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Real-world evidence on safety, effectiveness, and challenges, with attention to body mass index and sex

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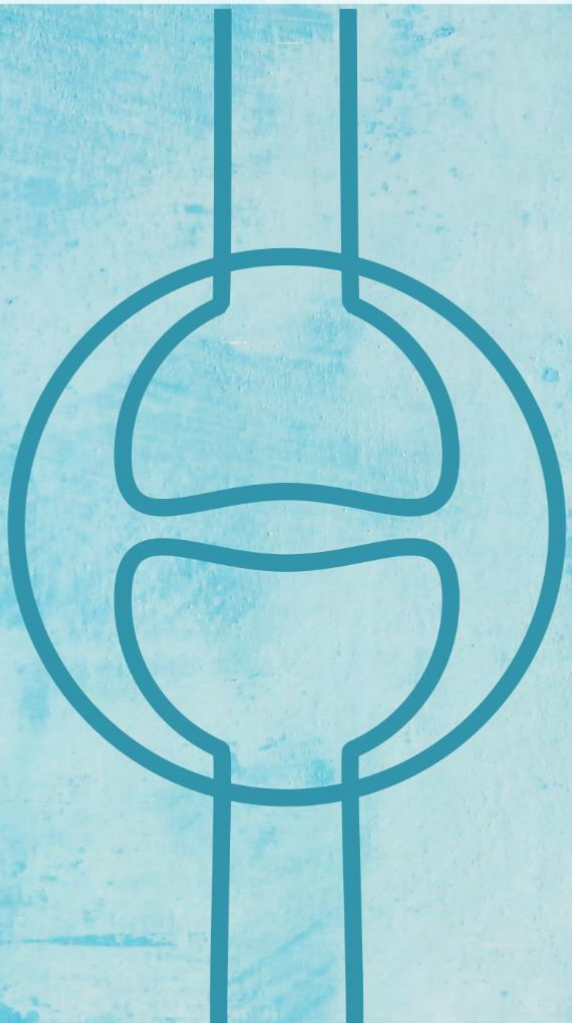

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Pharmacoepidemiology of rheumatic diseases

Real-world evidence on safety, effectiveness, and challenges, with attention to body mass index and sex

Enriqueta Vallejo-Yagüe

A thesis submitted to attain the degree of
DOCTOR OF SCIENCES of ETH Zurich
(Dr. sc. ETH Zurich)

presented by
ENRIQUETA VALLEJO-YAGÜE
Master in Pharmacoepidemiology and Pharmacovigilance, University of Alcala.
Licenciatura en Farmacia, Pharmacy Long-Cycle Degree, Complutense University of Madrid.

born on 24.05.1986

accepted on the recommendation of
Prof. Dr. Andrea M. Burden
Prof. Dr. Jörg Goldhahn

2022

Supervisor:
Prof. Dr. Andrea M. Burden

Assessment Committee:
Prof. Dr. Andrea M. Burden
Prof. Dr. Jörg Goldhahn

Enriqueta Vallejo-Yagüe

Pharmacist by training at the Complutense University of Madrid (2012). Training at Careggi University Hospital, Florence, in the galenic laboratory and department of medical devices (2011). Pharmaceutical R&D at Synovo GmbH (2012-2018), being Project Research Leader for the 7FP European-funded Project 'VISION – Prolonged inhibition of semaphorine3a pathway via a bio-degradable implant towards a better therapy for visual sensory impairments', and responsible person for the company's orphan drugs. Master in Pharmacoepidemiology and Pharmacovigilance by the University of Alcala, conducting the master thesis at the Medical School Twente (2017-2018). Doctoral thesis in the Pharmacoepidemiology group led by Prof. Andrea M. Burden at ETH Zurich. Passionate for healthcare and research. Lover of outdoor activities, traveling, dancing, and questioning unconscious/implicit bias. Ultimately, a fan of hiking in the Alps.

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The cover image was partially created modifying an original photo by Mona Eendra on Unsplash (https://unsplash.com/photos/vC8wj_Kphak).

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To Oli Walker,
for being a pillar when I need support,
the gate opener when I go to explore,
and my partner in crime, *mi compañero de vida*.

To my family,
for triggering my interest in research and self-improvement,
and for always being there for me.

To Dr Teresa S. Sánchez Pascua,
who handed me the keys to navigate a PhD.

"It is not only the question, but the way you try to solve it."

Maryam Mirzakhani

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Summary

Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are major chronic inflammatory immune-mediated rheumatic diseases. RA affects 0.45-0.66% of the European population,[1] and the prevalence of PsA in Europe is estimated to be 0.05-0.21%.[2] Both RA and PSA are associated with high physical disability and social burden for the patients, as well as health and socioeconomic challenges for society.[1,3,4] Thus, proper management of these diseases is crucial.

In the past decades, novel treatments for RA and PsA were introduced into clinical practice, advancing the treatment of patients for whom traditional treatments were not sufficient.[5–7] However, a substantial number of patients do not achieve clinical response.[5,8–12] Thus, with the effectiveness of treatments differing across patients, the selection of the optimal treatment remains challenging.[6,13] Additionally, there are patient groups who require special attention. For example, patients with abnormal body mass index (BMI), due to concerns regarding the association of obesity and worse management of rheumatic diseases.[14–19] Likewise, following the need to implement the gender perspective in medicine[20] and the evidence on sex-driven differences in the immune system,[21–25] studying female and male patients separately is of interest.

In this thesis, we investigated the safety of novel treatments of RA and PsA, and studied the RA and PsA population in Switzerland, with attention to BMI and sex, using real-word data (RWD). Additionally, we discussed challenges of this type of research and suggested solutions to address them.

First, we conducted a very timely safety study on the antirheumatic medications tofacitinib and baricitinib, using data from the World Health Organization (WHO). This built up on emerging safety concerns and supported the recommendation for cautious use of tofacitinib in patients with high thromboembolic risk (**Chapter 3**).[26]

Subsequently, we studied patients with RA and PsA in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) cohort, with attention to their BMI category. We observed that at the start of their first treatment escalation to biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD), RA and PsA patients with obesity had worse disease activity than those with normal weight (**Chapter 4**).[27] Furthermore, among PsA patients, obesity was associated with a halved reduced odds of achieving successful clinical outcome, compared to normal weight patients (**Chapter 5**)[28]. Among RA patients, we investigated the comparative effectiveness of treatments in patients who were overweight or obese. Initially, we did not observe differences

between the drugs. However, stratifying by sex we discovered a beneficial effect of infliximab versus adalimumab in female overweight patients, but the opposite in female patients with obesity. This was a relevant finding in female patients, which was otherwise 'hidden' when studying the overall cohort (**Chapter 6**).[29] Likewise, in an additional study, we identified a potential disparity in the decision on treatment upscale between male and female RA patients, which may explain the higher odds of reaching remission in men versus women (**Chapter 7**).[30] These findings supported the need for sex-stratified analyses and gender-studies in healthcare research.

Finally, with little guidance on measuring different types of RA response in observational data, we published a viewpoint to help distinguish between primary and secondary non-response, encouraging regulatory bodies to make this a priority (**Chapter 8**).[31] We believe this topic will mark a new era in RA research and clinical management.

Overall, this thesis adds to the body of evidence of RA and PsA in RWD. It contributes to the knowledge on safety and effectiveness of treatments, highlights potential gender bias in the treatment decision making, and opens up the discussion on the need of operational definitions for further research. It provides evidence to take into consideration the sex/gender, BMI, and clinical history (e.g., pre-existing risks) of the patients when taking clinical decisions or conducting research. Thus, these findings are a step forward in developing precision or personalized medicine approaches in rheumatology care, as they can shape clinical decisions and future research projects.

Zusammenfassung

Rheumatoide Arthritis (RA) und Psoriasis-Arthritis (PsA) sind schwere chronisch-entzündliche, immunvermittelte rheumatische Erkrankungen. Von RA sind 0,45-0,66% der europäischen Bevölkerung betroffen,[1] während die Prävalenz von PsA in Europa auf 0,05-0,21% geschätzt wird.[2] Sowohl RA als auch PsA sind mit schwerwiegenden körperlichen Behinderungen und sozialen Belastungen für die Patient:innen verbunden und haben gesellschaftliche Auswirkungen in gesundheitlicher und sozioökonomischer Hinsicht.[1,3,4] Daher ist ein gutes Management dieser Krankheiten von entscheidender Bedeutung.

In den vergangenen Jahrzehnten wurden neuartige Therapien für RA und PsA in die klinische Praxis eingeführt, wodurch die Behandlung von Patient:innen, für die herkömmliche Therapien nicht ausreichten, verbessert wurde.[5–7] Jedoch spricht eine beträchtliche Anzahl von Patient:innen nicht auf die Therapie an.[5,8–12] Da die Wirksamkeit der Therapien von Patient:in zu Patient:in unterschiedlich ist, bleibt die Auswahl der optimalen Behandlung eine Herausforderung.[6,13] Darüber hinaus gibt es bestimmte Patientengruppen, die bei der Therapiewahl besondere Aufmerksamkeit erfordern. Dies trifft beispielsweise auf Patient:innen zu, deren Body-Mass-Index (BMI) ausserhalb der Norm liegt, nachdem ein Zusammenhang zwischen Adipositas und einem reduzierten Ansprechen auf die Therapie der rheumatischen Erkrankung gezeigt wurde.[14–19] Ausserdem ist es aufgrund der Erkenntnisse über geschlechtsspezifische Unterschiede im Immunsystem notwendig,[21–25] weibliche und männliche Patienten getrennt zu betrachten und eine geschlechtsspezifische Analyse durchführen.

In dieser Arbeit untersuchten wir die Sicherheit neuartiger Behandlungen von RA und PsA und betrachteten dabei die Population der RA- und PsA-Patient:innen in der Schweiz unter Berücksichtigung des BMI und des Geschlechts, wobei wir Real-Word-Daten (RWD) verwendeten. Des Weiteren wurden spezifische Herausforderungen diskutiert, die dieser Studientyp mit sich bringt, und es wurden Vorschläge erarbeitet, wie man diese lösen könnte.

Als Reaktion auf neu auftretende Sicherheitsbedenken im Zusammenhang mit dem Antirheumatikum Tofacitinib untersuchten wir zunächst die Sicherheit von Tofacitinib und Baricitinib und stützten uns dabei auf Daten der Weltgesundheitsorganisation (WHO). Die Studie bestätigte die Sicherheitsbedenken und untermauerte die Empfehlung für einen vorsichtigen Einsatz von Tofacitinib bei Patient:innen mit hohem Thromboembolierisiko (**Kapitel 3**).[26]

Anschliessend betrachteten wir Patient:innen mit RA und PsA in der Swiss Clinical Quality Management in Rheumatic Diseases (SCQM), wobei wir besonderes Augenmerk auf den BMI legten.

Wir stellten fest, dass RA- und PsA- Patient:innen mit Adipositas eine höhere Krankheitsaktivität aufwiesen als normalgewichtige Patient:innen, wenn sie ihr erstes biologisches oder zielgerichtetes synthetisches krankheitsmodifizierendes Antirheumatikum (b/tsDMARD) erhielten (**Kapitel 4**).[27] Darüber hinaus war Adipositas bei PsA- Patient:innen ein Faktor, der mit einer um die Hälfte geringeren Wahrscheinlichkeit für einen erfolgreichen Verlauf verbunden ist, verglichen mit normalgewichtigen Patient:innen (**Kapitel 5**).[28] Auch für RA untersuchten wir die Wirksamkeit verschiedener Behandlungen bei übergewichtigen und adipösen Patient:innen. Zunächst konnten wir keine Unterschiede zwischen den Medikamenten feststellen, doch als wir nach Geschlecht stratifizierten, entdeckten wir bei übergewichtigen Patientinnen einen positiven Effekt von Infliximab gegenüber Adalimumab, bei Patientinnen mit Adipositas konnten wir jedoch das Gegenteil feststellen. Dies war ein wichtiger Befund bei weiblichen Patienten, der bei der Untersuchung der Gesamtkohorte unentdeckt geblieben wäre (**Kapitel 6**).[29] Ebenso konnten wir in einer weiteren Studie eine potenzielle Ungleichheit zwischen männlichen und weiblichen RA-Patienten in Bezug auf die Entscheidung, eine Behandlung mit b/tsDMARD zu beginnen, feststellen. Dies könnte erklären, warum bei männlichen Patienten die Wahrscheinlichkeit der Remission höher ist **(Kapitel 7**).[30] Diese Ergebnisse unterstreichen den Bedarf an geschlechtsspezifischen Analysen und Gender-Studien in der Gesundheitsforschung.

Da es keine offiziellen Leitlinien zur Messung der verschiedenen Arten von Behandlungserfolg gibt, veröffentlichten wir unsere Sichtweise zur Unterscheidung von primärem und sekundärem Nicht-Ansprechen auf die Therapie und forderten die Aufsichtsbehörden und die für die Erstellung von Behandlungsleitlinien zuständigen Fachgesellschaften auf, diesem Thema Priorität einzuräumen (**Kapitel 8**).[31] Wir glauben, dass dieses Thema eine neue Ära in der RA-Forschung und im klinischen Management einleiten wird.

Insgesamt erweitert diese Arbeit die Wissensbasis über RA und PsA im Zusammenhang mit RWD. Sie trägt zum Wissen über die Sicherheit und Wirksamkeit von Behandlungen bei, weist auf mögliche geschlechtsspezifische Verzerrungen bei der Entscheidungsfindung hin und eröffnet die Diskussion über die Notwendigkeit operativer Definitionen von primärem und sekundärem Nicht-Ansprechen auf die Therapie für die weitere Forschung. Sie liefert Anhaltspunkte dafür, dass sowohl bei der Therapie als auch bei der Forschung das Geschlecht, der BMI und die klinische Vorgeschichte (z. B. bereits bestehende Risiken) der Patient:innen berücksichtigt werden sollten. Somit sind diese Ergebnisse ein Schritt nach vorn bei der Entwicklung der Präzisionsmedizin bzw. personalisierten Medizin in der rheumatologischen Versorgung, da sie klinische Entscheidungen und künftige Forschungsprojekte beeinflussen können.

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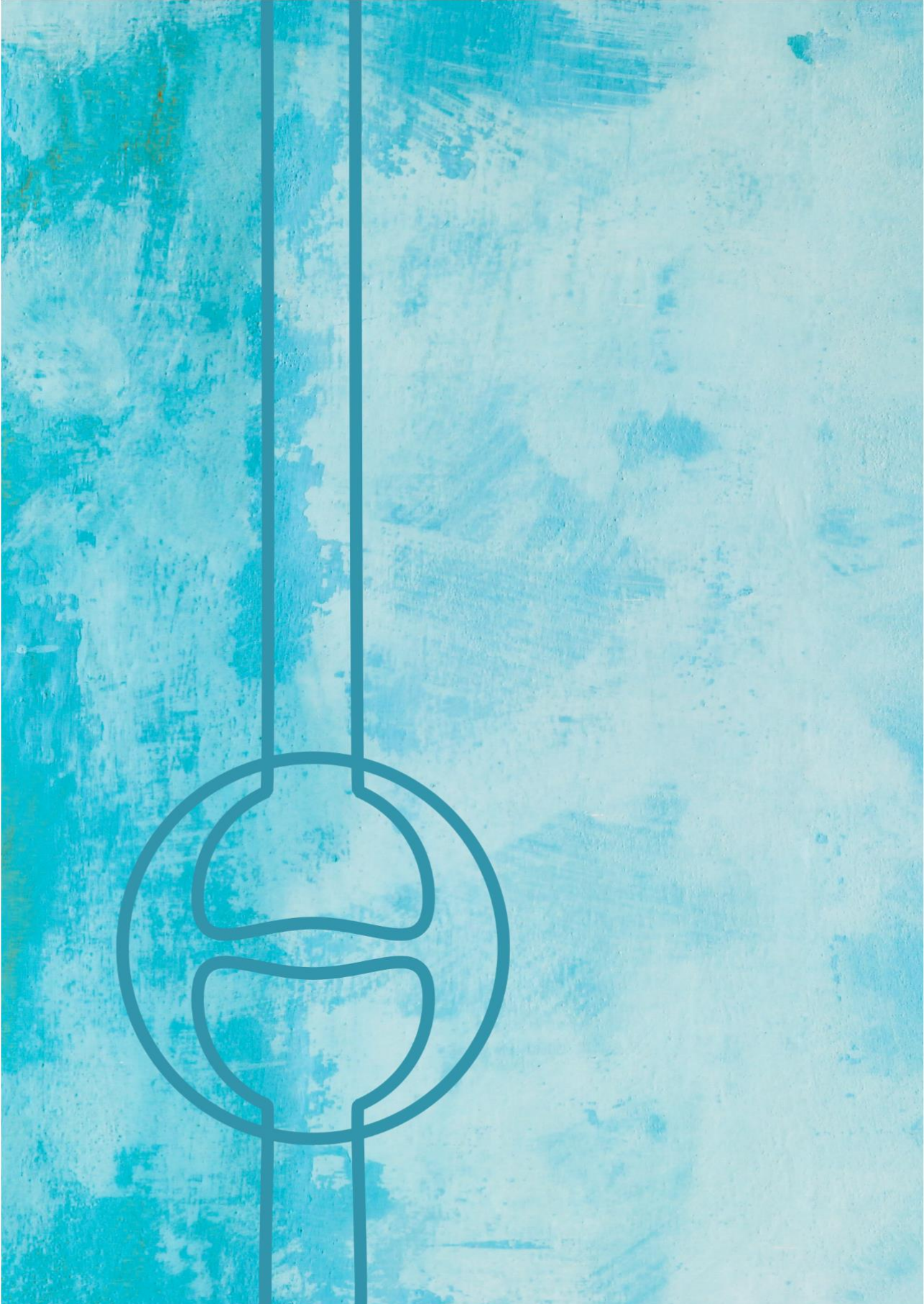

Chapter 1
Introduction

Introduction

Pharmacoepidemiology and real-world evidence

With the emerging and growth of digital technologies, an enormous amount of data is constantly being generated across the globe. This data-intensive landscape is embedded in many different fields, and it has gained a place in the healthcare practice, research, and development. Particularly, the existence of large clinical databases plays a crucial role in the development of observational studies in pharmacoepidemiology.

Pharmacoepidemiology is the scientific discipline that studies the use and effects of drugs in populations. It is a relatively new field, which emerged in the 1980s as a response to a public health need to monitor medicinal products.[1] However, it builds on top of two core well-funded sciences: pharmacology, the study of the action and effects of drugs, and epidemiology, the study of health-related questions at the population level. Additionally, pharmacoepidemiology also embraces and comprises medicine, statistics, and social sciences.[2] While pharmacoepidemiology comprises a wide and diverse set of study designs, observational studies in real-word data (RWD) may be considered its cornerstone. RWD is health-related data collected during routine clinical practice, to generate findings known as real-world evidence (RWE).[3]

Pharmacoepidemiologic studies in RWD are important to complement the evidence generated during pre-clinical and clinical phases of drug development. First, despite the high scientific relevance of randomised clinical trials (RCTs), these are conducted in a restricted patient profile, with limited exposure time, and under ideal conditions (e.g., regular visits, monitoring). Thus, even after optimal clinical development, it remains of interest to investigate the safety and effectiveness of drugs in a real-world setting. This means, for example, in a heterogeneous population and diverse patient profile, with comorbidities and/or comedication, and after longer exposures. Second, pharmacoepidemiologic studies in RWD can open the scope of drug research and provide settings and methods to explore the use and effects of drugs with goals and perspectives different than those from traditional drug development. For example, pharmacoepidemiologic studies can identify risk and prognostic factors, describe and investigate subpopulations of interest, depict drug utilization patterns (e.g., prescription patterns), address comparative effectiveness of treatments, evaluate interventions, etc. Ultimately, pharmacoepidemiologic studies can aid towards precision medicine,[4]

provide new insights on medicines and healthcare implementations, and therefore have an impact on recommendations (e.g., prescription decision-making) and policy or regulations.[3] In summary, RWE plays a role in the development, authorization, and supervision of drugs,[5] and the rapid growth of health-related data can aid to "answer questions previously thought infeasible."[6]

Real-world data sources

RWD may be collected for purposes other than research, for example, for administrative purposes, like the electronic healthcare records (EHRs; e.g., primary care data, hospital records) or insurance claims data. Alternatively, registries and pharmacovigilance databases are RWD sources collected primarily for research or drug monitoring, but not for one particular project. Thus, in RWE studies, the secondary use of data is common practice, and the data is commonly already collected at the moment when the research question is shaped and the study protocol is developed. Access to RWD requires approval from an ethics committee and the data holder, and usually an economic fee. Importantly, research on health records should be conducted in a purpose manner,[7] and following the principles of respect to persons, privacy, data fairness, and accountability.[8]

Despite the existence of several RWD sources, there is not completely perfect source and, therefore, knowing their strengths and limitations is key to develop appropriate RWE. The description of commonly used RWD sources is provided in **Figure 1.1**. In brief, EHRs are repositories of longitudinal medical data collected at primary care or at the hospital, often including diagnoses, prescriptions, and only sometimes laboratory or test results.[9] Claims data contain every healthcare encounter that is billable and reimbursed through a healthcare coverage or insurance company, and it includes diagnosis for medical consultations, dispensed pharmaceuticals, and tests and interventions (without the results).[9] Unlike EHRs or claims data, registries are longitudinal cohorts with the key inclusion criterion driven by diseases (disease registry) or medication (drug registry). Registries include clinical endpoints, such as detailed test results, information that is commonly missing in both primary care and claims data. Thus, registries are prospective cohorts that enable longitudinal follow-up on disease progression and treatment for the particular disease or medication of interest. An example of a rheumatology registry is the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM). Lastly, pharmacovigilance databases (e.g., VigiBase) are collections of individual safety reports (ICSRs), which are most commonly used for early drug safety monitoring.

For the purpose of this dissertation, we elaborate on two databases: the pharmacovigilance database VigiBase and the SCQM registry.

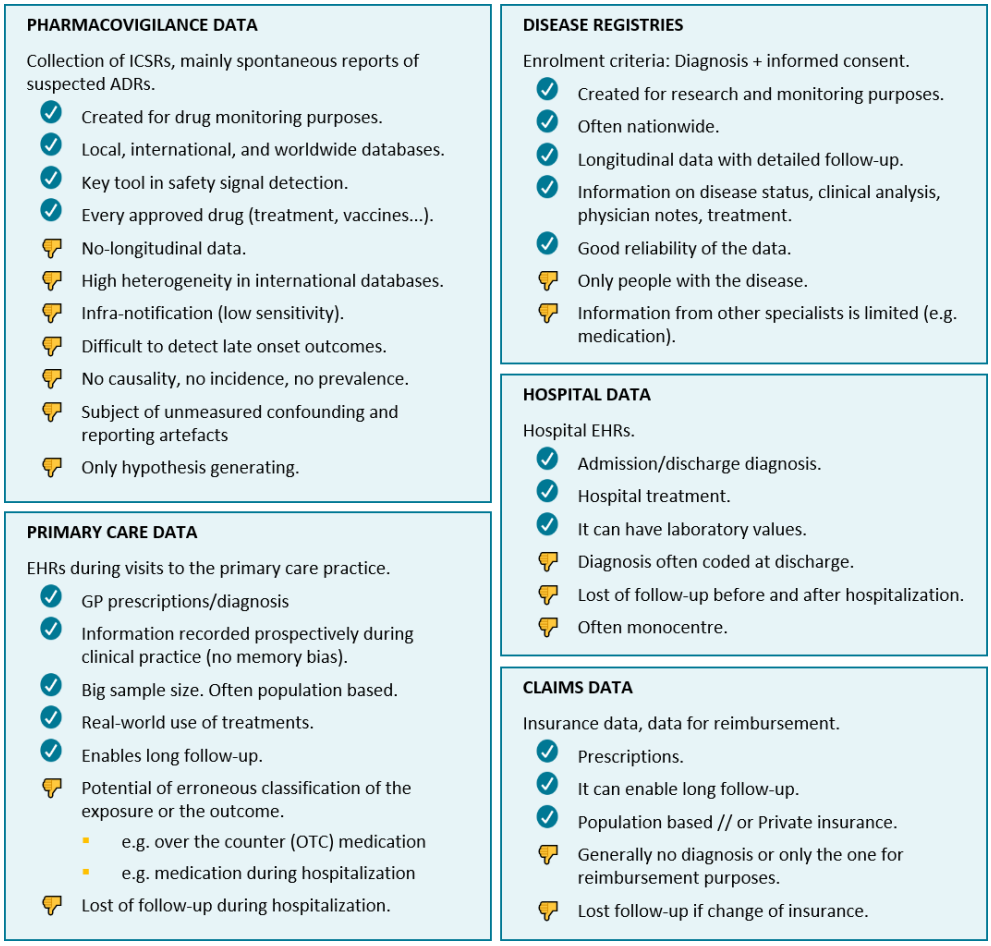

Figure 1.1 Real-world data (RWD) sources. Abbreviations: ICSRs individual case safety reports; ADRs adverse drug reactions; EHRs electronic healthcare records; GP general practitioner.

VigiBase, the WHO pharmacovigilance database

VigiBase,[10] the World Health Organization (WHO) global database of ICSRs, is the core pillar of the international drug surveillance or pharmacovigilance.

Pharmacovigilance is defined as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medicine-related problem."[11] In plain words, pharmacovigilance is a set of actions to monitor the safety of drugs, commonly applied to phase IV or post-marketing authorization phases of drug development.

VigiBase is the result from the collaboration between the WHO Program for International Drug Monitoring (PIDM) and the Uppsala Monitoring Centre (UMC), and it is the largest database of its kind.[10] VigiBase collects >30 million ICSRs from >120 countries.[12] These mainly include spontaneous reports of suspected adverse drug reactions (ADRs), although there is also a small percentage of reports from clinical trials and intense monitoring programs.[13] Most relevant information collected in ICSRs includes the patient's sex and age, the adverse event, and information on the suspected drug (name, dose, regimen), the suspected interacting drug, and any other concomitant drug (**Figure 1.2**).

Pharmacovigilance databases, like VigiBase, are particularly relevant for identification of new safety signals in a timely manner. *"A safety signal is information on a new or known adverse event that may be caused by a medicine and requires further investigation".*[14] It is important to highlight the "may be", since a safety signal indicates a potential risk that needs investigation, but it does not imply causality.

The analysis of ICSRs is often restricted to comparison of reporting rates, particularly, identifying disproportionate reporting. This consists on identifying when the reporting of a specific event for a specific drug is higher than expected, based on the reporting rate of that event for all other drugs.[15] Commonly used disproportionate statistical methods include the Reporting Odds Ratio (ROR) and the Information Component (IC).[16,17] Importantly, disproportionate reporting should not be mistaken for risk estimate.[13] When excessive reporting of an event for an specific drug is identified, if there is sufficient biological/scientific rational to support it, this may trigger a safety signal, which does not imply that there is a risk, but a potential risk that requires further investigation. Thus, it is important to highlight that they are valid for hypothesis generating, but not for hypothesis testing.[13]

Strengths of these pharmacovigilance databases are that every approved drug can be included, and they are the cornerstone tool in safety signal detection. However, intrinsic limitations of these databases include reporting bias, possible duplicated reports, confounding, and heterogeneity across time and regions.[13] As an example of reporting bias, the reporting of suspected ADRs may follow

different motivations, thus, it is not necessarily the same for new and old drugs, or known are unknown adverse events.

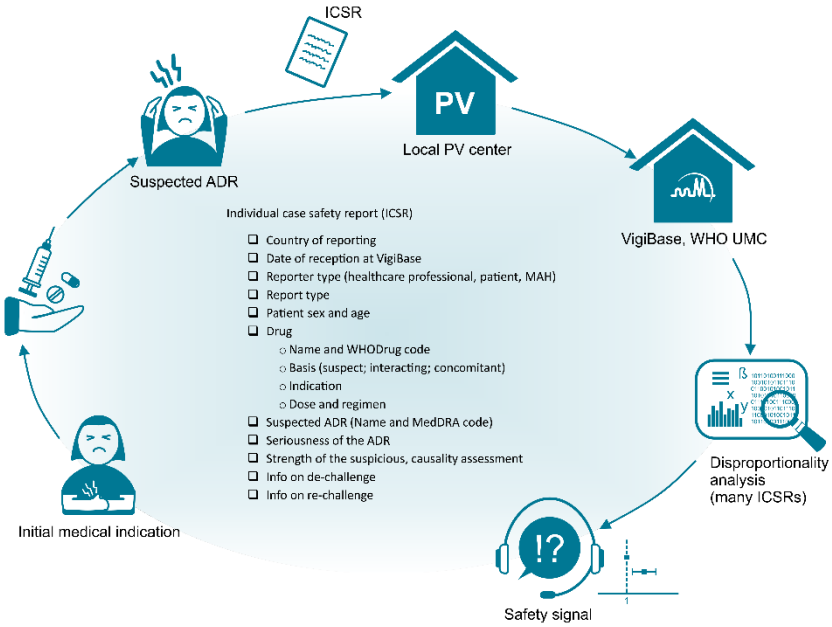

Figure 1.2 Flow diagram depicting the process from a suspected adverse drug reaction (ADR), to a pharmacovigilance safety signal. Starting at the bottom left, a patient with a medical need takes a medicine to address it, and subsequently suffers a suspected ADR. That information is submitted as an anonymised individual case safety report (ICSR) to the local pharmacovigilance (PV) centre, which in turn communicates it to VigiBase, the World Health Organization (WHO) global database of ICSR, at the Uppsala Monitoring Center (UMC). Subsequent disproportionality analysis on VigiBase, containing this and many other ICSRs, can highlight a potential safety signal if the reporting for this type of event is more frequent for the study drug compared to the rest of the drugs in the database, and there is a biological rational to support it. The safety signal is communicated and the development of other studies to address is suggested.

Swiss Clinical Quality Management (SCQM) registry

The Swiss Clinical Quality Management Foundation, in collaboration with the Swiss Rheumatology Association (SGR, '*Schweizerischen Gesellschaft für Rheumatologie*'), operates a research platform to facilitate long-term studies in inflammatory rheumatic diseases, named SCQM.

The SCQM is a national longitudinal population-based cohort of patients with rheumatic diseases in Switzerland, including rheumatoid arthritis (RA) and psoriatic arthritis (PsA), among others.[18] It was initiated in 1997 with the aim of improving inflammatory rheumatic diseases, as well as to aid rheumatologist and patients in the quality management of the disease.[18] Patients are invited to join by their rheumatologists, and participation is voluntary from both patients and clinicians. Following written informed consent, the patients are enrolled in SCQM, and they can withdraw their consent at any time.

The collected data is generated during patient consultations, where the physician performs standardised clinical assessments and the patient completes standardised questionnaires on disease activity, general health and socio-economic variables. Rheumatologists and patients are encouraged to perform annual consultations and are advised to perform intermediate controls at important changes in care (e.g., changes in disease activity or medication). SCQM participants, both rheumatologists and patients, benefit from the SCQM feedback in the format of a structured overview of the disease course with comprehensive graphs. Additionally, SCQM generates an anonymised database for research purposes, in accordance with the Swiss Data Protection.[19] A schematic representation of this process is illustrated in **Figure 1.3**.

For the purpose of this dissertation, we accessed the SCQM data, particularly the sections for demographics, medication, clinical visits, health associated conditions, and comorbidities. A detailed description of relevant variables is provided in **Chapter 4.**[20]

Strengths of this type of data include the possibility to address clinical endpoints, patient-reported outcomes (PROs), and laboratory results. Therefore, it is possible to investigate disease management and treatment response with clinically relevant outcomes, and without the need to use proxies such as treatment duration. Limitations include missingness, memory bias for PROs (e.g., comorbidities), and lack of direct information from clinical encounters besides the rheumatology visits.

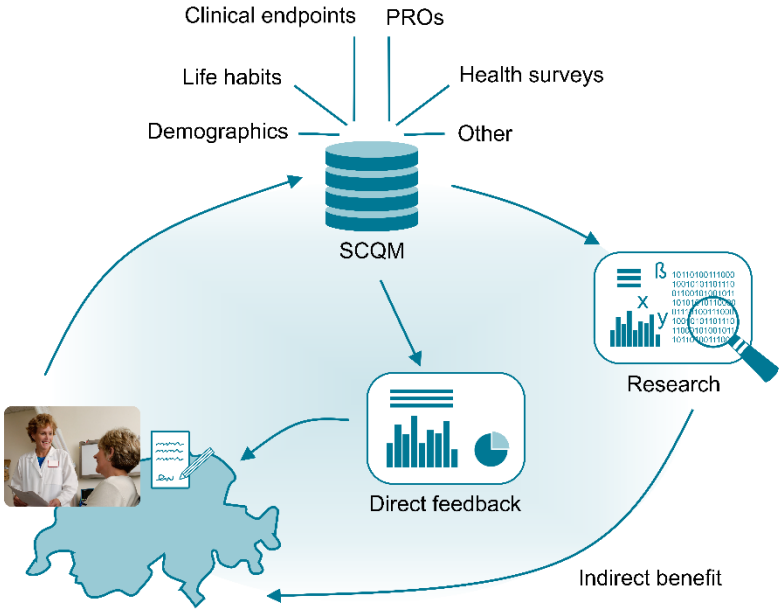

Figure 1.3 Example of flow diagram depicting a patient agreeing with participating in the Swiss Clinical Quality Management (SCQM) registry. Following written informed consent, the patient's data is, from them on, regularly recorded in SCQM. This generates direct feedback for both rheumatologist and patient, and provides anonymised data for research purposes upon approval by ethics committee and SCQM. Ultimately, participants in SCQM also benefit from the research findings. Abbreviations: PROs patient-reported outcomes. The photo from clinical practice was adapted from a public domain photo by National Cancer Institute on Unsplash.

Rheumatoid arthritis (RA)

Epidemiology and clinical picture of RA

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, primarily characterised by inflammation and pain in the joints of hands and feet.[21] RA affects 0.5-1% of the worldwide population[22–24] and 0.45-0.66% in Europe.[24] The RA prevalence increases with age,[25] and it affects women three times more often than men.[26]

The clinical picture of RA encompasses tender and swollen synovial joints, including small joints (finger and toes) and large joints (shoulder, elbow, knee, ankle),[21] and it may result in pain, stiffness, and impaired function of the joint.[27] Patients may also present high fatigue, weight-loss, and slight fever.[27] Ultimately, if not properly treated, RA can result in irreversible joint damage and disability,[28,29] and it can progress to extra-articular manifestations, like rheumatic vasculitis.[21]

Common comorbidities in patients with RA are depression, respiratory diseases, cardiovascular events, malignancies,[30] fatigue, hypertension, osteoporosis, osteoarthritis, and hyperlipidaemia.[31,32] Additionally, obesity has been associated with higher risk of developing RA[33] and worse disease progression and/or treatment response.[34–38]

Through physical impairment and pain, RA can affect the patients' social activities and quality of life. For example, it was estimated that 40% of persons with RA in Europe stopped working due to this rheumatic disease.[39]

Aetiology and pathogenesis of RA

While the aetiology of RA is not fully understood,[40] RA is considered a multifactorial disease, where both genetic and environmental factors play a role.[27] For example, specific variants of the class II human leukocyte antigen (HLA) have been associated to the development of RA.[28] And among environmental factors, smoking, silica exposure, infections, abnormal microbiota were associated to higher risk of developing RA,[28,29,40] as so did obesity.[33]

Joint involvement in RA is characterized by inflammation of the synovial membrane.[27] In healthy synovial joints, the bones are protected by articular cartilage, and the space between the bones (synovial cavity) is filled with the synovial fluid, which is contained by the synovial membrane and the articular capsule (**Figure 1.4**). In RA, there is abnormal elevated cell infiltration resulting in swollen synovial fluid.[27,28] This is believed to be preceded by the development of auto-immunity, or generation of antibodies (Abs) against modified self-proteins, which may occur for a long time before clinical symptoms.[28] Thus, there is appearance of autoantigens (Auto-Ag) and auto-Abs against them, such as

the anticitrullinated peptide antibodies (ACPAs, e.g., anti-cyclic citrullinated peptide, anti-CCP) or the rheumatoid factor (RF).[21]

The process from autoimmunity to synovial inflammation and subsequent bone damage was recently described in detail by Aletaha and Smolen.[21] In brief, the synovial inflammation in RA is driven by activated T cells, B cells, macrophages, and neutrophils, as well as auto-Ab with auto-Ag complexes, osteoclasts, reactive oxygen species (ROS), and inflammatory signalling like tumour necrosis factor alfa (TNFα, or TNF), interferon gamma (IFNγ), interleukin 6 (IL-6), and IL-1.[21,27,41]

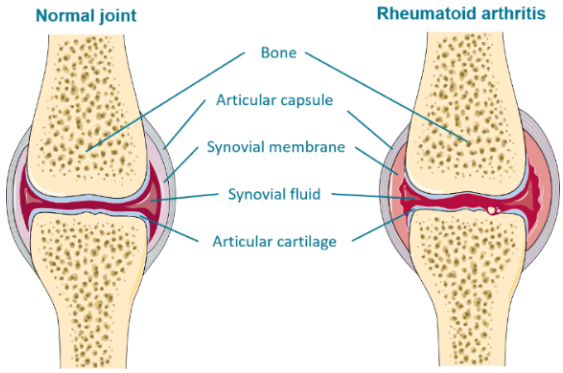

Figure 1.4 Synovial joint. Healthy joint on the left, and example of rheumatoid arthritis (RA) joint on the right. The figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.

Disease activity assessment in RA

Routine clinical management includes assessment of tender and swollen joint counts (TJC, SJC) counting a total of 28 joints as illustrated in **Figure 1.5**, as well as measuring levels of the acute phase reactants (inflammatory markers) erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), imaging, and collecting physician and patient assessments on the disease and its consequences.

RA disease activity is measured using composite disease activity scores, which enable interpretation based on thresholds. Thus, patients can be classified based on their disease activity as in remission, low or mild disease activity, moderate disease activity, and high disease activity. While there are numerous composite scores,[42] the most commonly used scores in Switzerland are the 28-joint Disease Activity Score (DAS28), and the Rheumatoid Arthritis Disease Activity Index 5 (RADAI-5).[43,44] Additionally, health-related quality of life surveys serve to assess the impact of RA on the patient's life. An example of this would be the Health Assessment Questionnaire (HAQ).[45]

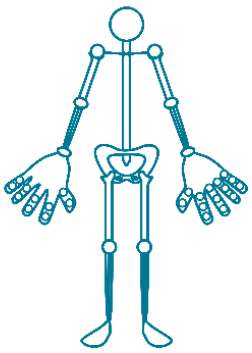

Figure 1.5 Illustration of the 28 joints assessed in patients with rheumatoid arthritis (RA) to assess the tender and swollen joint counts 28 (TJC28, SJC28).

Therapeutic approach for RA

Treatment of RA aims to minimize inflammation, prevent structural articular damage, reduce pain, maintain or improve the joint function, and improve the quality of life of the patients.

RA pharmacological management is driven by the treat-to-target (T2T) approach, which aims to achieve clinical remission, defined as "*the absence of signs and symptoms of significant inflammatory disease activity*", or alternatively, to achieve a minimum of low disease activity (LDA).[46] The T2T approach requires regular monitoring and change of treatment if the clinical aim is not achieved, or in the case of side effects.

After an RA diagnosis, patients are most commonly treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), among which methotrexate is the drug of choice.[47,48] Other csDMARDs used in RA are leflunomide, sulfasalazine, and hydroxychloroquine. Additionally, short-term glucocorticoids may be given for high disease activity. Following unsuccessful or no longer successful treatment with csDMARD, a switch of csDMARD or escalation to a biologic or targeted synthetic disease-modifying anti-rheumatic drug (b/tsDMARD) is suggested based on absence or presence of prognostic factors, respectively. Prognostic factors include high disease activity, high levels of acute phase reactants, high number of swollen joints, presence of auto-Abs, early erosions, and failure of ≥2 csDMARDs.[47] There are several b/tsDMARDs currently in the clinic (**Table 1.1**), prescribed as monotherapy or in combination with csDMARD. The TNF inhibitors were the first marketed, and they were the recommended preferable first biologic option until 2013,[49,50] when the European Alliance of Associations for Rheumatology (EULAR) also added the biologics abatacept, tocilizumab, and, under specific circumstances, rituximab, as suggested first options.[50] Current EULAR guidelines (2019) state similar efficacy between biologics and tsDMARDs, and therefore no longer

defines preferable options among the first-line b/tsDMARD.[47] Instead, EULAR recommends that the selection of first b/tsDMARD should be based on patient-related factors (e.g., comorbidities), patient's preference, and cost.[47] Thus, identifying risks associated with these medications is of interest to guide treatment decision making.

After starting a b/tsDMARD, it is expected that the patient will achieve improvement at 3-months and the clinical target at 6-months, otherwise, switching the b/tsDMARD is recommended.[47] At this stage, it may be that the type of response to the first b/tsDMARD could aid the decision on second treatment, but this requires further investigation.

Finally, pharmacologic treatment should be complemented with non-pharmacologic interventions,[51,52] such as exercise, physical and occupational therapy.[51]

Table 1.1 Biologics and targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) used for treatment of rheumatoid arthritis (RA) or psoriatic arthritis (PsA) in Switzerland (CH; Swissmedic) and/or the European Union (EU; European Medicines Agency, EMA) as per July 2019.

Active agent	Mode of action	1st MA CH	1st MA EMA	Indication RA	Indication PsA	Adm. route
Biologics						
Infliximab	TNF inhibitor	12.1999	08.1999	x	x	i.v. inf. (mg/kg)
Etanercept	TNF inhibitor	02.2000	02.2000	x	x	s.c.
Adalimumab	TNF inhibitor	04.2003	09.2003	x	x	s.c.
Certolizumab pegol	TNF inhibitor	06.2010	10.2009	x	x	s.c.
Golimumab	TNF inhibitor	09.2010	10.2009	x	x	s.c.
Rituximab	Anti-CD20	11.1997	06.1998	x	-	i.v. inf.
Abatacept	Anti-CD80 -CD86	08.2017	05.2007	x	x*	i.v. inf./ s.c.
Anakinra	Anti-IL1 receptor	-	03.2002	x*	-	s.c.
Tocilizumab	Anti-IL6 receptor	12.2008	01.2009	x	-	i.v. inf./ s.c.
Sarilumab	Anti-IL6 receptor	04.2018	06.2017	x	-	s.c.
Secukinumab	Anti-IL17A	02.2015	01.2015	-	x	s.c.
Ixekizumab	Anti-IL17A	12.2016	04.2016	-	x	s.c.
Ustekinumab	Anti-IL12/23	10.2010	01.2009	-	x	i.v. inf.
tsDMARDs						
Apremilast	PDE4 inhibitor	07.2015	01.2015	-	x	oral
Baricitinib	JAK inhibitor	06.2017	02.2017	x	-	oral
Tofacitinib	JAK inhibitor	07.2013	03.2017	x	x	oral

**Approved by the European Medicines agency (EMA), but not by Swissmedic.*

Abbreviations: MA Marketing authorization; CH Switzerland; EMA European Medicines agency; RA Rheumatoid arthritis; PsA Psoriatic arthritis; i.v. inf. intravenous infusion; s.c. subcutaneous; TNF tumour necrosis factor alpha; IL Interleukin; PDE4 Phosphodiesterase 4; JAK Janus Kinase.

Psoriatic arthritis (PsA)

Epidemiology and clinical picture of PsA

Psoriatic arthritis (PsA) is an immune-mediated inflammatory disease with a heterogeneous clinical picture.[53,54] PsA is characterized by musculoskeletal and dermatological manifestations,[55] and it includes five key domains: peripheral arthritis, axial disease, enthesitis, skin and nail psoriasis, and dactylitis.[56]

The prevalence of PsA is estimated to be 0.05% to 0.21% in the European population, and 0.06% to 0.25% in the United States (US).[57] Among persons with psoriasis, PsA is more frequent than in the general population, with a prevalence from 6% to 41%, increased incidence with longer duration of the psoriasis disease,[57] and increased risk in patients with overweight or obesity[58] However, PsA can be developed without prior presence of skin manifestations.[59] Female:male ratio in PsA is close to 1:1.[60]

The presentation of the different domains of the disease varies across patients, reflecting a very multifaceted disease.[61] Peripheral arthritis is present in the majority of people with PsA.[62] Axial disease, also known as psoriatic spondylitis, is characterized by inflammation in the spine, and its prevalence was reported 5-28% in early PsA, and 25-70% in long PsA duration.[62] Enthesitis, the inflammation of the entheses (sites where tendons and ligaments insert to the bone surface)[63] occurs in 30-50% of the PsA patients.[57,64] Psoriasis is present in the majority of PsA patients (80%), predominantly as plaque psoriasis (psoriasis vulgaris) and nail psoriasis.[64] Nail manifestations, present in 41-93% PsA patients, include pitting, onycholysis, oil spots, and splinter haemorrhages.[57,65] Dactylitis, also known as “sausage digit”, consist on uniform swelling of entire digit of the hands and/or feet, resulting in inflammation of joints, tendons, and soft tissue,[66] and it is present in 40-48% of the PsA patients.[57,66] Additionally, patients may also present PsA related-diseases (e.g., uveitis and inflammatory bowel disease), or other comorbidities.[55] Common comorbidities among patients with PsA include obesity, metabolic syndrome, and cardiovascular disease.[67,68]

The PsA disease affects the functional capacity and psychosocial health-related quality of life of patients, and it is a personal and social economic burden.[69]

Aetiology and pathogenesis of PsA

Both genetic and environmental factors are involved in the aetiology of PsA. For example, specific genetic variants of the class I HLA were associated to PsA,[70] as well as other non-HLA polymorphisms, like genes involved in IL-17 signalling.[54] Environmental factors described in PsA include bone or joint injury (mechano-inflammation),[70] obesity, infection,[54] and imbalance microbiome.[70]

A proposed description of pathologic pathways in different PsA phenotypes was described by FitzGerald et al.[54] In brief, key inflammatory cytokines in PsA are IL-23, IL-17, and TNF, and the activity of T cells has been described in different domains of the disease.[54] Additionally, high vascularity and neutrophil infiltration were also described in the synovial tissue in PsA patients.[71]

Disease activity assessment in PsA

Routine clinical management of PsA includes assessment of the musculoskeletal manifestations, for example, by addressing the tender and swollen joints counting a total of 68 (TJC28) and 66 (SJC66) joints, respectively (**Figure 1.6**). Additionally, overall inflammation (e.g., acute phase reactants ESR and CRP), and dermatological manifestations (e.g., skin extension affected by psoriasis) are also addressed.

To address the arthritis domain of PsA, disease activity measures originally developed for RA, like DAS28, were traditionally used.[72] The first composite measure developed and validated for PsA was the Disease Activity for Psoriatic Arthritis (DAPSA), which measures the arthritis activity including tender and swollen joints, patient-reported outcomes (PROs), and acute phase reactant.[73–75] While there are other composite scores used in PsA, it is likely that the most complete and meaningful one is the Minimal Disease Activity (MDA). The MDA is achieved when at least five of the following seven criteria are met: TJC ≤1; SJC ≤1; Psoriasis Area and Severity Index (PASI) ≤1 or body surface area (BSA) ≤3; patient's pain in a Visual Analogue Scale (VAS, 0 to 100) ≤15; patient global assessment (VAS, 0 to 100) ≤20; HAQ ≤0.5; tender entheseal points ≤1.[76] Finally, health-related surveys like the HAQ[45] may be used to assess the health-related quality of life in people with PsA.

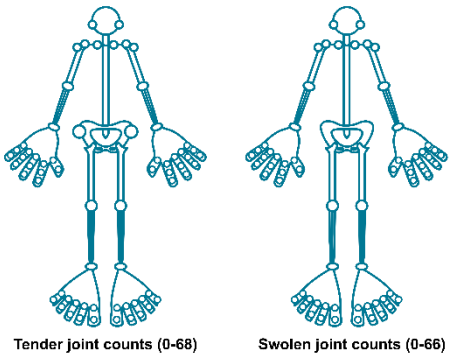

Figure 1.6 Illustration of the 68 joints (left) and 66 joints (right) assessed in patients with psoriatic arthritis (PsA) to assess the tender and swollen joint counts, respectively (TJC68, SJC66).

Therapeutic approach for PsA

Management of PsA aims to eliminate inflammation and optimise the patient's quality of life.[77] Therapeutic approaches should consider every domain of the disease, and target remission or, alternatively, LDA.[77]

The EULAR recommendations for the pharmacologic management of PsA[77] establishes the following: Non-steroidal anti-inflammatory drugs (NSAIDs) and local or systemic glucocorticoids may be used. However, patients with polyarthritis should start promptly with csDMARD treatment, and this should be considered in patients with mono- or oligoarthritis with poor prognostic factors (e.g., structural damage, high level of acute phase reactants, dactylitis or nail involvement). Following inadequate response to csDMARDs in these patients, biologics should be initiated. Likewise, in the presence of unequivocal enthesitis and insufficient response to NSAIDs, biologics should be considered. Among biologics, it is preferable to start with TNF inhibitors, unless there is skin involvement, in which case the IL-17 or IL-12/23 inhibitors are the preferable option. Following failure with csDMARD and biologic treatment, or when biologics are not appropriate, the tsDMARDs Janus Kinase (JAK) inhibitors are recommended. Finally, in patients with mild disease and inadequate response to csDMARD, for whom biologics or JAK inhibitors are not appropriate, the tsDMARD phosphodiesterase 4 (PDE4) inhibitor may be considered.[77] A list of b/tsDMARDs used in PsA is provided in **Table 1.1**.

Ultimately, PsA management requires a combination of both pharmacologic and non-pharmacologic interventions,[77] and due to the multifaceted aspect of the disease, its management requires a multidisciplinary care[55] and collaboration between healthcare professionals.[78]

Challenges in RA and PsA addressed in this thesis

Safety of new medications

In the past decades, the presence of b/tsDMARDs have revolutionized the pharmacologic management of rheumatic diseases. Compared to biologics, the tsDMARDs JAK inhibitors provide an alternative mode of action and route of administration for the treatment of rheumatic diseases (**Table 1.1**).

In early 2019, preliminary findings from a post-marketing safety trial on tofacitinib (study A3921133) suggested potential safety concerns for blood clots in the lungs and death in RA patients older than 50 years old, with pre-existing cardiovascular risk factor(s), and treated with high dose of tofacitinib.[79] Likewise, thromboembolic risk had been formerly discussed for baricitinib prior approval.[80] Thus, at that point in time, we addressed the rising safety concern by performing a pharmacovigilance study using data from VigiBase, the WHO global database of ICSRs (**Chapter 3**)[81]. We investigated tofacitinib and baricitinib, the two JAK inhibitors in used at the time.

Obesity in the context of RA and PsA

Obesity, defined by the WHO as body mass index (BMI) ≥30 kg/m^2,[82] affects 17% of the European population,[83] and it represents an increasing healthcare burden.[84] Despite common definition of obesity as excessive accumulation of body fat, it is also considered a low grade systemic inflammatory condition. Thus, concerns regarding the interplay between obesity and rheumatic diseases are emerging,[34,85–89] supported by their shared inflammatory character.

In the presence obesity, the white adipose tissue (WAT) behaves as an endocrine organ and secrets unbalanced levels of adipokines (adipose tissue-derived active substances), promoting inflammatory processes.[31,34] Elevated levels of proinflammatory adipokines like leptin, resistin, and visfatin have been described in obesity, as well as reduced levels of the anti-inflammatory adipokine adiponectin.[34,90] This results in differentiation of macrophages, promotion of type 1 T helper (Th1) cells response, increased levels of TNFα, IFN-γ, IL-12, IL-6 , IL-2, and IL1ß, and increased release of ROS by neutrophils.[34] Thus, sharing inflammatory pathological pathway with inflammatory rheumatic diseases, like RA or PsA, through activated T cells, macrophages, and neutrophils, as well as inflammatory signalling including TNFα, IFN-γ, and IL-6.

Among persons with RA and PsA, obesity prevalence was reported higher than in the general population[91,92] and, importantly, obesity was associated with worse disease management in patients with RA or PsA.[35–38]

According to recent meta-analyses, obese RA patients treated with TNF inhibitors had a 60-80% lower odds of remission compared to non-obese RA patients,[36,38] however, this difference was not significant in patients treated with abatacept, tocilizumab, or rituximab.[38] While this may suggest that non-TNF biologics may be a better option for treatment of RA patients with obesity, published studies only included users of the respective drug and assessed the impact of BMI categories.[93–98] Thus, it remains of interest to address the comparative effectiveness of TNF inhibitors versus non-TNF biologics in RA patients with obesity, as well as the comparative effectiveness across TNF inhibitors.

Compared to RA, the evidence on the impact of BMI on PsA is more limited. For example, the systematic review by Singh S. et al. investigated the impact of BMI on clinical response in patients with RA, psoriasis, PsA, and other rheumatic diseases, and included a total of 20 randomised clinical trials (RCTs) and 34 observational studies, but only one RCT and eight observational studies were on PsA (including those with additional patients with psoriasis), among which many had relatively small sample size (i.e., six had a sample size ≤330).[99] Additionally, Singh S. et al. joined together the PsA and psoriasis studies,[99] which we hypothesize that it was due to too few number of studies on these diseases independently. Therefore, further research is needed to confirm prior findings.

In summary, while it is well accepted that obese RA patients may have a different response to treatment than normal weight patients, selection of the most optimal treatment for these patients is still controversial and requires deeper study. Additionally, the evidence on the effect of BMI on the clinical response in PsA patients is insufficient and further studies on the topic remain of interest. And finally, evidence of BMI on rheumatic diseases in Switzerland is lacking, for both diseases. Thus, within this dissertation, we conducted studies on RA and PsA cohorts in Switzerland, with a focus on BMI (**Chapter 4**,[20] **Chapter 5**,[100] and **Chapter 6**[101]).

Sex and gender in the context of RA

Sex chromosomes, as well as hormonal levels, play a role in the regulation of the immune system.[102] This yields differences in the immune response between males and females.[103] In brief, a more reactive or immunocompetent immune system has been described in females compared to males, which may favour clearance of infections and higher response to vaccines, but it can also play a role in the more frequent development of inflammatory and autoimmune diseases in females.[102–104] Additionally, environmental factors can as well influence the immune system.[102]

To continue with this topic, it is important to distinguish and define the terms sex and gender. Sex is defined by biological or physiological attributes (e.g., chromosomes, genes, hormonal levels), and gender is defined by socially-constructed norms and behaviours.[105] According to sex, people are generally categorized as male and female. Conversely, gender is understood to be a spectrum of

identities.[106] However, lack of gender information in RWD often limits research to a dichotomous definition of gender (i.e., men, women). Importantly, both sex and gender are determinants of health.[107]

In the context of RA, the female:male ratio of 3:1[26] could be the consequence of biologically-driven sex differences in immunity.[108] Additionally, socially-constructed norms may as well influence disease prevalence by impacting exposure to risk factors. For example, a Danish study described different frequency of men and women among workers with occupational exposure to respirable crystalline silica.[109]

Among RA patients, besides the observed sex differences in prevalence, worse disease progression in female versus male patients was suggested.[110–112] On this regard, both sex and gender may influence this observation. For example, sex-based differences in pharmacodynamics and pharmacokinetics of drugs could be relevant. The volume of distribution and/or clearance of biologics are generally higher in males compared to females,[113] and while this could suggest potential lower effectiveness in males, it could as well lead to higher safety concerns for women, depending on the therapeutic range and dose of the drugs. Additionally, socially-constructed gender norms can impact health-related aspects.[114,115] For instance, they can impact the perception and reflection of the disease,[116] the prescription of pain medication,[117–120] and the time to referral to a specialist.[121] Thus, both sex and gender could influence differential clinical outcome between men and women.

In this thesis, we investigated the likelihood of achieving clinical response in males versus females with RA in the Swiss population, and further addressed which of the measured variables could explain the observed differences between both groups. Therefore, we conducted a sex comparative analysis in RA patients, integrating sex and gender dimensions, and importantly, we complemented the findings with mediation analyses (**Chapter 7**).[122] Additionally, we conducted sex-stratified analyses in a study on RA with focus on BMI (**Chapter 6**).[101]

Lack or loss of response

Despite the great advances in treatment of RA with the development of b/tsDMARDs with diverse mode of actions, selection of optimal treatment remains a trial-and-error approach. Additionally, many patients do not respond to treatment or lose response over time.[123–127] Reasons for the initial failure of treatment may be due to the interplay between the mechanism of action of the drug and the inflammatory drivers of the disease, which can vary across patients. However, different rational may explain the loss of response after previous initial treatment success. For example, the loss of response can be explained by the development of anti-drug Abs (ADAbs).[128–131] Therefore, we can distinguish two types of non-response or treatment failure, (1) primary non-response and (2)

secondary non-response. Primary non-response is defined as lack of initial response to treatment, while secondary non-response is defined as treatment failure after prior initial response to treatment.[132,133]

While the differences between primary and secondary non-response can seem conceptually clear, there is no agreement on practical definitions on primary and secondary non-response in research, nor clinical practice. Thus, the prevalence of primary versus secondary non-response is still largely unexplored.

Developing practical definitions of primary and secondary non-response is expected to enrich the knowledge on biologic treatment of RA and aid treatment decision making. For example, it was suggested that patients presenting primary response to a specific biologic but losing effectiveness over time (secondary non-responders), may respond well to a different biologic with a similar mode of action.[132] Conversely, patients with primary failure to a specific biologic may benefit more from a second biologic with an alternative mode of action.[132]

Within this thesis, we addressed the lack of agreement on definitions of primary and secondary non-response, and we suggested approaches to implement this in observational research in RWD (**Chapter 8**).[134]

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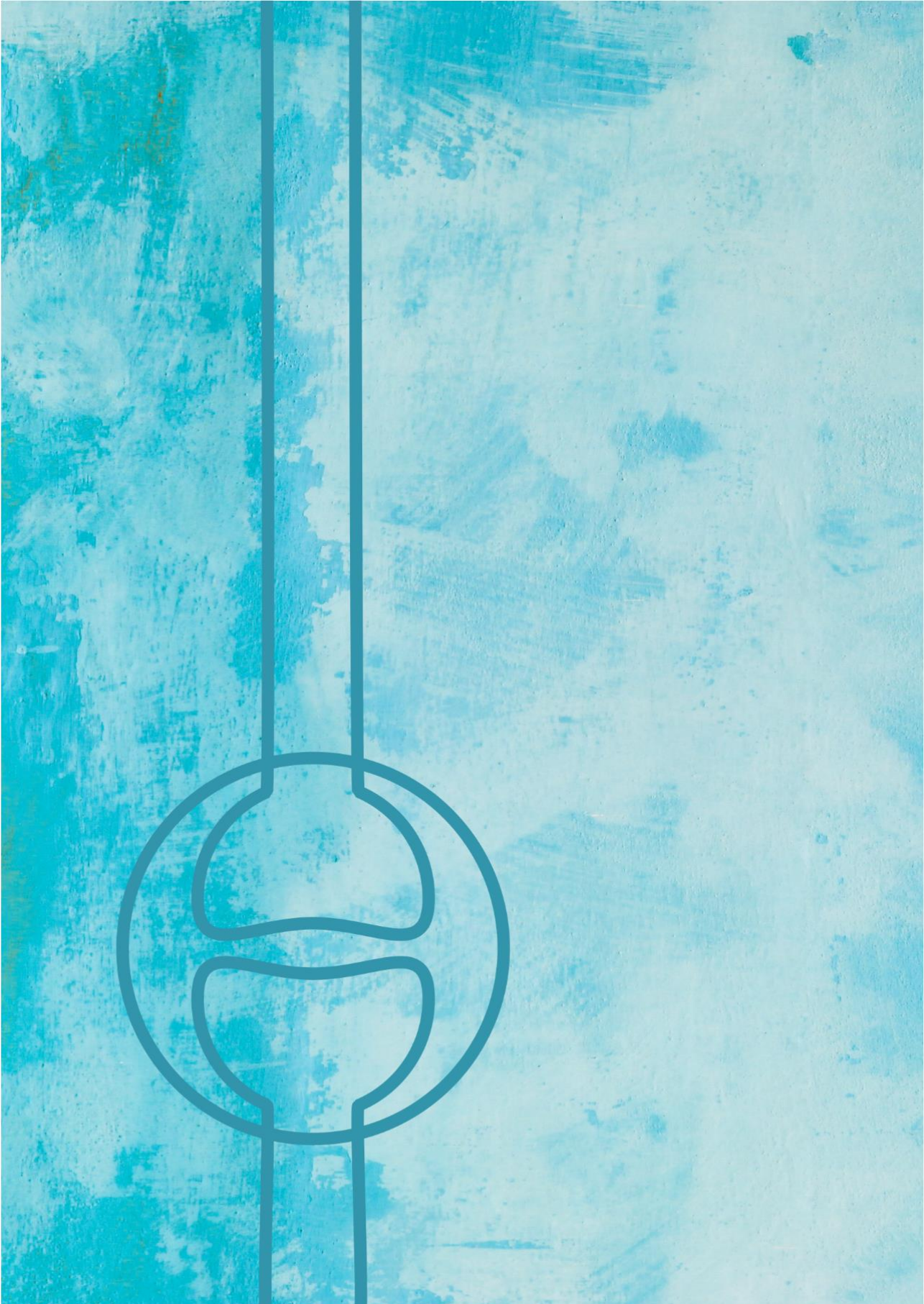

Chapter 2
Thesis goals

Thesis goals

The goal of this doctoral thesis was to address clinical and scientific gaps in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) at a population level. Particularly, this was addressed by targeting the below subgoals:

- To investigate the thromboembolic safety reporting of the Janus Kinase (JAK) inhibitors tofacitinib and baricitinib (**Chapter 3**).[1]
- To study the population of patients with RA and PsA in Switzerland, comparing those with abnormal body mass index (BMI) with those with normal weight (**Chapter 4**).[2]
- To assess the impact of BMI on the clinical response of PsA patients new-users of biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) in Switzerland. Secondarily, to assess the overlapping across several clinical outcomes (**Chapter 5**).[3]
- To assess the comparative effectiveness of biologics in RA patients stratified by their BMI category and sex, in Switzerland (**Chapter 6**).[4]
- To compare the clinical response in male versus female RA patients in Switzerland after start of their first b/tsDMARD (**Chapter 7**).[5]
- To address the methodological challenges of assessing RA primary and secondary non-response in observational studies, suggest options and open the room for discussion (**Chapter 8**).[6]

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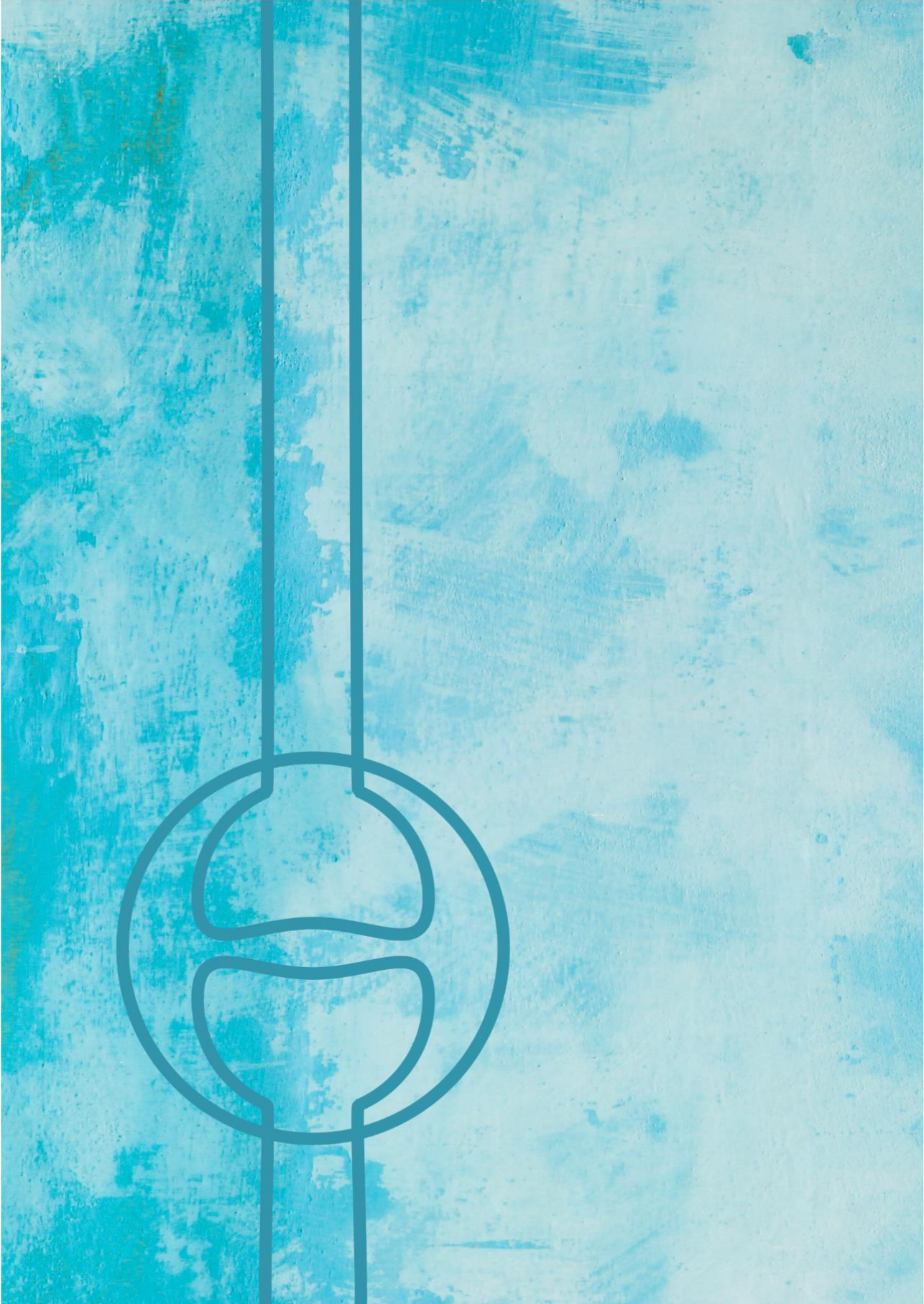

Chapter 3

Thromboembolic safety reporting of tofacitinib and baricitinib: an analysis of the WHO VigiBase

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ENRIQUETA VALLEJO-YAGÜE
STEFAN WEILER
RAPHAEL MICHEROLI
ANDREA M. BURDEN

Abstract

Introduction

The Janus kinase (JAK) inhibitors tofacitinib and baricitinib are new treatments for rheumatic diseases. Recent concerns regarding the risk of thrombosis have led to warnings by competent authorities. We therefore aimed to examine the thromboembolic safety signal for tofacitinib and baricitinib.

Methods

Individual case safety reports (ICSRs) for tofacitinib and baricitinib were retrieved from the World Health Organization global database VigiBase in April 2019. Primary outcomes were deep vein thrombosis (DVT) and pulmonary thrombosis (PT) or pulmonary embolism (PE). Patient demographics were summarised and then stratified by outcome. Disproportionality analyses were conducted by estimating the reporting odds ratios (RORs) and 95% confidence intervals (CIs) worldwide, and stratified by either Europe or the US.

Results

In both the tofacitinib (n = 40,017) and baricitinib (n = 2138) ICSRs, patients with reported DVT or PT/PE were older and had higher reporting of prothrombotic medications or antithrombotic treatments, suggesting a pre-existing thromboembolic risk/event. In Europe, tofacitinib was associated with increased reporting for DVT (ROR 2.37, 95% CI 1.23–4.56) and PT/PE (ROR 2.38. 95% CI 1.45–3.89). For baricitinib, a threefold increased reporting odds was observed for DVT (ROR 3.47, 95% CI 2.18–5.52) and PT/PE (ROR 3.44, 95% CI 2.43–4.88) in Europe. In the US, tofacitinib was only associated with an elevated ROR of PT (ROR 2.05, 95% CI 1.45–2.90) and no baricitinib ICSRs were reported.

