAG in Figure 4.1, there is no open path between E and O through C because C is a collider (a common effect of

E and O), which blocks the path. However, if we condition on the collider, through study design or statistical analysis, this path is opened and can give rise to a non-causal association. A consequence of selection bias is that the association between exposure and outcome in those actually studied will differ from the association in those we intended to study.

Non-representative selection of cases and controls is an obvious source of selection bias, where selection into the study is the collider. The exposure distribution in cases and controls should be representative of the exposure distribution in the population they were selected from (the study base), but this is not always the case because of e.g. difficulty to define the study base, non-response, or if exposure influences enrollment (due to screening for example).[145] A population-based study design using risk-set sampling with exposure and outcome information based on prospectively recorded data from national registers is likely to minimize many of these issues.

Differential loss to follow-up, or informative censoring, can also lead to selection bias when we only include patients who are not censored at end of follow-up in the analysis. This scenario is depicted in Figure 4.2A, where the exposure is initiation of anti-rheumatic treatment and the outcome is disease activity at 12 months, as in study II. Patients with lack of effect of the studied drug might change to another treatment before the 12-month evaluation, but excluding them from the analysis, and only keeping those who responded to treatment, will bias the results. By conditioning on a common effect of the exposure and a cause of the outcome, i.e. a collider, we open a backdoor path that will bias the association between exposure and outcome.[146] In study II, we used non-responder imputation to assign a negative response to subjects who stopped TNFi treatment before the 12-month evaluation, to avoid selection bias due to censoring. Similarly, selection bias can be a result of missing data for other reasons than loss to follow-up. Unless the subjects with missing data are a random sample of the study population, a complete-case analysis can lead to biased results (see section 4.4.5).

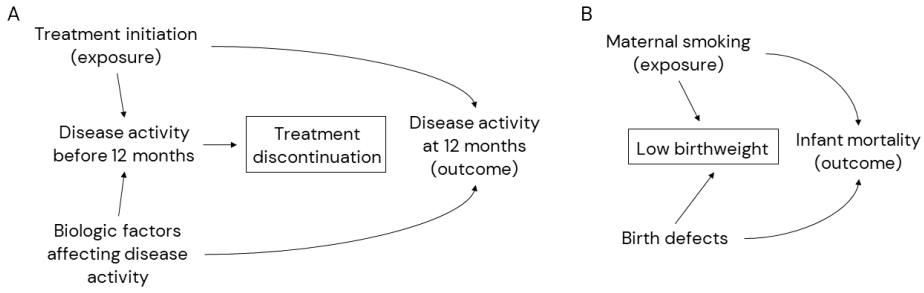

Figure 4.2 Directed acyclic graphs (DAGs) of collider-stratification bias, where conditioning (indicated by the box) on a common effect of the exposure and a cause of the outcome results in (A) informative censoring in a treatment evaluation study, and (B) the birthweight paradox in a study of infant mortality.

A similar structure for collider-stratification bias has also given rise to "the birthweight paradox", where mortality rates seems lower in low birthweight infants of smoking mothers compared to non-smoking mothers.[147] The explanation behind this paradox, visualized in Figure 4.2B, is that smoking is associated with both low birthweight and infant mortality, but other causes of low birthweight, such as birth defects, are even stronger causes of infant mortality. Mortality thus seems lower among those who are low birthweight due to maternal smoking, but it is not a true protective effect. Similar paradoxes can occur in any study of perinatal factors, or other factors, if we adjust for variables affected by the exposure of interest. It is therefore important to consider which variables are adjusted for in analysis, to avoid creating associations by collider stratification.

4.3.3 Information bias

Information bias stems from inability to correctly measure the variables under study. The direction and magnitude of the resulting bias from measurement error (of continuous variables) or misclassification (of categorical variables) varies. Non-differential misclassification means that the proportion of study subjects who are misclassified on for example exposure is independent of other variables. This generally leads to bias towards the null. If, on the other hand, the proportion of subjects who are misclassified is related to the outcome, misclassification is differential, which might bias the exposure-outcome association in any direction.[148]

There are several potential sources of information bias associated with the type of secondary data used in this thesis. When relying on data collected for other purposes, it is not possible to influence how and when variables are measured, or even which variables are recorded. When studying exposure to a drug, a filled prescription in the Prescribed Drug Register is not a guarantee that the drug was actually consumed. Misclassification of confounders, like measures of body-mass index (BMI) or smoking, decreases our ability to fully adjust for their effect on the exposure-outcome relationship, leading to residual confounding. An essential aspect is the classification of disease. Validation studies, where data in registers are compared to e.g. patient charts, is one way to determine the extent of disease misclassification in registers. At the same time, the use of prospectively recorded register data decreases the risk of differential misclassification. Recall bias, from differential reporting of exposures in cases and controls, would otherwise had been a risk in study IV, when studying perinatal risk factors for adult AS.

4.4 Statistical methods

The following sections briefly describes the statistical regression models applied within this thesis.

4.4.1 Logistic regression and conditional logistic regression

Logistic regression is commonly used in epidemiological studies to estimate odds ratios for associations between a given set of covariates and a binary outcome. While other alternatives for analyzing binary outcomes exist, as we shall see in the following sections, logistic regression is the appropriate choice in case-control studies, as the risk of the outcome in the source population is not known. Logistic regression is a generalized linear model with a logit link function where the outcome is modelled with a binomial distribution. Regression coefficients from the model are exponentiated into odds ratios.

When cases and controls are matched, e.g. on age and sex, it is possible and sometimes necessary to use a matched analysis. If the number of strata is high and the number of individuals in each stratum is small due to fine-level matching, problems with sparse data will occur with logistic regression.[149] A solution is to use conditional logistic regression, where the strata-specific parameters are eliminated by estimation of a conditional likelihood for each stratum considering the size of each stratum and the number of cases therein. The conditional likelihoods from each stratum are then multiplied to get the full conditional likelihood. As a consequence, it is not possible to estimate the effect of the matching variables on the outcome.[150] Conditional logistic regression was used in study I to estimate the familial aggregation of AS, and in study IV to identify perinatal and early-life risk factors for AS, both in the comparison with population controls and with unaffected siblings.

4.4.2 Modified Poisson regression

To estimate risk ratios for binary outcomes in cohort studies, a modified Poisson regression can be used.[151] In ordinary Poisson regression, it is assumed that the outcome follows a Poisson distribution, which a binary outcome does not. With the modified Poisson, however, it is not necessary to assume a Poisson distribution. The "modification" comes from using robust standard errors to correct for the misspecification.[152] Modified Poisson regression was used in study III to estimate relative risks of adverse pregnancy outcomes in women with axial SpA.

4.4.3 Linear regression for binary outcomes

Another method that can be used with a binary outcome is linear regression. While this might seem counterintuitive, as the outcome is not continuous, it comes with the main benefit that regression coefficients can be interpreted directly as differences in probabilities between the studied groups, after adjustments for any covariates added to

the model.[153] Linear regression was used in study II to compare the proportion of SpA patients with and without family history of SpA who reached low disease activity after one year of TNFi treatment. One common argument against using linear regression for a binary outcome is that it violates the homoscedasticity assumption (that the variance for the error term should be the same for all values of X), which will bias the resulting standard errors.[153] However, this can be mended by applying robust standard errors.

4.4.4 Survival analysis

Survival analysis concerns a group of methods used to analyze time-to-event data, where the event can be e.g. a diagnosis, treatment discontinuation, or death. People who do not experience the event during follow-up, or are lost to follow-up while still at risk of the event, are censored. Two methods commonly used in survival analysis are the Kaplan-Meier method and Cox proportional hazards regression.

The Kaplan-Meier estimator is a non-parametric estimator of the survival function, which describes the probability that a patient will be alive, or event-free, until a certain time.[154] The Kaplan-Meier estimator can be visualized with a Kaplan-Meier curve, plotted with survival probability on the y-axis and time on the x-axis. It is common to compare survival functions for two or more groups in the same Kaplan-Meier plot, and whether or not there is a significant difference between two curves can be tested using a log-rank test.

The Cox proportional hazards model is a regression model for survival data, modelling the hazard ratio over time. The hazard ratio compares the hazards in two groups, e.g. exposed and unexposed, in relation to a set of covariates. While the model does not make assumption regarding the shape of the baseline hazard, it comes with the assumption that the hazards in different subgroups are proportional over time, which is referred to as the "proportional hazards assumption".

Kaplan-Meier curves and Cox regression were used in study II to compare TNFi drug survival in SpA patients with and without family history of SpA.

4.4.5 Missing data and multiple imputation

A common problem in any epidemiological research is when some subjects do not have data recorded for all variables we wish to include in the analysis. An intuitive way to deal with missing data, and the standard procedure in many statistical software, is to simply exclude subjects with any missing variables, so called complete-case analysis. There are, however, often better approaches to handling missing data, as we soon shall see. But first, we must understand the different mechanisms behind missing data.

According to a framework developed by Rubin,[155] there are three main categories of missing data. When data is missing completely at random (MCAR), missingness is not associated with any other measured or unmeasured variable. The subjects with missing

data are a random sample of the full population. In a fictive study recording the weight of study subjects using a battery-powered scale, weight would be missing completely at random if weight could not be recorded on days when the scale was out of battery. This is the least problematic missing data mechanism, but it is also often unrealistic in real-world data. When data is said to be missing at random (MAR), missingness is associated with measured variables, but not, conditional on the measured variables, with the value of the missing variable itself. If females are less likely than males to have their weight recorded, but sex is recorded, weight will be MAR, and missing completely at random conditional on sex. When missingness is associated with the value of the missing variable itself, or another unmeasured variable, it is said to be missing not at random (MNAR). An example of MNAR would be if subjects who are overweight are less likely to have their weight recorded. If data are MAR or MNAR, a complete-case analysis can give biased results. Even if data is MCAR, restricting to subjects without missing data can dramatically reduce sample size, and thus also the precision of the regression coefficients.[156]

Another method to handle missing data, which is generally considered the best option, is multiple imputation. With imputation, missing values are replaced with plausible values based on data from other subjects in the sample. In multiple imputation with fully conditional specification, for each variable with missing data, the plausible variables are drawn from a distribution conditional on all other variables. The imputation process is repeated a specified number of times to create multiple complete datasets. Statistical analysis is performed in each of the imputed dataset, and estimates and standard errors are subsequently pooled. With this approach, the uncertainty of the imputed variables can be accounted for in the generated standard errors.[156]

Multiple imputation allows us to draw statistically valid inferences from our sample in the presence of missing data, but only when data is MCAR or MAR. It is not possible to test whether data for a specific variable is MAR or MNAR, thus researchers must use their subject matter knowledge to judge what is plausible. In cases of MNAR, more information on the missing variables or the causes of the missingness are needed to handle the missing data without introducing bias.[157]

4.5 Methods for specific studies

The following sections describes the methods for the thesis studies. It starts with a summary of the linkage of registers that was the data source for all four studies, and how we used this to identify our patients and comparators. For a more in-depth description of each study than provided here, please refer to the methods section of each article or manuscript.

4.5.1 Register linkage and identification of study population

Access to data from the registers described in section 4.1 is granted by the register-holding authorities contingent upon approval of ethical permission and successful application to extract data. To assemble the register linkage used in these studies, the Swedish National Board of Health and Welfare was instructed to identify all individuals who had received a diagnosis of either RA, SpA, PsA, or juvenile idiopathic arthritis at a healthcare visit registered in the National Patient Register from 2001, and all individuals with a filled prescription of specified bDMARDs in the Prescribed Drug Register from 2005. Additionally, all individuals in the SRQ, and RA patients from the EIRA study, were added to the list of index patients. The list of these individuals, and their personal identification numbers, were sent to Statistics Sweden, for them to randomly select five population controls for each arthritis case, of the same age, sex, and region of residence within Sweden using risk-set sampling. The population controls had to be alive and living in Sweden at the index date of the index patient. All first-degree relatives of index patients and population controls were also identified in the Multi-Generation Register. Data from the registers listed in section 4.1 were extracted for each individual, including first-degree relatives. Before the linkage was delivered to our research group, it was pseudonymized by replacing the personal identification number with a randomly assigned number, with the key kept at Statistics Sweden to enable linkage updates over time.

This register linkage was then used in various ways to identify the study population for the studies in this thesis, depending on the study objectives. For all studies, we used a stricter case definition than the one used when constructing the linkage to increase specificity for our outcome under study. In study I, we required two visits in the National Patient Register with an AS diagnosis, one being at a rheumatology or internal medicine clinic, or being registered in the SRQ. In study II, because we were studying markers of disease activity, we only included patients with SpA registered in the SRQ, where data on disease activity was available. Of note, we did not include patients with the SpA subtypes ReA or SpA associated with IBD. In study III and IV, we identified cases as those with one visit to a rheumatology or internal medicine clinic with either axial SpA (study III) or AS (study IV). For the case-control study IV, we used the existing controls in the linkage sampled by Statistics Sweden. In study I, also a case-control study, we wanted to increase the number of controls to 50 per case, because the exposure (having a first-degree relative with AS) would be so rare in controls. Thus, we re-sampled 50 controls per case from the total pool of controls in the linkage using risk-set sampling. In study III, which was a cohort study where births in women with axial SpA were matched with births from population comparators, we randomly selected births among the original (female) control individuals, matched on year of delivery, maternal age, and parity. Study II did not include any general population comparators.

4.5.2 Study I – Familial aggregation and heritability of AS

Study I was a nested case-control study aimed to estimate the familial aggregation and heritability of AS. Patients with AS were identified from the National Patient Register and the SRQ between 2001 and 2016. Each index patient was matched to 50 population controls of the same age and sex. First-degree relatives of index patients and controls were identified via the Multi-Generation Register, and their history of AS was evaluated in the National Patient Register (between 1987 and 2016) and the SRQ (2001 to 2016).

We used conditional logistic regression to estimate the familial aggregation as odds ratios for AS with the exposure being AS in a first-degree relative. Analyses were adjusted for region of residence in index patients and controls. Because of the clustered data structure, robust standard errors were used to correct the confidence intervals. The AS status in the relative was assessed independently of the time of AS onset in the index patient. In for example a pair of brothers with AS, each would occur in the analysis once as an index patient and once as an affected relative. We calculated the familial aggregation overall, but also depending on sex and type of kinship, and for having more than one relative with AS.

