KU Leuven
Biomedical Sciences Group
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KU LEUVEN

DOCTORAL SCHOOL
BIOMEDICAL SCIENCES

Exploring the multidimensional impact of rheumatoid arthritis on patients' lives: Can mobile health interventions provide solutions?

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Dissertation presented in partial fulfilment of the requirements for the degree of Doctor in Biomedical Sciences.

June 2024

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“It’s the questions we can’t answer that teach us the most. They teach us how to think. If you give a man an answer, all he gains is a little fact. But give him a question and he’ll look for his own answers.”

Patrick Rothfuss

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ABBREVIATIONS

ACPA	Anti-citrullinated protein antibody
AEGORA	App-based Education and GOal-setting in Rheumatoid Arthritis
ANCOVA	Analysis of covariance
APC	Antigen-presenting cell
AS	Ankylosing spondylitis
ASES	Arthritis Self-Efficacy Scale
bDMARD	Biologic disease-modifying antirheumatic drug
BMI	Body Mass Index
CareRA	Care in early Rheumatoid Arthritis
CDAI	Clinical Disease Activity Index
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying antirheumatic drug
DALYs	Disability-adjusted life years
DAS28	28-joint Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
eCRF	Electronic case report form
eHealth	Electronic health
EMR	Electronic medical record
ENAT	Educational Needs Assessment Tool
ESR	Erythrocyte sedimentation rate
EULAR	European League of Associations for Rheumatology
FLARE-RA	Flare Assessment in Rheumatoid Arthritis
GBD	Global Burden of Disease
HAQ	Health Assessment Questionnaire
HCQ	Hydroxychloroquine
HDA	High disease activity
HLA	Human leukocyte antigen
ICTRP	International Clinical Trials Registry Platform
IL	Interleukin
IPAQ-S	International Physical Activity Questionnaire Short form
IPQ-R	Revised Illness Perception Questionnaire
ITT	Intention-to-treat
JIA	Juvenile Idiopathic Arthritis
LDA	Low disease activity
MCID	Minimal clinically important difference
MCS	Mental Component Score
MDA	Moderate disease activity (RA) / Minimal disease activity (PsA)
MET	Metabolic Equivalent of Task
MFI	Multidimensional Fatigue Inventory
MHC	Major histocompatibility complex
mHealth	Mobile health
MMP	Matrix metalloproteinase
NOS	Newcastle-Ottawa Scale
NSAID	Non-steroidal anti-inflammatory drug
OA	Osteoarthritis
PCS (questionnaire)	Pain Catastrophizing Scale

PCS (SF-36)	Physical Component Score
PDA	Personal Digital Assistant
PGA	Patient's Global Assessment of disease activity
PhGA	Physician's Global Assessment of disease activity
PP	Per protocol
PRE	Patient-reported experience
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRO	Patient-reported outcome
PRP	Patient research partner
PsA	Psoriatic Arthritis
PSD	Persuasive Systems Design
PSQI	Pittsburgh Sleep Quality Index
QUAGOL	Qualitative Analysis Guide of Leuven
RA	Rheumatoid arthritis
RAID	Rheumatoid Arthritis Impact of Disease
RAPID3	Routine Assessment of Patient Index Data 3
RAQoL	Rheumatoid Arthritis Quality of Life
RCT	Randomised controlled trial
RDCI	Rheumatic Disease Comorbidity Index
REDCap	Research Electronic Data Capture
REMORA	Remote Monitoring of Rheumatoid Arthritis
RF	Rheumatoid factor
RQ	Research question
SDAI	Simplified Disease Activity Index
SF-36	Short Form-36
SMS	Short Message Service
SNP	Single-nucleotide polymorphism
SpA	Spondyloarthritis
SSZ	Sulphasalazine
T2T	Treat-to-target
TNFα	Tumour necrosis factor alpha
tsDMARD	Targeted synthetic disease-modifying antirheumatic drug
UCL	Utrecht Coping List
VAS	Visual Analogue Scale
WAT	Wearable activity tracker
WHO	World Health Organization
YLD	Years lived with disability

INTRODUCTION & OBJECTIVES

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory condition primarily characterised by inflammation of the synovial joints, particularly those of hands and feet(1). As one of the most common inflammatory joint diseases, RA represents a significant societal burden. When the disease is insufficiently controlled, people living with RA often experience joint pain, stiffness and swelling, as well as constitutional symptoms like fatigue. These symptoms can have a major impact on patients' quality of life and their ability to work or perform everyday activities. In many cases, uncontrolled joint inflammation in the context of RA eventually even leads to irreversible joint damage, giving rise to the classical image of hand deformities that is becoming increasingly rare in modern times. Indeed, major advances have been made in the management of RA in the past few decades, both through the introduction of new and more effective medication and through new insights into the optimal use of the available drugs. Nevertheless, RA is to this date still an uncurable disease with lifelong consequences for patients on both a personal and societal level.

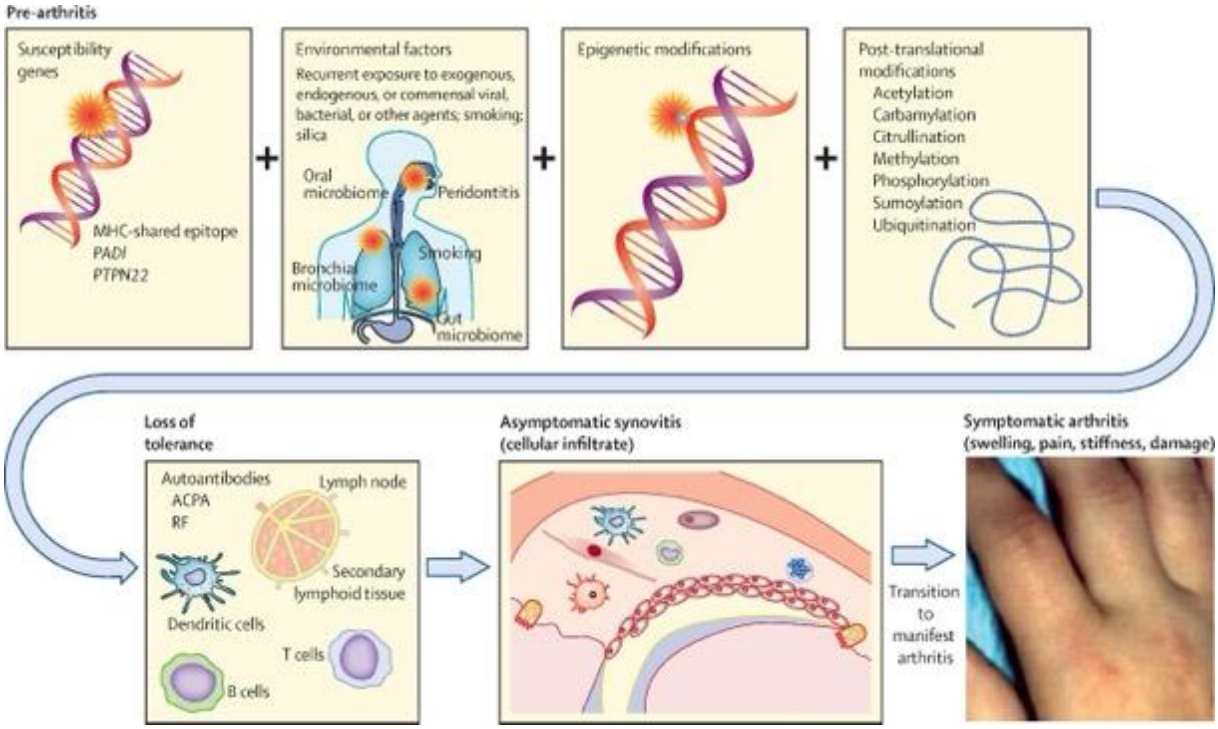
1. Epidemiology and societal impact

Musculoskeletal conditions rank among the most common health problems(2). Together, they account for more than 20% of the total years lived with disability (YLD) worldwide, which is second only to mental health problems(3). Within this group of musculoskeletal disorders, RA is the most common chronic inflammatory joint disease. Epidemiological studies in RA have mainly been conducted in Western countries, generally suggesting a prevalence in the range of 0.5-1%, although similar estimates have been reported elsewhere in the world, for instance in the Democratic Republic of the Congo(4,5). Overall, RA is 2-3 times more common among women, and although the disease can occur at any age, the first symptoms most commonly occur in the age group of 40-60 years(4). According to the Global Burden of Disease (GBD) Study, almost 20 million people across the world were estimated to be living with RA in 2020, and projections indicate that this number will continue to rise in the coming decades(6). Consequently, RA has a major societal impact, both in terms of disability and cost. RA accounted for approximately 3.1 million disability-adjusted life years (DALYs) in 2020(6), and estimates from the United States situated the annual societal cost of RA at over 19 billion dollars in 2005, rising to almost 40 billion dollars when including intangible costs associated with impaired quality of life(7). In other words, the personal and societal burden of RA is significant, and managing this burden begins with a basic understanding of the disease's pathophysiology.

2. Aetiology and pathophysiology: a brief overview

Autoimmune diseases are characterised by the presence of antibodies directed against the body's own tissues, so-called autoantibodies(8). RA is considered to be an autoimmune disease due to the presence of such autoantibodies, including rheumatoid factor (RF) antibodies, which are directed against human IgG, and the more specific anti-citrullinated protein antibodies (ACPA). However, the complexity and heterogeneity of this disease's pathophysiology are underlined by the existence of other RA-related autoantibodies, such as anti-carbamylated protein antibodies, and by the fact that up to one-in-three patients with RA are seronegative for both RF and ACPA(9). On the articular level, RA is characterised by synovial inflammation and hyperplasia and by destruction of periarticular bone and cartilage, eventually leading to irreversible joint deformities if the inflammatory process is not halted(10). However, much is yet to be learned about the causative events that might set these changes into motion. Indeed, RA's aetiology remains largely unclear, although it is thought to involve a complex interaction between genetic predisposition and environmental factors. These interactions eventually give rise to a stepwise autoimmune dysfunction, evolving from a preclinical stage to active disease (Figure 1)(11).

Figure 1. The natural history of rheumatoid arthritis.

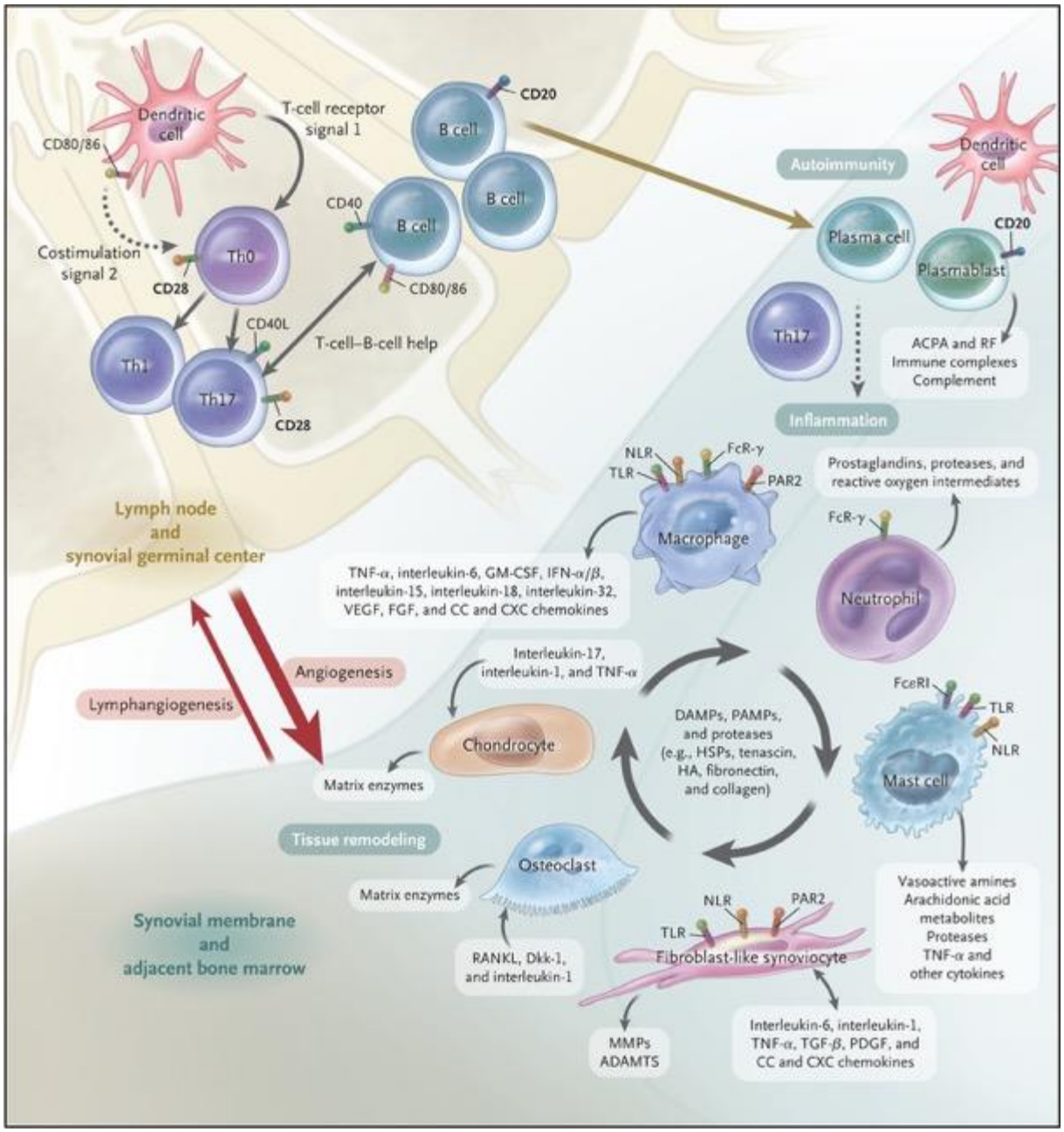


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That susceptibility to RA involves a genetic component is illustrated by twin studies, which have estimated the heritability of RA at around 60% and reported concordance rates of 10-15% among monozygotic twins(12). Genome-wide association studies have implicated many risk alleles in RA, most of which are related to immune regulatory pathways(13). Most of these RA risk alleles involve genes that encode major histocompatibility complex (MHC) molecules, which are involved in T-cell activation by antigen-presenting cells (APCs). Among these MHC-encoding risk alleles, susceptibility to RA is most strongly conferred by the so-called 'shared epitope', a common amino acid sequence in the human leukocyte antigen (HLA)-DRB1 locus(14). However, risk alleles for RA have been identified in many other immunological pathways, including single-nucleotide polymorphisms (SNPs) in the PTPN22 gene, and some of these alleles are associated with additional risk of developing RA through complex gene-gene interactions(15).

To make matters more complex, environmental triggers that interact with these genetic risk factors, possibly through epigenetic modification, appear equally important in the development of RA. Although numerous environmental factors have been linked with an increased risk of RA, including viral infections, periodontitis, occupational inhalants and the gut microbiome, the environmental trigger most consistently associated with RA is smoking(10,16). One hypothesis to explain this phenomenon is that exposure of the bronchial lining to tobacco smoke and other stressors induces post-translational citrullination of mucosal proteins(17). In genetically susceptible individuals, this then in turn results in a loss of self-tolerance and the production of autoantibodies directed against these citrullinated proteins, the so-called ACPA. Indeed, smoking and the presence of the shared epitope synergistically increase one's risk of developing ACPA-positive RA, while the risk factors and pathophysiology of seronegative RA remain to date much more elusive.

Figure 2. Immune processes within the joint in rheumatoid arthritis.



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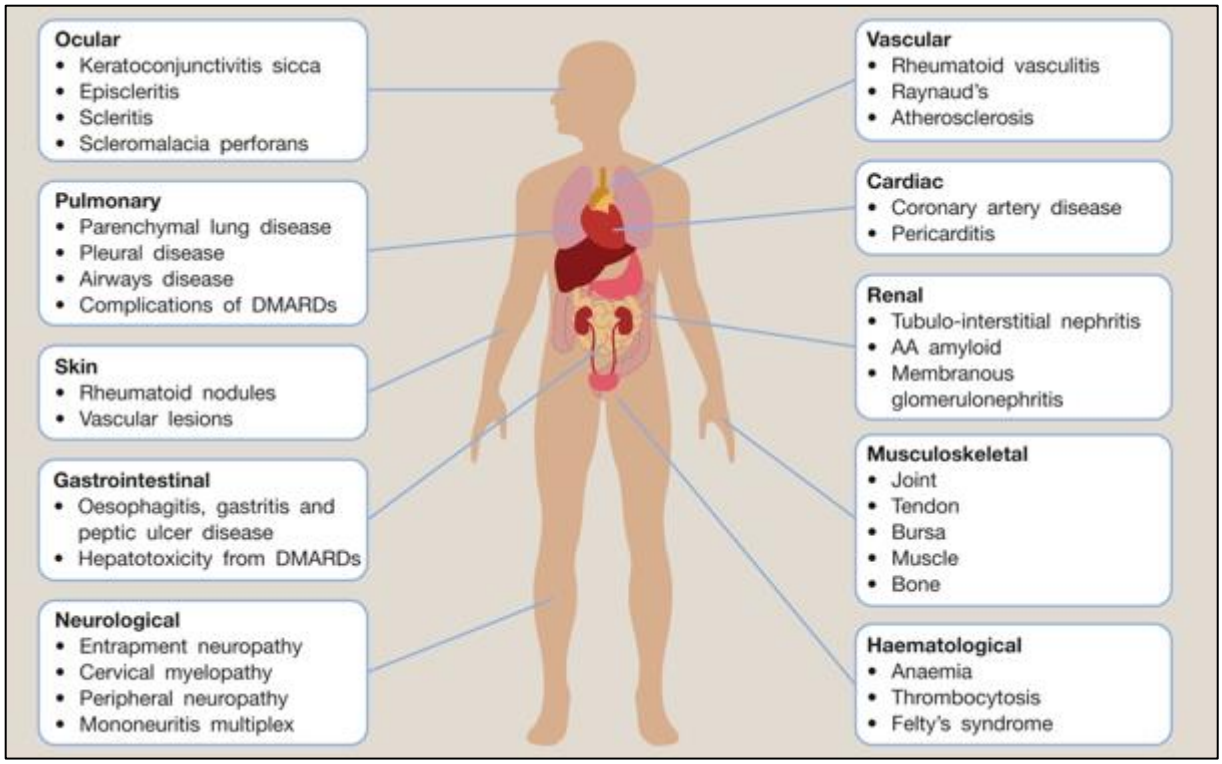
Interestingly though, studies have shown that autoantibodies like ACPA can be detected in the serum of patients with RA many years before the onset of clinical disease(18). Why these antibodies then go on to specifically cause localised inflammation in the synovial joints is much less clear, although it is presumed to arise from a multitude of biomechanical, microvascular and other local triggers(10). As soon as the synovial lesion is established however, a large number of T-cells, B-cells, plasma cells, dendritic cells, mast cells and granulocytes infiltrate the synovium and give rise to complex cell-cell interactions mediated by a multitude of pro-inflammatory cytokines and growth factors, including tumour necrosis factor (TNF)-alfa, interleukin (IL)-6 and IL-17 (Figure 2). During this process, B-cells are also activated, leading to the localised production of antibodies that contribute to sustained inflammation by activating the complement pathway. These interactions not only transform the paucicellular synovium into

a chronically inflamed, hyperplastic tissue or "pannus", but also initiate the process of bone and cartilage loss through increased expression of matrix metalloproteinases (MMPs), increased chondrocyte apoptosis and dysregulation of fibroblast, osteoblast and osteoclast activity.

3. Clinical presentation and diagnosis

As a result of this synovial inflammation, the clinical presentation of RA is mainly characterised by pain, swelling and stiffness of the peripheral joints(1). Typically, the affected joints are distributed in a polyarticular, symmetrical pattern with a predilection for the small joints of hands and feet, although numerous other joints may be equally affected. When the synovial inflammation persists for long enough, it usually leads to erosive damage to the joints and eventually even to irreversible joint deformities. However, RA is not solely a disease of the joint and may include several systemic manifestations, including fatigue, subcutaneous nodules, secondary Sjögren's syndrome, interstitial lung disease and rarely even vasculitis (Figure 3). In addition, RA is associated with an increased risk of cardiovascular disease and other comorbidities(19). Luckily though, improved management of RA in the past 20-30 years has reduced the impact these extra-articular manifestations and comorbidities traditionally had on mortality rates, and people living with RA now generally have a normal life expectancy(20,21).

Figure 3. Clinical manifestations of rheumatoid arthritis.



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Although laboratory and imaging tests are often helpful in the diagnostic process, RA is a clinical diagnosis, and there are no gold standard tests to confirm or rule out the disease. In the most typical case, the clinical suspicion of RA would be complemented by raised laboratory markers of inflammation like C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), the serological presence of RF and/or ACPA, and the appearance of typical erosions on X-ray imaging of hands and feet. In case of doubt or in more research-oriented settings, signs of active synovitis on other imaging modalities like ultrasound and magnetic resonance imaging

(MRI) can also be of use. However, only seldom are all these features present at the same time. For instance, biochemical inflammatory markers are not always raised, bony erosions are detected in only half of untreated patients or less within 6 months of symptom onset(23), and autoantibodies are present in only 2/3 patients as established above. Moreover, no diagnostic criteria for RA are currently available. For research purposes though, several sets of classification criteria for RA have been developed (Table 1), first by the American College of Rheumatology (ACR) in 1987 and later via a combined effort of the ACR and the European League of Associations for Rheumatology (EULAR) in 2010(24,25). These classification criteria differ primarily in the addition of the more specific ACPA test in the 2010 update and in the fact that these criteria depend less heavily on the presence of specific, but more long-term manifestations of RA like nodules and radiographic damage, allowing for earlier diagnosis at the cost of somewhat lower specificity.

Table 1. Classification criteria for rheumatoid arthritis.

1987 ACR classification criteria	**2010 ACR/ EULAR classification criteria**	
1. Morning stiffness (>1 hour)		**Score**
2. Arthritis of 3 or more joint areas	**A. Joint involvement**	
3. Arthritis of hand joints	1 large joint	0
4. Symmetric arthritis	2-10 large joints	1
5. Rheumatoid nodules	1-3 small joints	2
6. Serum RF	4-10 small joints	3
7. Radiographic changes	> 10 joints (at least 1 small joint)	5
Classification as RA if a patient satisfies at least 4/7 criteria AND criteria 1-4 have been present for at least 6 weeks.	**B. Serology**	
	Negative RF and negative ACPA	0
	Low-positive RF or low-positive ACPA	2
	High-positive RF or high-positive ACPA	3
	C. Acute-phase reactants	
	Normal CRP and normal ESR	0
	Abnormal CRP or abnormal ESR	1
	D. Duration of symptoms	
	< 6 weeks	0
	>= 6 weeks	1
	Classification as RA if a patient has at least 1 joint with definite clinical synovitis not better explained by another disease AND a score of at least 6/10.	

4. Pharmacological management: from past to present

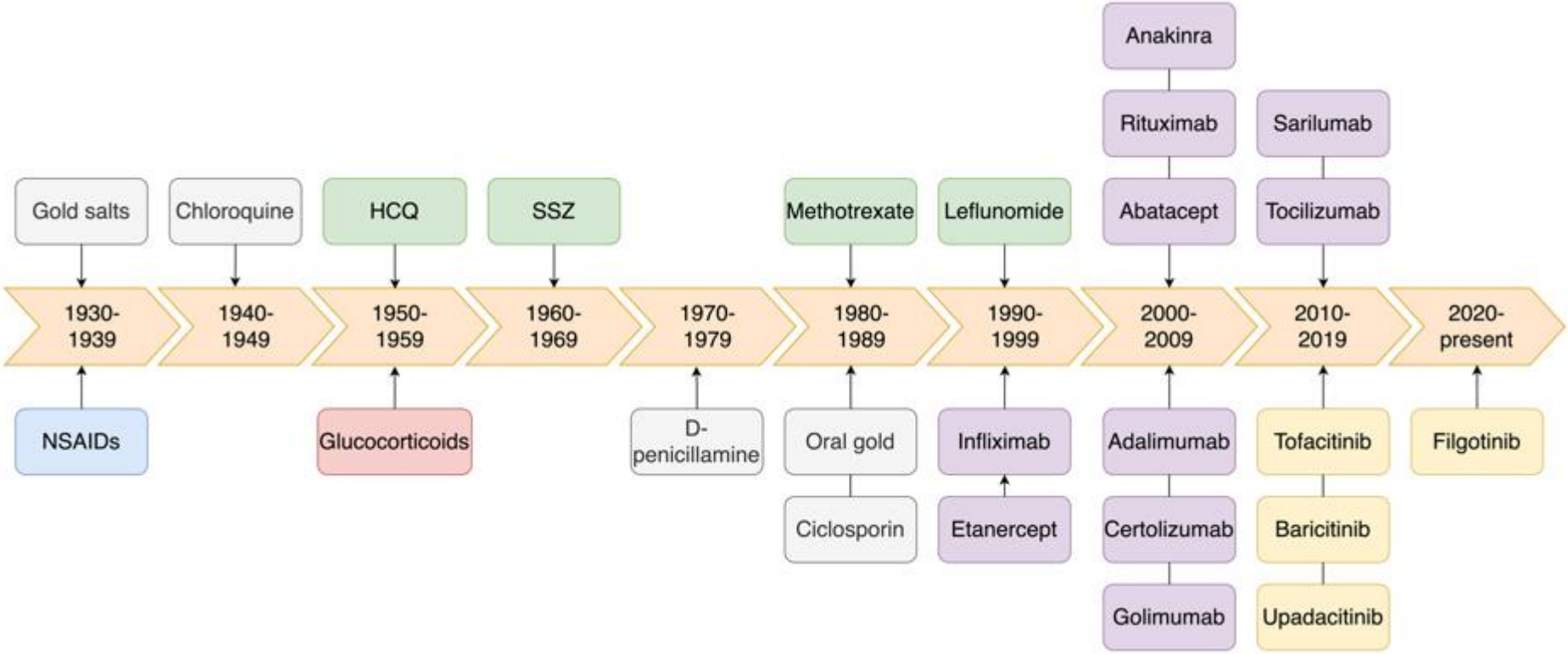
As can be appreciated from the updated classification criteria, making the diagnosis of RA early has become more important only in relatively recent times. Although there are descriptions of what appears to be RA dating as far back as ancient Egypt, RA was first described in the medical literature in the year 1800 by French surgeon Landré-Beauvais in his doctoral dissertation, referring to it as "asthenic gout"(26,27). Evidently, much has changed since then in the way this disease is treated (Figure 4). Since the 1990s in particular, there has been a true revolution in the management of RA, with both the advent of new and effective classes of disease-modifying antirheumatic drugs (DMARDs) and a novel approach to the way these drugs are applied.

4.1. The DMARD revolution

In the early 20th century, treatment options for RA were largely limited to symptomatic relief with analgesics, salicylates or NSAIDs, and non-pharmacological measures(28). The first notion that drug treatment might be able to actually modify the disease's progression came in the 1930s with the early experience with gold salts to treat RA(29). Another important landmark was the first introduction of glucocorticoids in the context of rheumatology, which came in the late 1940s and 1950s in the form of a series of studies, primarily from the Mayo Clinic, that showed clinical improvements beyond anything that had been achievable before(30). However, the discovery of glucocorticoids' spectacular efficacy in the treatment of RA was soon followed by the recognition of their important side effects, which went on to dictate the overall perception of these drugs for decades. In the following years, the first drugs that could effectively be termed disease-modifying were introduced, including hydroxychloroquine (HCQ) and sulphasalazine (SSZ) which are still used today(28).