Conclusion

This study supports the current recommendation for cautious use of tofacitinib in patients with high thromboembolic risk. Moreover, with a similar patient profile and elevated reporting for baricitinib, a potential class effect of JAK inhibitors cannot be ruled out.

Thromboembolic safety reporting of tofacitinib and baricitinib: an analysis of the WHO VigiBase

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ENRIQUETA VALLEJO-YAGÜE
STEFAN WEILER
RAPHAEL MICHEROLI
ANDREA M. BURDEN

Introduction

In the last decade, Janus kinase (JAK) inhibitors have emerged as novel targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs). These drugs work through the inhibition of one or more of the family of JAK enzymes: JAK1, JAK2, JAK3, or TYK2.[1] As of April 2019, two JAK inhibitors were approved for the management of rheumatoid arthritis (RA) - tofacitinib and baricitinib. Tofacitinib inhibits mainly JAK1 and JAK3, while baricitinib is a selective JAK1, JAK2 inhibitor.[2] Tofacitinib was approved by the US Food and Drug Administration (FDA) in 2012[3] and the European Medicines Agency (EMA) in 2017,[4] and is approved as 5 and 10 mg tablets[5,6] and extended-release tablets.[3] Conversely, baricitinib 2 and 4 mg daily was approved by the EMA in 2017,[7,8] yet only the 2 mg daily dose was approved by the FDA in 2018.[9]

The differential approval of baricitinib between the EMA and FDA was largely due to safety concerns regarding an increased risk for thromboembolic events that appeared to be dose-related. While the EMA included a warning on venous thromboembolism in the product information,[8,10] the FDA requested additional studies to assess the safety and efficacy of the two baricitinib doses (2 and 4 mg).[11] Following a pooled analysis of patients receiving baricitinib during clinical development (phase Ib through to phase III), an increased risk of thrombosis was identified and this contributed to the FDA decision to restrict approval to the 2 mg daily dose and include a black-box warning.[11-13]

In light of the safety concerns with baricitinib and to examine the potential for a class effect, the risk of thromboembolic events was assessed for other approved JAK inhibitors (tofacitinib, tofacitinib extended release, and ruxolitinib) in the FDA Adverse Event Reporting System (FAERS).[14] While this study did not identify elevated reporting rates for deep vein thrombosis (DVT) or pulmonary embolism (PE) individually, it was suggested that pulmonary thrombosis (PT) could be a potential safety issue for tofacitinib, with a reporting odds ratio (ROR) of 2.46 (95% confidence interval [CI] 1.55–3.91).[14]

A recent postmarketing ongoing safety trial (study A3921133) triggered concerns of blood clots in the lungs, and death in RA patients older than 50 years of age, with at least one cardiovascular risk factor and treated with high-dose tofacitinib.[15-17] Following these findings, both the FDA and EMA recently issued new boxed warnings for tofacitinib 10 mg twice-daily doses, citing recommendations to avoid use in patients with a high risk of thrombosis (such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilization).[15-20]

Surveillance of new drugs is a necessary practice to overcome the limited safety knowledge at the beginning of their use. Thus, as both tofacitinib and baricitinib are new medications, their safety in real-world data is limited, and both regulatory bodies and clinical researchers have raised concerns about their thromboembolic risk, we sought to investigate this further. We aimed to evaluate post-marketing surveillance data on the suspected adverse drug reactions (SADRs) collected in the World Health Organization (WHO) global database of individual case safety reports (ICSRs), VigiBase. This passive drug monitoring represents a key element in early signal detection for newly marketed drugs.[21] Thus, we sought to investigate whether the safety reporting for tofacitinib, with particular focus on thromboembolic events, supports the recent safety signal. Additionally, we aimed to similarly study the thromboembolic safety reports for baricitinib, particularly in Europe where both the 2 and 4 mg doses are available.

Methods

Data Source

Since 1968, VigiBase,[22,23] the WHO global database of ICSRs, constitutes the key asset of the WHO Programme for International Drug Monitoring. VigiBase collects, processes, and homogenizes worldwide SADRs. These SADRs are reported as ICSRs, by healthcare professionals and patients, to pharmacovigilance centers from more than 130 countries.[22] VigiBase includes mainly post-authorization unsolicited or spontaneous reports, but, to a lesser extent, it also contains reports from clinical studies or intensive monitoring programs.[22] The ICSRs in VigiBase include details on the demographics of the patient (age, sex), reporting country, and reporter description (e.g., healthcare

professional, patient). Additionally, all medications that could be potentially related to the SADR are reported at the time of the SADR, and are classified as the suspect drug, interacting drug, or comedication based on the expected causality. However, the duration or timing of each medication prior to the SADR is not accurately recorded in the databases. All reports can vary in completeness. Within the VigiBase, all potential SADRs are recorded and coded according to the Medical Dictionary for Regulatory Activities (MedDRA®) version 22.1, and all medications are coded according to WHODrug.

Study population

ICSRs including tofacitinib and baricitinib as suspect or interacting drugs were extracted on 1 April 2019 from the VigiBase database. All other ICSRs recorded in VigiBase were used as the reference group and were accessed through VigiLyze, a platform from Uppsala Monitoring Centre (UMC) enabling instant overview of the VigiBase information.

Outcomes of interest

The primary outcomes of interest were DVT and blood clots in the lungs. DVT was identified by the MedDRA® Preferred Term (MedDRA® PT) 'deep vein thrombosis'. The ICSRs mentioning blood clots in the lungs were identified by the MedDRA® PT 'pulmonary thrombosis' and 'pulmonary embolism', and these two terms were analysed as one single outcome (PT/PE). Thus, if an ICSR mentioned both events, it was counted as one. Subsequently, 'pulmonary thrombosis' (PT) and 'pulmonary embolism' (PE) were as well observed separately as two independent outcomes.

In a secondary analysis, we investigated other potential safety signals related to thromboembolism. These included the following MedDRA® PTs and High Level Terms (MedDRA® HLTs): 'peripheral embolism' (MedDRA® PT), 'retinal embolism and thrombosis' (MedDRA® HLT), 'ophthalmic artery thrombosis' (MedDRA® PT), 'ophthalmic vein thrombosis' (MedDRA® PT), 'renal embolism and thrombosis' (MedDRA® HLT), 'adrenal thrombosis' (MedDRA® PT), 'femoral artery embolism' (MedDRA® PT), 'spinal artery embolism' (MedDRA® PT), 'spinal artery thrombosis' (MedDRA® PT), 'subclavian artery embolism' (MedDRA® PT), 'subclavian vein thrombosis' (MedDRA® PT), 'subclavian artery thrombosis' (MedDRA® PT), 'coronary artery embolism' (MedDRA® PT), and 'coronary artery thrombosis' (MedDRA® PT). Additionally, to provide an overview of the safety profile of tofacitinib and baricitinib, the SADRs were described according to the MedDRA® System Organ Class (MedDRA® SOC).

Data analysis

The descriptive characteristics of the ICSRs were summarised using counts and proportions or means and standard deviations (SD), as appropriate, for tofacitinib and baricitinib separately. Within each medication, ICSRs were summarised overall and stratified by the primary outcome of interest (DVT or PT/PE). The reported dose or amount (milligrams) was calculated from those ICSRs providing the amount as milligrams or as 'DF dosage form'. The dose was calculated independently of the reported frequency due to high variability and missing data. Additionally, ICSRs mentioning more than one amount were considered as a missing amount. All comedications recorded in the VigiBase data were identified and a detailed list is provided in **Supplementary Table S3.1**. In a sensitivity analysis, we further observed the ICSRs filtering by spontaneous reporting (unsolicited reports) for both JAK inhibitors. ICSRs with a recorded age equal to 0 months and without any other hint of transplacental administration were set to 'missing age'.

To examine signals of disproportionate reporting (SDR) of the events of interest, we calculated the ROR with corresponding 95% CIs,[24] and the information component (IC) with the corresponding lower end of the 95% credibility interval (IC025).[25,26] These disproportionality methods aim to compare the observed versus expected reporting ratio for a specific event and a medicinal product.[27] The expected reporting ratio was calculated using the ICSRs of every other medicine in VigiBase. We conducted disproportionality analyses for the outcomes of interest and all MedDRA® SOCs, stratified by tofacitinib or baricitinib, using the VigiLyze data. Additionally, we completed a secondary analysis that stratified by reporting region to examine ICSRs originating from Europe and the US. This was done for two reasons. First, it was hypothesized that these would be the major contributors to the JAK inhibitor ICSRs. Second, this stratification would roughly match the areas covered by FDA and EMA regulations, where differential approval for baricitinib dose (2 and 4 mg) was observed. The analyses were conducted using the statistical software R,[28] and plots were performed using GraphPad Prism 8.[29]

Results

Descriptive analysis

We identified 42,155 ICSRs with tofacitinib or baricitinib as the suspect or interacting drug. Of these, 40,017 ICSRs were reported for tofacitinib and 2138 ICSRs for baricitinib. ICSRs were identified from 46 and 24 reporting countries for tofacitinib and baricitinib, respectively. For tofacitinib, the majority of reports were from the US (79.6%), followed by Canada (11.9%) and Europe (3.3%). Conversely, for baricitinib, 97.2% of ICSRs were from Europe, with no reports from the US or Canada. The included ICSRs were recorded from 1 June 2011 to 31 March 2019, and from 6 July 2014 to 31

March 2019, for tofacitinib and baricitinib, respectively. The characteristics of the ICSRs are described in **Table 3.1**, stratified by the outcome of interest. The mean age was 60.5 years (SD 12.5) for tofacitinib patients and 60.8 (SD 12.6) for baricitinib patients, and the majority were female (79.2% tofacitinib and 81.4% baricitinib). In two ICSRs, age was 0 months and there was no other hint of transplacental administration, thus, age was transformed to 'missing'. The majority of ICSRs stated RA as the indication for the JAK inhibitors.

When stratifying by outcome of interest, 49 tofacitinib ICSRs and 22 baricitinib ICSRs reported DVT (**Table 3.1**). These constituted 0.1% and 1.0% of the total ICSRs for tofacitinib and baricitinib, respectively. For PT/PE, we identified 114 tofacitinib ICSRs and 36 baricitinib ICSRs, which constituted 0.3% and 1.7% of the total ICSRs for tofacitinib and baricitinib, respectively. A higher frequency of elderly patients (> 65 years of age) was observed in ICSRs with reported DVT or PT/PE, versus the overall ICSRs for the studied drugs (**Table 3.1**). For ICSRs with a reported DVT or PT/PE, the mean age was slightly higher than the observed among all reports, with a mean of 61.2 years and 61.4 years for tofacitinib ICSRs with DVT and PT/PE, respectively, and a mean of 65.3 years and 66.4 years for baricitinib ICSRs with DVT or PT/PE, respectively. Additionally, ICSRs with DVT or PT/PE events showed higher reporting of medications associated with an elevated thromboembolic risk (**Table 3.1**). For tofacitinib, 12.2% (DVT) and 15.8% (PT/PE) reported hormonal treatment as a comedication, compared with 1.4% of the total tofacitinib ICSRs. Similarly, higher reporting of antidepressants and antithrombotics was reported among ICSRs with a DVT or PT/PE event, when compared with the overall reporting for each drug. Similar results were obtained in the sensitivity analysis of the 37,981 and 939 spontaneous ICSRs for tofacitinib and baricitinib, respectively. Descriptive results are provided in **Supplementary Table S3.2**.

Table 3.1. Characteristics of the individual case safety reports (ICSRs) with tofacitinib and baricitinib as suspect/interacting drugs, stratified by outcome of interest. Results as number and percentage, unless otherwise specified.

	Tofacitinib[a]			Baricitinib[b]		
Total ICSRs	Total (n=40,017)	DVT (n=49)	PT|PE (n=114)	Total (n=2,138)	DVT (n=22)	PT|PE (n=36)
Report type						
Spontaneous	37,981 (94.9)	36 (73.5)	97 (85.1)	939 (43.9)	17 (77.3)	28 (77.8)
Report from study	1,751 (4.4)	13 (26.5)	17 (14.9)	1,199 (56.1)	5 (22.7)	8 (22.2)
Other	285 (0.7)	..	..	..	..	..
Age (mean (SD))	60.5 (12.5)	61.2 (14.5)	61.4 (12.7)	60.8 (12.6)	65.3 (8.7)	66.4 (10.2)
0-17	98 (0.2)	..	..	..	..	..
18-49	5,919 (14.8)	8 (16.3)	13 (11.4)	175 (8.2)	1 (4.6)	1 (2.8)
50-64	14,877 (37.2)	13 (26.5)	41 (36.0)	369 (17.3)	7 (31.8)	10 (27.8)
65-74	7,928 (19.8)	14 (28.6)	39 (34.2)	221 (10.3)	5 (22.7)	7 (19.4)
> 75	3,338 (8.3)	6 (12.2)	4 (3.5)	111 (5.2)	1 (4.6)	7 (19.4)
Unknown age	7,857 (19.6)	8 (16.3)	17 (14.9)	1,262 (59.0)	8 (36.4)	11 (30.6)
Sex						
Female	31,705 (79.2)	33 (67.4)	85 (74.6)	1,740 (81.4)	17 (77.3)	29 (80.6)
Male	6,772 (16.9)	16 (32.7)	25 (21.9)	363 (17.0)	4 (18.2)	7 (19.4)
Unknown	1,540 (3.9)	..	4 (3.5)	35 (1.6)	1 (4.6)	..
Region of reporting						
USA	31,841 (79.6)	23 (46.9)	80 (70.2)	..	..	..
Europe	1,334 (3.3)	9 (18.4)	15 (13.2)	2,077 (97.2)	18 (81.8)	33 (91.7)
Other	6,842 (17.1)	17 (34.7)	19 (16.7)	61 (2.9)	4 (18.2)	3 (8.3)
Date of recording in VigiBase (year)						
2011	2 (0.0)	..	..	..	..	..
2012	11 (0.0)	..	..	..	..	..
2013	36 (0.1)	..	1 (0.9)	..	..	..
2014	2,257 (5.6)	13 (26.5)	15 (13.2)	5 (0.2)	..	..
2015	5,013 (12.5)	8 (16.3)	15 (13.2)	3 (0.1)	..	..
2016	5,597 (14.0)	2 (4.1)	13 (11.4)	4 (0.2)	..	..
2017	11,259 (28.1)	5 (10.2)	26 (22.8)	92 (4.3)	4 (18.2)	3 (8.3)
2018	15,246 (38.1)	17 (34.7)	36 (31.6)	1,347 (63.0)	9 (40.9)	21 (58.3)
2019	596 (1.5)	4 (8.2)	8 (7.0)	687 (32.1)	9 (40.9)	12 (33.3)

Table 3.1 (continued)

Total ICSRs	Tofacitinib[a] Total (n=40,017)	Tofacitinib[a] DVT (n=49)	Tofacitinib[a] PT|PE (n=114)	Baricitinib[b] Total (n=2,138)	Baricitinib[b] DVT (n=22)	Baricitinib[b] PT|PE (n=36)
Indication for tofacitinib/baricitinib						
Rheumatoid arthritis[c]	24,496 (61.2)	36 (73.5)	74 (64.9)	1,671 (78.2)	15 (68.2)	25 (69.4)
Other	2,824 (7.1)	7 (14.3)	23 (20.2)	17 (0.8)	..	4 (11.1)
Missing	12,697 (31.7)	6 (12.2)	17 (14.9)	450 (21.1)	7 (31.8)	7 (19.4)
Tofacitinib amount (mg)						
5	20377 (50.9)	21 (42.9)	56 (49.1)			
10	1431 (3.6)	13 (26.5)	17 (14.9)			
11	10469 (26.2)	5 (10.2)	11 (9.6)			
Other	537 (1.3)	1 (2.0)	1 (0.9)			
Unknown	7203 (18.0)	9 (18.4)	29 (25.4)			
Baricitinib amount (mg)						
2				268 (12.5)	5 (22.7)	4 (11.1)
4				1268 (59.3)	10 (45.5)	17 (47.2)
Other				46 (2.2)	2 (9.1)	2 (5.6)
Unknown				556 (26.0)	5 (22.7)	13 (36.1)
Number of co-medications per report						
(mean (SD))	3.2 (4.0)	8.4 (6.5)	5.8 (6.6)	2.5 (2.7)	3.5 (3.7)	4.9 (5.1)
(median [IQR])	1 [1-4]	7 [2-15]	3 [1-9]	1 [1-3]	1 [1-8]	1 [1-10]
< 5 reported medications	31,704 (79.2)	20 (40.8)	69 (60.5)	1820 (85.1)	15 (68.2)	22 (61.1)
5-9 reported medications	5,115 (12.8)	7 (14.3)	21 (18.4)	236 (11.0)	5 (22.7)	4 (11.1)
≥ 10 reported medications	3,198 (8.0)	22 (44.9)	24 (21.1)	82 (3.8)	2 (9.1)	10 (27.8)
Comedication[d]						
Glucocorticoids	5,297 (13.2)	23 (46.9)	23 (20.2)	390 (18.2)	6 (27.3)	7 (19.4)
sDMARD	10,184 (25.5)	26 (53.1)	44 (38.6)	449 (21.0)	6 (27.3)	8 (22.2)
bDMARD	3,293 (8.2)	8 (16.3)	16 (14.0)	64 (3.0)	..	1 (2.8)
Contraceptives/Estrogens /Progestogens	551 (1.4)	6 (12.2)	18 (15.8)	13 (0.6)	..	3 (8.3)
Antidepressants	2,409 (6.0)	14 (28.6)	23 (20.2)	74 (3.4)	1 (4.6)	4 (11.1)
Antithrombotic agents	1,685 (4.2)	12 (24.5)	21 (18.4)	94 (4.4)	1 (4.6)	2 (5.6)
Vitamin K antagonists	269 (0.7)	2 (4.1)	5 (4.4)	18 (0.8)	..	..
Platelet aggregation inhibitors (excl. heparin)	1,269 (3.2)	6 (12.2)	7 (6.1)	48 (2.3)	..	2 (5.6)
Heparins	31 (0.1)	2 (4.1)	1 (0.9)	7 (0.3)	..	..
Direct thrombin inhibitors	17 (0.0)	..	..	2 (0.1)	..	..
Direct factor Xa inhibitors	198 (0.5)	3 (6.1)	11 (9.7)	21 (1.0)	1 (4.6)	..

Table 3.1 (continued)

Abbreviations: DVT Deep Vein Thrombosis; PT|PE Pulmonary Thrombosis or Pulmonary Embolism; SD standard deviation; IQR interquartile range; USA United States of America; sDMARD synthetic disease modifying antirheumatic drug; bDMARD biologic disease modifying antirheumatic drug.

[a] ICSRs for tofacitinib identified between 01.06.2011 and 31.03.2019, from the VigiBase data extracted on 01.04.2019; [b] ICSRs for baricitinib identified between 06.07.2014 and 31.03.2019, from the VigiBase data extracted on 01.04.2019; [c] Terms used to identify RA as indication for the JAK inhibitors are included in Supplementary Table S4.1; [d] Detailed list of drugs constituting the reported comedication is included in Supplementary Table S4.1. Reported comedication corresponds with medication present at the time of the suspected adverse drug reaction or shortly before it. Thus, medication that could have had, potentially, an impact on the event, and it does not include medications prescribed after or as a result of the adverse event.

Disproportionality analysis

Figure 3.1 provides an overview of the disproportionality analysis to identify SADRs of tofacitinib ICSRs, with a detailed overview provided in **Supplementary Table S3.3**. For tofacitinib, the worldwide ROR for DVT was 0.49 (95% CI 0.37–0.64), with an IC of -1.03 (IC025 -1.49). A similar outcome was observed in the US, but, within Europe, the observed ROR was 2.37 (95% CI 1.23–4.56), with an IC of 1.14 (IC025 0.00). For suspected PT/PE events, the tofacitinib worldwide ROR was 0.84 (95% CI 0.70–1.00), with an IC of < 0. When stratified by region, the ROR in the US was 0.52 (95% CI 0.42–0.64) and the IC was -0.94 (IC025 -1.30). In contrast, the European ROR was 2.38 (95% CI 1.45–3.89), with an IC of 1.18 (IC025 0.34). Notably, within Europe, no PT SADRs were reported for tofacitinib, thus the overall estimate was attributable to the 16 cases of PE. In contrast, when examined individually in the US, a discrepancy between the disproportionality measured for PE (ROR 0.36, 95% CI 0.28–0.47) and PT (ROR 2.05, 95% CI 1.45–2.90) was observed.

The disproportionality analysis of baricitinib ICSRs is provided in **Figure 3.2** and **Supplementary Table S3.4**. The baricitinib worldwide ROR for DVT was 4.82 (95% CI 3.17–7.34) and the IC was 2.14 (IC025 1.43). The SDR was as well-elevated when considering only reports from Europe, with a ROR of 3.47 (95% CI 2.18–5.52) and IC of 1.69 (IC025 0.90). The disproportionality of PT/PE worldwide resulted in a ROR of 5.60 (95% CI 4.02–7.78) and IC of 2.38 (IC025 1.82), and in Europe, a ROR of 3.44 (95% CI 2.43–4.88) and IC of 1.71 (IC025 1.12). Every PT/PE event for baricitinib corresponded only with PE. No ICSRs for baricitinib were reported from the US.

Results from the secondary analysis examining other thromboembolic events are provided in **Supplementary Tables S3.3 and S3.4**. These secondary outcomes were infrequently reported for the studied drugs, as well as for all other drugs in the database.

The complete safety profile of tofacitinib and baricitinib SADRs is provided in **Supplementary Figures S3.1** and **S3.2**, respectively. For both tofacitinib and baricitinib, the MedDRA® SOC outcome 'infections and infestations' was associated with an elevated disproportionality of reporting.

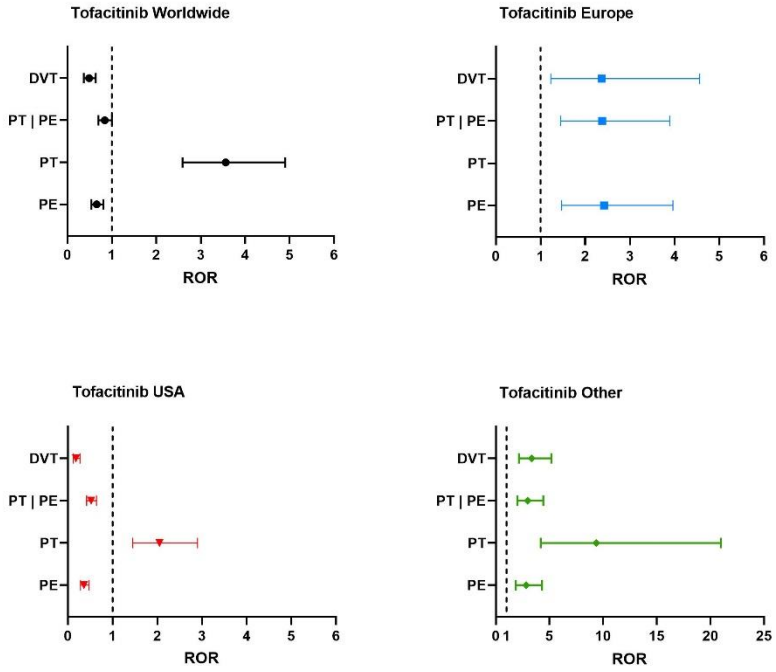

Figure 3.1 Disproportionality analysis of suspected thromboembolic events for tofacitinib compared with all other medications in the WHO VigiBase data. Outcomes of DVT or PT and/or PE were defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms version 22.1. Vertical bars on the ROR point estimate indicate the 95% confidence intervals. Abbreviations: ROR reporting odds ratio; DVT deep vein thrombosis; PT pulmonary thrombosis; PE pulmonary embolism

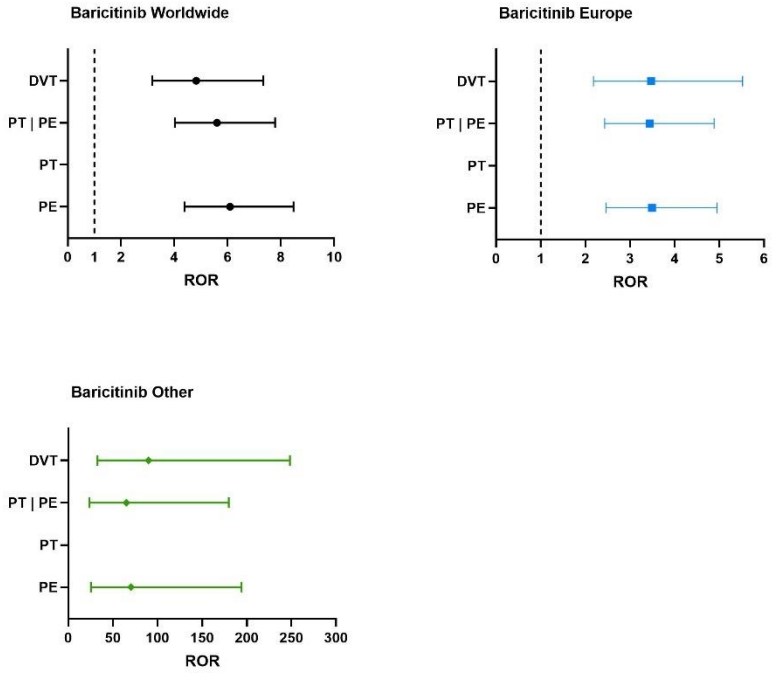

Figure 3.2 Disproportionality analysis of suspected thromboembolic events for baricitinib compared with all other medications in the WHO VigiBase data. Outcomes of DVT or PT and/or PE were defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) Preferred Terms version 22.1. Vertical bars on the ROR point estimate indicate the 95% confidence intervals. Abbreviations: ROR reporting odds ratio; DVT deep vein thrombosis; PT pulmonary thrombosis; PE pulmonary embolism.

Discussion

This real-world study identified that patients with a reported DVT or PT/PE as a SADR generally had risk factors associated with thromboembolic outcomes, such as older age and higher reporting of contraceptives, antidepressants, and antithrombotic agents, which could indicate a pre-existing thromboembolic risk or event. Additionally, a safety signal was identified for DVT and PT/PE for baricitinib in Europe. For tofacitinib, we observed a discrepancy between the US and Europe. Among European reports, we identified elevated reporting of DVT and PT/PE, similar to baricitinib. However, in the US, which accounted for the majority of ICSRs, tofacitinib was associated with a lower reporting for DVT and PE but an increased reporting for PT SADRs. Overall, the results of this study support the concerns regarding the use of tofacitinib in patients at risk of thromboembolism, and, despite current

regulatory discussions focusing on tofacitinib and limited existing real-world evidence for baricitinib, we cannot rule out a potential class effect due to the observed disproportionality in baricitinib ICSRs.

Our results on tofacitinib are in line with the results of Verden et al., using the US FAERS data to examine tofacitinib and ruxolitinib safety.[14] In the US FAERS data, PT showed an elevated reporting or disproportionality, with a ROR of 2.46, which was similar to the ROR of 2.05 observed in our study. However, in our analysis, we identified differential reporting when comparing Europe with the US. In our WHO data, the majority of DVT and PT/PE suspected outcomes for tofacitinib were reported from the US, and the disproportionality estimates from the US for tofacitinib in our study were similar to those found in the FAERS study. Conversely, in Europe, our results identified an increased ROR for DVT and PT/PE for tofacitinib. Due to the differential reporting between countries and outcomes, we believe that earlier safety signal detection using pharmacovigilance data would have been difficult for tofacitinib, particularly as the majority of ICSRs were reported from the US. However, the differential reporting by region warrants further exploration.

The descriptive analysis of the tofacitinib users reporting DVT and/or PT/PE as SADRs may reflect a subpopulation at an elevated risk for thromboembolic events, and is in line with recent communications by the EMA and FDA.[15-17,19,20] Tofacitinib users reporting DVT and/or PT/ PE exhibited risk factors of thrombosis, such as a slightly elevated mean age and a higher frequency of treatment with sex hormones and antithrombotics. The comedications reported in the WHO VigiBase are those that are taken at, or before, the time of the reported SADR. Thus, the elevated reporting of co-administered antithrombotics may suggest a patient population at high risk of thrombosis or even with a past thrombotic event. While these findings could suggest that patients with high thromboembolic risk may have developed DVT or PT/PE independently of tofacitinib, we cannot rule out that the administration of tofacitinib within this population was an additive risk factor. Thus, we would support the recent EMA and FDA communications to use tofacitinib with great caution in these high-risk populations.

Restricted use of tofacitinib in high-risk patient groups is also supported by safety concerns from the ongoing postmarketing safety trial (study A3921133), in which RA patients (> 50 years of age) who were already at high risk for venous thromboembolism were treated with high-dose tofacitinib or a tumour necrosis factor alpha (TNF) inhibitor.[17] At the interim analysis of this study, 19 cases (from 3884 patient-years) under tofacitinib treatment experienced a PE, compared with 3 (from 3982 patient-years) receiving a TNF inhibitor.[17] Similarly, Desai et al. identified that the number of events for venous thromboembolism was higher among tofacitinib users when compared with TNF inhibitors.[30] Conversely, a recent observational study, with limited power, reported similar incident

rates of thromboembolic events for tofacitinib and biologic disease-modifying antirheumatic drugs (bDMARDs).[31] Moreover, two recent meta-analyses of clinical trials did not show an increased thromboembolic risk with tofacitinib.[32,33] However, meta-analyses are limited by the intrinsic limitations of the included studies. While clinical trials are the gold standard for drug efficacy, they are limited by their ability to study rare adverse events (such as thromboembolic events), and their representativeness. Observational studies can address these restraints, but the availability of these studies for tofacitinib and cardiovascular events is limited, as identified by Sepriano and colleagues in a recent review,[34] where only a single observational study was included.[30]

Cumulatively, our results add to the growing body of literature and the recent communication from the EMA,[16,20] which suggest tofacitinib, particularly at higher doses, should be avoided in patients at high thromboembolic risk (e.g., > 65 years of age, history of cardiovascular disease, or treated with hormone replacement therapy).

To the best of our knowledge, this is the first real-world study on the safety profile of baricitinib. While the total number of ICSRs was considerably higher for tofacitinib, likely due to the longer approval time, the reporting of DVT and PT/PE SADRs was relatively higher for baricitinib. Similar to tofacitinib, we observed that ICSRs with a DVT or PT/PE were older, suggesting a high-risk profile; however, the absolute numbers were low, making broad conclusions challenging. Nevertheless, the disproportionality analyses of baricitinib ICSRs suggested higher than expected reporting for both DVT and PE at the European and worldwide level. There were no reports of any SADRs for baricitinib originating from the US, which is likely due to the limited observation time in the US for baricitinib (approved in June 2018[9] and data extraction in April 2019). Notably, in contrast to the EMA, the FDA did not approve the 4 mg dose of baricitinib due to unclear additional benefit versus the 2 mg dose, and also due to concerns of a dose effect in the safety profile, particularly for thromboembolism.[11,13] Similarly, Health Canada only approved baricitinib 2 mg in August 2018, also citing dose-related safety concerns and concluding that there was an inferiority of the safety–harm profile for the 4 mg dose.[35]

Thus, while we believe that the observed elevated reporting of DVT and PE SADRs for baricitinib should be taken with a high level of caution, as the premarket labelled concerns for DVT and PE[8,10,12] could have resulted in increased reporting of these drug-event combinations in Europe, further research is required. Moreover, in light of the results from the recent meta-analysis, which suggest that the occurrence of thromboembolic events appears to be higher with a 4 mg dose of baricitinib than a 2 mg dose,[32] the recent communication regarding a dose–response effect for tofacitinib, and the FDA decision to limit approval to the 2 mg formulation, we believe the use of baricitinib 4 mg should also be re-examined in Europe. In our data, we identified that the most commonly reported

amount for baricitinib was 4 mg. Unfortunately, pharmacovigilance data are not suited to explore the dose–response in more detail, and we were hindered by missing data.

Further research on the dose–response is of high interest as there remains debate on whether thromboembolic safety may be a class effect. This is largely centred on the lack of a clear mechanism of action. In an exploratory analysis to examine the mechanism of action, we included other thromboembolic events that could share a common mechanism. However, we did not identify an increase in reporting for either tofacitinib or baricitinib on these rare thromboembolic events. The lack of reporting of other thromboembolic-related outcomes (e.g., peripheral embolism) may suggest that the high reporting rate for baricitinib and DVT or PT/PE SADRs could have been triggered by previously reported and labelled safety concerns.[10] However, we identified that these secondary outcomes were poorly reported overall in the WHO VigiBase and therefore we cannot draw robust conclusions as a result of their absence in tofacitinib or baricitinib ICSRs. Nonetheless, our results identified elevated reporting of both DVT and PT/PE for tofacitinib and baricitinib in Europe, and therefore a shared mechanism in the sense of a class effect cannot be ruled out by our data. This finding is important, particularly regarding the monitoring of new JAK inhibitors currently in the pipeline, as well as the recent FDA- and EMA-approved upadacitinib (FDA-approved in August 2019[36]; EMA-approved in December 2019[37]).

Strengths and Limitations

A key element in pharmacovigilance, or safety surveillance of authorised drugs, is the collection and investigation of SADRs. The WHO VigiBase is the broadest pharmacovigilance database to study SADRs, as countries from all around the world submit data in an effort to join forces towards safeguarding patients' safety. Data are collected as ICSRs, which are mainly post-authorization unsolicited or spontaneous reports.[22] Therefore, this study contributes to the cumulative knowledge about the safety of JAK inhibitors using the biggest and one of most appropriate global databases for SADRs or ICSRs. Additionally, this database enables stratification by country of reporting, which resulted in a key asset for the analysis of our results. Due to the different authorization dates and prescription trends among countries, we consider that stratifying by country and individually observing the major contributors to the tofacitinib and baricitinib ICSRs provides a more informative result.

While VigiBase data are well-suited for studying safety reports, we are aware of the limitations that are intrinsic to the use of pharmacovigilance data. First, we acknowledge that causality cannot be determined, and RORs should not be interpreted as a measure of risk but rather as an indicator of a safety signal. The information within VigiBase comes from a variety of sources, and the likelihood

that a SADR is causally drug-related is not the same in all cases.[38] While we used RORs and ICs, which are measures to detect disproportionate reporting, we highlight that there are no universally established thresholds for identifying a clinically relevant signal. For the purpose of this study, we considered an outcome to have a higher than expected reporting if the ROR was >1 and the 95% CI did not encompass 1, and/or the IC025 was>0. However, as stated, while high reporting may suggest that the association between the event and the medicinal product is worth further investigation,[27] we recognize that it is not a measure of causality and should not be inferred as such. Rather, these results, supported by the current clinical warning by the EMA and FDA for tofacitinib,[15-20] and the thromboembolic concerns during the clinical development of baricitinib,[11-13] indicate a potential safety signal, which should be followed-up in a well-designed cohort study with an active comparator group. Along this line, we recognize that patients with RA, the most dominant indication for tofacitinib and baricitinib, have an elevated baseline risk for venous thromboembolism.[39] While future studies should examine the risk of thrombosis within RA patients, and using a suitable active comparator drug, we believe the results of this study should not be discounted on this basis. Within spontaneous reporting, events that are commonly associated with an underlying disease are unlikely to be categorised as SADRs, unless occurring following a new medication. Thus, it would be expected that health professionals treating RA patients would be aware of the associated risk, and therefore only report these events as SADRs when there is reasoning to suspect it as an adverse effect of the treatment; for example, if the event is in close temporal relationship to the start or dose increase of the treatment. While we were unable to identify an active comparator group, or stratify by disease, due to limitations with the data, we applied a traditional pharmacovigilance approach, whereby all other reports in the WHO serve as the comparison. Thus, our comparator group is not a 'health control' group. Rather, within our comparator group, we captured all non-tofacitinib and non-baricitinib medications, and may therefore include patient groups at similar, lower, or elevated thromboembolic risk.

Finally, reporting biases and confounding may be present.[22] Spontaneous reporting could be affected by changes in policy,[40] reporter type,[41] communications, prior knowledge about the product, and severity of the event, and may unevenly affect each medicinal product and each event. In this line, the preclinical-related concerns and existing label of potential risk[10] could have influenced the high reporting of thromboembolic events for baricitinib. Statistical adjustment to confounding factors is limited in pharmacovigilance data due to under-recording of comedications and indications. Moreover, certain risk factors for thromboembolic events, such as obesity, smoking status, or immobilization are not recorded in the database.

Conclusions

Results from this real-world pharmacovigilance analysis add to the ongoing clinical debate regarding the safety profile of tofacitinib and baricitinib. Patients with a DVT or PT/PE were older and more frequently reported use of prothrombotic medications (e.g., contraceptives) or existing clinically relevant risk factors of thromboembolism (e.g., treatment with antithrombotic agents). While, in Europe, tofacitinib was associated with an elevated reporting of DVT and PE, only increased reporting of PT was observed in the US. Similar elevated reporting for baricitinib was observed in Europe, however baricitinib reports from the US were not available at the time of data extraction.

To date, the real-world evidence regarding the safety of JAK inhibitors is lacking. While we acknowledge the inherent limitations of pharmacovigilance data, the results of this study suggest that the thromboembolic safety of JAK inhibitors requires ongoing real-world assessment to determine if a class- and dose-relationship exist.

Remarks on main author contributions: EV-Y contributed to the conceptualisation and methodology, data curation, formal analysis, visualisation, investigation, interpretation of the results, drafting and editing the manuscript, and critical revisions.

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Supplementary material

Supplementary Table S3.1 Definition of indication and comedication.

Rheumatoid arthritis indication was defined by the terms "rheumatoid arthritis", "rheumatoid arthritis, unspecified", "rheumatoid arthritis flare up", "rheumatoid arthritis aggravated", "arthritis rheumatoid", "ra", "seropositive rheumatoid arthritis", "seronegative rheumatoid arthritis", "seropositive ra", "seropositive rheumatoid arthritis, unspecified", "other rheumatoid arthritis", and "rheumatic arthritis acute".
Glucocorticoids include: Betamethasone, dexamethasone, fluocortolone, methylprednisolone, paramethasone, prednisolone, prednisone, triamcinolone, hydrocortisone, cortisone, prednylidene, rimexolone, deflazacort, cloprednol, meprednisone, and cortivazol.
sDMARDs include: Methotrexate, sulfasalazine, leflunomide, hydroxychloroquine, and chloroquine.
bDMARDs include: Infliximab, etanercept, adalimumab, certolizumab pegol, golimumab, rituximab, abatacept, anakinra, tocilizumab, and sarilumab.
Contraceptives/Estrogens/Progestogens include the following agents and their combinations: Desogestrel, levonorgestrel, etonogestrel, medroxyprogesterone, norethisterone, megestrol, estradiol, ethinylestradiol, estriol, estrogens, progesterone, dienogest, etynodiol, emergency contraceptives, intrauterine contraceptive device, and oral contraceptive nos.
Antidepressants include every medication classified as ATC-code N06A by the Anatomical Therapeutic Chemical (ATC) Classification System (13-12-2018). https://www.whocc.no/atc_ddd_index/?code=N06A
Antithrombotic agents include: Vitamin K antagonists include: Warfarin, phenprocoumon, and acenocumarol. Heparin group include: Enoxaparin, tinzaparin, heparin, and dalteparin. Platelet aggregation inhibitors excluding heparin include: Acetylsalicylic acid and combinations, clopidogrel, ticlopidine, ticagrelor, prasugrel, dipyridamole, cilostazol, and treprostinil. Direct thrombin inhibitors include: Dabigatran. Direct factor Xa inhibitors include: Rivaroxaban, apixaban, edoxaban.

Supplementary Table S3.2 Characteristics of the spontaneous individual case safety reports (ICSRs) for tofacitinib and baricitinib as suspect/interacting drugs stratified by outcome of interest. Sensitivity analysis filtering by only spontaneous reporting (unsolicited reports). Results as number and percentage, unless otherwise specified.

	Tofacitinib[a]			Baricitinib[b]		
Total spontaneous ICSRs	**Total** (n=37,981)	**DVT** (n=36)	**PT|PE** (n=97)	**Total** (n=939)	**DVT** (n=17)	**PT|PE** (n=28)
Age (mean (SD))	60.3 (12.40)	57.3 (14.60)	62.4 (11.96)	61.2 (13.00)	65.5 (9.30)	66.9 (10.20)
0-17	91 (0.2)	-	-	-	-	-
18-49	5670 (14.9)	8 (22.2)	10 (10.3)	115 (12.2)	1 (5.9)	1 (3.6)
50-64	14183 (37.3)	11 (30.6)	32 (33.0)	223 (23.7)	5 (29.4)	8 (28.6)
65-74	7371 (19.4)	8 (22.2)	35 (36.1)	140 (14.9)	4 (23.5)	6 (21.4)
> 75	3051 (8.0)	2 (5.6)	3 (3.1)	81 (8.6)	1 (5.9)	7 (25.0)
Unknown age	7,617 (20.0)	7 (19.4)	17 (17.5)	380 (40.5)	6 (35.3)	6 (21.4)
Sex						
Female	30,193 (79.5)	23 (63.9)	74 (76.3)	752 (80.1)	13 (76.5)	22 (78.6)
Male	6,302 (16.6)	13 (36.1)	19 (19.6)	152 (16.2)	3 (17.6)	6 (21.4)
Missing	1,486 (3.9)	-	4 (4.1)	35 (3.7)	1 (5.9)	-
Date of recording in VigiBase (year)						
2012	4 (0)	-	-	-	-	-
2013	5 (0)	-	-	-	-	-
2014	2,155 (5.7)	12 (33.3)	14 (14.4)	-	-	-
2015	4,765 (12.5)	5 (13.9)	8 (8.2)	-	-	-
2016	5,236 (13.8)	1 (2.8)	9 (9.3)	-	-	-
2017	10,784 (28.4)	4 (11.1)	25 (25.8)	73 (7.8)	3 (17.6)	2 (7.1)
2018	14,568 (38.4)	11 (30.6)	33 (34.0)	629 (67.0)	7 (41.2)	16 (57.1)
2019	464 (1.2)	3 (8.3)	8 (8.2)	237 (25.2)	7 (41.2)	10 (35.7)
Region of reporting						
USA	31,395 (82.7)	20 (55.6)	69 (71.1)	-	-	-
Europe	1,095 (2.9)	7 (19.4)	12 (12.4)	902 (96.1)	15 (88.2)	26 (92.9)
Other	5,491 (14.5)	9 (25.0)	16 (16.5)	37 (3.9)	2 (11.8)	2 (7.1)
Indication for tofacitinib/baricitinib						
Rheumatoid arthritis[c]	22,870 (60.2)	25 (69.4)	63 (64.9)	549 (58.5)	10 (58.8)	18 (64.3)
Other	1,476 (3.9)	4 (11.1)	11 (11.3)	58 (6.2)	7 (41.2)	6 (21.4)
Missing	13,635 (35.9)	7 (19.4)	23 (23.7)	332 (35.4)	-	4 (14.3)

Supplementary Table S3.2 (continued)

	Tofacitinib[a]			Baricitinib[b]		
	Total	**DVT**	**PT|PE**	**Total**	**DVT**	**PT|PE**
Daily dose (mean (SD))	7.26 (12.2)	6.75 (2.9)	6.87 (3.0)	3.47 (1.0)	3 (1.3)	3.22 (1.2)
Unknown	6,719 (17.7)	7 (19.4)	19 (19.6)	313 (33.3)	5 (29.4)	10 (35.7)
Number of medications per report						
Mean (SD)	3.0 (3.9)	8.0 (6.8)	5.6 (7.0)	2.6 (2.9)	2.7 (3.0)	5.2 (5.4)
Median [IQR]	1 [1-3]	5 [2-15]	2 [1-8]	1 [1-3]	1 [1-2]	1 [1-10]
< 5 reported medications	30,787 (81.1)	18 (50.0)	64 (66.0)	783 (83.4)	13 (76.5)	16 (57.1)
5-9 reported medications	4,416 (11.6)	2 (5.6)	13 (13.4)	109 (11.6)	4 (23.5)	4 (14.3)
≥ 10 reported medications	2,778 (7.3)	16 (44.4)	20 (20.6)	47 (5.0)	-	8 (28.6)
Comedication[d]						
Glucocorticoids	4452 (11.7)	16 (44.4)	16 (16.5)	113 (12)	4 (23.5)	5 (17.9)
sDMARD	9165 (24.1)	18 (50)	37 (37.1)	191 (20.3)	3 (17.7)	6 (21.4)
bDMARD	2977 (7.8)	7 (19.4)	17 (17.5)	35 (3.7)	-	1 (3.6)
Contraceptives/Estrogens/ Progestogens	518 (1.4)	5 (13.9)	15 (15.5)	11 (1.2)	-	2 (7.1)
Antidepressants	2295 (6.0)	13 (36.1)	18 (18.6)	35 (3.7)	1 (5.9)	3 (10.7)
Antithrombotic agents	1517 (4.0)	11 (30.6)	17 (17.5)	47 (5.0)	1 (5.9)	2 (7.1)
Vitamin K antagonists	236 (0.6)	2 (5.6)	5 (5.2)	7 (0.8)	-	-
Platelet aggregation inhib. excl. heparin	1140 (3.0)	5 (13.9)	3 (3.1)	27 (2.9)	-	2 (7.1)
Heparin group	22 (0.1)	2 (5.6)	1 (1)	3 (0.3)	-	-
Direct thrombin inhibitors	16 (0)	-	-	2 (0.2)	-	-
Direct factor Xa inhibitors	192 (0.5)	3 (8.3)	11 (11.3)	9 (1.0)	1 (5.9)	-

Abbreviations: DVT Deep Vein Thrombosis; PT|PE Pulmonary Thrombosis or Pulmonary Embolism; SD standard deviation; IQR interquartile range; USA United States of America; sDMARD synthetic disease modifier antirheumatic drug; bDMARD biologic disease modifier antirheumatic drug. [a] Spontaneous ICSRs for tofacitinib identified between 01.06.2011 and 31.03.2019, from the VigiBase data extracted on 01.04.2019. [b] Spontaneous ICSRs for baricitinib identified between 06.07.2014 and 31.03.2019, from the VigiBase data extracted on 01.04.2019. [c] Terms used to identify RA as indication for the JAK inhibitors are included in the Supplementary table S4.1. [d] Detailed list of drugs constituting the reported comedication is included in the Supplementary table S4.1. Reported comedication corresponds with medication present at the time of the suspected adverse drug reaction or shortly before it. Thus, medication that could have had, potentially, an impact on the event and do not include medications prescribed after or as a result of the adverse event.

Supplementary Table S3.3 Disproportionality analysis of tofacitinib individual case safety reports (ICSRs) included in VigiBase from 01.06.2011 to 31.03.2019, stratified by region of reporting.

TOFACITINIB 01.06.2011 to 31.03.2019		Tofacitinib		All other drugs				
		Event	No event	Event	No event	ROR (95% CI)	IC	IC025
Deep vein thrombosis (MedDRA-PT)	Worldwide	53	40058	34763	12763702	0.49 (0.37-0.64)	-1.03	-1.49
	Europe	9	1330	7411	2593011	2.37 (1.23-4.56)	1.14	0.00
	USA	24	31758	23454	5638155	0.18 (0.12-0.27)	-2.42	-3.11
	Other	20	6970	3898	4532536	3.34 (2-15-5.18)	1.65	0.90
Pulmonary thrombosis (MedDRA-PT) and Pulmonary embolism (MedDRA-PT)	Worldwide	126	39985	47880	12750585	0.84 (0.70-1.00)	-0.25	-0.55
	Europe	16	1323	13157	2587265	2.38 (1.45-3.89)	1.18	0.34
	USA	85	31697	29268	5632341	0.52 (0.42-0.64)	-0.94	-1.30
	Other	25	6965	5455	4530979	2.98 (2.01-4.42)	1.51	0.84
Pulmonary thrombosis (MedDRA-PT)	Worldwide	38	40073	3408	12795057	3.56 (2.59-4.90)	1.77	1.23
	Europe	0	1339	209	2600213	-	-	-
	USA	32	31750	2783	5658826	2.05 (1.45-2.90)	1.00	0.41
	Other	6	6984	416	4536018	9.37 (4.18-20.98)	2.50	1.08
Pulmonary embolism (MedDRA-PT)	Worldwide	92	40019	44653	12753812	0.66 (0.54-0.81)	-0.60	-0.95
	Europe	16	1323	12957	2587465	2.42 (1.47-3.96)	1.20	0.36
	USA	54	31728	26634	5634975	0.36 (0.28-0.47)	-1.46	-1.91
	Other	22	6968	5062	4531372	2.83 (1.86-4.30)	1.43	0.72
Peripheral embolism (MedDRA-PT)	Worldwide	3	40108	507	12797958	1.89(0.61-5.87)	0.74	-1.33
	Europe	0	1339	157	2600265	-	-	-
	USA	0	31782	263	5661346	-	-	-
	Other	3	6987	87	4536347	22.39 (7.08-70.79)	2.45	0.39
Retinal embolism and thrombosis (MedDRA-HLT)	Worldwide	2	40109	2244	12796221	0.28 (0.07-1.14)	-1.59	-4.18
	Europe	0	1339	779	2599643	-	-	-
	USA	2	31780	854	5660755	0.42 (0.10-1.67)	-1.08	-3.67
	Other	0	6990	611	4535823	-	-	-
Ophthalmic artery thrombosis (MedDRA-PT)	Worldwide	0	40111	0	12798465	-	-	-
Ophthalmic vein thrombosis (MedDRA-PT)	Worldwide	0	40111	64	12798401	-	-	-

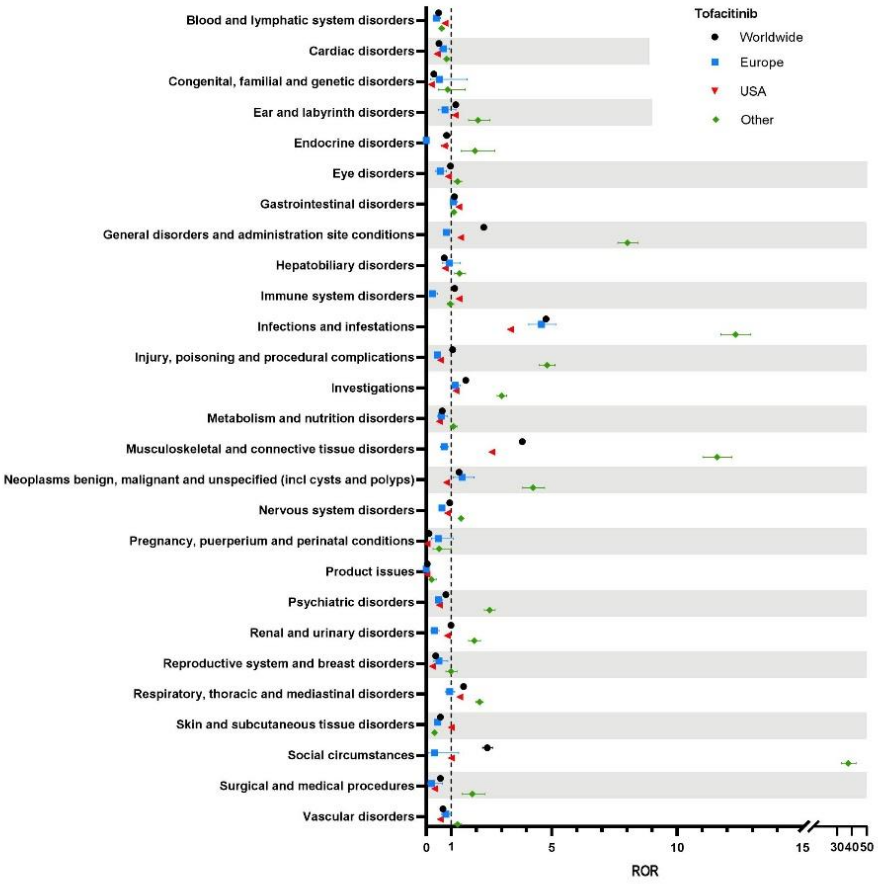
Supplementary Table S3.3 (continued)

TOFACITINIB 01.06.2011 to 31.03.2019		Tofacitinib		All other drugs		ROR (95% CI)	IC	IC025
		Event	No event	Event	No event			
Renal embolism and thrombosis (MedDRA-HLT)	Worldwide	1	40110	392	12798073	0.81 (0.11-5.79)	-0.20	-3.99
	Europe	0	1339	112	2600310			
	USA	0	31782	213	5661396			
	Other	1	6989	67	4536367	9.69 (1.34-69.80)	1.31	-2.47
Adrenal thrombosis (MedDRA-PT)	Worldwide	0	40111	4	12798461	-	-	-
Femoral artery embolism (MedDRA-PT)	Worldwide	0	40111	25	12798440	-	-	-
Spinal artery embolism (MedDRA-PT)	Worldwide	0	40111	2	12798463	-	-	-
Spinal artery thrombosis (MedDRA-PT)	Worldwide	0	40111	7	12798458	-	-	-
Subclavian artery embolism (MedDRA-PT)	Worldwide	0	40111	14	12798451	-	-	-
Subclavian vein thrombosis (MedDRA-PT)	Worldwide	0	40111	506	12797959	-	-	-
Subclavian artery thrombosis (MedDRA-PT)	Worldwide	0	40111	49	12798416	-	-	-
Coronary artery embolism (MedDRA-PT)	Worldwide	0	40111	92	12798373	-	-	-
Coronary artery thrombosis (MedDRA-PT)	Worldwide	2	40109	676	12797789	0.94 (0.24-3.78)	-0.07	-2.66
	Europe	0	1339	209	2600213	-	-	-
	USA	1	31781	349	5661260	0.51 (0.07-3.63)	-0.71	-4.49
	Other	1	6989	118	4536316	5.50 (0.77-39.38)	1.13	-2.65

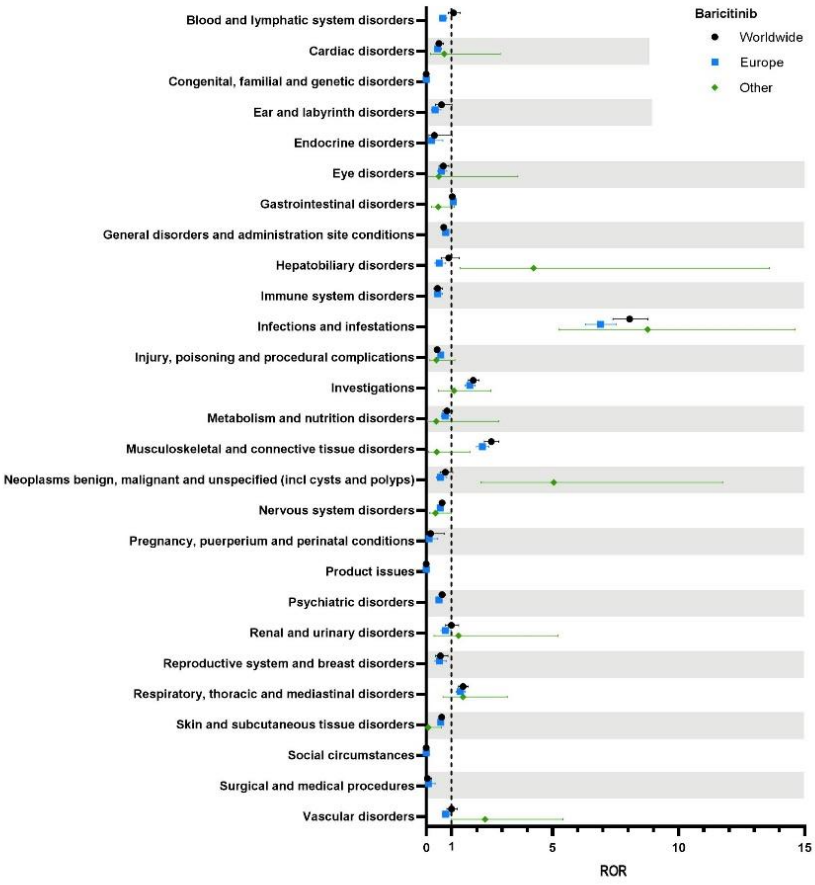
Abbreviations: ROR: Reporting odds ratio; CI: Confidence Interval; IC: Information component; MedDRA-PT: Medical Dictionary for Regulatory Activities – Preferred Term.

Supplementary Table S3.4 Disproportionality analysis of baricitinib individual case safety reports (ICSRs) included in VigiBase from 06.07.2014 to 31.03.2019, stratified by region of reporting.

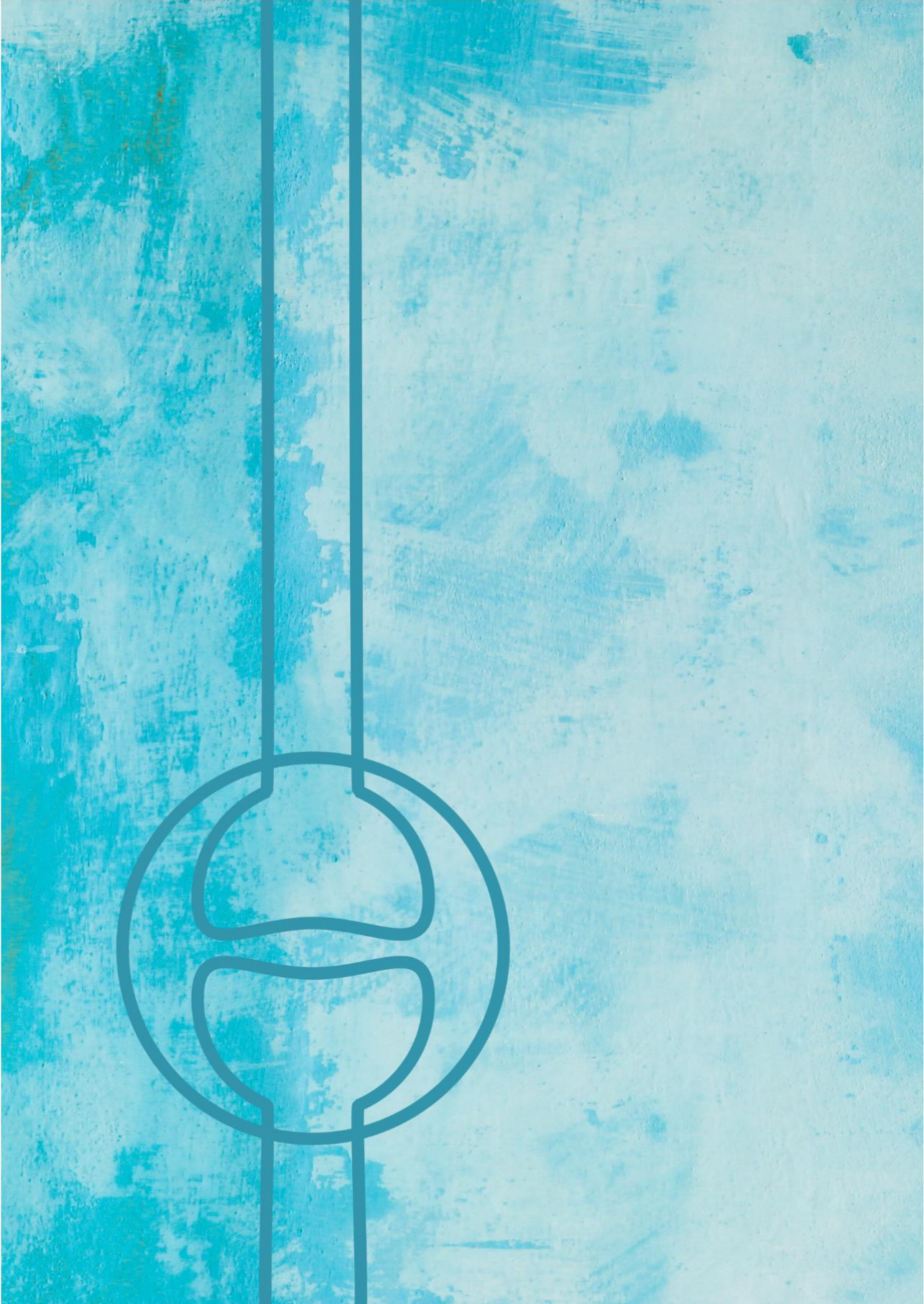
BARICITINIB		Baricitinib		All other drugs				
06.07.2014 to 31.03.2019		Event	No event	Event	No event	ROR (95% CI)	IC	IC025
Deep vein thrombosis (MedDRA-PT)	Worldwide	22	2116	21372	9908919	4.82 (3.17-7.34)	2.14	1.43
	Europe	18	2059	5260	2086007	3.47 (2.18-5.52)	1.69	0.90
	USA	0	0	13346	4274210	-	-	-
	Other	4	57	2766	3548702	90.03 (32.64-248.31)	3.04	1.27
Pulmonary thrombosis (MedDRA-PT) and Pulmonary embolism (MedDRA-PT)	Worldwide	36	2102	30300	9899991	5.60 (4.02-7.78)	2.38	1.82
	Europe	32	2045	9466	2081801	3.44 (2.43-4.88)	1.71	1.12
	USA	0	0	17018	4270538	-	-	-
	Other	4	57	3816	3547652	65.24 (23.66-179.90)	2.99	1.23
Pulmonary embolism (MedDRA-PT)	Worldwide	36	2102	27836	9902455	6.09 (4.38-8.47)	2.49	1.93
	Europe	32	2045	9330	2081937	3.49 (2.46-4.95)	1.73	1.14
	USA	0	0	14969	4272587	-	-	-
	Other	4	57	3537	3547931	70.39 (25.53-194.11)	3.00	1.24
Pulmonary thrombosis (MedDRA-PT)	Worldwide	0	2138	2569	9927722	-	-	-
Peripheral embolism (MedDRA-PT)	Worldwide	0	2138	299	9929992	-	-	-
Retinal embolism and thrombosis (MedDRA-HLT)	Worldwide	1	2137	1584	9928707	2.93 (0.41-20.85)	0.83	-2.95
	Europe	1	2076	559	2090708	1.80 (0.25-12.82)	0.51	-3.28
	USA	0	0	533	4287023	-	-	-
	Other	0	61	492	3550976	-	-	-
Ophthalmic artery thrombosis (MedDRA-PT)	Worldwide	0	2138	0	9930291	-	-	-
Ophthalmic vein thrombosis (MedDRA-PT)	Worldwide	0	2138	64	9930227	-	-	-
Renal embolism and thrombosis (MedDRA-HLT)	Worldwide	0	2138	270	9930021	-	-	-
Adrenal thrombosis (MedDRA-PT)	Worldwide	0	2138	3	9930288	-	-	-
Femoral artery embolism (MedDRA-PT)	Worldwide	0	2138	8	9930283	-	-	-
Spinal artery embolism (MedDRA-PT)	Worldwide	0	2138	1	9930290	-	-	-
Spinal artery thrombosis (MedDRA-PT)	Worldwide	0	2138	6	9930285	-	-	-
Subclavian artery embolism (MedDRA-PT)	Worldwide	0	2138	6	9930285	-	-	-
Subclavian vein thrombosis (MedDRA-PT)	Worldwide	0	2138	299	9929992	-	-	-
Subclavian artery thrombosis (MedDRA-PT)	Worldwide	0	2138	36	9930255	-	-	-
Coronary artery embolism (MedDRA-PT)	Worldwide	0	2138	59	9930232	-	-	-
Coronary artery thrombosis (MedDRA-PT)	Worldwide	0	2138	443	9929848	-	-	-



Supplementary Figure S3.1 Disproportionality analysis of suspected adverse drug reactions (ADRs) for tofacitinib, as compared to all other medications in the WHO VigiBase data. Outcomes defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) version 22.1. The reporting odds ratio (ROR) and 95% confidence intervals are provided, worldwide and stratified by region of reporting.



Supplementary Figure S3.2 Disproportionality analysis of suspected adverse drug reactions (ADRs) for baricitinib, as compared to all other medications in the WHO VigiBase data. Outcomes defined according to the Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) version 22.1. The reporting odds ratio (ROR) and 95% confidence intervals are provided, worldwide and stratified by region of reporting.



Chapter 4

Comparison of psoriatic arthritis and rheumatoid arthritis patients across body mass index categories in Switzerland

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ENRIQUETA VALLEJO-YAGÜE
THERESA BURKARD
BURKHARD MÖLLER
AXEL FINCKH
ANDREA M. BURDEN

Abstract

Abnormal body mass index (BMI) was associated with worse rheumatic markers in psoriatic arthritis (PsA) and rheumatoid arthritis (RA). Aiming to describe PsA and RA patients stratified by BMI, we performed a descriptive study in PsA and RA patients (two distinct cohorts) in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry. New users of biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) were stratified by BMI at the start of their treatment (underweight, normal weight, overweight, obese). The PsA underweight and normal weight categories were merged. Age at disease onset and further characteristics at the start of the first b/tsDMARD treatment were compared across BMI categories vs the corresponding normal weight group. The study included 819 PsA (36.5% overweight, 23.8% obese) and 3217 RA patients (4.4% underweight, 31.8% overweight, 17.0% obese). Compared to the corresponding normal weight group, PsA and RA obese patients had significantly ($p < 0.05$) higher C-reactive protein, worse disease activity, and lower quality of life (QoL). Obese PsA patients had significantly worse skin manifestation and pain, while obese RA patients had significantly higher erythrocyte sedimentation rate and tender joint counts, as well as lower seropositive prevalence. To conclude, obese PsA and RA patients presented worse disease activity and poorer QoL than those with normal weight.

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Introduction

Obesity represents an increasing healthcare burden worldwide;[1] it affects approximately 15% of the European population[2] and 11% of the Swiss population.[3] Understanding obesity as a low-grade systemic inflammatory condition, where the white adipose tissue behaves as an endocrine organ secreting adipokines responsible for immune and inflammatory processes,[4,5] suggests a common pathological pathway with immune-mediated inflammatory rheumatic diseases.

Concerns about obesity or high body mass index (BMI) hindering the management of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) patients have emerged in the past decade.[4,6-9] A higher prevalence of obesity was observed in PsA and RA patients compared to the general population,[10-13] with PsA patients having the highest observed prevalence among both diseases.[11,14] Obesity was associated with worse disease activity and disease management in both PsA and RA[12,15-21] and a detrimental response to anti-tumour necrosis factor alpha (anti-TNF) treatments.[15,17,18] Additionally, despite the association of weight loss with a better disease outcome in PsA patients,[22,23] a low BMI (underweight) was associated with worse RA disease activity.[10,24]

Epidemiological studies using real-world data and clinical studies in PsA and RA patients rarely stratify by BMI, body weight, or body fat distribution. In a systematic review that included randomised

clinical trials (RCTs) and observational studies assessing the failure to respond to anti-TNFs in adults with PsA, RA, spondyloarthropathies (SpA), and immune-mediated inflammatory diseases, the authors reported that less than 10% of eligible RCTs stratified by BMI at baseline.[18]

We believe that there is interest and room for contribution to the scientific knowledge with regard to patient differences across BMI categories. Thus, we aimed to investigate differences in patient characteristics across BMI strata in patients with PsA and RA at the start of their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment.

Materials and methods

Study design and data source

We performed a descriptive study of PsA and RA patients who were new users of b/tsDMARDs and were registered in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) database. The SCQM registry,[25] initiated in 1997, is a national longitudinal population-based cohort of rheumatic diseases in Switzerland that includes PsA and RA patients. Informed consent is obtained prior to enrolment and patients can withdraw their consent at any time. The data is generated during patient consultations and inserted by both the rheumatologist and the patient. The collected information includes physician- and patient-reported clinical endpoints (e.g., pain, skin manifestation, inflammatory markers), composite disease activity scores, health surveys, treatments, and comorbidities. Antirheumatic medication is recorded by the rheumatologist, including information on the start and stop dates of each treatment regimen.