Heritability for binary traits such as having or not having a disease can be estimated assuming an underlying, normally distributed liability to develop disease, where only individuals with liability above a certain threshold will fall ill (the liability-threshold model). A person's liability of disease is the sum of additive genetic effects and environmental factors.[45] While liability cannot be measured in practice, it is possible to estimate the correlation between relatives' liabilities to develop disease, the tetrachoric correlation, from the observed disease status in relatives.[158] Assuming that all correlation in relatives is due to additive genetics, and not for example shared environment, the heritability based on correlation between first-degree relatives is twice the tetrachoric correlation.[45]

In order to estimate the heritability of AS in study I, familial risk and AS prevalence in the population was first used to reconstruct the source population of controls. The prevalence of AS in Sweden has been previously estimated using the National Patient Register and is reported to be 0.18%.[20] We adjusted this figure to 0.11% to match the stricter case definition used in our study. Index patients and the reconstructed source population of controls were then placed into a 2x2 table based on exposure status, their tetrachoric correlation was calculated, and heritability was estimated as twice the tetrachoric correlation. We calculated heritability for both overall familial risks and sibling-specific risks, as siblings more equally are affected by calendar time trends such as truncations of the data. We also evaluated whether different values for the prevalence would affect our heritability estimate. Approximate 95% confidence intervals (CIs) around the heritability estimate were obtained by using the 95% confidence limits of the familial risk in the calculations.

4.5.3 Study II – Family history and TNFi treatment response

Study II was a cohort study designed to compare TNFi drug survival and treatment response in SpA patients with and without family history of SpA or other related conditions. From the SRQ, we identified patients with AS, PsA, or uSpA who started a first TNFi treatment between 2006 and 2018. Family history of SpA and other chronic inflammatory and non-inflammatory conditions was defined as having a first-degree relative diagnosed with a particular condition before start of treatment in the index patient. The relatives' medical history was assessed in the National Patient Register starting from 1987, with only inpatient data available before 2001. For most conditions, we only considered diagnoses given at a clinic with an appropriate medical specialty. For family history of psoriasis, filled prescriptions of anti-psoriatic drugs in the Prescribed Drug Register (from 2005 onwards) were also counted.

We evaluated treatment response in several different ways, with all analyses stratified by diagnosis in index patients (AS, PsA, or uSpA). Drug survival, i.e. the number of days a patient continued TNFi treatment, was assessed using Kaplan-Meier plots, and hazard ratios for drug discontinuation were calculated with Cox proportional hazards models. In the main analyses, we studied family history of AS in AS patients, family history of PsA in PsA patients, and family history of uSpA in uSpA patients, but we also assessed how family history of any SpA or other inflammatory or non-inflammatory conditions affected drug discontinuation.

Treatment response at three months was assessed as change from baseline in disease activity and functional status, measured with outcome measures such as BASDAI, ASDAS-CRP, and HAQ. Treatment response at 12 months was evaluated as a composite outcome of being on treatment and reaching certain pre-defined response criteria (e.g. low disease activity with BASDAI, or HAQ improvement >0.2 units). Differences between those with and without family history of their own diagnosis were estimated through linear regression with robust standard errors. For the dichotomous outcome at 12 months, the resulting estimates provided the difference in proportions reaching the response criteria (with 95% CIs) between the exposed and non-exposed.

Missing baseline covariates and treatment responses were imputed with multiple imputation (section 4.4.5), except at 12 months where we assigned a non-response to subjects who stopped TNFi treatment before the 12-month evaluation. All analyses were adjusted for age, sex, TNFi compound, country of birth, healthcare region, disease duration, SpA manifestations, baseline disease activity, co-medication, medical history, and socio-economic factors. Drug survival was additionally adjusted for family history of the other conditions included in the study.

4.5.4 Study III – Pregnancy outcomes in axial SpA

Study III was a cohort study comparing adverse pregnancy outcomes in births among women with axial SpA to births in the general population. Women with axial SpA were identified from the National Patient Register or the SRQ with ICD codes for either AS or uSpA. All singleton births in these women between April 2007 and December 2020 were identified in the Medical Birth Register. The study period was chosen so that all women would have prescription data in the Prescribed Drug Register in the year before pregnancy, and so that we could follow the children until one year of age. Each axial SpA birth was matched on year of delivery, maternal age, and parity to ten comparator births in women without chronic inflammatory arthritis from our register linkage.

We used modified Poisson regression (with robust standard errors) to estimate risk ratios for adverse pregnancy outcomes in axial SpA. Outcome data were collected from the Medical Birth Register, but information on serious infant infection was complemented with National Patient Register data. Analyses were adjusted for maternal height, early-pregnancy BMI, smoking, highest attained educational level, disposable income, and country of birth (Nordic or non-Nordic), in addition to the matching factors.

To study temporal trends in treatment patterns and adverse outcomes, proportions of births with specific treatments or outcomes each calendar year were plotted with loess curves. Loess, or locally weighted regression, is a non-parametric regression method that estimates the value of y at each x using weighted least square regression. At each x, the fit is based on the neighboring data points, weighting values by their distance to x, giving points close to x higher weight. This results in a smoothed trend curve.[159]

We aimed to find predictors of preterm birth by investigating associations between preterm birth and disease activity, treatment, and SpA manifestations in the women with axial SpA using modified Poisson regression. We also assessed whether the association to established risk factors for preterm birth differed in axial SpA compared to the general population, by including an interaction term between the risk factor and case status in the regression model.

4.5.5 Study IV – Perinatal and early-life risk factors for AS

Study IV was a nested case-control study of environmental risk factors for AS, with a sibling comparison design added to remove confounding from factors shared by siblings. AS cases were identified from the National Patient Register between 2001 and 2022, and included in the study if their birth was registered in the Medical Birth Register (i.e. those born in Sweden 1973 onwards). The same restriction was made for population controls from the register linkage, resulting in four controls per case.

We used conditional logistic regression to estimate odds ratios for AS in relation to perinatal and early-life factors, including infections until age 15, and number of siblings.

Perinatal factors were identified from the Medical Birth Register, and infections mainly from the National Patient Register. Number of full siblings and number of younger siblings were ascertained from the Multi-Generation Register, while number of older siblings was based on the parity variable in the Medical Birth Register (i.e. including older full siblings and maternal half-siblings). Analyses were adjusted for multiple birth, maternal age, maternal smoking, maternal BMI, maternal disposable income, maternal educational level, maternal inflammatory disease, and parental country of birth (both parents born in a Nordic country vs. not). Number of older siblings was additionally adjusted for number of younger siblings, and vice versa. We used multiple imputation to account for missing covariate data in the case-control analysis.

Exposures with statistically significant association to AS in the case-control analysis were subsequently included in the sibling comparison to test whether associations were a result of confounding from familial factors. For the AS cases, we identified all full siblings without a SpA diagnosis whose births were recorded in the Medical Birth Register. Conditional logistic regression conditioning on the family was used to compare associations to potential risk factors in AS cases and their siblings without a SpA diagnosis. Only siblings discordant in both exposure and outcome will contribute to the regression estimates. Analyses were adjusted for factors that can vary between siblings: maternal age at delivery, parity, year of birth, and sex.

4.6 Ethical considerations

The primary purpose of medical research, as stated in the Declaration of Helsinki, is to provide new knowledge on the etiology, development, and consequences of disease, and to find the optimal ways to prevent, diagnose, and treat illness.[160] Such research would ultimately not be possible without including human subjects. It is of highest importance, however, that research is conducted with respect for the subjects' health and rights. These are principles governed by law, as in the Swedish Ethical Review Act (2003:460), which mandates that research involving human subjects, biologic material from humans, or sensitive personal data must first be approved by the Ethical Review Authority.[161] Research may only be approved if its scientific value for the community is larger than the risk of personal harm to study subjects.

For register-based research, which involves processing of sensitive personal data, the largest threat for research subjects is to their personal integrity in case of a privacy breach. Several precautions must thus be taken to protect the integrity of the research subjects. According to the European Union's personal data protection legislation (GDPR), only data that is directly relevant and necessary for the scientific purpose should be processed.[162] Data used in this thesis are pseudonomized, meaning that personal identification numbers are replaced with a code, with the code key kept at the governmental register holders to allow updates to the data. When no longer needed, the

code key should be destroyed. It is the researcher's responsibility that data is stored on physically protected servers and that access to it is only possible by approved personnel. Results should only be presented on an aggregated level, to prevent identification of individuals.

The Ethical Review Act also mandates that informed consent must be collected from individuals participating in research. The law makes an exception, however, for research that only concerns *processing* of sensitive personal data.[161] This is a prerequisite to enable the use of national register data in research. Data are collected into these registers for all individuals in Sweden, without the possibility to opt out, and the national coverage is one of the reasons why these data sources are so powerful.

While the benefit of the research projects in this thesis may be limited for the individual research subject, the use of his or her personal data in medical research, together with hundreds or thousands of others', has great potential to generate new knowledge that can benefit other patients and society as a whole. By protecting data in accordance with current laws and regulations, and only conducting research with ethical approval, the research community can preserve peoples' trust, and register-based research can continue to be an ethically sound way to move medical research forward.

5 Results

5.1 Study I – Familial aggregation and heritability of AS

For this nested case-control study, we identified 13 795 individuals diagnosed with AS between 2001 and 2016 from either the National Patient Register or the SRQ. Each index patient was matched on age and sex to 50 general population controls. The index patients were born between 1909 and 2000, the male:female ratio was about 2:1, and 11.1% had at least one first-degree relative who also were diagnosed with AS. Among controls, only 0.6% had a first-degree relative diagnosed with AS.

The odds ratio (OR) for AS associated with having any first-degree relative with the disease was 19.4 (95% CI 18.1-20.8). Similar estimates were observed irrespective of sex and whether the affected relative was a sibling, parent, or child, except for a higher risk in females with a mother diagnosed with AS (Figure 5.1). The risk of AS associated with having more than one relative with AS was even more elevated (OR 68.0; 95% CI 51.3-90.1).

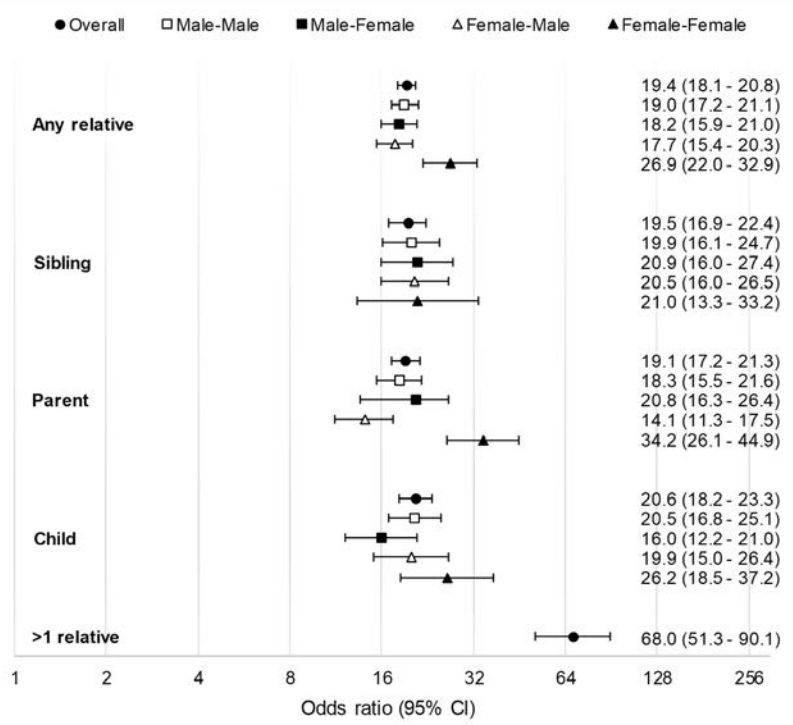

Figure 5.1 Familial ORs (95% CIs) for AS by type of relative and sex. For sex-specific estimates, e.g. 'male–female' refers to a male index patient and a female relative. Sibling/parent/child refers to a relative in relation to the index patient. This means that for example, estimates in the subgroup 'parent' are ORs of AS when having a parent with AS. [Reprinted from Rheumatology (Oxford) 2020;59:1695-702. CC BY-NC 4.0, 2019.]

We estimated heritability by using familial risks between siblings and assuming an AS population prevalence of 0.11%. This put AS heritability at 77% (95% CI 75-80%). Heritability estimates were quite robust to variations in e.g. AS prevalence, sex, and type of relative, though the estimates should be seen as an upper limit for the heritability, as shared environmental factors have not been taken into account.

5.2 Study II – Family history and TNFi treatment response

In this cohort study, we identified 9608 patients from the SRQ with a diagnosis of either AS, PsA, or uSpA, who started a first treatment with TNFi between 2006 and 2018. We considered family history separately among each of the disease groups and found that among 2568 AS patients, 292 (11%) had family history of AS, i.e. a first-degree relative diagnosed with AS. Furthermore, among 4282 PsA patients, 456 (11%) had family history of PsA. Finally, in the 2758 patients with uSpA, 137 (5%) had a family history of uSpA. Family history of any SpA was present in 17, 14, and 15% of AS, PsA, and uSpA patients, respectively.

When we compared clinical characteristics at treatment start for those with and without family history of their diagnosis, we found that patients with a family history were younger at recorded disease onset on average, but mean age when starting TNFi treatment did not differ between the groups. Thus, patients with family history, on average, had longer disease duration at the start of treatment.

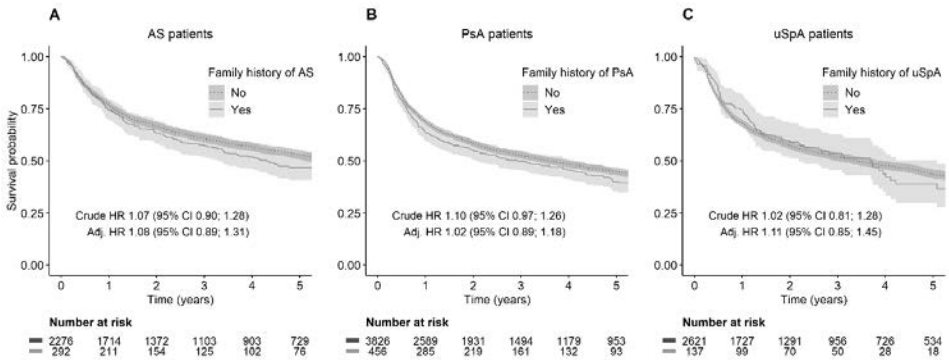

Figure 5.2 Kaplan-Meier plots for time to drug discontinuation during the first 5 years of TNFi treatment in (A) AS patients with and without a family history of AS, (B) PsA patients with and without a family history of PsA, and (C) uSpA patients with and without a family history of uSpA. Shaded bands are 95% confidence intervals. Hazard ratios (HRs) from Cox proportional hazards models, unadjusted and adjusted for age, sex, TNFi compound, country of birth, healthcare region, family history of other inflammatory and non-inflammatory conditions, disease duration, SpA manifestations, baseline disease activity, co-medication, medical history, and socioeconomic factors. [Reprinted from Scand J Rheumatol 2022;51:10-20. CC BY 4.0, 2021.]