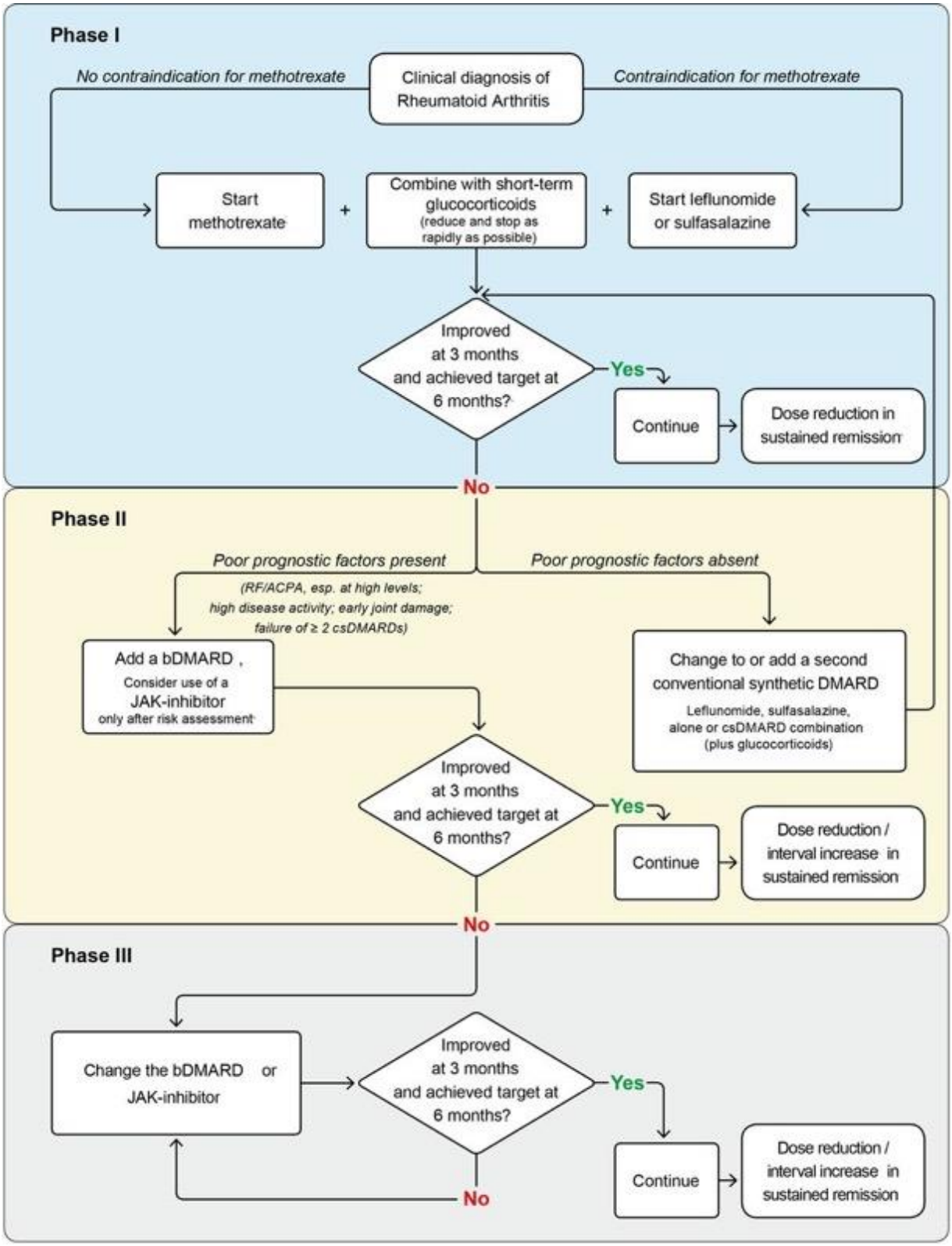
Despite the optimism associated with these advances, it took until the 1980s for the next crucial milestone to be achieved with the approval of methotrexate for the treatment of RA, fundamentally changing the way the disease is managed to this day. Developed as early as 1948, methotrexate gradually made its way into the rheumatology field over the subsequent decades through the realisation that among people suffering from psoriatic arthritis (PsA) it improved not only skin lesions but also arthritis(31). Randomised, placebo-controlled studies only took place in the 1980s though, and were followed by studies of combination therapies and the subsequent establishment of methotrexate as the cornerstone of the pharmacological management of RA(32,33). Although methotrexate is to date still considered the anchor drug for RA, the DMARD revolution truly took off in the 1990s when years of prior research into the key molecules involved in inflammatory processes ultimately resulted in the development of the first biologic DMARDs (bDMARDs)(34). Starting with the development of monoclonal antibodies targeting tumour necrosis factor alpha (TNFα), numerous different classes of bDMARDs - and more recently targeted synthetic DMARDs (tsDMARDs) - targeting various inflammatory mediators have since emerged and continue to be developed today.

Figure 4. Historical timeline of drug treatment for rheumatoid arthritis.



Blue = symptomatic treatment, red = glucocorticoids, green = conventional synthetic DMARDs, purple = biologic DMARDs, yellow = targeted synthetic DMARDs. Drugs indicated in grey are no longer routinely used to treat RA.
NSAIDs = non-steroidal anti-inflammatory drugs, HCQ = hydroxychloroquine, SSZ = sulphasalazine, DMARDs = disease-modifying antirheumatic drugs

Figure 5. EULAR recommendations for the management of rheumatoid arthritis, 2022 update.



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4.2. Treating-to-target and the window of opportunity

Despite this significant expansion of the pharmacological armamentarium, the drastic changes of the past 30 years in the treatment of RA have not been limited to drug development. Traditionally, the approach to treating patients with RA was pyramidal, gradually stepping up from analgesics to DMARDs when prior steps were insufficient to control symptoms(28). However, the introduction of methotrexate and several landmark trials in the 1990s and 2000s, such as COBRA(36), FIN-RACo(37) and BeST(38), have prompted a paradigm shift towards earlier and more intensive treatment of RA. Consequently, initiating DMARDs or even combinations of DMARDs and/or glucocorticoids as soon as the diagnosis is made has become the current standard of care(35,39). Indeed, it is now commonly recognised that treating RA early - preferably within the first 3 months of symptoms - results in a higher probability of achieving good clinical outcomes, a phenomenon that has come to be known as the "window of opportunity"(40). In a more recent evolution, this has prompted some research groups to investigate if starting DMARD therapy even earlier, before RA is clinically apparent, could prevent progression to the disease among people considered to be at risk of developing RA. This at-risk group is often called "clinically suspect arthralgia" and is a topic of considerable ongoing research(41).

However, aside from treating early and intensively, a third fundamental principle of modern RA treatment has proved to be equally important: treating-to-target. The treat-to-target (T2T) strategy implies that one sets a target of optimally controlled disease activity upfront and within a framework of shared decision-making with the patient, before regularly assessing this target and adapting treatment when it isn't achieved(42). Pivotal studies like the Tight Control for Rheumatoid Arthritis (TICORA) trial, published in 2004, have clearly illustrated that adhering to a T2T-strategy results in improved outcomes in terms of disease activity, physical function, radiographic progression and quality of life(43). Numerous trials have since confirmed these findings, and T2T-principles are now unequivocally integrated in international guidelines for the management of RA (Figure 5)(35,39). However, real-world evidence shows that consistently implementing a T2T-strategy in practice remains challenging, and there is still room for improvement in this regard(44).

Concretely, T2T implies that treatment should be aimed at achieving a state of optimally controlled disease activity, or remission. Based on the results of several pivotal trials, including COBRA(36), BeST(38), tREACH(45), IMPROVED(46), CareRA(47), IDEA(48), COBRA-light(49), NEO-RACo(50) and ARCTIC(51), current EULAR guidelines recommend initiating treatment with a conventional synthetic DMARD (csDMARD) like methotrexate with the addition of a step-down bridging scheme of glucocorticoids, the latter of which is to be tapered towards discontinuation whenever possible(35). This is contrasted by the ACR guidelines, which recommend initiating a csDMARD without glucocorticoids as the preferred first-line treatment(39), an illustration of the continuing debate over glucocorticoids in the rheumatology field. However, both guidelines agree that b- and tsDMARDs are still considered to be second-line therapy due to their higher cost and unclear added benefit over a csDMARD as first-line treatment, particularly when bridging with glucocorticoids(52).

5. Beyond the joints: disease activity and outcome measures

Naturally, the proposal of a T2T-strategy was only possible through the prior development of outcome measures that can be used to define a target like remission. In 1994, the Outcome Measures in RA Clinical Trials (OMERACT) group - later renamed Outcome Measures in Rheumatology - proposed a core set of outcomes to be collected in all RA clinical trials, which included pain, the patient's and physician's global assessment of disease activity (PGA/PhGA, usually on a visual analogue scale (VAS)), physical function, the number of swollen and tender

joints, an acute phase reactant like CRP or ESR, and - for longer trials – joint radiographs(53). Later, this list was expanded with the strong suggestion to additionally include a measure of fatigue(54). Using these outcomes, efforts were soon undertaken to derive quantitative measures of RA disease activity, which could then be used to define response to treatment as well as disease activity states like remission and low/moderate/high disease activity (LDA/MDA/HDA). This has resulted, among others, in the three composite disease activity scores that are currently most used for RA: Disease Activity Score based on 28 joints with CRP or ESR (DAS28-CRP/DAS28-ESR), Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI)(55–57). Although these scores are all derived from similar individual outcome parameters, there are some differences in their composition and in their cut-off points to define the various disease activity states (Table 2).
In 2011, a collaborative effort of ACR, EULAR and OMERACT used these outcomes and composite scores to propose a standardised definition for remission in RA, putting forward as preferred criterion either an SDAI of ≤3.3 or a Boolean definition where all of PGA, PhGA, CRP (in mg/dL) and the number of tender and swollen joints upon 28-joint examination (TJC28/SJC28) should simultaneously be ≤1(58). More recently though, the PGA threshold for Boolean remission was increased to ≤2(59), and there remains an active debate surrounding the optimal way to define remission within a T2T-setting(60–62).

Table 2. Composite disease activity scores for rheumatoid arthritis.

Index	Composition	Cut-off per disease activity state			
		Remission	**LDA**	**MDA**	**HDA**
DAS28*	Log-transformed, weighted sum of: PGA, TJC28, SJC28, CRP/ESR	< 2.6	2.6 – 3.2	>3.2 – 5.1	> 5.1
SDAI	PGA + PhGA + TJC28 + SJC28 + CRP	≤ 3.3	>3.3 – 11	>11 – 26	> 26
CDAI	PGA + PhGA + TJC28 + SJC28	≤ 2.8	>2.8 – 10	>10- 22	> 22

* Although differing cut-offs have been proposed for DAS28-CRP and DAS28-ESR, the values presented here are most commonly used. *DAS28 = Disease Activity Score based on 28 joints, SDAI = Simplified Disease Activity Index, CDAI = Clinical Disease Activity Index, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, TJC = tender joint count in 28 joints, SJC = swollen joint count in 28 joints, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, LDA = low disease activity, MDA = moderate disease activity, HDA = high disease activity*

6. Patient-experienced disease impact: through the looking glass

Despite their merits, it is increasingly clear that composite disease activity scores do not always fully reflect the impact and symptom burden patients experience when living with RA, or the goals patients aim to achieve with treatment(63). Useful tools to provide additional insight into these aspects are patient-reported outcome (PRO) measures, outcome instruments and questionnaires that are completed by patients themselves(64). Notable examples of these include the OMERACT core outcomes physical function – usually assessed with the Health Assessment Questionnaire (HAQ)(65) – and pain, fatigue and the PGA, which are often measured on a VAS (0-10 or 0-100). Among these, only the PGA is incorporated in the composite disease activity scores. Other PRO-instruments are designed to capture information on more complex concepts like quality of life, such as the Short Form-36 (SF-36) survey(66), or the broader impact of RA, for example the Rheumatoid Arthritis Impact of Disease (RAID)

questionnaire(67). Similarly, information about patients' experiences and perceptions of the process of care, rather than its outcome, can be captured with patient-reported experience (PRE) measures. PROs in particular are increasingly used in both clinical practice and rheumatology research, and this trend has contributed to the understanding that even in the modern age of treating-to-target, there is still some way to go to mitigate RA's impact on patients' lives.

6.1. The challenge of persisting disease impact

Through the availability of new and improved DMARDs and the increasing adoption of a T2T-strategy, the prognosis of RA has improved considerably in the last few decades. Remission is now a realistic and achievable goal for most patients, and the often-dramatic repercussions RA traditionally had have become rare occurrences. However, an increasing body of PRO-driven evidence illustrates that these improvements do not always translate into less patient-experienced disease impact(68). Reports from several randomised controlled trials (RCTs) and cohort studies have shown that many patients with RA continue to experience physical disability, pain and fatigue despite achieving the treatment targets of remission or LDA(69). Depending on the definition of remission and on the threshold used to define residual symptoms, as many as 20-50% of patients with RA who are in remission experience persisting pain and disability, with often even higher proportions when considering fatigue(70–74). Similarly, one-in-five patients with RA fail to meet the original Boolean definition of remission solely because of an elevated PGA, in turn driven by residual pain, physical disability and fatigue(75,76). Moreover, patients and rheumatologists do not always agree in their assessment of disease activity and treatment success, and this discordance may hamper shared decision-making when treating-to-target(77–79).

These findings are certainly not irrelevant, given that the first priority for people suffering from RA is to experience less symptoms and return to a normal life as soon as possible(80). Since in modern times, RA generally does not result in increased mortality, one could argue that the ultimate goal of RA treatment is to preserve and support patients' quality of life, and to help patients return to normality whenever possible. While adequate pharmacological treatment and control of the inflammatory disease process is usually a necessary prerequisite to attain this goal, the work clearly does not end there for many patients. There is a pressing need for more research to improve our understanding of RA's impact on patients' lives, and to explore strategies to both prevent and improve persistent impact.

6.2. Self-management and self-efficacy: patients hold the key

One approach to help patients cope with the impact of living with RA is to support them in their self-management of the disease and to empower them to take up a more active role in the shared decision-making process. Self-management behaviour encompasses the actions or approach a person takes to understand their disease and deal with the symptoms, consequences and impact it entails(81). RA is a chronic disease with lifelong consequences and an often-unpredictable course, with intermittent flares and sometimes even daily symptom variability(82). Interventions that support patients in their ability to manage these consequences have shown improvements in various health-related outcomes and might also reduce healthcare utilisation(83,84). Consequently, EULAR recently published a set of recommendations for the implementation of self-management strategies for inflammatory arthritis(85). Among others, these recommendations put forward patient education as the essential basis for self-management and recommended the inclusion of problem-solving or goal-setting principles, physical activity promotion, lifestyle advice, mental health support and digital tools in self-management interventions. As an overarching principle, EULAR also emphasised the

importance of self-efficacy as a crucial outcome for interventions to support self-management. Self-efficacy can be defined as one's confidence in their ability to manage a disease and its consequences(86). Higher self-efficacy has been found to have positive effects on various aspects of living with RA(87), and evidence supports the notion that self-efficacy can be improved with needs-based patient education and self-management support(88). However, a recent literature review on self-management interventions for inflammatory arthritis illustrated that patients' support needs are variable and most reported interventions are insufficiently theoretically founded(89). Moreover, despite EULAR's recommendations, this review found that the use of digital tools for self-management support is still underrepresented in the available literature.

6.3. Mobile health and digital tools: friend or foe?

In parallel with the rise of new drug therapies for RA, the past several decades have also brought an ongoing and worldwide technological revolution. Widespread internet connectivity, smartphones and wearable activity trackers (WATs) are inextricably linked with modern times, and with them have come opportunities to approach patient care in different ways. For instance, mobile health (mHealth) - or the use of smartphone applications in healthcare – can be used to provide self-management support in patients' own preferred time and space(90). Studies like the recent CareHand-trial have shown that this is a promising approach among patients with RA and can improve relevant patient outcomes like empowerment, physical activity and functioning(91,92).

Alternatively, smartphone applications can also provide a way for patients to record symptoms or their experience of disease impact on a regular basis, independently of scheduled clinical appointments(93). Again, recent evidence indicates that remote symptom monitoring does not only provide additional clinical information, but can also reduce healthcare utilisation by facilitating patient-initiated follow-up without necessarily compromising quality of care(94,95).

However, several challenges are associated with the use of smartphone applications for either interventional or remote monitoring purposes. For one, perhaps the greatest challenge of mHealth use in clinical practice and research is the ever-present problem of attrition and limited engagement with apps over time(96). For instance, estimates from non-healthcare industries suggest that almost 75% of app users disengage within 3 months, and recent studies within the rheumatology field have reported 3-month patient disengagement rates as high as almost 90% in some cases(96,97). A second challenge of mHealth use in practice is that, although research indicates that apps should be tailored to the needs of specific patient populations and ideally be co-developed by healthcare professionals and patients, most available mHealth-apps do not meet these essential criteria(98). Finally, qualitative studies have highlighted that patients often feel reluctant to engage in remote monitoring with apps because of fear that this might excessively confront them with their illness(99).

In other words, although there is clear potential to be found in apps with regard to both the provision of self-management support and the exploration of patient-experienced disease impact, further research is needed to explore if and how these challenges can be met.

RESEARCH OBJECTIVES

The overall objective of this thesis is to explore the impact of RA on patients' lives, its relationship with disease activity, and potential strategies to prevent or mitigate this impact.
In Part I*, this thesis will delve deeper into various ways that living with RA affects patients' wellbeing, with chapters dedicated to psychosocial wellbeing, fatigue and self-efficacy. These chapters will also study the relationship between these PROs and disease activity, and will attempt to contribute to a better understanding of those situations where patients continue to experience disease impact despite well-controlled inflammation.
In addition, this thesis will explore what both healthcare providers and patients can do to mitigate this impact. Part I will address this by investigating if prognostic factors can be identified early in the course of RA that could be acted upon to prevent persistent disease impact. In Part II, this thesis will focus on how mHealth-applications could fit into this equation. Specifically, Chapter 4 addresses the question if using smartphone apps can be a feasible approach to explore the patient-reported impact of RA in more detail. Finally, Chapter 5 will further elaborate on this question by reporting feasibility data from the randomised controlled trial AEGORA, which additionally explored in practice if mHealth-applications can also be used to support patients with RA in their self-management of experienced disease impact, with a focus on improving self-efficacy.

<u>This thesis will address the following research questions (RQ):</u>

1. How does patient-experienced disease impact relate to disease activity in RA, and can we prevent persistent disease impact by addressing prognostic factors in early disease?

   ➔ Part I: Chapters 1, 2 and 3

2. Can mobile health applications be a feasible approach to explore the impact of RA in more detail by remotely monitoring PROs?

   ➔ Part II: Chapters 4 and 5

3. Can mobile health applications improve patients' self-efficacy for managing RA and its impact, by providing multicomponent self-management support?

   ➔ Part II: Chapter 5

** All analyses of Part I, Chapters 1-3, are based on data from the 2-year Care in early RA (CareRA) trial, a multicentre, pragmatic RCT conducted in 13 Belgian rheumatology centres between 2009-2013, and its 3-year observational extension study CareRA-plus. This trial was designed to compare the effectiveness of different remission-induction DMARD-regimens, all consisting of methotrexate with/without additional csDMARDs and bridging step-down glucocorticoids, among patients with recently diagnosed RA. The primary results of CareRA and CareRA-plus have previously been published(47,100,101). More details on the study protocol and treatment regimens can be found in the Supplemental Materials of this thesis under Supplement 2.1. All background information relevant to the interpretation of the results of Chapter 1-3 of this thesis is addressed in the Methods section of the corresponding chapters.*

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PART I

Patient-reported outcomes as mirrors into experienced disease impact and its relationship with RA disease activity

“The sorrow which has no vent in tears may make other organs weep.”

Henry Maudsley

Chapter 1

Psychosocial wellbeing and rheumatoid arthritis disease activity: unravelling a complex interplay

This chapter was published as:
Doumen M, De Cock D, Pazmino S, Bertrand D, Joly J, Westhovens R, Verschueren P. Psychosocial Burden Predicts Sustained Remission in Early Rheumatoid Arthritis: Unraveling the Complex Interplay of Well-Being and Disease Activity. Arthritis Care Res 2023;75(4):758-767.

ABSTRACT

Objectives: To investigate how psychosocial aspects affect the probability of achieving sustained remission in early RA, and to explore the directionality of this relationship.

Methods: Data were analyzed from the randomized controlled CareRA-trial. Sustained remission was defined as continued DAS28-CRP <2.6 from weeks 16 to 104. Patients completed the Short Form 36 (SF-36), Revised Illness Perception Questionnaire (IPQ-R) and Utrecht Coping List (UCL). These psychosocial variables were studied at baseline and week 16 as predictors of sustained remission with logistic regression. Next, subgroups of patients in remission at week 16 were identified by Latent Profile Analysis (LPA) based on these psychosocial indicators. Time to first loss of remission was then compared between groups by Cox-proportional-hazards regression. Finally, directionality of associations between psychosocial indicators and DAS28-CRP was explored with cross-lagged panel models (CLPM).

Results: Sustained DAS28-CRP-remission was associated with higher SF-36-scores and less passive coping at baseline, and with higher SF-36-scores and more positive IPQ-R-outcomes at week 16. Among patients in DAS28-CRP-remission at W16 (n=287), two subgroups were identified: a low-psychosocial-burden group (n=231/287) and high-psychosocial-burden group (n=56/287). The low-psychosocial-burden group retained remission longer (HR 0.51 [0.35-0.73]). In the CLPM, temporal relationships between psychosocial wellbeing and DAS28-CRP were complex, bidirectional and disease-phase dependent.

Conclusion: Suboptimal psychosocial wellbeing and negative illness perceptions predicted lower probability of sustained remission in an early RA cohort. Illness perceptions appeared to become more clinically relevant with time. Finally, one-in-five patients showed worse psychosocial outcomes despite early remission, and these patients tended to lose remission earlier.

INTRODUCTION

Clinical outcomes of rheumatoid arthritis (RA) are continually improving, because of treating-to-target and the availability of novel disease-modifying antirheumatic drugs (DMARDs)(1–4). However, even when clinical treatment targets are met, many patients with RA still report ongoing symptoms, including pain and fatigue (5). Crucially, controlling these symptoms and being able to lead a 'normal' life despite their disease appear to be the most important goals for patients (6). It is therefore relevant to consider these unmet patient needs when assessing disease control, and to work towards patient-preferred goals (7). This could be facilitated by using patient-reported outcomes (PROs) to complement the evaluation of disease burden (8). Additionally, PROs like pain and physical function appear to be stronger predictors of remission than traditional prognostic factors such as autoantibodies or radiographic erosions (9,10).

However, while pain, fatigue and physical function are now widely collected as PROs for RA, less attention is often given to mental health and psychosocial wellbeing (11). Research has shown that suboptimal mental health persists in many patients with RA, despite successful treatment (7,12). Additionally, illness perceptions, particularly during early disease, contribute strongly towards adjustment to chronic illness (13). In RA, patients' perceptions about their disease also influence levels of pain and functioning (14,15). Furthermore, personality characteristics and psychological stressors during the early course of RA are known predictors of long-term anxiety and depressed mood (16). Despite this evidence, psychosocial wellbeing and illness perceptions are still rarely assessed in practice or even in clinical trials, and particularly not as specific endpoints informing person-centered interventions (17).

During the Care in Early RA (CareRA) trial, which compared several DMARD-regimens for early RA (18), numerous PROs relating to psychosocial wellbeing were collected. Results showed that psychosocial functioning after 1 year of treatment was mainly influenced by the initial treatment response (19,20). However, one-in-five patients in CareRA, despite responding well to treatment, continued to report signs of poor wellbeing, again reflecting unmet patient needs (21).

Nonetheless, it is often unclear whether these unmet needs should either be seen as a distinct issue, or as a disease-related complication that could in turn affect clinical disease control. For instance, although a negative association of depression and anxiety with remission has been suggested (22,23), it is less evident whether more general indicators of wellbeing also affect clinical outcomes. A better understanding of the relationship between psychosocial wellbeing, coping, illness perceptions and disease activity, and the directionality of these relations, could help clinicians to distinguish between patient needs that require pharmacological interventions and needs that are better addressed otherwise. Moreover, it remains unclear whether suboptimal psychosocial wellbeing should be intervened upon during the early stages of disease, or if this only later becomes more relevant.

Therefore, we aimed to assess how patients' psychosocial characteristics affect disease activity and remission or vice versa during the early course of RA.

METHODS

Study design and participants

We conducted a post-hoc analysis of the CareRA-trial. CareRA (EudraCT: 2008-007225-39) was a multicenter, prospective, two-year, pragmatic RCT comparing DMARD-regimens for early RA (18). In total, 379 patients were recruited from 13 Belgian rheumatology centers. All participants were diagnosed with RA <1 year ago and were DMARD-naïve at study initiation. Details on the study protocol and main results are published elsewhere (18,24). Briefly, all treatment arms consisted of methotrexate ± additional csDMARDs or bridging glucocorticoids. The ethics committee of each participating center approved the study protocol and all

participants provided written informed consent. This analysis included the entire CareRA-cohort and required no additional ethical approval.

Assessments

Participants were assessed at screening, baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104. At screening, demographic characteristics were collected and past or current co-morbidities of depression/anxiety were registered, defined as either a confirmed diagnosis or use of antidepressants. Each following assessment included tender and swollen joint counts, patient's and physician's global assessment of disease activity (PGA/PhGA) on a visual analogue scale (VAS), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). DAS28, CDAI and SDAI were calculated as composite scores (25,26). Moreover, numerous PROs were collected at different times, including pain and fatigue (VAS), the Health Assessment Questionnaire (HAQ), the Revised Illness Perception Questionnaire (IPQ-R) and the Short-Form 36 health survey (SF-36) (27–29). Coping was assessed at baseline and week 16 using the Utrecht Coping List (UCL) (30).

The IPQ-R measures 9 dimensions of illness perception: identity, consequences, timeline acute/chronic, timeline cyclical, treatment control, personal control, emotional representations, illness coherence and causes (28). Higher scores on illness coherence, treatment control and personal control represent a better understanding of RA and stronger beliefs in the ability of treatment or personal interventions to control the disease. Higher scores on emotional representations and consequences indicate stronger perceptions about the negative consequences of RA.

The SF-36 measures 8 dimensions of health divided into 4 physical dimensions (physical function, role physical, bodily pain, and general health; summarized in the physical component score PCS) and 4 mental dimensions (vitality, social functioning, role emotional, and mental health; summarized in the mental component score MCS) (29). Higher scores on SF-36 dimensions (0-100) indicate a better perceived health status.

Finally, the UCL measures seven coping strategies, with higher scores indicating more use of a certain strategy (30).

Outcomes

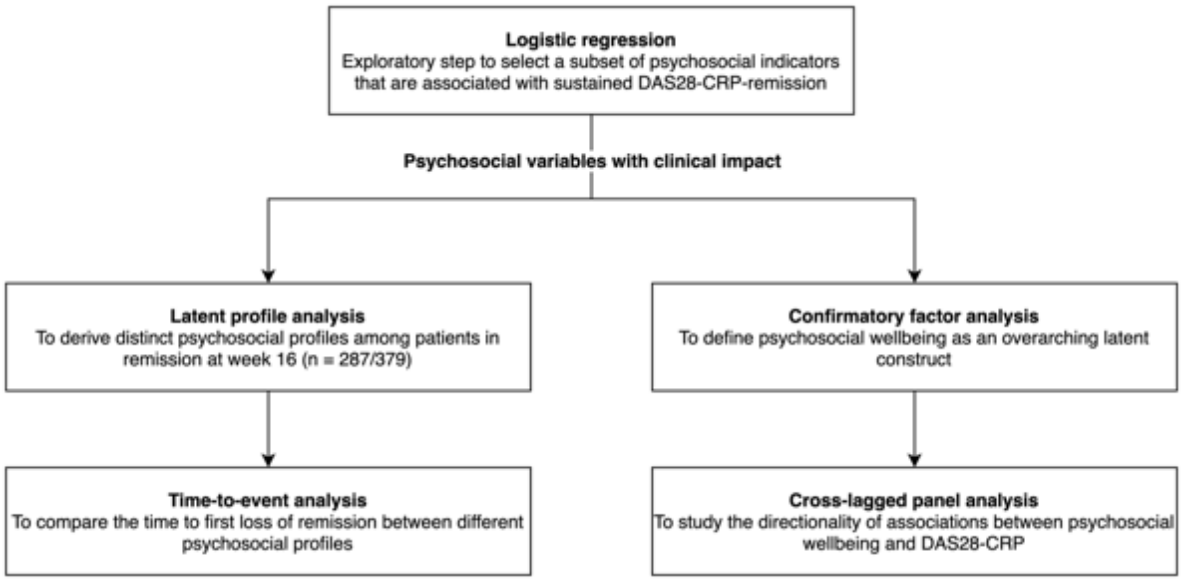
We aimed to investigate how indicators of psychosocial wellbeing affect the probability of achieving sustained remission in early RA, and additionally, how disease activity and psychosocial factors might interrelate over time. According to this research question, we selected the UCL, the mental health dimensions of the SF-36 and the IPQ-R-dimensions illness coherence, consequences, treatment control, personal control, and emotional representations as the most relevant psychosocial variables. Additionally, depression/anxiety was considered as a possible confounder. At each time point, remission was defined dichotomously as DAS28-CRP <2.6 (31). Sustained remission was defined as a continued state of remission from weeks 16 to 104. As a sensitivity analysis, results were compared for CDAI-remission, SDAI-remission and ACR-EULAR Boolean remission (26,32).

Statistical analysis

Descriptive statistics were reported as means (± SD), medians (± IQR) or proportions as appropriate. First, baseline clinical and demographic characteristics of patients achieving or not achieving sustained remission were compared using a t-test, Mann-Whitney-U-test or Chi-square test depending on data distribution. Variables that showed statistically significant differences between these groups were explored with multivariate logistic regression predicting sustained remission and adjusted for age, sex, treatment arm and the presence of autoantibodies.

Second, we constructed logistic regression models predicting the odds of sustained remission with the available psychosocial PROs as individual predictors, adjusted for age, sex, treatment arm, autoantibodies, and the two-component DAS28 (2C-DAS28) at the time of assessment. The 2C-DAS28 is a reweighted combination of swollen joint counts and CRP that represents joint inflammation rather than global disease activity (33). By adjusting for 2C-DAS28 instead of the four-component DAS28, we aimed to prevent collinearity between the PGA and other PROs. Similarly, individual regression models included only one of the psychosocial variables at any time. These prediction models were intended as an exploratory step to select, among the many available psychosocial indicators, the most clinically relevant PROs to include in the following analyses (Figure 1). Therefore, no correction for multiple comparisons was applied.

Figure 1. Flow chart of statistical analyses.