The study was reviewed by the ethics commission of the Canton of Zurich (KEK: Req-2020-00045). Since the researchers received pseudonymized data without access to the code key, a full ethics authorization was waived by the commission.

Study Population

PsA and RA patients registered in the SCQM database from 1 January 1997 to 31 July 2019 and starting their first b/tsDMARD treatment were included in the study. The first recorded start date of a b/tsDMARD treatment in the SCQM was defined as the index date. We excluded patients that started their b/tsDMARD treatment before their first registered visit in SCQM, as well as those without a measurement for weight and height at the index date (or within the 6 months prior to the index date). PsA and RA patients were treated as two distinct cohorts, which were analysed separately but following a similar approach.

Exposure

The primary exposure of interest in this analysis was patient BMI strata at the start of their first b/tsDMARD treatment. BMI (kg/m^2) was calculated using the weight and height recorded at the index date, or as close as possible to this date within the previous 6 months (**Supplementary Equation S4.1**). We stratified patients by their BMI according to the World Health Organization (WHO) classification as follows: underweight (BMI < 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), and obese (BMI ≥ 30).[26] The exposures of interest were the abnormal BMI categories (underweight, overweight, and obese), and the normal weight group was set as the comparator group.

Covariates

In both the PsA and RA patient cohorts, we included variables regarding disease onset, as well as patient characteristics, comorbidities, and medication use at the index date. Information on disease onset included age at first symptoms and age at diagnosis. Patient characteristics at the start of the first b/tsDMARD treatment (baseline characteristics) included demographics (e.g., sex, age), BMI, life habits, patient- and physician-reported clinical endpoints (e.g., pain, skin manifestation), composite disease activity scores, and health or quality of life (QoL) questionnaires. These variables were collected at the index date, or as close as possible to that date within a 6-month look-back window. Chronic comorbidities were included if they were ever reported in the patients' records before or on the index date. Treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and glucocorticoids were identified if present on the index date. Disease-specific clinical endpoints and composite disease activity scores differed slightly between the PsA and RA patient cohorts. In both PsA and RA, we included the 28-joint Disease Activity Score (DAS28) using the erythrocyte sedimentation rate (ESR) and DAS28 using C-reactive protein (CRP). While in the PsA cohort, Minimal Disease Activity (MDA), the Disease Activity Index for PsA (DAPSA), and the clinical DAPSA (cDAPSA) (DAPSA without CRP[27]) were additionally reported. Relevant formulas for composite disease activity scores and MDA are shown in the **Supplementary Equations S4.2–S4.6**.

Data analysis

All analyses were performed in each disease cohort separately. The BMI distribution was assessed in each disease cohort, and the prevalence of overweight and obese patients was plotted alongside the prevalence in the general Swiss population according to the Federal Statistical Office in Switzerland,[3] stratifying by sex.

Patients' age at disease onset and patient baseline characteristics were described in each disease cohort, stratifying by BMI category. Categorical variables were presented with counts (n, number of exposed patients) and percentages, and continuous variables were described using mean and

standard deviation (SD) or median and interquartile range (IQR). Abnormal BMI categories were compared to the corresponding normal weight group using a chi-squared test for categorical variables and t-test or Wilcoxon test for continuous variables. For these tests, missing values did not function as a grouping variable, they were dropped instead. Statistical significance was defined as $p < 0.05$.

Subsequently, among patients with a second b/tsDMARD treatment during the study period, we described the prescription patterns for the first and second b/tsDMARD treatments, stratifying by BMI.

In a post hoc analysis, we assessed the duration of first b/tsDMARD treatment across BMI categories and the reasons for treatment discontinuation. In this analysis, only patients with an available treatment stop date (or a start date of a second and different b/tsDMARD) were included.

The analyses and figures were performed using R statistical software, R Foundation for Statistical Computing (Vienna, Austria)[28] version 3.5.2 (20 December 2018), except for Figure 4.1, which was plotted using GraphPad Prism version 9.0.2 for Windows, GraphPad Software (San Diego, CA USA).[29]

Results

We identified 4865 (1003 PsA and 3862 RA) patients in the SCQM between 1997 and 2019 who were new users of a b/tsDMARD and had available baseline information. From those, 829 patients were excluded due to missing weight and height information at the baseline. The remaining 819 PsA and 3217 RA patients were included in the study. A flow diagram reflecting the selection process is presented as **Supplementary Figure S4.1**.

The prevalence of overweight and obese patients in our study, compared to the Swiss national population and stratified by sex, is shown in **Figure 4.1**. For both PsA and RA, the prevalence of obesity and overweight was higher than in the general Swiss population for both males and females. For PsA, obesity prevalence was 25.47% in women and 22.03% in men, and in RA, it was 17.0% in both women and men.

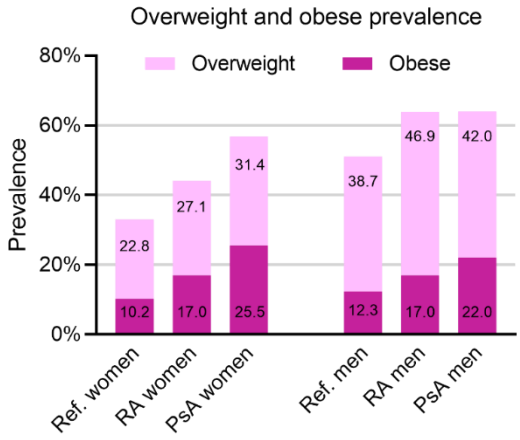

Figure 4.1 Overweight and obesity prevalence stratified by sex. The figure shows the findings from the studied rheumatoid arthritis (RA) and psoriatic arthritis (PsA) cohorts, along with the prevalence in the reference population (Ref.) according to the Swiss Federal Statistical Office, Übergewicht und Adipositas—Schweizerische Gesundheitsbefragung 2017—Korrigierte Version 25 September 2020|Publikation. Bundesamt für Statistik 2020. Available at: https://www.bfs.admin.ch/bfs/de/home/statistiken/gesundheit/erhebungen/sgb.assetdetail.14147705.html (accessed on 21 January 2021).

Patient Characteristics

Psoriatic Arthritis

Among the 819 PsA patients, only 13 patients (1.59%) had a BMI < 18.5; thus, due to the low numbers in the underweight category, we combined the underweight and normal weight groups in the PsA cohort. This resulted in 325 (39.68%) normal weight, 299 (36.51%) overweight, and 195 (23.81%) obese PsA patients (**Table 4.1**). Compared to the normal weight group, PsA patients categorised as overweight and obese were significantly older at the age of first symptoms and diagnosis.

Approximately half of the patients were women, with the lowest frequency of women in the underweight group (44.48%) and the highest in the normal weight category (56.31%). The mean age in the overweight group (50.55 years (SD 12.57)) was significantly higher than in the normal weight group (47.42 (SD 13.59)).

In the PsA cohort, anti-TNF drugs were the first b/tsDMARDs for 91.08% of normal weight, 91.64% of overweight, and 87.18% of obese patients (**Table 4.2**). Among those not treated with anti-TNFs, 68.97% normal weight, 64.00% overweight, and 68.00% obese patients received a tsDMARD (i.e.,

apremilast), and the remaining patients received a non-TNF biologic. History of cardiovascular event/disease and diabetes was more frequent in obese vs the normal weight patients. Further information on the patients' characteristics is provided in **Supplementary Table S4.1**. Here we show that the frequency of higher education and physical activity decreased with increasing BMI categories, but the frequency of smoking and alcohol consumption was similar between the BMI groups.

Table 4.1 Age at disease onset in the psoriatic arthritis (PsA) patient cohort.

	Normal weight	Overweight		Obese	
	(n=325)	(n=299)	p value	(n=195)	p value
Age at first symptoms (mean (SD))	38.04 (14.33)	41.35 (13.75)	0.004	40.73 (12.17)	0.031
missing	7 (2.15)	8 (2.68)		4 (2.05)	
Age at diagnosis (mean (SD))	41.81 (14.39)	45.21 (13.09)	0.002	45.00 (11.58)	0.010
missing	5 (1.54)	5 (1.67)		5 (2.56)	

Values are the number and column percentages, unless otherwise specified. The underweight, overweight, and obese categories were compared to the normal weight group using t-test. For the test, the missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation.

Table 4.2 Demographics, medication, and comorbidities of the psoriatic arthritis (PsA) patients at the start of their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment.

	Normal weight	Overweight		Obese	
	(n = 325)	(n = 299)	p value	(n = 195)	p value
Women	183 (56.31)	133 (44.48)	0.004	108 (55.38)	0.909
Age, years (mean (SD))	47.42 (13.59)	50.55 (12.57)	0.003	49.47 (10.80)	0.073
PsA duration, years	2.47	2.67	0.969	1.79	0.290
(median [IQR])	[0.60, 7.05]	[0.66, 7.58]		[0.68, 5.80]	
missing	5 (1.6)	5 (1.67)		5 (2.56)	
First b/tsDMARD					
anti-TNF biologic	296 (91.08)	274 (91.64)	0.900	170 (87.18)	0.369
other biologic	9 (2.77)	9 (3.01)		8 (4.1)	
tsDMARD	20 (6.15)	16 (5.35)		17 (8.72)	
csDMARD on index date	157 (48.31)	153 (51.17)	0.526	105 (53.85)	0.258
Glucocorticoids on index date	40 (12.31)	38 (12.71)	0.976	18 (9.23)	0.350
Other rheumatological disease	32 (9.85)	37 (12.37)	0.380	26 (13.33)	0.281
Fractures, surgeries	6 (1.85)	2 (0.67)	0.342	1 (0.51)	0.377
Skin problems, allergies, drug reactions	36 (11.08)	47 (15.72)	0.112	25 (12.82)	0.647
Infections	4 (1.23)	7 (2.34)	0.454	2 (1.03)	1.000
Cancerous tumour	7 (2.15)	5 (1.67)	0.884	7 (3.59)	0.484
Cardiovascular event/disease	27 (8.31)	40 (13.38)	0.056	33 (16.92)	0.005
Diabetes	4 (1.23)	8 (2.68)	0.307	10 (5.13)	0.017
Other metabolic problems	6 (1.85)	13 (4.35)	0.113	7 (3.59)	0.346
Depression/anxiety	13 (4.00)	17 (5.69)	0.426	10 (5.13)	0.700

Values are the number and column percentages, unless otherwise specified. Significance tests compared the overweight and obese categories to the normal weight group using chi-squared test for categorical variables and t-test for continuous variables, except for the Wilcoxon test for the PsA duration. For these tests, the missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation; IQR interquartile range; anti-TNF anti-tumour necrosis factor; tsDMARDs targeted synthetic disease-modifying antirheumatic drug; csDMARD conventional synthetic disease-modifying antirheumatic drug. Note: csDMARD and glucocorticoids indicate use on the index date, and not as ever having used them before.

Clinical characteristics of PsA patients at the start of the first b/tsDMARD treatment are presented in **Table 4.3**. Obese patients had significantly higher CRP than the normal weight category ($p = 0.020$), and no significant differences were observed in the rheumatoid factor (RF) and human leukocyte antigen B27 (HLA-B27) between the BMI strata. While the physician's global disease activity assessment was similar between BMI strata, the physician's global skin manifestation was significantly worse in the overweight and obese vs the normal weight group ($p < 0.02$). Similarly, compared to the normal weight group, patient-reported disease activity (0 to 10) was significantly worse in the obese group, and both overweight and obese patients reported significantly worse joint pain (0 to 10). Conversely, the mean number of tender joint counts (TJC) was similar among BMI categories. Furthermore, the mean number of swollen joint counts (SJC) was significantly higher in the overweight vs normal weight patients, but this was not consistent in the obese group. Additionally, no differences were observed across BMI groups regarding additional clinical manifestations (i.e., dactylitis, enthesitis, sacroilitis, spinal involvement, coxitis, peripheral arthritis, and nail manifestation).

The composite disease activity scores and health or QoL surveys of the PsA patients at the start of the first b/tsDMARD treatment are presented in **Table 4.4**. Overweight and obese patients presented worse disease activity, with significantly higher DAPSA (overweight 27.03 (SD 17.81), $p = 0.022$; obese 26.90 (SD 15.33), $p = 0.037$) compared to the normal weight group (23.23 (SD 15.46)). This was in line with the cDAPSA results and, likewise, significantly fewer patients had MDA in the overweight (1.67%, $p = 0.002$) and obese (2.05%, $p = 0.026$) vs normal weight patients (6.77%). However, DAS28 was only significantly higher in the overweight group. Regarding body function and QoL, obese patients, in comparison to the normal weight group, had consistently significantly worse measures on the following surveys: Health Assessment Questionnaire (HAQ), European Quality of Life-5 dimensions (EuroQoL EQ-5D), Dermatology Life Quality Index (DLQI), and Short Form containing 12 items (SF12) physical component summary (pcs). However, this was not observed in the SF12 mental component summary (mcs).

Table 4.3 Clinical characteristics of psoriatic arthritis (PsA) patients at the start of their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment.

	Normal weight	Overweight		Obese	
	(n=325)	(n=299)	p value	(n=195)	p value
RF+	14 (4.31)	10 (3.34)	0.667	5 (2.56)	0.423
missing	88 (27.08)	80 (26.76)		52 (26.67)	
HLA-B27+	40 (12.31)	28 (9.36)	0.319	22 (11.28)	1.000
missing	150 (46.15)	142 (47.49)		98 (50.26)	
ESR mm/h (median [IQR])	10.00 [5.00, 21.75]	12.00 [6.00, 22.25]	0.104	14.50 [6.00, 23.00]	0.081
missing	31 (9.54)	27 (9.03)		13 (6.67)	
CRP mg/dL (median [IQR])	0.50 [0.20, 0.90]	0.60 [0.30, 1.10]	0.152	0.79 [0.40, 1.20]	0.020
missing	40 (12.31)	36 (12.04)		18 (9.23)	
Physician global disease activity (mean (SD))	4.43 (2.03)	4.56 (1.86)	0.414	4.43 (1.85)	0.991
missing	17 (5.23)	9 (3.01)		6 (3.08)	
Physician global skin manifestation (0-3) (mean (SD))	0.93 (0.85)	1.11 (0.84)	0.012	1.12 (0.85)	0.019
missing	30 (9.23)	17 (5.69)		14 (7.18)	
Patient-reported disease activity (0-10) (mean (SD))	5.13 (2.72)	5.46 (2.54)	0.178	5.97 (2.60)	0.003
missing	89 (27.38)	59 (19.73)		48 (24.62)	
Joint pain last 24 hours (0-10) (mean (SD))	4.90 (2.65)	5.41 (2.39)	0.028	6.11 (2.41)	<0.001
missing	82 (25.23)	56 (18.73)		46 (23.59)	
Number tender joints 28 (mean (SD))	4.21 (5.11)	4.90 (5.52)	0.109	4.35 (5.10)	0.767
missing	12 (3.69)	6 (2.01)		10 (5.13)	
Number tender joints 68 (mean (SD))	8.07 (9.08)	8.97 (10.23)	0.267	8.65 (9.63)	0.518
missing	41 (12.62)	20 (6.69)		21 (10.77)	
Number swollen joints 28 (mean (SD))	2.73 (3.39)	3.65 (4.57)	0.005	2.88 (3.36)	0.627
missing	8 (2.46)	6 (2.01)		8 (4.1)	
Number swollen joints 66 (mean (SD))	4.62 (5.22)	5.78 (7.10)	0.026	4.76 (5.30)	0.769
missing	41 (12.62)	21 (7.02)		21 (10.77)	
Musculoskeletal manifestations	269 (82.77)	242 (80.94)	0.624	163 (83.59)	0.904
Manifestation dactylitis	114 (35.08)	119 (39.80)	0.256	80 (41.03)	0.206
Manifestation enthesitis	138 (42.46)	120 (40.13)	0.611	81 (41.54)	0.909
Manifestation sacroiliitis	80 (24.62)	71 (23.75)	0.873	34 (17.44)	0.071
Manifestation spinal involvement	91 (28.00)	78 (26.09)	0.655	48 (24.62)	0.458
Manifestation coxitis	18 (5.54)	9 (3.01)	0.176	17 (8.72)	0.222
Manifestation peripheral arthritis	170 (52.31)	158 (52.84)	0.957	113 (57.95)	0.246
Nail manifestation	68 (20.92)	71 (23.75)	0.453	56 (28.72)	0.056

Values are the number and column percentages, unless otherwise specified. Significance tests compared the overweight and obese categories to the normal weight group using chi-squared test for categorical variables and t-test for continuous variables, except for the Wilcoxon test for ESR and CRP. For the tests, the missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation; IQR interquartile range; RF+ rheumatoid factor positive; HLA-B27+ human leukocyte antigen B27 positive; ESR erythrocyte sedimentation rate; mm/h millimetres per hour; CRP—C-reactive protein; mg/dL milligrams per decilitre.

Table 4.4. Composite disease activity scores and health or quality of life surveys in psoriatic arthritis (PsA) patients at the start of their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment.

	Normal Weight	Overweight		Obese	
	(n = 325)	(n = 299)	p value	(n = 195)	p value
MDA	22 (6.77)	5 (1.67)	0.002	4 (2.05)	0.026
missing	64 (19.69)	41 (13.71)		36 (18.46)	
DAPSA (mean (SD))	23.23 (15.46)	27.03 (17.81)	0.022	26.90 (15.33)	0.037
missing	118 (36.31)	95 (31.77)		72 (36.92)	
cDAPSA without CRP (mean (SD))	22.16 (14.95)	25.64 (17.21)	0.023	26.03 (14.89)	0.020
missing	106 (32.62)	72 (24.08)		65 (33.33)	
DAS28-ESR (mean (SD))	3.30 (1.27)	3.57 (1.32)	0.014	3.43 (1.23)	0.273
missing	44 (13.54)	34 (11.37)		24 (12.31)	
DAS28-CRP (mean (SD))	3.26 (1.12)	3.52 (1.18)	0.011	3.41 (1.09)	0.191
missing	51 (15.69)	42 (14.05)		24 (12.31)	
HAQ (mean (SD))	0.71 (0.65)	0.75 (0.58)	0.375	0.89 (0.61)	0.003
missing	53 (16.31)	46 (15.38)		38 (19.49)	
Euro-QoL (mean (SD))	65.32 (17.81)	63.51 (17.38)	0.366	60.33 (20.31)	0.037
missing	169 (52.00)	145 (48.49)		90 (46.15)	
DLQI (mean (SD))	3.53 (5.35)	4.62 (6.08)	0.087	5.52 (7.66)	0.013
missing	167 (51.38)	137 (45.82)		87 (44.62)	
SF12-pcs (mean (SD))	39.06 (10.54)	38.23 (9.94)	0.368	35.78 (9.23)	0.001
missing	67 (20.62)	64 (21.4)		41 (21.03)	
SF12-mcs (mean (SD))	45.96 (11.36)	45.48 (11.46)	0.640	44.12 (11.67)	0.116
missing	67 (20.62)	64 (21.4)		41 (21.03)	

Values are the number and column percentages, unless otherwise specified. Significance tests compared the overweight and obese categories to the normal weight group using chi-squared test for categorical variables and t-test for continuous variables. For the tests, the missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation; MDA Minimal Disease Activity; DAPSA Disease Activity Index for Psoriatic Arthritis; DAS28 28-joint Disease Activity Score; ESR erythrocyte sedimentation rate; CRP C-reactive protein; HAQ Health Assessment Questionnaire; Euro-QoL European Quality of Life instrument; DLQI Dermatology Life Quality Index; SF12 Short-Form 12 health survey; pcs physical component summary; mcs mental component summary.

Rheumatoid Arthritis

Among the 3217 RA patients, 142 (4.41%), 1505 (46.78%), 1024 (31.83%), and 546 (16.97%) patients were classified as underweight, normal weight, overweight, and obese, respectively. The age of the RA patients at disease onset is provided in **Table 4.5**. The patients categorised as overweight and obese were significantly older than the normal weight group at the age of first symptoms and diagnosis, and the underweight group was significantly younger at both dates.

Demographics, medication, and comorbidities of the RA patients at the start of their first b/tsDMARD treatment are described in **Table 4.6**. At the start of the first b/tsDMARD treatment, both overweight (mean 57.63 years (SD 12.28), $p < 0.001$) and obese patients (mean 57.04 years (SD 11.65), $p < 0.001$) were significantly older than the normal weight group (53.86 (SD 14.60)), and the underweight group was significantly younger (49.37 (SD 16.47), $p = 0.001$). The first b/tsDMARD was an anti-TNF in 89.44% of underweight, 87.51% of normal weight, 85.06% of overweight, and 84.07%

of obese patients. Moreover, among those starting with another b/tsDMARD, 20.00% of underweight, 22.34% of normal weight, 24.18% of overweight, and 18.39% of obese patients received a tsDMARD, while the remaining patients received a non-TNF biologic. Prior history of cardiovascular event/disease, diabetes, other rheumatologic diseases, and depression were significantly more frequent in overweight and obese patients, and fractures were less frequent in obese patients. Other complementary information on patient characteristics is provided in **Supplementary Table S4.2**.

Clinical characteristics, composite disease activity scores, and health or QoL surveys of RA patients at b/tsDMARD start are presented in **Table 4.7**. Significantly fewer RF+ patients were observed in the obese (62.82%, p<0.001) vs normal weight group (72.16%). Likewise, prevalence of anti-CCP+ patients was significantly lower in obese (43.59%, p<0.001) than in normal weight patients (48.64%). Obese patients presented significantly higher ESR and CRP than the normal weight group. While the physician´s global disease activity assessment remained similar across RA BMI strata, the number of TJC was significantly increased in overweight and obese patients vs the normal weight group, and this was not consistent with the SJC.

Regarding disease activity, DAS28-ESR was significantly higher in overweight (4.39 [SD 1.41], p=0.007) and obese (4.41 [SD 1.35], p=0.011) in comparison to normal weight patients (4.23 [SD 1.42]), and this finding was in agreement with the DAS28-CRP results. Additionally, compared to normal weight patients, the overweight and obese patients presented worse QoL by HAQ, Euro-QoL, and SF12-pcs, but not SF12-mcs. Slightly worse HAQ and SF12-pcs may be observed in the underweight patients, however, this was not statistically significant.

Table 4.5 Age at disease onset in the rheumatoid arthritis (RA) patient cohort.

	Normal weight	Overweight		Obese		Underweight	
	(n=1505)	(n=1024)	p value	(n=546)	p value	(n=142)	p value
Age at first symptoms, years (mean (SD))	43.90 (15.46)	48.42 (13.98)	<0.001	48.52 (12.59)	<0.001	37.78 (16.68)	<0.001
missing	34 (2.26)	39 (3.81)		21 (3.85)		7 (4.93)	
Age at diagnosis, years (mean (SD))	45.36 (15.31)	50.10 (13.71)	<0.001	49.95 (12.67)	<0.001	39.86 (16.87)	<0.001
missing	34 (2.26)	33 (3.22)		19 (3.48)		8 (5.63)	

Values are the number and column percentages, unless otherwise specified. Significance tests compare underweight, overweight or obese categories to the normal weight group using t-test for continuous variables. For these tests, missing values did not function as a grouping variable. Abbreviations: n sample size; SD Standard deviation.

Table 4.6 Demographics, medication, and comorbidities of the rheumatoid arthritis (RA) patients at the start of their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) treatment.

	Normal weight	Overweight		Obese		Underweight	
	(n=1505)	(n=1024)	p value	(n=546)	p value	(n=142)	p value
Women	1237 (82.19)	664 (64.84)	<0.001	416 (76.19)	0.003	133 (93.66)	0.001
Age, years (mean (SD))	53.86 (14.60)	57.63 (12.28)	<0.001	57.04 (11.65)	<0.001	49.37 (16.47)	0.001
RA duration, years (median [IQR])	4.82 [1.67, 12.32]	4.08 [1.35, 10.75]	0.005	3.73 [1.38, 8.77]	0.001	6.94 [2.16, 14.47]	0.115
missing	34 (2.26)	33 (3.22)		19 (3.48)		8 (5.63)	
First b/tsDMARD			0.192		0.095		0.785
anti-TNF biologic	1317 (87.51)	871 (85.06)		459 (84.07)		127 (89.44)	
tsDMARD	42 (2.79)	37 (3.61)		16 (2.93)		3 (2.11)	
other biologic	146 (9.7)	116 (11.33)		71 (13.00)		12 (8.45)	
csDMARD on index date	1000 (66.45)	704 (68.75)	0.242	394 (72.16)	0.016	92 (64.79)	0.759
Glucocorticoids on index date	604 (40.13)	427 (41.7)	0.456	222 (40.66)	0.870	49 (34.51)	0.222
Other rheumatological disease	308 (20.47)	268 (26.17)	0.001	156 (28.57)	<0.001	22 (15.49)	0.192
Fractures, surgeries	151 (10.03)	80 (7.81)	0.067	36 (6.59)	0.021	14 (9.86)	1.000
Skin problems, allergies, drug reactions	18 (1.2)	11 (1.07)	0.927	8 (1.47)	0.796	2 (1.41)	1.000
Infections	22 (1.46)	17 (1.66)	0.816	12 (2.2)	0.338	1 (0.7)	0.718
Cancer tumour	27 (1.79)	26 (2.54)	0.253	12 (2.2)	0.683	1 (0.7)	0.535
Cardiovascular event/disease	216 (14.35)	274 (26.76)	<0.001	185 (33.88)	<0.001	13 (9.15)	0.113
Diabetes	36 (2.39)	49 (4.79)	0.002	48 (8.79)	<0.001	2 (1.41)	0.650
Other metabolic problems	36 (2.39)	55 (5.37)	<0.001	33 (6.04)	<0.001	0 (0)	0.118
Depression/anxiety	58 (3.85)	58 (5.66)	0.041	41 (7.51)	0.001	5 (3.52)	1.000

Values are the number and column percentages, unless otherwise specified. Significance tests compared the underweight, overweight, and obese categories to the normal weight group using chi-squared test for categorical variables and t-test for continuous variables, except for the Wilcoxon test for the RA duration. For the tests, the missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation; IQR interquartile range; anti-TNF anti-tumour necrosis factor; tsDMARDs targeted synthetic disease-modifying antirheumatic drug; csDMARD conventional synthetic disease-modifying antirheumatic drug. Note: csDMARD and glucocorticoids indicate use on the index date, and not as ever having used them before.

Table 4.7 Clinical characteristics, composite disease activity scores, and health or quality of life surveys of rheumatoid arthritis (RA) patients at start of first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD).

	Normal weight	Overweight		Obese		Underweight	
	(n=1505)	(n=1024)	p value	(n=546)		(n=1505)	(n=1024)
RF+	1086 (72.16)	700 (68.36)	0.219	343 (62.82)	<0.001	101 (71.13)	0.755
missing	53 (3.52)	58 (5.66)		28 (5.13)		4 (2.82)	
Anti-CCP+	732 (48.64)	489 (47.75)	0.317	238 (43.59)	<0.001	61 (42.96)	0.732
missing	427 (28.37)	278 (27.15)		136 (24.91)		49 (34.51)	
ESR mm/h (median [IQR])	18.00 [9.00, 32.00]	20.00 [10.00, 34.00]	0.103	20.00 [10.00, 33.00]	0.026	18.00 [8.00, 38.75]	0.919
missing	72 (4.78)	37 (3.61)		27 (4.95)		4 (2.82)	
CRP mg/dL (median [IQR])	0.80 [0.30, 1.40]	0.80 [0.30, 1.60]	0.089	0.90 [0.40, 1.52]	0.005	0.80 [0.20, 1.50]	0.723
missing	851 (56.54)	489 (47.75)		251 (45.97)		97 (68.31)	
Physician global disease activity (0-10) (mean (SD))	4.88 (2.14)	4.87 (2.14)	0.926	4.87 (1.99)	0.962	5.02 (2.13)	0.547
missing (%)	534 (35.48)	339 (33.11)		178 (32.6)		55 (38.73)	
Number of tender joints 28 (0-28) (mean (SD))	6.31 (6.32)	7.20 (6.97)	0.001	7.19 (6.70)	0.007	5.69 (6.15)	0.260
missing	10 (0.66)	6 (0.59)		3 (0.55)		2 (1.41)	
Number of swollen joints 28 (0-28) (mean (SD))	6.68 (5.90)	6.71 (5.63)	0.893	6.30 (5.50)	0.198	7.45 (6.66)	0.139
missing	7 (0.47)	2 (0.2)		2 (0.37)		1 (0.7)	
DAS28-ESR (mean (SD))	4.23 (1.42)	4.39 (1.41)	0.007	4.41 (1.35)	0.011	4.22 (1.57)	0.946
missing	81 (5.38)	43 (4.2)		29 (5.31)		6 (4.23)	
DAS28-CRP (mean (SD))	3.92 (1.20)	4.07 (1.21)	0.035	4.12 (1.12)	0.016	3.90 (1.13)	0.906
missing	860 (57.14)	495 (48.34)		252 (46.15)		98 (69.01)	
HAQ (mean (SD))	0.96 (0.71)	1.07 (0.72)	<0.001	1.18 (0.75)	<0.001	1.06 (0.74)	0.125
missing	122 (8.11)	104 (10.16)		71 (13)		11 (7.75)	
Euro-QoL (mean (SD))	65.85 (19.31)	60.75 (21.80)	<0.001	59.02 (22.79)	<0.001	64.74 (18.16)	0.735
missing	945 (62.79)	587 (57.32)		308 (56.41)		105 (73.94)	
SF12-pcs (mean (SD))	36.47 (10.27)	34.87 (9.57)	<0.001	34.16 (9.79)	<0.001	34.78 (10.62)	0.088
missing	262 (17.41)	208 (20.31)		131 (23.99)		24 (16.9)	
SF12-mcs (mean (SD))	46.01 (11.56)	45.31 (12.01)	0.185	44.80 (12.33)	0.070	45.34 (12.28)	0.552
missing	262 (17.41)	208 (20.31)		131 (23.99)		24 (16.9)	

Values are the number and column percentage, unless otherwise specified. Significance tests compare underweight, overweight or obese categories to the normal weight group using chi-squared test for categorical variables, and t-test for continuous variables, but Wilcoxon test for ESR and CRP. For tests, missing values did not function as a grouping variable. Abbreviations: n sample size; SD standard deviation; IQR interquartile range; RF+ rheumatoid factor positive; anti-CCP+ anti-cyclic citrullinated peptide positive; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28 28-joint Disease Activity Score; HAQ Health Assessment Question-ire; Euro-QoL European Quality of Life instrument; SF12 Short-Form 12 health survey; pcs physical component summary; mcs mental component summary.

Treatment trends, first and second b/tsDMARD

Psoriatic arthritis

In the PsA cohort, 385 patients (47.00%) had a second b/tsDMARD following treatment stop of the first b/tsDMARD. The distribution of paired first and second b/tsDMARDs used by these patients is illustrated in **Figure 4.2**, and counts to complement the figure are provided in the **Supplementary Table S4.3**. Among those with a recorded second b/tsDMARD, 94.84% of normal weight, 95.00% of overweight, and 90.00% of obese patients were treated with an anti-TNF as first b/tsDMARD. Among the patients starting with anti-TNF treatment, 84.35% of normal weight, 85.71% of overweight, and 88.89% of obese patients moved to the same or another anti-TNF as second treatment. The most common second b/tsDMARDs across the four BMI categories continued being the anti-TNFs adalimumab, etanercept, golimumab and infliximab.

In the post-hoc analysis, we identified 451 patients (175 normal weight patients, 173 overweight, and 103 obese) with available stop date of their first b/tsDMARD. Among those, the median years of treatment were 11.66 [IQR 3.91, 24.28], 11.47 [IQR 5.22, 26.68], and 9.59 [IQR 3.94, 20.78] for normal weight, overweight, and obese PsA patients respectively. No statistically significant differences were found in the duration of treatment across BMI groups. Reasons for treatment stop **(Supplementary Table S4.1**) were statistically different in the obese (p=0.024) versus normal weight strata.

Rheumatoid arthritis

In the RA cohort, 1546 patients (48.06%) received a second b/tsDMARD following treatment stop of the first b/tsDMARD. Their distribution of paired first and second treatments are shown in **Figure 4.3**, complemented with numerical values in **Supplementary Table S4.4**. Following anti-TNFs as first treatment [as was the case in 96.61% of underweight patients, 91.99% of normal weight; 89.14% of overweight; 86.49% of obese], a total of 78.95% of underweight, 64.15% of normal weight, 61.83% of overweight, and 58.04% of obese patients continued with anti-TNF as second b/tsDMARD. Overall, the most commonly used treatments as second b/tsDMARD were adalimumab and etanercept, but for the obese group, where rituximab was more frequently used than etanercept.

The post-hoc analysis identified 1787 patients (856 normal weight, 557 overweight, 307 obese, and 67 underweight) with available stop date for their first b/tsDMARD. Among those, the median years on treatment was 13.65 [IQR 5.79, 29.93], 13.24 [IQR 6.01, 32.03], 11.70 [IQR 5.31, 22.83], and 12.19 [IQR 5.14, 35.09] years for patients with normal weight, overweight, obesity, and underweight, respectively. In comparison to the normal weight group, obese patients had significantly shorter duration of treatment (p=0.006). The distribution of reasons for treatment stop (**Supplementary Table S4.2**) was significantly different in obese vs normal weight patients (p=0.007).

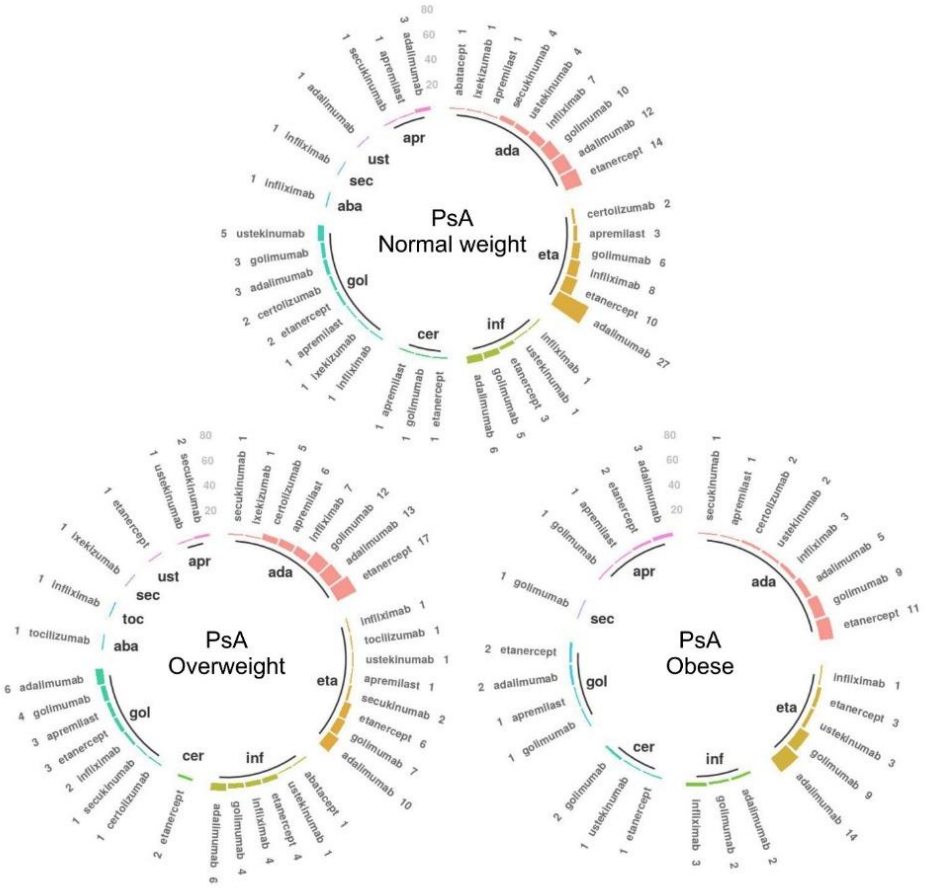

Figure 4.2 Treatment trends in the psoriatic arthritis (PsA) patients receiving a second biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD), stratifying by body mass index (n=385). The inner circle illustrates the first b/tsDMARD, and for each corresponding initial drug, the bars indicate the second b/tsDMARD treatment. Only patients with recorded second treatment are represented. Number of patients for each drug sequence are mentioned by each bar. Complementary data is provided in the **Supplementary Tables S4.3**. Abbreviations: PsA psoriatic arthritis; ada adalimumab; eta etanercept; inf infliximab; cer certolizumab; gol golimumab; aba abatacept; toc tocilizumab; sec secukinumab; ust ustekinumab; apr apremilast.

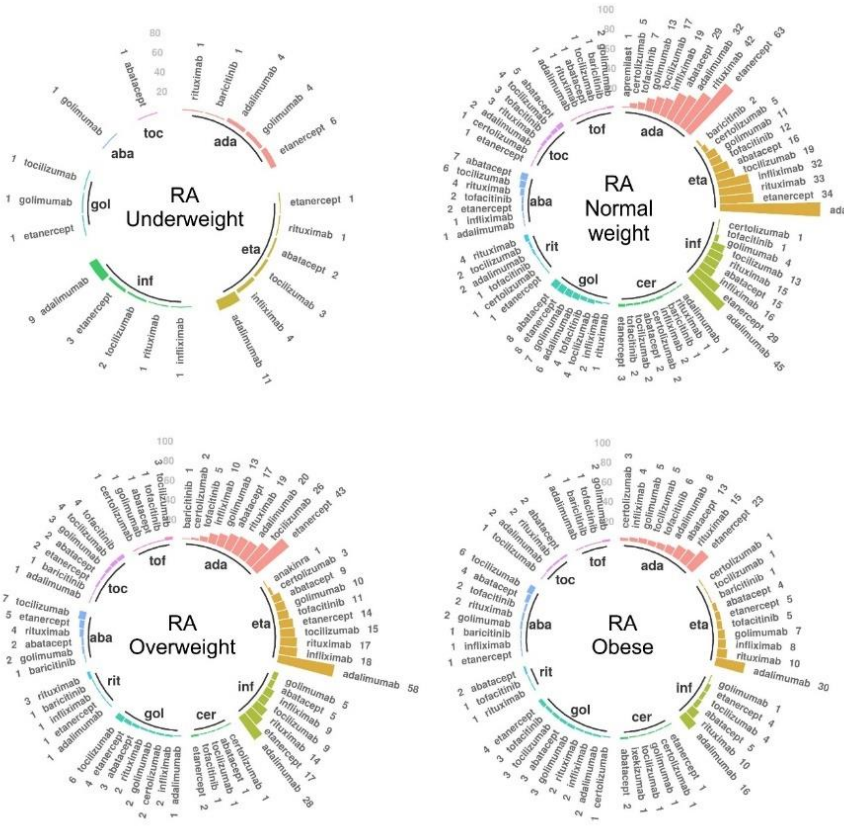

Figure 4.3 Treatment trends in the rheumatoid arthritis (RA) patients receiving a second biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD), stratifying by body mass index (n=1546). The inner circle illustrates the first b/tsDMARD, and for each corresponding initial drug, the bars indicate the second b/tsDMARD treatment. Only patients with recorded second treatment are represented. Number of patients for each drug sequence are mentioned by each bar. Complementary data is provided in the **Supplementary Tables S4.4**. Abbreviations: ada adalimumab; eta etanercept; inf infliximab; cer certolizumab; gol golimumab; rit rituximab; aba abatacept; toc tocilizumab; tof tofacitinib.

Discussion

To our knowledge, this is one of the largest studies to examine differences in patient characteristics among PsA patients across BMI strata, and we additionally provided a comparison to the RA population. In our analysis, we identified that obese patients were generally older at disease onset, and they had significantly higher CRP, worse disease activity scores, and lower QoL at the time of starting their first b/tsDMARD, compared to normal weight patients. Obese PsA patients also had worse skin manifestation and reported higher pain compared to the normal weight group. While in the RA cohort, the obese patients had higher ESR, higher TJC, but similar SJC, and smaller prevalence of RF+ patients. In both cohorts, anti-TNF drugs were the most commonly prescribed b/tsDMARD across every BMI category, and >84% PsA and >58% RA patients moved to the same or another anti-TNF (assuming gaps of ≥1-month as treatment stops).

Prevalence of BMI strata

We identified a higher obesity prevalence in our PsA (23.8% obese) and RA (17.0% obese) patient cohorts in comparison to the general Swiss population (Switzerland 2017, 11% obesity).[3] This is in accordance to prior studies. For example, obesity prevalence was 32% among PsA patients from Danish and Icelandic registries,[15] compared to the 14-17% and 22% of the general Danish and Icelandic populations respectively.[15,30,31] In Canadian studies, obesity prevalence was 35.4%-37% in PsA,[12,13] and 28% in RA, vs 18% in the general population.[11] And among RA patients in German cohorts obesity prevalence was 21.4%-23.8%, vs the 18.2% in the general population.[10] While we observed lower prevalence of obesity in both our cohorts compared to the above-mentioned studies, this may be explained by a less frequent obesity in our reference population. Additionally, our findings confirm the higher obesity prevalence among PsA vs RA patients, previously observed by other studies.[11,14]

While we aimed to provide stratified information on underweight patients in both cohorts, we were unable to do so in PsA due to the small sample size. With 13 patients being underweight (BMI <18.5), the prevalence in our cohort was 1.59%. Due to the lack of existing information on underweight PsA patients, it is unclear if this is comparable across international patient cohorts. Conversely, in our RA cohort, 4.4% patients were categorised as underweight. Comparing this prevalence with that in other studies, we observed a wide range of findings. In German cohorts, the prevalence of underweight patients was 1.1-2.2% in RA, vs the 0.8% in the reference population.[10] In a Dutch cohort of active RA, 8 patients (9.0%) had BMI<20 Kg/m^2,[32] and in a study in the US, 38 patients (4.9%) had BMI<20 Kg/m^2.[33] While there seems to be a lack of agreement on the prevalence of underweight patients in RA, this may be explained by the use of different BMI thresholds and measuring time-points throughout the course of the disease, the potentially different underweight

prevalence in the reference populations, as well as the restrictions posed by study-specific inclusion/exclusion criteria. Further evidence on underweight patients in both PsA and RA are certainly warranted.

Patient characteristics

Previous studies have reported that overweight and obese PsA and RA patients were older than the normal weight patients at disease onset,[10,13] and this was similarly observed in our study. While the reasons for a later onset age are unclear, it could be the consequence of failing to recognize rheumatic clinical signs when they could be attributed to heavy body weight.[13]

In an observational cohort study in Danish and Icelandic registries including 1271 PsA patients starting anti-TNFs, the authors reported that obese patients were older and had higher CRP, TJC, DAS28, HAQ, pain, and global disease assessment than non-obese patients at baseline, but not significantly higher SJC.[15] Similarly, in our study, PsA obese patients had higher CRP, worse pain, and worse HAQ, when compared to the normal weight group. However, SJC and DAS28 were only significantly higher in the overweight group, despite DAPSA showing significantly worse disease activity in both overweight and obese patients. This inconsistency between the PsA-specific DAPSA and the RA-derived DAS28 without specific adaptations to PsA in the obese group may be explained by the different components contributing to each score. First, DAPSA includes patient-assessment on disease activity and pain, which were significantly higher in obese patients. Second, if the potential underestimation of SJC in obese patients, due to excess of fat tissue around the joints, has a higher impact on the resulting DAS28 score than in DAPSA, this may also contribute to the observed significantly worse DAPSA score in both overweight and obese patients, but only significantly worse DAS28 in overweight, in comparison to the normal weight patients.

Among RA patients, some studies distinguished subjective (e.g., TJC, patient global assessment, and pain) and objective (e.g., CRP, ESR, and SJC) endpoints when comparing obese and non-obese patients.[19,34] For example, in a systematic review and meta-analysis in which DAS28 and HAQ were higher in obese patients, the authors suggested that the increased disease activity was mainly due to elevated subjective score components, such as TJC, and global pain and health assessments.[34] Additionally, another systematic review and meta-analysis also suggested that obesity may influence patient global disease assessment, pain, and QoL, but agreed that SJC are not higher in obese RA patients.[16] Albrecht et al. similarly observed increased DAS28 but not SJC among obese RA patients in comparison to the normal weight ones, but conversely with other studies, they also found higher ESR in obese patients.[10] In line with this, we identified worse DAS28, lower QoL, higher TJC, and no differences in SJC in obese compared to normal weight RA patients, but we also identified increased

CRP and ESR in the obese vs normal weight patients. Thus, we believe that the observed increased DAS28 in obese patients with RA was not only due to TJC, previously described as subjective endpoint, but also due to the enhanced inflammatory markers (CRP and ESR), or so-called objective endpoints.

The discussion of objective and subjective endpoints is likely important with the assessment of obese rheumatology patients. While in the clinic SJC is considered an objective measure, the excess or absence of fat tissue around the joints may influence the assessment on swelling, adding complexity to the practice and potentially reducing reliability of this measure in obese patients. This may explain the inconsistency observed between SJC and TJC among RA patients, as well as the controversial higher SJC in overweight vs obese among PsA patients. Additionally, in our RA cohort, we observed a tendency of higher SJC and lower TJC in underweight compared to normal weight patients, which contrasts the findings in obese patients. This SJC trend in underweight RA patients was also observed in German cohorts, but along with heterogeneous results on TJC.[10] Following the above-discussed potential impact of fat mass in the SJC, we believe that higher SJC in underweight patients could be the consequence of an easier detectable inflammation during clinical assessment and, conversely, SJC could potentially be underestimated in obese patients. Conversely, one may also consider that the disagreement among higher TJC, but similar SJC, in obese RA patients could be alternatively explained by hyperalgesia due to mood disorders like depression and subsequent fibromyalgia, which has been associated to obesity.[35]

Overall, obesity has been associated with pain, lower QoL, higher disability, depression,[36,37] cardiovascular risk,[38] and diabetes[39] in the general population. Obesity (adiposity) has been identified as a risk factor for PsA[40] and RA,[41] and higher frequency of lipid abnormalities (higher dyslipidaemia and serum triglycerides, and lower high-density lipoprotein (HDL)-cholesterol) has been identified in PsA patients.[42] This, together with the evidence of white adipose tissue enhancing immune and inflammatory processes,[4,5,43] and with the higher prevalence of obesity in PsA and RA patients vs the general population,[10-13] support the rational to believe that both the obesity and the rheumatology disease contribute to the patient status, and therefore may play a role in the assessed worse QoL and fragility observed in these patients. Additionally, the disagreement on the findings through QoL surveys including physical components (SF12-pcs, Euro-QoL), vs the SF12-mcs which solely assesses mental components, suggests that the findings on worse QoL in PsA/RA obese patients may be driven by the physical restrictions and less so from potentially decreased mental wellbeing.

Treatment trends

Existing studies have shown that obesity may be associated with detrimental response to anti-TNF treatments in PsA and RA patients, in comparison to non-obese or normal weight patients.[15,17,18]

Conversely, it has been suggested that high BMI does not influence the response to abatacept,[44-47] rituximab,[48] and tocilizumab[49,50] in RA. Thus, while we observed that anti-TNFs were the most frequent choice of b/tsDMARD treatment across every BMI category in both cohorts, there was a slight tendency for lower anti-TNF use among RA patients in higher BMI categories, which could indicate that clinical decision-making is in-line with these previous findings. However, this cannot be confirmed based on our results, and a time-series analysis may be more appropriate.

Strengths and limitations

This is one of the largest studies assessing differences in PsA patients across BMI categories, and provides further comparison to RA patients. To the best of our knowledge, the SCQM database is one of the few rheumatic disease registries with relatively complete information on patient weight and height, thereby enabling a stratification by BMI categories. Additionally, with obesity rates differing between countries,[3,51] we consider the Swiss population a sample of interest due to its relatively low, although increasing, prevalence of obesity in the general population [2017, 11%[3]]. However, BMI does not provide information on body composition,[52] and therefore, we acknowledge the potential misclassification for those patients for whom the BMI categories doesn't fairly represent their fat distribution. Ideally, we would like to have data from the hip/waist circumference, the skinfold thickness, and the bioelectrical impedance, which would provide a better assessment of unhealthy weight. However, this was not available in our data. Moreover, this information is rarely recorded during clinical practice, thus, this is likely unrealistic to be present in real-world data. Missing information of body mass composition may be especially relevant for the underweight group, resulting in lack of figures on cachexia (abnormal body composition). In cachexic patients, body fat (particularly belly fat) may remain stable or even increased despite muscle loss and weight loss.[53] Thus, it is possible that systemic inflammation in cachexic underweight patients may overlap with the rheumatic inflammation in a similar manner than in obese patients, despite the different phenotype. This could be better captured by more precise measures of body fat composition. However, we did not observe aggravated inflammatory markers in the underweight category vs the normal weight patients, which may suggest the absence of additional systemic inflammation in these patients.

While the SCQM is a comprehensive dataset, we acknowledge that there are limitations with data completeness. We may have incomplete information on non-rheumatic comorbidities as this information is self-reported by the patient and reporting systems have changed since the launching of SCQM. For example, while previous evidence suggests that the prevalence of depression is 9-22% in PsA[54-56] and 14-38% in RA patients,[57] we observed a lower prevalence (4-5.7% in PsA, and 3.5-7.5% in RA), supporting the believe that comorbidities may be underreported in our cohorts.

In both PsA and RA patients, we observed that obese patients were generally older than the normal weight patients, which could be due to increasing BMI with age, and therefore the interplay between age, BMI, and disease activity in PsA and RA patients deserves further attention. Additionally, we stratified patients according to their BMI at the start of b/tsDMARD, thus, for our analysis of differences in age at disease onset we assume that BMI remained constant from disease onset to start of b/tsDMARD.

Finally, the decision on what qualifies as a true treatment stop, or which length of treatment-free gap (between stop and re-start of same drug agent) should be considered as treatment continuation or as a true stop and re-start, may be arguable. In this study, we accepted a one-month grace period whereby patients with a stop and re-start of the same b/tsDMARD agent were considered as having continuous use. Therefore, the observed high proportion of patients with the same first and second b/tsDMARD may be explained by a misclassified stop (e.g., drug holidays), but it may as well be indicative of patients re-starting a therapy they previously did well on. Further research on the patterns of stopping b/tsDMARDs would be of interest.

Conclusions

In conclusion, this study provides a clinical picture of PsA and RA patients in Switzerland across different BMI categories. Obesity prevalence was higher in PsA and RA compared to the general Swiss population, and PsA and RA patients with obesity had worse disease activity and lower QoL in comparison to the corresponding normal weight groups. In the PsA cohort, the findings on disease activity (DAPSA) in obese patients were mainly driven by CRP and the patient-assessment on disease activity and pain, but results remained consistent when excluding CRP from the equation (cDAPSA). In the RA cohort, the results on disease activity (DAS28) in obese patients were primary attributable to TJC and ESR or CRP. Finally, these findings suggest to consider BMI when treating or studying PsA and RA patients.

Remarks on main author contributions: EV-Y contributed to the conceptualisation and methodology, data curation, formal analysis, visualisation, investigation, resources, interpretation of the results, drafting and editing the manuscript, and critical revisions.

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Supplementary material

Supplementary Equations S4

$$BMI = \frac{weight\ Kg}{height\ m^2} \quad (1)$$

$$DAS28esr = (0.56 \times \sqrt{tjc28}\ + 0.28 \times \sqrt{sjc28}\ + 0.7 \times ln(esr)) \times 1.08 + 0.16 \quad (2)$$

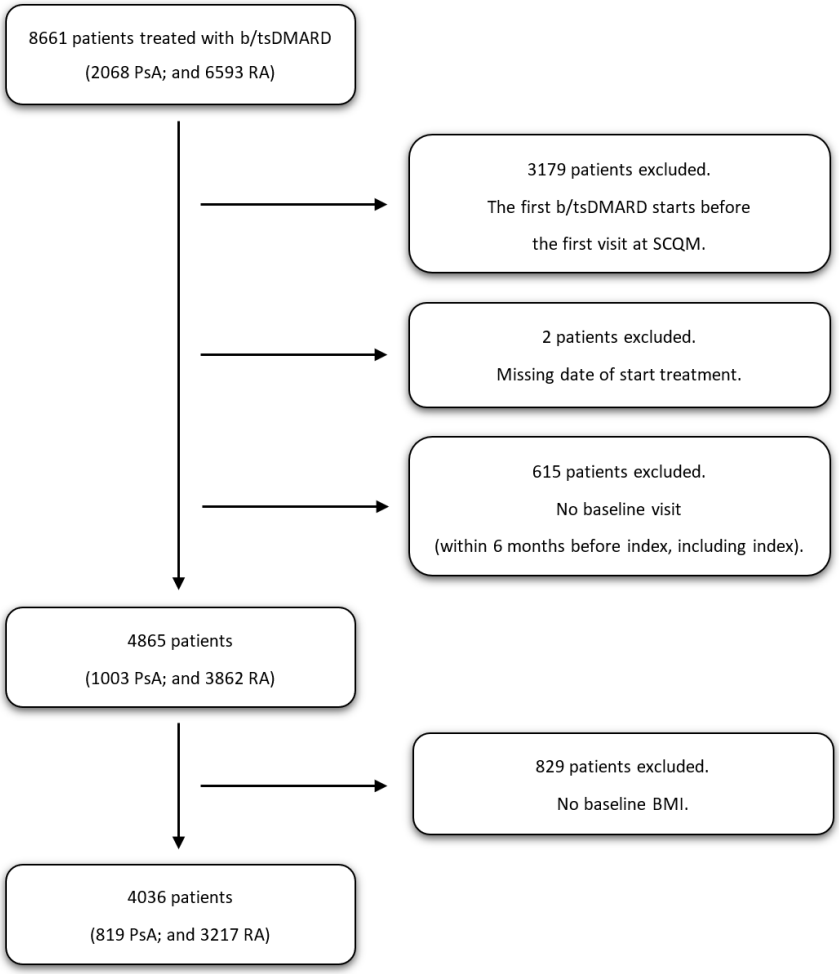
$$DAS28crp = \left(0.56 \times \sqrt{tjc28}\ + 0.28 \times \sqrt{sjc28}\ + 0.36 \times ln(crp + 1)\right) \times 1.10 + 1.15 \quad (3)$$

$$DAPSA = sjc66 + tjc68 + PatActivity + PatPain + crp \quad (4)$$

$$cDAPSA = sjc66 + tjc68 + PatActivity + PatPain \quad (5)$$

MDA is achieved if at least 5 of the following items score positive: PatActivity <2); PatPain <1.5); HAQ ≤0.5); sjc ≤1); tjc ≤1); enthenesis ≤1); Skin manifestation none or almost none. (6)

Abbreviations used in the above equations: BMI body mass index; DAS28 28-joint Disease Activity Score; DAPSA Disease Activity in Psoriasis Arthritis score; cDAPSA clinical DAPSA; MDA Minimal Disease Activity; sjc28 Number of swollen joints, counting 28; swc66 Number of swollen joints, counting 66; tjc28 Number of tender joints, counting 28; tjc68 Number of tender joints, counting 68; esr Erythrocyte sedimentation rate; crp C-reactive protein (mg/dl); PatActivity Patient's assessment of disease activity on average the last 24 hours (0 very well - 10 very poor); PatPain Patient's assessment of joint pain on average the last 24 hours (0 very well - 10 very poor).



Supplementary Figure S4.1 Flow chart reflecting the patient inclusion process. Abbreviations: PsA psoriatic arthritis; RA rheumatoid arthritis; b/tsDMARD biologic or targeted synthetic disease-modifying antirheumatic drug; SCQM Swiss Clinical Quality Management in Rheumatic Diseases; BMI body mass index.

Supplementary Table S4.1. Characteristics of psoriatic arthritis (PsA) patients starting first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD). Additional variables to complement **Table 4.2** and **Table 4.3**.

	Normal weight	Overweight		Obese	
	(n=325)	(n=299)	p value	(n=195)	p value
Family history	138 (42.46)	114 (38.13)	0.307	73 (37.44)	0.299
Smoker	82 (25.23)	92 (30.77)	0.292	54 (27.69)	0.911
missing	175 (53.85)	149 (49.83)		99 (50.77)	
Alcohol	12 (3.69)	20 (6.69)	0.173	8 (4.10)	1.000
missing	166 (51.08)	143 (47.83)		96 (49.23)	
Schooling			0.001		0.006
compulsory school	49 (15.08)	64 (21.4)		43 (22.05)	
vocational training	134 (41.23)	137 (45.82)		81 (41.54)	
high school university studies	83 (25.54)	43 (14.38)		28 (14.36)	
missing	59 (18.15)	55 (18.39)		43 (22.05)	
Daily time walking/bicycling/similar activities outdoors			0.143		0.007
none	5 (1.54)	10 (3.34)		11 (5.64)	
<30min	40 (12.31)	53 (17.73)		36 (18.46)	
30to60min	72 (22.15)	57 (19.06)		32 (16.41)	
>60min	41 (12.62)	37 (12.37)		20 (10.26)	
missing	167 (51.38)	142 (47.49)		96 (49.23)	
Power sports			0.019		<0.001
none	45 (13.85)	70 (23.41)		56 (28.72)	
<1h	32 (9.85)	26 (8.7)		18 (9.23)	
1to2h	53 (16.31)	35 (11.71)		18 (9.23)	
>2h	30 (9.23)	26 (8.7)		6 (3.08)	
missing	165 (50.77)	142 (47.49)		97 (49.74)	
Index year (mean (SD))	2011.46 (4.31)	2011.69 (3.99)	0.478	2012.12 (4.20)	0.087
Reason for 1st b/tsDMARD stop			0.382		0.024
adverse event	29 (8.92)	31 (10.37)		25 (12.82)	
not effective	72 (22.15)	83 (27.76)		46 (23.59)	
remission	16 (4.92)	16 (5.35)		1 (0.51)	
other/missing	58 (17.85)	43 (14.38)		31 (15.9)	
not info on stop date	150 (46.15)	126 (42.14)		92 (47.18)	

Values are the number and column percentage, unless otherwise specified. Significance tests compare overweight or obese categories to the normal weight group using chi-squared test for categorical variables, and t-test for continuous variables. For tests, missing values did not function as a grouping variable. Abbreviations: n sample size; SD Standard deviation.

Supplementary Table S4.2 Characteristics of rheumatoid arthritis (RA) patients starting first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD). Additional variables to complement **Table 4.5** and **Table 4.6**.

	Normal weight	Overweight		Obese		Underweight	
	(n=1505)	(n=1024)	p value	(n=546)	p value	(n=142)	p value
Family history	337 (22.39)	228 (22.27)	0.979	110 (20.15)	0.304	37 (26.06)	0.373
Smoker	412 (27.38)	328 (32.03)	0.260	170 (31.14)	0.280	27 (19.01)	0.569
missing	822 (54.62)	509 (49.71)		282 (51.65)		93 (65.49)	
Alcohol	87 (5.78)	67 (6.54)	0.660	23 (4.21)	0.252	7 (4.93)	0.892
missing	495 (32.89)	307 (29.98)		192 (35.16)		50 (35.21)	
Schooling			<0.001		<0.001		0.022
compulsory school	228 (15.15)	237 (23.14)		139 (25.46)		10 (7.04)	
vocational training	612 (40.66)	388 (37.89)		183 (33.52)		62 (43.66)	
university studies	170 (11.3)	85 (8.3)		31 (5.68)		21 (14.79)	
missing	495 (32.89)	314 (30.66)		193 (35.35)		49 (34.51)	
Daily time walking/bicycling/similar activities outdoors			0.495		0.037		0.077
none	127 (8.44)	91 (8.89)		63 (11.54)		17 (11.97)	
<30min	295 (19.6)	210 (20.51)		97 (17.77)		17 (11.97)	
30to60min	388 (25.78)	295 (28.81)		143 (26.19)		42 (29.58)	
>60min	247 (16.41)	154 (15.04)		69 (12.64)		21 (14.79)	
missing	448 (29.77)	274 (26.76)		174 (31.87)		45 (31.69)	
Power sports			0.073		0.007		0.436
none	501 (33.29)	393 (38.38)		201 (36.81)		53 (37.32)	
<1h	174 (11.56)	122 (11.91)		65 (11.9)		14 (9.86)	
1to2h	216 (14.35)	141 (13.77)		71 (13)		15 (10.56)	
>2h	159 (10.56)	86 (8.4)		31 (5.68)		12 (8.45)	
missing	455 (30.23)	282 (27.54)		178 (32.6)		48 (33.8)	
Index year (mean (SD))	2007.75 (5.09)	2008.52 (5.04)	<0.001	2009.05 (4.86)	<0.001	2006.36 (5.19)	0.002
Reason for 1st b/tsDMARD stop			0.111		0.007		0.562
adverse event	148 (9.83)	103 (10.06)		61 (11.17)		9 (6.34)	
not effective	297 (19.73)	214 (20.9)		125 (22.89)		25 (17.61)	
remission	57 (3.79)	45 (4.39)		28 (5.13)		7 (4.93)	
other/missing	354 (23.52)	195 (19.04)		93 (17.03)		26 (18.31)	
not info on stop date	649 (43.12)	467 (45.61)		239 (43.77)		75 (52.82)	

Values are the number and column percentage, unless otherwise specified. Significance tests compare overweight or obese categories to the normal weight group using chi-squared test for categorical variables, and t-test for continuous variables. For tests, missing values did not function as a grouping variable. Abbreviations: n sample size; SD Standard deviation.

Supplementary Table S4.3 First and second biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) among the psoriatic arthritis (PsA) patients. Only those PsA patients with recorded information on both treatments were included. Results as number and percentage.

1st biologic/ tsDMARD	2nd biologic/ tsDMARD	Normal weight (n=155)	Overweight (n=140)	Obese (n=90)
adalimumab		54 (34.84)	62 (44.29)	34 (37.78)
adalimumab	adalimumab	12 (22.22)	13 (20.97)	5 (14.71)
adalimumab	etanercept	14 (25.93)	17 (27.42)	11 (32.35)
adalimumab	infliximab	7 (12.96)	7 (11.29)	3 (8.82)
adalimumab	certolizumab	-	5 (8.06)	2 (5.88)
adalimumab	golimumab	10 (18.52)	12 (19.35)	9 (26.47)
adalimumab	abatacept	1 (1.85)	-	-
adalimumab	secukinumab	4 (7.41)	1 (1.61)	1 (2.94)
adalimumab	ixekizumab	1 (1.85)	1 (1.61)	-
adalimumab	ustekinumab	4 (7.41)	-	2 (5.88)
adalimumab	apremilast	1 (1.85)	6 (9.68)	1 (2.94)
etanercept		56 (36.13)	29 (20.71)	30 (33.33)
etanercept	adalimumab	27 (48.21)	10 (34.48)	14 (46.67)
etanercept	etanercept	10 (17.86)	6 (20.69)	3 (10.00)
etanercept	infliximab	8 (14.29)	1 (3.45)	1 (3.33)
etanercept	certolizumab	2 (3.57)	-	-
etanercept	golimumab	6 (10.71)	7 (24.14)	9 (30.00)
etanercept	tocilizumab	-	1 (3.45)	-
etanercept	secukinumab	-	2 (6.90)	-
etanercept	ustekinumab	-	1 (3.45)	3 (10.00)
etanercept	apremilast	3 (5.36)	1 (3.45)	-
infliximab		16 (10.32)	20 (14.29)	7 (7.78)
infliximab	adalimumab	6 (37.50)	6 (30.00)	2 (28.57)
infliximab	etanercept	3 (18.75)	4 (20.00)	-
infliximab	infliximab	1 (6.25)	4 (20.00)	3 (42.86)
infliximab	golimumab	5 (31.25)	4 (20.00)	2 (28.57)
infliximab	abatacept	-	1 (5.00)	-
infliximab	ustekinumab	1 (6.25)	1 (5.00)	-
certolizumab		3 (1.94)	2 (1.43)	4 (4.44)
certolizumab	etanercept	1 (33.33)	2 (100.0)	1 (25.00)
certolizumab	golimumab	1 (33.33)	-	2 (50.00)
certolizumab	ustekinumab	-	-	1 (25.00)
certolizumab	apremilast	1 (33.33)	-	-
golimumab		18 (11.61)	20 (14.29)	6 (6.67)
golimumab	adalimumab	3 (16.67)	6 (30.00)	2 (33.33)
golimumab	etanercept	2 (11.11)	3 (15.00)	2 (33.33)
golimumab	infliximab	1 (5.56)	2 (10.00)	-
golimumab	certolizumab	2 (11.11)	1 (5.00)	-
golimumab	golimumab	3 (16.67)	4 (20.00)	1 (16.67)
golimumab	secukinumab	-	1 (5.00)	-
golimumab	ixekizumab	1 (5.56)	-	-
golimumab	ustekinumab	5 (27.78)	-	-
golimumab	apremilast	1 (5.56)	3 (15.00)	1 (16.67)
abatacept		1 (0.65)	1 (0.71)	0 (0)
abatacept	infliximab	1 (100.00)	-	-
abatacept	tocilizumab	-	1 (100.00)	-
tocilizumab		-	1 (0.71)	-
tocilizumab	infliximab	-	1 (100)	-

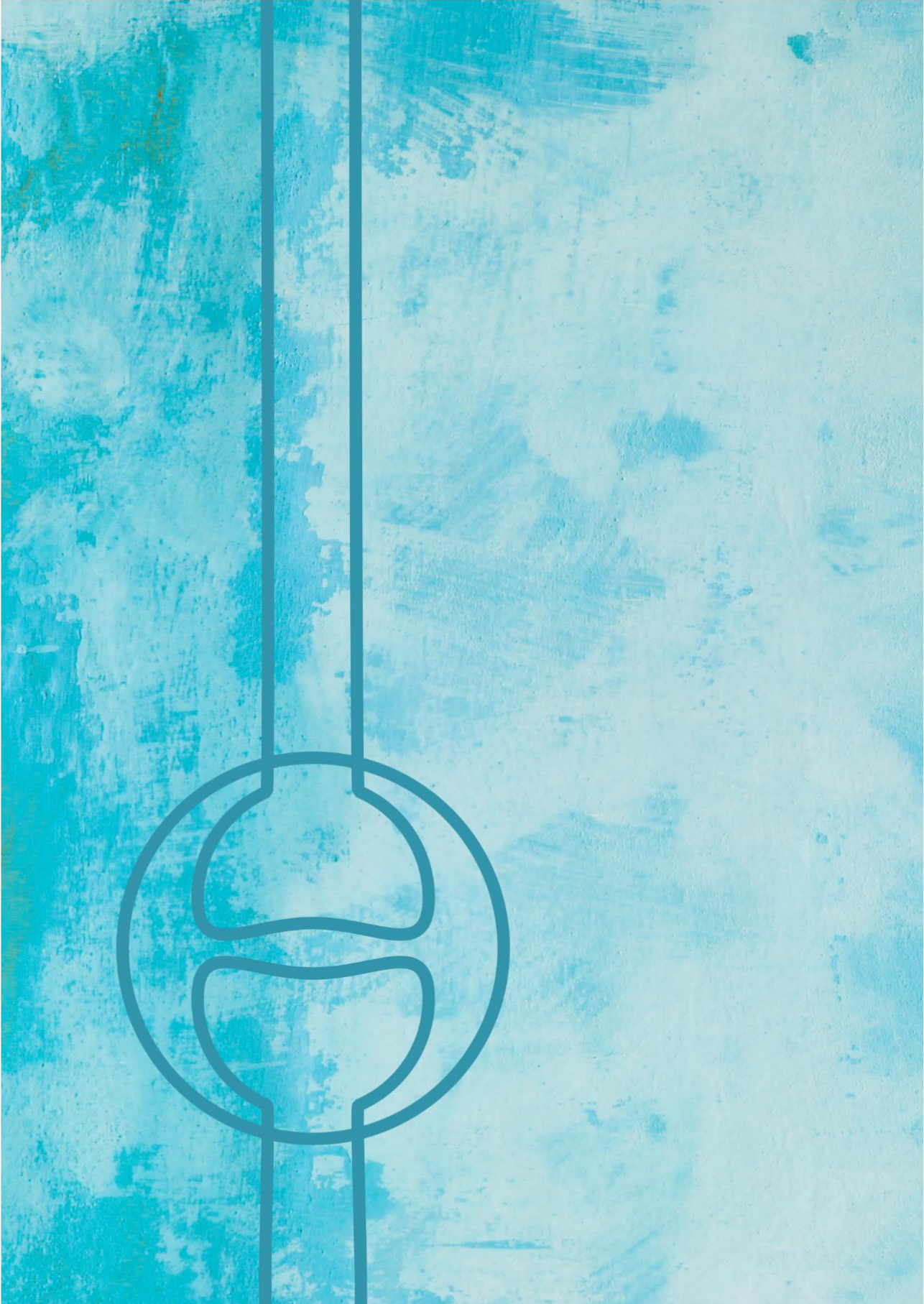
Supplementary Table S4.3 (continued)

1st biologic/ tsDMARD	2nd biologic/ tsDMARD	Normal weight (n=155)	Overweight (n=140)	Obese (n=90)
secukinumab		1 (0.65)	1 (0.71)	2 (2.22)
secukinumab	infliximab	1 (100.00)	-	-
secukinumab	golimumab	-	-	1 (50.00)
secukinumab	ixekizumab	-	1 (100.00)	-
secukinumab	tofacitinib	-	-	1 (50.00)
ustekinumab		1 (0.65)	1 (0.71)	0 (0)
ustekinumab	adalimumab	1 (100.00)	-	-
ustekinumab	etanercept	-	1 (100.00)	-
apremilast		5 (3.23)	3 (2.14)	7 (7.78)
apremilast	adalimumab	3 (60.00)	-	3 (42.86)
apremilast	etanercept	-	-	2 (28.57)
apremilast	golimumab	-	-	1 (14.29)
apremilast	secukinumab	1 (20.00)	2 (66.67)	-
apremilast	ustekinumab	-	1 (33.33)	-
apremilast	apremilast	1 (20.00)	-	1 (14.29)

Supplementary Table S4.4 First and second biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) among the rheumatoid arthritis (RA) patients. Only those RA patients with recorded information on both treatments were included. Results as number and percentage.