While there were some differences in drug survival between patients with different types of SpA, there were no differences in drug survival between those with and without family history of their diagnosis (Figure 5.2). We also calculated hazard ratios (HRs) for drug discontinuation in relation to family history of other types of SpA, as well as other inflammatory and non-inflammatory conditions. None of these were associated with drug discontinuation, except for family history of psoriasis in PsA (HR 1.10; 95% CI 1.00-1.22) and family history of dorsalgia in uSpA (HR 1.24; 95% CI 1.06-1.46, after adjustments for demographic, socioeconomic, and SpA-related factors).

Among patients remaining on treatment at 3 and 12 months, respectively, we compared treatment responses in those with and without family history of disease, but found no clinically meaningful differences between the groups.

5.3 Study III – Pregnancy outcomes in axial SpA

In this cohort study, we included 1580 singleton births in women diagnosed with axial SpA and 15 792 matched comparator births between April 2007 and December 2020. Background characteristics such as maternal BMI, smoking, and educational level were similar between the groups, but women in the axial SpA group were more often born in a Nordic country (92.7% vs. 79.6% in comparators).

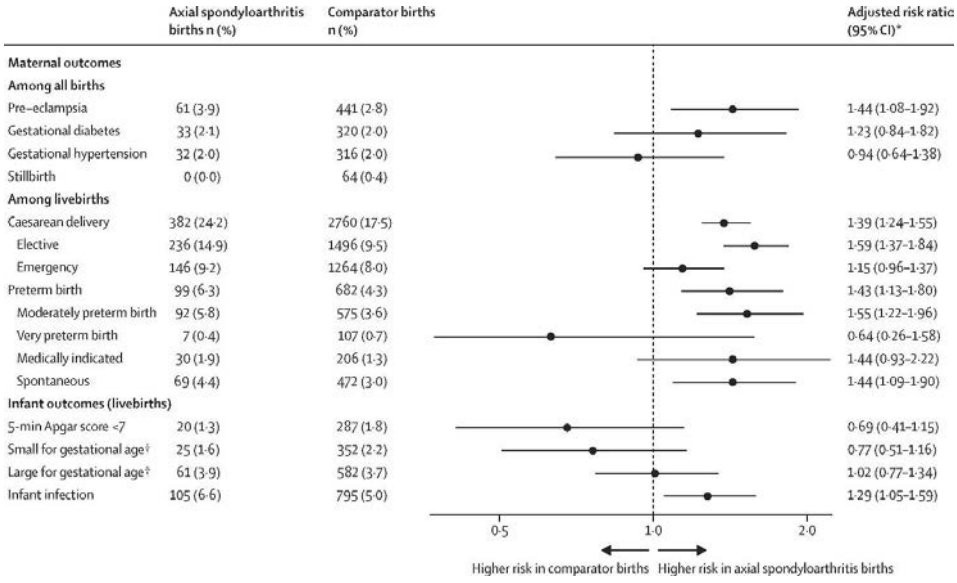

Figure 5.3. Relative risks of adverse pregnancy outcomes among births in women with axial SpA (n=1580) and matched comparator births (n=15 792), calculated using modified Poisson regression. *Adjusted for matching factors (year of delivery, maternal age, and parity) and maternal country of birth, height, BMI, smoking in early pregnancy, educational level, and disposable income. †One axial SpA birth and 13 comparator births were missing data for small for gestational age and large for gestational age. [Reprinted with permission from Lancet Rheumatol 2023;5:e121-e9. Copyright 2023 Elsevier Ltd.]

We found a higher risk of several adverse pregnancy outcomes in births by women with axial SpA compared to the general population comparators (Figure 5.3). The relative risk of pre-eclampsia was 1.44 (95% CI 1.08-1.92) after adjustments for year of delivery and a number of maternal characteristics. We also found a higher risk of preterm birth (RR 1.43; 95% CI 1.13-1.80), serious infant infection (RR 1.29; 95% CI 1.05-1.59), and elective cesarean delivery (RR 1.59; 95% CI 1.37-1.84).

Whereas these risks were evident when studying the whole cohort, the proportion of preterm births, serious infant infections, and cesarean deliveries decreased over the study period among people with axial SpA, while they mostly remained constant among comparators (Figure 5.4). At the end of the study period, the proportions of births with these adverse events in axial SpA even approached those of the general population. At the same time, the proportion of women treated with TNFi in the year before pregnancy increased by 2 percentage points annually, and from 2015 onwards the use of TNFi during pregnancy also increased markedly (Figure 5.5). In total, 216 women used TNFi at some point during pregnancy, though 62.5% of these discontinued before pregnancy week 14.

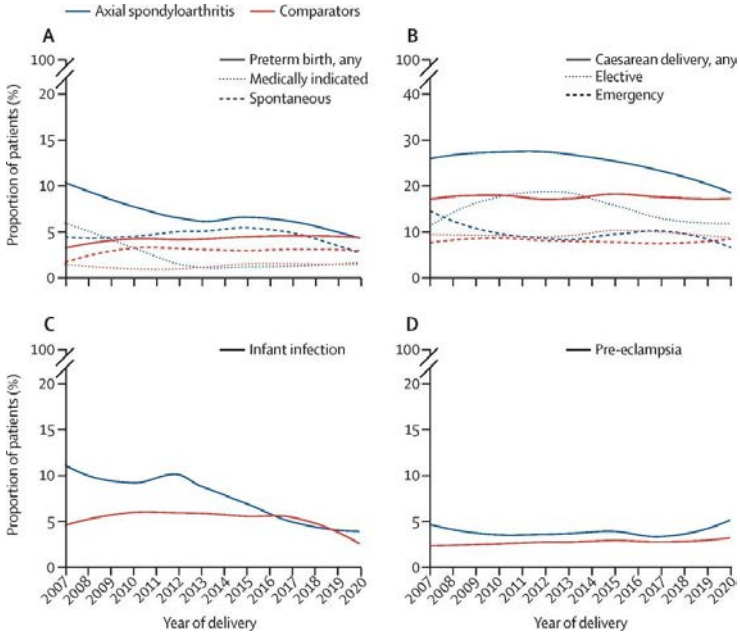

Figure 5.4 Proportion of (A) preterm births, (B) cesarean deliveries, (C) infant infections, and (D) pregnancies complicated by pre-eclampsia, in women with axial SpA and comparators by year of delivery. Lines are loess curves. [Reprinted with permission from Lancet Rheumatol 2023;5:e121-e9. Copyright 2023 Elsevier Ltd.]

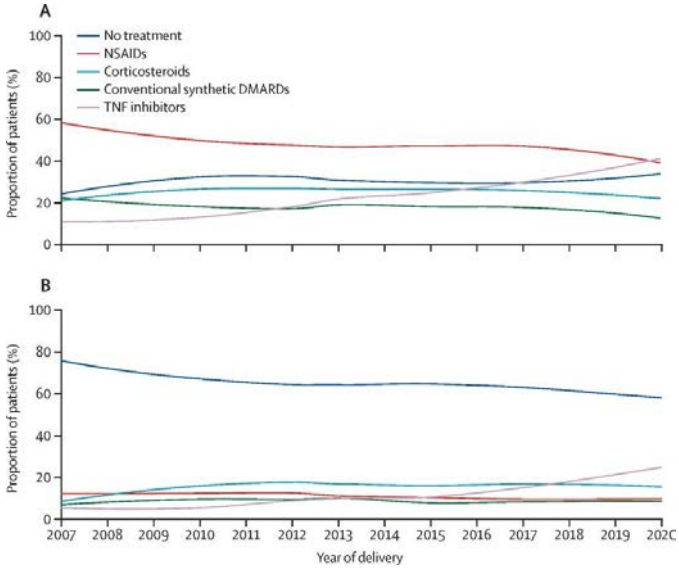

Figure 5.5 Proportion of births in women with axial SpA exposed to NSAIDs, corticosteroids, and DMARDs in (A) the year before pregnancy and (B) anytime during pregnancy, by year of delivery. Lines are loess curves. [Reprinted with permission from Lancet Rheumatol 2023;5:e121-e9. Copyright 2023 Elsevier Ltd.]

We studied whether different treatments, disease activity, and SpA manifestations were associated with preterm birth, infant infection, and pre-eclampsia, but were not able to find any significant associations. We also did not find any clinically significant differences in the association to established risk factors of preterm birth in axial SpA and comparators.

5.4 Study IV – Perinatal and early-life risk factors for AS

For the main case-control analysis in this study, we included 5612 AS patients and 22 042 population controls who were born 1973 or later and who were registered in the Medical Birth Register. When comparing exposures in cases and controls, we found no significant associations with perinatal factors related to fetal growth. We did however, find that multiple birth, being born in the winter months, having older siblings, serious childhood infection and history of a tonsillectomy in childhood were associated with an increased risk of AS in adulthood (Figure 5.6). Effect sizes were modest however, with odds ratios of 1.3 or less.

Risk factors	AS cases* (n=5612)	Controls* (n=22 042)	Adj. OR† (95% CI)
Maternal factors			
Maternal age, years	27.4 (5.0)	27.5 (5.1)	1.00 (0.99 to 1.00)
Maternal smoking‡	687 (24.4)	2774 (24.9)	0.99 (0.90 to 1.10)
Maternal BMI‡	22.6 (3.4)	22.8 (3.6)	0.99 (0.98 to 1.01)
Perinatal factors			
Gestational age, weeks	40 (2)	40 (2)	0.99 (0.97 to 1.00)
Weight for gestational age, SDs	-0.10 (1.12)	-0.10 (1.10)	1.01 (0.98 to 1.04)
Birth weight, grams§	3508 (563)	3513 (553)	1.00 (0.99 to 1.01)
Multiple birth	130 (2.3)	423 (1.9)	1.23 (1.01 to 1.50)
Caesarean delivery	624 (11.1)	2313 (10.5)	1.07 (0.97 to 1.18)
Maternal infection during pregnancy	134 (2.4)	477 (2.2)	1.08 (0.89 to 1.32)
Season of birth			
Dec-Feb	1399 (24.9)	5170 (23.5)	Reference
March-May	1615 (28.8)	6128 (27.8)	0.97 (0.90 to 1.05)
June-Aug	1381 (24.6)	5584 (25.3)	0.91 (0.84 to 0.99)
Sept-Nov	1217 (21.7)	5160 (23.4)	0.87 (0.80 to 0.95)
Number of siblings			
Full siblings			
None	881 (15.7)	3498 (15.9)	Reference
One	2557 (45.6)	9982 (45.3)	1.01 (0.92 to 1.11)
Two or more	2174 (38.7)	8562 (38.8)	1.01 (0.92 to 1.10)
Older siblings			
None	2164 (38.6)	9098 (41.3)	Reference
One	2172 (38.7)	8081 (36.7)	1.12 (1.04 to 1.22)
Two or more	1276 (22.7)	4863 (22.1)	1.15 (1.04 to 1.27)
Younger siblings			
None	3470 (61.8)	13155 (59.7)	Reference
One	1531 (27.3)	6245 (28.3)	0.97 (0.89 to 1.04)
Two or more	611 (10.9)	2642 (12.0)	0.91 (0.81 to 1.02)
Infections and procedures¶			
Serious childhood infection	1396 (24.9)	5006 (22.8)	1.13 (1.05 to 1.21)
Tonsillectomy	279 (5.0)	855 (3.9)	1.30 (1.13 to 1.49)
Appendectomy	126 (2.3)	573 (2.6)	0.87 (0.71 to 1.06)

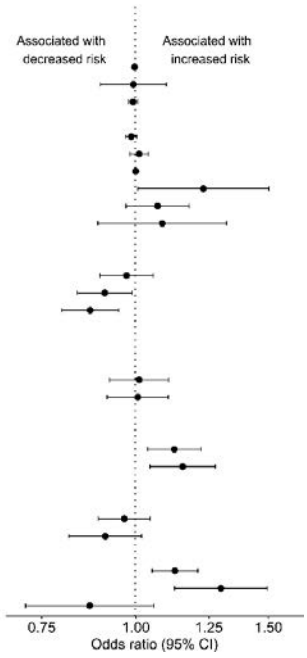

Figure 5.6 Odds ratios (ORs) for AS in relation to childhood infections and perinatal factors. Odds ratios from conditional logistic regression on 25 multiply imputed datasets with AS cases and population controls, matched on sex, year of birth, and region of residence. *Numbers are n (%) or mean (SD). †Adjusted for maternal age, maternal BMI, maternal smoking, parental country of birth, maternal disposable income, maternal educational level, maternal inflammatory disease (hospitalisation for SpA, IBD, psoriasis), and multiple birth, with the exception that no exposure was adjusted for itself. Number of older siblings additionally adjusted for number of younger siblings, and vice versa. ‡Analyses for smoking and BMI restricted to birth years from 1982 onwards. §Analysed per 100 grams. ¶Until age 15. 16 cases and their 72 matched controls excluded due to AS diagnosis in index case before age 16.

Around 70% of AS patients could also be included in the sibling comparison, where we compared exposures in 3965 AS patients and their 6070 siblings who had not received a SpA diagnosis during follow-up. In the sibling comparison, only having older siblings and childhood tonsillectomy remained associated with AS (Table 5.1). For multiple birth, season of birth, and serious infant infection, associations were attenuated in the sibling comparison.