Third, we performed a Latent Profile Analysis (LPA) to identify distinct psychosocial profiles among patients, based on normalized scores on the selected subset of PROs. LPA aims to discover hidden subgroups within observed data based on a set of continuous variables (34). Contrary to distance-based clustering algorithms, LPA models the probability of each patient belonging to a certain profile, which allows for more flexibility while also providing fit statistics. The optimal model and number of profiles were chosen based on Akaike and Bayesian Information Criterion (AIC/BIC), with lower numbers representing better model fit (35). By first selecting a relevant subset of PROs to include, LPA then allowed us to distinguish between patients with specific psychosocial profiles. This method was applied at week 16 specifically to the subgroup of patients who were in remission, to assess if differing psychosocial phenotypes could be found among these patients despite clinical disease control. Next, the clinical impact of such phenotypes was studied by comparing the time to first loss of remission between different profiles identified at week 16. This time-to-event analysis was based on Kaplan-Meier and Cox-proportional hazards regression with profile-membership as the predictor and adjusting for age, sex, treatment arm, and autoantibodies.
Finally, we explored the directionality of associations between the selected psychosocial indicators and DAS28-CRP. To reduce error due to repeated measurement of multiple variables, psychosocial wellbeing was first established as a latent construct loaded upon by the selected

psychosocial indicators with confirmatory factor analysis (CFA), and the stability of this construct over time (measurement invariance) was validated (Supplement 1.1 provides detailed methods) (36). Next, directionality and temporal nature of the association between the psychosocial wellbeing construct and DAS28-CRP was studied with a cross-lagged panel model (CLPM), adjusted for age, sex, treatment arm and autoantibodies. CLPMs can be applied to longitudinal data to estimate directionality of effects between variables at different points in time while adjusting for changes in the variables themselves, which might contribute to stronger causal claims (37).
Missing SF-36-items were first substituted with the respondent's average score on the same subscale's completed items when at least half of the items were answered, in accordance with the questionnaire's manual. Thereafter, missing data were assumed to be missing at random and imputed with multiple imputation (100 imputations, 16% total missingness, imputation by classification and regression trees). Before analysis, imputations were pooled into a single dataset containing the means of imputed values. A p-value <0.05 was considered as statistically significant for all analyses. Analyses were carried out in R Studio version 1.3.1093, with inclusion of the *mice*, *lavaan*, *tidyLPA* and *survival*-packages.

RESULTS

Patient characteristics

In total, 379 patients with early RA were included in CareRA between January 2009 and May 2013. Among these patients, 322 (85%) completed the two-year study. This post-hoc analysis included all 379 participants after imputation of missing data (Table 1).

Clinical predictors of sustained remission

Sustained DAS28-CRP-remission was achieved by 124/379 (33%) patients. Only 46/379 (12%) patients reached sustained CDAI-remission, and both sustained SDAI-remission and sustained remission based on ACR-EULAR Boolean criteria were attained in only 21/379 (6%) patients. However, although in most cases remission was not sustained until week 104, most patients did achieve DAS28-CRP-remission by week 16 or week 28 (Supplement 1.2).
Baseline demographic characteristics did not differ between the groups that did or did not achieve sustained DAS28-CRP-remission, except for a lower BMI in the sustained remission group (Table 1). However, patients who achieved sustained remission had, at baseline, a significantly lower DAS28-CRP, lower tender and swollen joint counts, lower PGA and PhGA, less pain and fatigue and lower HAQ. There were no statistically significant differences for CRP, ESR or the presence of depression/anxiety.
In multivariate analyses, BMI no longer predicted sustained remission, while lower baseline DAS28-CRP, tender and swollen joint counts, PGA, PhGA, pain and fatigue and HAQ remained associated with increased odds of sustained remission (Supplement 1.3).

Psychosocial predictors of sustained remission

In multivariate models, higher baseline scores on all SF-36 mental components were associated with increased odds of sustained remission (Table 2). In addition, the UCL-dimension of passive reacting negatively predicted sustained remission ($p = 0.037$), unlike other coping mechanisms. Finally, illness perceptions at baseline showed no statistically significant association with sustained remission, although a clear positive trend was seen for illness coherence ($p = 0.052$).

Table 1. Baseline characteristics of patients by sustained remission status.

	No sustained remission (n=255)	**Sustained remission (n=124)**	**p-value**
Demographic variables			
Age, years	52 (13)	52 (13)	0.77
BMI, kg/m^2	27 (4)	26 (4)	**0.039**
Women, n (%)	177 (69)	85 (69)	0.86
Smokers, n smoked ever (%)	146 (57)	63 (51)	0.15
RF positive, n (%)	170 (67)	82 (66)	0.92
ACPA positive, n (%)	168 (66)	81 (65)	0.91
Erosive disease, n (%)	65 (25)	32 (26)	0.95
Depression/anxiety, n (%)	8 (3)	4 (3)	0.96
Clinical variables			
DAS28-CRP	4.7 (1.2)	4.1 (1.2)	**<0.001**
TJC28, median (IQR)	9 (8)	5 (7)	**<0.001**
SJC28	7 (7)	5 (6)	**0.003**
PGA, mm (0-100)	58 (23)	49 (24)	**<0.001**
Pain, mm (0-100)	59 (24)	50 (24)	**<0.001**
Fatigue, mm (0-100)	52 (23)	40 (24)	**<0.001**
PhGA, mm (0-100)	55 (19)	47 (19)	**0.004**
ESR, mm/h, median (IQR)	25 (31)	21 (27)	0.12
CRP, mg/L, median (IQR)	26 (82)	15 (46)	0.08
HAQ (0-3), median (IQR)	1.1 (1.0)	0.8 (0.9)	**<0.001**

Results are reported as mean (SD) unless otherwise specified. *IQR = interquartile range, BMI = body mass index, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, DAS28 = Disease Activity Score in 28 joints, CRP = C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire*

Table 2. Psychosocial variables at baseline and week 16 predicting sustained remission.

	Baseline			Week 16		
Variable	**OR (95% CI)**	**Z-value**	**P-value**	**OR (95% CI)**	**Z-value**	**P-value**
SF-36						
SF-36MCS	1.33 (1.08 – 1.64)	2.61	**0.011**	1.84 (1.38 – 2.45)	4.15	**<0.001**
SF-36VT	1.25 (1.11 – 1.41)	3.67	**<0.001**	1.44 (1.25 – 1.65)	4.90	**<0.001**
SF-36SF	1.17 (1.07 – 1.28)	3.38	**<0.001**	1.42 (1.25 – 1.62)	5.15	**<0.001**
SF-36MH	1.23 (1.08 – 1.40)	3.02	**0.003**	1.48 (1.26 – 1.74)	4.50	**<0.001**
SF-36RE	1.06 (1.00 – 1.12)	2.04	**0.047**	1.19 (1.10 – 1.29)	4.16	**<0.001**
IPQ-R						
Illness coherence	1.06 (1.00 – 1.13)	1.92	0.052	1.11 (1.04 – 1.19)	2.73	**0.006**
Treatment control	1.07 (0.97 – 1.17)	1.30	0.188	1.18 (1.07 – 1.31)	2.65	**0.008**
Personal control	1.02 (0.96 – 1.09)	0.49	0.521	1.08 (1.00 – 1.17)	1.97	**0.048**
Emotional representations	0.98 (0.94 – 1.02)	-0.85	0.357	0.94 (0.90 – 0.98)	-2.77	**0.005**
Consequences	0.97 (0.92 – 1.02)	-1.18	0.277	0.88 (0.83 – 0.93)	-4.20	**<0.001**
UCL						
Active tackling	0.99 (0.92 – 1.06)	-0.24	0.841	1.07 (0.99 – 1.15)	1.38	0.156
Palliative reacting	0.98 (0.92 – 1.05)	-0.44	0.685	0.97 (0.91 – 1.05)	-1.09	0.303
Avoidance	0.98 (0.91 – 1.05)	-0.68	0.508	0.96 (0.89 – 1.04)	-1.35	0.175
Seeking social support	1.04 (0.97 – 1.12)	1.19	0.224	1.06 (0.98 – 1.15)	1.40	0.168
Passive reacting	0.92 (0.85 – 0.99)	-2.14	**0.037**	0.93 (0.86 – 1.01)	-1.76	0.086
Expression of emotion	1.01 (0.88 – 1.16)	0.32	0.727	1.10 (0.94 – 1.28)	0.99	0.340
Reassuring thoughts	0.98 (0.89 – 1.08)	-0.46	0.666	1.03 (0.93 – 1.13)	0.42	0.625

Results were obtained from multivariate logistic regression models with the specified variables as predictors and the odds of sustained DAS28-CRP-remission (from week 16 to week 104) as the dependent variable. All models contained age, sex, treatment arm, the presence of autoantibodies and 2C-DAS28 as covariates. *OR = odds ratio, CI = confidence interval; SF-36 = Short Form 36, MCS = mental component score, VT = vitality, SF = social functioning, MH = mental health, RE = role emotional; IPQ-R = Revised Illness Perception Questionnaire; UCL = Utrecht Coping List; 2C-DAS28 = two-component Disease Activity Score in 28 joints*

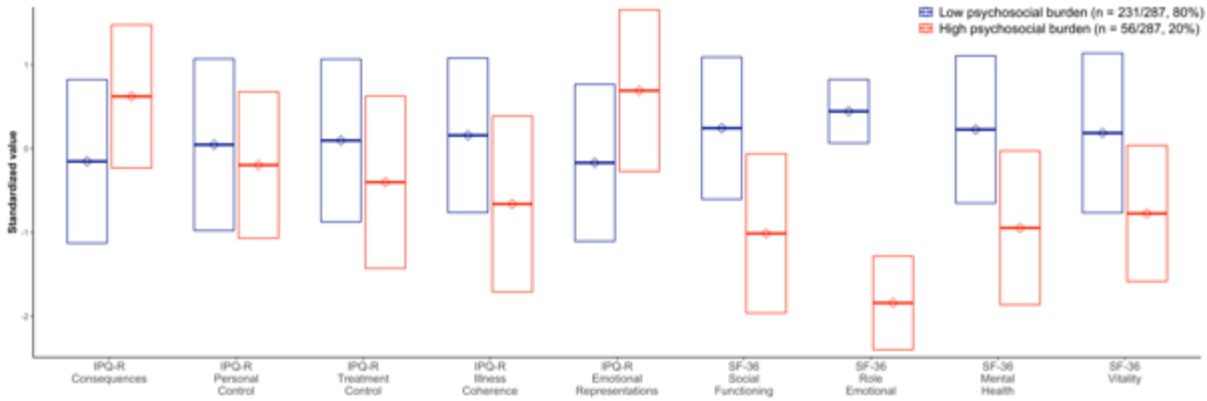
At week 16, better scores on all SF-36 mental components were associated with increased odds of sustained remission, with markedly higher odds ratios than at baseline (Table 2). Furthermore, contrary to baseline, more positive illness perceptions on all selected IPQ-R-dimensions at week 16 predicted sustained remission. However, at week 16, coping mechanisms were no longer significantly predictive. Therefore, the UCL was not included in the following analyses, and psychosocial wellbeing was defined in both the LPA and the CLPM by the four mental components of the SF-36 and all 5 available dimensions of the IPQ-R (Supplement 1.1B).

Psychosocial patient profiles

Figure 2 shows the results of LPA of patients in DAS28-CRP-remission at week 16 (n=287). Optimal model fit was achieved for 2 profiles with equal variances and covariances (Supplement 1.4). Although the normalized PRO-responses overlapped between profiles, the LPA distinguished between patients with low and high psychosocial burden despite being in remission. The low-psychosocial-burden profile consisted of 231/287 (80%) patients, the high-psychosocial-burden profile of 56/287 (20%) patients. Similar results were obtained when clustering patients in CDAI-remission. The limited number of patients in SDAI-remission and

ACR-EULAR Boolean remission did not allow for efficient clustering. However, when examining patients in low-disease-activity (LDA) (including remission) based on SDAI, results were similar to those for DAS28- and CDAI-remission.

Figure 2. Psychosocial profiles among patients in DAS28-CRP-remission at week 16, based on Latent Profile Analysis (LPA).



LPA of patients in DAS28-CRP-remission at week 16, based on 9 psychosocial variables. Crossbars represent mean ± SD. Optimal model fit was obtained for 2 profiles. The low-psychosocial-burden profile consisted of 231/287 patients (80%), the high-psychosocial-burden profile of 56/287 patients (20%). *IPQ-R = Revised Illness Perception Questionnaire; SF-36 = Short Form 36*

Sustainability of remission by psychosocial profile

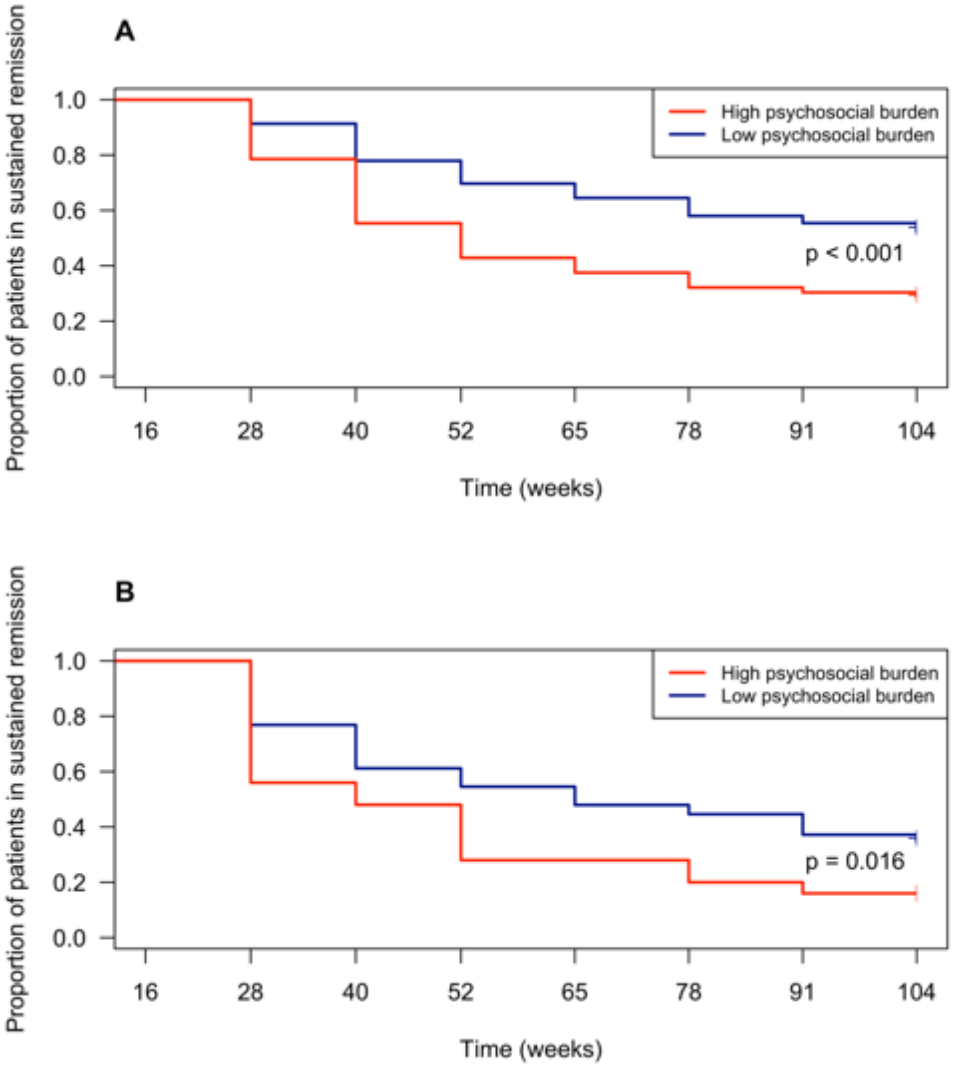
Among patients in DAS28-CRP-remission at week 16, the low-psychosocial-burden profile showed a significantly longer time to first loss-of-remission when compared with the high-psychosocial-burden group (HR 0.51 (0.35-0.73), $p < 0.001$) (Figure 3). Similar results were obtained for CDAI-remission (HR 0.54 (0.32-0.89), $p = 0.016$). Time-to-event tables are presented in Supplement 1.5. For patients in LDA or remission based on SDAI, results were comparable (Supplement 1.6).

The complexity of psychosocial wellbeing and disease activity

Although the factor structure for the latent construct of psychosocial wellbeing remained robust, factor loadings were allowed to change over time (configural invariance, Supplement 1.1). Specifically, factor loadings for the IPQ-R-dimensions increased over time from baseline, implying a gradually increasing influence of illness perceptions on psychosocial wellbeing.

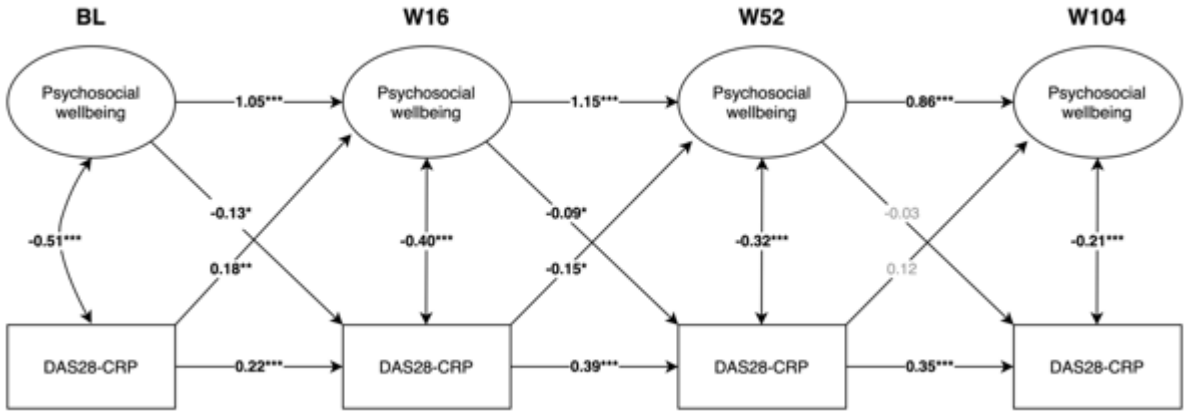
In the CLPM, better psychosocial wellbeing predicted lower DAS28-CRP at each following time point, except between weeks 52 and 104 (Figure 4). Moreover, DAS28-CRP negatively predicted future psychosocial wellbeing after similar adjustments. However, contrary to other time points, this effect was positive between baseline and week 16, with higher DAS28-CRP at baseline associated with better week 16 wellbeing.

Figure 3. Kaplan-Meier-curves for retention of DAS28-CRP-remission (A) or CDAI-remission (B) by psychosocial profile of patients in remission at week 16.



Profiles resulted from LPA of patients in remission at week 16 based on DAS28 (A) or CDAI (B). Significance was assessed by Cox-proportional hazards regression adjusting for age, sex, treatment arm, and autoantibody status. *LPA = Latent Profile Analysis, DAS28-CRP = Disease Activity Score in 28 joints, CDAI = Clinical Disease Activity Index*

Figure 4. Cross-lagged panel analysis of the association between psychosocial wellbeing and DAS28-CRP.



Displayed are three types of relations: within-time correlations (vertical arrows), within-construct or stability relations (horizontal arrows), and cross-lagged relations (diagonal arrows). Numbers shown are standardized regression coefficients. Paths of the observed psychosocial variables and covariates (age, sex, treatment arm and autoantibody status) were not shown for clarity.
** = p < 0.05, ** = p < 0.01, *** = p < 0.001*

DISCUSSION

Our results suggest that psychosocial wellbeing and illness perceptions, from as early as treatment initiation, are associated with the probability of achieving sustained remission in early RA, and that the relationship between disease activity and psychosocial factors is complex and disease-phase specific.

These results are in line with previous studies that have shown an association between mental health in early RA and the response to treatment (38). Interestingly, this is not limited to early disease, since mental health has also been shown to predict flares in patients with established RA during treatment tapering (39). Furthermore, conditions like fibromyalgia syndrome are linked with a higher prevalence of psychological vulnerability factors, including neuroticism, over resilience factors like optimism (40), and fibromyalgia-like traits such as pain catastrophizing and somatization have similarly been associated with impaired outcomes in RA (41,42). Nonetheless, the existing literature on RA has mainly focused on the influence of anxiety and depression on outcomes (43,44). To our knowledge, our approach is unique because we additionally assessed illness perceptions and coping mechanisms, and applied methods, like LPA and CFA, that studied the behavior and influence of multiple psychosocial indicators as one overarching construct, rather than as individual factors. Moreover, previous research has largely been unable to unravel the complex interplay between psychosocial and physical factors, both of which may influence each other in either direction. Our study not only reports a variety of longitudinally collected psychosocial indicators, but also applied methods that provide more information on the directionality of these relations. Specifically, our results suggest that psychosocial aspects and disease activity exert a complex, bidirectional influence on each other, with better psychosocial wellbeing predicting lower future disease activity and vice versa. Interestingly however, this relationship appeared to function differently during the earliest disease stages, with higher disease activity at baseline being associated with better wellbeing after 4 months in our study. While somewhat counterintuitive, this suggests a stronger beneficial effect of treatment on psychosocial wellbeing in those patients who initially

had the highest disease burden. Similarly, this finding might imply that psychosocial issues not directly related to disease activity are less responsive to antirheumatic treatment.
Of note, temporal relationships between wellbeing and disease activity were significant only during the first year of treatment. However, this is likely confounded by the considerably longer interval between assessments of psychosocial wellbeing during the trial's second year, possibly allowing for unrelated influences on wellbeing in the interim.
To add further insight into the complex interplay between psychosocial wellbeing and disease activity, our results also show that psychosocial wellbeing may differ among patients even when in remission, with approximately 20% of patients in DAS28-CRP- or CDAI-remission after 4 months of treatment showing markedly worse psychosocial outcomes at that time. The observation that these patients then tended to lose remission earlier than patients with a lower psychosocial burden further underlines the need for a continued attention for psychosocial wellbeing, even when clinical treatment targets are met. These findings add to those of a recent study that identified similar subgroups with either positive or negative illness perceptions among a mixed cohort of patients with early and established RA (45). However, our observation of such subgroups among patients in remission further emphasizes that psychosocial unmet needs are frequent and relevant even when the disease appears well-controlled. Therefore, future research should aim to develop tools to help clinicians to timely identify patients with such unmet needs in clinical practice.
Our results also provide a unique insight into the evolution of illness perceptions during the early stages of RA. Before treatment, illness perceptions appeared to be highly heterogeneous among patients, and were not convincing baseline predictors of sustained remission. At week 16, however, a distinct cluster of patients could be identified who exhibited more negative illness perceptions despite being in remission. Furthermore, all included IPQ-R-dimensions at week 16 were significantly associated with sustained remission, and the relative contribution of illness perceptions to psychosocial wellbeing in the CFA also increased over time. These findings suggest that illness perceptions need time to evolve, and gain in importance once the first treatment effects have taken hold. Indeed, it has previously been shown that a person's beliefs about their illness can evolve over time, because of changes in symptoms and efforts to cope with these (46). Moreover, a recent longitudinal study from the UK identified three distinct trajectories of evolving illness perceptions during the first treatment year in patients with early RA (47). Our results add to this by illustrating that a distinct subgroup of patients with negative illness perceptions can even be identified among patients who are in remission, and that patients belonging to this subgroup have less favorable clinical outcomes.
Of additional note, illness coherence in our study appeared to be more strongly associated with long-term disease control than other dimensions of illness perception before treatment initiation. This suggests that a correct understanding of the disease early on is key for successful management of RA, while the heterogeneity in other IPQ-R-dimensions might more strongly reflect temporary uncertainties in the early phase of the disease, which to many patients remains a destabilizing time. It is only later, after experiencing a satisfactory treatment response, that illness perceptions appear to become more uniformly shaped in most patients.
Our study has some limitations. First, we defined remission based on DAS28-CRP for our primary outcomes. A pitfall of DAS28-based remission is that it allows for some residual disease activity (48) compared to the more stringent ACR-EULAR Boolean remission or index definitions (32). However, we opted for DAS28-CRP-remission as primary outcome because it was also the primary outcome for the CareRA-trial's main analyses, and treatment during the trial was adapted when the minimal target of DAS28-LDA was not achieved. Furthermore, in our sensitivity analysis, defining remission based on CDAI produced comparable results to DAS28-based remission, which was also the case for SDAI-LDA. Regrettably, the limited number of patients achieving a sustained state of Boolean or SDAI-remission did not allow for

results to be reproduced for these definitions. Therefore, our results warrant further confirmation in a larger number of patients in stringent remission. Furthermore, we should note that our choice of sustained remission as the primary outcome, rather than remission at one given time, might have reduced the discriminatory power of our analyses. For instance, patients with a short-term flare-up in PGA or CRP, which might result from issues other than RA, did not achieve sustained remission according to our definition. To illustrate this, the number of patients achieving sustained CDAI-remission in our study was markedly higher than for sustained SDAI-remission, suggesting that some patients lost SDAI-remission at least once because of solitary CRP-increases unrelated to RA disease activity.

As a second limitation, a current diagnosis or treatment of depression/anxiety was surprisingly not associated with sustained remission in our study. These results are likely hampered by the relatively few patients with depression or anxiety in our cohort, when compared to other early RA cohorts. As a likely explanation, psychiatric co-morbidities were not screened for by a designated questionnaire but defined by anamnesis of medical history and review of medication. Consequently, it is likely that depression/anxiety were underreported in our study.

Third, missing data were imputed with multiple imputation, which assumes missingness at random. Before making this assumption, several exploratory analyses were conducted to discern systematic patterns of missingness. Moreover, efforts were made during the trial to minimize missingness, including frequent monitoring of data and specific participant education. In addition, participants who were lost to follow-up in CareRA were spread evenly across treatment arms, and reasons for discontinuation were mostly practical (18).

Finally, this study is a post-hoc analysis of a randomized controlled trial. Therefore, definite conclusions cannot be made about the causality of associations, and the number of patients in our cohort is rather limited when compared to large registry studies. However, the pragmatic nature of the CareRA-trial provided an early RA cohort that is very representative for daily practice. Furthermore, the extensive set of PROs collected at different times during early disease is a clear strength and allows for a unique translation of psychosocial burden and its clinical impact.

Conclusion

Indicators of suboptimal psychosocial wellbeing during early disease were associated with a lower probability of achieving and maintaining remission in an early RA clinical trial cohort, despite intensive treat-to-target therapy. Temporal relationships between disease activity and psychosocial wellbeing appeared to be complex, bidirectional and disease-phase dependent. Crucially, 20% of patients still exhibited worse psychosocial outcomes and more negative illness perceptions despite being in early clinical remission, and these patients tended to lose remission earlier than patients with more positive psychosocial profiles. Moreover, illness perceptions appeared to become more clinically relevant after 4 months of treatment, suggesting that the stressful period around diagnosis might not be the ideal time to evaluate psychosocial disease impact. Future research should focus on strategies to timely identify patients with unmet psychosocial needs in clinical practice and on person-centered interventions to target these needs.

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Chapter 2

Fatigue and its evolution under treatment for RA: understanding the roles of inflammation, perceived disease impact and early treatment response

This chapter was published as:
Doumen M, Pazmino S, Bertrand D, De Cock D, Joly J, Westhovens R, Verschueren P. Longitudinal trajectories of fatigue in early RA: the role of inflammation, perceived disease impact and early treatment response.
Ann Rheum Dis. 2022; 81(10):1385-1391.

ABSTRACT

Objectives: Fatigue is common in rheumatoid arthritis (RA). We aimed to explore its longitudinal course, predictors, and association with disease activity in early RA.

Methods: Data came from the 2-year treat-to-target trial Care in early RA (CareRA) and its 3-year extension. Fatigue was measured on visual analogue scale, Multidimensional Fatigue Inventory, and Short Form-36 (SF-36) Vitality. Longitudinal fatigue trajectories were identified with multivariate growth mixture modelling. Early predictors of fatigue, and the association of fatigue and its trajectories with disease activity and clinical/psychosocial outcomes, were studied with linear mixed models and multilevel mediation.

Results: We included 356 and 244 patients in 2-year and 5-year analyses, respectively. Four fatigue trajectories were identified: Rapid, Gradual, and Transient improvement, and Early Deterioration, including 10%, 14%, 56%, and 20% of patients. Worse pain, mental health and emotional functioning were seen in the Early Deterioration group. Higher pain, patient global assessment (PGA) and disability (HAQ), lower SF-36 mental components, and fewer swollen joints at baseline predicted higher fatigue over 5 years, while early disease remission strongly improved 5-year fatigue. The association between SDAI and fatigue was mediated by PGA, pain, mental health, and sleep quality.

Conclusions: Although fatigue evolves dynamically over time in early RA, most patients do not achieve sustained fatigue improvement despite intensive DMARD-therapy. Higher 5-year fatigue levels were seen in patients with more perceived disease impact and fewer swollen joints at baseline. Conversely, early inflammatory disease control strongly improved long-term fatigue, pointing towards an early window of opportunity to prevent persistent fatigue.

INTRODUCTION

Fatigue is common in rheumatoid arthritis (RA) and a major challenge in its management(1). Fatigue is an experience of severe tiredness or exhaustion not clearly caused by excessive energy expenditure(2). An estimated 10-20% of the general population regularly report significant fatigue, attributable to both physical and psychosocial causes(3–5). This burden is even more apparent in the rheumatic diseases, and 40-80% of patients with RA are affected by severe fatigue(6,7). Patients experience fatigue as overwhelming and unpredictable, inciting a vicious circle that strongly impacts quality of life(8). Moreover, people suffering from RA consider fatigue a crucial disease outcome and consistently rate it among the primary treatment goals in both established and early disease(9–11). Consequently, fatigue has long been recognized as an essential outcome to assess in RA-related trials(12,13).