1st biologic/tsDMARD	2nd biologic/tsDMARD	Normal weight (n = 749)	Overweight (n = 479)	Obese (n = 259)	Underweight (n = 59)
adalimumab (n (%))		228 (30.44)	156 (32.57)	82 (31.66)	16 (27.12)
adalimumab	adalimumab	32 (14.04)	20 (12.82)	8 (9.76)	4 (25.00)
adalimumab	etanercept	63 (27.63)	43 (27.56)	23 (28.05)	6 (37.50)
adalimumab	infliximab	19 (8.33)	10 (6.41)	4 (4.88)	-
adalimumab	certolizumab	5 (2.19)	2 (1.28)	3 (3.66)	-
adalimumab	golimumab	13 (5.70)	13 (8.33)	5 (6.10)	4 (25.00)
adalimumab	rituximab	42 (18.42)	19 (12.18)	15 (18.29)	1 (6.25)
adalimumab	abatacept	29 (12.72)	17 (10.90)	13 (15.85)	-
adalimumab	tocilizumab	17 (7.46)	26 (16.67)	5 (6.10)	-
adalimumab	apremilast	1 (0.44)	-	-	-
adalimumab	baricitinib	-	1 (0.64)	-	1 (6.25)
adalimumab	tofacitinib	7 (3.07)	5 (3.21)	6 (7.32)	-
etanercept (n (%))		266 (35.51)	156 (32.57)	72 (27.8)	22 (37.29)
etanercept	adalimumab	102 (38.35)	58 (37.18)	30 (41.67)	11 (50.00)
etanercept	etanercept	34 (12.78)	14 (8.97)	5 (6.94)	1 (4.55)
etanercept	infliximab	32 (12.03)	18 (11.54)	8 (11.11)	4 (18.18)
etanercept	certolizumab	5 (1.88)	3 (1.92)	1 (1.39)	-
etanercept	golimumab	11 (4.14)	10 (6.41)	7 (9.72)	-
etanercept	rituximab	33 (12.41)	17 (10.90)	10 (13.89)	1 (4.55)
etanercept	abatacept	16 (6.02)	9 (5.77)	4 (5.56)	2 (9.09)
etanercept	anakinra	-	1 (0.64)	-	-
etanercept	tocilizumab	19 (7.14)	15 (9.62)	1 (1.39)	3 (13.64)
etanercept	baricitinib	2 (0.75)	-	1 (1.39)	-
etanercept	tofacitinib	12 (4.51)	11 (7.05)	5 (6.94)	-
infliximab (n (%))		139 (18.56)	87 (18.16)	40 (15.44)	16 (27.12)
infliximab	adalimumab	45 (32.37)	28 (32.18)	16 (40)	9 (56.25)
infliximab	etanercept	29 (20.86)	17 (19.54)	4 (10)	3 (18.75)
infliximab	infliximab	16 (11.51)	9 (10.34)	-	1 (6.25)
infliximab	certolizumab	1 (0.72)	-	-	-
infliximab	golimumab	4 (2.88)	5 (5.75)	1 (2.5)	-
infliximab	rituximab	15 (10.79)	14 (16.09)	10 (25)	1 (6.25)
infliximab	abatacept	15 (10.79)	5 (5.75)	5 (12.5)	-
infliximab	tocilizumab	13 (9.35)	9 (10.34)	4 (10)	2 (12.5)
infliximab	tofacitinib	1 (0.72)	-	-	-
certolizumab (*n* (%))		16 (2.14)	6 (1.25)	7 (2.7)	0 (0)
certolizumab	adalimumab	1 (6.25)	-	-	-
certolizumab	etanercept	3 (18.75)	2 (33.33)	1 (14.29)	-
certolizumab	infliximab	2 (12.50)	-	-	-
certolizumab	certolizumab	2 (12.50)	1 (16.67)	1 (14.29)	-
certolizumab	golimumab	-	-	1 (14.29)	-
certolizumab	rituximab	1 (6.25)	-	-	-
certolizumab	abatacept	2 (12.50)	1 (16.67)	2 (28.57)	-
certolizumab	tocilizumab	2 (12.50)	1 (16.67)	1 (14.29)	-
certolizumab	ixekizumab	-	-	1 (14.29)	-
certolizumab	baricitinib	1 (6.25)	-	-	-
certolizumab	tofacitinib	2 (12.5)	1 (16.67)	-	-
golimumab (*n* (%))		40 (5.34)	22 (4.59)	23 (8.88)	3 (5.08)
golimumab	adalimumab	6 (15)	1 (4.55)	2 (8.70)	-
golimumab	etanercept	8 (20)	4 (18.18)	4 (17.39)	1 (33.33)
golimumab	infliximab	2 (5)	2 (9.09)	2 (8.70)	-

golimumab	certolizumab	-	2 (9.09)	1 (4.35)	-
Supplementary Table S4.4 (continued)		**Normal weight**	**Overweight**	**Obese**	**Underweight**
1st biologic/tsDMARD	**2nd biologic/tsDMARD**	**(n = 749)**	**(n = 479)**	**(n = 259)**	**(n = 59)**
golimumab	golimumab	7 (17.5)	2 (9.09)	3 (13.04)	1 (33.33)
golimumab	rituximab	1 (2.5)	2 (9.09)	2 (8.70)	-
golimumab	abatacept	8 (20)	3 (13.64)	3 (13.04)	-
golimumab	tocilizumab	4 (10)	6 (27.27)	3 (13.04)	1 (33.33)
golimumab	tofacitinib	4 (10)	-	3 (13.04)	-
rituximab (*n* (%))		11 (1.47)	7 (1.46)	4 (1.54)	0 (0)
rituximab	adalimumab	2 (18.18)	1 (14.29)	-	-
rituximab	etanercept	1 (9.09)	1 (14.29)	-	-
rituximab	infliximab	-	1 (14.29)	-	-
rituximab	certolizumab	1 (9.09)	-	-	-
rituximab	rituximab	4 (36.36)	3 (42.86)	1 (25)	-
rituximab	abatacept	-	-	2 (50)	-
rituximab	tocilizumab	2 (18.18)	-	-	-
rituximab	baricitinib	-	1 (14.29)	-	-
rituximab	tofacitinib	1 (9.09)	-	1 (25)	-
abatacept (n (%))		23 (3.07)	21 (4.38)	19 (7.34)	1 (1.69)
abatacept	adalimumab	1 (4.35)	-	-	-
abatacept	etanercept	2 (8.70)	5 (23.81)	1 (5.26)	-
abatacept	infliximab	1 (4.35)	-	1 (5.26)	-
abatacept	golimumab	-	2 (9.52)	2 (10.53)	1 (100)
abatacept	rituximab	4 (17.39)	4 (19.05)	2 (10.53)	-
abatacept	abatacept	7 (30.43)	2 (9.52)	4 (21.05)	-
abatacept	tocilizumab	6 (26.09)	7 (33.33)	6 (31.58)	-
abatacept	baricitinib	-	1 (4.76)	1 (5.26)	-
abatacept	tofacitinib	2 (8.70)	-	2 (10.53)	-
tocilizumab (*n* (%))		19 (2.54)	17 (3.55)	7 (2.70)	1 (1.69)
tocilizumab	adalimumab	2 (10.53)	1 (5.88)	2 (28.57)	-
tocilizumab	etanercept	1 (5.26)	2 (11.76)	-	-
tocilizumab	certolizumab	1 (5.26)	-	-	-
tocilizumab	golimumab	-	3 (17.65)	-	-
tocilizumab	rituximab	3 (15.79)	-	2 (28.57)	-
tocilizumab	abatacept	5 (26.32)	2 (11.76)	2 (28.57)	1 (100)
tocilizumab	tocilizumab	4 (21.05)	4 (23.53)	1 (14.29)	-
tocilizumab	baricitinib	-	1 (5.88)	-	-
tocilizumab	tofacitinib	3 (15.79)	4 (23.53)	-	-
tofacitinib (*n* (%))		7 (0.93)	7 (1.46)	5 (1.93)	0 (0)
tofacitinib	adalimumab	1 (14.29)	-	1 (20)	-
tofacitinib	certolizumab	-	1 (14.29)	-	-
tofacitinib	golimumab	2 (28.57)	1 (14.29)	2 (40)	-
tofacitinib	rituximab	1 (14.29)	-	-	-
tofacitinib	abatacept	1 (14.29)	1 (14.29)	-	-
tofacitinib	tocilizumab	1 (14.29)	3 (42.86)	-	-
tofacitinib	baricitinib	1 (14.29)	-	1 (20)	-
tofacitinib	tofacitinib	-	1 (14.29)	1 (20)	-



Chapter 5

Minimal Disease Activity and remission in psoriatic arthritis patients with elevated body mass index: an observational cohort study in the Swiss Clinical Quality Management cohort

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ENRIQUETA VALLEJO-YAGÜE
THERESA BURKARD
RAPHAEL MICHEROLI
ANDREA M. BURDEN

Abstract

Objective

To assess the impact of elevated body mass index (BMI) in the achievement of Minimal Disease Activity (MDA) and several definitions of remission in patients with psoriatic arthritis (PsA) in Switzerland. Secondarily, to assess the overlapping across the study outcomes.

Methods

This observational cohort study in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry included patients with PsA starting their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD) from 1997 to 30 June 2018. Exposure was BMI category at b/tsDMARD start: overweight, obese and normal weight (reference). Logistic regression was used to assess the achievement of MDA and remission at ≤12 months, as well as treatment persistence at 1 year, in overweight patients and patients with obesity compared with the normal weight group. Remission was defined by Disease Activity for Psoriatic Arthritis (DAPSA), clinical DAPSA (cDAPSA) and 28-joint Disease Activity Score (DAS28). Additionally, overlapping across study outcomes was investigated.

Results

The study included 306 (39.5%) normal weight patients, 285 (36.8%) overweight patients and 183 (23.6%) patients with obesity. Compared with the normal weight group, patients with obesity had lower odds of achieving MDA at ≤12 months (adjusted OR (ORadj) 0.45, 95% CI 0.24 to 0.82). This was consistent with the observed reduced odds of achieving DAPSA-remission (ORadj 0.42, 95% CI 0.21 to 0.85), cDAPSA-remission (ORadj 0.51, 95% CI 0.27 to 0.96) and DAS28-remission (ORadj 0.51, 95% CI 0.32 to 0.81) in patients with obesity versus normal weight patients. Among the 125 patients achieving MDA, the majority (81.8% normal weight, 80.0% overweight, 78.9% obese) achieved cDAPSA-remission. No differences were observed in the odds to achieving treatment persistence between the BMI strata.

Conclusions

Obesity halved the likelihood of achieving MDA and remission in patients with PsA with b/tsDMARDs compared with those with normal weight, while it did not impact treatment persistence. High overlapping of patients achieving the outcomes MDA and cDAPSA-remission was observed across every BMI group.

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ENRIQUETA VALLEJO-YAGÜE
THERESA BURKARD
RAPHAEL MICHEROLI
ANDREA M. BURDEN

Introduction

Psoriatic arthritis (PsA) is an immune-mediated rheumatic disease,[1] with an estimated prevalence of 0.05%–0.42%,[2–4] and 5%–41% among patients with psoriasis.[3] PsA is a complex and multifactorial disease,[5] for which pathological features include musculoskeletal involvement, such as inflammation of the peripheral joints (arthritis), the entheses (enthesitis), the axial skeleton (spondylitis) and the finger and toe digits (dactylitis), as well as extra-articular manifestations involving skin and nails, and potentially other organs.[6] Pharmacological treatments include conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs).[3] Treatment of PsA aims to maximise health-related quality of life (QoL), through targeting symptoms and structural damage,[7] and it is recommended to target low/minimal disease activity or remission.[6]

One of the most common comorbidities in patients with PsA is obesity,[1,8] and higher prevalence of obesity has been reported among patients with PsA (23%–37%) compared with the general population.[9–12] Among patients with PsA, obesity has been associated to lower probability of achieving MDA compared with patients with normal weight.[10,13,14] Similarly, patients with obesity who have PsA treated with tumour necrosis factor alfa (TNF) inhibitors showed higher risk of treatment

discontinuation compared with patients without obesity,[15] as well as lower odds of achieving treatment response compared with patients without obesity[15] or normal weight patients.[16]

The rationale behind the association between obesity and PsA has been previously discussed.[5,17,18] In short, obesity has been described as a low-grade inflammatory disease,[18] and both obesity and PsA share pathological inflammatory pathways.[5,18,19] Further evidence supporting the association between obesity and a worse PsA clinical outcome is the association of weight loss with higher rate of achieving MDA.[20] Additionally, obesity is a well-known contributor to the metabolic syndrome (MetS), and MetS was similarly associated with lower likelihood of achieving MDA in patients with PsA.[21]

Despite the growing evidence on the association between obesity and worse clinical response in patients with PsA, most published observational cohort studies on this topic had relatively small sample size. For example, a systematic review investigating the association between obesity and response in immune-mediated inflammatory diseases identified one randomised clinical trial and eight observational cohort studies in patients with PsA, but six of the included observational cohorts had a sample size ≤330.[16] Thus, further investigating this effect, especially in a different and bigger population cohort, remains of interest. Additionally, it is unclear whether the findings would remain consistent across outcome definitions.

Thus, we seek to contribute to the growing body of evidence by performing an observational cohort study aiming to assess the impact of body mass index (BMI) in the achievement of MDA and remission in patients with PsA. Additionally, by including several outcome definitions we aim to investigate the consistency of the findings when considering different aspects of the disease.

Methods

Study design and data source

We performed an observational cohort study in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry from 1 January 1997 to 31 July 2019. The SCQM is a national longitudinal population-based cohort of rheumatic diseases in Switzerland, initiated in 1997.[22] SCQM data are recorded during routine clinical practice, and include information on demographics, body height and weight, lifestyle habits, antirheumatic medication (with start and stop dates), clinical endpoints, patient-reported outcomes and health standardised surveys.[12,22] Diagnosis of PsA is recorded in SCQM following the physician's criteria.

Study population

Patients with PsA (≥18 years old) starting their first b/tsDMARD in the SCQM registry between 1 June 2020 and 30 June 2018 (inclusive) were included in the study. The first recorded start of b/tsDMARD in the SCQM was defined as the index date. Patients with a b/tsDMARD start date before their first registered visit at SCQM were excluded. Similarly, patients without a baseline record on height and weight were excluded.

Exposure

The exposure of interest was BMI category at the start of the patients' first b/tsDMARD. Baseline BMI (kg/m^2) was calculated using height and weight records (**Supplementary Equation S5.1**) at index date or as close as possible to this date within a 6-month look-back window. Measures of height and weight are taken in the clinic, during routine visits to the rheumatologist. Patients were classified based on BMI as normal weight (BMI <25 kg/ m^2), overweight (BMI 25.0–29.9 kg/m^2) and obese (BMI ≥30 kg/m^2). The normal weight group was the reference category.

Outcomes

The primary outcome was defined as achievement of Minimal Disease Activity (MDA) within the first year after the index date. MDA was achieved if at least five of the following seven criteria were met: number of tender joint counts (TJC) ≤1; number of swollen joint counts (SJC) ≤1; skin manifestation none or almost none; patient's joint pain by visual analogue scale (VAS, 0–100) ≤15; patient's assessment on PsA activity by VAS ≤20; Health Assessment Questionnaire (HAQ) ≤0.5; enthesis points ≤1.[23]

Secondary outcomes assessed within the first year were: achievement of Disease Activity for Psoriatic Arthritis (DAPSA) remission, defined as DAPSA ≤4; DAPSA-remission or low disease activity (DAPSA-remLDA), defined as DAPSA ≤14; clinical DAPSA (cDAPSA) remission, defined as cDAPSA ≤4 and 28-joint Disease Activity Score (DAS28) remission, defined as DAS28 <2.6. DAPSA, cDAPSA and DAS28 formulas are described in the **Supplementary Equations S5.2-S5.5**. DAS28-remission was calculated using erythrocyte sedimentation rate (ESR; DAS28-ESR), however, in cases where follow-up data on DAS28-ESR was missing, DAS28 with C reactive protein (CRP; DAS28-CRP) was used instead, if available.

As a tertiary outcome, persistence with the first b/tsDMARD at the end of month 12 was assessed. We allowed for a permissible gap of 1 month between treatment courses of the same b/tsDMARD, as illustrated in the **Supplementary Figure S5.1**.

Patients with missing information on the study outcomes during the follow-up were categorised as not having achieved the corresponding outcome. In a sensitivity analysis, we re-ran our analyses excluding patients with missing information on outcome during follow-up.

Follow-up

For primary and secondary outcomes, patients were followed from index date until achievement of outcome or a maximum follow-up of 12 months. For the tertiary outcome (treatment persistence), patients were followed until the earliest of the following: treatment stop, start of a new b/tsDMARD or end of observation period (12 months).

In a secondary analysis, all outcomes were assessed with a maximum follow-up of 9 months and 15 months. This was done to investigate if the findings would differ across shorter and longer follow-up times.

Covariates

Baseline variables included demographics, BMI, high education, ever smoking, antirheumatic medication (i.e., b/tsDMARD, csDMARD, corticosteroid), inflammatory markers or acute phase reactants (i.e., ESR, CRP), physician's assessment on disease activity and skin, patient-reported disease activity and pain, tender and swollen joint counts, composite disease activity scores (i.e., DAPSA, cDAPSA, DAS28-ESR), disease-specific manifestations (i.e., musculoskeletal manifestations, dactylitis, enthesitis, sacroilitis, spinal involvement, coxitis, peripheral arthritis, nail manifestation), health standardised surveys (i.e., HAQ, Short Form-12 (SF-12)) and comorbidities (i.e., cardiovascular event/disease, diabetes or other metabolic problems, depression/anxiety). Baseline variables were collected at index date, or as close as possible to that date within a 6-month look-back window, except for composite disease activity scores, disease-specific manifestations and health standardised surveys, which were collected with a 3-month look-back window; information on smoking, cardiovascular event/ disease and diabetes, which was included if ever reported prior or at index date and antirheumatic medication, which was collected on the index date.

Additional information on covariates is included in **Supplementary Text S5.1**.

Data analysis

Patient baseline characteristics were described, and the overweight and obese categories were compared with the normal weight group (reference group) using X^2 test for categorical variables and t-test, analysis of variance or Kruskal-Wallis test for continuous variables. For these tests, missing values did not function as a grouping variable. Statistical significance was defined as $p \leq 0.05$.

Subsequently, missingness for key baseline variables was addressed with multiple imputation by chained equation (MICE) using the mice package[24] in the R Statistical Software.[25] MICE was performed for each study outcome separately, using 50 imputations with 15 iterations for each set. Variables included in the imputations, their original missingness and corresponding applied imputation models are presented in the **Supplementary Table S5.1**. The 48.32% of the study population had complete information on every variable included in the MICE for the main analysis (**Supplementary Figure S5.2**). Convergence of imputations was assessed by visual inspection of density plots (**Supplementary Figure S5.3**).

To investigate the association between BMI categories and the study outcomes, multivariable logistic regression models were conducted (outcome specific) for individual imputed datasets, and the results were pooled to a single estimate according to Rubin's rules. These models were conducted first, including only sex and age as covariates, and second, adding clinical confounders (full-adjusted). Confounders were chosen based on clinical rational and direct acyclic graphs (**Supplementary Figure S5.4**), and included: sex (male; female), age, high education (yes/no), ever smoking (yes/no), b/tsDMARD (TNF inhibitor; other biologic; tsDMARD), csDMARD at index date (yes/no) and corticosteroid use at index date (yes/no). Additionally, sensitivity analyses were performed whereby we added the respective composite disease activity score or health standardised survey to the fully adjusted models for primary and secondary outcomes to assess their potential mediating impact on the analyses. Another sensitivity analysis addressed the 1-year outcomes after excluding patients with underweight (BMI <18.5 kg/m^2)

Lastly, to compare the overlapping across study outcomes, the proportion of patients achieving each outcome (per BMI group) was summarised, and the overlapping of patients achieving individual primary and secondary outcomes during the first year was illustrated with a Venn diagram.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Table 5.1 Patient characteristics at start of first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD), prior imputation, stratified by body mass index (BMI).

	Normal weight	Overweight		Obese	
	(n=306)	(n=285)	p value	(n=183)	p value
Sex, women	172 (56.21)	126 (44.21)	0.01	101 (55.19)	0.90
Age, years (mean (SD))	47.59 (13.20)	50.60 (12.52)	0.01	49.50 (11.03)	0.10
High education (high technical school or university)	80 (26.14)	42 (14.74)	0.00	27 (14.75)	0.01
missing	54 (17.65)	51 (17.89)		41 (22.4)	
Smoker (ever smoker)	77 (25.16)	84 (29.47)	0.28	54 (29.51)	0.35
Disease duration, years (mean (SD))	5.85 (8.07)	5.54 (6.98)	0.63	4.51 (6.02)	0.06
missing	6 (1.96)	6 (2.11)		5 (2.73)	
b/tsDMRAD			0.87		0.35
TNF inhibitor biologic[a]	279 (91.18)	262 (91.93)		160 (87.43)	
other biologic[b]	9 (2.94)	9 (3.16)		6 (3.28)	
tsDMARD[c]	18 (5.88)	14 (4.91)		17 (9.29)	
csDMARD at index	152 (49.67)	151 (52.98)	0.47	100 (54.64)	0.33
Corticosteroid (prednisone) at index	38 (12.42)	38 (13.33)	0.83	17 (9.29)	0.36
HLA-B27+	39 (12.75)	28 (9.82)	0.30	20 (10.93)	0.88
missing	141 (46.08)	132 (46.32)		92 (50.27)	
ESR (mm/h) (median [IQR])	10.00 [5.00, 22.00]	12.00 [6.00, 22.00]	0.15	15.00 [6.00, 23.00]	0.10
missing	38 (12.42)	43 (15.09)		24 (13.11)	
CRP (mg/dL) (median [IQR])	0.52 [0.20, 0.90]	0.60 [0.30, 1.10]	0.18	0.80 [0.40, 1.20]	0.03
missing	48 (15.69)	52 (18.25)		27 (14.75)	
Swollen joint counts (0-66) (mean (SD))	4.70 (5.31)	5.78 (7.17)	0.05	4.88 (5.34)	0.73
missing	36 (11.76)	18 (6.32)		18 (9.84)	
Tender joint counts (0-68) (mean (SD))	8.20 (9.23)	9.18 (10.36)	0.25	8.72 (9.80)	0.58
missing	36 (11.76)	18 (6.32)		19 (10.38)	
Physician global disease activity (1-10) (mean (SD))	4.42 (2.04)	4.58 (1.88)	0.32	4.41 (1.85)	0.96
missing	16 (5.23)	9 (3.16)		6 (3.28)	
Patient's assessment on PsA activity (1-10) (mean (SD))	5.08 (2.73)	5.57 (2.50)	0.05	6.05 (2.56)	0.00
missing	82 (26.8)	57 (20)		46 (25.14)	
Patient's joint pain (1-10) (mean (SD))	4.88 (2.65)	5.48 (2.39)	0.01	6.18 (2.36)	<0.001
missing	76 (24.84)	54 (18.95)		44 (24.04)	

Table 5.1 (continued)

	Normal weight	Overweight		Obese	
	(n=306)	(n=285)	p value	(n=183)	p value
Physician global skin manifestation			0.11		0.07
none	75 (24.51)	48 (16.84)		31 (16.94)	
almost none	55 (17.97)	55 (19.3)		34 (18.58)	
mild	56 (18.3)	66 (23.16)		36 (19.67)	
mild to moderate	35 (11.44)	30 (10.53)		18 (9.84)	
moderate	27 (8.82)	35 (12.28)		33 (18.03)	
moderate to severe	19 (6.21)	28 (9.82)		13 (7.10)	
severe	9 (2.94)	6 (2.11)		4 (2.19)	
missing	30 (9.80)	17 (5.96)		14 (7.65)	
Musculoskeletal manifestations	232 (75.82)	213 (74.74)	0.84	140 (76.5)	0.95
Dactylitis	101 (33.01)	106 (37.19)	0.33	66 (36.07)	0.55
Enthesitis	116 (37.91)	103 (36.14)	0.72	67 (36.61)	0.85
Sacroilitis	72 (23.53)	64 (22.46)	0.83	27 (14.75)	0.03
Spinal involvement	81 (26.47)	70 (24.56)	0.66	40 (21.86)	0.30
Coxitis	13 (4.25)	8 (2.81)	0.47	15 (8.2)	0.11
Peripheral arthritis	141 (46.08)	138 (48.42)	0.63	94 (51.37)	0.30
Nail manifestation	64 (20.92)	62 (21.75)	0.88	47 (25.68)	0.27
DAPSA (mean (SD))	23.14 (15.73)	27.94 (18.23)	0.01	26.56 (14.18)	0.07
missing	118 (38.56)	103 (36.14)		77 (42.08)	
cDAPSA (mean (SD))	22.04 (15.21)	26.39 (17.57)	0.01	25.60 (13.70)	0.04
missing	107 (34.97)	80 (28.07)		71 (38.80)	
DAS28-ESR (mean (SD))	3.34 (1.26)	3.61 (1.33)	0.02	3.44 (1.22)	0.43
missing	51 (16.67)	49 (17.19)		34 (18.58)	
SF-12 mcs (mean (SD))	45.87 (11.36)	45.11 (11.66)	0.49	43.85 (11.68)	0.11
missing	77 (25.16)	78 (27.37)		51 (27.87)	
SF-12 pcs (mean (SD))	38.95 (10.67)	37.63 (9.71)	0.18	35.79 (9.04)	0.01
missing	77 (25.16)	78 (27.37)		51 (27.87)	
HAQ (mean (SD))	0.71 (0.66)	0.79 (0.58)	0.20	0.93 (0.61)	0.00
missing	60 (19.61)	59 (20.70)		48 (26.23)	
Cardiovascular event/disease	26 (8.50)	39 (13.68)	0.06	31 (16.94)	0.01
Diabetes or other metabolic problems	10 (3.27)	20 (7.02)	0.06	14 (7.65)	0.05
Depression/anxiety	13 (4.25)	17 (5.96)	0.45	10 (5.46)	0.69

Table 5.1 (continued)

Values are the number and column percentage, unless otherwise specified. Significance tests compare overweight or obese categories to the normal weight group (reference) using chi-squared test for categorical variables, and t-test or ANOVA for continuous variables, but Kruskal-Wallis test for ESR and CRP. For these tests, missing values did not function as a grouping variable. Normal weight (BMI <25 kg/m2); Overweight (BMI 25.0-29.9 kg/m2); Obese (BMI≥30 kg/m2).

A adalimumab, etanercept, infliximab, certolizumab, golimumab;

b abatacept, secukinumab, tocilizumab, ustekinumab; c apremilast.

Abbreviations: BMI body mass index; p p-value; n sample size; SD Standard deviation; IQR Interquartile range; b/tsDMARD biologic or targeted synthetic disease-modifying antirheumatic drug; TNF tumour necrosis factor alpha; tsDMARD targeted synthetic disease modifying antirheumatic drug; csDMARD conventional synthetic disease modifying antirheumatic drug; HLA-B27+ human leukocyte antigen B27 positive; ESR erythrocyte sedimentation rate; mm/h millimetres per hour; CRP C-reactive protein; mg/dL milligrams per decilitre; PsA psoriasis arthritis; DAPSA Disease Activity Index for Psoriatic Arthritis; DAS28 28-joint Disease Activity Score; SF-12 Short-Form 12 health survey (SF-12); mcs mental component summary; pcs physical component summary; HAQ Health Assessment Questionnaire.

Results

The study included 774 adult patients with PsA starting their first b/tsDMARD. Supplementary **Figure S5.5** illustrates the cohort selection process. Among included patients, 306 (39.53%) were normal weight, 285 (36.82%) were overweight and 183 (23.64%) were obese. Baseline patient characteristics (prior to imputation) are presented in **Table 5.1**. Compared with the normal weight group, overweight patients had higher SJC, were less frequently women and had older mean age. Both overweight patients and patients with obesity had lower frequency of high education, and higher patient-reported disease activity and joint pain, while only patients with obesity had higher CRP levels. Compared with the normal weight category, DAPSA and DAS28 were elevated in the overweight group, while cDAPSA was higher in both overweight and obese BMI categories. HAQ and SF-12 with physical components were worse in the patients with obesity, and patients with obesity were more likely to have had a cardiovascular event/disease than the normal weight group.

Results from the logistic regression for the primary analysis are presented in **Figure 5.1**. Compared with the normal weight group, patients with obesity had significantly lower odds of achieving MDA within the first year, with an adjusted OR (ORadj) of 0.45 (95% CI 0.24 to 0.82). Similarly, both overweight patients and patients with obesity had >50% reduced odds of achieving DAPSA-remission (overweight ORadj 0.44 (95% CI 0.24 to 0.79) and obese ORadj 0.42 (95% CI 0.21 to 0.85)), compared with normal weight patients. Additionally, patients with obesity had reduced odds of achieving cDAPSA-remission (ORadj 0.51 (95% CI 0.27 to 0.96)) and DAS28-remission (ORadj 0.51 (95% CI 0.32 to 0.81)) within the first year.

No differences were observed across BMI categories on achievement of DAPSA-remLDA or treatment persistence at the end of month 12.

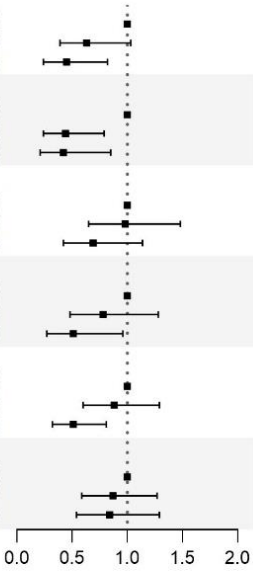
The secondary analyses showed that extending the maximum follow-up to 15 months resulted in similar findings to those from the 12 months analyses (**Table 5.2**). However, in the 9-month analyses, the associations of obesity with DAPSA-remission and with cDAPSA-remission were no longer significant (**Table 5.2**).

In the sensitivity analysis in which the respective composite disease activity score or health standardised survey was included in the model, the previously observed findings in the high BMI groups were attenuated, with the exception of obesity and achievement of MDA (**Supplementary Table S5.2**). The sensitivity analysis excluding patients with missing information on outcome during the 1-year follow-up yielded stronger reduced odds of achieving MDA and remission among abnormal BMI categories versus the normal weight group (**Supplementary Table S5.3**). The sensitivity analysis excluding the 12 patients with BMI <18.5 kg/m^2 yielded similar results to the main study findings (**Supplementary Table S5.4**).

The frequency of achieved outcomes (with 12 months follow-up) per BMI category are presented in **Figure 5.2**. Overall, 125 patients achieved MDA, 83 DAPSA-remission, 197 DAPSA-remLDA, 112 cDAPSA-remission and 275 DAS28-remission within the first year. Across all outcomes, patients with obesity had a lower prevalence of achieved outcomes. DAS28-remission and treatment persistence had the highest prevalence in all groups, with 37.58% and 59.80% achieved among normal weight patients and 27.87% and 51.37% among patients with obesity, respectively.

The overlap of patients achieving the outcomes during the first year is illustrated in **Figure 5.3**, complemented with numerical values in **Supplementary Table S5.5**. Among the 125 patients achieving MDA (66 normal weight, 40 overweight, 19 with obesity), 80 also achieved DAPSA-remission, of which 48 (72.73%) were normal weight, 20 (50.00%) were overweight and 12 (63.16%) were with obesity. Similarly, among patient with MDA, 54 (81.82%) normal weight, 32 (80.00%) overweight and 15 (78.95%) patients with obesity also achieved cDAPSA-remission. Additionally, MDA overlapped with every remission outcome in 45 (68.18%) normal weight, 18 (45.00%) overweight and 11 (57.89%) patients with obesity.

Outcome at ≤12 months unless otherwise specified	sample size, n	n (%) events	OR (95% CI)	ORadj (95% CI)	ORadj (95% CI)
MDA					
Normal weight	306	66 (21.6)	1 (ref.)	1 (ref.)	
Overweight	285	40 (14.0)	0.59 (0.38-0.91)	0.63 (0.39-1.03)	
Obese	183	19 (10.4)	0.43 (0.25-0.74)	0.45 (0.24-0.82)	
DAPSA-remission					
Normal weight	306	51 (16.7)	1 (ref.)	1 (ref.)	
Overweight	285	20 (7.0)	0.38 (0.22-0.66)	0.44 (0.24-0.79)	
Obese	183	12 (6.6)	0.36 (0.19-0.70)	0.42 (0.21-0.85)	
DAPSA-remLDA					
Normal weight	306	84 (27.5)	1 (ref.)	1 (ref.)	
Overweight	285	76 (26.7)	0.95 (0.65-1.37)	0.98 (0.65-1.48)	
Obese	183	37 (20.2)	0.67 (0.43-1.04)	0.69 (0.42-1.14)	
cDAPSA-remission					
Normal weight	306	57 (18.6)	1 (ref.)	1 (ref.)	
Overweight	285	39 (13.7)	0.69 (0.44-1.08)	0.78 (0.48-1.28)	
Obese	183	16 (8.7)	0.43 (0.24-0.77)	0.51 (0.27-0.96)	
DAS28-remission					
Normal weight	306	115 (37.6)	1 (ref.)	1 (ref.)	
Overweight	285	109 (38.2)	0.99 (0.70-1.39)	0.88 (0.6-1.29)	
Obese	183	51 (27.9)	0.64 (0.43-0.96)	0.51 (0.32-0.81)	
Treatment persistence at the end of month-12					
Normal weight	306	183 (59.8)	1 (ref.)	1 (ref.)	
Overweight	285	161 (56.5)	0.84 (0.60-1.17)	0.87 (0.59-1.27)	
Obese	183	94 (51.4)	0.71 (0.49-1.03)	0.84 (0.54-1.29)	



OR: odds ratio adjusting for: sex, age;

ORadj: odds ratio adjusting for: sex, age, high educational level, smoker, b/tsDMARD, csDMARD, corticosteroid.

n number; CI confidence interval; ref. reference; MDA Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSA-remission clinical DAPSA remission; DAS28-remission 28-joint disease activity score remission.

Figure 5.1 Results from the multivariable logistic regression investigating the association between body mass index categories and various clinical outcomes. Maximum follow-up 12 months. Abbreviations: MDA, Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSA-remission clinical DAPSA remission; DAS28-remission 28-joint Disease Activity Score remission; n number; OR odds ratio; ORadj adjusted odds ratio; b/tsDMARD biologic or targeted synthetic disease-modifying antirheumatic drug; csDMARD conventional synthetic disease-modifying antirheumatic drug; ref. reference.

Table 5.2 Result from the multivariable logistic regression investigating the association between body mass index (BMI) categories and various clinical outcomes, with maximum follow-up 9 months and 15 months.

		Sample size, n	Maximum follow-up 9-months			Maximum follow-up 15-months		
			n vents	OR	Oradj	n vents	OR	Oradj
MDA	Normal weight	306	45 (14.7)	1 (ref.)	1 (ref.)	86 (28.1)	1 (ref.)	1 (ref.)
	Overweight	285	21 (7.4)	0.47 (0.27-0.82)	0.52 (0.28-0.96)	61 (21.4)	0.67 (0.45-0.98)	0.75 (0.48-1.15)
	Obese	183	12 (6.6)	0.41 (0.21-0.80)	0.44 (0.21-0.94)	30 (16.4)	0.50 (0.31-0.80)	0.57 (0.34-0.96)
DAPSA remission	Normal weight	306	31 (10.1)	1 (ref.)	1 (ref.)	67 (21.9)	1 (ref.)	1 (ref.)
	Overweight	285	11 (3.9)	0.35 (0.17-0.72)	0.40 (0.18-0.88)	31 (10.9)	0.42 (0.26-0.68)	0.50 (0.30-0.84)
	Obese	183	8 (4.4)	0.41 (0.18-0.92)	0.49 (0.20-1.18)	17 (9.3)	0.37 (0.21-0.67)	0.47 (0.25-0.87)
DAPSA remLDA	Normal weight	306	47 (15.4)	1 (ref.)	1 (ref.)	117 (38.2)	1 (ref.)	1 (ref.)
	Overweight	285	37 (13)	0.81 (0.51-1.30)	0.88 (0.52-1.50)	104 (36.5)	0.91 (0.65-1.27)	0.90 (0.62-1.31)
	Obese	183	22 (12)	0.75 (0.43-1.29)	0.75 (0.40-1.40)	52 (28.4)	0.64 (0.43-0.95)	0.66 (0.42-1.03)
cDAPSA remission	Normal weight	306	36 (11.8)	1 (ref.)	1 (ref.)	77 (25.2)	1 (ref.)	1 (ref.)
	Overweight	285	22 (7.7)	0.62 (0.35-1.09)	0.70 (0.38-1.30)	53 (18.6)	0.65 (0.43-0.98)	0.75 (0.48-1.16)
	Obese	183	12 (6.6)	0.53 (0.27-1.06)	0.64 (0.31-1.35)	23 (12.6)	0.43 (0.26-0.72)	0.55 (0.32-0.95)
DAS28 remission	Normal weight	306	68 (22.2)	1 (ref.)	1 (ref.)	153 (50)	1 (ref.)	1 (ref.)
	Overweight	285	64 (22.5)	1.01 (0.68-1.49)	0.91 (0.58-1.43)	140 (49.1)	0.91 (0.65-1.28)	0.89 (0.61-1.3)
	Obese	183	29 (15.8)	0.67 (0.41-1.08)	0.50 (0.28-0.89)	70 (38.3)	0.62 (0.42-0.91)	0.57 (0.36-0.88)
Treatment persistence at end of follow-up	Normal weight	306	204 (66.7)	1 (ref.)	1 (ref.)	159 (52)	1 (ref.)	1 (ref.)
	Overweight	285	184 (64.6)	0.86 (0.60-1.21)	0.91 (0.60-1.36)	148 (51.9)	0.96 (0.69-1.34)	0.97 (0.67-1.42)
	Obese	183	111 (60.7)	0.77 (0.52-1.12)	0.91 (0.57-1.44)	81 (44.3)	0.73 (0.51-1.07)	0.87 (0.57-1.33)

OR: odds ratio adjusting for: sex, age;

ORadj: odds ratio adjusting for: sex, age, high educational level, smoker, b/tsDMARD, csDMARD, corticosteroid.

Abbreviations: n number; CI confidence interval; ref. reference; MDA Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSA-remission clinical DAPSA remission; DAS28-remission 28-joint Disease Activity Score remission.

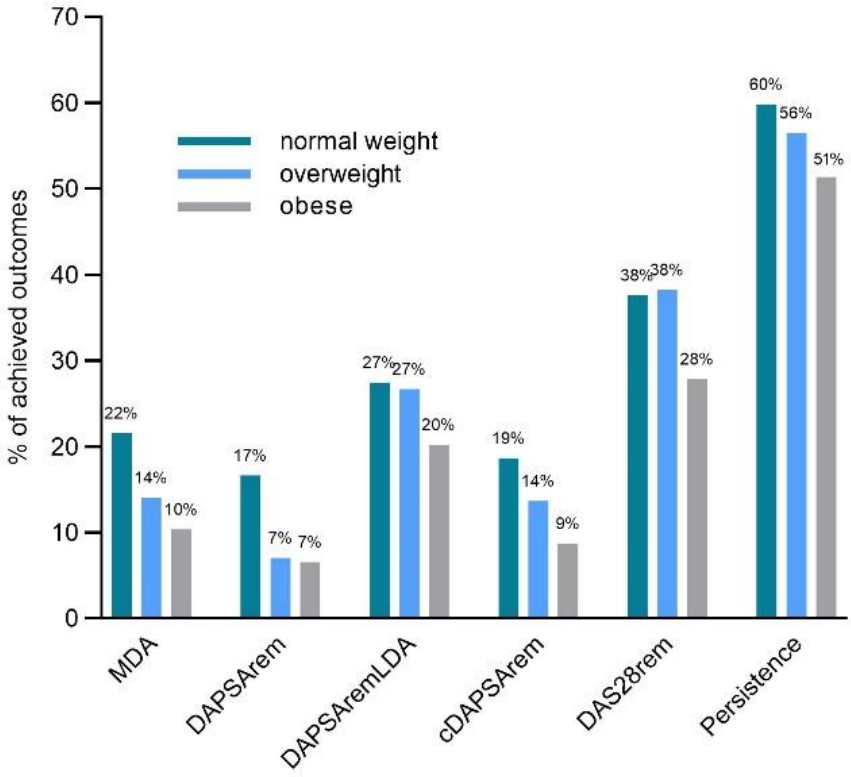


Figure 5.2 Distribution of patients achieving the study primary and secondary outcomes within the first year, and percentage of patients achieving treatment persistence at the end of month 12, stratified by body mass index category. Abbreviations: MDA Minimal Disease Activity; DAPSArem Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSArem clinical DAPSA remission; DAS28rem 28-joint Disease Activity Score remission.

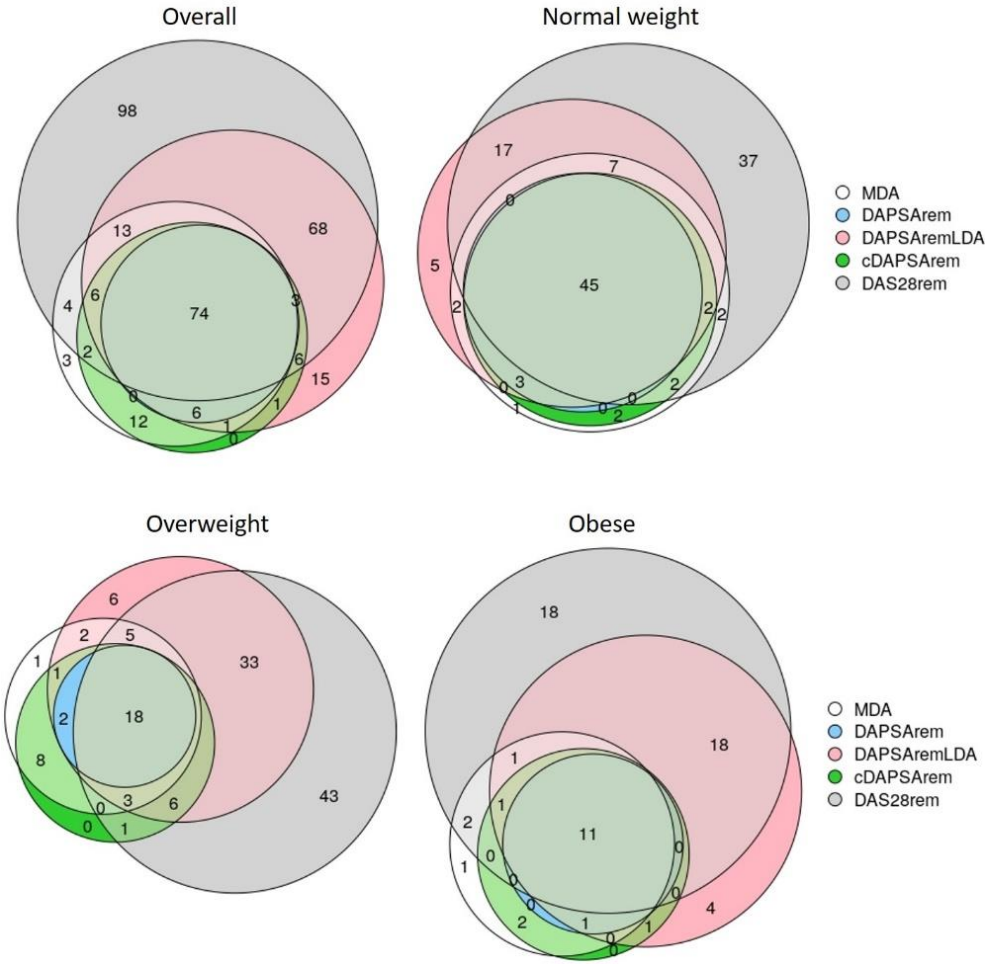


Figure 5.3 Venn diagram depicting the number of patients (counts) achieving the study individual primary and secondary outcomes within the first year, overall and stratifying by body mass index category. Abbreviations: MDA Minimal Disease Activity; DAPSArem Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSArem clinical DAPSA remission; DAS28rem 28-joint Disease Activity Score remission.

Discussion

This observational cohort study found that patients with obesity had a significant 49%–58% reduced odds of achieving MDA, DAPSA-remission, cDAPSA-remission and DAS28-remission within the first year, when compared with normal weight patients. Conversely, being overweight was only associated with a reduced odds of achieving DAPSA remission. In both high BMI categories, the association with achievement of DAPSA-remLDA within the first year and with 1-year treatment

persistence, were not statistically significant. Among patients who achieved MDA, the majority also achieved cDAPSA-remission.

Our findings on the association between obesity and lower probability of reaching MDA and remission are consistent with other longitudinal observational studies.[10,13,15] In the prospective study by Di Minno et al., obesity was associated with increased risk of not achieving MDA during a 12 months follow-up compared with patients with BMI <30 kg/m^2 (HR 4.90, 95% CI 3.04 to 7.87).[13] Eder et al. reported that, compared with normal weight patients (BMI <25 kg/m^2), overweight patients and patients with obesity had 34% and 47% significantly reduced odds of achieving MDA, respectively.[10] While we identified a similar OR in the overweight patients and patients with obesity, our results in the overweight group were not statistically significant. In the study by Højgaard et al, obesity was associated with 53% lower odds of achieving European Alliance of Associations for Rheumatology good or moderate (EGOM) response.[15] While we did not assess EGOM response, this is a DAS28-driven outcome, and the findings are in agreement with our observed association between obesity and 49% reduced odds for DAS28-remission. Conversely, Iannone et al. suggested no significant differences in DAS28-remission rates across BMI categories.[26] However, they had a small sample size (135 patients), and their observed lower remission rate in the obese vs normal weight patients was in line with our findings.

Additionally, results from Højgaard et al. showed that compared with patients without obesity (BMI <30 kg/m^2), patients with obesity were associated with a 60% higher risk of TNF inhibitor discontinuation during their study period (median follow-up of 1.5 years).[15] While our study did not yield an association between BMI and treatment persistence, these contrasting findings may be explained by the different methodologies. Højgaard et al. assessed the time to withdrawal using a survival model, which gives high attention to early outcomes, while we investigated persistence yes/no at a specific timepoint using logistic regression.

In our study, MDA was the main outcome as it covers several aspects from the disease presentation and consequences, and has been associated with patient's QoL and productivity.[27] Additionally, McGagh and Coates suggested that the 66/68 joint counts provide a more realistic picture of joint involvement in PsA, compared with the 28 joint counts, and highlighted the benefits of including patient-reported outcomes.[28] Based on this, we identified DAPSA-remission and cDAPSA-remission as optimal secondary outcomes. However, we expect that cDAPSA may be a better fit to study patients with abnormal BMI since obesity was associated with elevated CRP in the general population.[29–31] This is further supported by the high overlap of patients achieving MDA and cDAPSA-remission in our study, which was similar across every BMI group.

Regarding the observed higher frequency of achievement of DAS28-remission compared with other remission endpoints, this may be explained by its narrow focus on peripheral manifestations, potentially underestimating residual disease activity. Nevertheless, the consistency of the observed results on MDA and remission outcomes in the obese group suggests that obesity affects peripheral joints, as well as disease-specific manifestations and the patient's perspective. However, we note that the different outcome definitions led to contrasting results in the overweight group, suggesting that the effect of overweight on the PsA may not be fully captured by every remission definition. Similarly, the impact of obesity on PsA clinical response was not consistent with the more clinically accessible outcome low disease activity (DAPSA-remLDA).

The reasons for the lower response rates in patients with obesity could be multiple. High body weight can affect the clearance and volume of distribution of b/tsDMARDs.[32–34] Adipose tissue has a proinflammatory capacity,[35] which could negatively influence drug response. Finally, a relationship between mechanical stress and triggering of musculoskeletal inflammation (deep Köbner phenomenon) in PsA is discussed. Nevertheless, the observed lower odds of achieving MDA or remission in the obese group is of interest, and the consistency across the studied definitions of remission suggests that this effect may be reflected on several factors of the PsA disease.

Finally, as described elsewhere,[12] the prevalence of overweight and obesity were higher among patients with PsA in comparison to the general population in Switzerland (Switzerland 2017, people >15 years old, 31% overweight and 11% obese).[36] Higher obesity prevalence among patients with PsA in comparison to the reference population was in agreement with prior studies.[12]

Strengths and limitations

In addition to the large sample size and availability of BMI information (often lacking in real-world data), the key strength of this study is the use of several relevant clinical outcome definitions. While multiple approaches to assess PsA disease activity exist, no single one has been identified as sufficient[37] and the choice of the optimal measure remains challenging.[28] The consistency of the observed results on MDA and remission outcomes in the obese group reinforces the study findings. However, we did not look at unidimensional outcomes (e.g., dactylitis) and this remains of interest for future studies. Additionally, while standard MDA definition includes Psoriasis Activity and Severity Index ≤1 or Body Surface Area ≤3,[38] due to data restrictions our MDA definition included a skin manifestation of 'none' or 'almost none', as reported by the physician.

We did not require a minimum time between treatment start and outcome record. In a post hoc test, we identified that the median time to the record for MDA assessment was between 214 and 245 days, similar across the BMI groups. Additionally, patients could have records of the outcome

variable(s) at more than one visit during follow-up. When more than one record was available, all were assessed to identify if successful outcome was achieved.

Intrinsic to real-world data, missingness was a limitation. We addressed missingness at baseline with multiple imputation and missingness during follow-up with sensitivity analyses. Our results were mainly consistent among various sensitivity analyses. For example, the secondary analysis excluding patients who missed information on the outcome during follow-up (instead of treating them as non-achievers of the respective outcome), supported the observed effect of obesity towards MDA and remission, which was even accentuated in this sensitivity analysis. Among secondary analyses varying the duration of follow-up, the 15-month analyses showed consistence with the main findings, and the reduced effect found in the 9-month analyses may be explained by higher missingness of outcome information at shorter follow-up, and therefore lower number of observed events overall.

Limitations to consider when interpreting the results include the potential misclassification of patients in the BMI categories. While overweight and obesity are commonly defined by BMI,[39,40] this lacks information on body composition. Thus, although data on waist circumference, skinfold thickness and bioelectrical impedance may provide a better patient classification, this information is extremely limited in real-world data. Additionally, we classified patients with BMI <25 kg/m^2 as normal weight, including patients with BMI <18.5 kg/m^2, who may be classified as underweight. This was done due to low prevalence of underweight patients with PsA in SCQM[12] and is consistent with previous practice in PsA[10,26] and other inflammatory rheumatic diseases research in which the majority of studies combine normal and underweight patients.[41]

It was suggested that patients with obesity may benefit from other non-TNF b/tsDMARDs, however, the evidence is limited.[42] Nevertheless, our results of a lower odds of achieving remission may be largely driven by the high TNF inhibitor use in our cohort.

Finally, since weight loss in overweight patients and patients with obesity was identified as a predictor of MDA achievement,[20] it remains of interest to perform a similar study to this one but stratifying the overweight patients and patients with obesity by those with and without weight loss.

Conclusion

This study suggests that obesity in patients with PsA is associated with at least a 50% reduction in the likelihood of achieving MDA or remission within the first year after starting b/tsDMARD therapy, when compared with normal weight patients. The consistency of findings across definitions of remission suggests that obesity affects several factors of PsA disease. Conversely, obesity was neither associated with the likelihood of achieving low disease activity nor with treatment persistence. Finally,

comparative analyses of b/tsDMARDs within BMI groups is of interest and investigating the benefits of losing weight in this population remains of interest.

Remarks on main author contributions: EV-Y contributed to the conceptualisation and methodology, data curation, formal analysis, visualisation, investigation, resources, interpretation of the results, drafting and editing the manuscript, and critical revisions.

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Supplementary material

Supplementary Equations S5

$$BMI = \frac{weight\ Kg}{height\ m^2} \quad (1)$$

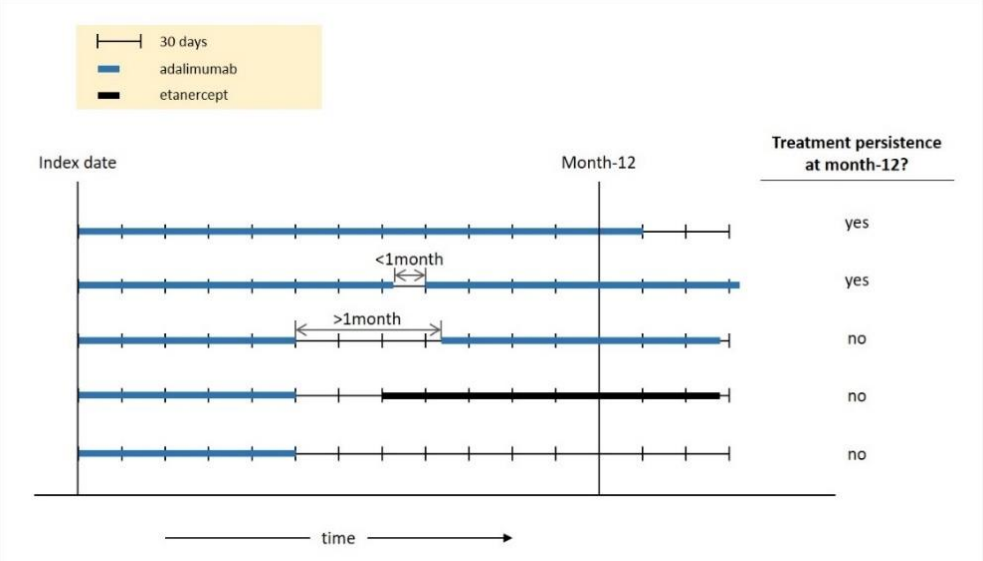
$$DAPSA = sjc66 + tjc68 + PatActivity + PatPain + CRP \quad (2)$$

$$cDAPSA = sjc66 + tjc68 + PatActivity + PatPain \quad (3)$$

$$DAS28ESR = \left(0.56 \times \sqrt{tjc28}\ + 0.28 \times \sqrt{sjc28}\ + 0.7 \times ln(ESR)\right) \times 1.08 + 0.16 \quad (4)$$

$$DAS28CRP = \left(0.56 \times \sqrt{tjc28}\ + 0.28 \times \sqrt{sjc28}\ + 0.36 \times ln(CRP + 1)\right) \times 1.10 + 1.15 \quad (5)$$

Abbreviations used in the above equations: DAPSA disease activity in psoriasis arthritis score; cDAPSA clinical DAPSA; DAS28 28-joint Disease Activity Score; sjc66 number of swollen joints, counting 66; sjc28 number of swollen joints, counting 28; tjc68 number of tender joints, counting 68; tjc28 number of tender joints, counting 28; CRP C-reactive protein (mg/dL); ESR erythrocyte sedimentation rate (mm/h); PatActivity patien''s assessment of disease activity (0 very well–- 10 very poor); PatPain patien''s joint pain (0 very well–- 10 very poor).



Supplementary Figure S5.1 Graphical representation of the assessment of treatment persistence at month-12 for an example patient who starts adalimumab as first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD).

Supplementary Text S5.1 Additional information on covariates.

High education was defined as 'höhere Fachschule' (university of applied sciences), or 'Universitätsstudium' (university study); and the no category for this variable was defined by 'obligatorische Schule' (compulsory school), 'Berufslehre' (apprenticeship), or 'Maturitätsschule' (3-4 year high school that enables direct admission to Universities school)'.

Smoker (ever smoker) was defined by at least one record of smoker prior index date.

Patient and physician assessments on disease activity, pain, or skin manifestations, as well as medication, disease specific manifestations (musculoskeletal manifestations, dactylitis, enthesitis, sacrolitis, spinal involvement, coxitis, peripheral arthritis, nail manifestations) and comorbidities are recorded as specific variables in SCQM.

Information on comorbidities was extracted from the SCQM health issues dataset or table, which contains patient reported information. Lack of disease or health issue was assumed unless otherwise stated. Cardiovascular event/disease included cerebrovascular disease, coronary heart disease, deep vein thrombosis, heart infarct, heart insufficiency, peripheral vascular disease, pulmonary embolism, hypertension, hypotension, other cardiovascular disease, and other heart disease, ever before the index date. Diabetes included type I and type II, ever before index date. Other metabolic problems included adrenal disease, thyroid disease, diseases of other endocrine glands, dysfunctions of water electrolyte balance or acid alkaline balance, hyperlipidaemia, and hyperuricemia, within the 6-months prior index date. Depression/anxiety includes depression and anxiety, within the 6-months prior index date.

Supplementay Table S5.1. Variables included in the multiple imputation.

Variable	Version 1, included	Version 2, included	Predicted	Predictor	Method	Missingness	Levels	Range
Outcome[a] (MDA/DAPSArem/DAPSAremLDA/Persistence)	√	-	-	√	-	-	yes; no.	-
Outcome[a] (DAS28rem)	-	√	-	√	-	-	yes; no.	-
Patient ID	√	√	-	-	-	-	-	1-774
BMI category	√	√	-	-	-	-	normal weight; overweight; obese.	-
BMI kg/m^2	√	√	-	√	-	-	-	16.56–- 51.42
Sex	√	√	-	√	-	-	female (women); male (men).	-
Age	√	√	-	√	-	-	-	18.37–- 84.65
Disease duration, years	√	√	√	√	pmm	17 (2.20)	-	0.04–- 47.31
High education	√	√	√	√	logreg	146 (18.86)	yes; no.	-
ESR mm/h	√	√	√	√	pmm	105 (13.57)	-	1–- 110
CRP mg/dL	√	√	√	√	pmm	127 (16.41)	-	0–- 11.10
Physicia''s global disease activity (0-10)	√	√	√	√	pmm	31 (4.01)	-	0–- 9
Physicia''s global skin manifestation	√	√	√	√	polyreg	61 (7.88)	none; almost none; mild; mild to moderate; moderate; moderate to severe; severe.	-
Patien''s assessment on disease activity (0-10) (PatActv)	√	√	√	√	pmm	185 (23.90)	-	0–- 10
Patien''s joint pain (0-10) (PatPain)	√	√	√	√	pmm	174 (22.48)	-	0–- 10
Number of swollen joints 28 (sjc28)	√	√	√	√	pmm	20 (2.58)	-	0–- 22
Number of swollen joints 66 (sjc66)	√	√	√	√	pmm	72 (9.30)	-	0–- 48

Supplementary Table S5.1 (continued)

Variable	Version 1, included	Version 2, included	Predicted	Predictor	Method	Missingness	Levels	Range
Number of tender joints 28 (tjc28)	√	√	√	√	pmm	28 (3.62)	-	0–- 28
Number of tender joints 68 (tjc68)	√	√	√	√	pmm	73 (9.43)	-	0–- 68
DAPSA	√	-	√	√[b]	passive imputation[d]	298 (38.5)	-	0.10–- 121
DAS28	-	√	√	√[c]	passive imputation[e]	99 (12.79)	-	0.20–- 7.60
HAQ (0-3)	√	√	√	√	pmm	167 (21.58)	-	0–- 3
SF-12mcus (0-100)	√	√	√	√	pmm	206 (26.61)		18.74-67.78
SF-12pcus (0-100)	√	√	√	√	pmm	206 (26.61)		16.74-61.25
b/tsDMARD	√	√	-	√	-	-	TNF inhibitor biologic; other biologic; tsDMARD.	-
csDMARD at index	√	√	-	√	-	-	yes; no.	-
Prednisone at index	√	√	-	√	-	-	yes; no.	-
Dactylitis	√	√	-	√	-	-	yes; no.	-
Sacroilitis	√	√	-	√	-	-	yes; no.	-
Enthesitis	√	√	-	√	-	-	yes; no.	-
Spinal involvement	√	√	-	√	-	-	yes; no.	-
Coxitis	√	√	-	√	-	-	yes; no.	-

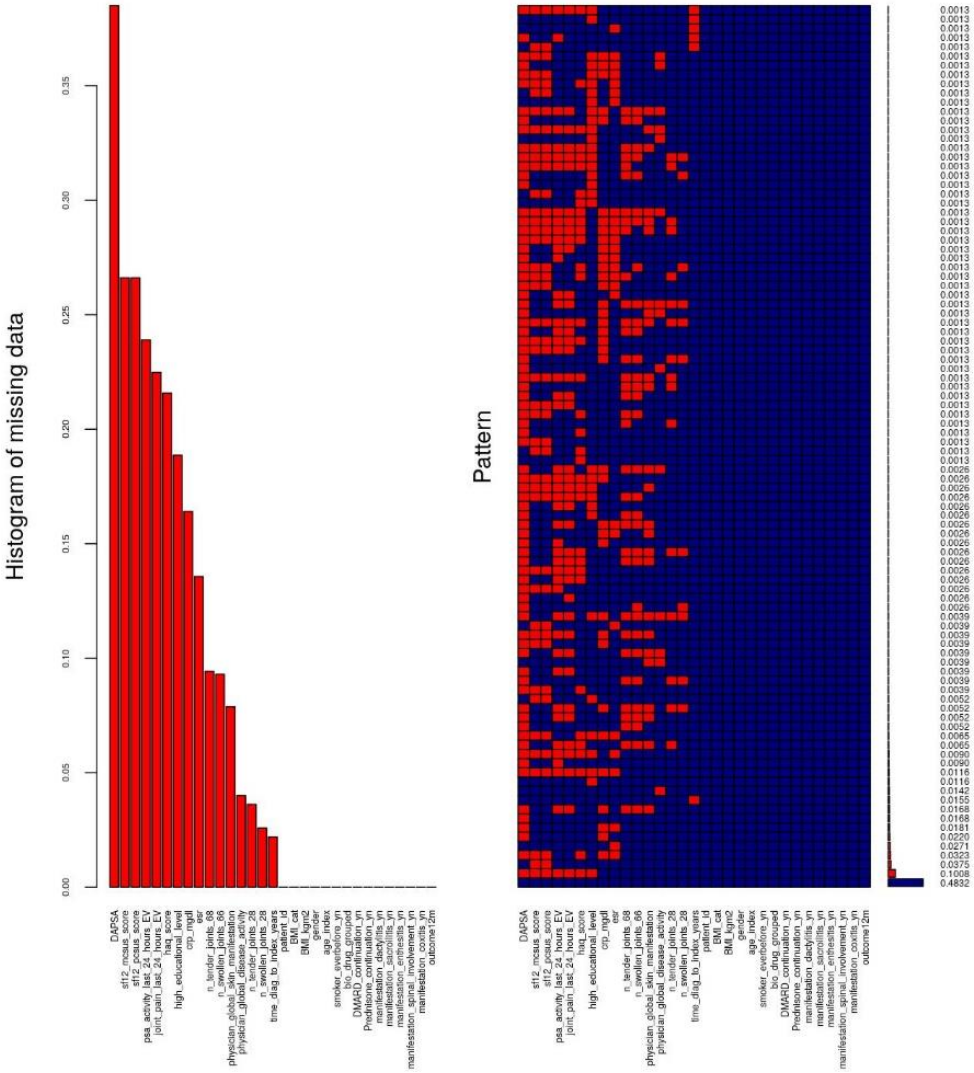
Abbreviations: BMI body mass index; ESR erythrocyte sedimentation rate; CRP C-reactive protein; PsA psoriasis arthritis; MDA Minimal Disease Activity; DAPSA Disease Activity Index for Psoriatic Arthritis; DAS28 28-joint Disease Activity Score; HAQ Health Assessment Questionnaire; b/tsDMARD biologic or targeted synthetic disease modifying antirheumatic drug;142sDMARDsD conventional synthetic disease modifying antirheumatic drug; TNF tumour necrosis factor alpha; tsDMARD targeted synthetic disease modifying antirheumatic drug; pmm predictive mean matching; logit logistic regression; polyreg polytomous logistic regression.