Table 5.1 Odds ratios (ORs) for AS from sibling comparison analysis, estimated using conditional logistic regression

Risk factor	AS cases* (n=3965)	SpA-free siblings* (n=6070)	OR (95% CI)	Adj. OR† (95% CI)
Multiple birth	118 (3.0)	208 (3.4)	1.06 (0.73-1.52)	1.09 (0.75-1.58)
Season of birth				
Dec-Feb	979 (24.7)	1461 (24.1)	Reference	Reference
March-May	1136 (28.7)	1725 (28.4)	0.99 (0.88-1.10)	0.99 (0.89-1.12)
June-Aug	978 (24.7)	1517 (25.0)	0.97 (0.86-1.09)	0.96 (0.85-1.08)
Sep-Nov	872 (22.0)	1367 (22.5)	0.99 (0.87-1.12)	0.96 (0.84-1.10)
No. of older siblings				
0	1462 (36.9)	1836 (30.2)	Reference	Reference
1	1589 (40.1)	2089 (34.4)	0.96 (0.89-1.03)	1.18 (1.06-1.31)
2 or more	914 (23.1)	2145 (35.3)	0.78 (0.70-0.86)	1.34 (1.09-1.65)
Serious childhood infection‡	1006 (25.5)	1503 (24.8)	1.05 (0.95-1.16)	1.04 (0.94-1.16)
Tonsillectomy‡	210 (5.3)	253 (4.2)	1.37 (1.12-1.68)	1.36 (1.10-1.67)

**Numbers are n (%). Numbers represent outcome-discordant siblings. Only siblings discordant for both exposure and outcome contribute to the regression estimates.*
†Adjusted for maternal age, year of birth, sex of child, and parity (except when exposure is number of older siblings).
‡Until age 15. 14 cases and their 18 SpA-free siblings excluded due to AS diagnosis in index case before age 16.

6 Discussion

This thesis consists of four studies examining various aspects of the etiology and prognosis of SpA, using family-based epidemiological methods. By taking advantage of the ample data available from Swedish national registers, including data on relatedness between Swedish residents, we were able to perform the largest studies to date on familial aggregation and heritability of AS, pregnancy outcomes in axial SpA, and on the association between family history of SpA and treatment response to TNFi. We were also, for the first time, able to study the association of perinatal factors and childhood infections with adult AS while controlling for childhood socio-economy in a sibling comparison analysis. Before putting the findings of these studies in context of the larger body of research, there are some methodological considerations to reflect on.

6.1 Methodological considerations

6.1.1 The use of registers in epidemiological research

National registers are powerful tools in epidemiological research. The nationwide coverage gives large study populations and reduced selection bias, while time and cost for data collection is minimized. The possibility to link data from different health and population registers enables adjustment for relevant confounders, and available information on the source population allows for random selection of population comparators. The possibility to identify first-degree relatives (in study I on familial aggregation) and siblings (in study IV on early-life risk factors) from registers with complete coverage is a major strength. In the absence of such infrastructure, one would have to rely on reports from index patients, or the willingness of relatives to participate in the study, which risks limiting its power and introducing bias. We were also able to follow the children of mothers with axial SpA in study III, in order to capture infections during their first year of life.

There are, nevertheless, limitations in using registers in epidemiological research. The National Patient Register only contains healthcare visits from specialized care, i.e. primary care is not included. There is risk of misclassification if patients are only seen in primary care. It is likely, however, that most patients with SpA are seen at least occasionally at a rheumatology clinic. All patients on anti-rheumatic treatment should according to Swedish guidelines be followed by a rheumatologist in specialized care.[25] Misclassification is more of a problem when identifying disease manifestations and comorbidities like psoriasis and diabetes, which to a larger extent are handled exclusively in primary care. We tried to overcome this issue in study II and III by including data on filled prescriptions of anti-psoriatic and anti-diabetic drugs from the Prescribed Drug Register in the definition of psoriasis and diabetes, respectively. When working with Swedish register data, one should also keep in mind that before 2001, only inpatient data is available from

the National Patient Register, and the Prescribed Drug Register started in mid-2005, which influences what type of questions are possible to answer.

SpA is a heterogeneous disease, and the current ICD classification (ICD-10), or earlier versions, do not capture the current view of SpA as one disease with predominantly axial or peripheral manifestations. This is the reason why we chose to focus on AS, the most well-characterized subtype of SpA, in studies I and IV, where we needed to identify cases many years back in time. In study III on pregnancy outcomes we aimed for a more contemporary cohort of axial SpA, by including a wider range of ICD codes. It is possible that this will have resulted in the inclusion of some women with mainly peripheral SpA, owing to the lack of specific diagnostic codes for this extremely under-researched group. In the next ICD edition (ICD-11), estimated to be adopted in Sweden during 2024, SpA will be coded as "inflammatory spondyloarthritis", with sub-codes for axial and peripheral spondyloarthritis.[163] It will likely take time, however, after ICD-11 has been implemented, before enough cases classified by these codes have accumulated to be used in research.

The level of clinical detail available from national registers is limited. Our main source of clinical data was the SRQ, where information on for example disease activity is entered longitudinally by the treating rheumatologist and the patient him or herself at healthcare visits. A validation study has shown that 86% of patients diagnosed with SpA in the National Patient Register who filled a prescription for a TNFi in the Prescribed Drug Register were also registered in the SRQ. Those on TNFi not covered by the SRQ did not differ by age or sex, but regional variation was noted.[140] The coverage of patients not on biologic treatment is unknown, but it is likely lower, and the patients included are not necessarily representative of all AS patients in terms of age, sex, disease activity etc. We used the SRQ as our only source of SpA cases in study II, where we wanted to study patients starting TNFi treatment and to evaluate their treatment response. Another important variable in SpA is HLA-B27, with potential influence on both inheritance and treatment response. While it is possible to register the HLA-B27 status of a patient into the SRQ, there was too much missing to allow us to use that variable.

The results from the studies in this thesis should be generalizable to most patients with axial SpA or AS in Sweden today, as a large proportion of them are expected to be captured in the National Patient Register. Results should further be generalizable to other countries with a similar healthcare environment, at least in the European setting or to countries with comparable HLA-B27 prevalence.

6.1.2 Methods to estimate heritability

Heritability can be estimated in different ways. As described in section 2.1.2, both family-based and SNP-based methods are used, where SNP-based methods tend to give lower estimates. Also among family-based methods, there are different approaches. In study I, we estimated heritability of AS based on the tetrachoric correlation between full siblings,

under the assumptions that mating in the population is random with regard to AS, that there is no dominance effect, and no influence of environmental factors shared between siblings. The last assumption is not likely to hold altogether, which is why our estimate should be seen as an upper limit for the heritability.

In order to separate the contribution of additive genetic factors and common environmental factor to the phenotypic variation, it is necessary to compare relatives with different degree of relatedness or shared childhood environment. A common approach is to contrast the phenotypic correlation in monozygotic and dizygotic twins. Monozygotic twins are expected to share 100% of their alleles, compared to 50% in dizygotic twins, while such a model assumes that both types of twins share environment to the same extent. It is thus possible to estimate the relative contribution of additive genetic factors, common environmental factors, and non-shared environmental factors.[158] We did not have access to twin data for this study, and even if we had, power would have been an issue for a relatively rare disease like AS. It is also possible to compare other types of relatives with different genetic and environmental correlation, like full and half-siblings. However, this also comes with strong assumptions regarding for example the extent of shared environment in childhood in maternal versus paternal half-siblings. We therefore decided to only use full siblings in our analysis of AS heritability.

6.1.3 Limitations of the sibling comparison design

A sibling comparison is intended to reduce confounding from factors that are otherwise difficult to adjust for, such as early childhood environment, maternal factors like inflammatory disease, and to some extent genetics, i.e. all factors shared by siblings. There are however other reasons than confounding from shared factors that can explain differences between a population estimate and a sibling comparison estimate. In the sibling comparison, only sibling pairs who are discordant for both exposure and outcome contribute to the effect estimate. This is a strong selection, which risks amplifying confounding from factors not shared by siblings.[164] We do not believe this to be a major problem in our analysis in study IV however, due to the nature of the exposures studied. Season of birth is rather randomly distributed, tonsillectomy and serious infection are rather uncommon, and number of older siblings will per definition differ between siblings.

An inherent property of sibling comparisons, also related to the selection of doubly discordant sibling pairs, is that random measurement error of the exposure will lead to stronger attenuation of the effect estimate in a sibling comparison that in a population sample.[164] In our case, we do not expect significant measurement error for multiple birth, season of birth, number of older siblings, and tonsillectomy. Serious childhood infection, which we defined as a hospitalization for an infection, could be an exception. One could imagine that several siblings might have suffered from the same contagious disease even

if only one was hospitalized. This might explain some of the attenuation seen for serious infections in the sibling comparison compared to the case-control analysis in study IV.

Carryover effects, where the exposure or outcome of one sibling affects those of another sibling, is also a potential source of bias in sibling comparisons.[165] Luckily, exposure-to-exposure carryover, which is the most probable type in our case, does not lead to bias. It is not likely that the childhood exposure of one sibling will affect the outcome (AS) of another in adulthood.

Taken together, sibling comparisons come with several limitations. These are important to consider when planning or interpreting results from a study with a sibling comparison design. With this knowledge at hand, sibling comparisons are a powerful way to test whether associations found in population samples are in fact explained by confounding from factors shared by siblings.

6.2 Findings in context

6.2.1 Familial aggregation of AS

One of the motivations behind this thesis was to challenge the prevailing view regarding familial aggregation and heritability of AS. Most previous studies in the field were based on clinical cohorts or volunteers from patient organizations, or on a small number of twins, but seldom including a control group. Resulting estimates were consequently rather variable but also, in our opinion, unreasonably high. There is an inherent risk of selection bias in studies explicitly recruiting affected families, as multicase families might be more willing to participate in such studies, which in turn inflates the familial risks reported. Our aim was to provide more precise estimates of the familial aggregation and heritability of AS using a large population-based sample, which also minimizes the risk of recall or selection bias.

By comparing the prevalence of AS in first-degree relatives of 13 795 AS patients and over 600 000 general population controls, we estimated the familial risk to 19.4 (95% CI 18.1-20.8). This is considerably lower than most previously reported estimates of familial risk. We show in study I and II that while 11% of Swedish AS patients have family history of AS (compared to 0.6% of controls), and 17% have a family history of any SpA, less than 5% of parents, siblings, and children, respectively, have received an AS diagnosis themselves. So despite that the familial aggregation of AS is remarkably high (though less so than previously reported), the risk of transferring the disease to one's children is still relatively low. This is an important point, as living with a heritable disease can affect one's decision to have children.[166]

Since study I was published in 2019, other publications on familial aggregation of axial SpA or AS have appeared, most notably one by van der Linden et al. investigating recurrence

rates of axial SpA over 35 years in first-degree relatives of AS cases recruited from the Swiss AS Patient Society.[167] In 1985, 363 index cases and 806 first-degree relatives consented to participate and underwent extensive examinations including HLA typing and pelvic radiography. In 2018, the former participants were contacted again, and asked to fill out a 157-item questionnaire, with a response rate of 41.6% (13.8% had already died). Their results are alarming: 27.1% of HLA-B27 positive first-degree relatives have developed axial SpA. In addition, they report a recurrence rate of over 80% among HLA-B27 positive children of HLA-B27 positive mothers, three times higher than in HLA-B27 positive fathers, which must be very disconcerting reading for any HLA-B27 positive woman with AS having, or thinking of having, children. In support of their conclusion that the risk for children to develop axial SpA is greater if the affected parent is a woman, they also cite our figures from study I, where we found 1.9% of children of AS fathers to have AS, compared to 2.4% of children of AS mothers. The comparability of results from these two studies can be questioned, however, considering the notable differences between the recurrence rates found in the respective studies.

There could be several possible explanations for these notable differences in the Swiss and Swedish study. We did not have access to HLA-B27 status for index patients and relatives, so our estimate includes both HLA-B27 positive and negative patients. The prevalence of HLA-B27 is estimated to 85-95% in AS patients, and around 10% in European populations. We can thus assume that at least 85% of our female AS mothers were HLA-B27 positive, and around 50% of their children. With an 80% recurrence rate, we would expect over 1400 AS cases among the 4189 daughters of our female index patients, compared to the 100 cases actually observed. Even if we consider possible sources of bias in our register data, such as milder cases only being handled in primary care and not registered in the National Patient Register, this is not sufficient to explain the discrepancy between results. Another possible explanation is what motivated our study in the first place: that the recruitment of families into studies on familial aggregation is a major risk of bias. It is not unlikely that among relatives receiving an invitation to fill out the Swiss follow-up questionnaire in 2018, those who have developed symptoms or received a diagnosis of axial SpA are more motivated to participate. Females seem to have been more likely to participate in the follow-up, as the proportion of female relatives changed from 52.9% in 1985 to 55.6% in 2018. Additionally, the sex distribution in children with axial SpA is opposite to the sex distribution of AS in the population for children of both male and female index patients. For male index patients, 15.2% of daughters and 9.4% sons responding to the questionnaire in 2018 reported that they had developed axial SpA. This further supports that selection has taken place. I would argue that these alarming numbers are a result of bias from the recruitment of affected relatives, possibly in combination with chance due to low numbers.

An increased transmission of disease from the least affected sex in diseases with a skewed sex distribution has been suggested previously, known as the "Carter effect", supposedly owing to that a stronger genetic liability or load is needed for the sex with lower prevalence to develop disease.[168] We did find a higher relative risk of AS in children of female index patients, but only in daughters, and especially in relation to the lower AS prevalence in females in the general populations. The recurrence rate was 1.3% if father had AS and 2.4% if mother had AS. Sons of AS patients had the same recurrence rate (2.5% if father had AS, and 2.4% if mother had AS) in our material. If female AS patients had a higher load of risk alleles, we would expect highest recurrence rates in sons of female AS patients, and also higher recurrence rates in siblings of female compared to male patients, but this is not supported by our data (Supplementary Table S2 of study I). Neither did van der Linden et al. find support for a higher genetic load in females when comparing polygenic risk scores between males and females.[167]

Our estimate of familial aggregation is in line with a previous Swedish study, which reported a sibling risk of 17 based on AS diagnoses from all hospitalizations in Sweden 1973 to 2004.[44] Only including hospitalized patients is likely to capture a more severe group of patients, but whether family history of disease is associated with severity is not clear. Interestingly, two population-based studies on familial aggregation of AS in Iceland seemingly contradict the Swedish findings. Based on all 256 AS patients in Iceland, they report familial risks between 75 and 94 in first-degree relatives.[42 43] We hypothesized that differences could be due to differing immigration rates in the two countries, or that all Icelandic cases were clinically verified and patients with PsA-associated axial disease excluded. We thus limited our study population to index patients born in Sweden (as Iceland has a lower immigration rate), only patients identified from the SRQ (with presumably higher diagnostic validity), and excluded patients ever diagnosed with psoriasis or PsA, but none of these factors could explain the difference between the countries. One could speculate that the limited number of cases in Iceland are more clustered, conveying a higher genetic load. In the Swedish data, we found that having more than one affected relative was associated with a familial risk of 68 (95% CI 51-90).