Although complementary care strategies like nurse-led care(14,15), peer mentoring(16) and cognitive behavioural therapy(17) could be beneficial, assessing and managing RA-related fatigue remains challenging. Fatigue is a multidimensional symptom whose causes, experience and impact are unique for each individual(18). Therefore, it is ideally assessed with multidimensional instruments(19). However, most studies measure fatigue on a visual analogue scale (VAS), which, despite being a reliable alternative(20), might lack detail about underlying mechanisms. To comprehensively assess RA-related fatigue, understanding its root causes is crucial. Although inflammation could be involved by influencing neurotransmitters(21), the relationship between RA disease activity and fatigue is complex and confounded by cognitive and psychosocial aspects(18). For instance, while fatigue can improve with disease-modifying antirheumatic drugs (DMARDs)(22), many patients still experience fatigue despite inflammatory disease control(23–25). More insight into contributors of persistent fatigue could highlight mechanisms other than inflammation and support management of this burden. Moreover, given its unpredictability, RA-related fatigue might evolve differently over time across specific patient subgroups(26–28).

Studies on contributors of RA-related fatigue should therefore include multidimensional fatigue measures, assessed longitudinally, starting in early disease and with multivariate methods that account for confounders(29). Moreover, contributors should be differentiated into either predisposing factors to support early identification of at-risk patients, or time-dependent associated factors, like inflammation, that could be modifiable with interventions(5). We aimed to identify predisposing and associated factors of RA-related fatigue by examining the longitudinal trajectory of multidimensional fatigue in early RA.

METHODS

Study design

Data were obtained from the Care in early RA (CareRA) trial and its extension CareRA-plus. CareRA was a 2-year, investigator-initiated, randomised controlled trial comparing several DMARD-regimens with/without glucocorticoid-bridging in DMARD-naïve patients with early RA. CareRA-plus was its 3-year observational extension. Details on the trial design have been published elsewhere (also see Supplement 2.1)(30,31). All participants completing CareRA were eligible for CareRA-plus. Protocols were approved by the participating centres' medical ethics committees, and all participants provided written informed consent.

Patient and public involvement

Although patients were not actively involved in designing the trial, patient-reported outcomes (PROs) to collect were selected based on daily contacts between the investigators and patients with RA, and these outcomes' relevance in early RA was confirmed in a qualitative study(9).

Outcomes

Assessment at screening included demographic characteristics, routine radiographs, rheumatoid factor and/or anti-citrullinated peptide antibodies, and comorbidities scored on the Rheumatic Diseases Comorbidity Index (RDCI). Clinical assessments during follow-up included tender/swollen joint counts (TJC28/SJC28), patient's/physician's global assessment of disease (PGA/PhGA), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). SDAI was derived as primary composite measure of disease activity(32). In addition, participants completed the Health Assessment Questionnaire (HAQ) and VAS for pain and fatigue at every visit, and the Short Form-36 (SF-36), Revised Illness Perception Questionnaire (IPQ-R) and Pittsburgh Sleep Quality Index (PSQI) at baseline and week 16, 52 and 104(33–35).

Starting from year 2, participants were assessed 6-monthly until year 5. Assessments during this phase were identical to the first 2 years, but PROs were limited to the HAQ and VAS for pain and fatigue.

Fatigue

Multiple measures of fatigue were collected, including a VAS (0-100) at every visit. Additionally, SF-36 Vitality (0-100, higher score implies less fatigue) and the Multidimensional Fatigue Inventory (MFI) were recorded at baseline and week 16, 52 and 104(36). The MFI is a 20-item questionnaire covering 5 dimensions of fatigue: General Fatigue (GF), Physical Fatigue (PF), Mental Fatigue (MF), Reduced Motivation (RM), and Reduced Activity (RA). Higher scores (4-20) indicate more fatigue.

Statistical analysis

Based on conceptual knowledge and data exploration, missingness (15% total) was assumed to be at random and handled with multiple imputation (m=20). Results were pooled using Rubin's rules wherever possible(37). Descriptive statistics were reported as means (SD) or proportions, and measures of fatigue at baseline were compared with Spearman correlation.

Before investigating distinct fatigue trajectories, we first studied the group-level evolution of fatigue (VAS) over time with linear mixed models (LMMs) including only participants with available 5-year data (Supplement 2.2A).

Based on these models, and because multidimensional fatigue measures were available during only this timeframe, the first 2 years were chosen to study longitudinal fatigue trajectories. We constructed a multivariate growth mixture model (GMM) following a three-step approach(38), with participant-specific random intercepts, and including as dependent variables the five dimensions of the MFI, SF-36 Vitality, and fatigue VAS. GMMs attempt to identify distinct classes of individuals with similar evolutions of one or more outcomes over time, while including random effects accounting for inter-individual, within-trajectory variance(39). Models were constructed for 2-5 trajectories with linear, quadratic, cubic and spline functions to model time. The optimal model was selected based on model fit statistics(40), and models deriving classes of <10% of participants were excluded to avoid overfitting (Supplement 2.3).

Second, after identifying trajectories, the longitudinal association of trajectory membership with clinical/psychosocial outcomes was studied with LMMs adjusted for age, sex, treatment type, autoantibodies, RDCI, and time-varying SDAI. Confidence intervals were derived through bootstrapping (5000 iterations of random sampling with replacement).

Third, baseline predictors of fatigue (VAS) over 2 and 5 years were studied with multivariable LMMs including participant-specific random intercepts and adjusted for age, sex, treatment type, and time. This method was chosen over predicting trajectory membership because it allowed to predict fatigue over the full 5-year follow-up. First, all candidate predictors were included simultaneously in an initial multivariable model and subsequently excluded through

a backwards-stepwise procedure based on predictors' statistical significance, model fit statistics, and conceptual reasons. Baseline PGA, PhGA, pain and HAQ were studied in separate models because of collinearity (Spearman r>0.60). Additionally, early treatment response was studied as a candidate predictor, defined as "early remission with sustained control", "secondary relapse", "delayed remission", or "non-remission" based on whether remission (SDAI ≤3.3) was achieved by week 16 with/without relapse before year 2. Considering treat-to-target recommendations, relapse was defined for this purpose as loss of low-disease-activity (SDAI >11)(41). Finally, the time-varying association of fatigue with clinical/psychosocial variables was studied in similar LMMs, adjusting for age, sex, treatment type, and time. The time-varying association between SDAI and fatigue (VAS) was then studied in more detail with a multilevel mediation analysis, including these clinical/psychosocial variables as candidate mediators and clustering within participants.
P-values were adjusted for multiple comparisons with Bonferroni-Holm correction where applicable, and p-values <0.05 were considered statistically significant. All analyses were carried out in R 4.0.3 (packages: *mice*, *lcmm*, *lme4*, *lavaan*, and *lavaanPlot*).

RESULTS
In total, 379 patients were included in CareRA, of which 23 were excluded from this analysis because they did not complete the baseline MFI (Supplement 2.4). All remaining 356 participants were included in the 2-year analyses after imputation. Of these, 244 entered CareRA-plus and were included in the 5-year analyses. Baseline characteristics of the 2-year and 5-year study populations were similar (Table 1).

Baseline fatigue
On average, participants reported moderate levels of fatigue at baseline, with a mean of 48/100 on both VAS and SF-36 Vitality, and scores of 10-14/20 on the different MFI-subscales. VAS fatigue was moderately to strongly correlated with more complex measures of fatigue (Supplement 2.5). However, it correlated less convincingly with measures of more cognitive fatigue, such as MFI-subscales Mental Fatigue (r=0.33), Reduced Motivation (r=0.36) and Reduced Activity (r=0.39).

Group-level fatigue evolution over 5 years
On average, fatigue (VAS) improved rapidly during the first 16 weeks, before reaching seemingly stable values (Supplement 2.2B). However, there continued to be significant changes over time at both the group and inter-individual level until year 2 (Supplement 2.2C). Between years 2 and 5, fatigue no longer changed significantly, implying that 5-year fatigue outcomes were mainly determined during the first 2 years of the trial.

Table 1. Baseline characteristics of participants included in analyses.

	2-year data available (n = 356)	**5-year data available (n = 244)**
Age, years	52 (13)	53 (13)
Women, n (%)	243 (68)	164 (67)
BMI, kg/m^2	26 (4)	27 (4)
RF-positive, n (%)	241 (66)	169 (69)
ACPA-positive, n (%)	237 (65)	176 (72)
Erosive disease, n (%)	95 (27)	67 (27)
RDCI (0-9)	0.8 (1.1)	0.9 (1.1)
Symptom duration, months	8 (12)	8 (13)
Fatigue		
VAS, mm (0-100)	48 (24)	47 (24)
MFI General Fatigue (0-20)	14 (4)	14 (4)
MFI Physical Fatigue (0-20)	14 (4)	14 (4)
MFI Mental Fatigue (0-20)	10 (4)	10 (4)
MFI Reduced Activity (0-20)	13 (4)	13 (4)
MFI Reduced Motivation (0-20)	11 (4)	11 (4)
SF-36 Vitality (0-100)	48 (20)	48 (20)
Clinical variables		
SDAI	37 (32)	38 (33)
DAS28-CRP	4.5 (1.3)	4.5 (1.3)
TJC28 (0-28)	9 (6)	9 (6)
SJC28 (0-28)	7 (5)	7 (5)
PGA, mm (0-100)	55 (24)	55 (23)
Pain, mm (0-100)	56 (24)	55 (23)
PhGA, mm (0-100)	52 (19)	50 (18)
CRP, mg/L	10 (24)	12 (26)
ESR, mm/h	30 (23)	31 (24)
HAQ (0-3)	1.0 (0.7)	1.0 (0.7)
SF-36 PCS (0-100)	33 (10)	34 (10)
SF-36 MCS (0-100)	47 (12)	47 (12)

Results are reported as mean (SD) unless otherwise specified. *BMI = body mass index, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, RDCI = Rheumatic Diseases Comorbidity Index, VAS = Visual Analogue Scale, MFI = Multidimensional Fatigue Inventory, SF-36 = Short Form-36, SDAI = Simple Disease Activity Index, DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire, PCS = Physical Component Score, MCS = Mental Component Score*

Table 2. Association of fatigue trajectory with outcomes over 2 years (A) and 5 years (B).

A.	**Gradual improvement (n = 50/356, 14%)**		**Transient improvement (n = 198/356, 56%)**		**Early deterioration (n = 71/356, 20%)**	
Outcome	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**
SDAI	0.66 (-2.61 to 3.93)	0.69 (0.96)	-0.10 (-0.07 to 0.04)	0.94 (0.94)	0.42 (-0.36 to 1.20)	0.79 (0.79)
Pain (VAS)	3.01 (-2.93 to 8.95)	0.32 (0.96)	6.57 (1.69 to 11.45)	***0.008 (0.06)***	9.82 (4.19 to 15.45)	**< 0.001 (0.004)**
HAQ	0.12 (-0.04 to 0.28)	0.14 (0.58)	0.08 (-0.06 to 0.22)	0.26 (0.53)	0.08 (-0.08 to 0.24)	0.27 (0.55)
SF-36 MH	-8.98 (-14.92 to -3.04)	**0.003 (0.018)**	-5.94 (-10.76 to -1.12)	***0.016 (0.10)***	-9.42 (-14.93 to -3.91)	**< 0.001 (0.005)**
SF-36 SF	-12.09 (-19.40 to -4.78)	**0.001 (0.007)**	-5.01 (-11.09 to 1.07)	0.11 (0.53)	-8.56 (-15.48 to -1.64)	***0.015 (0.06)***
SF-36 RE	-12.44 (-24.08 to -0.80)	0.04 (0.18)	-7.77 (-17.45 to 1.91)	0.12 (0.53)	-14.87 (-25.89 to -3.85)	**0.008 (0.04)**
PSQI global	0.66 (-0.69 to 2.01)	0.33 (0.96)	0.82 (-0.28 to 1.92)	0.15 (0.53)	1.10 (-0.15 to 2.35)	0.086 (0.26)
B.	**Gradual improvement (n = 40/244, 16%)**		**Transient improvement (n = 131/244, 54%)**		**Early deterioration (n = 52/244, 21%)**	
Outcome	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**
SDAI	-0.12 (-3.47 to 3.23)	0.95 (1.00)	-0.53 (-3.45 to 2.39)	0.72 (0.72)	0.64 (-2.61 to 3.89)	0.70 (0.70)
Pain (VAS)	1.87 (-5.48 to 9.22)	0.62 (1.00)	5.10 (-4.94 to 15.14)	0.12 (0.35)	9.77 (2.64 to 16.90)	**0.007 (0.021)**
HAQ	0.08 (-0.14 to 0.29)	0.47 (1.00)	0.11 (-0.09 to 0.31)	0.26 (0.52)	0.13 (-0.09 to 0.35)	0.25 (0.50)

Results were obtained from multivariate linear mixed models (LMM) with the reported outcome as the dependent variable and fatigue trajectory as the predictor (rapid improvement trajectory as the reference class). The SF-36 vitality dimension was not studied as an outcome since it was included as a determinant of the fatigue trajectories. All models were adjusted for age, sex, treatment arm, autoantibody status, SDAI, and RDCI as possible confounders. Confidence intervals were derived through bootstrapping (5000 iterations of random sampling with replacement).

* P-value adjusted for multiple comparisons with Bonferroni-Holm-correction. Since correction was applied separately for each trajectory and for 2 and 5-year outcomes, up to 7 p-values were considered in these adjustments.

SDAI = Simple Disease Activity Index, CRP = C-reactive protein, VAS = Visual Analogue Scale, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, MH = mental health, SF = social functioning, RE = emotional role functioning, PSQI = Pittsburgh Sleep Quality Index

Longitudinal fatigue trajectories and associated factors

Growth mixture analysis identified four latent trajectory classes for the evolution of multidimensional fatigue during the first 2 years (Figure 1). The Rapid Improvement group (n=37/356, 10%) showed a vast improvement in all fatigue measures over the first 16 weeks, before reaching stable values around week 52. In the Gradual Improvement trajectory (n=50/356, 14%), all measures of fatigue improved more steadily until week 104. Most participants (n=198/356, 56%) were characterized by a Transient Improvement in fatigue, where fatigue decreased over the first months, but any net improvement was lost by week 52. Finally, 20% of participants showed an Early Deterioration (n=71/356) of fatigue over the first 16 weeks, before reaching stable scores at higher levels than baseline.

Compared to the Rapid Improvement group, participants with an Early Deterioration trajectory reported higher pain (VAS) over both 2 and 5 years of follow-up and had significantly lower scores on SF-36 Mental health and Emotional role functioning after adjusting for confounders like SDAI and comorbidities (Table 2). Similarly, the Gradual Improvement group scored worse than Rapid Improvers on SF-36 Mental health and Social functioning over 2 years. Similar trends suggested worse outcomes for Transient Improvers, although these differences were not significant after adjusting for multiple comparisons. No differences were found between trajectories for SDAI, HAQ, or PSQI.

Predictors and associated factors of long-term fatigue

During variable selection, no predisposing effects on fatigue over both 2 and 5 years were found for autoantibodies, RDCI, symptom duration, erosive disease, or BMI (Supplement 2.6). Similarly, age, sex, and treatment type did not predict long-term fatigue but were kept in the final models as covariates.

In these final models, higher PGA, pain and HAQ, and lower SF-36 MCS at baseline were associated with more fatigue over both 2 and 5 years of follow-up (Table 3). Furthermore, higher 2-year and 5-year fatigue levels were seen in patients with a lower baseline SJC28 and in patients with delayed (n=98) or non-remission (n=121) rather than early remission with sustained control (n=85). Among patients with early remission, no difference in 2-year or 5-year fatigue was found with sustained control compared to secondary relapse (n=52).

In the time-varying LMMs, only pain, mental health and sleep quality were independently associated with fatigue over time (Supplement 2.7). Adjusted for other associated factors and multiple comparisons, SDAI, HAQ, IPQ-R, and the remaining SF-36 psychosocial dimensions were not associated with fatigue over time.

Moreover, the association between SDAI and fatigue (VAS) was fully mediated by PGA, pain, mental health, and sleep quality (Figure 2). Specifically, although there was a significant positive association between SDAI and VAS (standardized ß=0.39[0.31 to 0.46]), this association was fully explained by PGA (ß=0.19[0.10 to 0.28]) and pain (ß=0.18[0.11 to 0.26]), and to a lesser extent by SF-36 Mental health (ß=0.04[0.02 to 0.06]) and PSQI global score (ß=0.02[0.00 to 0.04]) (Supplement 2.8).

Table 3. Baseline and early predictors of fatigue (VAS) levels over time.

	Baseline – year 2 (n = 356)		**Baseline – year 5 (n = 244)**	
Baseline predictors	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**
BMI (kg/m^2)	0.43 (0.04 to 0.82)	***0.036 (0.14)***	-	-
PGA (0-100)	0.22 (0.14 to 0.30)	**< 0.001 (< 0.001)**	0.15 (0.05 to 0.25)	**0.002 (0.01)**
PhGA (0-100)	0.21 (0.09 to 0.33)	**0.001 (0.007)**	0.10 (-0.05 to 0.25)	0.20 (0.40)
SJC (0-28)	-0.64 (-1.13 to -0.15)	**0.010 (0.05)**	-0.91 (-1.56 to -0.26)	**0.006 (0.04)**
TJC (0-28)	0.18 (-0.25 to 0.61)	0.42 (0.84)	0.59 (0.04 to 1.14)	0.038 (0.15)
CRP (mg/dL)	0.02 (-0.06 to 0.10)	0.56 (0.84)	0.00 (-0.08 to 0.09)	0.92 (0.92)
Pain (0-100)	0.21 (0.13 to 0.29)	**< 0.001 (< 0.001)**	0.17 (0.08 to 0.26)	**< 0.001 (0.004)**
HAQ (0-3)	5.22 (2.18 to 8.26)	**0.001 (0.007)**	4.67 (1.08 to 8.26)	**0.011 (0.05)**
SF-36 MCS (0-100)	-0.36 (-0.52 to -0.20)	**< 0.001 (< 0.001)**	-0.42 (-0.60 to -0.24)	**< 0.001 (< 0.001)**
Treatment response$^{\perp}$				
Secondary relapse (n=52/356)	5.24 (-0.39 to 10.87)	0.07 (0.21)	5.37 (-1.04 to 11.78)	0.10 (0.30)
Delayed remission (n=98/356)	9.87 (4.91 to 14.83)	**< 0.001 (< 0.001)**	10.15 (4.39 to 15.91)	**< 0.001 (0.005)**
Non-remission (n=121/356)	21.66 (17.15 to 26.17)	**< 0.001 (< 0.001)**	20.89 (15.48 to 26.30)	**< 0.001 (< 0.001)**

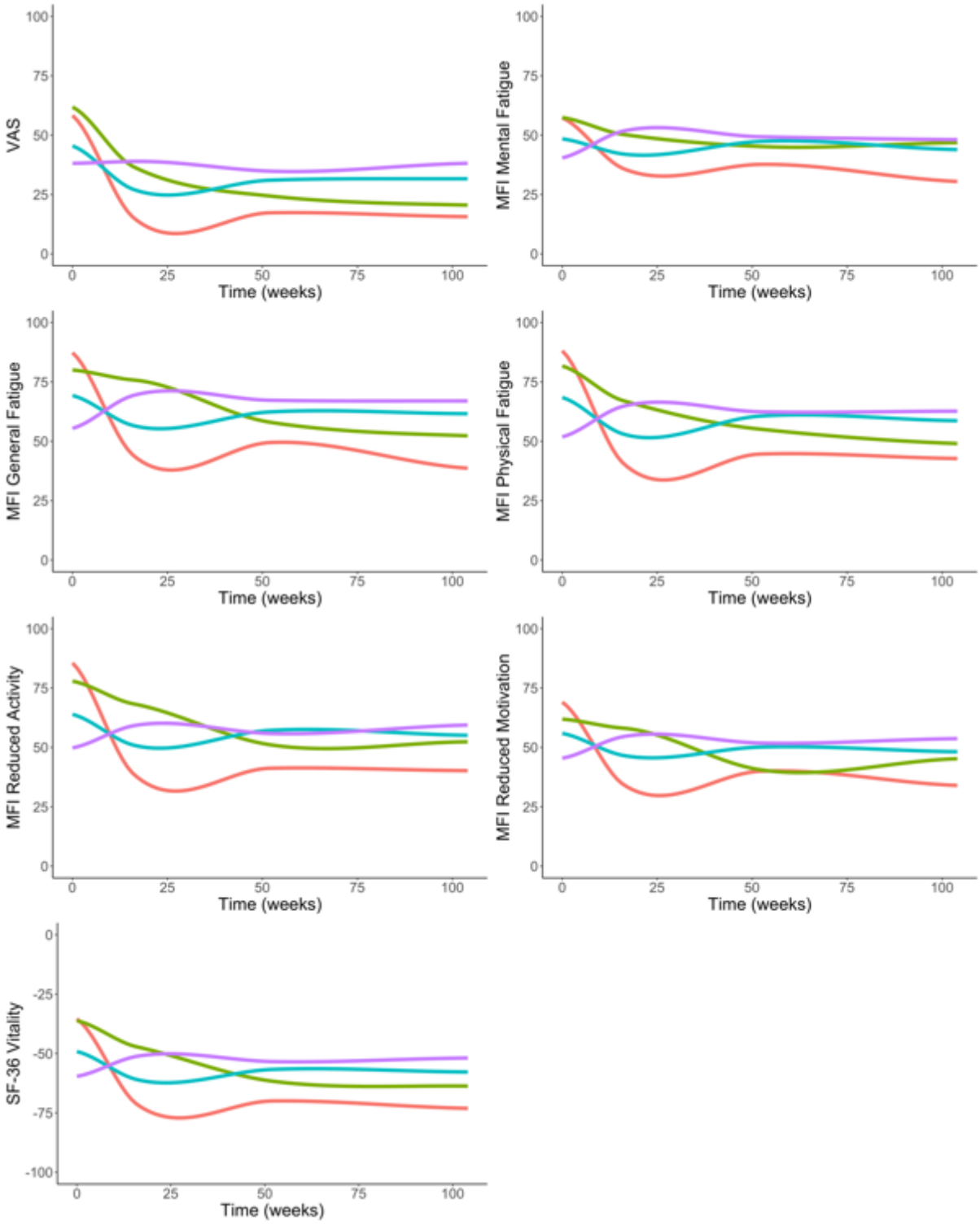
Results were obtained from multivariable linear mixed models (LMMs) with fatigue (VAS) as the dependent variable and a participant-specific random intercept. Fatigue (VAS) and SF-36 Vitality were not studied as baseline predictors since these models were intended to study average fatigue levels over time rather than fatigue evolution relative to baseline. PGA, PhGA, pain, and HAQ were included in separate models because of collinearity (Spearman r>0.60). All models were adjusted for age, sex, treatment type, and time as confounders.

* P-value adjusted for multiple comparisons with Bonferroni-Holm-correction. Since correction was applied separately for 2 and 5-year outcomes, up to 12 p-values were considered in these adjustments.

$^{\perp}$ Early remission with sustained control as reference category (n=85/356). This model was adjusted for age, sex, treatment type, time, and baseline SDAI.

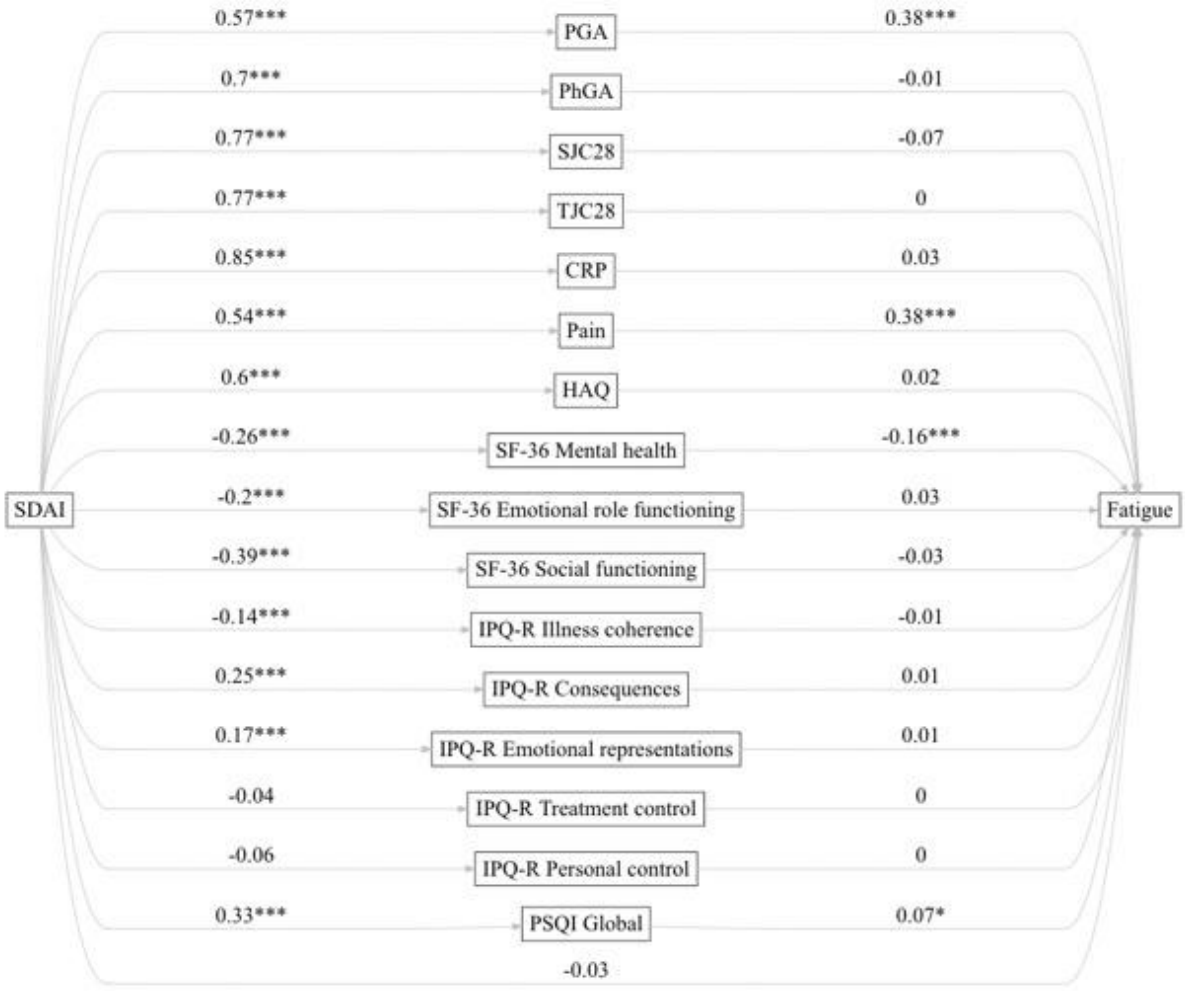
BMI = Body Mass Index, PGA = patient's global assessment, PhGA = physician's global assessment, SJC = swollen joint count, TJC = tender joint count, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, SF-36 MCS = Short Form-36 Mental Component Score, SDAI = Simple Disease Activity Index

Figure 1. Latent trajectories of fatigue evolution over the first 2 years in CareRA (n = 356).



Red = Rapid Improvement (10%); Green = Gradual Improvement (14%); Blue = Transient Improvement (56%); Purple = Early Deterioration (20%). Trajectories were derived through multivariate growth mixture modelling with participant-specific random intercepts and including as dependent variables the five dimensions of the MFI, SF-36 Vitality, and fatigue VAS. All fatigue outcomes were standardised (0-100) for comparability. *VAS = Visual Analogue Scale, MFI = Multidimensional Fatigue Inventory, SF-36 = Short Form-36*

Figure 2. Mediation analysis of the association between SDAI and fatigue (VAS) over time.



Results were obtained from multilevel mediation analysis studying the association between SDAI and fatigue (VAS) across baseline, week 16, 52 and 104, with participant-specific random intercepts (n = 356). Reported are the standardized regression coefficients with indicators of significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$).
VAS = Visual Analogue Scale, SDAI = Simple Disease Activity Index, PGA = patient's global assessment, PhGA = physician's global assessment, SJC28 = swollen joint count in 28 joints, TJC28 = tender joint counts in 28 joints, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, IPQ-R = Revised Illness Perception Questionnaire, PSQI = Pittsburgh Sleep Quality Index

DISCUSSION

To our knowledge, this study is the first to describe in detail the longitudinal course of fatigue in early RA with rigorous, multivariate growth modelling methods and based on multidimensional measures of fatigue. Our results suggest that fatigue evolves dynamically during the first treatment months but often remains a persistent symptom, with less than 25% of patients experiencing lasting improvements despite intensive DMARD-treatment. Remarkably, one-in-five patients in our study even experienced worsening fatigue during early treatment, and these patients also reported more pain and impaired mental health over time. Moreover, higher scores on pain, disability, PGA, and impaired mental health at baseline were associated with persistently higher fatigue over 5 years of follow-up. However, the strongest predictor of long-term fatigue in our study was early achievement of disease remission, even when disease activity later relapsed. Despite this, mediation analysis suggested that the relationship between disease activity and fatigue is complex and fully mediated by the PGA, pain, mental health, and sleep quality, implying a mainly indirect relation between fatigue and inflammation.