[a] Multiple imputation was run distinctly for each outcome; [b] DAPSA not used as predictor for: sjc66, tjc68, PatActivity, PatPain, CRP;

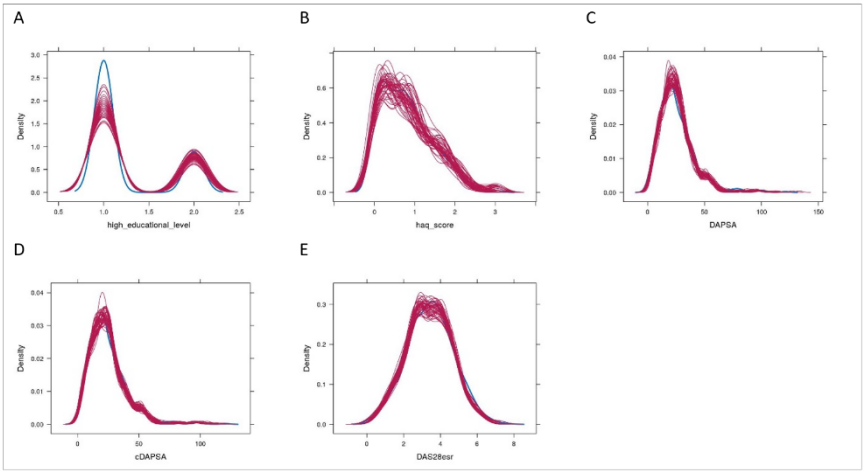
[c] DAS28 not used as predictor for: sjc28, tjc28, ESR;

[d] DAPSA passive imputation: $DAPSA = sjc66 + tjc68 + PatActivity + PatPain + CRP$

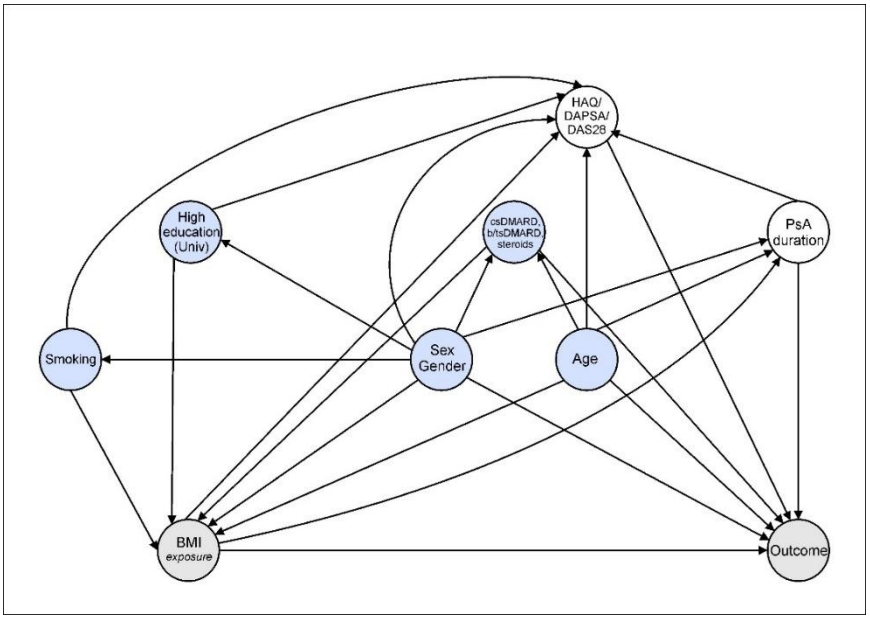
[e] DAS28 passive imputation: $DAS28ESR = \left(0.56 \times \sqrt{tjc28} + 0.28 \times \sqrt{sjc28} + 0.7 \times ln(ESR)\right) \times 1.08 + 0.16$



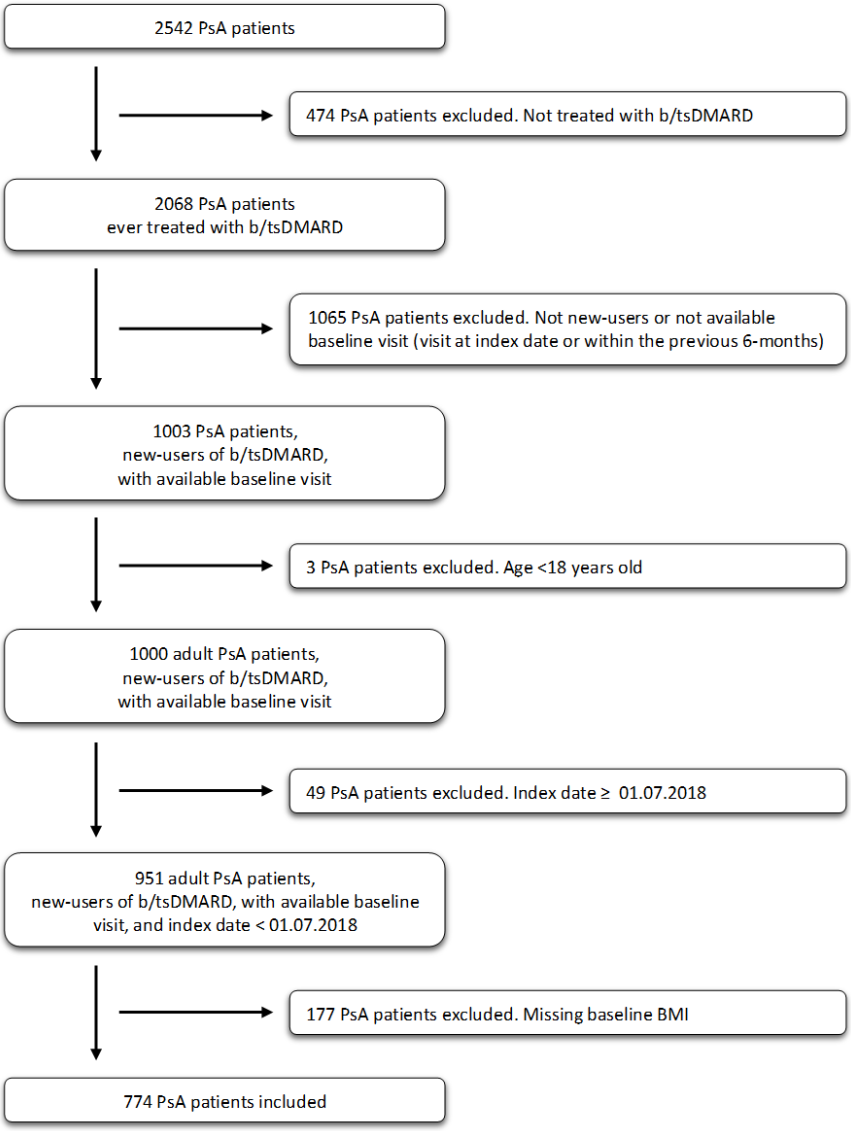
Supplementary Figure S5.2 Graphical representation of the missingness among baseline variables included in the imputations for primary analysis (i.e., achievement of Minimal Disease Activity (MDA) within the first year after index date). The 48.32% of patients had complete information on all the included variables. In the right figure, blue indicates availability of the data, and red missingness.



Supplementary Figure S5.3 Density plots for the imputed variables high educational level [A], Health Assessment Questionnaire (HAQ) [B], and Disease Activity Index for Psoriatic Arthritis (DAPSA) [C] for the primary outcome, achievement of Minimal Disease Activity (MDA) within the first year after index date. Additionally, density plot for the imputed clinical DAPSA (cDAPSA) [D] and 28-joint Disease Activity Score (DAS28) [E] for the secondary outcomes cDAPSA-remission and DAS28-remission within the first year of treatment, respectively. The variable distribution in the original dataset is shown in blue, and the corresponding distribution in each imputed dataset is shown in red.



Supplementary Figure S5.4 Direct acyclic graph (DAG) displaying the clinical rational for selection of confounders. The nodes represent the exposure, outcome and covariates, and the lines or edges represent the assumed relationship between them. Grey nodes represent the exposure and the outcome. Blue nodes represent the confounders included in the study full adjusted model. White nodes represent other variables included in sensitivity analyses.



Supplementary Figure S5.5 Flow chart reflecting the cohort selection based on inclusion and exclusion criteria.

Supplementary Table S5.2 Sensitivity analyses, including the respective composite disease activity score or health standardised survey in the multivariable logistic regression of each study outcome.

			Maximum follow-up 9-months		Maximum follow-up 12-months		Maximum follow-up 15-months	
		sample size, n	n events	oRadj[c] (95% CI)	n events	oRadj[c] (95% CI)	n events	oRadj[c] (95% CI)
MDA	Normal weight	306	45 (14.7)	1 (ref.)	66 (21.6)	1 (ref.)	86 (28.1)	1 (ref.)
	Overweight	285	21 (7.4)	0.67 (0.35-1.29)	40 (14.0)	0.69 (0.42-1.15)	61 (21.4)	0.85 (0.54-1.36)
	Obese	183	12 (6.6)	0.47 (0.19-1.14)	19 (10.4)	0.48 (0.25-0.96)	30 (16.4)	0.72 (0.4-1.27)
DAPSA remission	Normal weight	306	31 (10.1)	1 (ref.)	51 (16.7)	1 (ref.)	67 (21.9)	1 (ref.)
	Overweight	285	11 (3.9)	0.7 (0.29-1.72)	20 (7.0)	0.56 (0.28-1.1)	31 (10.9)	0.6 (0.33-1.08)
	Obese	183	8 (4.4)	0.78 (0.28-2.17)	12 (6.6)	0.49 (0.22-1.1)	17 (9.3)	0.49 (0.24-1)
DAPSA remLDA	Normal weight	306	47 (15.4)	1 (ref.)	84 (27.5)	1 (ref.)	117 (38.2)	1 (ref.)
	Overweight	285	37 (13.0)	0.91 (0.48-1.75)	76 (26.7)	1.03 (0.63-1.69)	104 (36.5)	0.79 (0.5-1.25)
	Obese	183	22 (12.0)	0.87 (0.41-1.85)	37 (20.2)	0.68 (0.38-1.22)	52 (28.4)	0.62 (0.36-1.04)
cDAPSA remission	Normal weight	306	36 (11.8)	1 (ref.)	57 (18.6)	1 (ref.)	77 (25.2)	1 (ref.)
	Overweight	285	22 (7.7)	1.04 (0.51-2.13)	39 (13.7)	0.91 (0.52-1.6)	53 (18.6)	0.78 (0.47-1.29)
	Obese	183	12 (6.6)	0.72 (0.28-1.81)	16 (8.7)	0.53 (0.25-1.11)	23 (12.6)	0.57 (0.3-1.07)
DAS28 remission	Normal weight	306	68 (22.2)	1 (ref.)	115 (37.6)	1 (ref.)	153 (50.0)	1 (ref.)
	Overweight	285	64 (22.5)	1.13 (0.68-1.9)	109 (38.2)	0.93 (0.6-1.43)	140 (49.1)	0.93 (0.6-1.42)
	Obese	183	29 (15.8)	0.67 (0.36-1.27)	51 (27.9)	0.62 (0.37-1.04)	70 (38.3)	0.69 (0.42-1.13)
Treatment persistence	Normal weight	306	204 (66.7)	1 (ref.)	183 (59.8)	1 (ref.)	159 (52.0)	1 (ref.)
	Overweight	285	184 (64.6)	0.92 (0.61-1.4)	161 (56.5)	0.88 (0.59-1.3)	148 (51.9)	1.04 (0.71-1.54)
	Obese	183	111 (60.7)	0.92 (0.56-1.49)	94 (51.4)	0.92 (0.58-1.46)	81 (44.3)	1.04 (0.66-1.64)

ORadj[c] odds ratio adjusting for sex, age, high educational level, smoker, b/tsDMARD, 146sDMARDsD, corticosteroid, and HAQ (for MDA) or DAPSA (for DAPSA-remission/DAPSA-remission/LDA) or DAS28 (for DAS28-remission).

Abbreviations: n number; CI confidence interval; ref. reference; MDA Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis remission; DAPSA-remLDA Disease Activity for Psoriatic Arthritis remission or low disease activity; cDAPSA-remission clinical Disease Activity for Psoriatic Arthritis remission; DAS28-remission 28-joint Disease Activity Score remission.

Supplementary Table S5.3 Sensitivity analysis, excluding patients without follow-up data on outcome. Multivariable logistic regression for each study outcome.

			Maximum follow-up 12-months, sensitivity analysis			
		sample size, n	n events	OR[a] (95% CI)	Oradj[b] (95% CI)	Oradj[c] (95% CI)
MDA	Normal weight	130	66 (50.8)	1 (ref.)	1 (ref.)	1 (ref.)
	Overweight	131	40 (30.5)	0.39 (0.23-0.66)	0.45 (0.25-0.80)	0.5 (0.26-0.93)
	Obese	81	19 (23.5)	0.28 (0.15-0.53)	0.33 (0.16-0.67)	0.37 (0.17-0.81)
DAPSA	Normal weight	113	51 (45.1)	1 (ref.)	1 (ref.)	1 (ref.)
remission	Overweight	113	20 (17.7)	0.23 (0.12-0.43)	0.25 (0.12-0.49)	0.37 (0.16-0.82)
	Obese	64	12 (18.8)	0.28 (0.13-0.59)	0.31 (0.14-0.71)	0.44 (0.17-1.13)
DAPSA	Normal weight	113	84 (74.3)	1 (ref.)	1 (ref.)	1 (ref.)
remLDA	Overweight	113	76 (67.3)	0.66 (0.37-1.19)	0.58 (0.3-1.12)	0.57 (0.26-1.29)
	Obese	64	37 (57.8)	0.48 (0.25-0.92)	0.44 (0.21-0.93)	0.42 (0.17-1.04)
cDAPSA	Normal weight	124	57 (46.0)	1 (ref.)	1 (ref.)	1 (ref.)
remission	Overweight	131	39 (29.8)	0.44 (0.26-0.75)	0.47 (0.26-0.85)	0.61 (0.31-1.21)
	Obese	74	16 (21.6)	0.32 (0.16-0.63)	0.36 (0.17-0.75)	0.44 (0.19-1.04)
DAS28	Normal weight	159	115 (72.3)	1 (ref.)	1 (ref.)	1 (ref.)
remisison	Overweight	153	109 (71.2)	0.86 (0.51-1.46)	0.55 (0.3-1.01)	0.57 (0.28-1.14)
	Obese	89	51 (57.3)	0.48 (0.27-0.86)	0.3 (0.15-0.6)	0.37 (0.17-0.81)

OR[a] odds ratio adjusting for: sex, age;

ORadj[b] odds ratio adjusting for: sex, age, high educational level, smoker, b/tsDMARD, 147sDMARDsD, corticosteroid.

ORadj[c] odds ratio adjusting for: sex, age, high educational level, smoker, b/tsDMARD,147sDMARDsD, corticosteroid, and HAQ (for MDA) or DAPSA (for DAPSA-remission/DAPSA-remission/LDA) or DAS28 (for DAS28-remission).

Abbreviations: n number; CI confidence interval; ref. reference; Abbreviations: n number; CI confidence interval; ref. reference; MDA Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis remission; DAPSA-remLDA Disease Activity for Psoriatic Arthritis remission or low disease activity; cDAPSA-remission clinical Disease Activity for Psoriatic Arthritis remission; DAS28-remission 28-joint Disease Activity Score remission

Supplementary Table S5.4 Sensitivity analyses, excluding the 12 patients with body mass index (BMI) <18.5 kg/m^2. Result from the multivariable logistic regression investigating the association between body mass index (BMI) categories and various clinical outcomes, with maximum follow-up 12-months.

Sensitivity analyses		Maximum follow-up 12-months			
(Excluding BMI<18.5)	sample size, n	n vents	OR	oRadj	
MDA	Normal weight	294	62 (21.1)	1 (ref.)	1 (ref.)
	Overweight	285	40 (14.0)	0.61 (0.39-0.95)	0.65 (0.40-1.06)
	Obese	183	19 (10.4)	0.44 (0.25-0.77)	0.45 (0.24-0.84)
DAPSA	Normal weight	294	47 (16)	1 (ref.)	1 (ref.)
remission	Overweight	285	20 (7.0)	0.40 (0.23-0.70)	0.46 (0.25-0.83)
	Obese	183	12 (6.6)	0.38 (0.20-0.75)	0.43 (0.21-0.88)
DAPSA	Normal weight	294	80 (27.2)	1 (ref.)	1 (ref.)
remLDA	Overweight	285	76 (26.7)	0.96 (0.66-1.40)	0.99 (0.65-1.50)
	Obese	183	37 (20.2)	0.68 (0.44-1.06)	0.70 (0.42-1.14)
cDAPSA	Normal weight	294	294 (18)	1 (ref.)	1 (ref.)
remission	Overweight	285	39 (13.7)	0.72 (0.46-1.14)	0.81 (0.49-1.33)
	Obese	183	16 (8.7)	0.45 (0.25-0.81)	0.53 (0.28-1.00)
DAS28	Normal weight	294	110 (37.4)	1 (ref.)	1 (ref.)
remission	Overweight	285	109 (38.2)	1.00 (0.71-1.42)	0.89 (0.61-1.31)
	Obese	183	51 (27.9)	0.65 (0.44-0.98)	0.51 (0.32-0.82)
Treatment persistence	Normal weight	294	179 (60.9)	1 (ref.)	1 (ref.)
at the end of follow-up	Overweight	285	161 (56.5)	0.81 (0.58-1.13)	0.83 (0.56-1.23)
	Obese	183	94 (51.4)	0.68 (0.47-0.99)	0.8 (0.52-1.24)

OR: odds ratio adjusting for: sex, age;

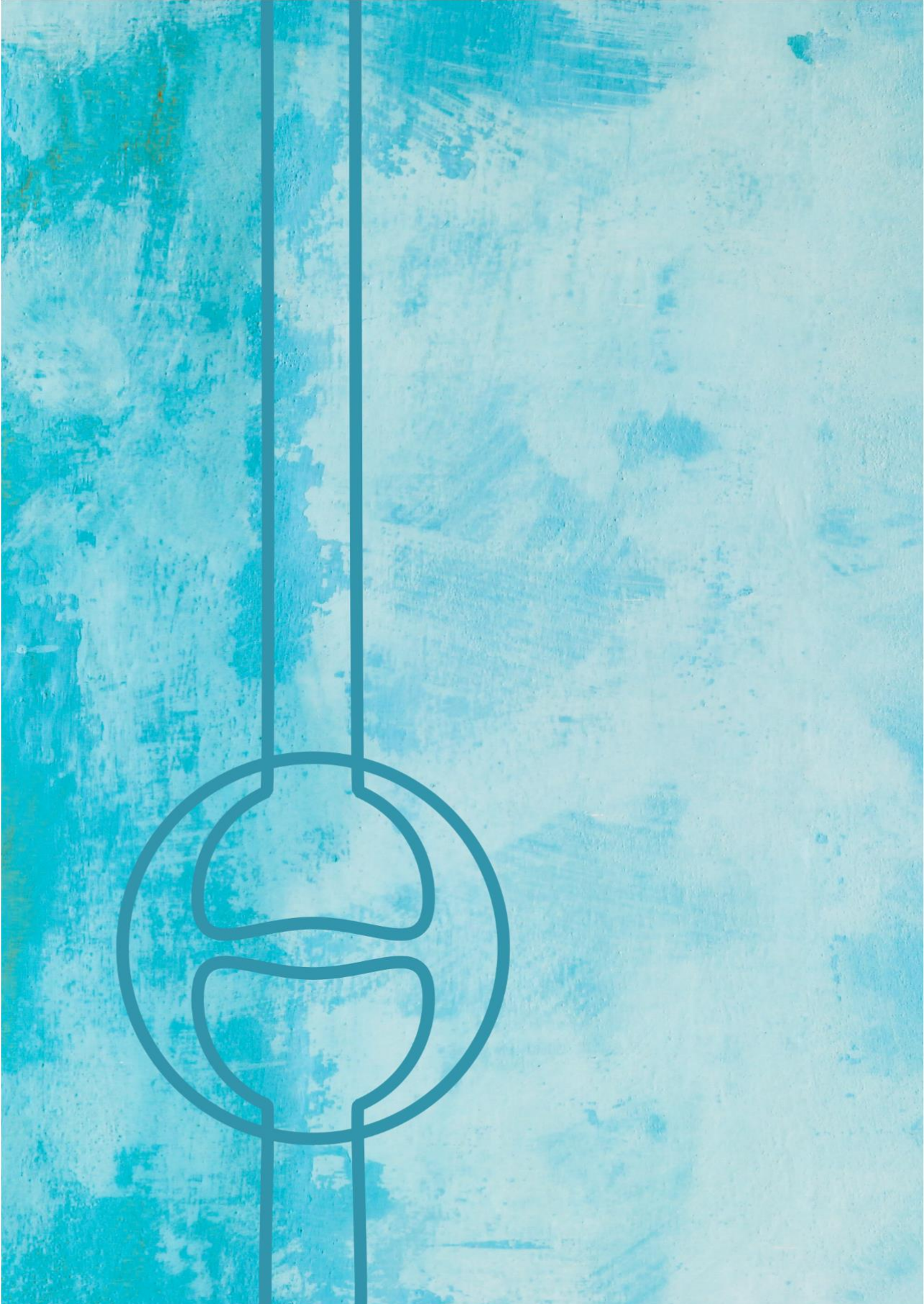
ORadj: odds ratio adjusting for: sex, age, high educational level, smoker, b/tsDMARD,148sDMARDsD, corticosteroid.

Abbreviations: n number; CI confidence interval; ref. reference; MDA Minimal Disease Activity; DAPSA-remission Disease Activity for Psoriatic Arthritis (DAPSA) remission; DAPSA-remLDA DAPSA remission or low disease activity; cDAPSA-remission clinical DAPSA remission; DAS28-remission 28-joint Disease Activity Score remission.

Supplementary Table S5.5 Number of patients, overall and stratified by body mass index (BMI) category, for each corresponding set of achieved outcomes within the first year. These numerical values complement the **Figure 5.4** Venn Diagram. Each patient may achieve none, one, or more outcomes. Each row includes patients with the same set of achieved outcomes. The symbol √ indicates that the corresponding outcome (column-wise) was achieved. Conversely, the symbol – indicates that the corresponding outcome was not achieved. To obtain the total number of patients achieving a specific outcome, every column with the corresponding outcome marked as achieved should be sum.

Achieved outcomes								
MDA	DAPSArem	DAPSAremLDA	cDAPSArem	DAS28rem	Overall (n=774) (counts)	Normal weight (n=306) (counts)	Overweight (n=285) (counts)	Obese (n=183) (counts)
√	-	-	-	-	3	1	1	1
√	-	√	-	-	4	2	2	0
√	-	-	-	√	4	2	0	2
√	-	√	-	√	13	7	5	1
√	-	-	√	-	12	2	8	2
√	-	√	√	-	1	0	1	0
√	-	-	√	√	2	2	0	0
√	-	√	√	√	6	2	3	1
√	√	√	√	-	6	3	2	1
√	√	√	√	√	74	45	18	11
-	-	√	-	-	15	5	6	4
-	-	-	-	√	98	37	43	18
-	-	√	-	√	68	17	33	18
-	-	√	√	-	1	0	0	1
-	-	-	√	√	1	0	1	0
-	-	√	√	√	6	0	6	0
-	√	√	√	√	3	3	0	0

Abbreviations: MDA Minimal Disease Activity; DAPSArem Disease Activity for Psoriatic Arthritis remission; DAPSAremLDA Disease Activity for Psoriatic Arthritis remission or low disease activity; cDAPSArem clinical Disease Activity for Psoriatic Arthritis remission; DAS28rem 28-joint Disease Activity Score remission.



Chapter 6

Comparative effectiveness of biologics in patients with rheumatoid arthritis stratified by body mass index and sex: a cohort study in SCQM

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ENRIQUETA VALLEJO-YAGÜE
THERESA BURKARD
AXEL FINCKH
ANDREA M. BURDEN
on behalf of the clinicians and patients of the
Swiss Clinical Quality Management Program

Abstract

Background

Obesity is associated with lower treatment response in patients with rheumatoid arthritis (RA). Among obese patients, abatacept was suggested as a preferable option to tumour necrosis factor alpha (TNF) inhibitors. Sex and gender differences in RA were described.

Objectives

To assess the comparative effectiveness of etanercept, infliximab, and abatacept, compared to adalimumab, in patients with RA stratified by body mass index (BMI) and sex.

Methods

Observational cohort study in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry (1997-2019). RA patients were classified in BMI-based cohorts: obese, overweight, and normal weight. Each BMI cohort was studied overall and stratified by sex. The study outcome was remission within 12-months, defined as a Disease Activity Score (DAS28) <2.6. Missingness was addressed using confounder-adjusted response rate with attrition correction (CARRAC). Logistic regression compared the effectiveness of etanercept, infliximab, and abatacept versus adalimumab.

Results

The study included 443 obese, 829 overweight, and 1243 normal weight RA patients. Across the BMI cohorts, there were no significant differences in the odds of remission at ≤12-months for the study drugs compared to adalimumab. However, among females, an inverse effect for infliximab was found, whereby overweight patients had higher odds of remission, while obese patients had lower odds of remission, compared to the respective adalimumab users.

Conclusions

Despite the previous hypothesis, treatment with abatacept showed similar odds of remission compared to adalimumab in all BMI cohorts. Conversely, compared to adalimumab, infliximab performed better in overweight female patients but worse in female patients with obesity. However, further validation is needed.

Comparative effectiveness of biologics in patients with rheumatoid arthritis stratified by body mass index and sex: a cohort study in SCQM

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ENRIQUETA VALLEJO-YAGÜE
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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, primarily characterised by joint damage, which can lead to disability.[1,2] Its pathogenesis and clinical presentation may vary between individuals and disease stages.[1] Following failure to achieve the therapeutic target with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), the European Alliance of Associations for Rheumatology (EULAR) recommends adding a biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD).[3] Supported by a recent systematic review,[4] the current EULAR guidelines have no preference for specific b/tsDMARD due to similar efficacy.[3]

Despite the advances in the treatment of RA and the availability of several b/tsDMARDs, up to 60% of patients will either not respond or lose response to therapy over time.[5–8] Thus, evidence-based decision on the optimal b/tsDMARD for each patient remains challenging. This is specifically important for RA patients with high body mass index (BMI) since obesity has been associated with worse disease activity and disease management in patients with RA,[9–14] and the prevalence of obesity was reported higher among RA cohorts compared to the reference populations.[15,16] There are

hypotheses to explain the reduced therapeutic response in patients with obesity. First, obesity is a low-grade systemic inflammatory condition,[17] which may share a common pathological pathway with immune-mediated diseases. Second, body weight can affect the drug's volume of distribution[18]. Third, the probability of developing anti-drug-antibodies (ADAbs) grows when body weight increases.[19] And fourth, obesity may affect and be affected by socially-constructed norms and behaviours with an impact on clinical management (e.g., weight stigma associated with less exercise[20]).

While previous studies have shown that obesity is associated with a detrimental response to tumour necrosis factor alpha (TNF) inhibitors,[10,14,21] it has been suggested that high BMI does not influence the response to the non-TNF biologic abatacept.[22–24] However, these studies assessed the impact of obesity on the treatment response solely among users of abatacept,[22–24] and often had small sample sizes.[22,24] Thus, it remains of interest to study the comparative effectiveness of TNF inhibitors versus abatacept in RA patients with obesity. Additionally, although similar effectiveness was suggested across TNF inhibitors in the general RA population,[25] it is unclear if this is the case in every BMI group.

Sex and gender-based differences in RA were described, including differences in the immune system, drug pharmacokinetics, treatment response rates, and immunity.[26–28] Therefore, sex-stratified analyses are of interest.

Thus, we decided to perform a comparative effectiveness analysis among RA patients who were new-users of biologics in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) cohort, stratified by BMI category and, secondarily, by sex.

Methods

Data source and study design

An observational cohort study in the SCQM registry from 1st January 1997 to 31st July 2019. The SCQM includes routinely collected data from rheumatology visits and patient-reported outcomes, including patient demographics, lifestyle habits, clinical endpoints, antirheumatic medication (with start and stop dates), patient-reported outcomes, and health standardised surveys.[16,29] More details have been described elsewhere.[16]

Study population

The study included adult (>18 years) RA patients registered in SCQM, who started adalimumab, etanercept, infliximab, or abatacept as their first b/tsDMARD between 1st January 1997 and 31st July 2018. Patients were stratified by BMI category at the start of treatment (index date). BMI categories were obese (BMI≥30 kg/m^2), overweight (≥25 and <30 kg/m^2), and normal weight (BMI ≥18.5 and <25

kg/m^2). Each BMI group was studied as an independent cohort, overall and stratified by sex (i.e., female, male). We excluded patients without a baseline BMI record and underweight patients (BMI <18.5 kg/m^2).

Exposure

The study exposure was the patient's first b/tsDMARD, including etanercept, infliximab, and abatacept, compared to adalimumab.

Outcome and follow-up

The primary outcome was clinical response during the treatment course with a maximum follow-up of 12-months. Clinical response was primarily defined as 28-joint Disease Activity Score (DAS28) remission (DAS28<2.6), which was calculated using the erythrocyte sedimentation rate (ESR, DAS28-ESR). Secondarily, clinical response was also assessed as DAS28 low disease activity (LDA), defined as DAS28<3.2; and Rheumatoid Arthritis Disease Activity Index-Five (RADAI-5) remission, defined as RADAI-5≤1.4. Treatment course was assessed using drug-specific extended time-windows after treatment stop. These were 42 days for adalimumab, 30 days for etanercept, 90 days for infliximab, and 60 or 30 days for i.v. and s.c. abatacept, respectively. Additionally, a permissible gap of up to 1-month between stop and re-start of the same treatment was accepted as treatment continuation. A schematic representation of the follow-up for the primary outcome can be seen in **Supplementary Figure S6.1**.

Additional secondary outcomes were the median change (Δ, delta) in unidimensional parameters between baseline and the best respective measurement during follow-up as described above. These included ΔESR, delta C-reactive protein (ΔCRP), delta tender joint counts (ΔTJC28), and delta swollen joint counts (ΔSJC28). Here, median values <0 reflect improvement and reduction of the respective values.

Following recent recommendations from EULAR,[30,31] missing information on primary and secondary outcomes was addressed using the confounder-adjusted response rate with attrition correction (CARRAC).[31] This consisted of multiple imputation by chain equation (MICE) that included baseline variables, treatment duration, and reason for treatment discontinuation. Additionally, missingness for the clinical response outcomes was also addressed in two other manners as sensitivity analyses: first, assuming that lack of information on outcome during follow-up was equivalent to not-achieving the outcome (MOIAN, Missing Outcome Information Assumed as No); and second, excluding patients who miss this information on outcome during follow-up (EPMOI, Excluding Patients Missing Outcome Information).

The tertiary outcome was treatment survival with a maximum follow-up of 5-years, overall and stratified by the reason for treatment stop adverse event(s), or remission, as recorded by the clinician. For this, we used the record of treatment stop without additional time extension and accepted ≤1-month gaps between stop and re-start of the same biologic as treatment continuation. Treatment stop was defined by a record of stop or by the start of a new b/tsDMARD. Otherwise, patients were censored at the time of stopping their participation at SCQM, at the end of the study period (31st July 2019), or 3-months after a visit with no subsequent visits for >2-years.

Covariates

Patient baseline characteristics were collected at the index date or within pre-defined look-back windows. Information on patient demographics, disease duration (time from RA diagnosis), seropositivity, swollen and tender joint counts (SJC28, TJC28), physician global disease activity (GDA), and body weight were collected within the 6-months prior index date. Inflammatory markers (ESR, CRP), disease activity score, and the Health Assessment Questionnaire (HAQ) were collected within the 3-months prior index date. Information on smoking (ever smoker), body height, and comorbidities were collected with an ever-before look-back window, except for records on fractures/surgeries/musculoskeletal system, which were collected within the 6-months prior index date. Information on pregnancy or breastfeeding was collected with a 12-month look-back window. Information on rheumatic medication was collected at the index date, including conventional synthetic disease-modifying antirheumatic drug (csDMARD) use, steroid use, and type of b/tsDMARD.

Statistical analysis

The obese, overweight, and normal weight groups were addressed as three distinctive cohorts. Patient baseline characteristics for each study cohort were described stratified by the exposure drug. The etanercept, infliximab, and abatacept groups were compared to the adalimumab group using chi-squared test for categorical variables and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

CARRAC was performed prior to the analysis of the clinical response outcomes and the change in unidimensional parameters. We performed 60 imputations on an outcome and cohort basis. We visually assessed the convergence of the imputations by mean and variance changes and addressed the overlapping of the distribution of continuous variables with density plots. Information on included variables and methods used in the imputations are described in **Supplementary Table S6.1,** and an example of visual assessment of the imputation of DAS28-ESR for the primary outcome (DAS28-remission) is depicted in **Supplementary Figure S6.2**.

Comparative effectiveness of the study drugs for the clinical response outcomes was assessed using logistic regression, with adalimumab as the reference group. Following the CARRAC, logistic regression was performed in each imputed dataset, and the results were subsequently pooled into a single estimate according to Rubin's rules. This regression was conducted, first, adjusting for age and sex, and second, adjusting for age, sex, index year, baseline DAS28, csDMARD at index, and steroid use at index. Sensitivity analyses were performed by MOIAN and EPMOI, followed by logistic regression calculating age and sex-adjusted odds ratio (OR).

Change in individual parameters (ΔESR, ΔCRP, ΔTJC28, ΔSJC28) was described using the median and interquartile range (IQR) and the Kruskal-Wallis test compared between the exposure drugs, using adalimumab as reference. Lastly, treatment survival was investigated with Kaplan-Meier curves for each cohort overall and stratified by reason of treatment stop (adverse event(s); remission) as recorded by the clinician. Treatment survival across drugs was compared using the log-rank test.

All analyses were independently performed for each BMI cohort (obese, overweight, and normal weight) overall and stratified by sex (female; male). The statistical analyses were performed with the R software, version 3.5.2.[33]

Results

The study included 2515 RA patients, among whom 443 (17.6%), 829 (33.0%), and 1243 (49.4%) were included in the obese, overweight, and normal weight cohorts, respectively (**Supplementary Figure S6.3**). The number of users of each study drug and their percentage within the study sub-cohorts (BMI cohorts stratified by sex) is depicted in **Figure 6.1**. The most commonly prescribed drugs were adalimumab and etanercept, followed by infliximab and abatacept. An increased use of abatacept was observed in the obese versus the normal weight cohort, especially among male patients.

Baseline characteristics for the obese and overweight cohorts are described in **Table 6.1**, and additional information is provided in **Supplementary Tables S6.3** and **S6.4**. Baseline characteristics for the normal weight cohort are described in **Supplementary Table S6.5**. In every BMI cohort, the median year of index date generally differed between the study drugs, with infliximab having the earliest and abatacept the latest. Etanercept users were very similar to adalimumab users in all BMI categories but had a significantly lower percentage of csDMARD use at index date in the obese and normal weight cohorts. Compared to the adalimumab group, infliximab users had significantly more frequent use of prednisone at index in every BMI cohort, significantly more frequent use of csDMARD at index, worse HAQ, and more frequent depression/anxiety in the overweight and normal weight

cohorts. In comparison to the adalimumab group, abatacept users were more frequently current or ever smokers in the overweight and obese cohorts and generally had more frequent history of hyperlipidemia and cardiac/cardiovascular event/disease and a tendency for more frequent diabetes. The characteristics stratified by BMI and sex are provided in **Supplementary Tables S6.6-S6.11**.

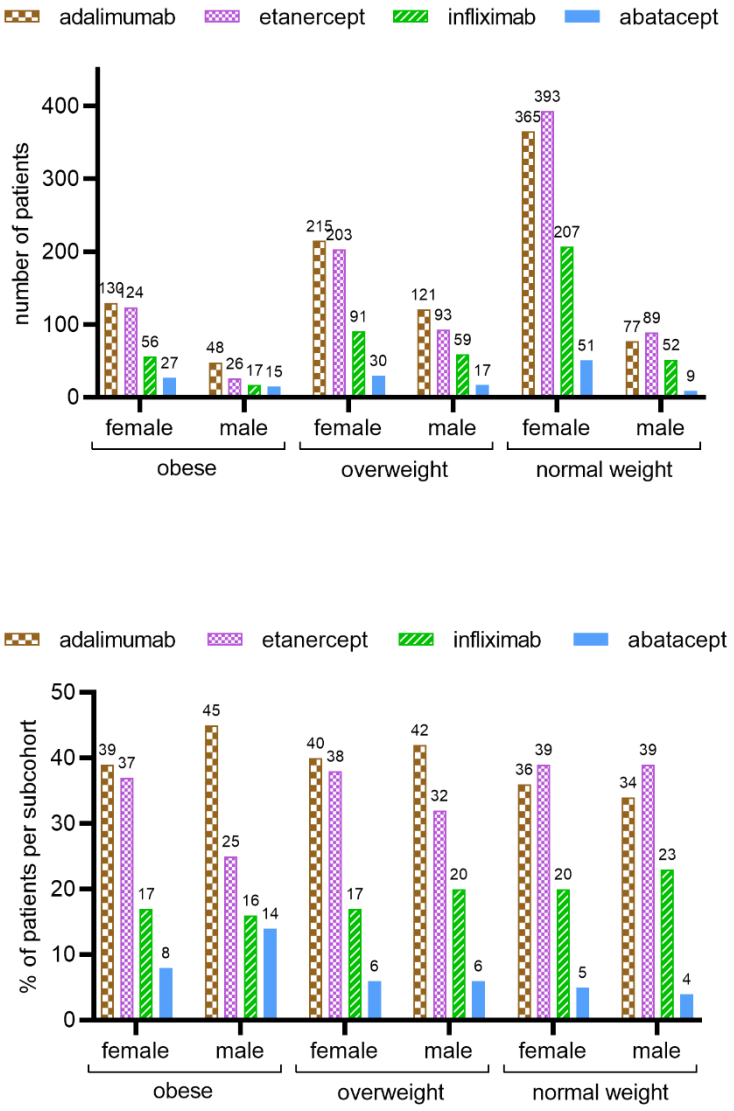

Figure 6.1 Number (top) and frequency (bottom) of patients using each study drug within each study sub-cohort (body mass index cohorts stratified by sex). The number on the columns indicates the number or percentage of patients, respectively.

Table 6.2 provides the results from the comparative effectiveness analysis for the clinical response outcomes (DAS28-remission; DAS28-LDA; RADAI-5-remission) in the overall BMI cohorts using CARRAC and MOIAN. The respective EPMOI analyses are presented in **Supplementary Table S6.12**. In the overall BMI cohorts, no significant differences were identified across the study drugs compared to adalimumab, with only one exception: In overweight patients, etanercept was associated with a reduced odds of achieving RADAI-5 remission (ORadj 0.44, 95%CI 0.22-0.90). This finding was consistent between both the sex- and age-adjusted model and the full-adjusted model, as well as consistent across the CARRAC, MOIAN, and EPMOI analyses.

Table 6.3 presents the analysis among females, including CARRAC and MOIAN. Additionally, EPMOI analyses are presented in **Supplementary Table S6.13**. Obese female patients treated with infliximab had lower odds of achieving DAS28-remission in the CARRAC age-adjusted model (OR 0.20, 95%CI 0.04-0.96), MOIAN (OR 0.26, 95%CI 0.04-0.97), and EPMOI (OR 0.20, 95%CI 0.03-0.79) analyses. However, this effect was not significant in the CARRAC full-adjusted analysis (ORadj 0.27, 95%CI 0.05-1.41). Conversely, in the overweight female cohort, higher odds of remission were observed with infliximab (ORadj 2.47, 95%CI 1.06-5.78). This effect was observed in the CARRAC full-adjusted and MOIAN analyses but not in the EPMOI analyses.

The stratification among males is provided in **Table 6.4**, and the EPMOI analyses are provided in **Supplementary Table S6.13**. Similar to the overall analysis, the overweight male users of etanercept had reduced odds of achieving RADAI-5 compared to adalimumab users. This was observed in the MOIAN and EPMOI analyses; however, not according to the CARRAC analysis.

The change in individual parameters is presented in **Table 6.5**. Among etanercept users, the overweight cohort had a significantly lower reduction (worse improvement) of CRP compared to the respective adalimumab group. This, however, was not significant when stratified by sex. For infliximab users, obese patients had significantly worse improvement on ESR and CRP, yet, in the normal weight cohort, there was a significantly higher improvement in ESR and a tendency for improvement in CRP when compared to adalimumab. The sex-stratified analysis showed that female patients with obesity had significantly worse improvement on ESR, while male obese patients had significantly worse improvement on CRP in comparison to the adalimumab users. Finally, no differences were found between abatacept and adalimumab.

Kaplan-Meier curves are depicted in **Supplementary Figure S6.4**. No differences in drug survival were identified across the study drugs.

Table 6.1 Obese and overweight cohorts, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
Obese cohort	**(n=178)**	**(n=150)**	**p value**	**(n=73)**	**p value**	**(n=42)**	**p value**
Women (%)	130 (73.0)	124 (82.7)	0.052	56 (76.7)	0.656	27 (64.3)	0.348
Age index (mean (SD))	56.60 (11.99)	56.98 (11.63)	0.777	55.86 (10.77)	0.644	59.27 (10.00)	0.183
RA duration, years (mean (SD))	6.72 (8.67)	7.75 (8.45)	0.285	7.92 (8.61)	0.331	5.80 (7.42)	0.531
Year of index date (mean (SD))	2007.85 (3.79)	2007.53 (4.56)	0.487	2005.68 (4.02)	<0.001	2013.19 (2.52)	<0.001
BMI kg/m^2 (mean (SD))	33.90 (3.86)	33.79 (3.85)	0.794	33.65 (3.09)	0.621	33.91 (3.99)	0.987
Ever smoker (%)	49 (27.5)	41 (27.3)	1.000	11 (15.1)	0.053	22 (52.4)	0.004
csDMARD at index date (%)	134 (75.3)	96 (64.0)	0.036	60 (82.2)	0.307	33 (78.6)	0.804
Prednisone at index date (%)	66 (37.1)	60 (40.0)	0.669	41 (56.2)	0.008	18 (42.9)	0.605
Seropositive [a] (%)	129 (72.5)	102 (68.0)	0.691	56 (76.7)	0.537	32 (76.2)	0.765
ESR (mean (SD))	24.22 (18.46)	23.73 (16.09)	0.809	29.43 (18.87)	0.053	22.00 (18.05)	0.518
CRP (mean (SD))	1.44 (1.20)	1.37 (1.42)	0.765	1.38 (1.08)	0.842	1.06 (0.97)	0.106
Tender joint counts 28 (mean (SD))	7.25 (6.92)	7.86 (6.75)	0.432	8.14 (7.20)	0.367	7.19 (6.66)	0.963
Swollen joint counts 28 (mean (SD))	6.75 (5.72)	6.63 (5.79)	0.865	7.38 (6.37)	0.449	5.73 (4.85)	0.317
Physician GDA (mean (SD))	4.94 (1.85)	4.93 (1.95)	0.950	5.29 (2.13)	0.344	4.09 (1.99)	0.024
DAS28-ESR (mean (SD))	4.40 (1.42)	4.54 (1.32)	0.406	4.72 (1.40)	0.118	4.18 (1.46)	0.399
RADAI-5 (mean (SD))	4.91 (2.04)	5.33 (2.18)	0.107	5.15 (2.12)	0.425	4.35 (2.36)	0.209
HAQ (mean (SD))	1.21 (0.74)	1.32 (0.73)	0.235	1.38 (0.77)	0.115	0.95 (0.70)	0.093
Osteoporosis [b]	24 (13.5)	23 (15.3)	0.750	11 (15.1)	0.898	4 (9.5)	0.663
Other rheumatological disease [c]	61 (34.3)	62 (41.3)	0.229	25 (34.2)	1.000	8 (19.0)	0.084
Psoriasis	2 (1.1)	2 (1.3)	1.000	1 (1.4)	1.000	0 (0.0)	1.000
Hyperlipidemia	15 (8.4)	11 (7.3)	0.873	5 (6.8)	0.871	10 (23.8)	0.011
Cardiac/cardiovascular event/disease [d]	84 (47.2)	84 (56.0)	0.139	32 (43.8)	0.730	30 (71.4)	0.008
Depression/anxiety [e]	25 (14.0)	31 (20.7)	0.150	12 (16.4)	0.772	7 (16.7)	0.849
Diabetes	17 (9.6)	23 (15.3)	0.154	9 (12.3)	0.669	8 (19.0)	0.140
Fractures, surgeries, musc. system	15 (8.4)	8 (5.3)	0.381	7 (9.6)	0.960	3 (7.1)	1.000

Table 6.1 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
Overweight cohort	**(n=336)**	**(n=296)**	**p value**	**(n=150)**	**p value**	**(n=47)**	**p value**
Women (%)	215 (64.0)	203 (68.6)	0.257	91 (60.7)	0.549	30 (63.8)	1.000
Age index (mean (SD))	57.28 (12.52)	57.81 (12.32)	0.589	56.87 (11.35)	0.734	62.99 (10.81)	0.003
RA duration, years (mean (SD))	7.10 (7.76)	8.45 (9.21)	0.050	7.66 (8.08)	0.477	6.60 (8.45)	0.690
Year of index date (mean (SD))	2007.68 (3.56)	2006.72 (5.02)	0.005	2005.93 (4.69)	<0.001	2012.32 (2.60)	<0.001
BMI kg/m2 (mean (SD))	27.16 (1.35)	27.21 (1.33)	0.643	27.13 (1.37)	0.829	27.19 (1.41)	0.885
Ever smoker (%)	94 (28.0)	76 (25.7)	0.575	43 (28.7)	0.962	22 (46.8)	0.014
csDMARD at index date (%)	226 (67.3)	189 (63.9)	0.414	126 (84.0)	<0.001	34 (72.3)	0.595
Prednisone at index date (%)	134 (39.9)	133 (44.9)	0.229	84 (56.0)	0.001	13 (27.7)	0.146
Seropositive [a] (%)	244 (72.6)	211 (71.3)	0.679	119 (79.3)	0.731	37 (78.7)	0.697
ESR (mean (SD))	24.82 (19.57)	25.87 (22.59)	0.555	25.44 (21.41)	0.766	28.92 (18.07)	0.221
CRP (mean (SD))	2.12 (3.25)	1.71 (3.10)	0.315	1.18 (1.68)	0.057	1.30 (1.48)	0.121
Tender joint counts 28 (mean (SD))	7.55 (6.90)	7.95 (7.69)	0.507	7.14 (6.85)	0.552	6.00 (5.88)	0.161
Swollen joint counts 28 (mean (SD))	6.90 (5.51)	6.68 (5.93)	0.639	7.92 (5.98)	0.077	5.82 (5.18)	0.219
Physician GDA (mean (SD))	4.92 (2.27)	4.90 (2.14)	0.907	5.56 (2.04)	0.033	4.28 (1.89)	0.091
DAS28-ESR (mean (SD))	4.47 (1.34)	4.42 (1.50)	0.690	4.42 (1.48)	0.747	4.49 (1.15)	0.933
RADAI-5 (mean (SD))	4.84 (2.08)	5.01 (2.17)	0.358	4.98 (2.18)	0.528	4.87 (2.35)	0.935
HAQ (mean (SD))	1.08 (0.70)	1.13 (0.74)	0.408	1.24 (0.72)	0.030	0.94 (0.69)	0.272
Osteoporosis [b]	59 (17.6)	61 (20.6)	0.382	33 (22.0)	0.303	11 (23.4)	0.442
Other rheumatological disease [c]	101 (30.1)	97 (32.8)	0.517	45 (30.0)	1.000	13 (27.7)	0.868
Psoriasis	2 (0.6)	3 (1.0)	0.887	0 (0.0)	0.857	1 (2.1)	0.816
Hyperlipidemia	16 (4.8)	25 (8.4)	0.086	8 (5.3)	0.967	7 (14.9)	0.016
Cardiac/cardiovascular event/disease [d]	123 (36.6)	117 (39.5)	0.501	58 (38.7)	0.740	21 (44.7)	0.363
Depression/anxiety [e]	31 (9.2)	42 (14.2)	0.068	27 (18.0)	0.009	2 (4.3)	0.390
Diabetes	26 (7.7)	19 (6.4)	0.625	8 (5.3)	0.443	8 (17.0)	0.068
Fractures, surgeries, musc. system	26 (7.7)	34 (11.5)	0.142	13 (8.7)	0.867	2 (4.3)	0.575

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; GDA global disease activity; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire: musc. musculoskeletal.

Table 6.1 (continued)

[a] Seropositivity was calculated using both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies; [b] Osteoporosis includes osteoporosis record or medication with bisphosphonates, denosumab, or teriparatide; [c] Other rheumatological disease includes gout, lupus, osteoarthritis, Sjogren syndrome, degenerative spine disease, degenerative spondylopathy, other connective tissue disease, other rheumatological disease; [d] Cardiac/cardiovascular event/disease includes myocardial infarction, heart infarct, heart failure, heart insufficiency, cardiac insufficiency, coronary heart disease, coronary cardiac disease, heart problem, heart disease, angina pectoris, rhythm disorder, artery intervention, stroke transient ischemic attack, cerebrovascular disease, deep venous thrombosis, peripheral vascular disease, pulmonary embolism, blood thinners, hypertension, hypotension, other cardiovascular disease, and medication with platelet aggregation inhibitors, antihypertensives, or statins; [e] Depression/anxiety includes record of the disease or medication with antidepressants.

Table 6.2 Comparative effectiveness analyses.

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Obese - overall	**DAS28-remission**						
	adalimumab	178	57	1 (ref.)	1 (ref.)	25	1 (ref.)
	etanercept	150	48	1.01 (0.48-2.12)	1.01 (0.43-2.40)	21	1.08 (0.57-2.03)
	infliximab	73	17	0.49 (0.18-1.32)	0.77 (0.26-2.34)	7	0.66 (0.25-1.54)
	abatacept	42	16	0.91 (0.30-2.82)	0.61 (0.16-2.25)	6	0.97 (0.34-2.43)
	DAS28-LDA						
	adalimumab	178	87	1 (ref.)	1 (ref.)	37	1 (ref.)
	etanercept	150	73	0.95 (0.47-1.90)	0.77 (0.33-1.80)	32	1.05 (0.61-1.80)
	infliximab	73	31	0.85 (0.36-1.99)	1.00 (0.36-2.74)	15	1.01 (0.50-1.95)
	abatacept	42	23	0.68 (0.24-1.97)	0.72 (0.19-2.74)	8	0.84 (0.34-1.91)
	RADAI-5-remission						
	adalimumab	178	32	1 (ref.)	1 (ref.)	11	1 (ref.)
	etanercept	150	22	0.95 (0.36-2.55)	1.05 (0.32-3.51)	9	1.01 (0.39-2.52)
	infliximab	73	10	1.01 (0.31-3.28)	0.64 (0.15-2.80)	5	1.13 (0.35-3.24)
	abatacept	42	9	1.21 (0.33-4.38)	5.43 (0.96-30.87)	4	1.56 (0.41-4.87)
Overweight - overall	**DAS28-remission**						
	adalimumab	336	111	1 (ref.)	1 (ref.)	55	1 (ref.)
	etanercept	296	93	0.83 (0.50-1.37)	0.97 (0.54-1.75)	44	0.9 (0.58-1.38)
	infliximab	150	59	1.15 (0.66-2.03)	1.77 (0.90-3.47)	33	1.45 (0.88-2.34)
	abatacept	47	18	1.18 (0.45-3.05)	0.70 (0.21-2.32)	8	1.18 (0.49-2.57)
	DAS28-LDA						
	adalimumab	336	170	1 (ref.)	1 (ref.)	84	1 (ref.)
	etanercept	296	135	0.63 (0.39-1.02)	0.83 (0.47-1.45)	62	0.79 (0.54-1.15)
	infliximab	150	80	0.89 (0.51-1.54)	1.52 (0.78-2.97)	44	1.25 (0.81-1.92)
	abatacept	47	27	1.15 (0.46-2.86)	0.98 (0.30-3.22)	13	1.22 (0.59-2.39)

Table 6.2 Comparative effectiveness analyses.

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Overweight - overall	**RADAI-5-remission**						
	adalimumab	336	75	1 (ref.)	1 (ref.)	35	1 (ref.)
	etanercept	296	47	0.43 (0.23-0.84)	0.44 (0.22-0.90)	16	0.49 (0.26-0.90)
	infliximab	150	31	0.82 (0.42-1.57)	0.79 (0.38-1.64)	18	1.17 (0.63-2.12)
	abatacept	47	11	1.33 (0.38-4.71)	1.48 (0.32-6.79)	4	0.82 (0.24-2.19)
Normal weight - overall	**DAS28-remission**						
	adalimumab	442	163	1 (ref.)	1 (ref.)	85	1 (ref.)
	etanercept	482	173	0.89 (0.61-1.31)	1.12 (0.71-1.77)	99	1.11 (0.80-1.54)
	infliximab	259	107	0.82 (0.53-1.28)	1.22 (0.71-2.11)	55	1.12 (0.76-1.65)
	abatacept	60	27	1.82 (0.82-4.08)	0.92 (0.34-2.49)	14	1.58 (0.80-2.98)
	DAS28-LDA						
	adalimumab	442	243	1 (ref.)	1 (ref.)	122	1 (ref.)
	etanercept	482	264	0.93 (0.64-1.37)	1.18 (0.74-1.88)	148	1.18 (0.89-1.58)
	infliximab	259	154	0.84 (0.54-1.30)	1.50 (0.86-2.62)	82	1.21 (0.86-1.69)
	abatacept	60	39	2.05 (0.87-4.84)	1.15 (0.39-3.35)	20	1.55 (0.85-2.76)
	RADAI-5-remission						
	adalimumab	442	109	1 (ref.)	1 (ref.)	49	1 (ref.)
	etanercept	482	125	1.15 (0.74-1.76)	1.08 (0.66-1.76)	69	1.37 (0.93-2.03)
	infliximab	259	71	1.11 (0.67-1.84)	1.16 (0.65-2.08)	38	1.40 (0.88-2.20)
	abatacept	60	17	1.36 (0.57-3.21)	1.79 (0.65-4.94)	9	1.62 (0.70-3.38)

OR odds ratio adjusted for sex and age.

ORadj odds ratio adjusted for sex, age, index year, baseline DAS28, csDMARD at index, steroid use at index.

** Median number of events among the imputed datasets.*

Abbreviations: CARRAC Confounder-Adjusted Response Rate with Attrition Correction; MOIAN Missing Outcome Information Assumed as No; ref reference; DAS28-remisison 28-joint Disease Activity Score remission; RADAI-5-remission Rheumatoid Arthritis Disease Activity Index-Five remission; n number.

Table 6.3 Comparative effectiveness analyses. Female cohorts.

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Obese - Female	**DAS28-remission**						
	adalimumab	130	39	1 (ref.)	1 (ref.)	16	1 (ref.)
	etanercept	124	34	0.88 (0.38-2.04)	0.78 (0.29-2.06)	16	1.05 (0.50-2.22)
	infliximab	56	6	0.20 (0.04-0.96)	0.27 (0.05-1.41)	2	0.26 (0.04-0.97)
	abatacept	27	11	1.15 (0.29-4.51)	0.73 (0.15-3.71)	4	1.28 (0.34-3.91)
	DAS28-LDA						
	adalimumab	130	65	1 (ref.)	1 (ref.)	27	1 (ref.)
	etanercept	124	57	0.81 (0.37-1.78)	0.64 (0.25-1.66)	26	1.02 (0.55-1.88)
	infliximab	56	17	0.53 (0.18-1.51)	0.48 (0.14-1.67)	8	0.65 (0.26-1.47)
	abatacept	27	16	0.78 (0.22-2.81)	0.92 (0.18-4.74)	6	1.03 (0.35-2.70)
	RADAI-5-remission						
	adalimumab	130	22	1 (ref.)	1 (ref.)	7	1 (ref.)
	etanercept	124	18	1.08 (0.35-3.33)	1.15 (0.30-4.34)	8	1.21 (0.42-3.55)
	infliximab	56	4	0.60 (0.11-3.30)	0.18 (0.02-2.12)	2	0.65 (0.10-2.79)
	abatacept	27	7	1.49 (0.32-6.94)	6.03 (0.75-48.54)	3	2.22 (0.45-8.69)
Overweight - Female	**DAS28-remission**						
	adalimumab	215	70	1 (ref.)	1 (ref.)	31	1 (ref.)
	etanercept	203	64	1.02 (0.54-1.90)	1.18 (0.57-2.41)	31	1.11 (0.64-1.91)
	infliximab	91	36	1.65 (0.81-3.37)	2.47 (1.06-5.78)	23	2.05 (1.11-3.76)
	abatacept	30	13	1.96 (0.69-5.61)	1.24 (0.33-4.67)	8	2.39 (0.92-5.76)
	DAS28-LDA						
	adalimumab	215	112	1 (ref.)	1 (ref.)	53	1 (ref.)
	etanercept	203	95	0.68 (0.38-1.23)	0.99 (0.51-1.93)	45	0.88 (0.56-1.39)
	infliximab	91	48	0.88 (0.44-1.76)	1.52 (0.67-3.45)	28	1.37 (0.79-2.34)
	abatacept	30	19	1.58 (0.55-4.50)	1.70 (0.44-6.60)	12	2.14 (0.94-4.73)
	RADAI-5-remission						
	adalimumab	215	45	1 (ref.)	1 (ref.)	19	1 (ref.)
	etanercept	203	33	0.51 (0.23-1.17)	0.52 (0.20-1.30)	11	0.59 (0.27-1.26)
	infliximab	91	20	1.16 (0.52-2.62)	1.22 (0.49-3.03)	13	1.72 (0.80-3.63)
	abatacept	30	8	2.04 (0.53-7.85)	3.13 (0.58-16.8)	4	1.60 (0.44-4.71)

Table 6.3 (continued)

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Normal weight - Female	**DAS28-remission**						
	adalimumab	365	133	1 (ref.)	1 (ref.)	69	1 (ref.)
	etanercept	393	140	0.85 (0.56-1.30)	1.03 (0.63-1.70)	78	1.08 (0.75-1.55)
	infliximab	207	76	0.76 (0.46-1.23)	1.22 (0.67-2.22)	42	1.11 (0.72-1.70)
	abatacept	51	23	1.99 (0.84-4.72)	0.86 (0.29-2.54)	13	1.76 (0.86-3.46)
	DAS28-LDA						
	adalimumab	365	194	1 (ref.)	1 (ref.)	96	1 (ref.)
	etanercept	393	212	0.99 (0.66-1.50)	1.2 (0.73-1.99)	119	1.24 (0.90-1.70)
	infliximab	207	113	0.89 (0.55-1.43)	1.59 (0.88-2.88)	66	1.33 (0.91-1.94)
	abatacept	51	32	2.09 (0.84-5.21)	1.09 (0.35-3.42)	17	1.65 (0.86-3.09)
	RADAI-5-remission						
	adalimumab	365	90	1 (ref.)	1 (ref.)	43	1 (ref.)
	etanercept	393	104	1.14 (0.71-1.81)	1.09 (0.65-1.84)	60	1.37 (0.90-2.09)
	infliximab	207	54	1.05 (0.61-1.81)	1.18 (0.63-2.20)	32	1.39 (0.84-2.27)
	abatacept	51	15	1.04 (0.41-2.68)	1.28 (0.42-3.91)	7	1.38 (0.53-3.11)

OR odds ratio adjusted for age.

ORadj odds ratio adjusted for age, index year, baseline DAS28, csDMARD at index, steroid use at index.

** Median number of events among the imputed datasets.*

Abbreviations: CARRAC Confounder-Adjusted Response Rate with Attrition Correction;; MOIAN Missing Outcome Information Assumed as No; ref reference; DAS28-remisison 28-joint Disease Activity Score remission; RADAI-5-remission Rheumatoid Arthritis Disease Activity Index-Five remission; n number.

Table 6.4 Comparative effectiveness analyses. Male cohorts.

			Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
		n all	n event*	OR	ORadj	n event	OR
Obese - Male	**DAS28-remission**						
	adalimumab	48	23	1 (ref.)	1 (ref.)	9	1 (ref.)
	etanercept	26	13	1.36 (0.28-6.61)	2.39 (0.19-30.15)	5	1.01 (0.28-3.39)
	infliximab	17	8	1.35 (0.28-6.47)	5.24 (0.55-50.01)	5	1.81 (0.48-6.37)
	abatacept	15	7	0.67 (0.09-4.75)	0.58 (0.03-10.00)	2	0.66 (0.09-3.01)
	DAS28-LDA						
	adalimumab	48	26	1 (ref.)	1 (ref.)	10	1 (ref.)
	etanercept	26	15	1.54 (0.31-7.63)	1.67 (0.12-22.91)	6	1.06 (0.31-3.34)
	infliximab	17	10	2.47 (0.47-12.97)	8.20 (0.75-90.07)	7	2.71 (0.81-9.09)
	abatacept	15	8	0.55 (0.08-3.93)	0.59 (0.03-11.23)	2	0.58 (0.08-2.57)
	RADAI-5-remission						
	adalimumab	48	12	1 (ref.)	1 (ref.)	4	1 (ref.)
	etanercept	26	4	0.48 (0.04-5.54)	0.27 (0.00-60.25)	1	0.44 (0.02-3.24)
	infliximab	17	5	1.91 (0.3-12.04)	3.23 (0.05-216.6)	3	2.36 (0.42-12.00)
	abatacept	15	3	0.75 (0.06-9.16)	31.26 (0.11-8838.89)	1	0.79 (0.04-5.88)
Overweight - Male	**DAS28-remission**						
	adalimumab	121	43	1 (ref.)	1 (ref.)	24	1 (ref.)
	etanercept	93	30	0.60 (0.25-1.43)	0.71 (0.24-2.09)	13	0.63 (0.29-1.31)
	infliximab	59	23	0.64 (0.25-1.67)	1.02 (0.32-3.27)	10	0.79 (0.34-1.75)
	abatacept	17	3	0 (0-Inf)	0 (0-Inf)	0	-
	DAS28-LDA						
	adalimumab	121	58	1 (ref.)	1 (ref.)	31	1 (ref.)
	etanercept	93	40	0.56 (0.25-1.30)	0.58 (0.20-1.71)	17	0.63 (0.32-1.23)
	infliximab	59	33	0.93 (0.37-2.33)	1.77 (0.53-5.98)	16	1.06 (0.51-2.12)
	abatacept	17	6	0.29 (0.03-3.15)	0.14 (0.01-2.29)	1	0.20 (0.01-1.05)
	RADAI-5-remission						
	adalimumab	121	34	1 (ref.)	1 (ref.)	16	1 (ref.)
	etanercept	93	16	0.33 (0.11-1.03)	0.37 (0.11-1.25)	5	0.37 (0.12-0.98)
	infliximab	59	12	0.44 (0.14-1.38)	0.33 (0.08-1.32)	5	0.6 (0.19-1.62)
	abatacept	17	2	0 (0-Inf)	0 (0-Inf)	0	-

Table 6.4 (continued)

		n all	Main analyses (CARRAC)			Sensitivity analyses (MOIAN)	
			n event*	OR	ORadj	n event	OR
Normal weight - Male	**DAS28-remission**						
	adalimumab	77	34	1 (ref.)	1 (ref.)	16	1 (ref.)
	etanercept	89	34	1.25 (0.47-3.32)	1.72 (0.51-5.76)	21	1.27 (0.60-2.75)
	infliximab	52	29	1.03 (0.32-3.29)	1.08 (0.24-4.73)	13	1.12 (0.47-2.64)
	abatacept	9	4	1.17 (0.09-14.72)	1.23 (0.07-22.1)	1	0.58 (0.03-3.87)
	DAS28-LDA						
	adalimumab	77	53	1 (ref.)	1 (ref.)	26	1 (ref.)
	etanercept	89	49	0.67 (0.23-1.92)	1.09 (0.23-5.10)	29	0.99 (0.51-1.91)
	infliximab	52	37	0.51 (0.14-1.83)	0.69 (0.12-3.89)	16	0.81 (0.37-1.73)
	abatacept	9	7	2.15 (0.17-27.7)	4.01 (0.12-136.57)	3	1.16 (0.22-4.96)
	RADAI-5-remission						
	adalimumab	77	18	1 (ref.)	1 (ref.)	6	1 (ref.)
	etanercept	89	21	1.21 (0.36-4.02)	1.10 (0.25-4.83)	9	1.37 (0.47-4.28)
	infliximab	52	14	1.55 (0.40-5.93)	1.03 (0.19-5.47)	6	1.47 (0.43-4.99)
	abatacept	9	4	10.81 (0.68-172.46)	15.15 (0.58-395.29)	2	3.81 (0.49-21.44)

OR odds ratio adjusted for age.

ORadj odds ratio adjusted for age, index year, baseline DAS28, csDMARD at index, steroid use at index.

** Median number of events among the imputed datasets.*

Abbreviations: CARRAC Confounder-Adjusted Response Rate with Attrition Correction; MOIAN Missing Outcome Information Assumed as No; ref reference; Inf infinite; DAS28-remisison 28-joint Disease Activity Score remission; RADAI-5-remission Rheumatoid Arthritis Disease Activity Index-Five remission; n number.

Table 6.5 Median change (delta, Δ) on individual clinical endpoints between baseline and the end of follow-up.

		Adalimumab	Etanercept		Infliximab		Abatacept	
				p value		p value		p value
Overall	**Obese**							
	ΔESR	-3.00 [-11.50, 1.00]	-4.50 [-16.00, 1.00]	0.596	-0.50 [-5.00, 14.75]	0.044	-1.00 [-8.00, 2.00]	0.574
	ΔCRP	-0.20 [-1.00, 0.00]	-0.45 [-0.94, -0.10]	0.389	0.35 [-0.24, 0.50]	0.047	-0.23 [-0.59, 0.00]	0.366
	ΔTJC28	-3.00 [-6.00, 0.00]	-3.00 [-6.50, -0.50]	0.668	-1.00 [-6.00, 0.00]	0.642	-6.00 [-10.00, -0.75]	0.131
	ΔSJC28	-2.00 [-7.00, -1.00]	-4.00 [-7.00, -0.50]	0.479	-2.00 [-5.50, -0.50]	0.648	-4.00 [-7.00, -2.00]	0.562
	Overweight							
	ΔESR	-4.00 [-12.00, 2.00]	-3.00 [-12.00, 2.00]	0.738	-3.50 [-15.25, 2.00]	0.989	-8.00 [-13.00, -5.00]	0.301
	ΔCRP	-0.40 [-1.40, 0.00]	0.00 [-0.50, 0.00]	0.019	-0.28 [-0.73, -0.00]	0.452	-0.35 [-0.67, 0.00]	0.435
	ΔTJC28	-3.00 [-6.75, 0.00]	-3.00 [-8.00, 0.00]	0.713	-3.00 [-7.50, 0.00]	0.882	-3.50 [-8.75, -1.00]	0.627
	ΔSJC28	-3.00 [-7.00, -1.00]	-3.00 [-7.00, 0.00]	0.613	-4.00 [-8.50, -1.00]	0.306	-3.00 [-5.50, -0.50]	0.631
	Normal weight							
	ΔESR	-3.00 [-14.00, 1.00]	-4.00 [-13.00, 1.00]	0.942	-8.00 [-18.00, 0.00]	0.040	-8.00 [-17.00, 0.00]	0.290
	ΔCRP	-0.15 [-0.60, 0.00]	-0.10 [-0.90, 0.00]	0.808	-0.41 [-1.45, 0.00]	0.173	-0.10 [-0.64, 0.00]	0.701
	ΔTJC28	-3.00 [-7.00, 0.00]	-2.00 [-6.00, 0.00]	0.208	-3.00 [-8.50, 0.00]	0.217	-4.00 [-8.00, -2.00]	0.158
	ΔSJC28	-3.00 [-7.00, -0.50]	-3.00 [-6.00, 0.00]	0.302	-5.00 [-9.00, -1.00]	0.005	-3.00 [-7.75, -1.00]	0.688
Female	**Obese female**							
	ΔESR	-3.00 [-10.00, 1.00]	-4.00 [-15.00, 1.00]	0.631	0.50 [-5.00, 19.75]	0.020	0.00 [-3.00, 3.00]	0.150
	ΔCRP	-0.10 [-0.67, 0.00]	-0.40 [-0.80, -0.10]	0.225	0.05 [-0.79, 0.50]	0.564	-0.23 [-0.40, 0.00]	0.616
	ΔTJC28	-3.00 [-6.00, 0.00]	-3.00 [-7.00, -1.00]	0.797	0.00 [-4.00, 2.00]	0.123	-6.00 [-10.00, 0.00]	0.502
	ΔSJC28	-2.00 [-7.00, -1.00]	-3.00 [-7.00, 0.00]	0.851	-1.00 [-4.00, 0.00]	0.123	-2.00 [-4.00, 0.00]	0.738
	Overweight female							
	ΔESR	-5.00 [-15.00, 1.00]	-2.00 [-10.75, 2.00]	0.361	-4.00 [-15.25, 2.00]	0.811	-8.00 [-12.75, -1.25]	0.708
	ΔCRP	-0.30 [-0.90, 0.00]	0.00 [-0.38, 0.01]	0.072	-0.30 [-0.50, 0.00]	0.756	-0.30 [-0.60, 0.00]	0.668
	ΔTJC28	-2.50 [-7.00, 0.00]	-3.00 [-9.00, 0.00]	0.649	-3.00 [-8.00, 0.00]	0.794	-5.50 [-8.75, -1.00]	0.508
	ΔSJC28	-3.00 [-7.00, -1.00]	-3.00 [-7.00, 0.00]	0.598	-4.00 [-8.00, -1.00]	0.787	-3.00 [-5.75, -1.00]	0.614
	Normal weight female							
	ΔESR	-4.00 [-13.75, 1.00]	-3.00 [-12.00, 1.00]	0.762	-10.00 [-18.00, -1.00]	0.019	-8.00 [-17.00, -3.00]	0.266
	ΔCRP	-0.10 [-0.50, 0.00]	-0.10 [-0.90, 0.00]	0.914	-0.70 [-1.60, 0.00]	0.063	0.00 [-0.45, 0.00]	0.544
	ΔTJC28	-3.00 [-7.00, 0.00]	-2.00 [-6.75, 0.00]	0.470	-4.00 [-8.50, 0.00]	0.271	-4.00 [-8.00, -2.00]	0.283
	ΔSJC28	-3.00 [-7.00, 0.00]	-3.00 [-6.00, 0.00]	0.551	-6.00 [-9.00, -1.50]	0.001	-3.00 [-7.75, -1.00]	0.718

Table 6.5 (continued)		Adalimumab	Etanercept		Infliximab		Abatacept	
				p value		p value		p value
Male	**Obese male**							
	ΔESR	-2.00 [-17.75, 0.25]	-6.00 [-25.00, 0.00]	0.509	-1.50 [-7.00, -0.25]	0.774	-8.00 [-28.50, -0.50]	0.422
	ΔCRP	-1.10 [-1.75, -0.05]	-1.80 [-3.17, -1.05]	0.357	0.65 [0.43, 0.88]	0.037	-0.35 [-0.69, 0.00]	0.361
	ΔTJC28	-2.50 [-6.75, 0.75]	-2.00 [-4.00, 0.00]	0.935	-4.00 [-8.50, -1.25]	0.279	-6.00 [-12.50, -3.50]	0.119
	ΔSJC28	-2.00 [-6.50, -0.25]	-4.50 [-6.75, -2.25]	0.221	-6.50 [-7.75, -2.00]	0.253	-6.00 [-7.50, -2.00]	0.203
	Overweight male							
	ΔESR	-3.50 [-10.25, 2.00]	-5.00 [-16.00, 0.00]	0.435	-3.00 [-12.50, 2.00]	0.859	-8.00 [-16.00, -6.50]	0.245
	ΔCRP	-0.61 [-1.63, -0.18]	-0.20 [-0.65, 0.00]	0.253	-0.20 [-0.80, -0.01]	0.563	-0.90 [-2.10, 0.40]	0.734
	ΔTJC28	-3.00 [-4.25, -0.75]	-3.00 [-6.00, 0.00]	0.951	-2.00 [-7.00, 0.00]	0.913	-1.00 [-5.25, -0.25]	0.543
	ΔSJC28	-2.50 [-5.25, -1.00]	-2.00 [-6.00, -0.25]	0.761	-5.00 [-9.00, -1.00]	0.190	-3.00 [-4.00, 0.00]	0.777
	Normal weight male							
	ΔESR	-2.50 [-19.00, 0.25]	-8.00 [-14.50, 0.50]	0.645	-2.50 [-10.25, 0.00]	0.947	-12.50 [-30.75, 4.25]	0.880
	ΔCRP	-0.20 [-0.85, 0.00]	-0.40 [-0.90, 0.00]	0.824	-0.10 [-0.26, 0.00]	0.681	-0.70 [-1.12, -0.17]	0.560
	ΔTJC28	-3.00 [-6.75, 0.00]	0.00 [-3.50, 0.50]	0.169	-2.00 [-6.75, 0.00]	0.583	-5.50 [-7.25, -3.50]	0.282
	ΔSJC28	-2.50 [-6.50, -1.00]	-2.00 [-4.00, 0.00]	0.268	-1.00 [-7.00, 0.00]	0.417	-4.50 [-5.75, -2.75]	0.774

Significance tests compare each drug of interest to adalimumab, using Kruskal-Wallis test.