6.2.2 Heritability of AS

Previous studies have put the heritability of AS somewhere between 50-70% (based on SNPs) and 94-99% (from twin studies).[46-48] While SNP-based studies are known to underestimate heritability, as explained in section 2.1.2, twin models can lead to overestimations because of the assumption that monozygotic and dizygotic twins share environment to the same extent. We report a heritability estimate based on data from nationwide registers that is in between those based on SNPs and twins. From the familial risks of AS in Swedish siblings, we estimate heritability to be 77% (95% CI 73-80%), and results are within the same range when based on familial risks for any first-degree relative, and by sex. Since our method ignores the contribution of common environmental factors

on similarity between siblings, it is still an overestimation and can be seen as an upper limit for AS heritability.

6.2.3 What does a family history entail?

While study I focused on the risk of AS associated with having family history of AS, study II investigated whether family history had any predictive value for TNFi treatment response in SpA patients, without finding an association. So what does a family history entail? Disease occurrence in more than one family member can be a result of both genetic and shared environmental influences, but the shared environmental influences have not been extensively studied. In AS, over 100 genes have been associated with disease, with the most influential one being HLA-B27, explaining about 20% of AS heritability,[5] and one third of the familial risk according to our back-of-the-envelope calculations in study I. A family history of AS or axial SpA is associated with HLA-B27 positivity in patients with suspected or confirmed axial SpA, with possible variations by geographical region or ethnicity.[51 52 169] A family history of AS has also been associated with an axial SpA diagnosis in some cohorts, but this association is weaker. Once the HLA-B27 status was known, family history was not independently associated with a diagnosis.[170] That family history actually has little predictive value for a diagnosis is in line with the relatively low recurrence rates noted in study I. The other SpA subtypes included in the ASAS definition of family history are less associated with HLA-B27, and has shown even less predictive value towards an axial SpA diagnosis, with only uveitis being a possible exception.[51 170]

While we, and others before us, did not find a significant association between family history of AS and TNFi treatment response, HLA-B27 positivity has been shown to predict a better treatment response to TNFi in AS patients.[171–173] Frölish et al. suggest that this is in part mediated by factors associated with the phenotype HLA-B27-positive patients display, such as higher CRP.[173] Results from a study using machine-learning algorithms on data from ten clinical trials to predict treatment response to TNFi, also show that the predictive value of HLA-B27 ranks low compared to factors like CRP, BASDAI, patient global assessment, and age.[174] Family history was not among the exposures included in that study, but would likely have scored even lower in terms of predictive value. We did not have the power in study II to investigate whether family history of treatment response per se, i.e. how relatives had responded to TNFi treatment, was predictive of a patient's own treatment response. Such an association has been found for RA, at least for drug survival, but this could be a result of both genetic and social influences.[175]

Thus, family history of AS is still one piece of the diagnosis puzzle, especially if HLA-B27 status is unknown, but its importance should not be overemphasized. Only one in ten AS patients had family history of AS in our studies.

6.2.4 Early-life risk factors

In study IV, on perinatal factors and childhood infections as risk factors for AS, we found that having older siblings and a history of tonsillectomy in childhood were associated with adult AS. Results were consistent after adjustment for family-shared confounding in a sibling comparison. We interpret older siblings as a proxy for exposure to childhood infections. Older siblings have been associated with an increased risk of especially respiratory infections during the first years of life in several studies.[176-178] For serious childhood infection, on the other hand, the significant association with AS in the case-control analysis was attenuated in the sibling comparison. If we suspect childhood infections to play a role in the etiology of AS, is this not evidence for the opposite? Not necessarily. Serious childhood infection in study IV was defined as having received an ICD code corresponding to an infection either in the Medical Birth Register at birth, or from an inpatient visit in the National Patient Register until age 15. If possible, we would have liked to include also milder infections that did not require hospitalization, but this data was not available. In this regard, we can consider serious infection as a proxy for any infection, but with significant measurement error. A known feature of the sibling comparison design is that attenuation of an association due to random measurement error is larger in exposure-discordant siblings than in a case-control sample. Thus, the observed attenuation does not necessarily indicate that the case-control estimate is confounded, but it could also be a result of random measurement error. For the other exposures included in the sibling comparison, i.e. multiple birth, season of birth, older siblings, and tonsillectomy, we do not expect measurement error to be a large problem.

Performing an equally well-powered sibling comparison study, with excellent coverage for many perinatal and early-life exposures, had not been possible without the national registers. Our results strengthen the hypothesis that childhood infections play a role in the etiology of AS. It should be noted, however, that the effect sizes were rather small, and there are likely many environmental factors that contribute to disease development in genetically predisposed individuals.

6.2.5 Pregnancy and treatment in SpA

Study III, on pregnancy outcomes in axial SpA, was not included in the original study plan for this thesis, but we decided at half-time that it would fit under the thesis' family theme. Not only did this study give me a chance to learn more about perinatal epidemiology and the Medical Birth Register, but it was also evident when we first discussed it in 2020 that there was a real research gap concerning pregnancy outcomes in SpA. By the time the study came to be in 2022, more publications on this topic had started to appear, including three reviews (two with meta-analyzes) summarizing the existing literature.[106 118 119] They showed even more clearly that there was a lack of large, population-based studies on pregnancy outcomes in SpA. Our results indicate, in line with the systematic reviews, that

axial SpA is associated with an increased risk of especially pre-eclampsia and preterm birth, but also of infections in the infant.

In study III, we were able to show that while the rates of preterm birth, cesarean delivery, and infant infection remained constant in general population comparators during the study period, the proportion of adverse outcomes in women with axial SpA in Sweden have decreased over these 14 years, approaching similar levels as in the general population. As much as we would like to attribute this change to the effect of better treatments, we did not have the power to test whether high disease activity was associated with a higher risk of preterm birth, or whether those on TNFi treatment had less adverse events. Such an association might also be confounded by indication, as those with highest disease activity are more likely to continue TNFi treatment when becoming pregnant. Our data show that the majority of women do not take any treatment during pregnancy, conceivably owing to a concern from both the women and their rheumatologists regarding the safety for the child. We would still claim that the increased use of effective treatments is the most likely explanation to the decrease in adverse pregnancy outcomes observed in the Swedish axial SpA population during the last decade. The proportion of women treated with TNFi in the year before pregnancy has increased from 2010, and the proportion treated at some point during pregnancy has increased from around 2015. While the number of pregnancies exposed to TNFi might be too small to explain the whole decrease in adverse outcomes, low disease activity when entering pregnancy is probably also beneficial even if treatment is stopped at conception. A recent study with prospectively collected data for 322 pregnancies in women with axial SpA followed at specialist centers in four European counties reported rates of adverse outcomes similar to those expected in the general population.[179] These women were tightly monitored during pregnancy, and 21% continued TNFi treatment in the third trimester, which likely contributed to the favorable outcomes.

One exception to the optimistic trend seen for adverse pregnancy outcomes in study III is pre-eclampsia, for which we saw a constantly increased risk in axial SpA pregnancies compared to general population comparators corresponding to a risk ratio of 1.44 (95% CI 1.08-1.92). Around the time study III was accepted, another study on the risk of pre-eclampsia in Swedish and Danish women with RA, PsA, and axial SpA was published, reporting a significant risks for pre-eclampsia in RA and PsA but not in axial SpA (OR 1.17 [0.76-1.78]).[180] The 431 Swedish axial SpA pregnancies included were from women in the SRQ, giving birth 2007-2017, and should thus overlap with our study population. Differences could be due to chance, considering the confidence intervals of the estimates from these two studies. An alternative explanation could be that women in the SRQ, and the Danish counterpart DANBIO, are not representative of all women with axial SpA in the population. The total proportion of women on TNFi treatment pre-pregnancy and at any time during pregnancy in the Swedish/Danish study are similar to those in the very last

years of our study. The odds ratio for pre-eclampsia was also higher in Sweden than Denmark, though the difference was not statistically significant. Even though not visible from our data, there might still be a beneficial effect of treatment also on the risk of pre-eclampsia in axial SpA.

So what can we say about treatment during pregnancy in women with axial SpA? Well-treated and well-monitored patients tend to do better. Current treatment guidelines from the European Alliance of Associations for Rheumatology (EULAR) and the American College of Rheumatology (ACR) recommend the use of TNFi until week 20 (or until third trimester in ACR recommendations) if needed, and certolizumab pegol can be used throughout pregnancy.[127 129] The main concern now regarding TNFi use in pregnancy is the risk of infections in the mother, and in particular in the infant due to placental transfer of these immune-modulating molecules during the last part of pregnancy. Currently, children exposed to TNFi after pregnancy week 22 are advised not receive live vaccines during their first six months of life as this might result in infection.[127] Certolizumab pegol has another molecular structure than the other TNFi, minimizing placental transfer, which is why it is preferred over the other TNFi in late pregnancy. The increased risk of serious infant infection found in study III is most likely not associated with TNFi exposure, as infections were most common in the beginning of the study period while TNFi use in late pregnancy only occurred during the very last years of the study. The low number of exposed births did not allow us to study the risk of infection associated with TNFi use in the third trimester specifically. The number of studies on this topic have increased dramatically over the last years, however, especially for women with other diseases like RA and IBD, and they indicate that the risk of infant infection is low after TNFi exposure in utero.[181–183] In a 2023 update of the British Society for Rheumatology guideline on drug prescribing in pregnancy, the conclusion is that there is now evidence enough to recommend continuation of all five TNFi drugs throughout pregnancy in women with rheumatic diseases.[184] For other b/tsDMARDs, safety data is still too limited to recommend use during pregnancy,[127 184] but as for TNFi, more observational data will be available over time, to help rheumatologists and patients make evidence-based decisions in order to improve outcomes for both mother and child.

7 Conclusions

The studies in this thesis had not existed had it not been for the wealth of data available in the Swedish health and populations registers. The ability to follow individuals over decades of their lives, linking information from before birth to adult health and demographics in registers with near complete coverage is invaluable to research. For the studies in this thesis, a key factor was the possibility to link information within families: across generations, among siblings, and from mother to child.

Specifically, we found that:

- The risk of AS is 20 times increased among first-degree relatives of AS patients compared to the general population. For those with more than one first-degree relative with AS, the risk is multiple times higher.
- The heritability of AS, i.e. the proportion of liability to develop AS in the populations that is due to genetics, is 80% or less. This is a high number, but lower than what has been reported previously.
- Despite being a strong risk factor for disease development, family history of SpA was not associated with clinical presentation at the start of treatment with biologic DMARDs, nor with drug survival or treatment response in SpA patients starting a first biologic DMARD.
- Pregnant women with axial SpA were at increased risk of pre-eclampsia and preterm birth, and a significantly higher proportion delivered by cesarean section. Infants born to women with axial SpA were at increased risk of serious infection during their first year of life.
- Reassuringly, the risk of adverse pregnancy outcomes have decreased among women with axial SpA in Sweden over the last two decades, approaching the same rates as in the general population. This happened in parallel with an increased use of biologic DMARDs, both in the axial SpA population as a whole and during pregnancy.
- History of a tonsillectomy in childhood and having older siblings were independently associated with development of AS in adulthood, even after adjustment for family-shared confounders. This strengthens the hypothesis that childhood infections play a role in the etiology of AS.

8 Points of perspective

The aim of this thesis was to contribute to the knowledge on etiology and prognosis of SpA in order to inform future etiological research and clinical practice. The findings reported herein have some implications of value both for the understanding of disease origin and in the clinical setting.

- The findings in study I of an upper limit of AS heritability around 80% can guide future etiological research and possibly help to close the gap between family-based and SNP-based heritability estimates.
- We have provided more precise, and less alarming, estimates on the familial aggregation and risk of passing on disease to one's children compared to figures previously available. Still, the 80% heritability and 20 times increased familial risk can be difficult for patients to interpret. Clinicians discussing the topic of heredity with patients must put the familial risk in perspective of the low AS prevalence in the population.
- As shown in study II, family history of SpA on its own has limited value with regards to prediction of which patients will respond to treatment with TNFi. Research is currently moving away from these types of single-factor studies, instead moving towards precision medicine, applying artificial intelligence and machine learning to predict the best treatment based on a person's genes, environment, and lifestyle factors. Future research will tell whether family history (self-reported or collected from registers) can contribute to the prediction under such circumstances.
- The association between childhood infections and adult-onset AS reported in study IV raises several interesting questions. First, these results should preferably be replicated in other populations. Future research should also investigate whether this association is restricted to specific classes of infections, e.g. respiratory tract infections, or certain infectious agents. Whether the timing of infections are important, and how antibiotic treatment affect the association, are other issues to address. The type of data needed to answer these questions, however, might be difficult to obtain. A re-evaluation of associations in Swedish data is warranted when enough patients with data on antibiotic prescription in childhood have accumulated, though that will take several decades. Another option is to make use of records from primary care, including lab results, to identify a wider range of infections. While this data is less structured then the information in the National Patient Register, it would be a very valuable source of information to researchers.
- The encouraging trend of improvement over time in pregnancy outcomes in women with axial SpA observed in study III, which coincided with an increased use of TNFi before and during pregnancy, gives support to current clinical guidelines recommending to minimize disease activity during pregnancy, even if it means

continuing treatment. There is a need for rheumatologists to monitor their patients closely before and during pregnancy, in order to observe potential changes in disease activity and adjust treatment accordingly. We noted in study III that a majority of patients did not have a visit recorded in the SRQ in the year before or during pregnancy where disease activity or inflammation were captured. While there might have been more visits taking place than actually entered into the SRQ, entering data into the register for these pregnant patients will be of major importance for future research differentiating effects from disease activity and new b/tsDMARDs on pregnancy outcomes.