Several studies in early RA cohorts have suggested that the first treatment months are the most influential to determining long-term fatigue. Although long-term follow-up studies have identified improvements in group-level fatigue during the first year of treatment, fatigue remained largely unchanged during subsequent years(42,43). In a recent publication from the CATCH-cohort, the average improvement in fatigue was most pronounced during the first 3 months of treatment(44). Similarly, in our study, group-level fatigue improved predominantly during the first 4 months, whereas no significant changes were apparent between year 2 and year 5.

However, we found important inter-individual variation in fatigue evolution over time, characterized by either rapid, gradual, or transient improvement, or by early deterioration. These longitudinal trajectories depict fatigue as a persistent symptom, with most patients experiencing only temporary improvement. This is in line with previous longitudinal studies on RA-related fatigue, which have either reported stable trajectories over time(27,28) or found that only up to a third of patients experienced an improving trajectory(26,43). However, the trajectories we identified seem more dynamic, possibly because fatigue was assessed in detail during early disease, with both short assessment intervals and multidimensional instruments. For instance, 20% of our participants not only made no sustained improvement in fatigue, but even experienced worsening fatigue during the first treatment months. To our knowledge, only one study has reported a similar deterioration of fatigue during the early course of RA, although this did not result in a distinct trajectory(43). Our findings contribute to the awareness of a crucial unmet need for patients with RA, particularly since worsening fatigue was associated with more pain and impaired mental health irrespective of disease activity. Furthermore, ample research has shown that fatigue often persists despite improved treatment, and even when achieving disease remission(23,25,42,45).

Stated differently, the association between disease activity and fatigue appears more complex than one might assume. We found that disease activity was indeed positively correlated with fatigue over time, but this association was fully mediated by the PGA and pain, and to a lesser extent by mental health and sleep quality. Conversely, joint counts and classical inflammatory markers played no apparent role in this association. These findings add to several studies reporting that fatigue is predominantly associated with pain, sleep, and psychological aspects like mood and self-efficacy, whereas inflammatory markers seem to contribute little to this association directly(46–48). Similarly, it has been suggested that improvements in fatigue with DMARDs are largely due to improved pain(7).

Because of these associations between fatigue and other PROs, it is unsurprising that most studies have identified PGA, pain, and mental health as baseline predictors of fatigue(26,43,49). Our findings confirm this, with higher baseline pain, PGA, and HAQ, and lower SF-36 MCS associated with consistently higher levels of fatigue over 5 years of follow-up. Strikingly though, a higher baseline swollen joint count predicted lower long-term fatigue. These findings add to recent results of the ARCTIC-trial, in which more swollen joints and higher ultrasound inflammation at baseline were associated with less fatigue at year 2, while a predisposing effect was seen for PGA(50). Together, results of both trials could indicate that RA-related fatigue is a composite of inflammation-driven fatigue and fatigue with a stronger psychosocial background. Nevertheless, to improve long-term fatigue outcomes, it appears particularly important to achieve disease control early, likely through positive effects on both these pathways(51). For instance, both our study and the ARCTIC-trial identified early remission as the strongest predictor of long-term fatigue. In our study, this effect was evident from early on to even 5 years of follow-up. Moreover, our results add the crucial insight that these beneficial effects of early remission on long-term fatigue remain even when relapses of disease activity later occur, pointing towards an early window of opportunity to prevent long-term fatigue in RA.

Our study has some limitations. Whereas during the first two trial years fatigue was measured frequently with multiple instruments, fatigue assessments during CareRA-plus were limited to a 6-monthly VAS. Consequently, our finding of a more stable fatigue course during this timeframe might be influenced by study design.

However, several strengths add credibility to our findings. Most studies assess fatigue on a VAS or numeric rating scale. While our results showed that a VAS correlates well with measures of general and physical fatigue, it seemed to capture aspects related to mental fatigue and motivation less convincingly. We assessed fatigue not only through several multidimensional instruments, but also longitudinally for up to 5 years in a pragmatic clinical trial representative for an early RA patient population. Moreover, fatigue was measured frequently during the first treatment months and studied with rigorous statistical methods, providing a uniquely detailed picture of its complexity in early RA.

Conclusion

We showed that fatigue is a dynamic but persistent symptom in early RA, with less than 25% of patients making lasting improvements despite intensive DMARD-treatment, and one-in-five patients even experiencing worsening fatigue during the first months. However, achieving early disease remission strongly improved fatigue over up to 5 years of follow-up, even when disease activity later relapsed. Thus, the first step to managing fatigue in early RA should be to seize this window of opportunity for prompt inflammatory disease control. Nonetheless, the association between disease activity and fatigue seems to be mainly explained by pain, mental health, and sleep quality. Moreover, higher fatigue over time was seen in patients who at baseline had more perceived disease impact and fewer swollen joints. Clinicians should thus reserve specific attention for the psychosocial determinants of fatigue and timely consider additional non-pharmacological approaches, particularly when no rapid improvement is made with pharmacotherapy.

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Chapter 3

Towards self-management of disease impact: exploring the building blocks of self-efficacy

This chapter was published as:
Doumen M, De Cock D, Pazmino S, Bertrand D, Joly J, Westhovens R, Verschueren P. Treatment response and several patient-reported outcomes are early determinants of future self-efficacy in rheumatoid arthritis.
Arthritis Res Ther 2021; 23(1):269.

ABSTRACT

Background: Self-efficacy, or patients' confidence in their ability to control disease and its consequences, was recently prioritised in EULAR-recommendations for inflammatory arthritis self-management strategies. However, it remains unclear which factors influence self-efficacy in early rheumatoid arthritis (RA).

Methods: Data were analysed from the 2-year RCT Care in early RA (CareRA),which studied remission-induction treatment regimens for early RA. Participants completed the Arthritis Self-Efficacy Scale (ASES), Short Form 36 (SF-36), Revised Illness Perception Questionnaire (IPQ-R), Utrecht Coping List (UCL), RAQoL and Health Assessment Questionnaire (HAQ). Depending on time to first remission (DAS28-CRP <2.6) and persistence of remission, treatment response was defined as persistent response, secondary failure, delayed response, late response, or non-response. The association between ASES-scores and clinical/psychosocial factors was explored with Spearman-correlation and multivariate linear mixed models. Baseline predictors of week 104 ASES were identified with exploratory linear regression followed by multiple regression of significant predictors adjusted for DAS28-CRP, HAQ, treatment arm, treatment response, cumulative CRP/SJC28, and demographic/serologic confounders.

Results: All 379 patients had a recent diagnosis of RA and were DMARD-naïve at study initiation. Most patients were women (69%) and RF/ACPA-positive (66%) and the mean (SD) age was 52 (13) years. For all tested outcome measures, better perceived health correlated with higher self-efficacy. While patient-reported factors (HAQ, SF-36, RAQoL, IPQ-R, pain, fatigue, and patient's global assessment) showed moderate/strong correlations with ASES-scores, correlations with physician-reported factors (physician's global assessment, SJC28), TJC28 and DAS28-CRP were weak. Only more favourable outcomes on patient-reported factors and DAS28-CRP were associated with higher ASES-scores at each time point. An earlier, persistent treatment response predicted higher ASES-scores at both week 52 and 104. Significant baseline predictors of week 104 ASES included HAQ; SF-36 Mental Component Score, Vitality, Mental Health and Role Emotional; IPQ-R Illness coherence, Treatment control, Emotional representations and Consequences; UCL Passive reacting and the RAQoL.

Conclusions: Patient-reported outcomes and treatment response were early determinants of long-term self-efficacy in an early RA trial. These results provide further relevance for the window of opportunity in an early treat-to-target strategy and could help to timely identify patients who might benefit from self-management interventions.

INTRODUCTION

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis and it considerably impacts patients' daily functioning and quality of life (1). Although remission of RA has become a realistic treatment target, around one-in-five patients still report ongoing symptoms even when the disease appears clinically well-controlled (2,3). Since adequate control of ongoing symptoms like pain and fatigue is a crucial goal for patients, it is essential to not only induce remission by early and intensive treatment, but also to timely address these unmet patient needs (4). In addition to pain and fatigue, the unmet needs of patients with RA often include psychosocial factors such as the impact on mental health and social functioning (5). Recently, there has been an increasing awareness that these psychosocial aspects have a significant influence on patients' perceived symptoms and quality of life (6–8).

As in every chronic disease, an important long-term aspect in the care for patients with RA is self-efficacy, defined as the confidence in one's ability to carry out a task with the desired outcome (9). For patients with RA, self-efficacy mainly relates to confidence in their ability to better control the disease and its consequences with actions they can take themselves. Self-efficacy is therefore a major contributor to self-management behaviour and active coping, which in turn are promoters of psychological adjustment to chronic illness (10). In other words, patients who are more self-efficacious can be more actively involved in the management of their disease, in a process of shared decision-making (11). Shared decision-making involves patients working together with rheumatologists to provide the best possible care with regard to both scientific evidence and patient-specific goals and preferences (12). In recent years, shared decision-making and disease self-management have gained increasing attention, both in usual care and as the cornerstone of innovative care models like patient-initiated consultations and mobile health (mHealth) guided follow-up (13). Consequently, self-efficacy was identified as a priority in the recent EULAR-recommendations for the implementation of self-management strategies for inflammatory arthritis (14). Moreover, with a view to improved shared decision-making, numerous intervention studies have shown that self-efficacy beliefs are not static personality traits but can be improved with personalised patient education and psychological support (15–17).

Therefore, it is important to gain a clear understanding of which factors influence self-efficacy in RA. Stronger self-efficacy beliefs have been associated with lower levels of pain, fatigue, physical disability, and emotional distress (18). Moreover, a negative association between disease severity and self-efficacy has previously been reported (19). Finally, feeling more self-efficacious seems to be related to psychosocial wellbeing in patients with early RA (20).

However, the studies reporting these associations are characterised by considerable heterogeneity in outcome measures, and most of those studies have been limited to describing cross-sectional correlations (21). Moreover, few studies have been able to identify predictors of self-efficacy in patients with RA, and the predictors that have been suggested have often not been confirmed in other publications (21–23).

Therefore, we aimed to investigate which disease-related and psychosocial factors are associated with self-efficacy across time in patients with RA. Moreover, we looked specifically at the early stages of disease, where effective interventions might have the largest impact.

METHODS

Study design and participants

This study was an observational post-hoc analysis of the Care in early RA (CareRA) trial. CareRA (EudraCT number: 2008-007225-39) was a prospective, multicentre, two-year, open-label pragmatic randomised controlled trial comparing different remission-induction treatment regimens for early RA (24). The trial included 379 patients from 13 Belgian rheumatology centres. All included patients had a recent diagnosis of RA (<1 year ago) and had not received

disease-modifying antirheumatic drugs (DMARDs) before study initiation. Details on the study protocol and primary outcomes have been published elsewhere (24,25). In short, each treatment arm consisted of methotrexate with or without additional conventional synthetic DMARDs (csDMARDs), and with or without temporary glucocorticoids. The ethics committee of all participating centres approved the study protocol and all included patients provided written informed consent. For this observational study, which included the entire CareRA-cohort, no additional ethical approval was required.

Assessments and outcomes

The primary aim of this study was to identify clinical and psychosocial factors associated with self-efficacy across time, as well as early predictors of self-efficacy, in patients with early RA. Self-efficacy was measured by the 2-subscale version of the Arthritis Self-Efficacy Scale (ASES) at week 52 and week 104 (26). The pain (PSE) and other symptoms (OSE) subscales measure the patient's perceived confidence in their ability to control arthritis pain, and to control symptoms of arthritis other than pain, respectively, with other means than medication. PSE and OSE were scored separately and summed to derive a total ASES-score. Scores on both the PSE and OSE subscales range from 1-10 ('very uncertain' to 'very certain'). The total ASES-score thus ranges from 2-20, with higher scores indicating stronger self-efficacy beliefs.

Clinical variables: Participants were clinically assessed at screening, baseline, week 4, 8, 16, 28, 40, 52, 65, 78, 91 and 104 to collect tender and swollen joint counts (TJC28/SJC28), patient's and physician's global assessment of disease activity (PGA/PhGA) on a visual analogue scale (VAS) of 100mm, and laboratory markers of inflammation including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Patients' demographic characteristics were recorded at baseline, including comorbidity burden in the form of the Rheumatic Diseases Comorbidity Index (RDCI) (27). Disease Activity Score in 28 joints with CRP (DAS28-CRP) was calculated as a composite disease activity measure (28), and DAS28-CRP <2.6 was defined as remission for all analyses (29). Treatment was initiated at the baseline visit. Treatment response was specified as a categorical variable with 5 levels: 1) persistent response, defined as sustained remission from week 16 to week 104; 2) secondary failure, defined as remission by week 16 with later loss of remission; 3) delayed response, defined as a first remission between week 16 and week 52; 4) late response, defined as a first remission after week 52; and 5) non-response, defined as no remission within 104 weeks.

Psychosocial variables: In addition to the ASES, numerous other patient-reported outcomes (PROs) were collected at different timepoints. These include, among others, at baseline, week 16, 52 and 104: pain and fatigue on a VAS of 100mm, physical function measured by the Health Assessment Questionnaire (HAQ), illness perceptions assessed by the Revised Illness Perception Questionnaire (IPQ-R) and multidimensional quality of life as reflected by the Short Form 36 health survey (SF-36) and the RAQoL (30–33). Furthermore, coping strategies were collected at baseline and week 16 using the Utrecht Coping List (UCL) (34).

The IPQ-R measures 9 dimensions of illness perception (31). Among these, the dimensions of illness coherence, personal control, treatment control, emotional representations and perceived consequences were selected as most relevant to our research question. Higher scores on illness coherence imply a better understanding of the disease, while higher outcomes on personal control and treatment control indicate a higher perceived likelihood of personal interventions or treatment controlling the disease. By contrast, higher scores on emotional representations and consequences represent a stronger perceived impact of the disease's negative consequences.

The SF-36 measures 8 dimensions of health: 4 physical dimensions (physical function, role physical, bodily pain, and general health; compiled into a physical component score (PCS)) and 4 mental dimensions (vitality, social function, role emotional and mental health; compiled into a mental component score (MCS)) (32). Higher scores on each of the SF-36 dimensions (0-100) imply better patient-perceived health. For this study, we placed particular emphasis on the SF-36 mental components, since the physical dimensions were considered to be well-represented by other included PROs. The RAQoL is an RA-specific quality of life (QoL) instrument consisting of 30 'yes/no'-questions, resulting in a score of 0-30 with higher scores indicating lower QoL (33). Finally, the UCL assesses seven distinct coping strategies, with higher scores corresponding with more use of a certain strategy (34).

Statistical analysis

Missing PRO-data were first handled as outlined in the individual questionnaire manuals. Next, missing data were assumed to be missing at random and imputed with multiple imputation by classification and regression trees (total missingness 16%, n=100 imputations). Analyses were carried out in each imputed dataset and then pooled using Rubin's rules. Descriptive statistics were reported as means (± SD), medians (± IQR) or proportions depending on data distribution. Correlations between ASES-scores and the selected clinical and psychosocial variables were reported as Spearman coefficients.

To describe the association of the selected clinical and psychosocial variables with total ASES-scores across time, linear mixed models (LMM) with a random intercept were constructed. This method makes optimal use of longitudinal data by considering repeated observations within individual patients, allowing for a different baseline value for each patient. Because ASES was only collected at 2 timepoints, we did not include a random slope for time in these mixed models. All LMMs were multivariate models adjusting for concurrent DAS28-CRP and HAQ, as well as time, treatment arm, age, sex, and the presence of rheumatoid factor (RF) or anti-citrullinated peptide antibodies (ACPA) as covariates. When the independent variable of interest was a component of the DAS28-CRP, the other DAS28-CRP-components were included as individual covariates instead of DAS28-CRP.

To identify baseline predictors of long-term self-efficacy, we first constructed exploratory, univariate linear regression models using the total ASES-score at week 104 as the dependent variable and the selected clinical and psychosocial variables at baseline, including the individual questionnaire dimensions, as predictors. Statistically significant predictors of week 104 ASES ($p < 0.05$) were then included as independent variables in multiple linear regression models adjusted for categorical treatment response, treatment arm, age, sex, the presence of RF or ACPA and baseline HAQ and DAS28-CRP (or its components) as relevant covariates. In addition, these models were also adjusted for the cumulative sum of CRP and SJC28 levels across the 2 years of follow-up, as longitudinal markers of disease-related inflammation. To account for the increased risk of type I error due to multiple comparisons (n=18 prediction models were constructed), a Bonferroni-correction was applied, setting the significance level at $\alpha = 0.003$ instead of 0.05 for all analyses following the exploratory step. Finally, a mediation analysis was carried out to gain a better understanding of how treatment response could affect self-efficacy, when considering other treatment-related predictors collected at the same time points as the ASES. Confidence intervals for the mediation analysis were obtained through bootstrapping (5000 iterations of random sampling with replacement). All statistical analyses were carried out in R Studio version 1.3.1093, with inclusion of the packages *mice, lmerTest, lavaan and lavaanPlot*.

RESULTS

Patient characteristics

A total of 379 patients with early RA were included in CareRA between January 2009 and May 2013, 322 (85%) of whom completed the two-year study. After imputation of missing data, all 379 patients were included in this post-hoc analysis. All patients had a recent diagnosis of RA and were DMARD-naïve at study initiation, with a mean (SD) DAS28-CRP of 4.8 (1.3) at baseline. The majority of patients were women (69%) and RF or ACPA-positive (66%) and the mean (SD) age was 52 (13) years. Table 1 presents baseline demographic, clinical and patient-reported outcome characteristics.

Table 1. Baseline characteristics of participants included in CareRA (n = 379).

	Distribution
Demographic variables	
Age, years	52 (13)
BMI, kg/m2	26 (4)
Women, n (%)	262 (69)
Smokers, n smoked ever (%)	209 (55)
RF positive, n (%)	252 (66)
ACPA positive, n (%)	249 (66)
Erosive disease, n (%)	97 (26)
RDCI, mean (SD)	0.84 (1.15)
Clinical variables	
DAS28-CRP	4.8 (1.3)
TJC28, median (IQR)	7 (8)
SJC28	6 (8)
PGA, mm (0-100)	55 (24)
Pain, mm (0-100)	56 (24)
Fatigue, mm (0-100)	48 (24)
PhGA, mm (0-100)	52 (19)
ESR, mm/h, median (IQR)	23 (30)
CRP, mg/L, median (IQR)	21 (78)
HAQ (0-3), median (IQR)	1 (1)

Results are reported as mean (SD) unless otherwise specified. *IQR = interquartile range, BMI = body mass index, RF = rheumatoid factor, ACPA = anti-citrullinated peptide antibody, RDCI = Rheumatic Diseases Comorbidity Index, DAS28 = Disease Activity Score in 28 joints, CRP = C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, ESR = erythrocyte sedimentation rate, HAQ = Health Assessment Questionnaire*

Factors associated with self-efficacy

Table 2 presents coefficients for the correlation between both ASES-subscales and the selected clinical and patient-reported variables at all available time points. As expected, the ASES PSE and OSE subscales were strongly correlated with each other ($r_S = 0.72$), and with the total score (since this is the sum of the two subscales). For all included outcome measures, better perceived

health was associated with stronger self-efficacy beliefs. In general, patient-reported variables (HAQ, SF-36 component scores, RAQoL, IPQ-R, pain, fatigue, and PGA) showed moderate to strong correlations with OSE, and in most cases these correlations were notably stronger than those with PSE. By contrast, physician-reported variables (PhGA, SJC28), TJC28 and DAS28-CRP were only weakly correlated with both ASES-subscales. Furthermore, laboratory measures of inflammation (CRP and ESR) showed only very weak correlations with ASES-scores. None of the included variables showed a substantially stronger correlation with PSE than with OSE.

Table 2. Spearman coefficients for the correlation between ASES-subscales and clinical and psychosocial variables at all available time points.

	ASES Pain	**ASES Symptoms**	**ASES Other**	**ASES Total**
DAS28-CRP	-0.35	-0.33		-0.37
HAQ	**-0.48**	**-0.55**		**-0.55**
Pain (VAS)	**-0.46**	**-0.46**		**-0.50**
Fatigue (VAS)	**-0.45**	**-0.51**		**-0.51**
PGA (VAS)	**-0.46**	**-0.47**		**-0.51**
SF-36 PCS	**0.58**	**0.61**		**0.64**
SF-36 MCS	0.33	**0.52**		**0.44**
IPQ-R Illness Coherence	0.37	**0.50**		**0.46**
IPQ-R Treatment Control	**0.40**	**0.46**		**0.46**
IPQ-R Personal Control	0.29	0.27		0.30
IPQ-R Consequences	**-0.58**	**-0.64**		**-0.65**
IPQ-R Emotional Representations	**-0.46**	**-0.59**		**-0.56**
RAQoL	**-0.57**	**-0.68**		**-0.67**
PhGA (VAS)	-0.32	-0.34		-0.36
TJC28	-0.32	-0.31		-0.34
SJC28	-0.19	-0.17		-0.20
CRP	-0.07	-0.06		-0.07
ESR	-0.07	-0.07		-0.08

ASES = Arthritis Self-Efficacy Scale, DAS28 = Disease Activity Score in 28 joints, HAQ = Health Assessment Questionnaire, VAS = Visual Analogue Scale, PGA = patient's global assessment of disease activity, SF-36 = Short-Form 36, PCS = physical component score, MCS = mental component score, IPQ-R = Revised Illness Perception Questionnaire, PhGA = physician's global assessment of disease activity, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate

In the multivariate longitudinal models, only better scores on patient-reported variables and DAS28-CRP were significantly associated with higher total ASES-scores across time, which was not the case for physician-reported and laboratory measures of disease activity (Table 3). In the case of DAS28-CRP and RAQoL, these associations interacted with HAQ: more specifically, the additional effect of DAS28-CRP or RAQoL on the total ASES-score decreased with increasing HAQ-scores. A combination of DAS28-CRP, HAQ, age, sex, treatment arm, auto-antibody status and different individual PROs explained 60%-69% of the total variance in the total ASES-score across time.

Table 3. Variables associated with total ASES-score across time, based on multivariate linear mixed models.

Variable	Coefficient (95% CI)	P-value[⊥]	Conditional R^2	Interactions
DAS28-CRP	-0.22 (-0.32, -0.11)	<**0.001**	0.614	HAQ*
HAQ	-1.06 (-1.27, -0.84)	<**0.001**	0.610	-
Pain (VAS)	-0.14 (-0.19, -0.09)	<**0.001**	0.603	-
Fatigue (VAS)	-0.15 (-0.19, -0.10)	<**0.001**	0.606	-
PGA (VAS)	-0.16 (-0.21, -0.11)	<**0.001**	0.594	-
SF-36 MCS	0.40 (0.29, 0.50)	<**0.001**	0.607	-
IPQ-R Illness Coherence	0.12 (0.09, 0.15)	<**0.001**	0.617	-
IPQ-R Treatment Control	0.16 (0.12, 0.20)	<**0.001**	0.619	-
IPQ-R Personal Control	0.09 (0.06, 0.11)	<**0.001**	0.608	-
IPQ-R Consequences	-0.17 (-0.19, -0.15)	<**0.001**	0.690	-
IPQ-R Emotional Representations	-0.11 (-0.12, -0.09)	<**0.001**	0.634	-
RAQoL	-0.11 (-0.12, -0.09)	<**0.001**	0.640	HAQ**
PhGA (VAS)	-0.12 (-0.19, -0.04)	**0.002**	0.613	-
TJC28	-0.01 (-0.06, 0.03)	0.590	0.594	-
SJC28	0.01 (-0.04, 0.07)	0.630	0.594	-
CRP	0.00 (-0.01, 0.01)	0.550	0.594	-
ESR	0.00 (0.00, 0.01)	0.320	0.597	-

[⊥]Bonferroni-correction for multiple comparisons was applied, setting the significance level at $p < 0.003$.
* Interaction (ß = 0.24; 95% CI = 0.12-0.36; $p < 0.001$) implies that the additional effect of DAS28-CRP on self-efficacy (SE) decreases with increasing HAQ
** Interaction (ß = 0.05; 95% CI = 0.03-0.08; $p < 0.001$) implies that the additional effect of RAQoL on SE decreases with increasing HAQ
ASES = Arthritis Self-Efficacy Scale, DAS28 = Disease Activity Score in 28 joints, HAQ = Health Assessment Questionnaire, VAS = Visual Analogue Scale, PGA = patient's global assessment of disease activity, SF-36 MCS = Short-Form 36 mental component score, IPQ-R = Revised Illness Perception Questionnaire, PhGA = physician's global assessment of disease activity, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate

Predictors of self-efficacy

Patients who achieved a more favourable treatment response had higher total ASES-scores at week 104 (Figure 1, Table 4). Highest ASES-scores were seen in the persistent response group, followed by the groups with secondary failure, delayed response, late response, and non-response, respectively. In the multivariate prediction models, after adjusting for baseline HAQ and DAS28-CRP, treatment arm, auto-antibody status, cumulative inflammation and demographics, treatment response remained a significant predictor of total ASES-scores at week 104 (Table 5). In a mediation analysis, the effect of treatment response on later self-efficacy was mediated by IPQ-R dimensions Consequences and Personal control; the RAQoL; and VAS for fatigue, while there was no significant mediation by CRP, SJC28, PGA, HAQ, VAS for pain, SF-36 MCS or other IPQ-R dimensions (Figure 2, Supplement 3.1). Although there was a significant total effect, the direct effect of treatment response on later ASES-scores was not significant after adjusting for these mediators.

In addition to treatment response, better perceived health status at baseline for the following PROs was independently associated with higher ASES-scores at week 104 in both univariate and multivariate models: HAQ (ß = -0.73, $p < 0.001$); SF-36-dimensions MCS (ß = 0.31, p <

0.001), Vitality (ß = 0.16, p < 0.001), Mental Health (ß = 0.21, p < 0.001) and Role Emotional (ß = 0.07, p < 0.001); IPQ-R-dimensions Illness coherence (ß = 0.07, p < 0.001), Treatment control (ß = 0.09, p = 0.003), Emotional representations (ß = -0.07, p < 0.001) and Consequences (ß = -0.07, p < 0.001); the UCL-dimension of Passive reacting (ß = -0.08, p < 0.001); and the RAQoL (ß = -0.04, p = 0.001).
However, the predictive effects of sex; baseline VAS for PGA, PhGA, pain or fatigue; the SF-36-dimension Social Function; the IPQ-R-dimension Personal control and the UCL-dimension Active tackling were no longer significant after adjusting for multiple comparisons and covariates (Table 4, Table 5).

Table 4. Baseline and treatment-related predictors of total ASES-score at week 104, based on univariate models.

Variable	Coefficient (95% CI)	P-value	Variable	Coefficient	P-value
Clinical/demographic			**IPQ-R**		
Age	0.01 (0.00, 0.02)	0.056	Illness coherence	0.09 (0.06, 0.13)	**<0.001**
Sex (male)	0.36 (0.06, 0.66)	**0.021**	Treatment control	0.11 (0.05, 0.17)	**<0.001**
Ab-status (+)	-0.03 (-0.37, 0.31)	0.856	Personal control	0.08 (0.04, 0.12)	**<0.001**
Erosive disease (+)	0.14 (-0.19, 0.46)	0.409	Emotional repr.	-0.09 (-0.11, -0.07)	**<0.001**
RDCI	-0.05 (-0.17, 0.07)	0.442	Consequences	-0.09 (-0.13, -0.06)	**<0.001**
Treatment type	0.00 (-0.11, 0.10)	0.981	**UCL**		
Treatment response	-0.51 (-0.66, -0.36)	**<0.001**	Seeking social support	0.04 (0.00, 0.08)	0.065
HAQ	-0.57 (-0.76, -0.37)	**<0.001**	Passive reacting	-0.11 (-0.15, -0.06)	**<0.001**
DAS28-CRP	-0.07 (-0.18, 0.04)	0.222	Active tackling	0.05 (0.01, 0.09)	**0.028**
PGA (VAS)	-0.13 (-0.19, -0.07)	**<0.001**	Palliative reacting	-0.02 (-0.06, 0.02)	0.364
TJC28	-0.01 (-0.03, 0.02)	0.543	Avoidance	-0.04 (-0.08, 0.01)	0.093
SJC28	0.01 (-0.01, 0.04)	0.356	Expr. of emotion	-0.03 (-0.11, 0.05)	0.484
CRP	0.00 (-0.01, 0.00)	0.108	Reassuring thoughts	0.02 (-0.04, 0.08)	0.504
ESR	0.00 (-0.01, 0.01)	0.782	**SF-36**		
PhGA (VAS)	-0.09 (-0.16, -0.02)	**0.021**	MCS	0.41 (0.29, 0.53)	**<0.001**
Pain (VAS)	-0.12 (-0.18, -0.06)	**<0.001**	VT	0.25 (0.19, 0.32)	**<0.001**
Fatigue (VAS)	-0.14 (-0.20, -0.09)	**<0.001**	SF	0.16 (0.11, 0.21)	**<0.001**
RAQoL			MH	0.27 (0.20, 0.34)	**<0.001**
RAQoL	-0.07 (-0.09, -0.05)	**<0.001**	RE	0.09 (0.06, 0.12)	**<0.001**

Results were obtained from univariate linear regression models predicting total ASES-score at week 104. For this exploratory stage, no correction for multiple comparisons was applied.
ASES = Arthritis Self-Efficacy Scale, RDCI = Rheumatic Diseases Comorbidity Index, HAQ = Health Assessment Questionnaire, DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein, PGA = patient's global assessment of disease activity, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PhGA = physician's global assessment of disease activity, VAS = Visual Analogue Scale, SF-36 = Short-Form 36, MCS = mental component score, VT = Vitality, SF = Social Function, MH = Mental Health, RE = Role Emotional, IPQ-R = Revised Illness Perception Questionnaire, UCL = Utrecht Coping List

Table 5. Baseline and treatment-related predictors of total ASES-score at week 104, based on multivariate models.