Abbreviations: p p-value; n number, sample size; ESR erythrocyte sedimentation rate; CRP C-reactive protein; TJC28 tender joint counts counting 28; SJC28 swollen joint counts counting 28.

Discussion

This observational cohort study in the SCQM registry included 443 obese, 829 overweight, and 1243 normal weight RA patients treated with adalimumab, etanercept, infliximab, or abatacept as their first b/tsDMARD. In the overall BMI cohorts, similar achievement of DAS28-remission was observed between the studied biologics compared to adalimumab. Results were consistent across various methods and outcomes. However, when stratified by sex, infliximab appeared to perform better among overweight females but worse in obese females in comparison to adalimumab. Additionally, lower odds of achievement of RADAI-5-remission were observed in overweight users of etanercept compared to adalimumab.

Our findings in the overall BMI cohorts were in agreement with published studies on the RA general population.[4,34–36] For example, a recent observational cohort study of RA patients who were new-users of b/tsDMARDs showed no statistical differences in effectiveness between TNF inhibitors and non-TNF biologics.[34] Conversely, a study on new-users of adalimumab, etanercept, infliximab, and abatacept reported comparable rates of effectiveness across the study drugs (24%, 28%, 23%, 26%, respectively) but also indicated a lower relative risk of effectiveness for infliximab compared to the other drugs.[37] In our study, we observed no differences between the clinical response to infliximab and adalimumab in the overall BMI cohorts. However, when stratifying by sex, a contradictory effect was observed in the female cohorts. Infliximab female users with overweight had increased odds of achieving DAS28-remission in comparison to the respective adalimumab group, contrary to the results in the obese female patients, for whom infliximab performed worse than adalimumab. This finding in the obese female users of infliximab was observed in every model but for the CARRAC fully adjusted analyses, in which overfitting is expected due to the very low number of events for this particular finding.

Despite the influence that the body weight has on the volume of distribution of infliximab,[18] the weight-adjusted dose of this treatment may explain the higher benefit of infliximab versus adalimumab in overweight female patients. However, while one would expect that increasing body fat would have a consistent response, studies among cohorts of RA patients treated with infliximab reported an association between obesity and worse response,[38,39] consistent with findings from other TNF inhibitors.[10] Additionally, there may be other factors that influence the low response of infliximab in obese patients. For example, obesity was described as a predictor of hypoalbuminemia,[40] and serum albumin levels have been inversely associated with the clearance of infliximab.[18] Thus, lower levels of albumin in obese patients may result in higher clearance of infliximab and, therefore, reduced effectiveness. Additionally, infliximab clearance is not linearly correlated to weight.[19] Thus,

appropriate dose adjustment in overweight patients but altered pharmacokinetics in the presence of highly elevated BMI may explain the conflicting effect observed between the overweight and obese female cohorts. Moreover, our findings on the change of individual parameters suggest that the lower achievement of DAS28-remission in obese female patients with infliximab vs adalimumab may be driven by a significantly lower improvement in inflammation, despite similar improvement in tender and swollen joint counts. This may explain the inconsistency between DAS28-remission and RADAI-5-remission in these patients. RADAI-5 is a patient-driven score, which correlates with tender joint counts, but has a low correlation with ESR.[41] Thus, despite the validity of RADAI-5 as measurement of disease activity, both scores provide a different assessment of the disease, and the inconsistency between them should not undervalue either. Finally, due to the inflammatory character of obesity, which can result in elevated levels of TNF,[17] it may be that infliximab does not sufficiently reduce the excess inflammation.

Conversely to the above-discussed results in the female cohort, male patients treated with infliximab and adalimumab had similar odds of achieving remission, irrespectively of their BMI category. This sex difference may be explained by the smaller sample size of the male cohorts. Additionally, sexual dimorphism in body fat may as well play a role. In brief, there are differences in body fat distribution (e.g., males tend to have more visceral adipose tissue, while females have more subcutaneous adipose tissue), adipocyte function, hormonal levels and genetics (with consequent differences in the immune system) between males and females.[42–44] Thus, this may explain the observed sex differences in response to RA treatment. While further elucidation of this effect in the context of infliximab response is of interest, we consider it beyond the scope of this paper.

Abatacept has been suggested as a preferable drug candidate to treat patients with elevated BMI due to an alternative mode of action. This is supported by the systematic review from Shan and Zhang, which reported reduced odds of response in RA patients with obesity treated with TNF inhibitors but not in patients treated with abatacept.[14] Four studies have assessed the impact of BMI on the treatment response in RA patients treated with abatacept, all suggesting that BMI does not impact the clinical response to abatacept in RA.[21–24] In addition to this, the pharmacokinetics of abatacept were consistently described regardless of BMI,[21] despite abatacept being a lipophilic drug.[22] This may suggest that the lower response reported in obese patients treated with TNF inhibitors may relate to the mechanistic pathway of these treatments and not solely to their body distribution. For example, body weight was described as a predictor of the formation of ADAbs in RA patients treated with infliximab, potentially explained by the higher TNF-infliximab complexes due to the additional TNF consequence of the adipose tissue.[19] Therefore, non-TNF biologics open up as potential optimal treatments in obese RA patients. However, while this seemed promising, we did not observe any

direct benefit of being treated with abatacept versus adalimumab in any of the study cohorts. This is in agreement with the observed comparable efficacy between abatacept and adalimumab in a head-to-head randomised trial.[45] Therefore, we trust that current evidence does not justify a superiority of abatacept versus adalimumab in RA patients with obesity.

Regarding etanercept versus adalimumab, the study results showed >50% reduced odds of achieving RADAI-5-remission among etanercept users with overweight in comparison to the respective adalimumab group. However, this effect was not observed for the DAS28 outcomes, and a rationale to explain it is lacking. While this could have been a chance finding, the consistency of this result across the different analysis types (CARRAC, MOIAN, EPMOI) suggests that further investigation is of interest.

Strengths and limitations

The number of head-to-head trials is increasing,[35] and studies on the comparative effectiveness of b/tsDMARDs in real-world-setting are limited but rising. However, to our knowledge, this is the first real-world comparative effectiveness observational cohort study on biologics in RA patients stratified by BMI category. Additionally, this is one of the first studies after the very recent recommendation from EULAR to use CARRAC to address missingness during follow-up.[30,31] Thus, we contribute to the validation of this recommendation while still providing traditional approaches alongside the CARRAC findings.

A limitation of this study is the restriction to only four biologics. This decision was driven by the limited sample size for other b/tsDMARDs due to different times of approval in Switzerland and, importantly, due to former guidelines suggesting TNF inhibitors as preferable first b/tsDMARD choice until 2013.[46,47] While a prevalence-user design would have enabled to investigate more treatments, we discarded this option to avoid confounding by indication, for example, driven by the expected different response to second-line treatments based on the type of response to the first b/tsDMARD (i.e., primary versus secondary non-response[48]). Finally, although underweight patients were a population of interest, sample size-wise was not feasible to address this research question in these patients.

Conclusions

Patients treated with etanercept, infliximab, or abatacept, had similar odds of achieving DAS28-remission compared to those treated with adalimumab, irrespectively of the BMI category, with the exception of infliximab in female patients. Compared to adalimumab, higher odds of DAS28 remission were observed in overweight female patients treated with infliximab, while, conversely, lower odds

were observed in female obese users of infliximab. Additionally, the differential odds of achieving RADAI-5 remission between etanercept and adalimumab in overweight patients requires further attention. Ultimately, while the study findings suggested differential effectiveness of biologics depending on the BMI and sex of the patient, the selection of an optimal biologic in patients with abnormal BMI remains of interest, and the role of infliximab and etanercept depending on BMI may be further investigated.

Remarks on main author contributions: EV-Y contributed to the conceptualisation and methodology, data curation, formal analysis, visualisation, investigation, resources, interpretation of the results, drafting and editing the manuscript, and critical revisions.

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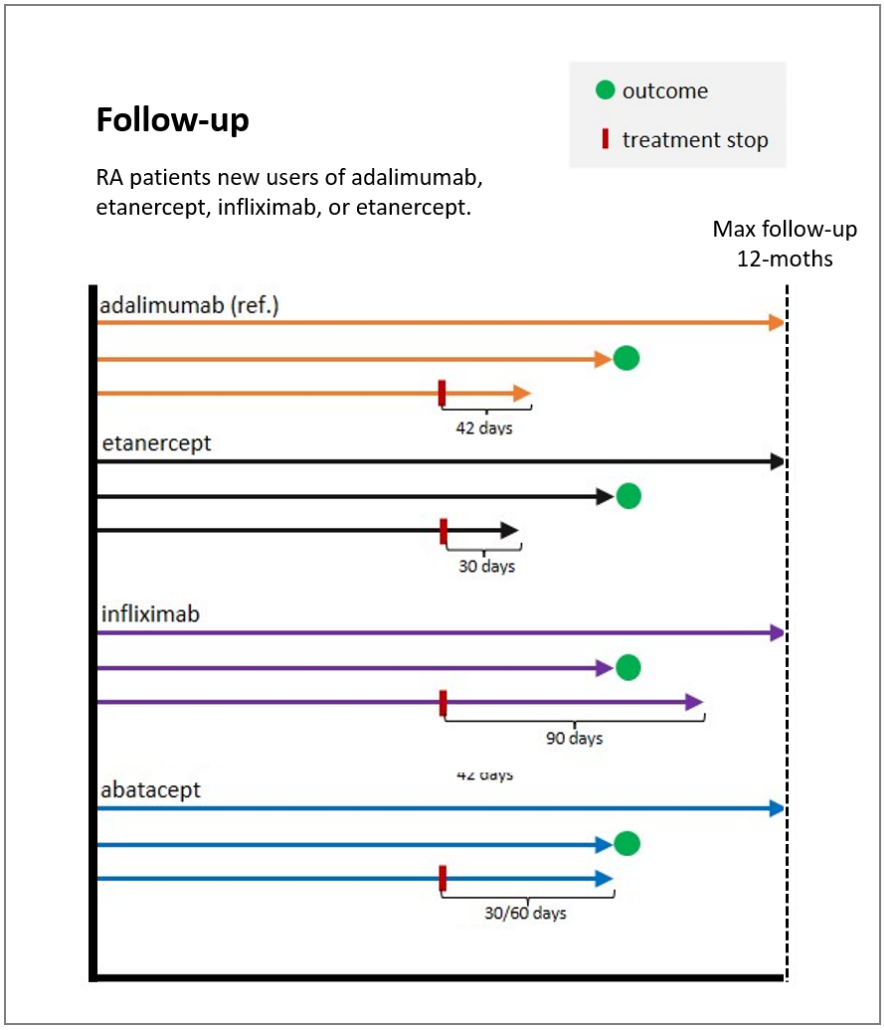
Supplementary material



Supplementary Figure S6.1 Comparative effectiveness analysis. Abbreviations: RA rheumatoid arthritis; BMI body mass index; m months.

Supplementary Table S6.1 Variables included in the multiple imputation, conducted on outcome and cohort basis.

Variable	Included for DAS28 outcomes	Included for RADAI-5 outcome	Included for individual	Predicted	Predictor	Method	Levels
Baseline variables:							
Biologic agent	yes	yes	yes	-	yes	-	adalimumab; etanercept; infliximab; abatacept.
Sex[a]	yes[a]	yes[a]	yes[a]	-	yes[a]	-	female; male.
Age	yes	yes	yes	-	yes	-	-
BMI kg/m^2	yes	yes	yes	-	yes	-	-
Smoker ever before	yes	yes	yes	-	yes	-	yes; no.
Disease duration, years	yes	yes	yes	yes	yes	pmm	-
Year of index date	yes	yes	yes	-	yes	-	-
csDMARD at index	yes	yes	yes	-	yes	-	yes; no.
Prednisone at index	yes	yes	yes	-	yes	-	yes; no.
Seropositivity	yes	yes	yes	yes	yes	logreg	yes; no.
ESR	yes	yes	yes	yes	yes	pmm	-
CRP	-	-	yes	yes	yes	pmm	-
SJC28	yes	yes	yes	yes	yes	pmm	-
TJC28	yes	yes	yes	yes	yes	pmm	-
DAS28-ESR	yes	yes	yes	yes	yes[b]	passive imputation[c]	-
RADAI-5	yes	yes	yes	yes	yes	pmm	-
HAQ	yes	yes	yes	yes	yes	pmm	-
Follow-up variables:							
Treatment duration (time to stop or censor)	yes	yes	yes	-	yes	-	-
Treatment stop, or censor	yes	yes	yes	-	yes	-	censor; stop.
Reason for treatment stop (or switch)	yes	yes	yes	yes	yes	polyreg	adverse event; not effective; remission; other; stop/censor >3years.
DAS28-ESR_{fu}	yes	-	-	yes	yes	pmm	-
RADAI-5_{fu}	-	yes	-	yes	yes	pmm	-
ESR_{fu}	-	-	yes	yes	yes	pmm	-
CRP_{fu}	-	-	yes	yes	yes	pmm	-
$TJC28_{fu}$	-	-	yes	yes	yes	pmm	-
$SJC28_{fu}$	-	-	yes	yes	yes	pmm	-
Outcome DAS28-remission	yes	-	-	yes	-	passive imputation [ESR_{fu}<2.6 → yes]	yes; no.
Outcome DAS28-LDA	yes	-	-	yes	-	passive imputation [ESR_{fu}<3.2 → yes]	yes; no.

Supplementary Table S6.1 (continued)

Variable	Included for DAS28 outcomes	Included for RADAI-5 outcome	Included for individual	Predicted	Predictor	Method	Levels
Follow-up variables (continued):							
Outcome RADAI-5	-	yes	-	yes	-	passive imputation [$RADAI_{fu} \leq 1.4 \rightarrow$ yes]	yes; no.
Outcome ΔESR	-	-	yes	yes	-	passive imputation [ESR_{fu} - $ESR_{baseline}$]	-
Outcome ΔCPR	-	-	yes	yes	-	passive imputation [CRP_{fu} - $CRP_{baseline}$]	-
Outcome ΔTJC28	-	-	yes	yes	-	passive imputation [$TJC28_{fu}$ - $TJC28_{baseline}$]	-
Outcome ΔSJC28	-	-	yes	yes	-	passive imputation [$SJC28_{fu}$ - $SJC28_{baseline}$]	-

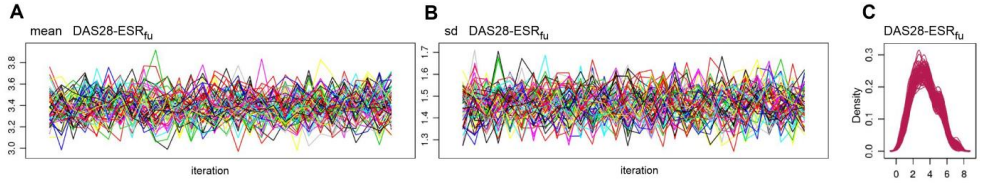
When unspecified, variables correspond to baseline data. Otherwise, it is specified as fu (follow-up) or outcome.

[a] Sex not included as variable in the sex-stratified cohorts.

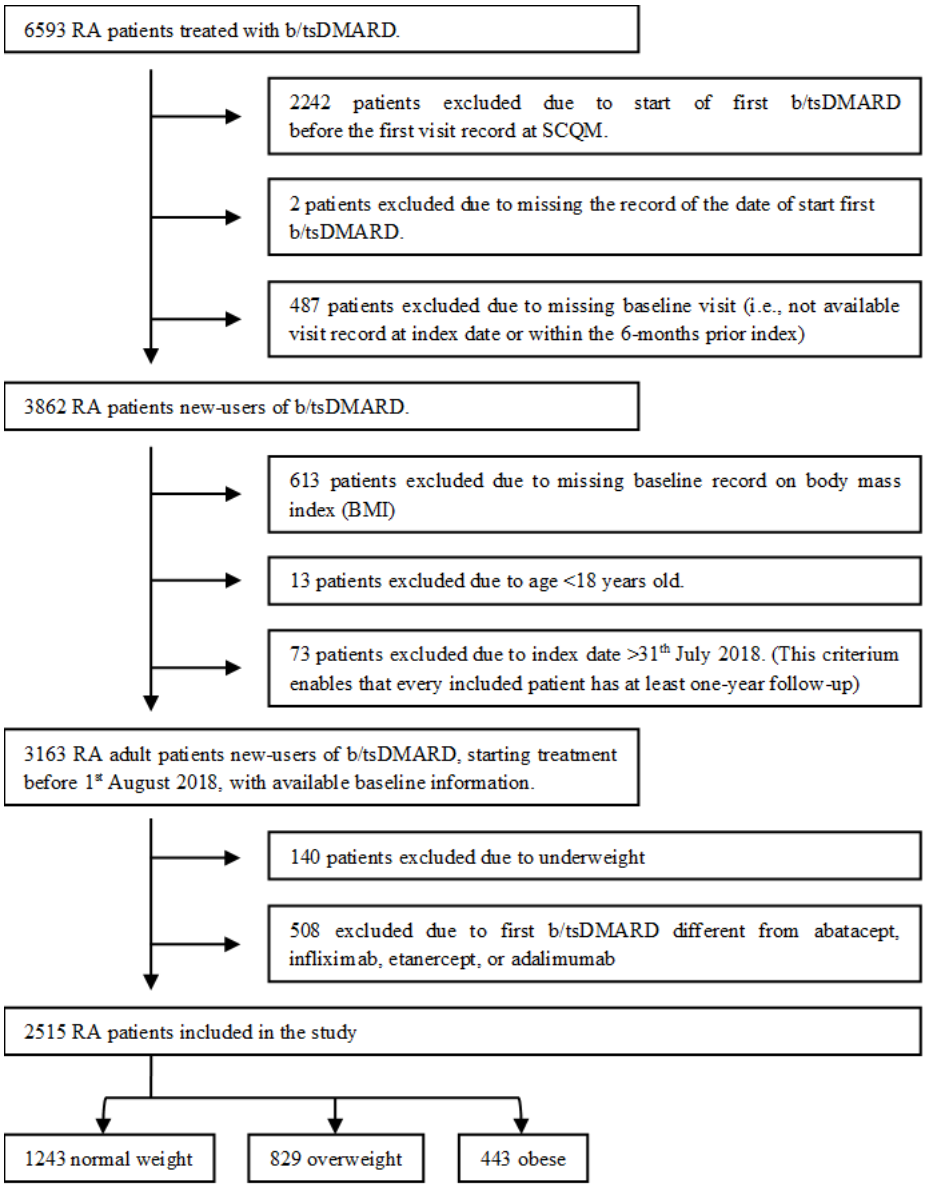
[b] Baseline DAS28 not used as predictor for baseline ESR, TJC28, and SJC28.

[c] Baseline DAS28 passive imputation: $DAS28ESR = \left(0.56 \times \sqrt{tjc28} + 0.28 \times \sqrt{sjc28} + 0.7 \times ln(ESR)\right) \times 1.08 + 0.16$

Abbreviations: DAS28 28-joint Disease Activity Score; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; fu follow-up; logreg logistic regression; pmm predictive mean matching.



Supplementary Figure S6.2 Visualisation of the coverage of the multiple imputation by chain equations (MICE) or confounder-adjusted response rate with attrition correction (CARRAC), of the outcome DAS28-remission in the obese cohort with a maximum follow-up of 12-months, particularly the variation of the mean (A) and standard deviation (B) of the DAS28-ESR at follow-up. On the right, density plot depicting the distribution of the DAS28-ESR at follow-up (C). Distribution in the original data set is depicted with a blue line, and distribution in each imputed dataset is depicted with a red line per dataset. (Blue line not visible, covered by the red lines). Abbreviations: sd standard deviation; DAS28 28-joint Disease Activity Score; ESR erythrocyte sedimentation rate; fu follow-up.



Supplementary Figure S6.3 Flow chart of the inclusion and exclusion criteria. Abbreviations: RA rheumatoid arthritis; b/tsDMARD biologic or targeted synthetic disease modifying antirheumatic drug; SCQM Swiss Quality Management of Rheumatic Diseases; BMI body mass index.

Supplementary Table S6.3 Obese cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OBESE	**(n=178)**	**(n=150)**	**p value**	**(n=73)**	**p value**	**(n=42)**	**p value**
Women (%)	130 (73.0)	124 (82.7)	0.052	56 (76.7)	0.656	27 (64.3)	0.348
Age index (mean (SD))	56.60 (11.99)	56.98 (11.63)	0.777	55.86 (10.77)	0.644	59.27 (10.00)	0.183
RA duration, years (mean (SD))	6.72 (8.67)	7.75 (8.45)	0.285	7.92 (8.61)	0.331	5.80 (7.42)	0.531
missing/unknown	5 (2.8)	7 (4.7)		4 (5.5)		0 (.00)	
Year of index date (mean (SD))	2007.85 (3.79)	2007.53 (4.56)	0.487	2005.68 (4.02)	<0.001	2013.19 (2.52)	<0.001
BMI kg/m^2 (mean (SD))	33.90 (3.86)	33.79 (3.85)	0.794	33.65 (3.09)	0.621	33.91 (3.99)	0.987
High educational level (%)	11 (6.2)	4 (2.7)	0.268	4 (5.5)	1.000	4 (9.5)	0.690
missing/unknown	58 (32.6)	57 (38.0)		27 (37.0)		13 (31.0)	
Ever smoker (%)	49 (27.5)	41 (27.3)	1.000	11 (15.1)	0.053	22 (52.4)	0.004
csDMARD at index date (%)	134 (75.3)	96 (64.0)	0.036	60 (82.2)	0.307	33 (78.6)	0.804
Prednisone at index date (%)	66 (37.1)	60 (40.0)	0.669	41 (56.2)	0.008	18 (42.9)	0.605
Seropositive (%)	129 (72.5)	102 (68.0)	0.691	56 (76.7)	0.537	32 (76.2)	0.765
missing/unknown	20 (11.2)	21 (14.0)		8 (11.0)		1 (2.4)	
ESR (mean (SD))	24.22 (18.46)	23.73 (16.09)	0.809	29.43 (18.87)	0.053	22.00 (18.05)	0.518
missing/unknown	14 (7.9)	18 (12.0)		5 (6.8)		7 (16.7)	
CRP (mean (SD))	1.44 (1.20)	1.37 (1.42)	0.765	1.38 (1.08)	0.842	1.06 (0.97)	0.106
missing/unknown	105 (59.0)	88 (58.7)		54 (74.0)		6 (14.3)	
Tender joint counts 28 (mean (SD))	7.25 (6.92)	7.86 (6.75)	0.432	8.14 (7.20)	0.367	7.19 (6.66)	0.963
missing/unknown	8 (4.5)	11 (7.3)		2 (2.7)		5 (11.9)	
Swollen joint counts 28 (mean (SD))	6.75 (5.72)	6.63 (5.79)	0.865	7.38 (6.37)	0.449	5.73 (4.85)	0.317
missing/unknown	9 (5.1)	11 (7.3)		2 (2.7)		5 (11.9)	
Physician global disease activity (mean (SD))	4.94 (1.85)	4.93 (1.95)	0.950	5.29 (2.13)	0.344	4.09 (1.99)	0.024
missing/unknown	70 (39.33)	68 (45.33)		35 (47.95)		9 (21.43)	
DAS28-ESR (mean (SD))	4.40 (1.42)	4.54 (1.32)	0.406	4.72 (1.40)	0.118	4.18 (1.46)	0.399
missing/unknown	15 (8.43)	18 (12)		5 (6.85)		8 (19.05)	
DAS28-CRP (mean (SD))	4.45 (1.15)	4.36 (1.08)	0.648	3.78 (1.10)	0.026	4.06 (1.22)	0.113
missing/unknown	105 (58.99)	88 (58.67)		54 (73.97)		7 (16.67)	
RADAI-5 (mean (SD))	4.91 (2.04)	5.33 (2.18)	0.107	5.15 (2.12)	0.425	4.35 (2.36)	0.209
missing/unknown	28 (15.73)	35 (23.33)		8 (10.96)		16 (38.1)	

Supplementary Table S6.3 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
OBESE	**(n=178)**	**(n=150)**	**p value**	**(n=73)**	**p value**	**(n=42)**	**p value**
HAQ (mean (SD))	1.21 (0.74)	1.32 (0.73)	0.235	1.38 (0.77)	0.115	0.95 (0.70)	0.093
missing/unknown	23 (12.92)	30 (20)		6 (8.22)		15 (35.71)	
Osteoporosis	24 (13.5)	23 (15.3)	0.750	11 (15.1)	0.898	4 (9.5)	0.663
Fibromyalgia	2 (1.1)	8 (5.3)	0.059	0 (0.0)	0.898	1 (2.4)	1.000
Other rheumatological disease	61 (34.3)	62 (41.3)	0.229	25 (34.2)	1.000	8 (19.0)	0.084
Psoriasis	2 (1.1)	2 (1.3)	1.000	1 (1.4)	1.000	0 (0.0)	1.000
Hyperlipidemia	15 (8.4)	11 (7.3)	0.873	5 (6.8)	0.871	10 (23.8)	0.011
Cardiac/cardiovascular event/disease	84 (47.2)	84 (56.0)	0.139	32 (43.8)	0.730	30 (71.4)	0.008
Cancer	7 (3.9)	4 (2.7)	0.744	1 (1.4)	0.513	4 (9.5)	0.270
Depression/anxiety	25 (14.0)	31 (20.7)	0.150	12 (16.4)	0.772	7 (16.7)	0.849
Diabetes	17 (9.6)	23 (15.3)	0.154	9 (12.3)	0.669	8 (19.0)	0.140
Fractures, surgeries, musculoskeletal system	15 (8.4)	8 (5.3)	0.381	7 (9.6)	0.960	3 (7.1)	1.000

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

Additional information on seropositivity and comorbidities: Seropositivity was calculated using both rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies. Osteoporosis includes osteoporosis record or medication with bisphosphonates, denosumab, or teriparatide; Other rheumatological disease includes gout, lupus, osteoarthritis, Sjogren syndrome, degenerative spine disease, degenerative spondylopathy, other connective tissue disease, other rheumatological disease; Cardiac/cardiovascular event/disease includes myocardial infarction, heart infarct, heart failure, heart insufficiency, cardiac insufficiency, coronary heart disease, coronary cardiac disease, heart problem, heart disease, angina pectoris, rhythm disorder, artery intervention, stroke transient ischemic attack, cerebrovascular disease, deep venous thrombosis, peripheral vascular disease, pulmonary embolism, blood thinners, hypertension, hypotension, other cardiovascular disease, and medication with platelet aggregation inhibitors, antihypertensives, or statins; Depression/anxiety includes record of the disease or medication with antidepressants.

Supplementary Table S6.4 Overweight cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OVERWEIGHT	**(n=336)**	**(n=296)**	**p value**	**(n=150)**	**p value**	**(n=47)**	**p value**
Women (%)	215 (64.0)	203 (68.6)	0.257	91 (60.7)	0.549	30 (63.8)	1.000
Age index (mean (SD))	57.28 (12.52)	57.81 (12.32)	0.589	56.87 (11.35)	0.734	62.99 (10.81)	0.003
RA duration, years (mean (SD))	7.10 (7.76)	8.45 (9.21)	0.050	7.66 (8.08)	0.477	6.60 (8.45)	0.690
missing/unknown	12 (3.57)	7 (2.36)		4 (2.67)		3 (6.38)	
Year of index date (mean (SD))	2007.68 (3.56)	2006.72 (5.02)	0.005	2005.93 (4.69)	<0.001	2012.32 (2.60)	<0.001
BMI kg/m^2 (mean (SD))	27.16 (1.35)	27.21 (1.33)	0.643	27.13 (1.37)	0.829	27.19 (1.41)	0.885
High educational level (%)	29 (8.6)	21 (7.1)	0.833	12 (8.0)	0.892	6 (12.8)	0.629
missing/unknown	98 (29.2)	106 (35.8)		41 (27.3)		11 (23.4)	
Ever smoker (%)	94 (28.0)	76 (25.7)	0.575	43 (28.7)	0.962	22 (46.8)	0.014
csDMARD at index date (%)	226 (67.3)	189 (63.9)	0.414	126 (84.0)	<0.001	34 (72.3)	0.595
Prednisone at index date (%)	134 (39.9)	133 (44.9)	0.229	84 (56.0)	0.001	13 (27.7)	0.146
Seropositive (%)	244 (72.6)	211 (71.3)	0.679	119 (79.3)	0.731	37 (78.7)	0.697
missing/unknown	47 (14.0)	41 (13.9)		12 (8.0)		5 (10.6)	
ESR (mean (SD))	24.82 (19.57)	25.87 (22.59)	0.555	25.44 (21.41)	0.766	28.92 (18.07)	0.221
missing/unknown	39 (11.61)	21 (7.09)		9 (6)		9 (19.15)	
CRP (mean (SD))	2.12 (3.25)	1.71 (3.10)	0.315	1.18 (1.68)	0.057	1.30 (1.48)	0.121
missing/unknown	208 (61.9)	181 (61.15)		101 (67.33)		6 (12.77)	
Tender joint counts 28 (mean (SD))	7.55 (6.90)	7.95 (7.69)	0.507	7.14 (6.85)	0.552	6.00 (5.88)	0.161
missing/unknown	33 (9.82)	12 (4.05)		5 (3.33)		4 (8.51)	
Swollen joint counts 28 (mean (SD))	6.90 (5.51)	6.68 (5.93)	0.639	7.92 (5.98)	0.077	5.82 (5.18)	0.219
missing/unknown	33 (9.82)	12 (4.05)		5 (3.33)		3 (6.38)	
Physician global disease activity (mean (SD))	4.92 (2.27)	4.90 (2.14)	0.907	5.56 (2.04)	0.033	4.28 (1.89)	0.091
missing/unknown	136 (40.48)	140 (47.3)		73 (48.67)		7 (14.89)	
DAS28-ESR (mean (SD))	4.47 (1.34)	4.42 (1.50)	0.690	4.42 (1.48)	0.747	4.49 (1.15)	0.933
missing/unknown	41 (12.2)	21 (7.09)		9 (6)		9 (19.15)	
DAS28-CRP (mean (SD))	4.28 (1.20)	4.19 (1.31)	0.584	4.01 (1.27)	0.189	3.98 (1.07)	0.161
missing/unknown	209 (62.2)	181 (61.15)		101 (67.33)		7 (14.89)	
RADAI-5 (mean (SD))	4.84 (2.08)	5.01 (2.17)	0.358	4.98 (2.18)	0.528	4.87 (2.35)	0.935
missing/unknown	73 (21.7)	44 (14.9)		24 (16)		16 (34)	

Supplementary Table S6.4 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
OVERWEIGHT	**(n=336)**	**(n=296)**	**p value**	**(n=150)**	**p value**	**(n=47)**	**p value**
HAQ (mean (SD))	1.08 (0.70)	1.13 (0.74)	0.408	1.24 (0.72)	0.030	0.94 (0.69)	0.272
missing/unknown	63 (18.75)	38 (12.84)		14 (9.33)		14 (29.79)	
Osteoporosis	59 (17.6)	61 (20.6)	0.382	33 (22.0)	0.303	11 (23.4)	0.442
Fibromyalgia	0 (0.0)	9 (3.0)	0.004	5 (3.3)	0.004	2 (4.3)	0.007
Other rheumatological disease	101 (30.1)	97 (32.8)	0.517	45 (30.0)	1.000	13 (27.7)	0.868
Psoriasis	2 (0.6)	3 (1.0)	0.887	0 (0.0)	0.857	1 (2.1)	0.816
Hyperlipidemia	16 (4.8)	25 (8.4)	0.086	8 (5.3)	0.967	7 (14.9)	0.016
Cardiac/cardiovascular event/disease	123 (36.6)	117 (39.5)	0.501	58 (38.7)	0.740	21 (44.7)	0.363
Cancer	6 (1.8)	13 (4.4)	0.093	1 (0.7)	0.586	2 (4.3)	0.572
Depression/anxiety	31 (9.2)	42 (14.2)	0.068	27 (18.0)	0.009	2 (4.3)	0.390
Diabetes	26 (7.7)	19 (6.4)	0.625	8 (5.3)	0.443	8 (17.0)	0.068
Fractures, surgeries, musculoskeletal system	26 (7.7)	34 (11.5)	0.142	13 (8.7)	0.867	2 (4.3)	0.575

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Scores using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.5 Normal weight cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
NORMAL WEIGHT	**(n=442)**	**(n=482)**	**p value**	**(n=259)**	**p value**	**(n=60)**	**p value**
Women (%)	365 (82.6)	393 (81.5)	0.744	207 (79.9)	0.438	51 (85.0)	0.776
Age index (mean (SD))	53.24 (13.78)	54.32 (14.68)	0.253	53.15 (14.28)	0.936	61.97 (14.34)	<0.001
RA duration, years (mean (SD))	8.29 (9.16)	8.66 (8.96)	0.537	9.82 (9.32)	0.036	9.15 (10.51)	0.506
missing/unknown	10 (2.26)	13 (2.7)		6 (2.32)		2 (3.33)	
Year of index date (mean (SD))	2007.33 (3.46)	2005.82 (4.90)	<0.001	2004.81 (4.04)	<0.001	2012.72 (2.68)	<0.001
BMI kg/m^2 (mean (SD))	22.17 (1.77)	22.07 (1.82)	0.413	22.17 (1.82)	0.973	22.43 (1.74)	0.278
High educational level (%)	50 (11.3)	47 (9.8)	0.630	24 (9.3)	0.702	6 (10.0)	0.579
missing/unknown	140 (31.7)	165 (34.2)		96 (37.1)		11 (18.3)	
Ever smoker (%)	122 (27.6)	119 (24.7)	0.351	55 (21.2)	0.075	18 (30.0)	0.814
csDMARD at index date (%)	316 (71.5)	265 (55.0)	<0.001	208 (80.3)	0.012	38 (63.3)	0.250
Prednisone at index date (%)	168 (38.0)	193 (40.0)	0.572	124 (47.9)	0.013	27 (45.0)	0.367
Seropositive (%)	325 (73.5)	379 (78.6)	0.175	208 (80.3)	0.012	46 (76.7)	0.456
missing/unknown	56 (12.7)	50 (10.4)		32 (12.4)		2 (3.3)	
ESR (mean (SD))	23.49 (20.10)	25.78 (23.17)	0.134	26.11 (24.61)	0.149	26.87 (22.18)	0.288
missing/unknown	58 (13.12)	43 (8.92)		24 (9.27)		14 (23.33)	
CRP (mean (SD))	1.28 (1.57)	1.32 (1.61)	0.855	1.44 (1.98)	0.561	1.47 (1.92)	0.506
missing/unknown	299 (67.65)	350 (72.61)		200 (77.22)		13 (21.67)	
Tender joint counts 28 (mean (SD))	6.70 (6.41)	6.69 (6.66)	0.989	6.59 (6.75)	0.837	6.44 (5.59)	0.783
missing/unknown	40 (9.05)	26 (5.39)		18 (6.95)		8 (13.33)	
Swollen joint counts 28 (mean (SD))	6.56 (5.67)	6.83 (6.09)	0.506	8.42 (6.92)	<0.001	6.17 (5.31)	0.635
missing/unknown	39 (8.82)	26 (5.39)		16 (6.18)		7 (11.67)	
Physician GDA (mean (SD))	4.98 (2.12)	5.14 (2.17)	0.397	5.23 (2.18)	0.269	4.40 (1.75)	0.101
missing/unknown	200 (45.25)	230 (47.72)		131 (50.58)		18 (30)	
DAS28-ESR (mean (SD))	4.29 (1.40)	4.30 (1.43)	0.926	4.35 (1.57)	0.619	4.33 (1.18)	0.836
missing/unknown	60 (13.57)	44 (9.13)		26 (10.04)		15 (25)	
DAS28-CRP (mean (SD))	4.11 (1.22)	4.14 (1.13)	0.827	3.98 (1.19)	0.483	4.02 (1.18)	0.650
missing/unknown	301 (68.1)	351 (72.82)		202 (77.99)		14 (23.33)	
RADAI-5 (mean (SD))	4.61 (2.22)	4.69 (2.14)	0.61	4.59 (2.10)	0.888	4.34 (1.81)	0.434
missing/unknown	88 (19.9)	63 (13.1)		45 (17.4)		16 (26.7)	

Supplementary Table S6.5 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
NORMAL WEIGHT	**(n=442)**	**(n=482)**	**p value**	**(n=259)**	**p value**	**(n=60)**	**p value**
HAQ (mean (SD))	0.96 (0.70)	1.03 (0.72)	0.173	1.12 (0.72)	0.010	0.78 (0.64)	0.089
missing/unknown	80 (18.1)	59 (12.24)		29 (11.2)		14 (23.33)	
Osteoporosis	88 (19.9)	101 (21.0)	0.755	61 (23.6)	0.297	23 (38.3)	0.002
Fibromyalgia	1 (0.2)	1 (0.2)	1.000	4 (1.5)	0.124	0 (0.0)	1.000
Other rheumatological disease	99 (22.4)	118 (24.5)	0.504	70 (27.0)	0.197	16 (26.7)	0.566
Psoriasis	5 (1.1)	2 (0.4)	0.382	2 (0.8)	0.946	0 (0.0)	0.892
Hyperlipidemia	9 (2.0)	14 (2.9)	0.525	3 (1.2)	0.573	7 (11.7)	<0.001
Cardiac/cardiovascular event/disease	78 (17.6)	115 (23.9)	0.025	56 (21.6)	0.233	31 (51.7)	<0.001
Cancer	4 (0.9)	9 (1.9)	0.337	6 (2.3)	0.234	4 (6.7)	0.005
Depression/anxiety	30 (6.8)	46 (9.5)	0.160	30 (11.6)	0.040	6 (10.0)	0.523
Diabetes	6 (1.4)	21 (4.4)	0.012	4 (1.5)	1.000	4 (6.7)	0.023
Fractures, surgeries, musculoskeletal system	43 (9.7)	60 (12.4)	0.227	38 (14.7)	0.064	3 (5.0)	0.341

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.6 Obese female cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OBESE FEMALE	**(n=130)**	**(n=124)**	**p value**	**(n=56)**	**p value**	**(n=27)**	**p value**
Age index (mean (SD))	56.70 (12.45)	56.27 (11.65)	0.778	55.87 (11.33)	0.669	60.33 (10.55)	0.159
RA duration, years (mean (SD))	6.92 (8.60)	7.19 (7.66)	0.798	7.97 (8.91)	0.460	6.33 (7.94)	0.744
missing/unknown	5 (3.85)	5 (4.03)		2 (3.57)		0 (0)	
Year of index date (mean (SD))	2007.86 (3.80)	2008.00 (4.52)	0.791	2006.16 (4.12)	0.007	2013.63 (2.20)	<0.001
BMI kg/m^2 (mean (SD))	34.25 (4.13)	34.12 (4.07)	0.792	33.71 (3.10)	0.376	34.69 (4.65)	0.626
High educational level (%)	10 (7.7)	3 (2.4)	0.187	3 (5.4)	1.000	3 (11.1)	0.804
missing/unknown	36 (27.7)	49 (39.5)		23 (41.1)		8 (29.6)	
Ever smoker (%)	34 (26.2)	31 (25.0)	0.947	8 (14.3)	0.113	12 (44.4)	0.095
csDMARD at index date (%)	95 (73.1)	83 (66.9)	0.352	45 (80.4)	0.384	21 (77.8)	0.791
Prednisone at index date (%)	42 (32.3)	51 (41.1)	0.184	29 (51.8)	0.019	12 (44.4)	0.324
Seropositive (%)	94 (72.3)	84 (67.7)	0.408	44 (78.6)	0.620	18 (66.7)	0.247
missing/unknown	15 (11.5)	14 (11.3)		5 (8.9)		1 (3.7)	
ESR (mean (SD))	25.50 (18.54)	24.62 (16.21)	0.704	30.59 (17.45)	0.097	19.79 (14.28)	0.156
missing/unknown	11 (8.46)	17 (13.71)		5 (8.93)		3 (11.11)	
CRP (mean (SD))	1.32 (1.11)	1.30 (1.29)	0.931	1.35 (1.04)	0.922	0.96 (0.86)	0.169
missing/unknown	75 (57.69)	70 (56.45)		39 (69.64)		3 (11.11)	
Tender joint counts 28 (mean (SD))	7.38 (6.64)	7.91 (6.70)	0.540	8.19 (7.39)	0.473	5.54 (5.12)	0.202
missing/unknown	6 (4.62)	11 (8.87)		2 (3.57)		3 (11.11)	
Swollen joint counts 28 (mean (SD))	6.82 (5.37)	6.48 (5.69)	0.634	7.06 (6.59)	0.804	4.08 (3.62)	0.018
missing/unknown	7 (5.38)	11 (8.87)		2 (3.57)		3 (11.11)	
Physician GDA (mean (SD))	5.11 (1.92)	4.96 (1.89)	0.624	5.19 (2.11)	0.863	3.43 (1.60)	<0.001
missing/unknown	48 (36.92)	53 (42.74)		29 (51.79)		6 (22.22)	
DAS28-ESR (mean (SD))	4.54 (1.31)	4.58 (1.27)	0.819	4.78 (1.36)	0.284	3.95 (1.26)	0.048
missing/unknown	12 (9.23)	17 (13.71)		5 (8.93)		4 (14.81)	
DAS28-CRP (mean (SD))	4.45 (1.09)	4.29 (1.08)	0.458	3.81 (1.16)	0.041	3.79 (1.13)	0.019
missing/unknown	75 (57.69)	70 (56.45)		39 (69.64)		4 (14.81)	
RADAI-5 (mean (SD))	5.02 (1.99)	5.46 (2.27)	0.146	5.06 (2.15)	0.913	4.44 (2.27)	0.270
missing/unknown	22 (16.9)	32 (25.8)		7 (12.5)		9 (33.3)	

Supplementary Table S6.6 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
OBESE FEMALE	**(n=130)**	**(n=124)**	**p value**	**(n=56)**	**p value**	**(n=27)**	**p value**
HAQ (mean (SD))	1.25 (0.77)	1.36 (0.73)	0.329	1.40 (0.77)	0.271	1.10 (0.65)	0.408
missing/unknown	17 (13.08)	28 (22.58)		6 (10.71)		8 (29.63)	
Osteoporosis	20 (15.4)	20 (16.1)	1.000	10 (17.9)	0.839	3 (11.1)	0.785
Fibromyalgia	2 (1.5)	8 (6.5)	0.091	0 (0.0)	0.874	1 (3.7)	1.000
Other rheumatological disease	44 (33.8)	48 (38.7)	0.499	16 (28.6)	0.593	5 (18.5)	0.182
Psoriasis	2 (1.5)	1 (0.8)	1.000	1 (1.8)	1.000	0 (0.0)	1.000
Hyperlipidemia	10 (7.7)	9 (7.3)	1.000	4 (7.1)	1.000	4 (14.8)	0.418
Cardiac/cardiovascular event/disease	63 (48.5)	69 (55.6)	0.308	24 (42.9)	0.587	19 (70.4)	0.063
Cancer	6 (4.6)	3 (2.4)	0.544	1 (1.8)	0.610	2 (7.4)	0.905
Depression/anxiety	21 (16.2)	28 (22.6)	0.255	9 (16.1)	1.000	4 (14.8)	1.000
Diabetes	11 (8.5)	18 (14.5)	0.187	8 (14.3)	0.348	4 (14.8)	0.508
Fractures, surgeries, musculoskeletal system	12 (9.2)	7 (5.6)	0.397	5 (8.9)	1.000	1 (3.7)	0.572

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.7 Obese male cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OBESE MALE	**(n=48)**	**(n=26)**	**p value**	**(n=17)**	**p value**	**(n=15)**	**p value**
Age index (mean (SD))	56.36 (10.77)	60.36 (11.12)	0.136	55.82 (8.97)	0.855	57.37 (8.94)	0.743
RA duration, years (mean (SD))	6.18 (8.90)	10.54 (11.39)	0.079	7.71 (7.68)	0.551	4.85 (6.55)	0.597
missing/unknown	0 (0)	2 (7.69)		2 (11.76)		0 (0)	
Year of index date (mean (SD))	2007.83 (3.79)	2005.31 (4.19)	0.010	2004.12 (3.30)	0.001	2012.40 (2.92)	<0.001
BMI kg/m^2 (mean (SD))	32.96 (2.84)	32.24 (1.96)	0.257	33.47 (3.15)	0.534	32.52 (1.79)	0.577
High educational level (%)	1 (2.1)	1 (3.8)	1.000	1 (5.9)	1.000	1 (6.7)	1.000
missing/unknown	22 (45.8)	8 (30.8)		4 (23.5)		5 (33.3)	
Ever smoker (%)	15 (31.2)	10 (38.5)	0.712	3 (17.6)	0.446	10 (66.7)	0.032
csDMARD at index date (%)	39 (81.2)	13 (50.0)	0.011	15 (88.2)	0.777	12 (80.0)	1.000
Prednisone at index date (%)	24 (50.0)	9 (34.6)	0.305	12 (70.6)	0.237	6 (40.0)	0.703
Seropositive (%)	35 (72.9)	18 (69.2)	0.325	12 (70.6)	1.000	14 (93.3)	0.493
missing/unknown	5 (10.4)	7 (26.9)		3 (17.6)		0 (0.0)	
ESR (mean (SD))	20.82 (18.00)	19.92 (15.29)	0.833	25.94 (22.87)	0.358	26.82 (24.51)	0.362
missing/unknown	3 (6.25)	1 (3.85)		0 (0)		4 (26.67)	
CRP (mean (SD))	1.81 (1.41)	1.88 (2.13)	0.929	1.65 (1.91)	0.882	1.27 (1.17)	0.276
missing/unknown	30 (62.5)	18 (69.23)		15 (88.24)		3 (20)	
Tender joint counts 28 (mean (SD))	6.89 (7.69)	7.65 (7.07)	0.679	8.00 (6.75)	0.602	10.23 (8.22)	0.179
missing/unknown	2 (4.17)	0 (0)		0 (0)		2 (13.33)	
Swollen joint counts 28 (mean (SD))	6.54 (6.64)	7.31 (6.30)	0.634	8.41 (5.67)	0.307	8.77 (5.46)	0.273
missing/unknown	2 (4.17)	0 (0)		0 (0)		2 (13.33)	
Physician GDA (mean (SD))	4.42 (1.55)	4.73 (2.41)	0.649	5.55 (2.25)	0.089	5.25 (2.14)	0.185
missing/unknown	22 (45.83)	15 (57.69)		6 (35.29)		3 (20)	
DAS28-ESR (mean (SD))	4.05 (1.65)	4.36 (1.52)	0.435	4.56 (1.54)	0.268	4.65 (1.78)	0.287
missing/unknown	3 (6.25)	1 (3.85)		0 (0)		4 (26.67)	
DAS28-CRP (mean (SD))	4.45 (1.36)	4.81 (1.02)	0.509	3.55 (0.07)	0.374	4.58 (1.26)	0.789
missing/unknown	30 (62.5)	18 (69.23)		15 (88.24)		3 (20)	
RADAI-5 (mean (SD))	4.61 (2.15)	4.80 (1.77)	0.725	5.44 (2.09)	0.195	4.12 (2.69)	0.574
missing/unknown	6 (12.5)	3 (11.5)		1 (5.9)		7 (46.7)	

Supplementary Table S6.7 (continued) OBESE MALE	Adalimumab (n=48)	Etanercept (n=26)	p value	Infliximab (n=17)	p value	Abatacept (n=15)	p value
HAQ (mean (SD))	1.10 (0.65)	1.17 (0.71)	0.692	1.35 (0.80)	0.221	0.61 (0.72)	0.062
missing/unknown	6 (12.5)	2 (7.69)		0 (0)		7 (46.67)	
Osteoporosis	4 (8.3)	3 (11.5)	0.973	1 (5.9)	1.000	1 (6.7)	1.000
Fibromyalgia	0 (0.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)	-
Other rheumatological disease	17 (35.4)	14 (53.8)	0.198	9 (52.9)	0.327	3 (20.0)	0.423
Psoriasis	0 (0.0)	1 (3.8)	0.754	17 (100.0)	-	15 (100.0)	-
Hyperlipidemia	5 (10.4)	2 (7.7)	1.000	1 (5.9)	0.946	6 (40.0)	0.025
Cardiac/cardiovascular event/disease	21 (43.8)	15 (57.7)	0.367	8 (47.1)	1.000	11 (73.3)	0.088
Cancer	1 (2.1)	1 (3.8)	1.000	0 (0.0)	1.000	2 (13.3)	0.275
Depression/anxiety	4 (8.3)	3 (11.5)	0.973	3 (17.6)	0.542	3 (20.0)	0.433
Diabetes	6 (12.5)	5 (19.2)	0.664	1 (5.9)	0.763	4 (26.7)	0.365
Fractures, surgeries, musculoskeletal system	3 (6.2)	1 (3.8)	1.000	2 (11.8)	0.839	2 (13.3)	0.735

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.8 Overweight female cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OVERWEIGHT FEMALE	**(n=215)**	**(n=203)**	**p value**	**(n=91)**	**p value**	**(n=30)**	**p value**
Age index (mean (SD))	56.84 (13.10)	58.48 (12.58)	0.192	57.29 (11.20)	0.776	61.73 (11.82)	0.054
RA duration, years (mean (SD))	7.26 (8.00)	8.94 (9.59)	0.056	7.61 (7.61)	0.726	6.36 (9.46)	0.586
missing/unknown	10 (4.65)	4 (1.97)		1 (1.1)		2 (6.67)	
Year of index date (mean (SD))	2007.57 (3.44)	2006.69 (4.93)	0.034	2005.97 (4.66)	0.001	2012.00 (2.82)	<0.001
BMI kg/m^2 (mean (SD))	27.16 (1.36)	27.27 (1.35)	0.434	27.13 (1.39)	0.837	27.02 (1.37)	0.602
High educational level (%)	10 (4.7)	11 (5.4)	0.686	6 (6.6)	0.692	3 (10.0)	0.487
missing/unknown	61 (28.4)	73 (36.0)		25 (27.5)		7 (23.3)	
Ever smoker (%)	46 (21.4)	43 (21.2)	1.000	21 (23.1)	0.862	12 (40.0)	0.044
csDMARD at index date (%)	150 (69.8)	129 (63.5)	0.213	76 (83.5)	0.018	23 (76.7)	0.573
Prednisone at index date (%)	84 (39.1)	85 (41.9)	0.629	50 (54.9)	0.015	7 (23.3)	0.142
Seropositive (%)	158 (73.5)	141 (69.5)	0.703	72 (79.1)	1.000	23 (76.7)	1.000
missing/unknown	27 (12.6)	31 (15.3)		6 (6.6)		2 (6.7)	
ESR (mean (SD))	25.35 (18.20)	25.59 (20.70)	0.907	24.94 (19.45)	0.866	26.55 (17.86)	0.771
missing/unknown	28 (13.02)	9 (4.43)		7 (7.69)		8 (26.67)	
CRP (mean (SD))	1.75 (2.56)	1.42 (1.91)	0.357	1.15 (1.82)	0.239	0.96 (1.12)	0.149
missing/unknown	138 (64.19)	123 (60.59)		60 (65.93)		6 (20)	
Tender joint counts 28 (mean (SD))	7.44 (6.64)	8.39 (8.08)	0.206	7.34 (7.21)	0.916	6.41 (6.18)	0.447
missing/unknown	23 (10.7)	5 (2.46)		4 (4.4)		3 (10)	
Swollen joint counts 28 (mean (SD))	6.70 (5.16)	6.87 (5.90)	0.763	7.68 (5.68)	0.158	5.56 (4.69)	0.274
missing/unknown	22 (10.23)	5 (2.46)		4 (4.4)		3 (10)	
Physician GDA (mean (SD))	4.90 (2.22)	5.06 (2.15)	0.587	5.36 (1.85)	0.204	3.87 (1.79)	0.036
missing/unknown	84 (39.07)	95 (46.8)		44 (48.35)		7 (23.33)	
DAS28-ESR (mean (SD))	4.53 (1.19)	4.47 (1.55)	0.644	4.47 (1.42)	0.725	4.52 (1.17)	0.975
missing/unknown	29 (13.49)	9 (4.43)		7 (7.69)		8 (26.67)	
DAS28-CRP (mean (SD))	4.22 (1.17)	4.33 (1.35)	0.573	4.06 (1.17)	0.521	4.04 (1.03)	0.499
missing/unknown	138 (64.19)	123 (60.59)		60 (65.93)		6 (20)	
RADAI-5 (mean (SD))	4.97 (2.03)	5.08 (2.14)	0.647	5.30 (2.18)	0.268	4.99 (2.13)	0.976
missing/unknown	16 (7.4)	10 (4.9)		1 (1.1)		2 (6.7)	

Supplementary Table S6.8 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
OVERWEIGHT FEMALE	**(n=215)**	**(n=203)**	**p value**	**(n=91)**	**p value**	**(n=30)**	**p value**
HAQ (mean (SD))	1.17 (0.69)	1.20 (0.75)	0.757	1.27 (0.75)	0.334	0.94 (0.69)	0.149
missing/unknown	37 (17.21)	21 (10.34)		9 (9.89)		10 (33.33)	
Osteoporosis	45 (20.9)	51 (25.1)	0.367	22 (24.2)	0.634	7 (23.3)	0.950
Fibromyalgia	0 (0.0)	9 (4.4)	0.005	5 (5.5)	0.003	2 (6.7)	0.007
Other rheumatological disease	70 (32.6)	71 (35.0)	0.675	29 (31.9)	1.000	9 (30.0)	0.942
Psoriasis	1 (0.5)	2 (1.0)	0.960	0 (0.0)	1.000	1 (3.3)	0.581
Hyperlipidemia	6 (2.8)	14 (6.9)	0.082	5 (5.5)	0.409	2 (6.7)	0.568
Cardiac/cardiovascular event/disease	77 (35.8)	80 (39.4)	0.511	35 (38.5)	0.757	12 (40.0)	0.807
Cancer	5 (2.3)	9 (4.4)	0.355	1 (1.1)	0.798	1 (3.3)	1.000
Depression/anxiety	26 (12.1)	33 (16.3)	0.280	20 (22.0)	0.042	1 (3.3)	0.261
Diabetes	12 (5.6)	10 (4.9)	0.936	6 (6.6)	0.938	4 (13.3)	0.224
Fractures, surgeries musculoskeletal system	13 (6.0)	28 (13.8)	0.013	6 (6.6)	1.000	1 (3.3)	0.857

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.9 Overweight male cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
OVERWEIGHT MALE	**(n=121)**	**(n=93)**	**p value**	**(n=59)**	**p value**	**(n=17)**	**p value**
Age index (mean (SD))	58.05 (11.43)	56.35 (11.64)	0.285	56.22 (11.64)	0.318	65.22 (8.63)	0.014
RA duration, years (mean (SD))	6.83 (7.35)	7.35 (8.26)	0.628	7.74 (8.86)	0.475	7.01 (6.58)	0.924
missing/unknown	2 (1.65)	3 (3.23)		3 (5.08)		1 (5.88)	
Year of index date (mean (SD))	2007.88 (3.77)	2006.77 (5.24)	0.073	2005.86 (4.78)	0.002	2012.88 (2.12)	<0.001
BMI kg/m^2 (mean (SD))	27.16 (1.33)	27.09 (1.27)	0.698	27.14 (1.36)	0.931	27.49 (1.47)	0.349
High educational level (%)	19 (15.7)	10 (10.8)	0.505	6 (10.2)	0.354	3 (17.6)	1.000
missing/unknown	37 (30.6)	33 (35.5)		16 (27.1)		4 (23.5)	
Ever smoker (%)	48 (39.7)	33 (35.5)	0.629	22 (37.3)	0.885	10 (58.8)	0.217
csDMARD at index date (%)	76 (62.8)	60 (64.5)	0.909	50 (84.7)	0.004	11 (64.7)	1.000
Prednisone at index date (%)	50 (41.3)	48 (51.6)	0.174	34 (57.6)	0.058	6 (35.3)	0.833
Seropositive (%)	86 (71.1)	70 (75.3)	1.000	47 (79.7)	0.719	14 (82.4)	0.261
missing/unknown	20 (16.5)	10 (10.8)		6 (10.2)		3 (17.6)	
ESR (mean (SD))	23.93 (21.76)	26.53 (26.71)	0.459	26.18 (24.18)	0.543	32.19 (18.41)	0.151
missing/unknown	11 (9.09)	12 (12.9)		2 (3.39)		1 (5.88)	
CRP (mean (SD))	2.68 (4.05)	2.38 (4.80)	0.752	1.24 (1.45)	0.146	1.78 (1.81)	0.378
missing/unknown	70 (57.85)	58 (62.37)		41 (69.49)		0 (0)	
Tender joint counts 28 (mean (SD))	7.75 (7.35)	6.94 (6.64)	0.427	6.83 (6.32)	0.419	5.31 (5.47)	0.205
missing/unknown	10 (8.26)	7 (7.53)		1 (1.69)		1 (5.88)	
Swollen joint counts 28 (mean (SD))	7.25 (6.08)	6.24 (6.01)	0.247	8.28 (6.45)	0.312	6.24 (6.00)	0.520
missing/unknown	11 (9.09)	7 (7.53)		1 (1.69)		0 (0)	
Physician GDA (mean (SD))	4.97 (2.38)	4.54 (2.08)	0.315	5.87 (2.32)	0.086	4.82 (1.94)	0.814
missing/unknown	52 (42.98)	45 (48.39)		29 (49.15)		0 (0)	
DAS28-ESR (mean (SD))	4.36 (1.56)	4.31 (1.39)	0.829	4.35 (1.58)	0.962	4.44 (1.14)	0.848
missing/unknown	12 (9.92)	12 (12.9)		2 (3.39)		1 (5.88)	
DAS28-CRP (mean (SD))	4.37 (1.26)	3.86 (1.14)	0.061	3.92 (1.46)	0.217	3.89 (1.16)	0.182
missing/unknown	71 (58.68)	58 (62.37)		41 (69.49)		1 (5.88)	
RADAI-5 (mean (SD))	4.58 (2.16)	4.85 (2.26)	0.428	4.55 (2.12)	0.937	4.68 (2.76)	0.881
missing/unknown	30 (24.8)	18 (19.4)		6 (10.2)		5 (29.4)	

Supplementary Table S6.9 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
OVERWEIGHT MALE	**(n=121)**	**(n=93)**	**p value**	**(n=59)**	**p value**	**(n=17)**	**p value**
HAQ (mean (SD))	0.90 (0.70)	0.97 (0.68)	0.514	1.20 (0.69)	0.011	0.93 (0.72)	0.875
missing/unknown	26 (21.49)	17 (18.28)		5 (8.47)		4 (23.53)	
Osteoporosis	14 (11.6)	10 (10.8)	1.000	11 (18.6)	0.290	4 (23.5)	0.324
Fibromyalgia	0 (0)	0 (0))	-	0 (0)	-	0 (0)	-
Other rheumatological disease	31 (25.6)	26 (28.0)	0.820	16 (27.1)	0.973	4 (23.5)	1.000
Psoriasis	1 (0.8)	1 (1.1)	1.000	0 (0.0)	1.000	0 (0.0)	1.000
Hyperlipidemia	10 (8.3)	11 (11.8)	0.524	3 (5.1)	0.641	5 (29.4)	0.027
Cardiac/cardiovascular event/disease	46 (38.0)	37 (39.8)	0.903	23 (39.0)	1.000	9 (52.9)	0.362
Cancer	1 (0.8)	4 (4.3)	0.226	0 (0.0)	1.000	1 (5.9)	0.583
Depression/anxiety	5 (4.1)	9 (9.7)	0.178	7 (11.9)	0.102	1 (5.9)	1.000
Diabetes	14 (11.6)	9 (9.7)	0.825	2 (3.4)	0.126	4 (23.5)	0.324
Fractures, surgeries, musculoskeletal system	13 (10.7)	6 (6.5)	0.394	7 (11.9)	1.000	1 (5.9)	0.847

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.10 Normal weight female cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
NORMAL WEIGHT FEMALE	**(n=365)**	**(n=393)**	**p value**	**(n=207)**	**p value**	**(n=51)**	**p value**
Age index (mean (SD))	53.03 (13.95)	53.84 (14.78)	0.438	53.70 (14.18)	0.583	61.81 (13.39)	<0.001
RA duration, years (mean (SD))	8.86 (9.45)	8.96 (9.31)	0.894	10.49 (9.72)	0.054	9.99 (10.98)	0.439
missing/unknown	9 (2.47)	9 (2.29)		5 (2.42)		1 (1.96)	
Year of index date (mean (SD))	2007.10 (3.20)	2005.84 (4.84)	<0.001	2004.61 (4.11)	<0.001	2012.78 (2.80)	<0.001
BMI kg/m^2 (mean (SD))	22.08 (1.76)	21.97 (1.78)	0.365	22.07 (1.81)	0.963	22.24 (1.70)	0.556
High educational level (%)	38 (10.4)	28 (7.1)	0.191	17 (8.2)	0.708	6 (11.8)	1.000
missing/unknown	113 (31.0)	134 (34.1)		77 (37.2)		10 (19.6)	
Ever smoker (%)	91 (24.9)	80 (20.4)	0.156	37 (17.9)	0.066	14 (27.5)	0.829
csDMARD at index date (%)	260 (71.2)	222 (56.5)	<0.001	167 (80.7)	0.017	33 (64.7)	0.428
Prednisone at index date (%)	145 (39.7)	160 (40.7)	0.839	100 (48.3)	0.057	22 (43.1)	0.754
Seropositive (%)	266 (72.9)	308 (78.4)	0.401	169 (81.6)	0.013	39 (76.5)	0.376
missing/unknown	49 (13.4)	38 (9.7)		24 (11.6)		1 (2.0)	
ESR (mean (SD))	23.20 (19.08)	24.74 (22.92)	0.347	28.03 (24.61)	0.014	25.87 (18.95)	0.416
missing/unknown	47 (12.88)	39 (9.92)		21 (10.14)		13 (25.49)	
CRP (mean (SD))	1.24 (1.49)	1.21 (1.62)	0.899	1.45 (2.05)	0.487	1.49 (2.05)	0.417
missing/unknown	256 (70.14)	285 (72.52)		162 (78.26)		12 (23.53)	
Tender joint counts 28 (mean (SD))	6.77 (6.42)	6.86 (6.79)	0.864	6.66 (6.51)	0.847	6.98 (5.80)	0.842
missing/unknown	33 (9.04)	22 (5.6)		15 (7.25)		7 (13.73)	
Swollen joint counts 28 (mean (SD))	6.66 (5.70)	6.75 (6.05)	0.849	8.74 (6.92)	<0.001	6.62 (5.54)	0.965
missing/unknown	34 (9.32)	22 (5.6)		14 (6.76)		6 (11.76)	
Physician GDA (mean (SD))	5.04 (2.11)	5.14 (2.21)	0.624	5.15 (2.04)	0.646	4.46 (1.79)	0.128
missing/unknown	175 (47.95)	192 (48.85)		103 (49.76)		16 (31.37)	
DAS28-ESR (mean (SD))	4.33 (1.34)	4.28 (1.45)	0.644	4.51 (1.48)	0.160	4.48 (0.97)	0.507
missing/unknown	48 (13.15)	39 (9.92)		22 (10.63)		14 (27.45)	
DAS28-CRP (mean (SD))	4.11 (1.17)	4.05 (1.09)	0.683	4.03 (1.23)	0.716	4.13 (1.15)	0.929
missing/unknown	257 (70.41)	285 (72.52)		163 (78.74)		13 (25.49)	
RADAI-5 (mean (SD))	4.62 (2.17)	4.67 (2.16)	0.788	4.65 (2.05)	0.888	4.21 (1.66)	0.264
missing/unknown	73 (20.00)	55 (13.99)		41 (19.81)		14 (27.45)	

Supplementary Table S6.10 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
NORMAL WEIGHT FEMALE	**(n=365)**	**(n=393)**	**p value**	**(n=207)**	**p value**	**(n=51)**	**p value**
HAQ (mean (SD))	0.99 (0.72)	1.05 (0.73)	0.263	1.21 (0.70)	0.001	0.76 (0.57)	0.056
missing/unknown	65 (17.81)	51 (12.98)		26 (12.56)		12 (23.53)	
Osteoporosis	78 (21.4)	87 (22.1)	0.867	51 (24.6)	0.427	22 (43.1)	0.001
Fibromyalgia	0 (0.0)	1 (0.3)	1.000	3 (1.4)	0.088	0 (0)	-
Other rheumatological disease	82 (22.5)	99 (25.2)	0.427	59 (28.5)	0.131	14 (27.5)	0.539
Psoriasis	4 (1.1)	1 (0.3)	0.327	1 (0.5)	0.772	0 (0.0)	1.000
Hyperlipidemia	6 (1.6)	10 (2.5)	0.542	1 (0.5)	0.414	6 (11.8)	<0.001
Cardiac/cardiovascular event/disease	60 (16.4)	89 (22.6)	0.040	44 (21.3)	0.186	26 (51.0)	<0.001
Cancer	3 (0.8)	8 (2.0)	0.275	4 (1.9)	0.444	3 (5.9)	0.027
Depression/anxiety	27 (7.4)	40 (10.2)	0.223	25 (12.1)	0.085	6 (11.8)	0.421
Diabetes	2 (0.5)	9 (2.3)	0.089	2 (1.0)	0.956	3 (5.9)	0.010
Fractures, surgeries, musculoskeletal system	40 (11.0)	51 (13.0)	0.458	33 (15.9)	0.113	2 (3.9)	0.189

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.11 Normal weight male cohort, patient characteristics at baseline, stratified by first b/tsDMARD adalimumab, etanercept, infliximab, and abatacept.