9 Acknowledgements

I had a dream about becoming an epidemiologist, and now as this thesis is ready to be printed and my PhD journey is coming to an end, I start to realize that sometimes dreams come true! Obviously, this would not have been possible without the guidance, encouragement, and support from my colleagues, family, and friends.

First and foremost, I want to thank my main supervisor **Thomas Frisell**. I am so glad that you dared to give me this opportunity, despite my lack of relevant experience. You always waved me in whenever I appeared at your office door, be it for coding advice or a therapy couch when a PhD was the least of my worries. I can only hope that someday I will be able to lead others the way you have led me: with endless enthusiasm, always happy to share your wisdom, making me feel capable and pushing me towards independence in the end.

To my supervisor **Karin Hellgren**. Thank you for teaching me everything rheumatology-related, for offering your thoughtful input even from the other side of the world, for being so supportive of me and always leaving me with positive energy. I could not have asked for a better team of supervisors!

I have truly enjoyed my time at KEP, much thanks to the amazing people that make KEP to what it is. This journey would not have been the same without my fellow (past and present) PhD students: **Kelsi Smith**, thank you for being a good friend, making time to start the day with a cup of tea, and for the proofreading! To **Peter Alping**, for your kindness and smartness that have brightened my workdays. To **Andrei Barbulescu**, for being on my team from the start, before there officially was one. To **Simon Steiger**, for all the talks on baking, birds and life in general that made my last year at KEP, and the kappa writing, more delightful. To **Marina Dehara, Karin Gunnarsson, Viktor Molander, Viet Ngoc Nguyen, Eleni Tsamantioti, Weng Ian Che**, **Viktor Wintzell**, **Huiling Xu**, **Arda Yilal, Renata Zelic**, **Anton Öberg Sysojev** and the rest: I am so glad I got to share this special time of my life with you. Thank you for making KEP a both friendly and enlightening place.

To Team Frisell (**Simon**, **Suvi**, **Elisa**, **Peter**, **Andrei**, **Malik**, and **Thomas**) for valuable discussions at our methods club, and a feeling of belonging.

My other colleagues at KEP: **Hannah Bower**, **Bénédicte Delcoigne**, **Daniela Di Giuseppe**, and **Helga Westerlind**, for the rheuma conference company and covid time Zoom fikas in particular, and **Pernilla Appelquist**, **Johan Askling**, **Gustav Bruze**, **Matti Bryder, Michael Fored, Fredrik Granath, Helena Nord, Monica Ringheim, Kristin Waldenlind** and more for knowledge-sharing and engaging lunch room discussions. To **Elizabeth Arkema** for an inspiring career pep talk and agreeing to chair my defense!

To my co-authors **Ulf Lindström** and **Olof Stephansson**: Thank you for taking the time to engage in my studies, offering valuable input despite your busy schedules.

To my mentor **Jessica Beser**, for showing me that there is a life full of opportunities outside academia.

To my friends! If you have read all the way here, perhaps you finally understand what I have been doing these years. Or, you skipped a few pages, but I love you anyway! To my family! The Morins (**Lena**, **Gunnar**, **Eric**, **Verónica** and **Lasse**), for backing us up when I needed to focus and for inspiring me on my way to become the latest Dr. Morin. My sister **Ebba**, for endless support and discussions on (PhD) life, for mentoring me through all my worries, and for proofreading my kappa in the end. My brother **Karl**, for your wit and kindheartedness. To my parents, **Gunnel** and **Olle**, none of this would have been possible if it had not been for you. You always encouraged me to follow my dreams, and you are always there for me! Thank you!

Finally, to my husband **Thomas**. You were the one who boosted me into applying to this PhD in the first place, and I am so glad you did. You were also my only coworker in the home office for a significant part of it, and I cannot think of anyone else I would rather have spent covid isolation with. Älskar dig!

10 References

1. Carron P, De Craemer A-S, Van den Bosch F. Peripheral spondyloarthritis: a neglected entity—state of the art. *RMD Open* 2020;6(1):e001136.

2. Navarro-Compan V, Sepriano A, El-Zorkany B, van der Heijde D. Axial spondyloarthritis. *Ann Rheum Dis* 2021;80(12):1511-21.

3. Merriam-Webster. "spondyl" [Internet]. 2023 [cited 2023 16 June]. Available from: https://www.merriam-webster.com/dictionary/spondyl.

4. Moll JM, Haslock I, Macrae IF, Wright V. Associations between ankylosing spondylitis, psoriatic arthritis, Reiter's disease, the intestinal arthropathies, and Behcet's syndrome. *Medicine (Baltimore)* 1974;53(5):343-64.

5. Ellinghaus D, Jostins L, Spain SL, Cortes A, Bethune J, Han B, et al. Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nat Genet* 2016;48(5):510-8.

6. Sieper J, Braun J, Dougados M, Baeten D. Axial spondyloarthritis. *Nat Rev Dis Primers* 2015;1(1):15013.

7. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic Arthritis. *N Engl J Med* 2017;376(10):957-70.

8. Zochling J, Smith EU. Seronegative spondyloarthritis. *Best Pract Res Clin Rheumatol* 2010;24(6):747-56.

9. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27(4):361-8.

10. Feldtkeller E, Khan MA, van der Heijde D, van der Linden S, Braun J. Age at disease onset and diagnosis delay in HLA-B27 negative vs. positive patients with ankylosing spondylitis. *Rheumatol Int* 2003;23(2):61-6.

11. Lindstrom U, Exarchou S, Sigurdardottir V, Sundstrom B, Askling J, Eriksson JK, et al. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish National Patient Register. *Scand J Rheumatol* 2015;44(5):369-76.

12. Amor B, Dougados M, Mijiyawa M. [Criteria of the classification of spondylarthropathies]. *Rev Rhum Mal Osteoartic* 1990;57(2):85-89.

13. Dougados M, van der Linden S, Juhlin R, Huitfeldt B, Amor B, Calin A, et al. The European Spondylarthropathy Study Group preliminary criteria for the classification of spondylarthropathy. *Arthritis Rheum* 1991;34(10):1218-27.

14. Rudwaleit M, van der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The Assessment of SpondyloArthritis international Society classification criteria for peripheral spondyloarthritis and for spondyloarthritis in general. *Ann Rheum Dis* 2011;70(1):25-31.

15. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society

classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68(6):777-83.

16. Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H. Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum* 2006;54(8):2665-73.

17. Deodhar A, Reveille JD, van den Bosch F, Braun J, Burgos-Vargas R, Caplan L, et al. The Concept of Axial Spondyloarthritis: Joint Statement of the Spondyloarthritis Research and Treatment Network and the Assessment of SpondyloArthritis international Society in Response to the US Food and Drug Administration's Comments and Concerns. *Arthritis Rheum* 2014;66(10):2649-56.

18. Stolwijk C, van Onna M, Boonen A, van Tubergen A. Global Prevalence of Spondyloarthritis: A Systematic Review and Meta-Regression Analysis. *Arthritis Care Res (Hoboken)* 2016;68(9):1320-31.

19. Haglund E, Bremander AB, Petersson IF, Strombeck B, Bergman S, Jacobsson LT, et al. Prevalence of spondyloarthritis and its subtypes in southern Sweden. *Ann Rheum Dis* 2011;70(6):943-8.

20. Exarchou S, Lindstrom U, Askling J, Eriksson JK, Forsblad-d'Elia H, Neovius M, et al. The prevalence of clinically diagnosed ankylosing spondylitis and its clinical manifestations: a nationwide register study. *Arthritis Res Ther* 2015;17:118.

21. Exarchou S, Wallman JK, Di Giuseppe D, Klingberg E, Sigurdardottir V, Wedrén S, et al. The National Prevalence of Clinically Diagnosed Psoriatic Arthritis in Sweden in 2017. *J Rheumatol* 2023;50(6):781-88.

22. Scotti L, Franchi M, Marchesoni A, Corrao G. Prevalence and incidence of psoriatic arthritis: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2018;48(1):28-34.

23. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. *Ann Rheum Dis* 2023;82(1):19-34.

24. Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. *Nat Rev Rheumatol* 2022;18(8):465-79.

25. Svensk Reumatologisk Förening. Riktlinjer för läkemedelsbehandling vid axial spondylartrit och psoriasisartrit 2022 [Internet]. 2022 [cited 2023 7 June]. Available from: https://svenskreumatologi.se/wp-content/uploads/2022/03/riktlinjer-axial-spondylartrit-och-psoriasisartrit-220127.pdf.

26. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, Dougados M, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* 2020;79(6):700-12.

27. Ash Z, Gaujoux-Viala C, Gossec L, Hensor EMA, FitzGerald O, Winthrop K, et al. A systematic literature review of drug therapies for the treatment of psoriatic arthritis: current evidence and meta-analysis informing the EULAR

recommendations for the management of psoriatic arthritis. *Ann Rheum Dis* 2012;71(3):319-26.

28. Sepriano A, Regel A, van der Heijde D, Braun J, Baraliakos X, Landewe R, et al. Efficacy and safety of biological and targeted-synthetic DMARDs: a systematic literature review informing the 2016 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *RMD Open* 2017;3(1):e000396.

29. Baraliakos X, Gensler LS, D'Angelo S, Iannone F, Favalli EG, de Peyrecave N, et al. Biologic therapy and spinal radiographic progression in patients with axial spondyloarthritis: A structured literature review. *Ther Adv Musculoskelet Dis* 2020;12:1759720x20906040.

30. Boers N, Michielsens CAJ, van der Heijde D, den Broeder AA, Welsing PMJ. The effect of tumour necrosis factor inhibitors on radiographic progression in axial spondyloarthritis: a systematic literature review. *Rheumatology (Oxford)* 2019;58(11):1907-22.

31. Karmacharya P, Duarte-Garcia A, Dubreuil M, Murad MH, Shahukhal R, Shrestha P, et al. Effect of Therapy on Radiographic Progression in Axial Spondyloarthritis: A Systematic Review and Meta-Analysis. *Arthritis Rheum* 2020;72(5):733-49.

32. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. *Rheumatology (Oxford)* 2020;59(Supplement_1):i37-i46.

33. Ortolan A, Webers C, Sepriano A, Falzon L, Baraliakos X, Landewé RB, et al. Efficacy and safety of non-pharmacological and non-biological interventions: a systematic literature review informing the 2022 update of the ASAS/EULAR recommendations for the management of axial spondyloarthritis. *Ann Rheum Dis* 2023;82(1):142-52.

34. Deodhar A, Van den Bosch F, Poddubnyy D, Maksymowych WP, van der Heijde D, Kim TH, et al. Upadacitinib for the treatment of active non-radiographic axial spondyloarthritis (SELECT-AXIS 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2022;400(10349):369-79.

35. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol* 1994;21(12):2286-91.

36. van der Heijde D, Lie E, Kvien TK, Sieper J, Van den Bosch F, Listing J, et al. ASDAS, a highly discriminatory ASAS-endorsed disease activity score in patients with ankylosing spondylitis. *Ann Rheum Dis* 2009;68(12):1811-8.

37. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23(2):137-45.

38. Ekdahl C, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis. Use of a Swedish version of the Stanford Health Assessment Questionnaire. *Scand J Rheumatol* 1988;17(4):263-71.

39. Schoels MM, Aletaha D, Alasti F, Smolen JS. Disease activity in psoriatic arthritis (PsA): defining remission and treatment success using the DAPSA score. *Ann Rheum Dis* 2016;75(5):811-8.

40. Dernis E, Said-Nahal R, D'Agostino MA, Aegerter P, Dougados M, Breban M. Recurrence of spondylarthropathy among first-degree relatives of patients: a systematic cross-sectional study. *Ann Rheum Dis* 2009;68(4):502-7.

41. Brown MA, Laval SH, Brophy S, Calin A. Recurrence risk modelling of the genetic susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2000;59(11):883-6.

42. Geirsson AJ, Kristjansson K, Gudbjornsson B. A strong familiality of ankylosing spondylitis through several generations. *Ann Rheum Dis* 2010;69(7):1346-8.

43. Thjodleifsson B, Geirsson AJ, Bjornsson S, Bjarnason I. A common genetic background for inflammatory bowel disease and ankylosing spondylitis: a genealogic study in Iceland. *Arthritis Rheum* 2007;56(8):2633-9.

44. Sundquist K, Martineus JC, Li X, Hemminki K, Sundquist J. Concordant and discordant associations between rheumatoid arthritis, systemic lupus erythematosus and ankylosing spondylitis based on all hospitalizations in Sweden between 1973 and 2004. *Rheumatology (Oxford)* 2008;47(8):1199-202.

45. Falconer DS, Mackay TFC. Introduction to quantitative genetics. 4th ed. Harlow: Longman 1996.

46. Brown MA, Kennedy LG, MacGregor AJ, Darke C, Duncan E, Shatford JL, et al. Susceptibility to ankylosing spondylitis in twins: the role of genes, HLA, and the environment. *Arthritis Rheum* 1997;40(10):1823-8.

47. Pedersen OB, Svendsen AJ, Ejstrup L, Skytthe A, Harris JR, Junker P. Ankylosing spondylitis in Danish and Norwegian twins: occurrence and the relative importance of genetic vs. environmental effectors in disease causation. *Scand J Rheumatol* 2008;37(2):120-6.

48. Huang X-F, Li Z, De Guzman E, Robinson P, Gensler L, Ward MM, et al. Genomewide Association Study of Acute Anterior Uveitis Identifies New Susceptibility Loci. *Invest Ophthalmol Vis Sci* 2020;61(6):3.

49. Yang J, Zeng J, Goddard ME, Wray NR, Visscher PM. Concepts, estimation and interpretation of SNP-based heritability. *Nat Genet* 2017;49(9):1304-10.

50. Li Q, Chandran V, Tsoi L, O'Rielly D, Nair RP, Gladman D, et al. Quantifying Differences in Heritability among Psoriatic Arthritis (PsA), Cutaneous Psoriasis (PsC) and Psoriasis vulgaris (PsV). *Sci Rep* 2020;10(1):4925.

51. Ez-Zaitouni Z, Hilkens A, Gossec L, Berg IJ, Landewé R, Ramonda R, et al. Is the current ASAS expert definition of a positive family history useful in identifying axial spondyloarthritis? Results from the SPACE and DESIR cohorts. *Arthritis Res Ther* 2017;19:118.