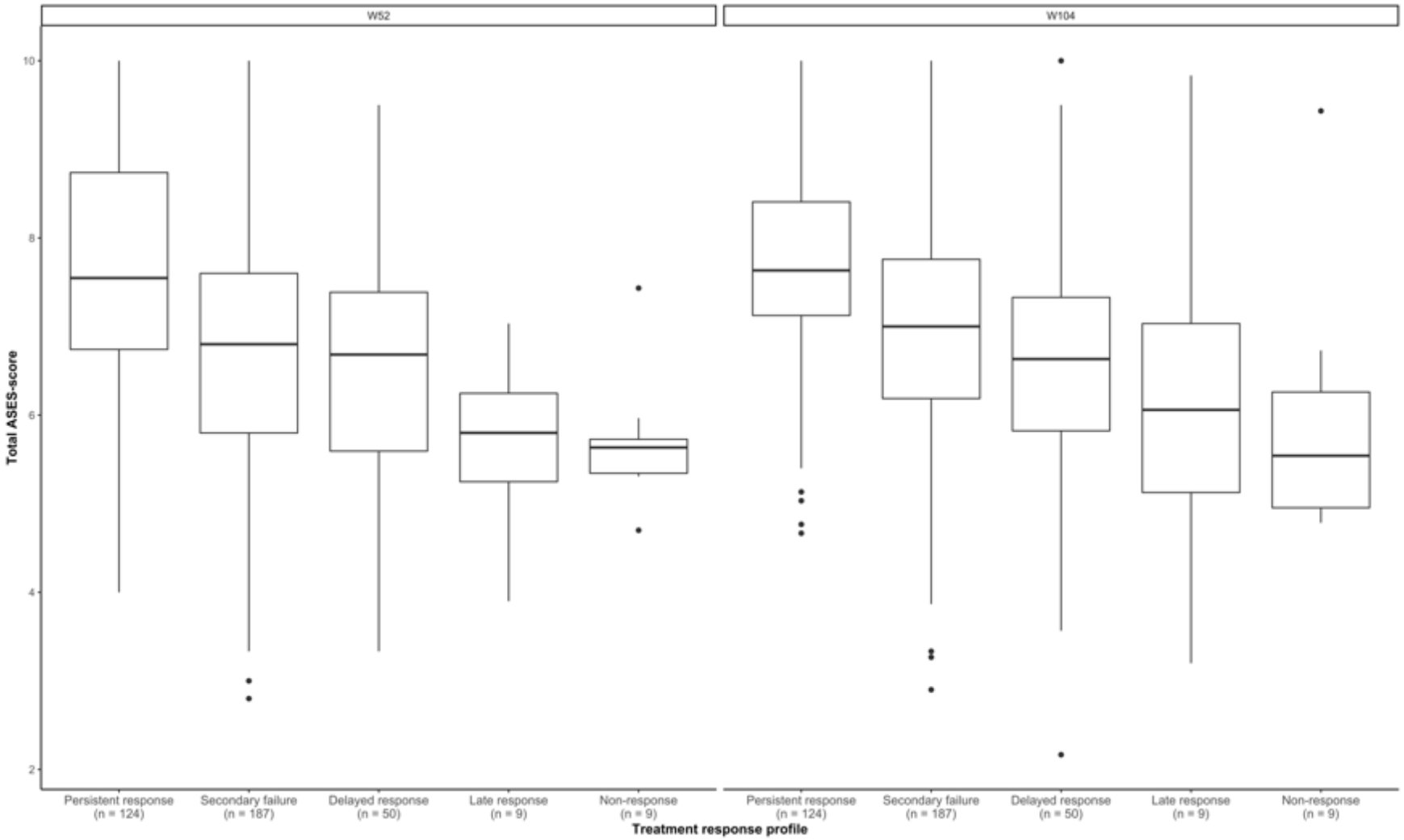
Variables	Coefficient (95% CI)	P-value[⊥]	Adjusted R^2
Clinical/demographic			
Sex (male)	0.32 (0.03, 0.60)	0.030	0.178
Treatment response	-0.46 (-0.65, -0.27)	**<0.001**	0.178
HAQ	-0.73 (-0.97, -0.49)	**<0.001**	0.178
Pain (VAS)	-0.04 (-0.11, 0.03)	0.316	0.177
Fatigue (VAS)	-0.06 (-0.12, 0.01)	0.083	0.182
PGA	-0.01 (-0.08, 0.07)	0.733	0.182
PhGA	-0.01 (-0.11, 0.09)	0.607	0.175
SF-36			
MCS	0.31 (0.19, 0.43)	**<0.001**	0.230
Vitality	0.16 (0.08, 0.24)	**<0.001**	0.210
Social Function	0.08 (0.02, 0.15)	0.008	0.191
Mental Health	0.21 (0.13, 0.28)	**<0.001**	0.235
Role Emotional	0.07 (0.04, 0.10)	**<0.001**	0.218
IPQ-R			
Illness coherence	0.07 (0.04, 0.10)	**<0.001**	0.215
Treatment control	0.09 (0.03, 0.14)	**0.002**	0.197
Personal control	0.05 (0.01, 0.09)	0.008	0.191
Emotional representations	-0.07 (-0.10, -0.05)	**<0.001**	0.261
Consequences	-0.07 (-0.10, -0.03)	**<0.001**	0.208
UCL			
Passive reacting	-0.08 (-0.12, -0.04)	**<0.001**	0.186
Active tackling	0.03 (-0.01, 0.07)	0.090	0.182
RAQoL	-0.04 (-0.07, -0.02)	**0.001**	0.199

Results were obtained from multivariate linear regression models predicting total ASES-score at week 104 by predictors that were significant in univariate analyses, and adjusting for age, sex, treatment type and response, auto-antibody status, cumulative CRP, cumulative SJC28 and baseline HAQ and DAS28-CRP or its components. Treatment response was treated as an ordinal variable with lower values representing earlier and more persistent response.

[⊥]Bonferroni-correction for multiple comparisons was applied, setting the significance level at $p < 0.003$.

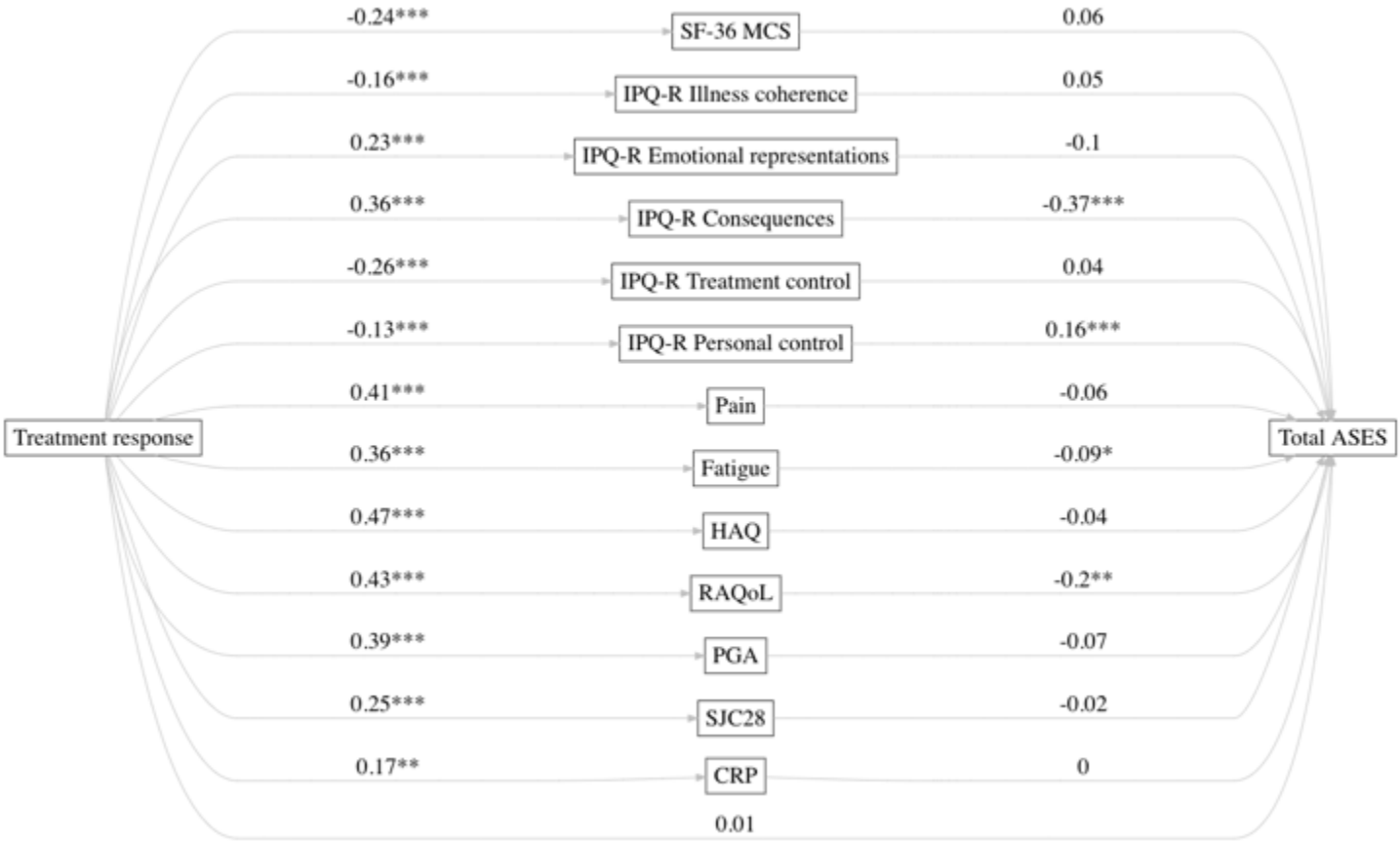
ASES = Arthritis Self-Efficacy Scale, SF-36 = Short-Form 36, MCS = mental component score, IPQ-R = Revised Illness Perception Questionnaire, UCL = Utrecht Coping List

Figure 1. Total ASES-score at week 52 and week 104, stratified by treatment response profile.



Response to treatment was associated with total scores on the Arthritis Self-Efficacy Scale (ASES) at week 52 and week 104, with more favourable responses to treatment resulting in stronger self-efficacy beliefs after both 1 and 2 years of treatment.

Figure 2. Mediators of the association between treatment response and total ASES-score at week 104.



Reported are the standardised regression coefficients with indicators of significance (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). Treatment response was treated as an ordinal variable with lower values representing earlier and more persistent response. *ASES = Arthritis Self-Efficacy Scale, SF-36 = Short-Form 36, MCS = mental component score, IPQ-R = Revised Illness Perception Questionnaire, HAQ = Health Assessment Questionnaire, PGA = patient's global assessment of disease activity, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein*

DISCUSSION

In our study, the self-efficacy beliefs of patients with early RA were more strongly associated with the response to treatment and with patient-reported outcomes - including pain, fatigue, physical function, mental health, illness perceptions and quality of life – than with physician-reported and laboratory measures of disease activity. Furthermore, our results suggest that psychosocial factors, even early in the disease course, can predict long-term self-efficacy beliefs independently of treatment response or objective measures of disease activity.

Of particular interest is our finding that better response to treatment appears to be an independent contributor to stronger long-term self-efficacy beliefs in patients with early RA. Current treatment guidelines for RA recommend starting treatment early and intensively, aiming to achieve remission or at least low disease activity within a certain 'window of opportunity' (35,36). The importance of the window of opportunity has been further emphasised by previous research showing that early achievement of treatment targets also results in better psychosocial outcomes (37). Our findings illustrate that this appears to be equally the case for self-efficacy beliefs, with patients who demonstrated an early and persistent treatment response scoring highest on the ASES after both 1 and 2 years of treatment.

Interestingly, although we did find a correlation between measures of disease activity and self-efficacy at both available timepoints, disease activity and symptoms like pain and fatigue at baseline were not predictive of future self-efficacy. Moreover, the association of early and persistent treatment response with later self-efficacy remained robust even after adjusting for cumulative markers of inflammation. Finally, the results of our mediation analysis suggest that the effect of early and persistent treatment response on self-efficacy is mainly indirect. Treatment response seems to exert its influence primarily through improvements in various psychosocial outcomes and illness perceptions, but not through improvements in pain, physical function, inflammation or swollen joint counts. These findings illustrate that the experience of achieving a satisfactory response to treatment seemingly plays a larger role in building self-management confidence than through better control of disease activity or inflammation as such.

In addition, our results show moderate to strong correlations between several PROs and self-efficacy. These findings are in line with those of a recent meta-analysis, which demonstrated significant associations between the ASES and key areas of functioning in patients with RA or osteoarthritis (18). However, the associations reported by studies included in this meta-analysis were rather heterogeneous, and most of these studies did not investigate outcome measures relating to illness perceptions or coping. Remarkably, only few studies have investigated associations between self-efficacy and psychological factors beyond QoL or depression/anxiety, but these studies have mostly shown a relation between higher self-efficacy and positive affect, acceptance of illness or active coping (38,39). Our findings similarly suggest that optimal illness coherence, more positive illness perceptions and less emotional impact of disease are associated with stronger self-efficacy beliefs.

Furthermore, the ASES-subscale measuring self-efficacy for symptoms other than pain (OSE) showed markedly stronger correlations with most patient-reported measures of health and QoL, including fatigue, when compared to the pain-subscale (PSE). Only for pain, DAS28-CRP and PGA were correlations with OSE and PSE comparable. These findings suggest that experiencing adequate control of pain and disease activity equally influences patients' confidence in their ability to manage pain or other symptoms, whereas self-efficacy for symptoms other than pain appears to depend more on QoL in a broader psychosocial sense. This difference between ASES-subscales has been reported before, and further underlines that managing pain and other symptoms, like fatigue, are perceived by patients with RA as different challenges, which in turn are influenced by different factors (18,21).

It is notable that previous research has identified physical function as one of the factors strongly associated with self-efficacy beliefs (40). Our findings confirm this association but suggest a more complex interplay between both concepts. For instance, in the longitudinal models, the association between DAS28-CRP and ASES-scores across time interacted with HAQ, with the additional effect of DAS28-CRP on self-efficacy decreasing with increasing HAQ. Thus, the association between disease activity and self-efficacy appears to become less important when the patient experiences a heavier burden of physical disability. Interestingly, analogous results were obtained for the association between QoL (measured by the RAQoL) and self-efficacy. It is important to emphasise that self-efficacy represents one's confidence, rather than one's ability, to successfully perform a task (9). In other words, our results suggest that when a patient's physical function is heavily impaired, it is the patient's perceived lack of ability to function that primarily affects their confidence to self-manage.

Finally, our study identified a number of early predictors of long-term self-efficacy beliefs in patients with RA. Interestingly, psychosocial factors were the strongest early predictors of future self-efficacy, rather than perceived pain, fatigue or classic measures of disease activity such as joint counts or biochemical inflammation. For instance, better perceived mental health and QoL, more positive illness perceptions and a less passive coping style before treatment initiation were associated with stronger self-efficacy beliefs after 2 years of treatment. These results are in line with previous research that has shown an important influence of psychological health on self-efficacy or vice versa (23,41). However, it is particularly noteworthy that patients' self-efficacy beliefs following treatment appear to be influenced by psychological well-being, coping and illness perceptions as early as the time of treatment initiation. These results suggest that patients with certain psychosocial characteristics, such as a passive coping style or a stronger emotional impact of disease, are at risk to maintain a lower confidence in their ability to manage their disease, even when treatment has proved effective. Since confidence to self-manage is crucial to facilitate treatment strategies that actively involve and empower the patient (14), our findings further underline the importance of a person-centred, holistic treatment approach to complement pharmacological treatment, even early in the disease course. A number of studies have already shown that patients' self-efficacy beliefs can be improved by needs-based patient education and psychological interventions (42,43). Our study provides further evidence that early attention to specific psychosocial risk factors might help to identify those patients that could benefit the most from these interventions.

Our study has some limitations. First, not all PROs were collected at every visit. For instance, coping mechanisms were only assessed at baseline and week 16, while the ASES was collected at week 52 and week 104. Therefore, a cross-sectional correlation between coping and self-efficacy could not be obtained. Furthermore, because the ASES was not collected at baseline, conclusions could not be made about changes in self-efficacy after treatment or the effect of psychosocial predictors on changes in self-efficacy from baseline. However, baseline ASES-scores would be less relevant to our research question, since it could be argued that self-efficacy needs time to develop, and patients likely cannot be expected to feel self-efficacious before treatment has even been initiated.

Second, coping was assessed by the Utrecht Coping List. Although the UCL is a validated instrument to measure coping, it has not yet been validated within a population of patients with RA. Therefore, it is possible that the choice of psychometric instrument has an additional influence on the obtained results.

Third, this study is an exploratory post-hoc analysis of data from a trial on pharmacological treatment strategies, rather than the result of a psychological or educational intervention. Therefore, we cannot draw conclusions about the possible causal nature of the reported associations.

However, our study does provide a unique insight into the relationship between psychosocial wellbeing and self-efficacy. For instance, our assessment of psychosocial wellbeing is based on various PROs relating to mental health, social functioning, illness perceptions and coping strategies. Moreover, self-efficacy was measured by a validated instrument at 2 different timepoints during the early disease course.

Conclusions

In conclusion, our findings suggest a possible role for psychosocial characteristics and the response to treatment as early determinants of the long-term self-efficacy beliefs of patients with RA. These results could be seen as further evidence on the importance of the window of opportunity in an early treat-to-target strategy. In addition, our findings suggest that attention to psychosocial factors could help to timely identify patients who might benefit the most from interventions to improve self-efficacy, or to identify the optimal target audience for treatment strategies that rely heavily on patient self-management. However, further research is needed to confirm these findings in the context of a prospective interventional trial aiming to improve self-efficacy.

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Part I - Epilogue

Validation of findings in the CareRA2020 cohort

This chapter is based on unpublished data, to be submitted as:

- Doumen M, et al. Early responders to remission-induction treatment with methotrexate and bridging glucocorticoids report lower Rheumatoid Arthritis Impact of Disease over 2 years: secondary analysis of the CareRA2020 trial.

In the preceding chapters, we have shown that various patient-reported outcomes (PROs) are associated with RA disease activity in complex and bidirectional ways. For instance, we found that less perceived disease impact, more positive illness perceptions and better psychosocial wellbeing during the early stages of disease were associated with more sustained remission, while inversely, patients who achieved earlier control of disease activity tended to experience less fatigue and more confidence in their self-management abilities later on.
However, these analyses were all based on data from the Care in early RA (CareRA) trial. In this Epilogue to Part I, we present an abridged view of our findings relating to PROs from the more recent Care in early RA 2020 (CareRA2020) trial, which included patients from an early, DMARD-naïve RA population similar to the original CareRA cohort. This Epilogue chapter was intended as a validation of Part I's conclusions in a different patient cohort, and was based in particular on methods similar to those outlined in Chapter 2.

Early responders to remission-induction treatment with methotrexate and bridging glucocorticoids report lower Rheumatoid Arthritis Impact of Disease over 2 years: secondary analysis of the CareRA2020 trial.

Background: Despite considerable advances in the management of rheumatoid arthritis (RA), many patients continue to experience an impact of the disease even when treatment is successful in terms of controlling disease activity. However, recent evidence from the Care in early RA (CareRA) trial and other early RA cohorts has shown that long-term patient-reported outcomes are improved when patients achieve remission early(1–3). As a tool to measure the patient-reported impact of RA, the Rheumatoid Arthritis Impact of Disease (RAID) instrument was developed via a EULAR initiative(4).

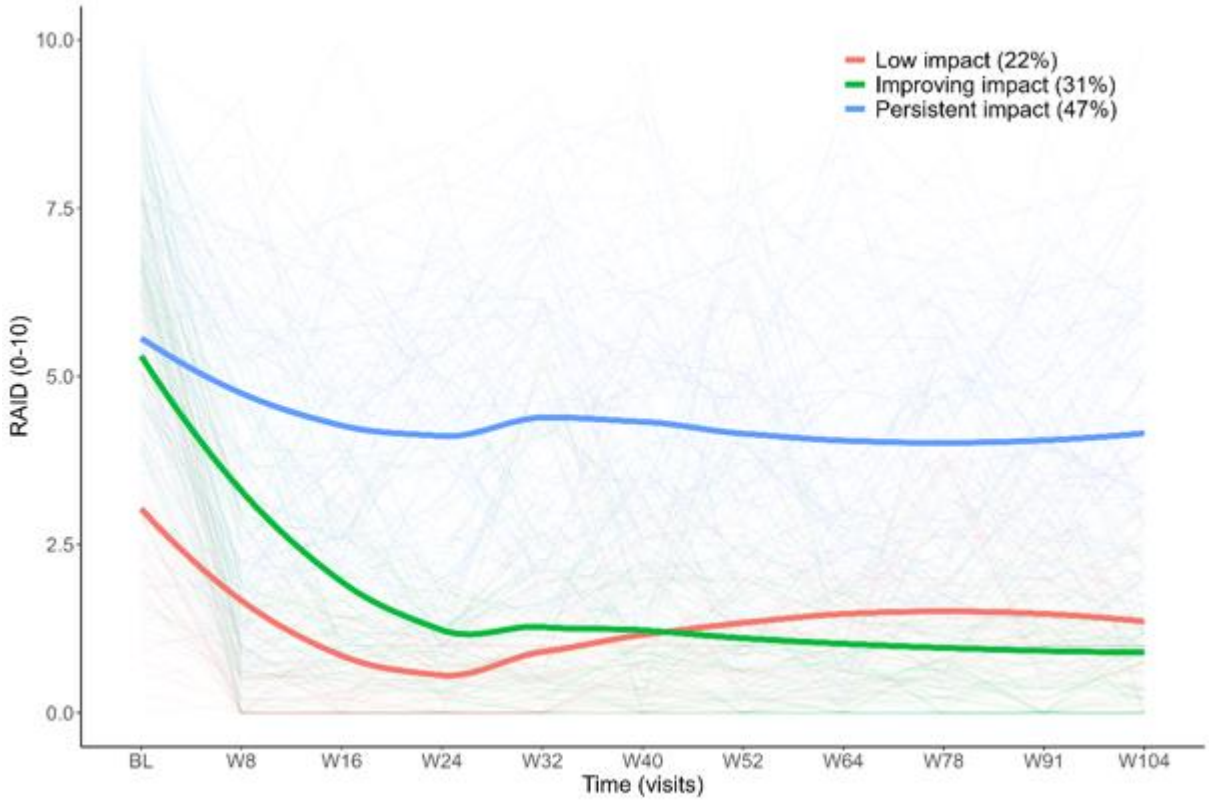
Objectives: We aimed to explore the longitudinal course of RA-related impact, assessed using the RAID instrument, among patients with RA first starting DMARD therapy, and to confirm the prognostic value of early treatment response for this outcome.

Methods: This was a secondary analysis of the recently completed 2-year multicentre randomised controlled trial CareRA2020. All included patients were DMARD naïve and received treatment with methotrexate and bridging glucocorticoids (COBRA-Slim). Within a time window between weeks 8 and 32, participants were classified as either early responders or early insufficient responders based on the achievement of DAS28-CRP $\leq$3.2 from week 8 onwards and <2.6 by week 32. Early insufficient responders were then randomised to addition of leflunomide or a 6-month remission-induction course of etanercept. A treat-to-target approach was practiced during the complete trial period. Within the total trial population, we derived longitudinal trajectories of the RAID score (0-10, with higher scores reflecting more impact) using growth mixture modelling, which implies that patients were clustered into different groups based on their individual evolution of the RAID over time. Baseline variables and classification as early responder to the initial COBRA-Slim regimen were then studied as predictors of the RAID score over 2 years using a linear mixed model (LMM).

Results: In total, 252 patients were included in this analysis, 142 of whom (56%) were early responders to COBRA-Slim. CareRA2020 included a typical early RA population with a mean (SD) age of 54 (14) years, a mean (SD) DAS28-CRP of 5.0 (1.3) at baseline and a median (IQR) symptom duration of 4 (6) months, while 69% were women and 76% were seropositive. Mean (SD) total RAID score at baseline was 5.6 (2.4). Three distinct RAID trajectories were identified (Figure 1): Low impact, Improving impact and Persistent impact, consisting of 22%, 31% and 47% of patients, respectively. In the LMM (Table 1), baseline patient global assessment and Health Assessment Questionnaire scores were positively associated with RAID scores over 2 years. By contrast, significantly lower RAID scores were reported over 2 years by early responders to COBRA-Slim when compared to early insufficient responders.

Conclusion: Almost one-in-two patients in this early RA trial experienced persisting disease impact despite intensive DMARD treatment in a protocolised treat-to-target setting. However, lower long-term disease impact was seen with early achievement of treatment targets, confirming similar findings with other patient-reported outcomes from the preceding CareRA trial and other early RA cohorts.

Figure 1. Latent trajectories of Rheumatoid Arthritis Impact of Disease (RAID) evolution over 2 years.



BL = baseline, W = week

Table 1. Predictors of Rheumatoid Arthritis Impact of Disease (RAID) score over 2 years.

Predictors	***β (95% CI)***	***p-value (**)***
Age (years)	-0.02 (-0.03 to -0.00)	0.011 (0.099)
Sex (female)	0.25 (-0.10 to 0.61)	0.164 (1.000)
RF/ACPA (+)	0.23 (-0.19 to 0.64)	0.282 (1.000)
Erosions (+)	-0.22 (-0.61 to 0.18)	0.284 (1.000)
Comorbidities (+)	0.10 (-0.30 to 0.49)	0.636 (1.000)
Baseline PGA (0-10)	**0.27 (0.17 to 0.37)**	**<0.001 (<0.001)**
Baseline TJC (0-28)	-0.02 (-0.06 to 0.02)	0.347 (1.000)
Baseline SJC (0-28)	-0.00 (-0.04 to 0.04)	0.928 (1.000)
Baseline CRP (mg/dL)	-0.03 (-0.09 to 0.03)	0.314 (1.000)
Baseline HAQ (0-3)	**0.65 (0.34 to 0.96)**	**<0.001 (<0.001)**
Baseline PhGA (0-10)	0.02 (-0.08 to 0.12)	0.643 (1.000)
Early responders*	**-1.45 (-1.80 to -1.10)**	**<0.001 (<0.001)**

Results of a single linear mixed model with the total RAID score as time-varying dependent variable and the listed predictors as fixed independent variables. The model was additionally fitted with a participant-specific random intercept and a random slope for time.
* Compared to early insufficient responders.
** Adjusted for multiple comparisons (Bonferroni-Holm method).
CI = confidence interval, RF = Rheumatoid factor, ACPA = anti-citrullinated protein antibodies, PGA = patient global assessment, TJC = tender joint count, SJC = swollen joint count, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, PhGA = physician global assessment

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PART II

Mobile health applications as tools to monitor disease impact and to support its self-management

“People’s beliefs about their abilities have a profound effect on those abilities.”

Albert Bandura

Chapter 4

Mobile health to remotely monitor disease impact in rheumatoid arthritis: challenges and opportunities

This chapter was published as:

- Doumen M, Westhovens R, Pazmino S, Bertrand D, Stouten V, Neys C, Creten N, Van Laeken E, Verschueren P, De Cock D. The ideal mHealth-application for rheumatoid arthritis: qualitative findings from stakeholder focus groups. BMC Musculoskelet Disord 2021; 22(1):746.

- Doumen M, De Cock D, Van Lierde C, Betrains A, Pazmino S, Bertrand D, Westhovens R, Verschueren P. Engagement and attrition with eHealth tools for remote monitoring in chronic arthritis: a systematic review and meta-analysis. RMD Open 2022; 8(2):e002625.

Chapter 4.1

The ideal mHealth-application for rheumatoid arthritis: qualitative findings from stakeholder focus groups*

* In light of consistency, the term "compliance" in the published version of the manuscript was adapted to "engagement" throughout this thesis manuscript.

ABSTRACT

Background: Shifts in treatment strategies for rheumatoid arthritis (RA) have made ambulatory care more labour-intensive. These developments have prompted innovative care models, including mobile health (mHealth) applications. This study aimed to explore the perceptions of mHealth-inexperienced stakeholders concerning these applications in RA care.

Methods: We performed a qualitative study by focus group interviews of stakeholders including RA patients, nurses specialised in RA care and rheumatologists. The qualitative analysis guide of Leuven (QUAGOL), which is based on grounded theory principles, was used to thematically analyse the data. In addition, the Persuasive Systems Design (PSD) model was used to structure recommended app-features.