	Adalimumab	Etanercept		Infliximab		Abatacept	
NORMAL WEIGHT MALE	**(n=77)**	**(n=89)**	**p value**	**(n=52)**	**p value**	**(n=9)**	**p value**
Age index (mean (SD))	54.24 (12.98)	56.40 (14.14)	0.309	50.97 (14.60)	0.185	62.91 (19.86)	0.078
RA duration, years (mean (SD))	5.57 (7.12)	7.31 (7.06)	0.122	7.15 (6.95)	0.220	3.91 (4.36)	0.521
missing/unknown	1 (1.3)	4 (4.49)		1 (1.92)		1 (11.11)	
Year of index date (mean (SD))	2008.47 (4.32)	2005.73 (5.16)	<0.001	2005.58 (3.70)	<0.001	2012.33 (1.94)	0.010
BMI kg/m^2 (mean (SD))	22.58 (1.76)	22.55 (1.90)	0.897	22.57 (1.81)	0.965	23.55 (1.61)	0.120
High educational level (%)	12 (15.6)	19 (21.3)	0.430	7 (13.5)	0.977	0 (0.0)	0.278
missing/unknown	27 (35.1)	31 (34.8)		19 (36.5)		1 (11.1)	
Ever smoker (%)	31 (40.3)	39 (43.8)	0.760	18 (34.6)	0.643	4 (44.4)	1.000
csDMARD at index date (%)	56 (72.7)	43 (48.3)	0.002	41 (78.8)	0.561	5 (55.6)	0.493
Prednisone at index date (%)	23 (29.9)	33 (37.1)	0.415	24 (46.2)	0.089	5 (55.6)	0.238
Seropositive (%)	59 (76.6)	71 (79.8)	0.214	39 (75.0)	0.708	7 (77.8)	1.000
missing/unknown	7 (9.1)	12 (13.5)		8 (15.4)		1 (11.1)	
ESR (mean (SD))	24.89 (24.56)	30.08 (23.86)	0.193	18.84 (23.48)	0.185	31.62 (35.13)	0.488
missing/unknown	11 (14.29)	4 (4.49)		3 (5.77)		1 (11.11)	
CRP (mean (SD))	1.42 (1.84)	1.78 (1.54)	0.426	1.40 (1.84)	0.979	1.36 (1.18)	0.933
missing/unknown	43 (55.84)	65 (73.03)		38 (73.08)		1 (11.11)	
Tender joint counts 28 (mean (SD))	6.34 (6.39)	5.96 (6.03)	0.706	6.31 (7.66)	0.977	3.50 (3.02)	0.220
missing/unknown	7 (9.09)	4 (4.49)		3 (5.77)		1 (11.11)	
Swollen joint counts 28 (mean (SD))	6.10 (5.56)	7.19 (6.26)	0.254	7.20 (6.85)	0.330	3.62 (2.88)	0.221
missing/unknown	5 (6.49)	4 (4.49)		2 (3.85)		1 (11.11)	
Physician GDA (mean (SD))	4.75 (2.18)	5.12 (2.03)	0.377	5.58 (2.70)	0.155	4.14 (1.68)	0.482
missing/unknown	25 (32.47)	38 (42.7)		28 (53.85)		2 (22.22)	
DAS28-ESR (mean (SD))	4.07 (1.64)	4.36 (1.34)	0.241	3.71 (1.73)	0.263	3.64 (1.82)	0.488
missing/unknown	12 (15.58)	5 (5.62)		4 (7.69)		1 (11.11)	
DAS28-CRP (mean (SD))	4.12 (1.38)	4.59 (1.25)	0.193	3.79 (1.09)	0.455	3.49 (1.26)	0.249
missing/unknown	44 (57.14)	66 (74.16)		39 (75)		1 (11.11)	
RADAI-5 (mean (SD))	4.56 (2.46)	4.79 (2.04)	0.550	4.36 (2.28)	0.654	5.03 (2.49)	0.638
missing/unknown	15 (19.5)	8 (9)		4 (7.7)		2 (22.2)	

Supplementary Table S6.11 (continued)	**Adalimumab**	**Etanercept**		**Infliximab**		**Abatacept**	
NORMAL WEIGHT MALE	**(n=77)**	**(n=89)**	**p value**	**(n=52)**	**p value**	**(n=9)**	**p value**
HAQ (mean (SD))	0.85 (0.63)	0.96 (0.64)	0.326	0.77 (0.67)	0.496	0.89 (0.97)	0.882
missing/unknown	15 (19.48)	8 (8.99)		3 (5.77)		2 (22.22)	
Osteoporosis	10 (13.0)	14 (15.7)	0.780	10 (19.2)	0.476	1 (11.1)	1.000
Fibromyalgia	1 (1.3)	0 (0.0)	0.942	1 (1.9)	1.000	0 (0.0)	1.000
Other rheumatological disease	17 (22.1)	19 (21.3)	1.000	11 (21.2)	1.000	2 (22.2)	1.000
Psoriasis	1 (1.3)	1 (1.1)	1.000	1 (1.9)	1.000	0 (0.0)	1.000
Hyperlipidemia	3 (3.9)	4 (4.5)	1.000	2 (3.8)	1.000	1 (11.1)	0.892
Cardiac/cardiovascular event/disease	18 (23.4)	26 (29.2)	0.501	12 (23.1)	1.000	5 (55.6)	0.096
Cancer	1 (1.3)	1 (1.1)	1.000	2 (3.8)	0.729	1 (11.1)	0.497
Depression/anxiety	3 (3.9)	6 (6.7)	0.643	5 (9.6)	0.343	0 (0.0)	1.000
Diabetes	4 (5.2)	12 (13.5)	0.123	2 (3.8)	1.000	1 (11.1)	1.000
Fractures, surgeries, musculoskeletal system	3 (3.9)	9 (10.1)	0.214	5 (9.6)	0.343	1 (11.1)	0.892

Values are the number and column percentage, unless otherwise specified. Significance tests compare each drug of interest to Adalimumab, using chi-squared test for categorical variables, and t-test for continuous variables. For these tests, missing values did not function as a grouping variable.

Abbreviations: SD standard deviation; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease modifying antirheumatic drug; ESR erythrocyte sedimentation rate; CRP C-reactive protein; DAS28-ESR 28-joint Disease Activity Score using erythrocyte sedimentation rate; DAS28-CRP 28-joint Disease Activity Score using C-reactive protein; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five; HAQ Health Assessment Questionnaire.

For additional information on seropositivity and comorbidities see footnote in Supplementary Table S6.3.

Supplementary Table S6.12 Sensitivity analyses excluding patients who miss information on outcome during follow-up (EPMOI, Excluding Patients Missing Outcome Information), overall BMI cohorts.

		Sensitivity analyses (EPMOI)		
		n all	n event	OR
Obese - overall	**DAS28-remission**			
	adalimumab	71	25	1 (ref.)
	etanercept	64	21	1.01 (0.49-2.11)
	infliximab	32	7	0.49 (0.17-1.26)
	abatacept	18	6	0.91 (0.28-2.73)
	DAS28-LDA			
	adalimumab	71	37	1 (ref.)
	etanercept	64	32	0.95 (0.48-1.89)
	infliximab	32	15	0.85 (0.36-1.98)
	abatacept	18	8	0.68 (0.23-1.95)
	RADAI-5-remission			
	adalimumab	63	11	1 (ref.)
	etanercept	56	9	0.95 (0.35-2.53)
	infliximab	28	5	1.01 (0.29-3.14)
	abatacept	20	4	1.21 (0.30-4.13)
Overweight - overall	**DAS28-remission**			
	adalimumab	147	55	1 (ref.)
	etanercept	136	44	0.83 (0.50-1.36)
	infliximab	81	33	1.15 (0.65-2.02)
	abatacept	23	8	1.18 (0.44-2.98)
	DAS28-LDA			
	adalimumab	147	84	1 (ref.)
	etanercept	136	62	0.63 (0.39-1.02)
	infliximab	81	44	0.89 (0.51-1.54)
	abatacept	23	13	1.15 (0.47-2.91)
	RADAI-5-remission			
	adalimumab	133	35	1 (ref.)
	etanercept	121	16	0.43 (0.22-0.82)
	infliximab	80	18	0.82 (0.42-1.55)
	abatacept	13	4	1.33 (0.34-4.47)
Normal weight – overall	**DAS28-remission**			
	adalimumab	204	85	1 (ref.)
	etanercept	256	99	0.89 (0.61-1.31)
	infliximab	147	55	0.82 (0.52-1.28)
	abatacept	29	14	1.82 (0.81-4.10)
	DAS28-LDA			
	adalimumab	204	122	1 (ref.)
	etanercept	256	148	0.93 (0.63-1.37)
	infliximab	147	82	0.84 (0.54-1.30)
	abatacept	29	20	2.05 (0.89-5.04)
	RADAI-5-remission			
	adalimumab	186	49	1 (ref.)
	etanercept	243	69	1.15 (0.75-1.77)
	infliximab	134	38	1.11 (0.67-1.83)
	abatacept	30	9	1.36 (0.55-3.13)

OR odds ratio adjusted for sex and age.

Abbreviations: EPMOI Excluding Patients Missing Outcome Information; n number; ref reference; DAS28-remisison 28-joint Disease Activity Score remission; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five.

Supplementary Table S6.13 Sensitivity analyses excluding patients who miss information on outcome during follow-up (EPMOI, Excluding Patients Missing Outcome Information), female and male BMI cohorts.

		Sensitivity analyses (EPMOI)		
		n all	n event	OR
Obese - female	**DAS28-remission**			
	adalimumab	50	16	1 (ref.)
	etanercept	54	16	0.88 (0.38-2.03)
	infliximab	22	2	0.20 (0.03-0.79)
	abatacept	12	4	1.15 (0.27-4.32)
	DAS28-LDA			
	adalimumab	50	27	1 (ref.)
	etanercept	54	26	0.81 (0.37-1.76)
	infliximab	22	8	0.53 (0.18-1.48)
	abatacept	12	6	0.78 (0.21-2.84)
	RADAI-5-remission			
	adalimumab	44	7	1 (ref.)
	etanercept	47	8	1.08 (0.35-3.38)
	infliximab	19	2	0.60 (0.08-2.84)
	abatacept	14	3	1.49 (0.28-6.51)
Overweight - female	**DAS28-remission**			
	adalimumab	92	31	1 (ref.)
	etanercept	96	31	1.02 (0.55-1.90)
	infliximab	52	23	1.65 (0.81-3.37)
	abatacept	19	8	1.96 (0.68-5.58)
	DAS28-LDA			
	adalimumab	92	53	1 (ref.)
	etanercept	96	45	0.68 (0.38-1.23)
	infliximab	52	28	0.88 (0.44-1.76)
	abatacept	19	12	1.58 (0.57-4.69)
	RADAI-5-remission			
	adalimumab	85	19	1 (ref.)
	etanercept	86	11	0.51 (0.22-1.15)
	infliximab	52	13	1.16 (0.51-2.60)
	abatacept	11	4	2.04 (0.49-7.61)

		Sensitivity analyses (EPMOI)		
		n all	n event	OR
Obese - male	**DAS28-remission**			
	adalimumab	21	9	1 (ref.)
	etanercept	10	5	1.36 (0.29-6.51)
	infliximab	10	5	1.35 (0.29-6.38)
	abatacept	6	2	0.67 (0.08-4.25)
	DAS28-LDA			
	adalimumab	21	10	1 (ref.)
	etanercept	10	6	1.54 (0.33-7.76)
	infliximab	10	7	2.47 (0.52-14.08)
	abatacept	6	2	0.55 (0.07-3.51)
	RADAI-5-remission			
	adalimumab	19	4	1 (ref.)
	etanercept	9	1	0.48 (0.02-4.04)
	infliximab	9	3	1.91 (0.3-11.65)
	abatacept	6	1	0.75 (0.03-6.83)
Overweight - male	**DAS28-remission**			
	adalimumab	55	24	1 (ref.)
	etanercept	40	13	0.6 (0.25-1.40)
	infliximab	29	10	0.64 (0.24-1.63)
	abatacept	4	0	-
	DAS28-LDA			
	adalimumab	55	31	1 (ref.)
	etanercept	40	17	0.56 (0.24-1.28)
	infliximab	29	16	0.93 (0.37-2.33)
	abatacept	4	1	0.29 (0.01-2.53)
	RADAI-5-remission			
	adalimumab	48	16	1 (ref.)
	etanercept	35	5	0.33 (0.10-0.96)
	infliximab	28	5	0.44 (0.13-1.29)
	abatacept	2	0	-

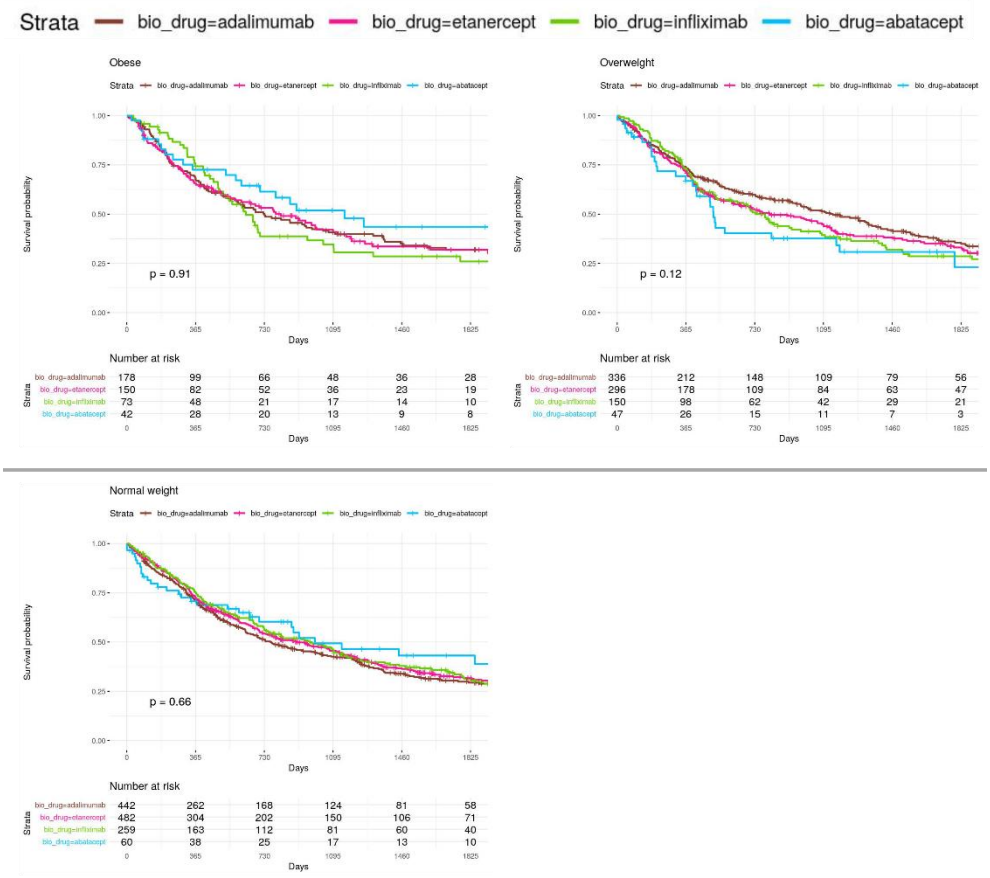
Supplementary Table S6.13 (continued)

		Sensitivity analyses (EPMOI)		
		n all	n event	OR
Normal weight - female	**DAS28-remission**			
	adalimumab	170	69	1 (ref.)
	etanercept	212	78	0.85 (0.56-1.30)
	infliximab	124	42	0.76 (0.46-1.23)
	abatacept	25	13	1.99 (0.84-4.77)
	DAS28-LDA			
	adalimumab	170	96	1 (ref.)
	etanercept	212	119	0.99 (0.66-1.50)
	infliximab	124	66	0.89 (0.55-1.43)
	abatacept	25	17	2.09 (0.86-5.46)
	RADAI-5-remission			
	adalimumab	157	43	1 (ref.)
	etanercept	203	60	1.14 (0.72-1.82)
	infliximab	114	32	1.05 (0.61-1.81)
	abatacept	27	7	1.04 (0.38-2.57)

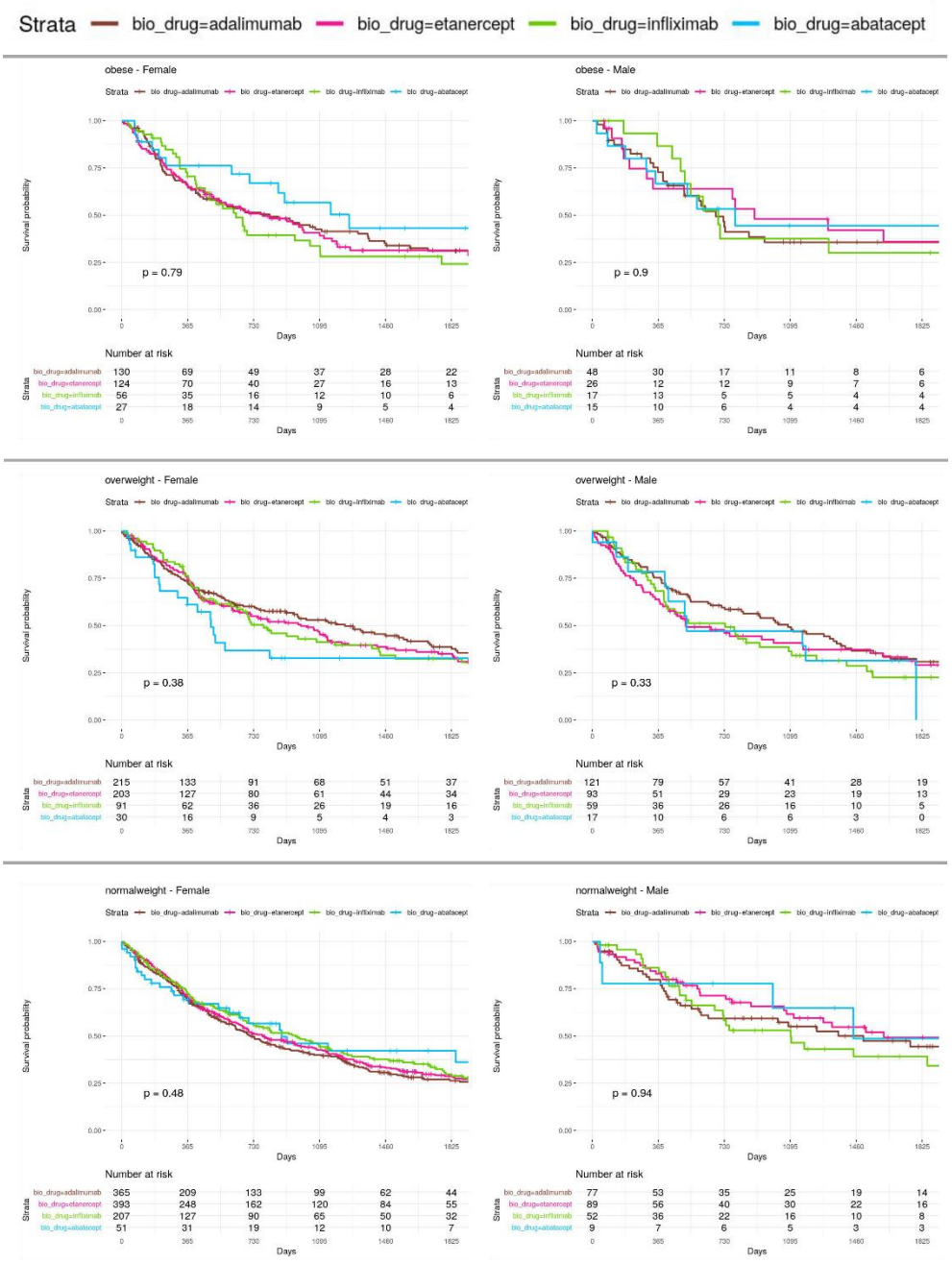
		Sensitivity analyses (EPMOI)		
		n all	n event	OR
Normal weight - male	**DAS28-remission**			
	adalimumab	34	16	1 (ref.)
	etanercept	44	21	1.25 (0.48-3.33)
	Infliximab	23	13	1.03 (0.33-3.27)
	Abatacept	4	1	1.17 (0.05-12.24)
	DAS28-LDA			
	adalimumab	34	26	1 (ref.)
	etanercept	44	29	0.67 (0.23-1.87)
	Infliximab	23	16	0.51 (0.14-1.81)
	Abatacept	4	3	2.15 (0.21-50.93)
	RADAI-5-remission			
	adalimumab	29	6	1 (ref.)
	etanercept	40	9	1.21 (0.37-4.14)
	infliximab	20	6	1.55 (0.40-5.96)
	abatacept	3	2	10.81 (0.77-289.43)

OR odds ratio adjusted for age.

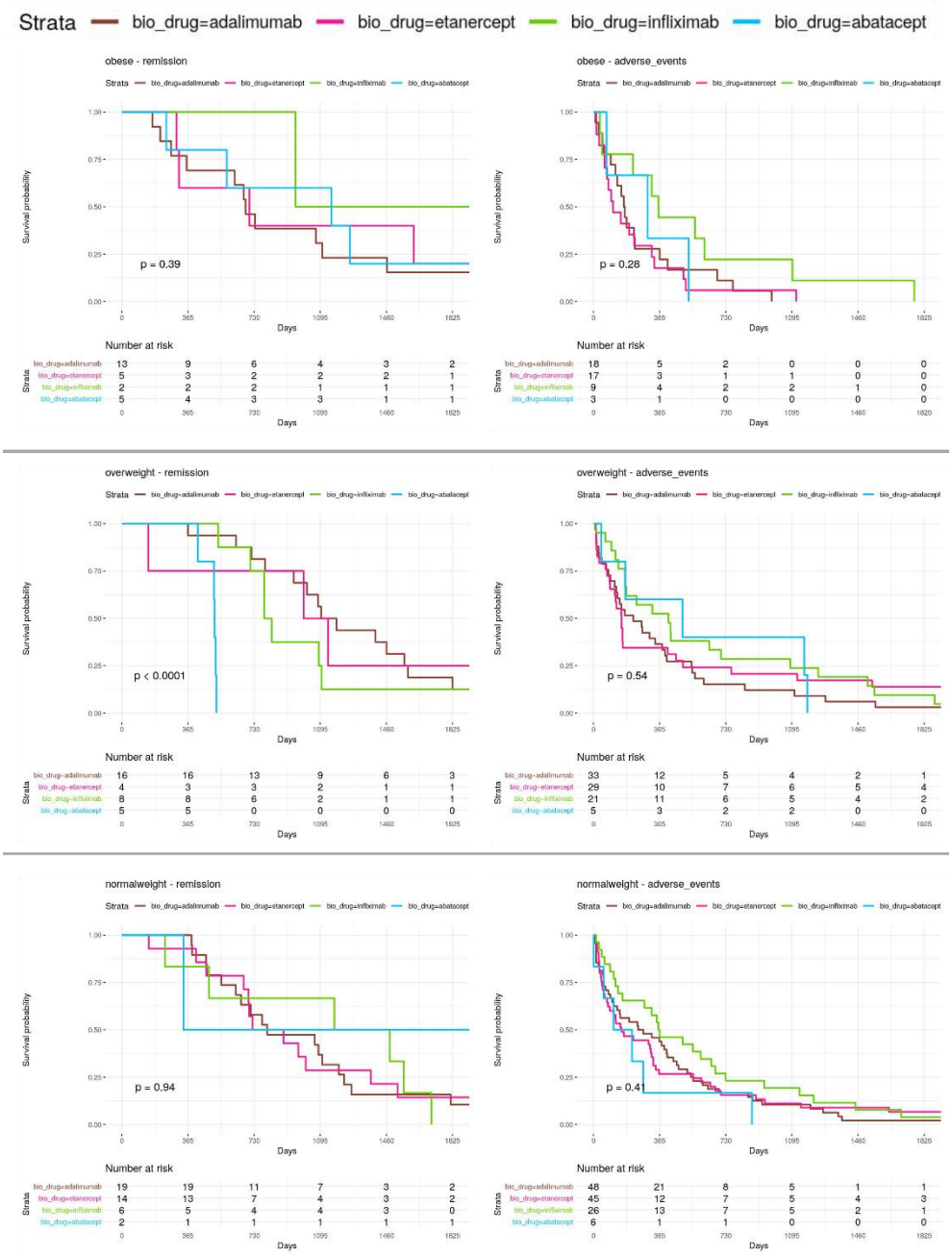
Abbreviations: EPMOI Excluding Patients Missing Outcome Information; n number; ref reference; DAS28-remisison 28-joint Disease Activity Score remission; RADAI-5 Rheumatoid Arthritis Disease Activity Index-Five.



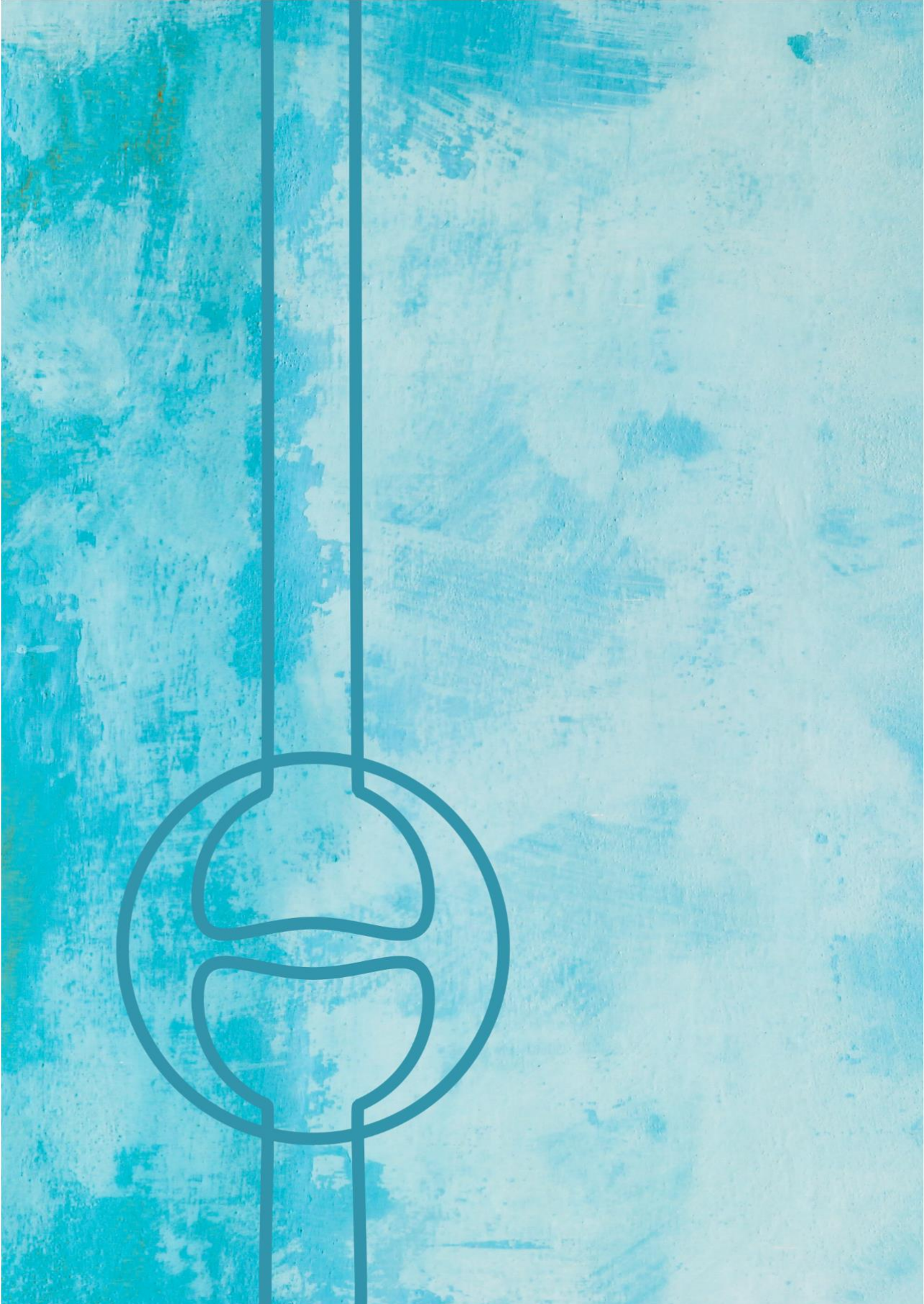
Supplementary Figure S6.4 part I Kaplan-Meier curves for drug survival in the BMI cohorts. Log-rank p value indicated in each graph, and frequency table described below each respective graph.



Supplementary Figure S6.4 part II Kaplan-Meier curves for drug survival in the BMI cohorts stratified by sex. Log-rank p value indicated in each graph, and frequency table described below each respective graph.



Supplementary Figure S6.4 part III Kaplan-Meier curves for drug survival in the BMI cohorts stratified by reason of treatment stop as adverse event(s) or remission as recorded by the clinician. Log-rank p value indicated in each graph, and frequency table described below each respective graph.



Chapter 7

Lower odds of remission among women with rheumatoid arthritis: a cohort study in the Swiss Clinical Quality Management cohort

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ENRIQUETA VALLEJO-YAGÜE*
JULIA N. PFUND*
THERESA BURKARD
CAROLE CLAIR
RAPHAEL MICHEROLI
BURKHARD MÖLLER
AXEL FINCKH
ANDREA M. BURDEN
**both authors contributed equally*

Abstract

Objective

To compare the likelihood of achieving remission between men and women with rheumatoid arthritis (RA) after starting their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD).

Methods

This cohort study in the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry included RA patients starting their first b/tsDMARD (1997-31/04/2018). The odds of achieving remission at ≤12-months, defined by 28-joint Disease Activity Score (DAS28) <2.6, were compared between men and women. Secondary analyses were adjusted for age and seropositivity, and we investigated potential mediators or factors that could explain the main findings.

Results

The study included 2839 (76.3%) women and 883 (23.7%) men with RA. Compared to women, men were older at diagnosis and b/tsDMARD start, but had shorter time from diagnosis to b/tsDMARD (3.4 versus 5.0 years, p<0.001), and they had lower DAS28 at b/tsDMARD start. Compared to women, men had 21% increased odds of achieving DAS28-remission, with odds ratio (OR) 1.21, 95% confidence interval (CI) 1.02-1.42. Adjusting for age and seropositivity yielded similar findings (adjusted OR 1.24, 95%CI 1.05-1.46). Analyses of potential mediators suggested that the observed effect may be explained by the shorter disease duration and lower DAS28 at treatment initiation in men versus women.

Conclusion

Men started b/tsDMARD earlier than women, particularly regarding disease duration and disease activity (DAS28), and had higher odds of reaching remission. This highlights the importance of early initiation of second line treatments, and suggests to target an earlier stage of disease in women to match the benefits observed in men.

Lower odds of remission among women with rheumatoid arthritis: a cohort study in the Swiss Clinical Quality Management cohort

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ENRIQUETA VALLEJO-YAGÜE*
JULIA N. PFUND*
THERESA BURKARD
CAROLE CLAIR
RAPHAEL MICHEROLI
BURKHARD MÖLLER
AXEL FINCKH
ANDREA M. BURDEN
**both authors contributed equally*

Introduction

Rheumatoid arthritis (RA), with a prevalence of 0.5 to 1.0%,[1] affects women three times more frequently than men.[2,3] While the reason for this unbalanced frequency between women and men is not fully understood, it is known as the result from multiple factors, including both biologically-driven sex concepts and socially constructed gender factors. Sex-based factors include observed differences in the immune response and hormonal levels between sexes.[4–7] Comparing adult men and women, antibody production and cell-mediated immunity are generally enhanced in women.[7,8] Particularly, T cell activation and proliferation, CD4/CD8 ratio, B cells, and immunoglobulins are increased in women, while men present higher levels of CD8+ T cells and regulatory T (Treg) cells.[7] Additionally, levels of estrogen (which fluctuate during the menstrual cycle) have a dose-, density-, and distribute-dependent role in the immune-response,[7] with low levels enhancing it, and high levels (characteristic of pregnancy stage) having immune inhibitory effect.[8] Conversely, progesterone and testosterone have anti-inflammatory effects.[7,8] Furthermore, besides the sex-based factors, socially constructed

gender bias and stereotypes may also play a role in the development of RA by influencing environmental or behavioural factors.[4] For example, smoking, associated to increased risk of incidence of seropositive-RA,[9] is more common among men than women in Switzerland.[10]. And while women may seek health consultation earlier, they tend to be prescribed lower dose[11] or less appropriate pain medication than men.[12–15] Likewise, a later referral from first physician encounter to the arthritis clinic was reported for women versus men.[16]

In addition to the differences in RA prevalence in men and women, previous studies have found differences in the presentation and management of RA. Among RA patients, an increased disease severity and higher pain levels in women, compared to men, have been reported in several studies.[17–22] Moreover, observational studies showed a stronger clinical response and higher likelihood of achieving remission in men compared to women.[23–28] However, these findings were not always consistent depending on the study design. For example, Jawaheer et al. found that men, compared to women, had higher odds of achieving sustained remission in early RA but not in established RA.[24,26] Likewise, Couderc et al. found inconsistent results on regard to remission rates and response across men and women depending on the follow-up time-point.[29] Additionally, a recent meta-analysis of randomised clinical trials (RCTs) for biologics reported no significant differences in response rates between women and men.[30]

Thus, investigating the influence of sex and gender on the course of RA remains of interest. In this study we characterised women and men with RA at the time of starting their first biologic or targeted synthetic disease-modifying antirheumatic drug (b/tsDMARD), and aimed to assess the impact of sex/gender in the subsequent clinical response.

Materials and methods

Study design and data source

We conducted an observational cohort study using data from the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry. The SCQM registry, established in 1997, is a Swiss multicenter longitudinal cohort of patients with rheumatic diseases.[31] Patients are invited to enter the registry by their treating rheumatologist. Patients provide written informed consent, and they can withdraw their consent at any point. Following consent, information from routine visits is recorded.[32] Within these visits, clinical endpoints (e.g., inflammatory markers, disease activity score), patient-reported outcomes (e.g., pain), and treatments are recorded. Similarly, patient demographics, comorbidities, and other health-related notes are collected. Additional surveys are filled out by the patients regularly (e.g., Health Assessment Questionnaire (HAQ)[33]).

Pseudonymized data, without access to the code key, was provided by the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) registry to the researchers. Therefore, the commission of the Canton of Zurich (KEK: Req-2020-00045) waived the need for a full ethics authorization.

Study population

The study included adult RA patients (≥18 years old) registered in the SCQM and who started their first b/tsDMARD between 1997 and April 30st 2018 (15-months before the end of the data collection period, July 31st 2019). The start of the first b/tsDMARD was considered the index date. Patients with a b/tsDMARD treatment start before their first visit registered in SCQM were excluded. Additionally, patients without a recorded visit at index date or within the previous 6-months (i.e., the baseline visit) were excluded.

Exposure

The study exposure was the sex of the patients. While this is registered in the SCQM as female and male, we refer to these categories as women and men. Additionally, since both biologically-driven sex concepts and socially constructed gender factors may play a role in the study of this exposure groups, we refer to our exposure as sex/gender.

Outcomes

The primary outcome was 28-joint Disease Activity Score (DAS28)[33] remission within the first 12-months after the index date, defined as DAS28<2.6.[34] DAS28-remission was calculated using erythrocyte sedimentation rate (ESR; DAS28-ESR). When DAS28-ESR was missing in follow-up visits, DAS28 using C-reactive protein (CRP; DAS28-CRP) was used instead, if available. Formulas for DAS28 are provided in **Supplementary Equations S7.1**.

Secondary outcomes were 1) the achievement of DAS28 low disease activity (LDA) or remission (DAS28-rem/LDA) within the first 12-months, defined as DAS28<3.2; 2) the achievement of Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5) remission within the first 12-months, defined as RADAI-5 ≤1.4.[34]

For all outcomes, patients with missing records of the respective outcome during follow-up were considered as non-achievers of that outcome. To challenge this assumption, we performed a sensitivity analysis in which patients with missing follow-up information on the respective outcome were excluded.

Follow-up

Patients were followed until achievement of the outcome, or for a maximum of 12-months. Sensitivity analyses that restricted and extended the maximum follow-up to 9- and 15-months, respectively, were performed.

Covariates

Patients' age at first symptoms and RA diagnosis were collected. Baseline patient characteristics were recorded at index date (start of first b/tsDMARD) or as close as possible to this date within a pre-defined look-back window. Patient demographics, body mass index (BMI), disease duration (time from RA diagnosis), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibodies, number of swollen joint counts counting 28 (SJC28), number of tender joint counts counting 28 (TJC28), and physician global disease activity were collected with a 6-month look-back window. Inflammatory markers (ESR, CRP), disease activity scores (DAS28-ESR, DAS28-CRP, RADAI-5), and the Health Assessment Questionnaire (HAQ)[33] were collected with a 3-month look-back window. Information on treatment was collected at index date, including conventional synthetic disease-modifying antirheumatic drugs (csDMARD) and steroid use, and type of b/tsDMARD. Records on ever smoking, post-menopause, and comorbidities were collected if ever-before, except for fractures/surgeries/musculoskeletal system records and infections, which had a 6-month look-back window. Information on pregnancy or breastfeeding had a 12-month look-back window.

RF and anti-CCP values were combined as seropositivity, which was positive if either was positive, negative if both were negative, and missing otherwise. Missingness in ever smoking, pregnancy/breastfeeding, post-menopause record, and comorbidities, were categorised as absent.

Statistical methods

Patient characteristics were described for women and men separately. To compare differences, findings in men were compared to those in women using chi-squared test for categorical variables, and t-test or Kruskal-Wallis test for continuous variables.

Multiple imputation with chained equations (MICE) was used to complete relevant baseline variables. We performed 55 imputations and the 41.2% of patients had complete information in every included variable. The variables included in the MICE, their role, their missingness, and the used imputed methods are detailed in **Supplementary Table S7.1**. Convergence was checked visually. Density plots depicting the overlapping of the distribution of key variables in the original and imputed datasets are presented in **Supplementary Figure S7.1**.

To assess the likelihood of achieving the study outcomes in men versus women (reference group), logistic regression was performed in each imputed dataset, and subsequently, results were combined using Rubin's rule. These analyses were done crude and adjusted for age and seropositivity.

We identified as potential mediators or factors to explain an association between sex/gender and the study outcomes the following baseline covariates: DAS28, disease duration, BMI, and rheumatic medication. While mediators should not be included in the main model to assess the impact of an exposure on an outcome because they would disturb the findings, performing additional mediation analyses aids elucidating the pathways to explain the effect of an exposure on an outcome.[35] Thus, we performed mediation analyses to investigate the influence of the identified potential mediators on the impact of sex/gender on the achievement of DAS28-remission at ≤12-months. The above-mentioned potential mediators were treated as categorical variables, which were: moderate or high disease activity versus lower (DAS28≥3.2 versus DAS28<3.2); late versus early RA disease duration (RA duration >2-years versus ≤2-years); elevated BMI versus normal weight (BMI≥25 versus BMI<25); csDMARD use at index date (yes versus no); and steroid use at index date (yes versus no). Since adjusting for exposure-outcome confounders in mediation analyses may introduce additional biases,[35] we did not adjust for exposure-outcome confounders.

The mediation analyses were performed independently for each potential mediator, and they included the following steps: I) Logistic regression to investigate the association between sex/gender and the potential mediator; II) Logistic regression to investigate the association between sex/gender and DAS28-remission when the potential mediator is included in the model;[36] Directed Acyclic Graphs (DAGs) showing the dependencies between the study exposure, outcome, and potential mediators were depicted in **the Supplementary Figures S7.2 and S7.3**. When step-I showed no association between sex/gender and the potential mediator, further steps were not conducted. Finally, we concluded that there was a mediation effect when the findings from the respective mediation analysis showed an attenuated risk estimate compared to that from the main analysis.[36]

Based on reviewer comments, we assessed the median change between follow-up and baseline (delta: follow-up value - baseline) for individual clinical endpoints and composite disease activity scores in a post-hoc analysis. For this analysis, only patients with information on the respective variables at both baseline and follow-up were included (complete case). When more than one measurement of a specific variable was available during follow-up (365 days), the best one was chosen.

All the analyses were performed with the R software, version 3.5.2.[37] MICE was conducted using the R package mice, version 3.13.0.[38]

Ethics statement

This study was reviewed by the ethics commission of the Canton of Zurich (KEK: Req-2020-00045). Pseudonymized data, without access to the code key, was provided by the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) to the researchers. Therefore, the commission waived the need for a full ethics authorization.

Results

The study included 3722 RA adult patients, of which 2839 (76.3%) were women and 883 (23.7%) were men. The flow chart for inclusion/exclusion criteria is depicted in **Figure 7.1**. Patient's age at first symptoms and diagnosis, and baseline characteristics are presented in **Table 7.1**. Compared to women, men were older at first symptoms, diagnosis, and start of first b/tsDMARD. While both strata had similar time from first symptoms to diagnosis, men's median time from diagnosis to the start of b/tsDMARD was shorter than the time in women (3.4 years versus 5.0 years). At baseline, men were more likely to be overweight (47.2% versus 27.0%) and a had higher frequency of ever smoking (49.2% versus 30.6%), compared to women. Conversely, men had a lower disease activity at baseline (DAS28-ESR 4.2 versus 4.4, p<0.001), and lower (better) median HAQ score (0.9 vs 1.0, p<0.001) and lower median TJC (4.0 vs. 5.0, p=0.02), compared to women. When assessing patient responses to disease activity and pain level (on a scale from 1-10), we note that men had less reported pain (4.6 vs. 4.9, p=0.05), and lower self-assessed activity of their rheumatic disease (4.8 vs. 5.1, p=0.004) compared to women. Additionally, while men had higher frequency of hyperlipidemia, diabetes, and cardiovascular disease or cardiac events, women had significantly higher frequency of history of fibromyalgia, osteoporosis, and depression/anxiety.

Results from the main logistic regressions are presented in **Figure 7.2**. Compared to women, men had higher odds of achieving DAS28-remission within the first 12-months, with unadjusted odds ratio (OR) of 1.21 and 95% confidence interval (CI) 1.02-1.42. Adjusting for age and seropositivity led to similar results, with adjusted OR (ORadj) 1.24 (95% CI 1.05-1.46). Secondary outcomes DAS28-rem/LDA and RADAI-5 remission did not show a significant difference between men and women. Sensitivity analyses with 9- and 15-months follow-up showed similar results as those at 12-months for all three outcomes (**Table 7.2**).

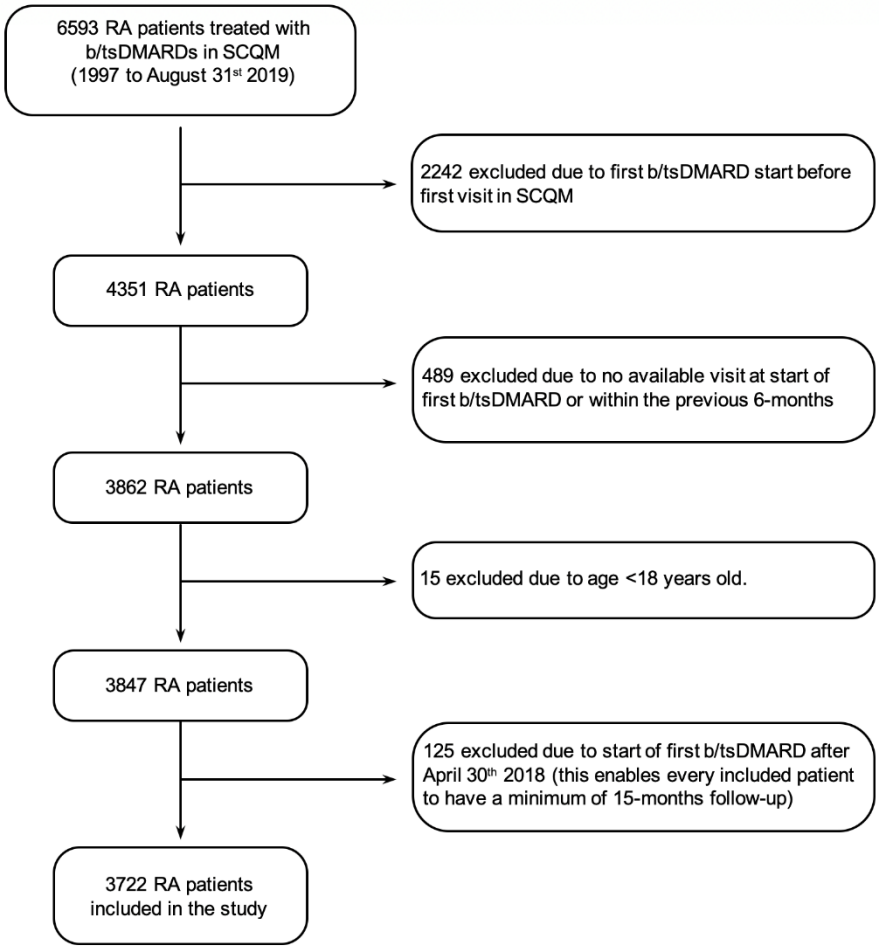

Figure 7.1 Flowchart of inclusion/exclusion criteria for the study population. Abbreviations: RA rheumatoid arthritis; b/tsDMARD biologic or targeted synthetic disease-modifying antirheumatic drug; SCQM Swiss Clinical Quality Management in Rheumatic Diseases.

Table 7.1 Patient characteristics.

	Women (n = 2839)	Men (n = 883)	p value
Patient characteristics at disease start			
Age at first symptoms (mean (SD))	45.4 (15.0)	48.1 (14.0)	<0.001
missing (%)	105 (3.7)	28 (3.2)	
Age at diagnosis (mean (SD))	47.0 (14.8)	49.7 (13.6)	<0.001
missing (%)	89 (3.1)	32 (3.6)	
Baseline patient characteristics (start of first b/tsDMARD)			
Age at start of first b/tsDMARD, years (mean (SD))	55.4 (13.7)	56.5 (12.4)	0.029
Time from symptoms to diagnosis, years (median [IQR])	0.4 [0.1, 1.3]	0.3 [0.1, 1.0]	0.278
missing (%)	168 (5.9)	46 (5.2)	
RA duration, time from diagnosis to first b/tsDMARD, years (median [IQR])	5.0 [1.7, 12.0]	3.4 [1.2, 9.9]	<0.001
missing (%)	91 (3.2)	35 (4.0)	
BMI (kg/m^2) (mean (SD))	25.2 (5.2)	26.5 (4.1)	<0.001
missing (%)	465 (16.4)	143 (16.2)	
BMI category (% from available)			<0.001
normal weight	1198 (50.5)	255 (34.5)	
overweight	642 (27.0)	349 (47.2)	
obese	404 (17.0)	127 (17.2)	
underweight	130 (5.5)	9 (1.2)	
Smoker ever before (%)	869 (30.6)	434 (49.2)	<0.001
Targeted treatment type (%)			0.499
TNF inhibitor biologic	2395 (84.4)	755 (85.5)	
other biologic	362 (12.8)	100 (11.3)	
tsDMARD	82 (2.9)	28 (3.2)	
Steroid use at index date (%)	1103 (38.9)	371 (42.0)	0.101
csDMARD use at index date (%)	1954 (68.8)	619 (70.1)	0.500
RF+ (%)	1957 (72.0)	607 (71.9)	0.986
missing (%)	122 (4.3)	39 (4.4)	
Anti-CCP+ (%)	1337 (64.3)	423 (65.3)	0.687
missing (%)	760 (26.8)	235 (26.6)	
ESR (median [IQR])	20.0 [10.0, 32.0]	18.0 [8.0, 34.0]	0.005
missing (%)	354 (12.5)	95 (10.8)	
CRP (mg/dL) (median [IQR])	0.8 [0.3, 1.4]	0.8 [0.4, 2.1]	0.001
missing (%)	1592 (56.1)	462 (52.3)	
Swollen joint count 28 (median [IQR])	6.0 [2.0, 10.0]	5.0 [2.0, 10.0]	0.603
missing (%)	49 (1.7)	15 (1.7)	
Tender joint count 28 (median [IQR])	5.0 [2.0, 11.0]	4.0 [1.0, 10.0]	0.020
missing (%)	54 (1.9)	21 (2.4)	

Table 7.1 (continued)	**Women (n = 2839)**	**Men (n = 883)**	**P value**
PRO Activity of rheumatic disease today (0-10) (mean (SD))	5.1 (2.6)	4.8 (2.7)	0.004
missing	549 (19.3)	175 (19.8)	
PRO Activity of rheumatic disease last 6 months (0-10) (mean (SD))	5.8 (2.5)	5.6 (2.5)	0.052
missing	570 (20.1)	178 (20.2)	
PRO How do you feel your health condition is today? (0-10) (mean (SD))	5.0 (2.5)	4.9 (2.5)	0.476
missing	574 (20.2)	175 (19.8)	
PRO Pain level today (0-10) (mean (SD))	4.9 (2.8)	4.6 (2.8)	0.047
missing	538 (19.0)	172 (19.5)	
Physician global disease activity (mean (SD))	4.8 (2.1)	4.8 (2.1)	0.883
missing (%)	1047 (36.9)	307 (34.8)	
DAS28-CRP (mean (SD))	4.1 (1.2)	4.1 (1.2)	0.471
missing (%)	1624 (57.2)	477 (54.0)	
DAS28-ESR (mean (SD))	4.4 (1.4)	4.2 (1.5)	<0.001
missing (%)	388 (13.7)	108 (12.2)	
RADAI-5 (mean (SD))	4.8 (2.1)	4.6 (2.2)	0.028
missing (%)	651 (22.9)	189 (21.4)	
HAQ (median [IQR])	1.0 [0.5, 1.6]	0.9 [0.4, 1.4]	<0.001
missing (%)	605 (21.3)	190 (21.5)	
Pregnancy/breastfeeding	0 (0)	-	-
Post-menopause	896 (31.6)	-	-
Comorbidities			
Fibromyalgia	54 (1.9)	4 (0.5)	0.004
Osteoporosis	601 (21.2)	111 (12.6)	<0.001
Other rheumatological disease	773 (27.2)	219 (24.8)	0.167
Hyperlipidemia	136 (4.8)	80 (9.1)	<0.001
Diabetes	133 (4.7)	89 (10.1)	<0.001
Cardiovascular disease / cardiac event	886 (31.2)	340 (38.5)	<0.001
Cancer	77 (2.7)	21 (2.4)	0.674
Depression/anxiety	353 (12.4)	66 (7.5)	<0.001
Fractures, surgeries, musculoskeletal system	240 (8.5)	60 (6.8)	0.131
Infections	41 (1.4)	16 (1.8)	0.535
Latent inactive tuberculosis	46 (1.6)	16 (1.8)	0.812

Values are the counts and percentages unless stated otherwise. Abbreviations: b/tsDMARD biologic or targeted synthetic disease-modifying antirheumatic drug; RA rheumatoid arthritis; BMI body mass index; TNF tumour necrosis factor; tsDMARD targeted synthetic disease-modifying antirheumatic drug; csDMARD conventional synthetic disease-modifying antirheumatic drug; RF rheumatoid factor; Anti-CCP anti cyclic citrullinated peptide; ESR erythrocyte sedimentation rate; CRP C-reactive protein; PRO patient reporting outcome; DAS28 28-joint Disease Activity Score; RADAI-5 rheumatoid arthritis disease activity index-5; HAQ health assessment questionnaire.

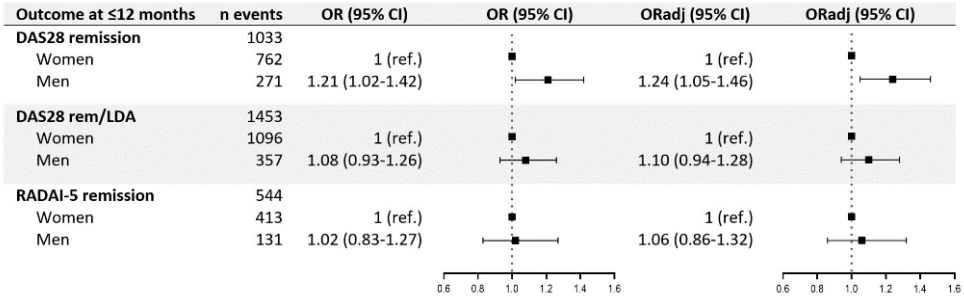

Figure 7.2 Logistic regression assessing the effect of sex/gender on the study outcomes, with 12-month maximum follow-up. Abbreviations: n number; OR odds ratio; ORadj odds ratio adjusted for age and seropositivity; DAS28 28-joint Disease Activity Score; rem/LDA remission or low disease activity; RADAI-5 Rheumatoid Arthritis Disease Activity Index-5.

Sensitivity analysis excluding patients without follow-up information on the outcome (**Supplementary Table S7.2**), showed an even higher likelihood of men versus women on achievement of DAS28-remission within the first year (OR 1.36 [95% CI 1.12-1.64]). Likewise, this resulted in higher odds of men achieving DAS28-rem/LDA (OR 1.23 [95% CI 1.02-1.50]), whereas the findings for RADAI-5 remission remained non-significant.

Results from the mediation analyses are shown in **Table 7.3**, and **Supplementary Figure S7.3**. Among the investigated potential mediators, men were associated with lower odds of baseline DAS28≥3.2 and RA duration >2-years, and higher odds of having BMI≥25 in comparison to women. Subsequently, adding baseline DAS28 (threshold 3.2) to the main analysis removed the significance from the previously observed association between sex/gender and DAS28-remission. Similar observation was made for RA duration (threshold 2-years). Thus, baseline DAS28 and RA duration were identified as factors which may explain the association between sex/gender and DAS28-remisison at ≤12-months. Conversely, adding BMI to the main analysis did not attenuate, nor dismissed, the main findings.

Results from the post-hoc analysis assessing changes in individual clinical endpoints and composite disease activity scores are provided in **Supplementary Table S7.3**. We did not identify any significant differences, apart from CRP, which had substantial missingness.

Table 7.2 Sensitivity analysis. Logistic regression assessing the effect of sex/gender on the study outcomes, with maximum follow-up of 9- and 15-months.

Outcome	Outcome at ≤9-months			Outcome at ≤15-months		
	n events	OR (95% CI)	ORadj (95% CI)	n events	OR (95% CI)	ORadj (95% CI)
DAS28 remission	613			1208		
Women	447	1 (ref.)	1 (ref.)	888	1 (ref.)	1 (ref.)
Men	166	1.24 (1.02-1.51)	1.24 (1.02-1.51)	320	1.25 (1.07-1.46)	1.28 (1.09-1.50)
DAS28 rem/LDA	868			1680		
Women	653	1 (ref.)	1 (ref.)	1268	1 (ref.)	1 (ref.)
Men	215	1.08 (0.90-1.29)	1.09 (0.91-1.30)	412	1.08 (0.93-1.26)	1.10 (0.95-1.28)
RADAI-5 remission	281			672		
Women	218	1 (ref.)	1 (ref.)	507	1 (ref.)	1 (ref.)
Men	63	0.92 (0.69-1.24)	0.95 (0.71-1.27)	165	1.06 (0.87-1.28)	1.09 (0.90-1.33)

Abbreviations: n number; OR odds ratio; ORadj odds ratio adjusted for age and seropositivity; DAS28 28-joint Disease Activity Score; rem/LDA remission or low disease activity; RADAI-5 Rheumatoid Arthritis Disease Activity Index-5.

Table 7.3 Summary findings from the mediation analyses (steps I and II), and findings from the main analysis for reference.

	Main analysis		Mediation analyses	
	E -> O		Step I (E -> M)	Step II (E + M -> O)
	OR (95%CI)	ORadj (95%CI)	OR (95%CI)	OR (95%CI)
Mediation analysis for baseline DAS28≥3.2				
Female	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Male	1.21 (1.02-1.42)	1.24 (1.05-1.46)	0.65 (0.53-0.78)	1.15 (0.96-1.38)
DAS28<3.2	-	-	-	1 (ref.)
DAS28≥3.2	-	-	-	0.36 (0.30-0.43)
Mediation analysis for RA disease duration at index date >2years				
Female	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Male	1.21 (1.02-1.42)	1.24 (1.05-1.46)	0.71 (0.60-0.83)	1.17 (0.99-1.39)
RA≤2years	-	-	-	1 (ref.)
RA>2years	-	-	-	0.74 (0.64-0.87)
Mediation analysis for baseline BMI≥25				
Female	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Male	1.21 (1.02-1.42)	1.24 (1.05-1.46)	2.29 (1.93-2.72)	1.31 (1.09-1.58)
BMI<25	-	-	-	1 (ref.)
BMI≥25	-	-	-	0.73 (0.62-0.86)
Mediation analysis for csDMARD use at index				
Female	1 (ref.)	1 (ref.)	1 (ref.)	-
Male	1.21 (1.02-1.42)	1.24 (1.05-1.46)	1.06 (0.90-1.25)	-
Mediation analysis for steroid use at index				
Female	1 (ref.)	1 (ref.)	1 (ref.)	-
Male	1.21 (1.02-1.42)	1.24 (1.05-1.46)	1.14 (0.98-1.33)	-

Abbreviations: E study exposure (sex/gender); O study outcome (DAS28-remission at ≤12-months); M potential mediator; DAS28 28-joint Disease Activity Score; OR Odds ratio; ORadj odds ratio adjusted for age and seropositivity; csDMARD conventional synthetic disease-modifying antirheumatic drugs.

Discussion

This study on 3722 RA patients new-users of b/tsDMARD had 76% women and 24% men. At baseline, men were older and presented higher frequency of overweight and ever smoking compared to women. Conversely, women had longer disease duration (5.0 versus 3.4 years in men), more active disease (DAS28, RADAI-5), and more frequent history of fibromyalgia, osteoporosis, and depression/anxiety. Men were more likely to achieve DAS28-remission within one year, in comparison to women. Our analyses suggested that this benefit in men may be explained by the differences in baseline disease activity (DAS28) and disease duration at start of first b/tsDMARD. Conversely, no differences were observed between men and women on their likelihood of achieving low disease activity (DAS28-rem/LDA) or RADAI-5 remission.

Results from our analyses showed 21% higher odds of DAS28-remission in men versus women, which was consistent with previous studies. For example, an observational cohort study with 2879 RA patients treated with tumour necrosis factor alpha (TNF) inhibitor (etanercept/infliximab) in a British registry suggested that women were 40% significantly less likely to achieve DAS28-remission.[27] Similarly, another study in the same registry, seeking to identify predictors for infliximab response at 12-months, reported women to be significantly associated with lower DAS28 improvement compared to men.[28] Conversely, two studies of RA patients treated with rituximab and abatacept, respectively, showed no significant differences between men and women and their likelihood of achieving DAS28-remission.[29,39] However, these last-mentioned studies included in their main analyses adjustment for baseline disease activity and disease duration. While the authors treated these variables as confounders, we identified them as mediators, and adjustment for mediators in their analyses is expected to attenuate or remove the observed effect of the study exposure. Additionally, findings from the rituximab study showed higher remission rates in men compared to women,[29] and the un-adjusted results from the abatacept study showed significantly reduced odds of achieving DAS28-remission in women compared to men at 6-, 12-, and 24-months, with an OR 0.56 (95% CI 0.37 to 0.87) in women at 12-months.[39]

Similarly, a recent meta-analysis of RCTs of biologics did not find statistically significant difference in the American College of Rheumatology 20 (ACR20) rates between men and women. While both DAS28-remisson and ACR20 are commonly used clinical outcomes in RA, they are different in nature. The ACR20 is a relative score, defined by a 20% improvement in various disease attributes (e.g., SJC28, TJC28, pain, HAQ, CRP).[34] Thus, ACR20 outcome is taking the baseline disease activity and HAQ into consideration. This, together with the above-mentioned role of the baseline disease activity as

mediator in the association between sex/gender and clinical outcome, may explain why no differences were found between men and women when using ACR20 as outcome.

Our mediation analyses suggested baseline disease activity and disease duration as mediators of the effect of sex/gender on the achievement of DAS28-remisison. More concretely, the observed lower odds of having moderate or higher disease activity at baseline (DAS28≥3.2) and lower odds of a disease duration >2-years at start of b/tsDMARD explained the observed association between men and higher odds of achieving DAS28-remissison compared to women.

In our study, men were prescribed b/tsDMARD with a median 1.6 years shorter disease duration than women. This significant temporal gap between men and women escalating treatment was consistent with other observational studies on RA patients treated with biologics.[29,39,40]

The study by Arkema et al. in the Swedish national biologics registry ARTIS suggested that, compared to men, women started TNF inhibitor therapy at a higher level of patient-reported outcomes (TJC28, patient's global assessment, pain, HAQ) but at similar level of physician-reported outcomes (SJC28, physician's global assessment).[40] Our study reflected a similar trend, with women having worse symptoms or patient-reported outcomes (TJC28, RADAI-5), while similar physician-reported outcomes (SJC28, physician global disease activity), in comparison to men at baseline.

Thus, although overall decision on step-up to b/tsDMARD in the Swiss practice is done based on disease activity, we observed discrepancies on composite disease activity scores (DAS28, RADAI-5) and individual clinical features between the study groups. Hypotheses to explain these phenomena may include differential physician-driven and/or patient-driven aspects on treatment decision-making.

Although patient-reported outcomes, like pain or tenderness, are key features on RA disease management, sex-driven differences (e.g., hormonal level; expression of pain receptors) and socially-constructed gender stereotypes may affect their perception, expression, and interpretation across patients.[41] Studies on sex, gender, and pain reported that, while chronic pain syndromes are more frequent in women, and women generally report more and worse pain than men, there are numerous examples of women's pain being discounted or underplayed in healthcare,[12,13,42–46] and women often receive less or less appropriate pain medication.[12–15] While our findings show similar type of b/tsDMARD and similar frequency of comedication with csDMARD and steroids between men and women, the shorter disease duration and lower disease activity in men at b/tsDMARD start, compared to women, reflects a potential treatment gap between the study groups. Additionally, in the context

of pain, we may discuss depression, as a common comorbidity with pain[14] and fibromyalgia. In our study, the female/male ratio for fibromyalgia was four to one (1.9% of women versus 0.5% of men), and frequency of depression/anxiety was 12.4% in women and 7.5% in men. While overall these frequencies are low, this along with the observed higher tender joints in women, suggest that women may have had higher pain at the start of their first b/tsDMARD, in comparison to men. And yet, it may be that a more frequent mention to pain by women may have led physicians to unconsciously "raise the bar" and undervalue the patient's observations, a move that by itself may "increase the voice" of the patient, all in all turning into a vicious circle from which healthcare professionals should seek to escape.

In addition to the above-discussion on patient-reported outcomes, we may as well discuss the levels of inflammatory markers in both study groups. Conversely to the study by Arkema et al.,[40] we observed higher ESR in women versus men at baseline, whereas in both theirs and our study, baseline CRP was higher in men. Both ESR and CRP are acute phase reactants commonly used in the clinic as biomarkers of inflammation. Both increase with age,[47] may be differently affected by sex and BMI,[48] and have different half-life.[49] It was suggested that ESR is more influenced by sex (elevated in females) and age, while the CRP levels may be affected by smoking, high blood pressure, and high BMI.[50] This could partially explain our higher baseline CRP in the male population, with higher BMI and prevalence of cardiovascular history and smoking. Likewise, it could partially explain the observed higher baseline ESR level in women. While evidenced interpretation of the controversy between the baseline findings on ESR and CRP remain unclear, our CRP results may be taken with caution due to the high missingness (>50% at baseline), and the elevated ESR levels (which agreed with the elevated tender joint counts and RADAI-5 score in women) depicted a more active disease in women *versus* men at start of treatment.

It remains of interest to investigate the impact of sex on the b/tsDMARD mode of action. RA clinical guidelines do not differentiate treatment regimen based on sex,[41] and although further sex-specific pharmacological research remains of interest, this lays out of the scope and capacity of our study design. However, independently of sex-specific mechanisms, according to our study findings, a higher threshold for prescription of b/tsDMARD in women *versus* men may partially explain the observed gap on treatment. While this could be prescriber-driven, we also note that observations from our practice in Switzerland also describe women patients as more reluctant to b/tsDMARDs and prescription of injectable therapies compared to men.

Ultimately, the study findings suggest that earlier step-up treatment with b/tsDMARD in women could potentially increase their odds of remission and it is consistent with the suggestions that earlier treatment with biologics leads to higher likelihood of successful clinical outcome.[51]

Results for our secondary outcome DAS28-rem/LDA showed no differences across men and women. While this could simply be due to the more approachable threshold of DAS28-rem/LDA compared to DAS28-remisison, exclusion of the patients without follow-up information on outcome (sensitivity analysis) tilted the odds towards a favorable result for men. This suggests a differential distribution of patients lacking follow-up information on outcome between sexes. Therefore, the study findings on DAS28-rem/LDA should be taken with caution. On regard to the outcome RADAI-5 remission, men and women had similar odds of achieving RADAI-5 remission in both the main and the sensitivity analysis. RADAI-5 is a mainly patient-driven score, and therefore, it reflects the patient's perception of their own disease, unlike the DAS28, which mostly contains values measured by the physicians (3-item formula for DAS28, **Supplementary S1 Equations**). Thus, these two outcomes measured two different clinical goals. A complete understanding on the RADAI-5 results remains of interest.

Strengths and limitations

Key strengths of this study include the large sample size and the addition of the mediation analyses, which aid the discussion and understanding of the findings. An additional strength is the appropriateness of the SCQM data to address the research question. While missing values are always a burden in real-world data, key covariates were sufficiently complete so that their missingness could be successfully addressed by MICE. The decision to consider patients missing follow-up information on outcome as not outcome achievers was tested with a sensitivity analysis, which supported the study findings on DAS28-remission. We would have excluded patients in remission at baseline, however, to avoid having different sample size in each imputed dataset, we decided against it. We did not quantify the effect of the mediation; thus, it may be that the two identified mediators fully explain the observed association between sex/gender and remission, or there could be other mediators that we did not foresaw. For example, we did not explore the role of depression or fibromyalgia in the mediation analyses. And we acknowledge that the comorbidities (e.g., fibromyalgia) may be underreported.