52. Boel A, van Lunteren M, López-Medina C, Sieper J, van der Heijde D, van Gaalen FA. Geographical prevalence of family history in patients with axial spondyloarthritis and its association with HLA-B27 in the ASAS-PerSpA study. *RMD Open* 2022;8(1):e002174.

53. Reveille JD, Zhou X, Lee M, Weisman MH, Yi L, Gensler LS, et al. HLA class I and II alleles in susceptibility to ankylosing spondylitis. *Ann Rheum Dis* 2019;78(1):66-73.

54. Molto A, Sieper J. Peripheral spondyloarthritis: Concept, diagnosis and treatment. *Best Pract Res Clin Rheumatol* 2018;32(3):357-68.

55. Lim CSE, Sengupta R, Gaffney K. The clinical utility of human leucocyte antigen B27 in axial spondyloarthritis. *Rheumatology (Oxford)* 2018;57(6):959-68.

56. International Genetics of Ankylosing Spondylitis C, Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45(7):730-8.

57. Jacques P, Lambrecht S, Verheugen E, Pauwels E, Kollias G, Armaka M, et al. Proof of concept: enthesitis and new bone formation in spondyloarthritis are driven by mechanical strain and stromal cells. *Ann Rheum Dis* 2014;73(2):437.

58. Jacques P, McGonagle D. The role of mechanical stress in the pathogenesis of spondyloarthritis and how to combat it. *Best Pract Res Clin Rheumatol* 2014;28(5):703-10.

59. Videm V, Cortes A, Thomas R, Brown MA. Current Smoking is Associated with Incident Ankylosing Spondylitis — The HUNT Population-based Norwegian Health Study. *J Rheumatol* 2014;41(10):2041-48.

60. Li W, Han J, Qureshi AA. Smoking and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis* 2012;71(6):804-8.

61. Wendling D, Prati C. Spondyloarthritis and smoking: towards a new insight into the disease. *Expert Rev Clin Immunol* 2013;9(6):511-16.

62. Manasson J, Scher JU. Spondyloarthritis and the Microbiome: New Insights From an Ancient Hypothesis. *Curr Rheumatol Rep* 2015;17(2):10.

63. Costello ME, Ciccia F, Willner D, Warrington N, Robinson PC, Gardiner B, et al. Brief Report: Intestinal Dysbiosis in Ankylosing Spondylitis. *Arthritis Rheumatol* 2015;67(3):686-91.

64. Klingberg E, Magnusson MK, Strid H, Deminger A, Ståhl A, Sundin J, et al. A distinct gut microbiota composition in patients with ankylosing spondylitis is associated with increased levels of fecal calprotectin. *Arthritis Res Ther* 2019;21:248.

65. Montoya J, Matta NB, Suchon P, Guzian MC, Lambert NC, Mattei JP, et al. Patients with ankylosing spondylitis have been breast fed less often than healthy controls: a case-control retrospective study. *Ann Rheum Dis* 2016;75(5):879-82.

66. Barker DJ. Adult consequences of fetal growth restriction. *Clin Obstet Gynecol* 2006;49(2):270-83.

67. Silva IdS, Stavola BD, McCormack V, Collaborative Group on Pre-Natal Risk Factors and Subsequent Risk of Breast Cancer. Birth Size and Breast Cancer Risk: Re-analysis of Individual Participant Data from 32 Studies. *PLoS Med* 2008;5(9):e193.

68. Zazara DE, Arck PC. Developmental origin and sex-specific risk for infections and immune diseases later in life. *Semin Immunopathol* 2019;41(2):137-51.

69. Mostafavi B, Akyuz S, Jacobsson ME, Nilsen LV, Theander E, Jacobsson LH. Perinatal characteristics and risk of developing primary Sjögren's syndrome: a case-control study. *J Rheumatol* 2005;32(4):665-8.

70. Carlens C, Jacobsson L, Brandt L, Cnattingius S, Stephansson O, Askling J. Perinatal characteristics, early life infections and later risk of rheumatoid arthritis and juvenile idiopathic arthritis. *Ann Rheum Dis* 2009;68(7):1159-64.

71. Jacobsson LT, Jacobsson ME, Askling J, Knowler WC. Perinatal characteristics and risk of rheumatoid arthritis. *BMJ* 2003;326(7398):1068-9.

72. Mandl LA, Costenbader KH, Simard JF, Karlson EW. Is birthweight associated with risk of rheumatoid arthritis? Data from a large cohort study. *Ann Rheum Dis* 2009;68(4):514-8.

73. Parks CG, D'Aloisio AA, DeRoo LA, Huiber K, Rider LG, Miller FW, et al. Childhood socioeconomic factors and perinatal characteristics influence development of rheumatoid arthritis in adulthood. *Ann Rheum Dis* 2013;72(3):350-6.

74. Lindstrom U, Forsblad-d'Elia H, Askling J, Kristensen LE, Lie E, Exarchou S, et al. Perinatal characteristics, older siblings, and risk of ankylosing spondylitis: a case-control study based on national registers. *Arthritis Res Ther* 2016;18:16.

75. Lindstrom U, Exarchou S, Lie E, Dehlin M, Forsblad-d'Elia H, Askling J, et al. Childhood hospitalisation with infections and later development of ankylosing spondylitis: a national case-control study. *Arthritis Res Ther* 2016;18:240.

76. Chao WC, Lin CH, Chen YM, Jiang RS, Chen HH. Association between tonsillitis and newly diagnosed ankylosing spondylitis: A nationwide, population-based, case-control study. *PLoS One* 2019;14(8):e0220721.

77. Baudoin P, Van Der Horst-Bruinsma IE, Dekker-Saeys AJ, Weinreich S, Bezemer PD, Dijkmans BAC. Increased risk of developing ankylosing spondylitis among first-born children. *Arthritis Rheum* 2000;43(12):2818-22.

78. Brophy S, Taylor G, Calin A. Birth order and ankylosing spondylitis: no increased risk of developing ankylosing spondylitis among first-born children. *J Rheumatol* 2002;29(3):527.

79. Brahe CH, Ornbjerg LM, Jacobsson L, Nissen MJ, Kristianslund EK, Mann H, et al. Retention and response rates in 14 261 PsA patients starting TNF inhibitor treatment-results from 12 countries in EuroSpA. *Rheumatology (Oxford)* 2020;59(7):1640-50.

80. Lindstrom U, Olofsson T, Wedren S, Qirjazo I, Askling J. Biological treatment of ankylosing spondylitis: a nationwide study of treatment trajectories on a patient level in clinical practice. *Arthritis Res Ther* 2019;21:128.

81. Ornbjerg LM, Brahe CH, Askling J, Ciurea A, Mann H, Onen F, et al. Treatment response and drug retention rates in 24 195 biologic-naive patients with axial spondyloarthritis initiating TNFi treatment: routine care data from 12 registries in the EuroSpA collaboration. *Ann Rheum Dis* 2019;78:1536-44.

82. Arends S, Brouwer E, van der Veer E, Groen H, Leijsma MK, Houtman PM, et al. Baseline predictors of response and discontinuation of tumor necrosis factor-alpha blocking therapy in ankylosing spondylitis: a prospective longitudinal observational cohort study. *Arthritis Res Ther* 2011;13:R94.

83. Baraliakos X, Szumski A, Koenig AS, Jones H. The role of C-reactive protein as a predictor of treatment response in patients with ankylosing spondylitis. *Semin Arthritis Rheum* 2019;48(6):997-1004.

84. Davis JC, Jr., Van der Heijde DM, Dougados M, Braun J, Cush JJ, Clegg DO, et al. Baseline factors that influence ASAS 20 response in patients with ankylosing spondylitis treated with etanercept. *J Rheumatol* 2005;32(9):1751-4.

85. Glintborg B, Ostergaard M, Dreyer L, Krogh NS, Tarp U, Hansen MS, et al. Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor alpha therapy: results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011;63(2):382-90.

86. Glintborg B, Ostergaard M, Krogh NS, Dreyer L, Kristensen HL, Hetland ML. Predictors of treatment response and drug continuation in 842 patients with ankylosing spondylitis treated with anti-tumour necrosis factor: results from 8 years' surveillance in the Danish nationwide DANBIO registry. *Ann Rheum Dis* 2010;69(11):2002-8.

87. Kristensen LE, Gulfe A, Saxne T, Geborek P. Efficacy and tolerability of anti-tumour necrosis factor therapy in psoriatic arthritis patients: results from the South Swedish Arthritis Treatment Group register. *Ann Rheum Dis* 2008;67(3):364-9.

88. Kristensen LE, Karlsson JA, Englund M, Petersson IF, Saxne T, Geborek P. Presence of peripheral arthritis and male sex predicting continuation of anti-tumor necrosis factor therapy in ankylosing spondylitis: an observational prospective cohort study from the South Swedish Arthritis Treatment Group Register. *Arthritis Care Res (Hoboken)* 2010;62(10):1362-9.

89. Rudwaleit M, Claudepierre P, Wordsworth P, Cortina EL, Sieper J, Kron M, et al. Effectiveness, safety, and predictors of good clinical response in 1250 patients treated with adalimumab for active ankylosing spondylitis. *J Rheumatol* 2009;36(4):801-8.

90. Vieira-Sousa E, Eusebio M, Avila-Ribeiro P, Khmelinskii N, Cruz-Machado R, Rocha TM, et al. Real-world Longterm Effectiveness of Tumor Necrosis Factor Inhibitors in Psoriatic Arthritis Patients from the Rheumatic Diseases Portuguese Register. *J Rheumatol* 2020;47(5):690-700.

91. Haddad A, Gazitt T, Feldhamer I, Feld J, Cohen AD, Lavi I, et al. Treatment persistence of biologics among patients with psoriatic arthritis. *Arthritis Res Ther* 2021;23:44.

92. Lindström U, Olofsson T, Wedrén S, Qirjazo I, Askling J. Impact of extra-articular spondyloarthritis manifestations and comorbidities on drug retention of a first TNF-inhibitor in ankylosing spondylitis: a population-based nationwide study. *RMD Open* 2018;4(2):e000762.

93. Glintborg B, Højgaard P, Lund Hetland M, Steen Krogh N, Kollerup G, Jensen J, et al. Impact of tobacco smoking on response to tumour necrosis factor-alpha inhibitor treatment in patients with ankylosing spondylitis: results from the Danish nationwide DANBIO registry. *Rheumatology (Oxford)* 2015;55(4):659-68.

94. Micheroli R, Hebeisen M, Wildi LM, Exer P, Tamborrini G, Bernhard J, et al. Impact of obesity on the response to tumor necrosis factor inhibitors in axial spondyloarthritis. *Arthritis Res Ther* 2017;19:164.

95. Yahya F, Gaffney K, Hamilton L, Lonsdale E, Leeder J, Brooksby A, et al. Tumour necrosis factor inhibitor survival and predictors of response in axial spondyloarthritis-findings from a United Kingdom cohort. *Rheumatology (Oxford)* 2018;57(4):619-24.

96. Alazmi M, Sari I, Krishnan B, Inman RD, Haroon N. Profiling Response to Tumor Necrosis Factor Inhibitor Treatment in Axial Spondyloarthritis. *Arthritis Care Res (Hoboken)* 2018;70(9):1393-99.

97. Nørgaard M, Larsson H, Pedersen L, Granath F, Askling J, Kieler H, et al. Rheumatoid arthritis and birth outcomes: a Danish and Swedish nationwide prevalence study. *J Intern Med* 2010;268(4):329-37.

98. Stephansson O, Larsson H, Pedersen L, Kieler H, Granath F, Ludvigsson JF, et al. Congenital abnormalities and other birth outcomes in children born to women with ulcerative colitis in Denmark and Sweden. *Inflamm Bowel Dis* 2010;17(3):795-801.

99. Huang W, Wu T, Jin T, Zhang Y, Wang J, Qi J, et al. Maternal and fetal outcomes in pregnant women with rheumatoid arthritis: a systematic review and meta-analysis. *Clin Rheumatol* 2023;42(3):855-70.

100. Leung KK, Tandon P, Govardhanam V, Maxwell C, Huang V. The Risk of Adverse Neonatal Outcomes With Maternal Inflammatory Bowel Disease: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2021;27(4):550-62.

101. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum* 2008;59(9):1241-8.

102. Ostensen M, Husby G. A prospective clinical study of the effect of pregnancy on rheumatoid arthritis and ankylosing spondylitis. *Arthritis Rheum* 1983;26(9):1155-9.

103. Ursin K, Lydersen S, Skomsvoll JF, Wallenius M. Disease activity during and after pregnancy in women with axial spondyloarthritis: a prospective multicentre study. *Rheumatology (Oxford)* 2018;57(6):1064-71.

104. van den Brandt S, Zbinden A, Baeten D, Villiger PM, Ostensen M, Forger F. Risk factors for flare and treatment of disease flares during pregnancy in rheumatoid arthritis and axial spondyloarthritis patients. *Arthritis Res Ther* 2017;19:64.

105. Ostensen M, Romberg O, Husby G. Ankylosing spondylitis and motherhood. *Arthritis Rheum* 1982;25(2):140-3.

106. Maguire S, O'Dwyer T, Mockler D, O'Shea F, Wilson F. Pregnancy in axial spondyloarthropathy: A systematic review & meta-analysis. *Semin Arthritis Rheum* 2020;50(6):1269-79.

107. Skomsvoll JF, Ostensen M, Irgens LM, Baste V. Obstetrical and neonatal outcome in pregnant patients with rheumatic disease. *Scand J Rheumatol Suppl* 1998;107:109-12.

108. Wallenius M, Skomsvoll JF, Irgens LM, Salvesen K, Nordvåg BY, Koldingsnes W, et al. Pregnancy and delivery in women with chronic inflammatory arthritides with a specific focus on first birth. *Arthritis Rheum* 2011;63(6):1534-42.

109. Jakobsson GL, Stephansson O, Askling J, Jacobsson LT. Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016;75(10):1838-42.

110. Zbinden A, van den Brandt S, Østensen M, Villiger PM, Förger F. Risk for adverse pregnancy outcome in axial spondyloarthritis and rheumatoid arthritis: disease activity matters. *Rheumatology (Oxford)* 2018;57(7):1235-42.

111. Mørk S, Voss A, Möller S, Bliddal M. Spondyloarthritis and Outcomes in Pregnancy and Labor: A Nationwide Register-Based Cohort Study. *Arthritis Care Res (Hoboken)* 2021;73(2):282-88.