Results: In total, 2 focus groups with nurses (total n=16), 2 with patients (n=17) and 2 with rheumatologists (n=25) took place. Six overarching themes emerged from the analysis. Efficiency of care and enabling patient empowerment were the two themes considered as expected benefits of mHealth-use in practice by the stakeholders. In contrast, 4 themes emerged as possible barriers of mHealth-use: the burden of chronic app-use, motivational aspects, target group aspects, and legal and organisational requirements. Additionally, recommendations for an ideal mHealth-app could be structured into 4 domains (Primary Task Support, Dialogue Support, Social Support and System Credibility) according to the PSD-framework. Most recommended features were related to improving ease of use (Task Support) and System Credibility.

Conclusions: Although mHealth-apps were expected to improve care efficiency and stimulate patient empowerment, stakeholders were concerned that mHealth-app use could reinforce negative illness behaviour. For mHealth-apps to be successful in practice, challenges according to stakeholders were avoiding long-term poor engagement, finding the target audience and tailoring a legal and organisational framework. Finally, the ideal mHealth-application should above all be trustworthy and easy to use.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition that primarily results in joint pain and swelling as well as functional disability and impaired quality of life (1). Current recommendations for the management of RA state that treatment should be started early and intensively to a target of remission or low disease activity (LDA) (2). This treat-to-target (T2T) strategy and novel disease-modifying antirheumatic drugs (DMARDs) have considerably improved clinical outcomes in RA. However, in order to achieve optimal outcomes, pharmacological treatment should be started within a certain window of opportunity (3), while specific additional patient needs should simultaneously be addressed (4). Nonetheless, early access to specialised rheumatological care is not always readily available (5). In part due to the introduction of more labour-intensive T2T-strategies and person-centred care, some countries face a relative shortage of practicing rheumatologists (6). Additionally, in many countries, the role of other healthcare professionals, including nurse-specialists, is not firmly established in care trajectories for patients with RA (7). Therefore, attention is turning towards new care models for RA, including the use of mobile health (mHealth) applications, such as mobile apps and wearables.

In recent years, an ongoing evolution in technology and digitalisation has resulted in an ever-increasing number of mHealth-applications (8). In addition, wearable activity trackers (WATs) are emerging as a promising tool to monitor biometric data (9). When routinely integrated into health care and linked to electronic medical patient files, these mHealth-applications and WATs could prove to be an added value in (tele)monitoring treatment adherence, adverse treatment effects or symptoms and disease activity in RA (10). Specifically, remote monitoring of a well-selected set of patient-reported outcomes (PROs) and wearable-obtained physical parameters could provide continuous information on a patient's health status (11). Since the T2T-strategy implies a need for frequent assessment of treatment response, such a remote monitoring approach holds promise to predict the need for urgent clinic visits in patients with high disease activity, but also to reduce the number of clinical visits for well-controlled patients (12). By consequence, remote monitoring of symptoms through mHealth-applications could present a possible cost-saving measure (13), even though the potential impact on quality of care warrants further investigation.

Most patients with rheumatic diseases seem to consider that an mHealth-application could be beneficial to their health, although such an app should be needs-tailored and co-developed by healthcare professionals (14,15). Moreover, it appears crucial to patients for an mHealth-app to facilitate communication with their caregivers, to provide disease-specific information and to reinforce social support (16). However, most available apps do not meet these criteria (17) and care models based on these applications have to date only sparsely been introduced in practice (18). Moreover, previous studies have raised concerns about user disengagement with mHealth-applications, illustrating the need to study ideal app-content to optimise engagement (19). Finally, the opinions of stakeholders other than patients, such as nurses and rheumatologists, have received little attention in mHealth-literature.

Therefore, perceptions of multiple stakeholders including both patients and healthcare providers on mHealth-applications need to be assessed ahead of the development of an integrated mHealth-app for routine rheumatology care. To this end, this study aimed to explore the expectations and opinions of mHealth-inexperienced patients, nurses and rheumatologists on the possible benefits, barriers and essential features of an ideal mHealth-application in the care for patients with RA.

METHODS

We conducted a cross-sectional qualitative study investigating stakeholder perceptions on mHealth-applications in RA care. Patients with RA, rheumatologists and rheumatology nurses were identified as stakeholders and included in semi-structured focus group interviews. A focus group method was specifically chosen to stimulate constructive discussion and to make optimal use of group dynamics (20). The study protocol was approved by the University Hospitals Leuven Ethics Committee and all participants gave informed consent before participation.

Study design and participant recruitment

Patients were invited for focus group interviews at the University Hospitals Leuven, Belgium, Rheumatology clinic or via representatives of RA patient associations, whom we contacted via email. This way, not only patients in follow-up at an academic hospital were included, but also patients in non-academic or private practice care. Practicing rheumatologists were invited to participate during local peer quality groups, which are mandatory for physician accreditation in Belgium. Rheumatology nurses were recruited through the Flemish working group on rheumatology nursing and the Belgian Health Professionals association. We conducted 5 focus group interviews in four different municipalities across the region of Flanders, Belgium, between January and March 2020. One additional focus group of rheumatologists was conducted via Zoom due to the Covid19-pandemic. Interviews were semi-structured, and all were coordinated by the same moderator (DDC) and two observers (RVM & MVDP).

Rheumatologists, rheumatology nurses and two patient research partners were involved in the construction of the interview guide. The interviews were initiated with several exploratory open-ended queries, inquiring about stakeholders' initial perceptions about mHealth-applications, before going into more specific follow-up questions relating to possible benefits, barriers and recommended features of an mHealth-application for RA. During the focus groups, notes were taken by the observers to record participant body language and behavioural cues. All focus groups were audio-recorded, transcribed verbatim and anonymised for analysis.

Analysis

Two independent investigators (MD & DDC) coded and analysed the transcripts in accordance with the methodology outlined in the Qualitative Analysis Guide of Leuven (QUAGOL) (21) and guided by an experienced researcher (RW). Three patient research partners validated the final results of this analysis.

According to the principles of grounded theory underlying the QUAGOL-method, the initial codes were grouped into a conceptual framework of themes that was subsequently confirmed alongside all individual transcripts. This framework was then deconstructed into perceived benefits and barriers for the implementation of mHealth-applications in the care for patients with RA. Additionally, recommended features of an mHealth-application according to all stakeholders were grouped into a separate framework. In order to identify features that contribute to user engagement, this framework was iteratively compared with the existing literature on persuasive principles. Persuasive principles are design techniques that motivate users of a system, such as an app, to adhere to a specific target behaviour, such as continued app-use (22). In mHealth-literature, ample experience exists with the Persuasive Systems Design (PSD) model by Oinas-Kukkonen and Harjumaa (22–26), which is one of the different theories based on persuasive principles.

Persuasive Systems Design (PSD)
The PSD-model proposes 28 persuasive design principles divided into 4 categories: Primary Task Support, Dialogue Support, Social Support and System Credibility. Primary Task Support constitutes all persuasive principles intended to support the user in carrying out their primary task, including the reduction of complex behaviour into simpler tasks. Dialogue Support refers to principles that provide a degree of feedback to the user, including praise, rewards and reminders. Social Support includes all principles that attempt to motivate users by leveraging social influence. Finally, System Credibility principles, including trustworthiness and a sense of authority, aim to increase the persuasiveness of a system by making it more credible.

RESULTS

In total, 2 focus groups consisting of rheumatology nurses (n=16), 2 of patients (n=17) and 2 of rheumatologists (n=25) were conducted. None of the stakeholders were experienced in the use of mHealth-applications. Expected benefits and barriers for the implementation of mHealth-applications in the care for patients with RA were identified across all stakeholders and grouped into the following 6 overarching themes: efficiency of care, enabling patient empowerment, the burden of chronic app-use, motivational aspects, target group aspects and legal and organisational requirements (Table 1). Additionally, recommended features of an mHealth-application for RA were grouped according to the PSD-framework (Table 2).

Table 1. Expected benefits and barriers of mHealth-apps for RA, according to mHealth-inexperienced patients, nurses and rheumatologists.

BENEFITS	BARRIERS
Efficiency of care	**The burden of chronic app-use**
Efficiency of care organisation (P)	Negative illness behaviour (P, N, R)
Efficiency of patient-caregiver interaction (N, R)	Chronicity (P)
	Motivational aspects
	Engagement and attrition (P, N, R)
	A tsunami of mHealth-apps (R)
	Need for instruction and guidance (N)
Enabling patient empowerment	**Target group aspects**
Visualising disease variability (P, N, R)	Lack of symptoms (P, N, R)
Patient-centred goals (R)	Symptom recognition (P, N)
Improving illness coherence (P, N, R)	Accessibility and acceptability (P, N, R)
Trust in care (P)	Evolving disease characteristics (R)
	Legal and organisational requirements
	Privacy concerns (N, R)
	Workload and financial compensation (R)

P = patients; N = rheumatology nurses; R = rheumatologists

Benefits

Efficiency of care

Efficiency of care organisation

Patients considered that implementing mHealth-applications into clinical practice might reduce the number of necessary visits to the rheumatology clinic. For instance, some patients expected an mHealth-application could be used as a decision-support tool to help rheumatologists prioritise patients in need of more urgent attention.

> *"Knowing that some patients have to wait a long time for an appointment, while we are only there to say we're doing well... Maybe this could help to make way for these other people." (Pt 4, patient group 1)*

Efficiency of patient-caregiver interaction

In addition, both nurses and rheumatologists emphasised the benefits such applications could provide for efficient communication with their patients. Specifically, all caregivers agreed that being able to review data collected in between clinic visits, together with their patients, could improve the clarity of their interactions.

> *"(With an overview of the data) you could refer to a flare the patient seems to have had 2 months ago, and the patient can then respond, 'yes, that was the case because of this…'." (R 9, rheumatologist group 2)*

Rheumatologists and nurses both expected this to save valuable time during consultations, again improving efficiency. However, caregivers strongly emphasised that an mHealth-application should never replace genuine social interaction.

Enabling patient empowerment

Visualising disease variability

Patients, nurses as well as rheumatologists considered the potential of an mHealth-application to record symptoms or measures of disease activity in between clinic visits as a crucial benefit. All stakeholder groups agreed that these additional insights into the variability of a patient's disease could improve the quality of care for patients with RA.

> *"When I visit the rheumatologist on a day that I'm feeling fine, I've already forgotten how bad I felt 2 weeks before." (Pt 1, patient group 2)*

Patient-centred goals

Moreover, by being able to look at symptoms or physical data submitted by a patient during and immediately related to their daily life activities, rather than retrospectively discussing them, rheumatologists expected to gain a more comprehensive picture of what is really important to their patient. This way, they considered that an mHealth-application could help to clarify particular personal goals that patients might be reluctant to discuss with their physician during a consultation.

> *"To emphasise the goals of our patients that are rarely discussed during a consultation. The landmarks that a patient might aspire to: being able to play with their grandchildren, or play tennis even if they're 82 years old, etc." (R 1, rheumatologist group 1)*

Improving illness coherence
Just as rheumatologists believed mHealth-apps could improve their understanding of patients' needs, it was also assumed that these applications could help patients to better understand themselves. For instance, the ability to confront patients with symptoms they had previously reported was perceived by caregivers as a means of improving patients' illness coherence.

> *"I think it could help to teach patients to look at their disease in the right way." (N 2, nurse group 2)*

In addition, patients strongly believed that the provision of personalised education through an mHealth-application could benefit their understanding of the disease, a sentiment that was confirmed by both nurses and rheumatologists.

Trust in care
Some patients expressed that having access to an mHealth-application would make them feel safer, since it provides more information and a more comprehensive picture of their disease course to caregivers.

> *"What if something's wrong and you don't know for sure? Well, this way you know, because your nurse and your rheumatologist are always informed." (Pt 3, patient group 2)*

Barriers
The burden of chronic app-use
Negative illness behaviour
All stakeholder groups expressed concern that asking patients to frequently rate their symptoms with an mHealth-application could facilitate negative aspects of illness behaviour. For instance, both nurses and rheumatologists worried that patients paying excessive attention to their symptoms might aggravate the disease's impact on their daily lives.

> *"People shouldn't be occupied with this every single day, because eventually your disease becomes the only thing you're concerned about. After a while, you'll become your disease." (N 3, nurse group 2)*

Patients voiced similar concerns and feared that an mHealth-application that requires them to rate their symptoms too frequently would leave them feeling deprived of their freedom or even "trapped" by their disease.

Chronicity
Some patients related these fears to the chronic nature of RA and worried that committing to an mHealth-guided follow-up strategy would therefore imply a life-long obligation.

Motivational aspects
Engagement and attrition
Patients, nurses and rheumatologists all expected attaining sufficient patient engagement with an mHealth-application to be a challenge. Moreover, all stakeholders expressed concerns that engagement with such an app would inevitably decrease over time.

> *"When it starts to become a drag, you'll stop using it." (Pt 7, patient group 2)*

Additionally, nurses were particularly concerned that some patients, when prompted to remotely report disease symptoms through an app, would tend to over- or understate the severity of their symptoms in an attempt to prompt or avoid clinic visits, respectively.

A tsunami of mHealth-apps
Rheumatologists indicated that the recent emergence of a large number of mHealth-applications might hamper patients' inclination to use a particular app of interest.

Need for instruction and guidance
Nurses emphasised that time and effort would need to be invested to teach patients how to use an mHealth-application.

Target group aspects
Lack of symptoms
Patients expected a lack of symptoms would hamper their motivation to register data into an mHealth-application. Therefore, most patients assumed the early or active stages of RA would be the ideal window to target with such an application, which was confirmed by both nurses and rheumatologists.

> *"If you feel fine and there are no concerns, I suppose you won't keep remembering to use the app." (Pt 5, patient group 1)*

Symptom recognition
Nonetheless, it was acknowledged by patients that remotely recording symptoms requires a certain amount of experience in recognising exactly which symptoms are disease-related, which is often more difficult in the early stages of disease.

> *"I can understand that recognising the symptoms could be more difficult for patients who have only recently been diagnosed or even don't have a definitive diagnosis yet." (Pt 3, patient group 2)*

Uniting both these views, some caregivers believed an mHealth-guided care strategy could be useful to both patients with early and more established RA, suggesting an evolution from a complementary role of mHealth-apps in early disease to a more autonomous role later on in the disease course.

> *"I think it could serve more as an 'extra' in the early disease, and maybe later on, when things are a bit more stable, it could replace some aspects of care." (N 3, nurse group 2)*

Accessibility and acceptability
Access to digital technologies and internet connection, as well as having a certain digital literacy, was identified by all stakeholders as a barrier for mHealth-applications. In some focus groups, older age was proposed as an example of this. Moreover, nurses indicated that language barriers and cultural differences could pose an additional challenge.

Evolving disease characteristics
Rheumatologists were concerned that remote follow-up with an mHealth-application would not be able to capture comorbidities or even changes in the defining characteristics of a patient's underlying disease, implying that, at some point in time, the app could be reflecting signs and symptoms of a different health problem.

> *"If at some point the diagnosis changes and is no longer correctly reflected by the app, I think that could pose a major problem. What if the diagnosis of inflammatory arthritis is not correct, or the disease has evolved into something else?" (R 16, rheumatologist group 2)*

Legal and organisational requirements

Privacy concerns

While patients did not express a reluctance to share their personal data in the context of an mHealth-application, both nurses and rheumatologists were particularly concerned about the security of patients' health information.

> *"I can imagine some patients would be afraid their data would become available to insurers. These patients might rate their symptoms differently, fearing certain consequences." (N 6, nurse group 2)*

In part relating to these privacy concerns, rheumatologists strongly emphasised the need for an mHealth-application to be developed by healthcare providers and patients, rather than by commercial enterprises. This way, rheumatologists expected to retain more control over the content of such an application and the data processed by it.

Workload and financial compensation

Some rheumatologists were concerned that an mHealth-application would significantly increase the amount of patient data to be processed, consequently increasing their workload, while these activities are not currently reimbursed. Therefore, they felt that a tailored legal framework would be needed, including an adaptation of the remuneration system, for mHealth-guided care to be feasible.

Recommended features of an mHealth-application

Table 2 provides a summary of recommended features for an ideal mHealth-application based on the suggestions of patients with RA, rheumatology nurses and rheumatologists in this study. The recommended features were grouped according to the framework of the PSD-model.

Primary Task Support

Reducing the amount and frequency of data to be entered by patients was identified as a priority for all stakeholders. Furthermore, data entry should be a quick and efficient process, while a degree of automation in both entering and processing of the data was preferred by rheumatologists. Patients, nurses and rheumatologists all expected visual or graphical feedback of disease activity scores or symptoms over time to improve patients' engagement with apps. Finally, both patients and rheumatologists suggested to personalise the frequency and content of requested data entry according to a patient's disease activity, for instance extending the interval of symptom registration for patients with a stable disease.

Dialogue Support

All stakeholder groups preferred an mHealth-application to provide reminders when data entry is due. Moreover, patients indicated they would feel more comfortable with mHealth-guided follow-up if the application would send out an alert when the results indicate an increase in disease activity, for instance suggesting them to contact their healthcare provider.

Social Support
While patients did not expect an mHealth-app to facilitate communication with their peers, a direct communication with healthcare providers was identified by patients as a priority for an mHealth-app. The option of a 'free-text box' to further specify certain symptoms was suggested as a means to promote this.

System Credibility
Nurses and rheumatologists strongly emphasised the need for an mHealth-application to be based on validated measures of disease activity. However, the interpretation of remotely monitored disease activity measures was perceived as a challenge, due to the subjective nature of many of these measures. Furthermore, care providers considered an mHealth-application should be integrated with electronic medical patient files or even linked to specific interventions, including physical therapy programs or the monitoring of medication adherence. For patients, it was particularly important to be convinced that their data would actually be used for their benefit.

DISCUSSION

In this cross-sectional qualitative study, we investigated the perceptions and recommendations of 'app-naïve' stakeholders on mHealth-applications in the care for patients with RA.
All stakeholders agreed on some expected benefits mHealth-applications could provide to clinical practice. Firstly, both patients and healthcare providers were convinced that using mHealth-apps could save valuable time and improve the efficiency of ambulatory care. Additionally, patients acknowledged that remote monitoring of RA disease activity via an app could allow rheumatologists to prioritise the allocation of clinic visits to those patients who need it most. These findings are in line with results from a recently published study, which showed this strategy was acceptable to patients with established RA when demand exceeded capacity (27). Secondly, all stakeholders in our study were confident that mHealth-apps could enable patient empowerment by providing patients with more insight into the evolution of disease activity, as well as by conferring personalised education and enhancing patients' trust in their caregivers. Moreover, patients recognised that, by collecting information about their daily lives via an app, they could grant healthcare providers a more comprehensive picture of what matters most to them. As studies have shown, being able to discuss the results of remote monitoring with their physician is highly valued by patients as a contributor to patient-caregiver interaction (11,28). All these factors might contribute to improved illness coherence, a crucial step towards patient empowerment (29).
In spite of these benefits, our study highlights a number of important barriers for mHealth-applications to become an integral part of daily clinical care for RA patients, including the necessity of an appropriate legal framework. For instance, concerns were raised towards data privacy, and who would be able to access patient information. Clear information should thus be provided towards all stakeholders to ensure trustworthy data processing. Moreover, several expected barriers for the implementation of mHealth-applications were specifically related to remote symptom monitoring. First, rheumatologists were concerned mHealth-based symptom monitoring would increase their workload. Therefore, mHealth-applications should aim to streamline the existing responsibilities of healthcare providers, for instance by providing more data, and should not result in additional tasks. Second, patients, nurses and rheumatologists all expressed concerns that frequently assessing disease symptoms entails a risk of reinforcing negative illness behaviour. Patients also worried this would confront them more often with the chronic nature of their disease. Similarly, in a recent study, patients who were interviewed after testing a novel mHealth-app, indicated that the app reminded them too much of their disease, resulting in an internal resistance to use the app (30). Third, all stakeholders in our study were

Table 2. Recommended features of mHealth-applications for RA according to stakeholders, grouped into categories of the PSD-model.

	Patients	Nurses	Rheumatologists
Primary Task Support			
Data reduction	♦	♦	♦
Efficient data entry	♦	♦	♦
Automated processes			♦
Personalised frequency of data entry	♦		♦
Graphical or visual feedback of evolution	♦	♦	♦
Dialogue Support			
Reminders for data entry	♦	♦	♦
Alerts in case of red flags	♦	♦	♦
Suggestions of action in case of red flags	♦		
Social Support			
Direct communication with healthcare providers	♦		
Free-text box	♦		
System Credibility			
Integration with electronic medical patient files		♦	♦
Link with interventions		♦	♦
Monitoring of medication adherence		♦	♦
Purpose and relevance of data entry	♦	♦	♦
Valid measurement instruments		♦	♦

PSD = Persuasive Systems Design

concerned about using data perceived to be subjective and highly patient-specific, such as levels of pain and fatigue. All these expected barriers illustrate the need to carefully consider in what way and how intensively an optimal mHealth-app should track disease activity.

As a final expected barrier, our study participants identified engagement with apps as a challenge and expected this to further decline over time. Indeed, although previous research on mHealth in RA has shown generally high engagement rates, a decline in app-use over time has been suggested (31–33). Interestingly, most stakeholders in our study assumed engagement would be particularly low when the disease is well-controlled. While it was suggested that the early stages of disease would therefore present the ideal window for mHealth-guided symptom-tracking, our results also show that a degree of experience in recognising disease symptoms appears crucial. Strikingly, while recent studies on mHealth-interventions have been very heterogeneous in nature, only one study has to date investigated an mHealth-guided

intervention in patients with early or active disease (12,18). Therefore, the ideal target population for an mHealth-application remains a matter of debate.
In addition to perceived benefits and barriers for the implementation of mHealth-apps, our study participants also identified a number of features the ideal mHealth-application should provide. To explore the expected impact of these features on user engagement, we divided proposed features into 4 categories according to the PSD-model (22). Although it could be argued that improving user engagement should also depend on support and empowerment, rather than being limited to persuasive designs, this model nonetheless provides a useful framework to identify motivational app-features. A recent study based on the PSD-model concluded that most mHealth-apps for chronic arthritis would benefit from more emphasis on Social Support and Dialogue Support-techniques (23). In contrast, most features recommended by stakeholders in our study were related to improving Primary Task Support and System Credibility, such as efficient data entry and a secure link with medical records. We should note that features related to these categories could have partly been prompted by specific interview questions, such as "do you think these applications could be used to monitor your disease?" Nevertheless, all stakeholders emphasised the need for an mHealth-application to facilitate communication between patients and care providers, illustrating that Social Support-features would indeed be highly valued by such an app's intended primary users. In contrast, communication between patients themselves via mHealth-apps was not mentioned in our focus groups, even though peer mentoring has been shown to be important to patients (34,35). Similarly, not many existing mHealth-apps supply such a platform towards patient communication or a patient community (23,36). Reasons for this are unknown, although this could be due to privacy concerns or even due to system credibility. However, peer support might prove to be an important facilitator for app-use and should be explored more in future research.
Our study has some limitations. Firstly, participants were interviewed in focus groups. While focus groups are an efficient method to interactively explore participants' perceptions, some participants might have felt less comfortable to speak openly than they would have in individual interviews. However, focus groups provide a setting that often allows for constructive reasoning among stakeholders, which was of particular importance to gather specific recommendations on app-content. Moreover, two separate focus groups were conducted for each stakeholder group and exhibited comparable results, illustrating the robustness of our findings. Secondly, detailed demographic characteristics of participants could not be provided, since the collection of these data was not included in the study protocol. However, our focus groups did include patients from both academic and private practice or non-academic care settings, and patients from various age groups. None of the included patients had a recently diagnosed RA. Moreover, specific efforts were made to include nurses and rheumatologists with varying levels of experience as well as different practice settings across several different regions. Finally, most of our study participants had little or no experience with mHealth-applications. These results should therefore not be interpreted as experience-based suggestions for improvement. However, this 'app-naïve' study population is also a major strength of this study. This way, the opinions, concerns and recommendations for an mHealth-application, as perceived by its intended users, could serve as a blueprint to develop the optimal mHealth-app. Moreover, by investigating the perceptions of rheumatologists and rheumatology nurses in addition to patients with RA, our study provides a more representative overview of what all its intended users expect an mHealth-application to offer. In addition, the robustness of our findings was improved by analysing the results with an interdisciplinary research team, guided by the QUAGOL. Finally, patient research partners were involved in every stage of this study, providing additional credibility to our results.

Conclusion

This study investigated possible benefits, barriers, and recommendations for the implementation of mHealth-applications in the care for patients with RA, as perceived by mHealth-inexperienced patients, rheumatologists, and rheumatology nurses. Participants expected mHealth-apps to improve the efficiency of care and enable patient empowerment but were concerned that these apps could reinforce negative illness behaviour and assumed engagement would be a challenge. A number of app-features were recommended to overcome these challenges. Finally, while the ideal target audience for an mHealth-app remains to be further determined, a tailored legal and organisational framework should be in place for these applications to become a part of routine care for patients with RA.

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Chapter 4.2

Engagement and attrition with eHealth tools for remote monitoring in chronic arthritis: a systematic review and meta-analysis

ABSTRACT

Objectives. Although electronic health (eHealth) tools are potentially useful for remote disease monitoring, barriers include concerns of low engagement and high attrition. We aimed to summarise evidence on patients' engagement and attrition with eHealth tools for remotely monitoring disease activity/impact in chronic arthritis.

Methods. A systematic literature search was conducted for original articles and abstracts published before September 2022. Eligible studies reported quantitative measures of patients' engagement with eHealth instruments used for remote monitoring in chronic arthritis. Engagement rates were pooled using random effects meta-analysis.

Results. Of 8246 references, 45 studies were included: 23 using smartphone applications, 13 evaluating wearable activity trackers, 7 using Personal Digital Assistants (PDA), 6 including web-based platforms, and 2 using Short Message Service (SMS). Wearable-based studies mostly reported engagement as the proportion of days the tracker was worn (70% pooled across 6 studies). For other eHealth tools, engagement was mostly reported as completion rates for remote patient-reported outcomes (PROs). The pooled completion rate was 80%, although between-study heterogeneity was high (I^2 93%) with significant differences between eHealth tools and frequency of PRO-collection. Engagement significantly decreased with longer study duration, but attrition varied across studies (0-89%). Several predictors of higher engagement were reported. Data on the influence of PRO-reporting frequency were conflicting.

Conclusion. Generally high patient engagement was reported with eHealth tools for remote monitoring in chronic arthritis. However, we found considerable between-study heterogeneity and a relative lack of real-world data. Future studies should use standardised measures of engagement, preferably assessed in a daily practice setting.

INTRODUCTION

Chronic arthritis is an umbrella term for several inflammatory and non-inflammatory musculoskeletal conditions that rank among the most prevalent chronic diseases worldwide and represent a considerable societal burden(1). People suffering from chronic arthritis are faced with pain, stiffness, fatigue and functional decline, negatively affecting their quality of life and social participation(2). These symptoms fluctuate over time and can even persist when the disease is clinically well-controlled, often giving rise to discordance between patients' and physicians' views on disease activity(3). Consequently, potentially relevant information about the disease's impact between clinic visits is insufficiently captured in routine care(4). Moreover, following shifts to targeted treatment strategies, managing chronic inflammatory arthritis increasingly requires lifelong follow-up on a regular basis(5). However, the resulting increase in demand has not been met with a corresponding expansion of the rheumatology workforce, leading to increasing referral times and rising pressure on the conventional care model(6).

Possible solutions to some of these challenges could be found in the form of eHealth, defined as the use of information and communication technologies to support health care(7). Recent years have brought a revolution of technological innovations, including the widespread availability of internet connectivity, smartphones, and wearable activity trackers, all of which could provide health-care practitioners and researchers with opportunities to improve patient care(8). One potential strategy is to use eHealth tools like these to monitor patients with chronic arthritis remotely. Remote monitoring can be implemented in a synchronous setting, where patients and care providers remain in real-time contact through digital communication tools like telephone or video calls. Alternatively, this strategy can be approached asynchronously, which implies that the eHealth tool collects information, such as patient-reported outcomes (PROs), that is only later accessed by the care provider(9). Particularly in an asynchronous setting, eHealth tools could provide researchers or care providers with a unique window into the day-to-day variability of disease activity and its impact on patients(10). Such information has also shown potential to facilitate patient-initiated follow-up, as opposed to prescheduled clinic visits(11), ultimately contributing to reduced health-care utilisation(12). Finally, there is an ongoing evolution in technology that allows patients to self-sample capillary blood for biochemical markers like urate or C-reactive protein, and recent studies have shown promising feasibility for such devices(13–15).

However, despite their potential benefits, the implementation of eHealth tools in routine rheumatology care is associated with several challenges, including concerns about vulnerable populations, legal and organisational barriers, and respondent fatigue(16). Among these, arguably the biggest challenge of eHealth studies is missing data due to attrition and limited patient engagement, potentially biasing study results and hampering larger-scale implementation(17). Consequently, it is crucial to comprehensively describe how engagement with eHealth tools is currently measured, how reliably patients use and continue to use these tools, and which population-based or study-specific factors are associated with eHealth engagement.

The objective of this systematic review was to summarise the available evidence on patients' engagement and attrition with eHealth tools for remote monitoring of disease activity or impact in chronic arthritis. For these purposes, this review focused on asynchronous eHealth interventions, rather than on tools intended for remote consultations.