Although we would have liked to investigate DAS28-CRP remission in parallel to the studied DAS28-ESR remission, we were limited by the high missingness in CRP. Additionally, although a recent study in the Veterans Affairs RA (VARA) registry (10.2% women) suggested that their observed lower likelihood of achieving DAS28-ESR remission in women versus men was driven by ESR and that ESR

could be biased in sex studies due to the influence of sex on ESR;[52] the rheumatology guidelines do not distinguish between DAS28-ESR and DAS28-CRP.[48] Moreover, the threshold currently used for DAS28 remission was created and validated using DAS28-ESR.[50] Thus, since the real-world RA population has 70% women (conversely to the VARA registry), it is expected that DAS28-ESR remission remains an optimal measure for our research question.

While we acknowledge a gender concept beyond the binary, due to data limitations we were restricted to the study of women and men as a binary category. Additionally, when discussing the study results in the context of other findings, since the concepts sex and gender were often interchanged in biomedical literature,[53] and the terms women/men and female/male were indistinctly used, we compared other studies' women and female patients with our women cohort, and men and male patients with our men cohort.

Finally, following the sex differences in the immune function and the effects of sex hormones on the immune response, described elsewhere,[53–55] a limitation of this study was the absence of sex hormonal data. Additionally, studying the effects of pregnancy, post-partum, and menstrual cycles on the study outcome in women (or people with cycles) remains of interest. For example, it has been suggested that the risk of RA could be reduced during pregnancy,[55] however, our study population did not include any patient with record of pregnancy (nor breastfeeding) at baseline.

Conclusions

The study findings indicated that when starting their first b/tsDMARD, men had a shorter disease duration and lower disease activity (DAS28-ESR, RADAI) in comparison to women. Likewise, compared to women, men presented higher odds of achieving DAS28-remission within the first year. Finally, findings from mediation analyses indicate these discrepancies in the treatment decision making regarding start of first b/tsDMARD in men and women patients as potential explanation for the observed response gap between the sex groups. Thus, these findings suggest that step-up to b/tsDMARD treatment at an earlier disease stage in women, similar to the observed practice in men, may bring women the beneficial effect observed in the men group.

Remarks on main author contributions: EV-Y contributed to the conceptualisation and methodology, data curation, formal analysis, visualisation, investigation, resources, interpretation of the results, drafting and editing the manuscript, and critical revisions.

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Supplementary material

Supplementary Equations S7.1

$$DAS28_{ESR} = (0.56 \times \sqrt{tjc28} + 0.28 \times \sqrt{sjc28} + 0.7 \times ln(ESR)) \times 1.08 + 0.16 \quad (1)$$

$$DAS28_{CRP} = \left(0.56 \times \sqrt{tjc28} + 0.28 \times \sqrt{sjc28} + 0.36 \times ln(CRP + 1)\right) \times 1.10 + 1.15 \quad (2)$$

Abbreviations: DAS28 Disease Activity Score 28; tjc28 Number of tender joints, counting 28; sjc28 Number of swollen joints, counting 28; ESR Erythrocyte sedimentation rate (mm/h); CRP C-reactive protein (mg/dL).

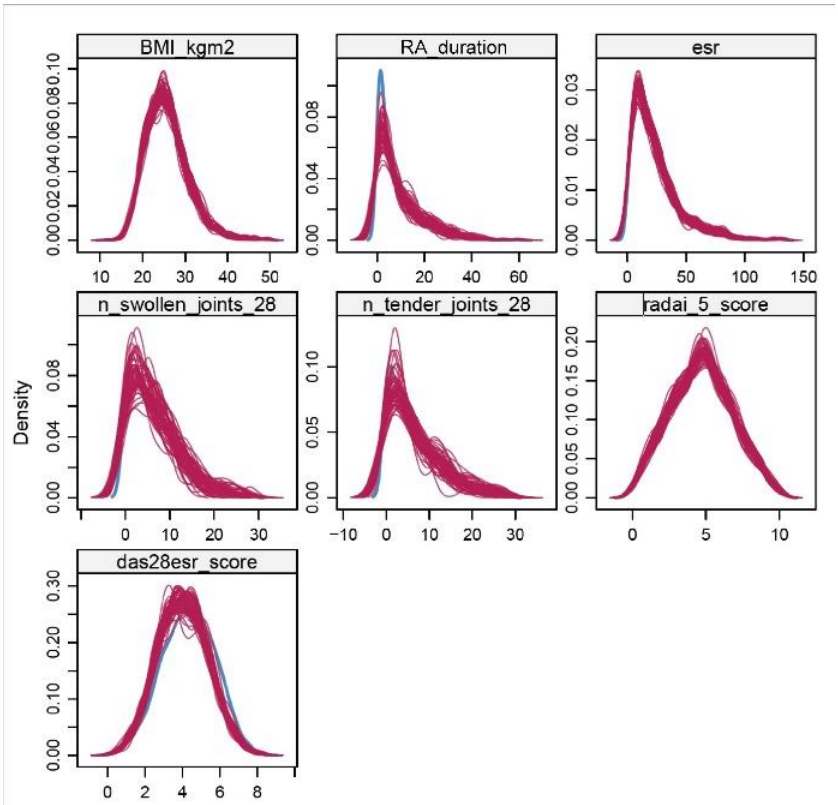
Supplementary Table S7.1 Details about the variables and methods used in the multiple imputations by chain equations (MICE). The 41.2% of the patients had complete information on every variable included in the MICE.

Variable	Predicted	Used as predictor	Method	Missingness	Levels
Sex	-	yes	-	0%	women; men
BMI	yes	yes	pmm	16.3%	-
Age at index	-	yes	-	0%	-
RA disease duration	yes	yes	pmm	3.4%	-
Smoker ever before	-	yes	-	0%	yes; no
b/tsDMARDs	-	yes	-	0%	TNF inhibitor; other biologic; tsDMARD
csDMARD use	-	yes	-	0%	yes; no
Glucocorticoid use	-	yes	-	0%	yes; no
RF	yes	yes	logreg	4.3%	yes; no
Anti-CCP	yes	yes	logreg	26.7%	yes; no
Seropositivity	yes	yes[a]	logreg	9.9%	yes; no
ESR	yes	yes	pmm	12.1%	-
SJC28	yes	yes	pmm	1.7%	-
TJC28	yes	yes	pmm	2.0%	-
RADAI-5	yes	yes	pmm	22.6%	-
DAS28-ESR	yes	yes[b]	pmm	13.3%	-
Outcome	-	yes	-	0%	yes; no

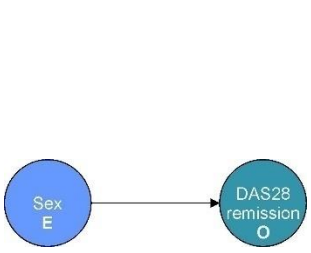
[a] *Excluded as predictor in models for RF and anti-CCP.*

[b] *Excluded as predictor in for SJC28, TJC28 and ESR.*

Abbreviations: BMI body mass index; b/tsDMARD biologic or targeted synthetic disease modifying antirheumatic drug; TNF tumour necrosis factor; csDMARD conventional synthetic disease modifying antirheumatic drug; RF rheumatoid factor; Anti-CCP anti-cyclic citrullinated peptide antibodies; ESR erythrocyte sedimentation rate; SJC28 number of swollen joint counts counting 28; TJC28 number of tender joint counts counting 28; RADAI-5 Rheumatoid Arthritis Disease Activity Index-5; DAS28 Disease Activity Score 28; logreg logistic regression; pmm predictive mean matching.

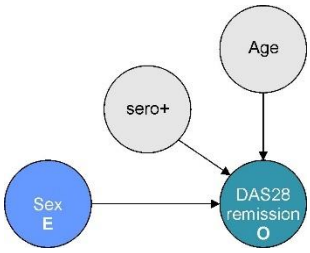


Supplementary Figure S7.1 Density plots depicting the distribution of key variables in the original dataset (blue) and the imputed datasets (red). Abbreviations: BMI body mass index; RA_duration rheumatoid arthritis duration; esr erythrocyte sedimentation rate; n_swollen_joints_28 number of swollen joints counting 28; n_teder_joints_28 number of tender joints counting 28; radai_5_score Rheumatoid Arthritis Disease Activity Index-5; DAS28_score Disease Activity Score 28.



E -> O

	OR (95%CI)
Female	1 (ref.)
Male	1.21 (1.02-1.42)



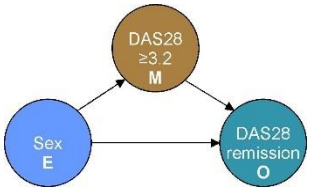
E + age + seropositive -> O

	ORadj (95%CI)
Female	1 (ref.)
Male	1.24 (1.05-1.46)

Adjusted for age and seropositivity.

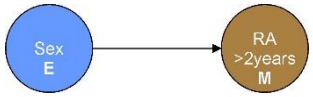
Supplementary Figure S7.2 Directed acyclic graphs (DAGs) showing the dependencies between the study exposure sex/gender (E; blue balloons), the study outcome DAS28-remission (O; green balloons), and the covariates age and seropositivity (grey balloons). Each DAG is accompanied by the respective odds ratio (OR) or adjusted OR (ORadj) with 95% confidence interval (CI). Abbreviations: DAS28 Disease Activity Score 28; sero+ seropositivity.

	E -> M OR (95%CI)
Female	1 (ref.)
Male	0.65 (0.53-0.78)

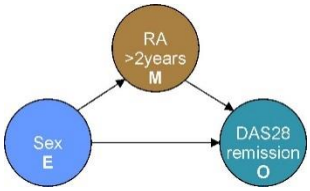


	E + M -> O OR (95%CI)
Female	1 (ref.)
Male	1.15 (0.96-1.38)
DAS28<3.2	1 (ref.)
DAS28≥3.2	0.36 (0.30-0.43)

Supplementary Figure S7.3 Directed acyclic graphs (DAGs) showing the dependencies between the study exposure sex/gender (E; blue balloons), the study outcome DAS28-remission (O; green balloons), and the potential mediators (M; brown balloons), for the association between sex/gender and DAS28-remission. Each DAG is accompanied by the respective odds ratio (OR) with 95% confidence interval (CI). Abbreviations: DAS28 Disease Activity Score 28; RA rheumatoid arthritis; BMI body mass index; csDMARD conventional synthetic disease-modifying antirheumatic drug; E exposure; O outcome; M mediator.

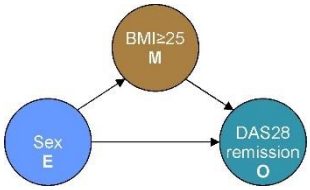


	E -> M
	OR (95%CI)
Female	1 (ref.)
Male	0.71 (0.60-0.83)

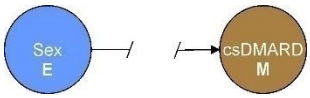


	E + M -> O
	OR (95%CI)
Female	1 (ref.)
Male	1.17 (0.99-1.39)
RA≤2years	1 (ref.)
RA>2years	0.74 (0.64-0.87)

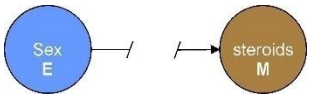
	E -> M
	OR (95%CI)
Female	1 (ref.)
Male	2.29 (1.93-2.72)



	E + M -> O
	OR (95%CI)
Female	1 (ref.)
Male	1.31 (1.09-1.58)
BMI<25	1 (ref.)
BMI≥25	0.73 (0.62-0.86)



	E -> M
	OR (95%CI)
Female	1 (ref.)
Male	1.06 (0.90-1.25)



	E -> M
	OR (95%CI)
Female	1 (ref.)
Male	1.14 (0.98-1.33)

Supplementary Figure S7.3 (continued)

Supplementary Table S7.2 Sensitivity analysis, excluding patients without any record on the outcome information during follow-up. Logistic regression assessing the effect of sex/gender on the study outcomes, with maximum follow-up of 12-months.

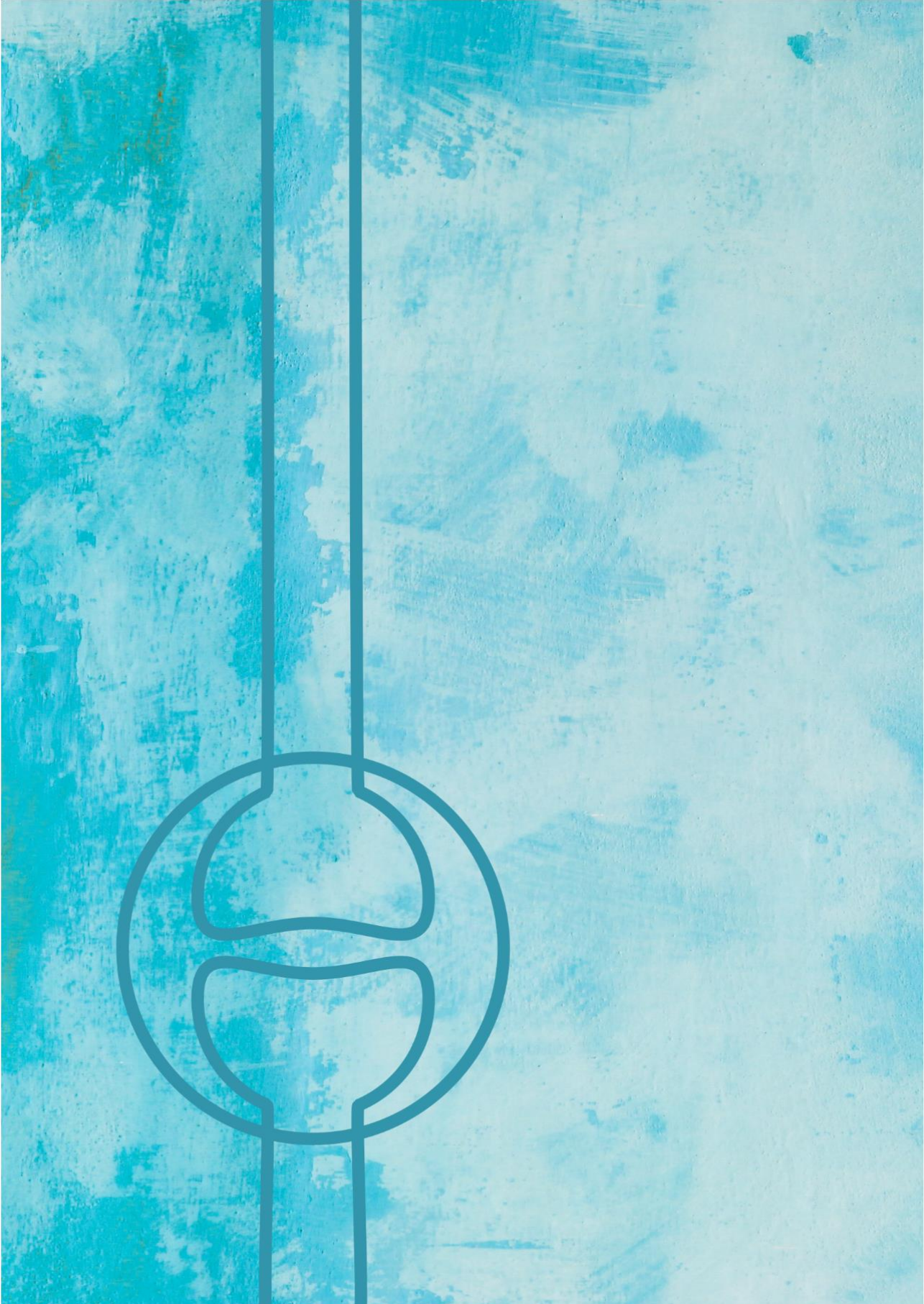
Sensitivity analysis Outcome at ≤12-months	n sample size	n events	OR (95% CI)	ORadj (95% CI)
DAS28-remission	2464	1033		
Women		762	1 (ref.)	1 (ref.)
Men		271	1.36 (1.12-1.64)	1.39 (1.15-1.68)
DAS28-rem/LDA	2464	1453		
Women		1096	1 (ref.)	1 (ref.)
Men		357	1.23 (1.02-1.50)	1.25 (1.03-1.52)
RADAI-5-remission	2169	544		
Women		413	1 (ref.)	1 (ref.)
Men		131	1.06 (0.85-1.34)	1.09 (0.87-1.37)

Abbreviations: n number; OR odds ratio; ORadj odds ratio adjusted for age and seropositivity; DAS28 Disease Activity Score 28; rem/LDA remission or low disease activity; RADAI-5 Rheumatoid Arthritis Disease Activity Index-5.

Supplementary Table S7.3 Post-hoc analysis. Changes in individual clinical endpoints and composite disease activity scores (delta: follow-up value - baseline). As a note, median values below zero reflect improvement, reduction of the scores.

	Women (n=2839)	Men (n=883)	p value
ΔESR (median [IQR])	-4.00 [-14.00, 0.00]	-5.00 [-17.00, 0.00]	0.226
missing	1220 (42.97%)	386 (43.71%)	
ΔCRP (median [IQR])	-0.20 [-0.90, 0.00]	-0.30 [-1.40, 0.00]	0.030
missing	2039 (71.82%)	612 (69.31%)	
ΔTJC28 (median [IQR])	-3.00 [-7.00, 0.00]	-2.00 [-6.00, 0.00]	0.228
missing	908 (31.98%)	311 (35.22%)	
ΔSJC28 (median [IQR])	-3.00 [-7.00, 0.00]	-3.00 [-7.00, 0.00]	0.727
missing	903 (31.81%)	306 (34.65%)	
ΔDAS28-ESR (median [IQR])	-1.30 [-2.20, -0.30]	-1.20 [-2.40, -0.40]	0.745
missing	1258 (44.31%)	404 (45.75%)	
ΔDAS28-CRP (median [IQR])	-1.45 [-2.20, -0.60]	-1.40 [-2.30, -0.50]	0.720
missing	2073 (73.02%)	633 (71.69%)	
ΔRADAI5 (median [IQR])	-1.40 [-3.00, -0.20]	-1.40 [-3.00, -0.20]	0.997
missing	1522 (53.61%)	471 (53.34%)	

Abbreviations: IQR interquartile range; ESR erythrocyte sedimentation rate; CRP C-reactive protein; TJC28 tender joint count 28; SJC28 swollen joint count; DAS28 disease activity score 28; RADAI-5 rheumatoid arthritis disease activity index-5



Chapter 8

Primary and secondary non-response: in need of operational definitions in observational studies

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ENRIQUETA VALLEJO-YAGÜE
EDWARD C. KEYSTONE
SREEMANJARI KANDHASAMY
RAPHAEL MICHEROLI
AXEL FINCKH
ANDREA M. BURDEN

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RAPHAEL MICHEROLI
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ANDREA M. BURDEN

Introduction

Treatment response to biologics and targeted synthetic disease-modifying antirheumatic drugs in rheumatoid arthritis (RA) patients can be classified as primary or secondary non-response, based on evidence of an initial response. Conceptually, primary non-response is generally considered if the drug was ineffective, with no clinical response within the initial treatment period, while secondary non-response would be considered if, after an initial response, the effectiveness is lost over time.[1–4] Despite these generally accepted definitions, there is no consensus on how to operationalise these concepts. Consequently, the current observational evidence is highly heterogeneous and the prevalence of primary versus secondary failure remains largely unknown.

The underlying mechanisms for primary and secondary non-response may differ,[3,5] thus, we believe that defining the type of non-response is key to improving patient care. While primary non-response may be due to a mechanistic failure, secondary non-response may be driven by immunogenicity. Previous studies have shown that both the type of non-response and the development of antidrug antibodies (ADAbs) are important factors when predicting the success of the second biologic.[6,7] Thus, developing clear definitions of how to operationalise primary and secondary non-response is essential to accelerate research that aims to predict the optimal therapy for a given

patient,[5] which will, in turn, improve clinical practice recommendations. For example, if a patient is a primary non-responder to a tumour necrosis factor inhibitor (anti-TNF), the best practice would likely be to switch to a biologic with different mechanism of action. However, if the patient was able to achieve clinical response prior to failure (secondary non-responder), it would be reasonable to proceed with another anti-TNF. Additionally, following the growing postmarketing research targeting comparative effectiveness of treatments in RA, agreement on operational definitions would improve cross-study comparisons. Thus, we believe that unifying this terminology would benefit the clinical practice, clinical trials and postmarketing research, and a unique operational procedure for those three scenarios would be ideal. However, since translating clinical concepts into studies in real-world data represents extra challenges, we drive our discussion in the context of observational research.

In this viewpoint, we discuss the concepts of primary and secondary non-response, with special attention to its implementation in observational data, and we suggest recommendations for future research. Ultimately, we hope this discussion will trigger expert committees to develop standard terminology for these concepts as a step towards harmonising study results.

Conceptual challenges

Despite the limited publications distinguishing between primary and secondary non-response, a common method used in observational studies consists on establishing a time point to assess primary response using composite disease activity scores. Once primary response is achieved, maintenance or deterioration of the disease status can be studied by assessing disease activity at later time points.[8–12] While some publications use a 3-month time point,[8,11] there is high tendency to identify primary response within the first 6 months.[2,4,10,12] The European Alliance for Associations of Rheumatology (EULAR) recommends to switch biological treatment if at 3 months there is no improvement and at 6 months the target (low disease activity or remission) has not been reached.[13] In observational studies using registry data, not all patients have recorded visits with the same frequency, and visits with complete information may be restricted to a year and/or half-year visit (and occasionally longer periods). This can result in missing data on measurements to quantify treatment response, especially when assessing short time periods, such as 3 months. Thus, 6 months is likely ideal to aid with limitations intrinsic to real-world data, while remaining in-line with clinical guidelines.

While assessing primary response at 6 months is straightforward and generally accepted, there is less agreement on how, or when, to define secondary non-response. For example, what evidence of an initial response is needed, and for how long should this response be held? These questions are pivotal for determining if patients who quickly lose their response belong to the same category as those who relapse after a period of evidenced sustained response. We argue here, that there may be

important differences, and therefore, conceptualising these patients as different categories seems reasonable. Following this argument, one may consider that maintaining evidenced positive effect for a period of ≥12 months from treatment initiation, or having two consecutive positive measurements with a minimum time interval, could be understood as clinically relevant sustained response. This leaves a period between 6 and 12 months that may require specific characterisation. Thus, we identify three response categories of interest, and propose the following three-level classification to differentiate response:

> **Primary non-response:** Lack of response within the first 6 months of treatment.
>
> **Early secondary non-response:** Primary response followed by failure to maintain a positive effectiveness outcome for at least 12 months from treatment initiation or to achieve two consecutive positive measurements with a minimum time interval.
>
> **Late secondary non-response:** Loss of response after having sustained a positive effectiveness outcome for ≥12 months from treatment initiation, or after two consecutive positive measurements with a minimum time interval.

This conceptualisation is illustrated in **Figure 8.1**. Additionally, five case examples of patient trajectories are presented in **Figure 8.2**. For instance, the second example in **Figure 8.2** represents a patient who is classified as primary responder based on the evidence of EULAR good response at 4 months (≤6 months), however, this response is not sustained at 12 months and the patient does not have two consecutive successful response measures with minimal time interval, thus, the patient would therefore be classified as an early secondary non-responder.

While we propose a model based on researcher-defined primary and secondary non-response in observational data using timelines, alternative approaches could be used. For example, one approach may be to use physicians' judgement on primary and secondary non-response (i.e., physician-reported reason for treatment stop/switch), if available. However, this will vary vastly based on the individual physician interpretation. In a study by Keystone et al,[4] there were discrepancies in the time periods of reported primary and secondary non-response between two Canadian registries, indicating a lack of consensus among physicians on the operational definitions. Thus, it is evident that there is significant need for work in this area. However, we acknowledge that if agreement on a more harmonised definition of primary and secondary non-response in clinical practice is achieved, this may be implemented in registries, hoping to improve the use of physician's reason for treatment discontinuation to study response. Alternatively, treatment discontinuation for non-safety related reasons within the above-discussed time frames may be an option to assess response if effectiveness instruments are missing in the data.

Overview and next steps

The underlying mechanisms for treatment failure may differ between patients with primary non-response and patients in whom effectiveness is lost over time.[3,5] Additionally, the type of response may help treatment decision making.[5] This supports the need for standard definitions of primary and secondary non-response, and reflects important considerations for driving our operational definitions. While there is a general consensus to identify primary response within the first 6 months of treatment,[2,4,10,12] there is no agreement on how to assess secondary non-response. Additionally, it remains unclear if patients losing the effectiveness of a treatment after a brief response are similar to those losing it after a sustained beneficial effect. Thus, as outlined above, in addition to the primary non-response, we recommend considering two categories for secondary non-response (early vs late), and we described an approach for assessing the type of response based on timelines.

While the use of timelines may be subject to potential misclassification (e.g., if comedication with steroids blurs measurements of response), time frames are often used to assess treatment response and it would mean an easy transition from current standards. In the future, alternative data-driven (machine learning) strategies and therapeutic drug monitoring studies identifying ADAb levels may be used to complement the proposed approach. However, until further research is completed, the proposed classification and timelines can provide a guidance to improve the transparency and homogeneity in research.

Standardising the terminology of primary and secondary non-response is common to all aspects of rheumatology research (observational and interventional). Thus, unifying this terminology will benefit the clinical practice, clinical trials and postmarketing research. Here, we focused on observational research due to the complexity of using secondary data, such as disease or biological registries. While these data include detailed information on rheumatic treatment and disease-specific variables, enabling assessment of disease progression,[14] data on ADAbs may be lacking and loss to follow-up present significant challenges. We acknowledge that due to the great heterogeneity between data sources (e.g., different composite disease activity scores) and treatments (e.g., rituximab), a single operational definition of primary and secondary non-response in observational studies may be unrealistic. However, there are some common methodological approaches, particularly related to timing of measurement and categorisation terminology.

Thus, while there are remaining challenges in developing standard terminology and operational definitions of primary and secondary non-response, we believe expert-driven guidelines from organisms such as EULAR, the American College of Rheumatology, or Outcomes Measures in Rheumatology, would be a beneficial step forward. Additionally, data-driven approaches and further

evidence from therapeutic drug monitoring studies on immunogenicity will contribute to guideline development as it becomes available. However, until consensus is reached, we urge researchers to improve clarity in the reported methodology, particularly on the timing of how non-response was measured in observational studies in order to improve cross-study comparisons between those with similar outcome definitions.

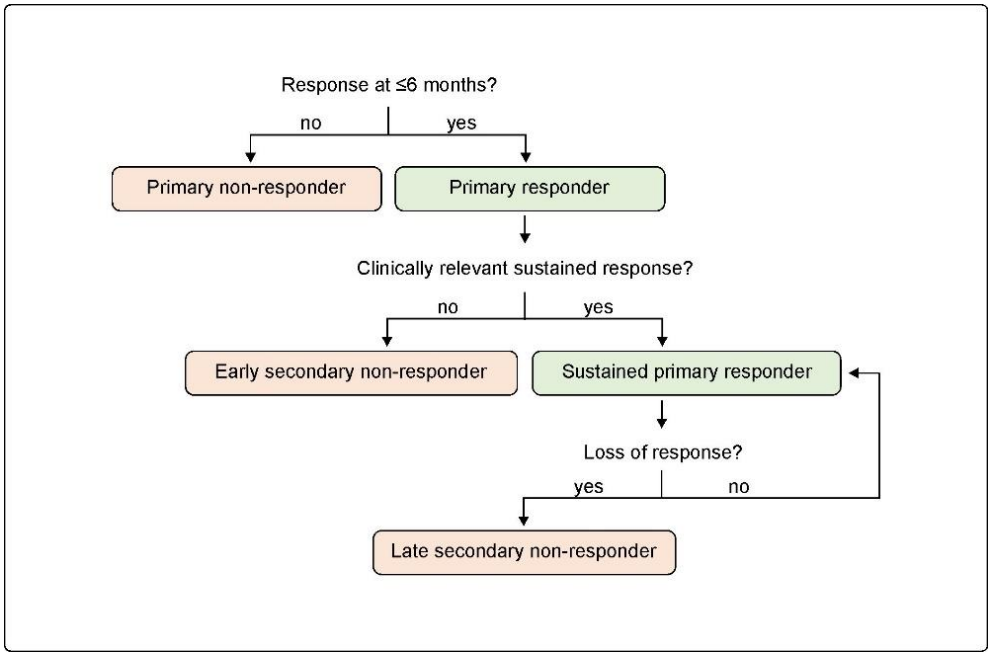

Figure 8.1 Decision tree to classify treatment response to biologics and targeted synthetic disease-modifying antirhematic drugs in rheumatoid arthritis based on evidence of an initial response, assuming a clinically relevant sustained response as prerequisite prior late secondary non-response. Patients discontinuing treatment due to remission or safety reasons are not reflected in the decision tree.

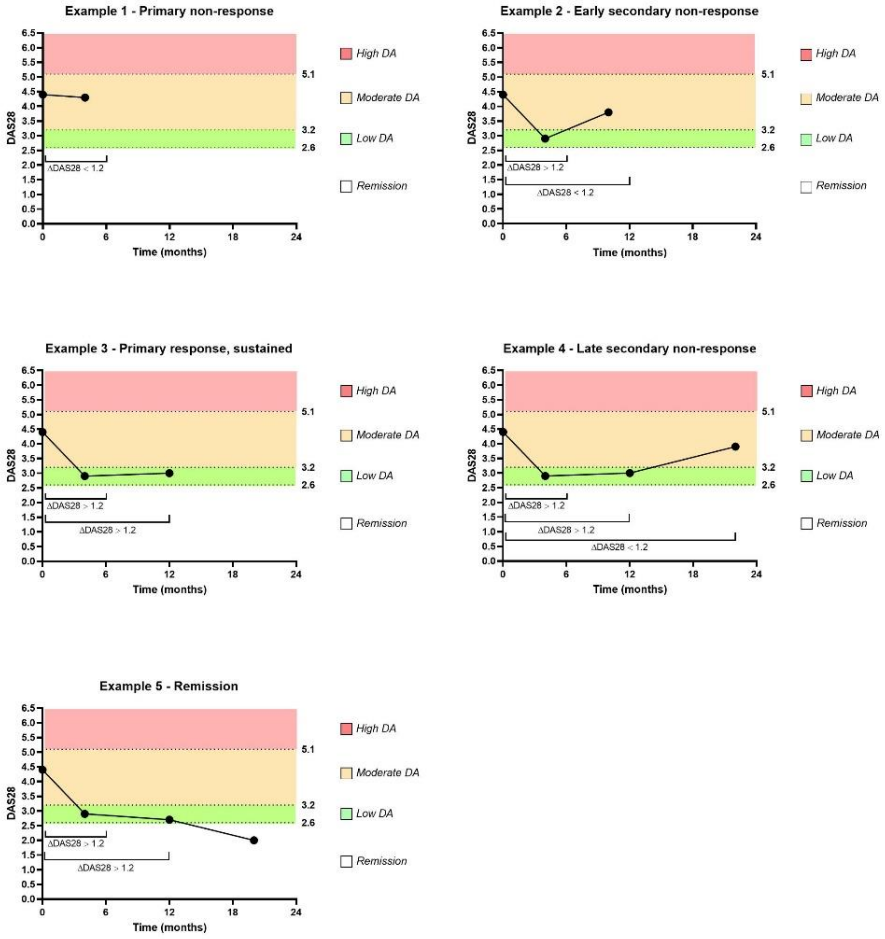

Figure 8.2 Examples of patient trajectory of treatment response for studies on rheumatoid arthritis patients in real-world data registries. Response as per European Alliance for Associations of Rheumatology (EULAR) good response, defined as Disease Activity Score 28 (DAS28) change >1.2 with achieved DAS28 ≤3.2. Example one does not achieve response at ≤6 months, representing a primary non-responder. Examples 2–5 are primary responders, with response to treatment at ≤6 months. In example 2, despite primary response, the effectiveness is lost before the 12-month time point, thus, the patient classifies as early secondary non-responder. Examples 3 and 4 have sustained response for at least 12 months, or had two consecutive positive measurements at ≤12 months. Once achieved sustained response, example four loses it over time, characterising as late secondary non-responder. Example five eventually ends in remission (DAS28 <2.6).

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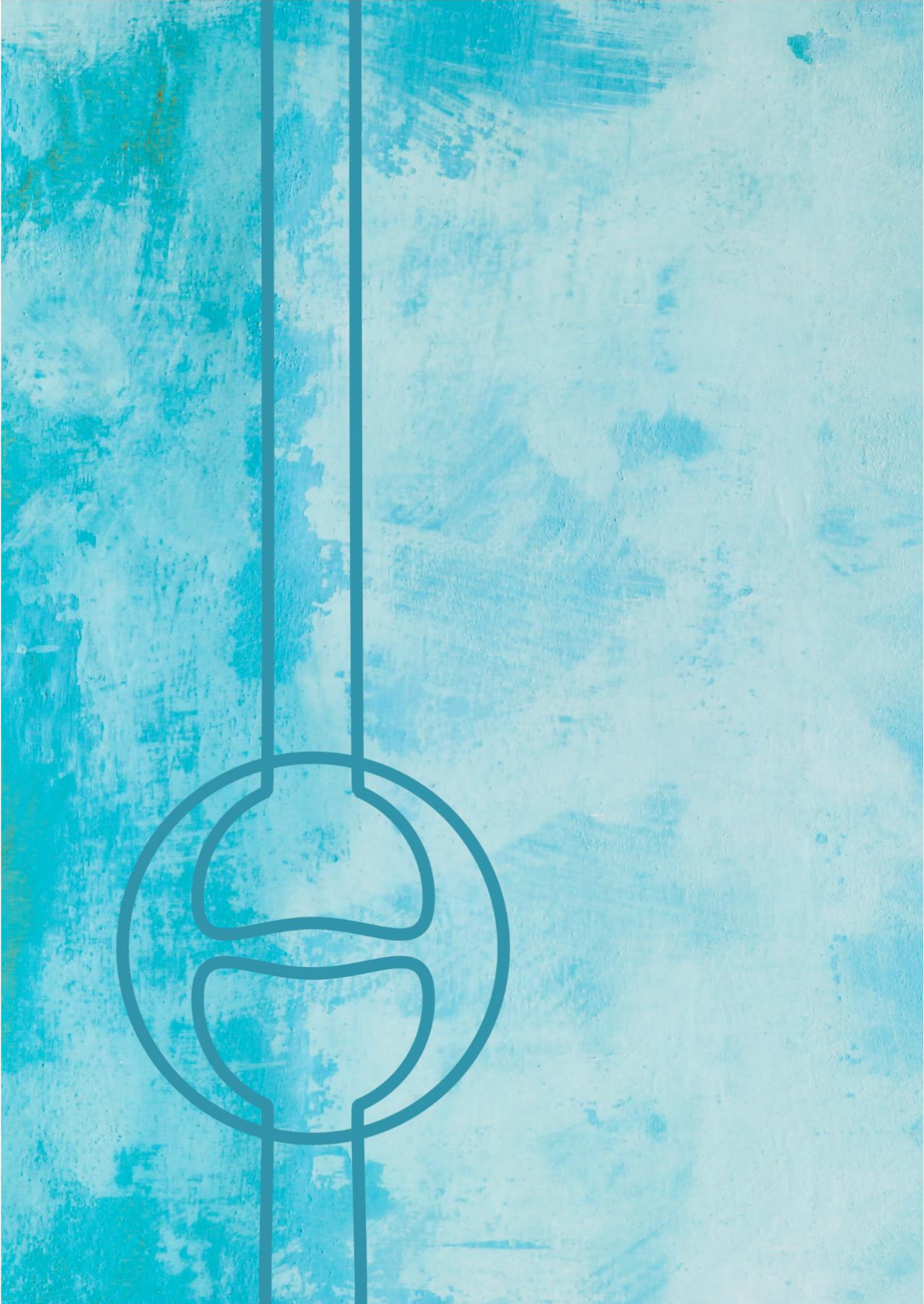

Chapter 9
General discussion

General discussion

Summary of findings

In this thesis, we addressed clinical and scientific gaps in rheumatoid arthritis (RA) and psoriatic arthritis (PsA). This included: a study investigating the safety of Janus Kinase (JAK) inhibitors (**Chapter 3**);[1] a descriptive study of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) patients in Switzerland with attention to body mass index (BMI) category (**Chapter 4**);[2] a study addressing the impact of BMI on clinical response of PsA patients (**Chapter 5**);[3] a comparative effectiveness analysis of biologics in RA patients stratified by BMI and sex (**Chapter 6**);[4] a study comparing the odds of achieving clinical response in male versus female RA patients (**Chapter 7**);[5] and a viewpoint or opinion paper on the need for operational definitions of primary and secondary non-response in RA for pharmacoepidemiologic research (**Chapter 8**).[6]

In **Chapter 3**, following rising concerns on the potential thromboembolic risk of the JAK inhibitor tofacitinib in early 2019, we conducted a study on VigiBase, the World Health Organization (WHO) global database of individual case safety reports (ICSRs), to assess whether the reporting of thromboembolic suspected adverse drug reactions (ADRs) was more frequent for tofacitinib than for other drugs. Additionally, we also studied the other approved JAK inhibitor at the time, baricitinib. The study findings reflected higher than expected reporting of thromboembolic events for tofacitinib and baricitinib, and we observed that patients reporting thromboembolic events were older and had co-medication that suggested previous high cardiovascular risk.[1]

Our research on the Swiss Clinical Quality Management in Rheumatic Diseases (SCQM) cohort showed a higher prevalence of obesity among patients with PsA (23.8% obese) and RA (17.0% obese) compared to the general adult population in Switzerland (Switzerland 2017, 11% obesity).[2,7] Additionally, among RA and PsA patients starting treatment with biologic or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs), those with obesity had worse disease activity and lower quality of life in comparison to the corresponding normal weight groups (**Chapter 4**).[2] Among PsA patients, obesity halved the odds of achieving minimal disease activity (MDA) or remission within the first year after starting their first b/tsDMARD therapy, compared to normal weight patients (**Chapter 5**).[3]

In **Chapter 6**, we investigated the comparative effectiveness of adalimumab, etanercept, infliximab, and abatacept as first b/tsDMARD in RA patients stratified by BMI category (using adalimumab as reference). Across every BMI group, there were no significant differences between the studied drugs. However, after stratifying by sex, we observed a beneficial response to infliximab versus adalimumab in overweight female patients, but the opposite (worse response to infliximab) in the obese females cohort.[4]

In **Chapter 7**, we compared the clinical response in male versus female patients with RA, and we observed that, within the year after starting their first b/tsDMARD, male patients had 54.8% higher probability (i.e., 21% higher odds) of achieving remission compared to female patients. Additionally, the study findings suggested that this difference could be explained by the shorter disease duration and lower disease activity in male versus female patients at the start of their first b/tsDMARD. Thus, earlier step-up to b/tsDMARD treatment in female patients could benefit them and reduce the observed sex difference.[5]

Finally, aiming to trigger discussion and agreement on the practical definitions of primary and secondary non-response in RA, we published with clinical experts a view point on our opinion and suggestions to move forward (**Chapter 8**).[6]

Impact and relevance

The studies within this dissertation generated new real-world evidence (RWE) on the clinical management of RA and PsA. In addition to the individual relevance discussed within each respective chapter, these studies jointly addressed clinical and scientific gaps in the management of RA and PsA from a population perspective and contributed to the knowledge on safety and effectiveness of therapeutic approaches. Additionally, they ultimately contributed to the needed body of evidence for approaching precision medicine in these diseases.

Precision medicine, defined as personalized or individualized targeted healthcare initiatives,[8] is at very early stages in rheumatology.[9] Thus, while implementing optimal precision medicine (e.g., including molecular or genetic profiling) does not yet seem feasible in current rheumatology practice, the results of this thesis may point towards it by addressing it from a wider perspective. For instance, taking into consideration the patient's characteristics like comorbidities or expected risk profile, as well as BMI, and sex/gender is expected to bring the field closer to personalized health care. Additionally, our research addressed operational definitions for the type of response to a first b/tsDMARD, which is expected to aid the selection of second b/tsDMARD, thus contributing to targeted health care.

In the current rheumatology scene, there is little guidance on which treatment would be optimal for which patient, thus safety warnings or contraindications are pivotal in guiding which treatments to avoid based on patient's profile. Here, our pharmacovigilance study on the JAK inhibitors tofacitinib and baricitinib contributed in a very timely manner to the body of evidence that will decide the fate of the use of these treatments. Our findings supported the emerged communications from regulatory authorities to limit the use of tofacitinib in patients with pre-existing high thromboembolic risk,[10,11] and the recently started safety review to investigate the thromboembolic risk for every approved JAK inhibitor by the European Medicines Agency (EMA).[12] Moreover, studies to elucidate the mechanism behind the observed thromboembolic risk of tofacitinib have emerged,[13] and although the biological explanation remains unknown,[13,14] the discussion on the safety of JAK inhibitors versus biologics remains active in the literature.[14,15] We trust that the ongoing scientific and regulatory interest in the topic will provide additional evidence to better understand and describe this effect and, therefore, it is expected that this will ultimately aid the treatment decision making for b/tsDMARDs in RA and PsA, particularly on regard to JAK inhibitors.

Moving on from safety to effectiveness, while the interplay between obesity and immune-mediated rheumatic diseases has been discussed,[16–21] related evidence in PsA was limited to a few studies.[22–25] Thus, our research on the impact of BMI on the clinical outcome of PsA patients enriched the evidence generated in this disease, which has historically 'borrowed' knowledge from RA and other rheumatic diseases. Our findings were in agreement with previous evidence,[22–25] and contributed to the latest PsA research agenda from the European Alliance of Associations for Rheumatology (EULAR), which states interest on investigating metabolic syndrome – for which obesity is an important contributor[26] – and its link with PsA disease activity.[27]

In RA, there is no current preference for particular b/tsDMARD, thus, identifying factors that would allow clinicians to make the best treatment decisions remains of interest.[28] Following our research findings, we suggest both sex and BMI for this purpose. For example, compared to adalimumab, we would discourage the use of infliximab in female RA patients with obesity, but suggest it as preferable option in overweight female RA patients. This would imply sex- and weight-specific therapeutic guidance. Importantly, this finding highlights the benefits of stratifying our population by sex and BMI, since otherwise this differential effectiveness between drugs would not have been observable. In conclusion, taking sex and BMI into consideration is expected to contribute to personalization of the RA therapeutics.

The biological and societal factors underlying sex and gender differences in RA disease course and prognosis are poorly understood.[29,30] Our research highlighted differences in prescription between

male and female patients, which may partially explain their different odds of achieving clinical remission in Switzerland. While we acknowledge that biological sex differences could also play a role in the observed disparity in remission, our analyses suggested that the earlier scale-up to b/tsDMARD in male patients could explain their higher benefit after starting this treatment, compared to the female patients. Thus, it is of interest to identify the factors underlying this discrepancy in treatment prescription in order to address them and improve clinical outcomes in female patients.

In the context of Switzerland, our findings regarding obesity in RA and PsA are particularly relevant, because they depict a reality that would only get worse if the prevalence of obesity - which doubled from 1992 to 2017[31] - continues rising in the general population. Additionally, incorporating sex and gender in health sciences is only emerging in Switzerland, for example, through the ongoing sex and gender integration in the Swiss medical curriculum.[32–34]

Finally, RWE builds up on cumulative scientific evidence, and therefore, agreement on definitions and procedures is crucial for subsequent correlation of findings across studies. While there is extensive literature on the general response in RA patients, the evidence on primary versus secondary non-response remains limited.[6] Thus, we expect that our proposed practical definitions to classify these types of response will pioneer the future discussions and development of protocols for this purpose.

Limitations

The strengths and limitations for each individual study were described in each specific chapter. Thus, here we provide an overview of challenges or points to consider in observational research in real-world data (RWD), with attention to those relevant to our research.

Missingness and loss of follow-up

In RWD, information or values for included variables may not be recorded for every participant and/or every time-point, resulting in missing data.[35] Missing values could be the result of the reporter forgetting, not knowing, or not wanting to report/collect particular information, or they could be the result of human or software errors. Additionally, in SCQM, missing data may also be the consequence of not addressing every test and survey in every visit, not every visit being recorded, and not having a consistent time between visits. Likewise, there is potential loss of follow-up if the patient changes rheumatology clinic, stops participation in the cohort, or dies.

In cohort studies, data can be missing at baseline and during follow-up. There are several methods to deal with missing values, although the majority of published studies lack information on this regard.[36] Traditionally, many studies excluded patients with missing information on key variables,

conducting "complete-case analyses".[36] However, this approach reduces sample size and, importantly, these results can be biased.[35] Alternatively, one can use the nearest available observation (NAO), or impute or predict the missing values. The study by Mongin et al., which compared methods of missing data imputation in RA databases, recommended to use multiple imputation to predict missing baseline variables, and use the NAO for missing data during follow-up.[37] Following this recommendation, we used last observation carried forward (within predefined look-back windows based on clinical rational) and multiple imputation with chain equation (MICE) to complete the baseline covariates in our cohort studies. After MICE, we conducted the statistical analysis in each imputed dataset and joined the estimate using Rubin's rule,[38] which accounts for the variability across the imputed datasets. With regard to the missing values during follow-up, we were already using NAO-like by design (i.e., the outcome value was collected during a time-frame), and yet, we still had missingness. Thus, to deal with missingness during follow-up, we assumed that patients missing information on clinical endpoint during follow-up were not-achievers of the clinical target, therefore, not achievers of the successful clinical endpoint. Additionally, to assess this assumption, we conducted sensitivity analyses excluding patients who missed information on follow-up (**Chapter 5**[3] and **Chapter 7**). However, earlier this year, another study from Mongin et al. compared methods to address missing information on clinical endpoints during follow-up, and recommended MICE with confounding and treatment cessation reasons as an optimal method.[39] This method was called Confounder-Adjusted Response Rate with Attrition Correction (CARRAC), and it was included in the 2022 EULAR recommendations for observational studies investigating comparative effectiveness of drugs in rheumatology.[40] Therefore, we followed this recommendation and implemented CARRAC in our comparative effectiveness study (**Chapter 6**[4]). Additionally, we also performed in this study our previous two approaches as sensitivity analyses. This way, we generated evidence with the new recommended model, while we also provided results obtained in traditional manners.

Biases and confounding

Observational studies can be prone to systematic errors, like selection bias, information bias, and confounding.

We here acknowledge potential selection biases that could not be addressed. First, VigiBase, like any other database of suspected ADRs, is subject to reporting bias.[41] While underreporting is overall expected for ICSRs, the level of underreporting can vary between drugs and events,[41] and it is not predictable, nor measurable. Differences in the level of reporting between drugs can lead to false findings (towards to and away from the null) when comparing their reporting rates. Thus, results from this type of study should be taken with caution and they are only valid for hypothesis generating and

not for hypothesis testing.[41] Second, in SCQM, patients are invited by their rheumatologists to join the database. Thus, only patients treated by rheumatologists who have an agreement with the SCQM can join. Additionally, rheumatologists and patients participating may have their own motives to join, and this may distinguish them from those deciding against it (volunteer bias). While this could affect the external validity of the SCQM cohort when compared to the complete population of patients with rheumatic diseases in Switzerland, the SCQM includes participants from all around the country and includes private and academic clinics. Thus, we trust the validity of SCQM as a representative nationwide cohort in Switzerland.

Regarding information bias, we may mention a potential misclassification of our participants according to their BMI. Although overweight and obesity are commonly defined by BMI,[42,43] this measure using height and weight is only a proxy for percentage of body fat.[44] BMI does not provide information on body composition[45] and its relationship with body fat percentage can vary between populatons.[45,46] Additionally, a higher body fat percentage has been described in RA patients compared to healthy controls with similar BMI.[45] Thus, normal weight or overweight patients with rheumatoid cachexia (low muscle mass and elevated fat mass[47]) could have been misclassified. While reduced BMI cut-off points for the classification of overweight and obese persons with RA were suggested,[45,47] we used the worldwide accepted WHO cut-off points.[42,43] We did this to keep our research consistent with other studies addressing similar research questions to ours. Additionally, although other measures like hip/waist circumference, skinfold thickness, and bioelectrical impedance would have been more appropriate than BMI, these were not available in SCQM and are overall scarce in RWD.

Additional potential misclassification was driven by the lack of data on gender in SCQM. Thus, when investigating biological and social implications on clinical remission in male compared to female RA patients, we were limited to the interpretation of gender as a dichotomous variable, with males understood as men, and females as women. This hinders research and presents ethical concerns and inequity. Fortunately, there are emerging expert discussions on how to collect gender information in RWD, which it will likely shape registries like SCQM in the future.

Finally, another information bias is the recall bias, which may be present in the SCQM data for the patient-reported outcomes (PROs) regarding non-rheumatology health issues and medication. Likewise, in VigiBase, it may affect the reporting of comedication in ICSRs, especially if the recording is done some time after the event.

Confounding is an intrinsic limitation of observational studies in general, and especially relevant in studies seeking to assess causal effects. To address this in our cohort studies, we identified confounders using clinical rational and directed acyclic graphs (DAGs), and we addressed them through adjustment. While we could do this with measured confounders, residual confounding may be a possibility. Additionally, to avoid confounding by indication, we restricted our population in the cohort studies to new-users of b/tsDMARDs and avoided the use of prevalent-user designs.

Outlook

Following our safety study,[1] the regulatory decisions for tofacitinib,[10,11] and the ongoing efforts to depict the biological rational for this association,[13,14] the next steps will consist of investigating the thromboembolic safety concern in every approved JAK inhibitor for immune-mediated rheumatic and dermatological diseases.[12] We suggest a few methodological options to investigate this. First, continue the monitoring of the JAK inhibitors' ICSRs in VigiBase. Second, close monitoring programs, such as observational studies prospectively collecting safety data from JAK inhibitor users. While this could be approached using existing rheumatology registries, we trust that the collection of safety events in SCQM is not sufficient to address this research question. Thus, in Switzerland, a dedicated drug registry or appendix to the SCQM would be needed. Third, a randomised safety study including the population at risk. These or similar initiatives are expected as part of the Phase IV risk management plan from the corresponding marketing authorization holders (MAHs), however, academic researchers are also invited to contribute to this research. Ultimately, it is expected that if new safety restrictions are in place, this will impact the use of these drugs and influence treatment decision guidelines.

Following our research using the SCQM data, it would be of interest to assess if there was a correlation on the increased prevalence of obesity in PsA/RA and the general population in Switzerland in the past decades. Additionally, for RA, next steps would include validation of our suggested definitions of primary and secondary non-response, and investigating if the type of response to the first b/tsDMARD could aid decision on second b/tsDMARD. Likewise, studies that remain of interest after our PsA research include sex-stratified analyses and comparative effectiveness of b/tsDMARDs, as performed in the RA cohort. Additionally, normalized definitions for PsA and its phenotypes would help to homogenize research and to develop targeted strategies for the different phenotypes.

We highlighted RA and PsA patients with elevated BMI as a subpopulation of interest in research and clinical practice, and we therefore encourage researchers to stratify their analyses by BMI category when feasible. However, to properly approach obesity in the context of RA and PsA, we

acknowledge that it would be important to revisit the definition of obesity. Since obesity meets the criteria typically attributed to diseases (e.g., district clinical picture and pathophysiology, increased associated risk of comorbidities and mortality), a better definition of obesity, beyond the simply BMI threshold, is needed for better diagnosis in the clinic,[48] as well as for better definition in observational research. Additionally, following the detrimental impact of BMI on rheumatic diseases, it seems reasonable that patients sharing both obesity and RA or PsA would benefit from a holistic healthcare approach targeting both diseases independently and jointly. This means a collaboration between rheumatologists and endocrinologists. In this regard, we would recommend rheumatology registries to expand their reach and invite clinicians other than rheumatologist to join and contribute, and/or build bridges with other data sources with the possibility of linking patients. Ultimately, to provide RA and PsA patients with the best healthcare, it is important to remove the stigma associated with obesity. Despite current scientific evidence of the complexity of obesity as a low-grade systemic inflammatory disease,[16,48,49] there is still a common belief that obesity is a self-inflicted condition; and it remains a social misconception that obesity can easily be solved with reduced eating and exercise.[50] Weight-based bias has been described in healthcare and public narratives,[48,51] and weight stigma hinders the health of affected persons, for example, it was associated with worse depression and anxiety.[48,51] Thus, although we did not assess, nor discuss weight-based bias in our studies, we expect that understanding and targeting obesity as a disease, instead of a self-inflicted condition, would benefit how obesity is targeted from a healthcare and research perspective and, ultimately, will benefit patients with obesity and rheumatic diseases.

Our sex-based studies strongly supported the need to integrate sex and gender dimensions into rheumatology practice and research. Although from the scientific and social perspective this may seem obvious, incorporating sex and gender in health sciences is only just emerging. For example, in overall medicine and pharmacology, there was historical acceptance of the male's anatomy, clinical signs, and symptoms as the norm,[52–54] limited use of female animals in preclinical drug research[55,56], and strong under-representation of women in clinical trials[57,58], which resulted in higher frequency of misdiagnosis[56] and side effects in women versus men.[56,59] Fortunately, sex comparative studies are gaining attention. However, beyond this, we suggest performing sex-stratified research as a primary basic step towards precision medicine. This way, we could normalise sex-specific aspects that are often not taken into consideration in the overall population. For example, during the course of these doctoral studies, we realised that fundamental biological mechanisms intrinsic to the female body, such as the menstrual cycle or the menopause, are often ignored or treated as comorbidities in health research. In the SCQM registry, information on pregnancy, breastfeeding, and menopause is collected within the dataset for health issues, and it is likely under-reported. This reflects a bias against female-

specific life-factors and promotes the historical misconception of the female body as a deviation from the norm. Additionally, despite the high impact that hormonal levels could have on inflammatory-driven diseases[60,61] (e.g., oestrogen, which fluctuates during the menstrual cycle),[62] these factors are barely never recorded in RWD, and therefore are under-researched.

Lastly, due to the interplay between sex and gender, it is important to acknowledge the relevance of both. Separating the specific impact of sex and gender on a clinical outcome is very challenging. However, sex-stratified randomised clinical trials (RCTs) may be a good approach to assess sex-specific differences and aid developing sex-specific treatment algorithms.[30] Complementarily, RWD mirrors a reality in which both biological aspects and social norms, behaviours, and beliefs, play a role in health. For example, our identified disparities in the decision to upscale treatment to b/tsDMARDs in male and female patients, resulting in different clinical response, may reflect behavioural trends as well as implicit bias from both patient and prescriber. Thus, a deeper understanding of the factors involved in this gender disparity could light up the way to approach them.

In conclusion, sex-specific studies are a must, and taking into consideration the comorbidities or pre-existing risks, BMI, sex/gender, and/or treatment history in RA and PsA patients is expected to benefit research and rheumatology practice. Therefore, we encourage the need to routinely address these factors in both research and the clinic.

Conclusions

In this thesis, we generated and discussed RWE to address safety, effectiveness, and methodological challenges in RA and PsA. First, we conducted a pharmacovigilance study that supported the recent restriction of the use of tofacitinib in patients with pre-existing high thromboembolic risk, and suggested to investigate a potential class effect (**Chapter 3**).[1] Next, we conducted a series of pharmacoepidemiologic studies on RA and PsA patients from the SCQM cohort, which depicted a higher prevalence of obesity among RA and PsA patients compared to the general population in Switzerland (**Chapter 4**),[2] an association of obesity with worse clinical outcome in PsA patients (**Chapter 5**),[3] a differential response to infliximab in female RA patients depending on their BMI category (**Chapter 6**),[4] and a potential disparity in the decision of treatment upscale between male and female RA patients, together with higher odds of clinical remission in males compared to females (**Chapter 7**)[5]. Therefore, we highlighted differences on clinical outcome and treatment response based on BMI category, and depicted sex and gender differences worth addressing. Thus, this suggested BMI, sex and gender as patient characteristics to be considered for a more tailored research and management of these rheumatic diseases. Lastly, we identified the need for operational

definitions to study primary and secondary non-response to RA treatments in RWD, and we provided a review and recommendations for this issue (**Chapter 8**).[6]

Moving forward, we expect that better understanding of the safety profile of JAK inhibitors will have an impact on treatment guidelines. We foresee that obesity will be more often tackled as a comorbidity worth stratifying by in clinical and RWD research. We expect that the understanding of immune-mediated diseases and its management will be improved when a sex-based approach is normalised and when we start addressing sex-specific factors and gender-bias in a regular manner, both in the clinic and in research. We expect a continuation on the discussion on primary and secondary non-response. Ultimately, we hope that all these steps will jointly contribute to a better care of RA and PsA patients and will constitute a step closer to precision medicine in these rheumatic diseases.

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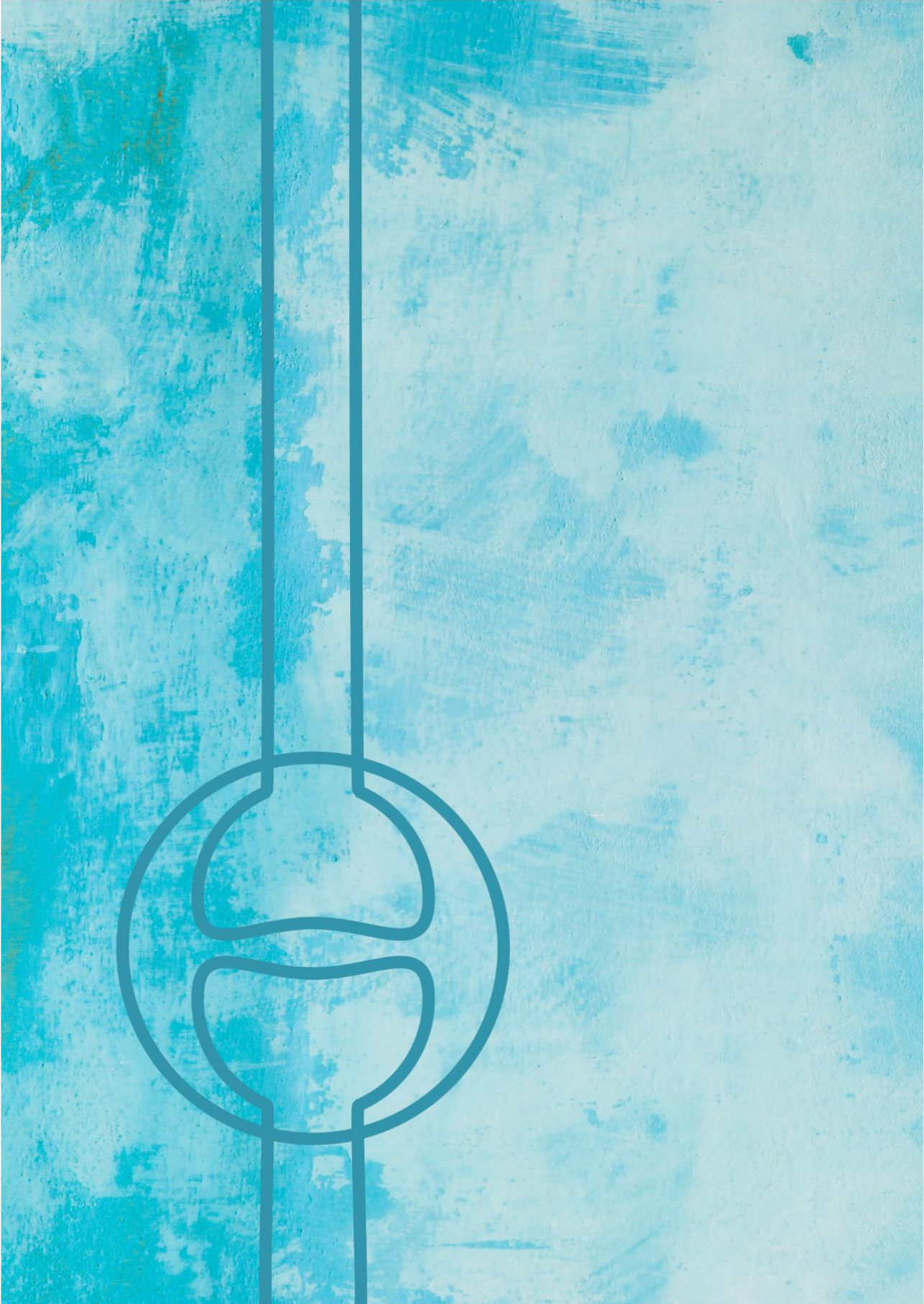

Chapter 10
Appendices

Scientific publications

- **Vallejo-Yagüe E***, Pfund JN*, Burkard T, et al. Lower odds of remission among women with rheumatoid arthritis: A cohort study in the Swiss Clinical Quality Management cohort. PLOS ONE 2022; 17: e0275026. doi.org/10.1371/journal.pone.0275026 (*both authors contributed equally)
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Abbreviations: EULAR Annual European congress of Rheumatology; ICPE International Society for Pharmacoepidemiology (ISPE) Annual Conference; ECTS European Calcified Tissue Society.

Preprint

- **Vallejo-Yague E,** Burkard T, Finckh A, Burden AM, on behalf of the clinicians and patients of the Swiss Clinical Quality Management Program. Comparative effectiveness of biologics in patients with rheumatoid arthritis stratified by body mass index and sex: a cohort study in SCQM. medRxiv 2022; Preprint. 2022.09.30.22280396. doi.org/10.1101/2022.09.30.22280396

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Lo bonito de la vida
es la gente que conocemos
y las montañas que conquistamos junt@s.

Abbreviations

7FP	Seventh Framework Programme
Ab	Antibody
aba	Abatacept
ACPA	Anticitrullinated peptide antibody
ACR	American College of Rheumatology
ada	adalimumab
ADAb	Anti-drug antibody
ADR	Adverse drug reaction
Ag	Antigen
anti-CCP	Anti-cyclic citrullinated peptide
anti-TNF	Anti-tumour necrosis factor alfa (TNF), or TNF inhibitor
apr	Apremilast
ATC	Anatomical Therapeutic Chemical
b/tsDMARD	Biologic or targeted synthetic disease-modifying antirheumatic drug
BMI	Body mass index
BSA	Body surface area
CARRAC	Confounder-Adjusted Response Rate with Attrition Correction
cDAPSA	Clinical Disease Activity for Psoriatic Arthritis
cDAPSArem	Clinical Disease Activity for Psoriatic Arthritis (CDAPSA) remission
cer	Certolizumab
CH	Switzerland
CI	Confidence interval
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DAG	Directed acyclic graph
DAPSA	Disease Activity for Psoriatic Arthritis
DAPSArem	Disease Activity for Psoriatic Arthritis (DAPSA) remission
DAPSA-remLDA (DAPSAremLDA)	Disease Activity for Psoriatic Arthritis (DAPSA) remission or low disease activity (LDA)
DAS28	28-joint Disease Activity Score
DAS28-CRP	28-joint Disease Activity Score (DAS28), calculated using C-reactive protein (CRP)
DAS28-ESR	28-joint Disease Activity Score (DAS28), calculated using erythrocyte sedimentation rate (ESR)
DAS28rem	28-joint Disease Activity Score (DAS28) remission
DE	German
DF	Dosage form
DLQI	Dermatology Life Quality Index
DVT	Deep vein thrombosis
e.g.	for example, '*exempli gratia*'
ECTS	European Calcified Tissue Society

EGOM	European Alliance of Associations for Rheumatology (EULAR) good or moderate
EHRs	Electronic healthcare records
EMA	European Medicines Agency
EN	English
EPMOI	Excluding Patients Missing Outcome Information
ESR	Erythrocyte sedimentation rate
eta	Etanercept
ETH	Swiss Federal Institute of Technology, '*Eidgenössische Technische Hochschule*'
EU	European Union
EULAR	European Alliance of Associations for Rheumatology
Euro-QoL	European Quality of Life
Euro-QoL	European Quality of Life instrument
EuroQoL EQ-5D	European Quality of Life-5 dimensions
FAERS	Food and Drug Administration Adverse Event Reporting system
FDA	Food and Drug Administration
fu	Follow-up
GDA	Global disease activity
gol	Golimumab
GP	General practitioner
HAQ	Health Assessment Questionnaire
HDL	Lower high-density lipoprotein
HLA	Human leukocyte antigen
HLA-B27	Human leukocyte antigen B27
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard ratio
i.e.	that is, '*id es*t'
i.v. inf.	Intravenous infusion
IC	Information Component
IC025	Lower end of the 95% credibility interval for the inforation component (IC)
ICPE	International Society for Pharmacoepidemiology (ISPE) Annual Conference
ICSR	Individual case safety reports
IFNγ	Interferon gamma
IL	Interleukin
inf	Infliximab
IQR	Interquartile range
ISPE	International Society for Pharmacoepidemiology
ISPE	International Society for Pharmacoepidemiology
JAK	Janus Kinase

LDA	Low disease activity
LLT	Lowest Level Term
logreg	Logistic regression
MAH	Marketing authorization holder
MDA	Minimal Disease Activity
MedDRA	Medicinal Dictionary for Regulatory Activities
MetS	metabolic syndrome
MICE	Multiple imputation with chain equation
MOIAN	Missing Outcome Information Assumed as No
n	Number
NAO	Nearest available observation
NSAID	Non-steroidal anti-inflammatory drugs
OR	Odds ratio
ORadj	Adjusted odds ratio
PASI	Psoriasis Area and Severity Index
PatActivity	Patient's assessment of disease activity on average the last 24 hours (0 very well - 10 very poor)
PatPain	Patient's assessment of joint pain on average the last 24 hours (0 very well - 10 very poor)
PDE4	Phosphodiesterase 4
PE	Pulmonary embolism
PIDM	Programme for International Drug Monitoring
pmm	predictive mean matching
PRO	Patient reported outcome
Prof.	Professor
PsA	Psoriatic arthritis
PT	Preferred Term
PT	Pulmonary thrombosis
PV	Pharmacovigilance
QoL	Quality of life
RA	Rheumatoid arthritis
RADAI-5	Rheumatoid Arthritis Disease Activity Index-Five
RCT	Randomised clinical trial
ref.	Reference
rem	Remission
RCT	Randomised clinical trial
RF	Rheumatoid factor
ROR	Reporting Odds Ratio
ROS	Reactive oxygen species
RWD	Real-world-data
RWE	Real-world evidence
s.c.	Subcutaneous
SADR	Suspected adverse drug reaction

SCQM	Swiss Clinical Quality Management in Rheumatic Diseases
SD (sd)	Standard deviation
SDR	Signals of disproportionate reporting
sec	secukinumab
SF12-mcs	Short-Form 12 health survey - mental component summary
SF12-pcs	Short-Form 12 health survey - physical component summary
SGR	Swiss Rheumatology Association, 'Schweizerischen Gesellschaft für Rheumatologie'
SJC (sjc)	Swollen joint counts
SJC28 (sjc28)	Swollen joint counts, counting 28 joints
SJC66 (sjc66)	Swollen joint counts, counting 66 joints
SOC	System Organ Class
SpA	Spondyloarthropathies
T2T	Treat-to-target
Th1	Type 1 T helper cell
TJC (tjc)	Tender joint counts
TJC28 (tjc28)	Tender joint counts, counting 28 joints
TJC68 (tjc68)	Tender joint counts, counting 68 joints
TNF (TNFα)	Tumour necrosis factor alfa
toc	Tocilizumab
tof	Tofacitinib
Treg	T regulatory
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
TYK2	Tyrosine Kinase 2
UK	United Kingdom
UMC	Uppsala Monitoring Centre
US (USA)	United States (United States of America)
ust	ustekinumab
VARA	Veterans Affairs RA
VAS	Visual Analogue Scale
vs	Versus
WAT	White adipose tissue
WHO	World Health Organization
X^2	Chi-squared

Other

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