112. Unal C, Fadiloglu E, Tanacan A, Zaim OC, Beksac MS. Retrospective evaluation of pregnancies with ankylosing spondylitis in a tertiary center in Turkey. *Int J Rheum Dis* 2020;23(1):101-05.

113. Park EH, Lee JS, Kim YJ, Lee SM, Jun JK, Lee EB, et al. Pregnancy outcomes in Korean women with ankylosing spondylitis. *Korean J Intern Med* 2021;36(3):721-30.

114. Keeling SO, Bowker SL, Savu A, Kaul P. A Population-level Analysis of the Differing Effects of Rheumatoid Arthritis and Spondyloarthritis on Peripartum Outcomes. *J Rheumatol* 2020;47(2):197-203.

115. Timur H, Tokmak A, Turkmen GG, Ali Inal H, Uygur D, Danisman N. Pregnancy outcome in patients with ankylosing spondylitis. *J Matern Fetal Neonatal Med* 2016;29(15):2470-4.

116. Strouse J, Donovan BM, Fatima M, Fernandez-Ruiz R, Baer RJ, Nidey N, et al. Impact of autoimmune rheumatic diseases on birth outcomes: a population-based study. *RMD Open* 2019;5(1):e000878.

117. Maguire S. Response to Bernardy et al. comment on "pregnancy in axial spondyloarthropathy: A systematic review and meta-analysis. *Semin Arthritis Rheum* 2021;51(5):e2-e4.

118. Mokbel A, Lawson DO, Farrokhyar F. Pregnancy outcomes in women with ankylosing spondylitis: a scoping literature and methodological review. *Clin Rheumatol* 2021;40(9):3465-80.

119. Hamroun S, Hamroun A, Bigna JJ, Allado E, Forger F, Molto A. Fertility and pregnancy outcomes in women with spondyloarthritis: a systematic review and meta-analysis. *Rheumatology (Oxford)* 2022;61(4):1314-27.

120. Smith CJF, Bandoli G, Kavanaugh A, Chambers CD. Birth Outcomes and Disease Activity During Pregnancy in a Prospective Cohort of Women With Psoriatic Arthritis and Ankylosing Spondylitis. *Arthritis Care Res (Hoboken)* 2020;72(7):1029-37.

121. Polachek A, Polachek Shlomi I, Spitzer K, Pereira D, Ye JY, Chandran V, et al. Outcome of pregnancy in women with psoriatic arthritis compared to healthy controls. *Clin Rheumatol* 2019;38(3):895-902.

122. Broms G, Haerskjold A, Granath F, Kieler H, Pedersen L, Berglind IA. Effect of Maternal Psoriasis on Pregnancy and Birth Outcomes: A Population-based Cohort Study from Denmark and Sweden. *Acta Derm Venereol* 2018;98(8):728-34.

123. Remaeus K, Stephansson O, Johansson K, Granath F, Hellgren K. Maternal and infant pregnancy outcomes in women with psoriatic arthritis: a Swedish nationwide cohort study. *BJOG* 2019;126(10):1213-22.

124. Bharti B, Lee SJ, Lindsay SP, Wingard DL, Jones KL, Lemus H, et al. Disease Severity and Pregnancy Outcomes in Women with Rheumatoid Arthritis: Results from the Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project. *J Rheumatol* 2015;42(8):1376-82.

125. de Man YA, Hazes JM, van der Heide H, Willemsen SP, de Groot CJ, Steegers EA, et al. Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009;60(11):3196-206.

126. Hellgren K, Secher AE, Glintborg B, Rom AL, Gudbjornsson B, Michelsen B, et al. Pregnancy outcomes in relation to disease activity and anti-rheumatic treatment strategies in women with rheumatoid arthritis: a matched cohort study from Sweden and Denmark. *Rheumatology (Oxford)* 2022;61(9):3711-22.

127. Götestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C, et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75(5):795-810.

128. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006;40(5):824-9.

129. Sammaritano LR, Bermas BL, Chakravarty EE, Chambers C, Clowse MEB, Lockshin MD, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. *Arthritis Rheumatol* 2020;72(4):529-56.

130. Broms G, Kieler H, Ekbom A, Gissler M, Hellgren K, Lahesmaa-Korpinen AM, et al. Anti-TNF treatment during pregnancy and birth outcomes: A population-based study from Denmark, Finland, and Sweden. *Pharmacoepidemiol Drug Saf* 2020;29(3):316-27.

131. Redeker I, Strangfeld A, Callhoff J, Marschall U, Zink A, Baraliakos X. Maternal and infant outcomes in pregnancies of women with axial spondyloarthritis compared with matched controls: results from nationwide health insurance data. *RMD Open* 2022;8(2):e002146.

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

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

134. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf* 2007;16(7):726-35.

135. Cnattingius S, Källén K, Sandström A, Rydberg H, Månsson H, Stephansson O, et al. The Swedish medical birth register during five decades: documentation of the content and quality of the register. *Eur J Epidemiol* 2023;38(1):109-20.

136. Ludvigsson JF, Almqvist C, Bonamy AK, Ljung R, Michaëlsson K, Neovius M, et al. Registers of the Swedish total population and their use in medical research. *Eur J Epidemiol* 2016;31(2):125-36.

137. Ekbom A. The Swedish Multi-generation Register. *Methods Mol Biol* 2011;675:215-20.

138. Ludvigsson JF, Svedberg P, Olén O, Bruze G, Neovius M. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. *Eur J Epidemiol* 2019;34(4):423-37.

139. Eriksson JK, Askling J, Arkema EV. The Swedish Rheumatology Quality Register: optimisation of rheumatic disease assessments using register-enriched data. *Clin Exp Rheumatol* 2014;32(5 Suppl 85):S-147-9.

140. Wadstrom H, Eriksson JK, Neovius M, Askling J. How good is the coverage and how accurate are exposure data in the Swedish Biologics Register (ARTIS)? *Scand J Rheumatol* 2015;44(1):22-8.

141. Wacholder S, Hartge P. Case–Control Study. In: Encyclopedia of Biostatistics. John Wiley & Sons, Ltd 2005.

142. Langholz B. Case–Control Study, Nested. In: Encyclopedia of Biostatistics. John Wiley & Sons, Ltd 2005.

143. Vandenbroucke JP, Pearce N. Case-control studies: basic concepts. *Int J Epidemiol* 2012;41(5):1480-9.

144. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;10(1):37-48.

145. Shapiro S, Rosenberg L. Bias in Case–Control Studies. In: Encyclopedia of Biostatistics. John Wiley & Sons, Ltd 2005.

146. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;15(5):615-25.

147. Hernández-Díaz S, Schisterman EF, Hernán MA. The Birth Weight "Paradox" Uncovered? *Am J Epidemiol* 2006;164(11):1115-20.

148. Lash TL, VanderWeele TJ, Haneause S, Rothman K. Modern Epidemiology. 4th ed. Philadelphia, PA: Wolters Kluwer Health 2021.

149. Pearce N. Analysis of matched case-control studies. *BMJ* 2016;352:i969.

150. Hosmer DW, Lemeshow S, Sturdivant RX. Applied logistic regression. 3rd ed. Hoboken, NJ: John Wiley & Sons 2013.

151. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159(7):702-6.

152. Talbot D, Mésidor M, Chiu Y, Simard M, Sirois C. An Alternative Perspective on the Robust Poisson Method for Estimating Risk or Prevalence Ratios. *Epidemiology* 2023;34(1):1-7.

153. Hellevik O. Linear versus logistic regression when the dependent variable is a dichotomy. *Quality & Quantity* 2009;43(1):59-74.

154. Borgan Ø. Kaplan–Meier Estimator. In: Encyclopedia of Biostatistics. John Wiley & Sons, Ltd 2005.

155. Little RJA, Rubin DB. Statistical analysis with missing data. 2nd ed. Hoboken, N.J: Wiley 2002.

156. Austin PC, White IR, Lee DS, van Buuren S. Missing Data in Clinical Research: A Tutorial on Multiple Imputation. *Can J Cardiol* 2021;37(9):1322-31.

157. van Buuren S. Flexible Imputation of Missing Data. 2nd ed. Boca Raton, FL.: CRC Press 2018. Available from: https://stefvanbuuren.name/fimd/.

158. Tenesa A, Haley CS. The heritability of human disease: estimation, uses and abuses. *Nat Rev Genet* 2013;14(2):139-49.

159. Cleveland WS. Robust Locally Weighted Regression and Smoothing Scatterplots. *Journal of the American Statistical Association* 1979;74(368):829-36.

160. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *JAMA* 2013;310(20):2191-94.

161. Lag om etikprövning av forskning som avser människor (SFS 2003:460) Stockholm: Utrikesdepartementet.

162. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) OJ L199.

163. World Health Organization (WHO). International Classification of Diseases, Eleventh Revision (ICD-11) [Internet]. 2023 [cited 2023 22 August]. Available from: https://icd.who.int/browse11.

164. Frisell T, Öberg S, Kuja-Halkola R, Sjölander A. Sibling Comparison Designs: Bias From Non-Shared Confounders and Measurement Error. *Epidemiology* 2012;23(5):713-20.

165. Sjölander A, Frisell T, Kuja-Halkola R, Öberg S, Zetterqvist J. Carryover Effects in Sibling Comparison Designs. *Epidemiology* 2016;27(6):852-8.

166. Pelaez-Ballestas I, Romero-Mendoza M, Burgos-Vargas R. If three of my brothers have ankylosing spondylitis, why does the doctor say it is not necessarily hereditary? The meaning of risk in multiplex case families with ankylosing spondylitis. *Chronic Illn* 2016;12(1):58-70.

167. van der Linden SM, Khan MA, Li Z, Baumberger H, Zandwijk Hv, Khan MK, et al. Recurrence of axial spondyloarthritis among first-degree relatives in a prospective 35-year-follow-up family study. *RMD Open* 2022;8(2):e002208.

168. Carter CO, Evans KA. Inheritance of congenital pyloric stenosis. *J Med Genet* 1969;6(3):233-54.

169. van Lunteren M, Sepriano A, Landewé R, Sieper J, Rudwaleit M, van der Heijde D, et al. Do ethnicity, degree of family relationship, and the spondyloarthritis subtype in affected relatives influence the association between a positive family history for spondyloarthritis and HLA-B27 carriership? Results from the worldwide ASAS cohort. *Arthritis Res Ther* 2018;20:166.

170. van Lunteren M, van der Heijde D, Sepriano A, Berg IJ, Dougados M, Gossec L, et al. Is a positive family history of spondyloarthritis relevant for diagnosing axial spondyloarthritis once HLA-B27 status is known? *Rheumatology (Oxford)* 2019;58(9):1649-54.

171. Baraliakos X, Koenig AS, Jones H, Szumski A, Collier D, Bananis E. Predictors of Clinical Remission under Anti-tumor Necrosis Factor Treatment in Patients with Ankylosing Spondylitis: Pooled Analysis from Large Randomized Clinical Trials. *J Rheumatol* 2015;42(8):1418-26.

172. Maneiro JR, Souto A, Salgado E, Mera A, Gomez-Reino JJ. Predictors of response to TNF antagonists in patients with ankylosing spondylitis and psoriatic arthritis: systematic review and meta-analysis. *RMD Open* 2015;1(1):e000017.

173. Fröhlich F, Micheroli R, Hebeisen M, Kissling S, Bürki K, Exer P, et al. HLA-B27 as a predictor of effectiveness of treatment with TNF inhibitors in axial spondyloarthritis: data from the Swiss Clinical Quality Management Registry. *Clin Rheumatol* 2023;42(5):1267-74.

174. Wang R, Dasgupta A, Ward MM. Predicting Probability of Response to Tumor Necrosis Factor Inhibitors for Individual Patients With Ankylosing Spondylitis. *JAMA Netw Open* 2022;5(3):e222312.

175. Frisell T, Saevarsdottir S, Askling J. Does a family history of RA influence the clinical presentation and treatment response in RA? *Ann Rheum Dis* 2016;75(6):1120-25.

176. Latzin P, Frey U, Roiha HL, Baldwin DN, Regamey N, Strippoli MP, et al. Prospectively assessed incidence, severity, and determinants of respiratory symptoms in the first year of life. *Pediatr Pulmonol* 2007;42(1):41-50.

177. Vissing NH, Chawes BL, Rasmussen MA, Bisgaard H. Epidemiology and Risk Factors of Infection in Early Childhood. *Pediatrics* 2018;141(6):e20170933.

178. von Linstow M-L, Holst KK, Larsen K, Koch A, Andersen PK, Høgh B. Acute respiratory symptoms and general illness during the first year of life: A population-based birth cohort study. *Pediatr Pulmonol* 2008;43(6):584-93.

179. Meissner Y, Strangfeld A, Molto A, Forger F, Wallenius M, Costedoat-Chalumeau N, et al. Pregnancy and neonatal outcomes in women with axial spondyloarthritis: pooled data analysis from the European Network of Pregnancy Registries in Rheumatology (EuNeP). *Ann Rheum Dis* 2022;81(11):1524-33.

180. Secher AEP, Granath F, Glintborg B, Rom A, Hetland ML, Hellgren K. Risk of pre-eclampsia and impact of disease activity and antirheumatic treatment in women with rheumatoid arthritis, axial spondylarthritis and psoriatic arthritis: a collaborative matched cohort study from Sweden and Denmark. *RMD Open* 2022;8(2):e002445.

181. Desai RJ, Bateman BT, Huybrechts KF, Patorno E, Hernandez-Diaz S, Park Y, et al. Risk of serious infections associated with use of immunosuppressive agents in

pregnant women with autoimmune inflammatory conditions: cohort study. *BMJ* 2017;356:j895.

182. Geldhof A, Slater J, Clark M, Chandran U, Coppola D. Exposure to Infliximab During Pregnancy: Post-Marketing Experience. *Drug Saf* 2020;43(2):147-61.

183. Truta B, Leeds IL, Canner JK, Efron JE, Fang SH, Althumari A, et al. Early Discontinuation of Infliximab in Pregnant Women With Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2020;26(7):1110-17.

184. Russell MD, Dey M, Flint J, Davie P, Allen A, Crossley A, et al. British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids. *Rheumatology (Oxford)* 2023;62(4):e48-e88.