METHODS

This systematic review was conducted in accordance with the Cochrane Handbook and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines(18). The protocol was registered on PROSPERO (CRD42021267936).

Eligibility criteria

Studies were eligible for inclusion if they were conducted in patients with chronic arthritis, defined as either rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriatic arthritis (PsA), osteoarthritis (OA), gout or juvenile idiopathic arthritis (JIA). Records not reporting delineable outcome data for any of these populations were excluded. Participants of all ages were eligible. Moreover, studies were considered only if they included any eHealth instrument for asynchronous remote monitoring purposes, and additionally provided information on patients' objectively measured engagement, adherence, or compliance with the use of this eHealth instrument. Records were excluded if engagement was solely self-reported or if no information on data completeness was reported. As an eHealth tool, we considered any application of information and communication technology in the context of health or health-related fields(7).

Study design

We included randomised controlled trials (RCTs), observational studies, and case-control studies published in English and in peer-reviewed journals. Given the rapid evolution of this research field, we additionally included conference abstracts adhering to the eligibility criteria, and updated the search a second time. To allow for maximal comparability, we did not consider purely qualitative studies.

Outcomes

The primary outcome was any quantitative assessment of patients' engagement or adherence with the reported eHealth instrument. As secondary outcomes, we aimed to summarise the evidence on attrition, defined as a loss of participant engagement over time, and to describe demographic, disease-related, or study-related factors associated with engagement or attrition.

Search strategy and study selection

We systematically searched the following databases from inception to the 29th of May 2021 (updated to the 31st of August 2022): Embase, PubMed, Cochrane Central, CINAHL, Web of Science, Clinicaltrials.gov, and the International Clinical Trials Registry Platform (ICTRP). The search string was developed in collaboration with biomedical reference librarians of KU Leuven Libraries and was based on key words and free-text entries combining the concepts of "chronic arthritis" AND "eHealth" (Supplement 4.1). Additionally, we screened the reference lists of included reports as a backward citation search.

Duplicates were removed with Endnote V20.1. First, all records were screened by title and abstract independently by two reviewers (CVL and MD), using Rayyan QRCI (https://www.rayyan.ai/). Finally, the full texts were screened for all remaining articles. A third reviewer (DDC) was consulted to resolve conflicts.

Data extraction

Two reviewers (CVL and MD) independently extracted data from included studies into a Microsoft Excel database. The following data were considered: general study characteristics (first author, publication year, study design, and study duration); population characteristics (number of participants, age, sex, and diagnosis); eHealth-related characteristics (type of eHealth tool, outcomes collected by the tool, requested frequency of outcome collection, and

incentives for use of the tool); and engagement or attrition-related characteristics (definition and quantitative outcome).

Data synthesis
Meta-analysis was performed for engagement outcomes available in ≥3 studies. As we expected high between-study heterogeneity, a random-effects model (restricted maximum likelihood method with Hartung-Knapp adjustment) was applied to estimate the pooled effect across studies with similar engagement outcomes. An inverse variance method was used for weighting each study in the meta-analysis. The proportion of variability in effect estimates due to between-study heterogeneity was summarised using Tau^2 and I^2. Logit-transformed proportions were used for variance stabilisation. If ≥10 studies were available and relevant subgroups were sufficiently large, heterogeneity among studies with similar engagement outcomes was further explored by subgroup analyses for the type of eHealth tool, the outcome collection frequency, diagnosis, and study design (RCT or observational/case-control study). Additionally, the impact of study duration was explored with univariable meta-regression. Finally, sensitivity analyses were performed by excluding abstracts. Meta-analysis was conducted with R (v2021.09.1), using the *meta* package.

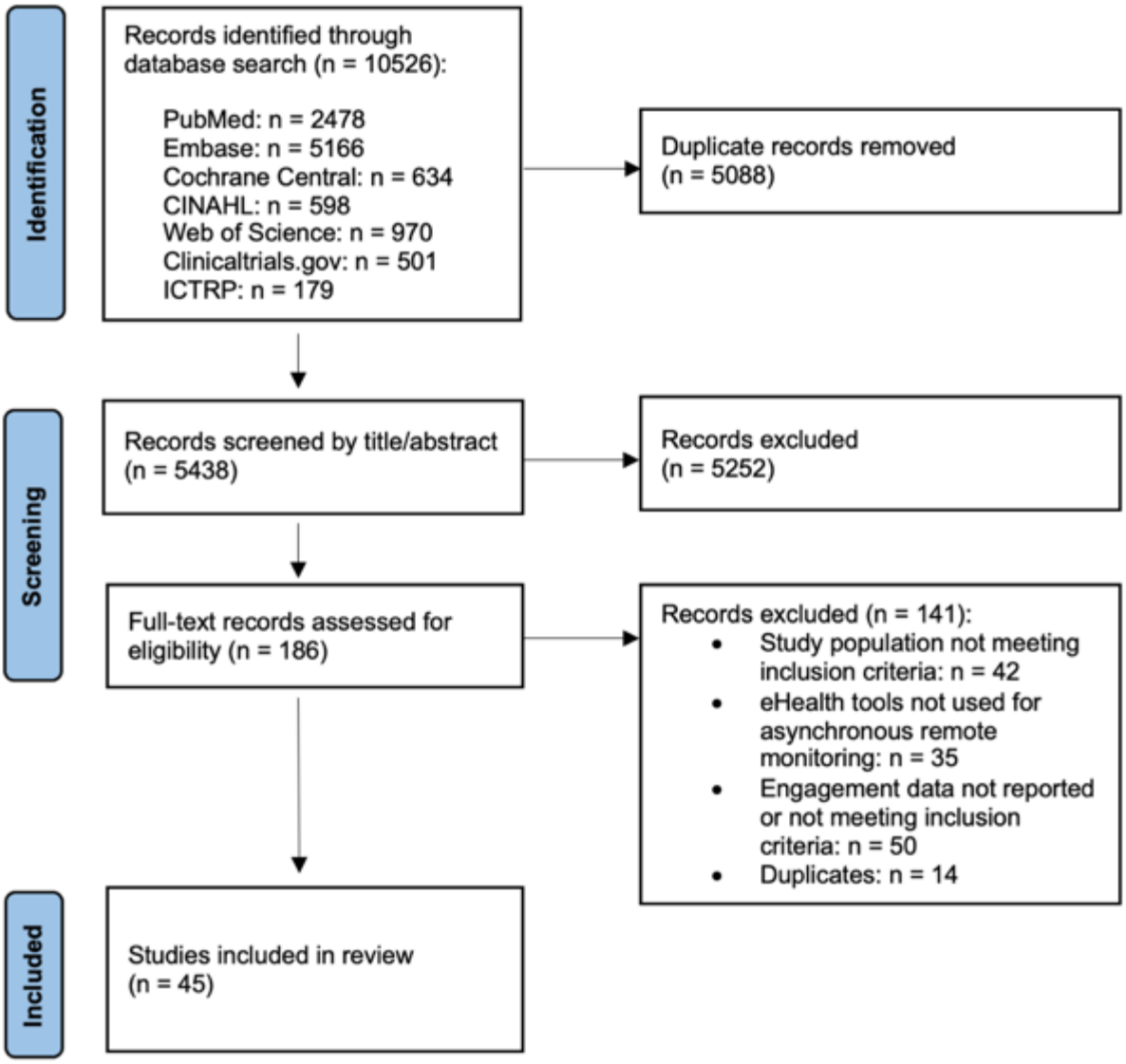
Risk of bias assessment
Risk of bias was assessed for all included studies for which a full text was available, using the Newcastle-Ottawa scale (NOS) for cohort studies and the PEDro scale for randomised controlled trials(19,20).

RESULTS
Search results
The systematic search resulted in 10526 potentially relevant records (Figure 1). After deduplication, 5438 articles were screened by title and abstract, 186 of which were eligible for full-text screening. Among these, 45 articles were eventually included in the final review, with publication dates ranging from 2008 to 2022. No additional records meeting the inclusion criteria were identified through backward citation searching.

Study characteristics and risk of bias
A total of 14341 patients were included across the 45 eligible studies (Table 1). Of these 45 studies, 32 were observational studies, 8 were RCTs or post-hoc analyses thereof, 2 were case-control studies, and 3 were conference abstracts. Sixteen (36%) studies were conducted in an RA population, 13 (29%) in an OA population, 9 (20%) in JIA, 2 (4%) in a population with gout, and 3 (7%) in patients with ankylosing spondylitis (AS) or axial SpA, while 4 (9%) studies included mixed populations. The reported mean age of included participants ranged from <18 years in the JIA studies to over 60 years in several OA-focused studies. Most studies included a predominantly female patient population. Only six articles included mostly men with either gout(21,22), JIA(23), SpA(24,25), or OA(26).
Study durations varied considerably across the included studies, ranging from 7 days to up to one year. Moreover, a large degree of heterogeneity was seen in the studies' approach to patient recruitment. Although most studies recruited participants during a physical clinic visit, 13 studies (29%) approached eligible participants through fully digital channels such as email, social media, Short Message Service (SMS) messages, or online surveys.
Finally, risk of bias was assessed for all 42 studies with full-text availability (Supplement 4.2). Overall, included studies had a moderate risk of bias when considering the outcome of participant engagement. The main source of bias was selection bias, with most studies including only participants who had both access to smartphones or computers and sufficient

experience using them. Furthermore, some studies recruited participants based on a self-reported physician's diagnosis of arthritis(27–33), particularly when a fully digital recruitment approach was taken, and most studies lacked control groups.

Figure 1. PRISMA flowchart of systematic review.



Characteristics of reported eHealth tools

In all, 23 studies (51%) evaluated the use of a smartphone application, while 13 studies (29%) reported on the use of wearable activity trackers, 7 (16%) provided participants with a Personal Digital Assistant (PDA) e-diary, 6 (13%) used a web-based platform, and 2 (4%) were based on an SMS messaging system (Table 1). Generally, in studies evaluating activity trackers, participant data such as step counts and physical activity were collected continuously while wearing the tracker. By contrast, other eHealth tools primarily collected PROs, usually in the form of questionnaires sent to participants via the system. However, these eHealth systems differed significantly in the specific type of outcome measures collected, in the frequency of requested PRO-reporting, and in the incentives provided to participants to adhere to this

reporting frequency. For instance, 7 studies (16%) asked participants to complete PROs three times each day, whereas once-a-day reporting was requested in 19 studies (42%), weekly reporting in 14 (31%), and monthly reporting in 6 (13%). Some systems allowed data entry at any time, for instance in case of a flare, while one study asked participants to choose their preferred reporting frequency at baseline(34). Finally, incentives to participants for providing complete data ranged from financial compensation and regular compliance checks in some studies to no incentives whatsoever in others.

Participant engagement with eHealth tools

Engagement was defined in several ways across the included studies (Table 1). Some studies defined engagement categorically or based on the proportion of patients providing data above a certain threshold of completeness.

However, where applicable, most articles reported a completion rate for the collected PRO-data, defined as the proportion of all requested data entries in the study that were effectively completed by participants. Meta-analysis of the 34 studies that reported completion rates (Figure 2) resulted in a pooled global completion rate of 80% [95% CI: 73-85%] with high between-study heterogeneity (Tau^2 0.78; I^2 93%).

Subgroup analysis (Figure 3) showed significant differences between eHealth tools (p for interaction <0.01), with a pooled completion rate of 73% [95% CI: 64-80%] in studies using smartphone applications, 91% [95% CI: 81-96%] in studies using PDA e-diaries, 81% [95% CI: 54-94%] in studies evaluating a web-based platform, and 71% [95% CI: 29-94%] in studies using an SMS messaging system. Additionally, two studies involved PRO registration via a smartwatch app and reported a pooled completion rate of 79%.

PRO completion rates also differed according to the requested frequency of data collection (p for interaction = 0.02), with a pooled completion rate of 86% [95% CI: 77-92%] for daily, 70% [95% CI: 57-81%] for weekly, and 71% [95% CI: 50-86%] for monthly intervals (Figure 4). In studies collecting data more than once per day, a pooled completion rate of 69% [95% CI: 56-80%] was reported. Additional subgroup meta-analyses (Supplement 4.3) showed no apparent differences in PRO completion rates according to diagnosis (including only studies in an RA population) and study design (comparing RCTs and observational studies).

Finally, studies using a wearable activity tracker mostly defined engagement as the proportion of days the tracker was actively worn. Across the 6 studies for which this was reported(21,30,35–38), the pooled proportion of days worn was 70% [95% CI: 39-90%] with high between-study heterogeneity (Tau^2 1.18; I^2 86%) (Figure 5).

In sensitivity analyses excluding abstracts, meta-analysis resulted in a pooled global PRO-completion rate of 80% (unchanged to when considering all records) and a pooled proportional tracker wear time of 77% (compared to 70% when considering all records) (Supplement 4.4).

Attrition

In total, 20 studies reported on attrition, defined as a loss of participant engagement over time (Table 2). Among these, 14 studies (70%) defined attrition as the difference between the start and end of the study in PRO-completion rate or in the amount of time the wearable tracker was worn. The remaining 6 articles reported on attrition either as the proportion of participants who were no longer active with the eHealth system by the end of the study, or as the proportion who did not meet a minimal threshold of data completeness.

Generally, attrition rates were highly variable, ranging from no change in completion rate over time in a PDA e-diary study nested within a large phase III drug trial(39) to as much as 89% drop-out in a smartphone feasibility study that recruited participants exclusively through social media(27). Overall, longer study durations were associated with lower completion rates (p=0.029 in univariable meta-regression) (Supplement 4.5).

Figure 2. Forest plot of pooled completion rates for PROs collected with eHealth tools.

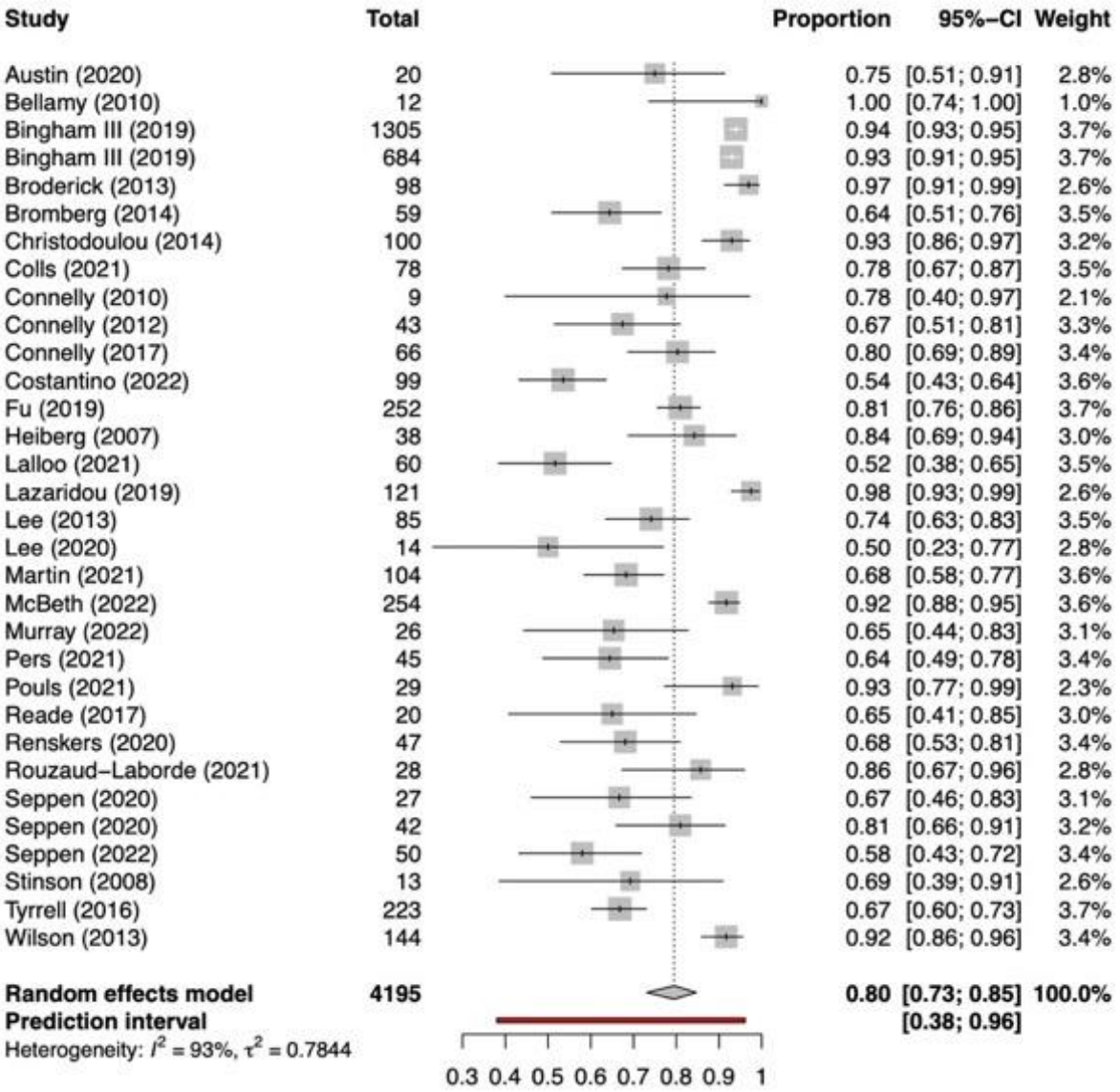


Figure 3. Forest plot of pooled completion rates according to eHealth tool.

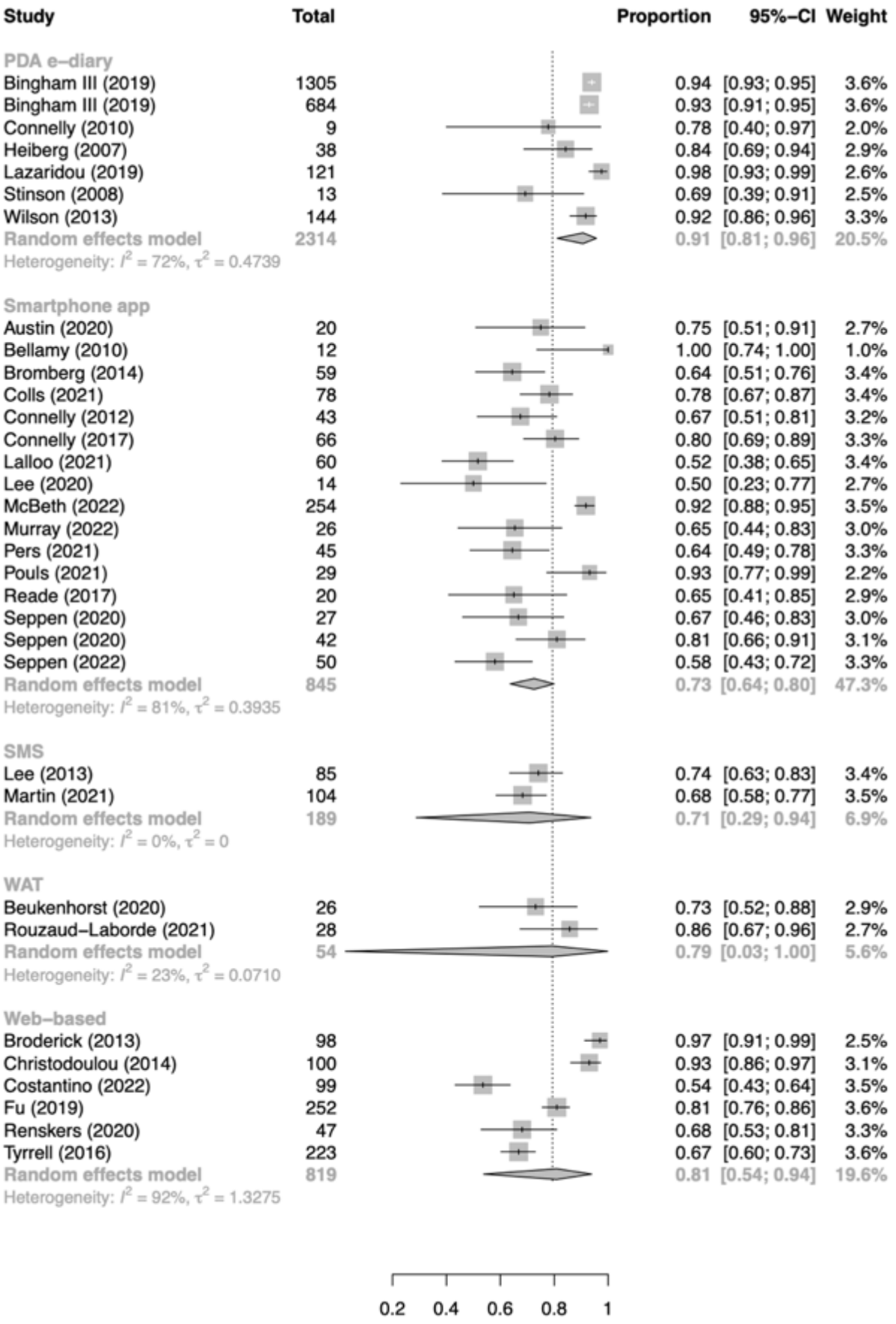


Figure 4. Forest plot of pooled completion rates according to PRO collection frequency.

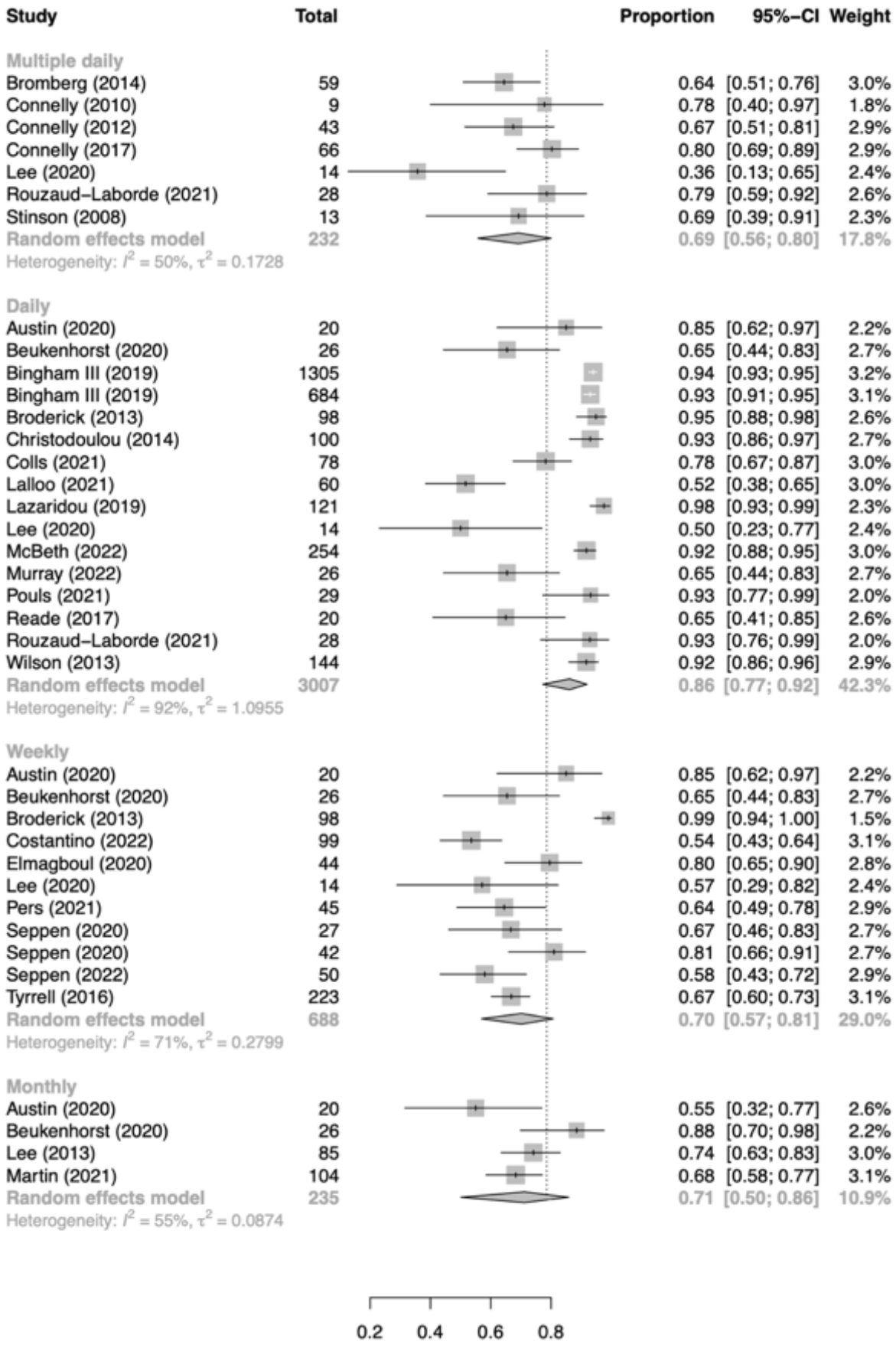
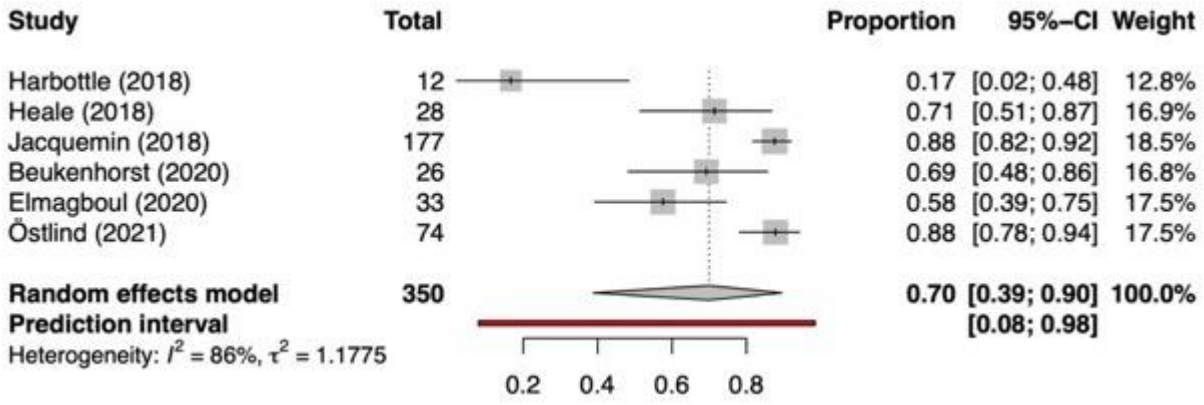


Figure 5. Forest plot of pooled proportion of study days a wearable activity tracker was actively worn.



Factors facilitating or hindering engagement

Facilitators or barriers to eHealth engagement were reported in 17 (38%) of the included studies (Table 3), but only 13 of these studies provided quantitative assessments.

First, evidence for the influence of demographic or disease-related aspects on engagement was largely inconsistent. Overall, higher levels of engagement were reported for older adults and for children rather than adolescents with JIA. However, while one study found women with chronic arthritis to be more engaged than men(31), no such difference was apparent in others(28,40). Similarly, higher completion rates were reported with lower disease activity in an established RA population(40), whereas the inverse was found in a recent study on SpA(25), and qualitative data suggested that a lack of symptoms might hinder engagement(41). Additionally, one study found higher completion rates for patients treated with biological disease-modifying drugs(32), while this finding was contradicted in another report(25). Moreover, engagement was not affected by the diagnosis itself in any of the included studies with mixed populations. Conflicting results were also reported for the influence of employment status, with one study reporting more dropouts in non-employed participants(32), whereas another found lower completion rates in fully employed patients(42).

In addition, several studies indicated that the approach to outcome collection might influence participants' engagement. For instance, less time-intensive PRO-reporting schedules, such as weekly rather than daily reporting, were associated with higher completion rates in 5 out of 6 studies for which this information was available(30,32,43–45). Moreover, higher engagement was found when feedback was provided to patients about the data they reported, either by discussing them in clinic or through data visualisation in the eHealth tool itself. Specifically, the PARADE study reported a 4% difference in attrition in favour of participants who had daily access to their data compared to those who did not(27). Similarly, using a smartphone app to provide visual feedback on step counts resulted in increased engagement with a wearable activity tracker in another report(46). Interestingly however, using reminders to prompt data entry did not appear to have a clear effect on participant engagement in both studies that investigated this(11,25).

DISCUSSION

In this systematic review, we summarised the evidence on patients' engagement with eHealth systems used to remotely monitor disease activity or impact in chronic arthritis. Relatively high levels of eHealth engagement were reported across 45 included studies, which primarily consisted of observational cohorts and randomised controlled trials. The pooled global completion rate for remotely monitored PROs was 80%, while wearable activity trackers were worn for a pooled global proportion of 70% of study days, rising to 77% in a sensitivity analysis excluding abstracts.

In general, these results are in line with engagement data from remote monitoring studies in other chronic diseases, including diabetes, obesity, and mental health conditions(47). However, between-study heterogeneity for engagement outcomes was high in both previous research and in our review. This considerable heterogeneity encountered between studies represents a first major challenge in the current landscape of eHealth research. Among the included studies, much variability was apparent in study population and duration, ranging from only a few days to one year, as well as in the incentives to participants for providing complete data, and even in how engagement was defined and measured. Furthermore, some studies used an entirely digital recruitment approach without physical contact between patients and investigators, for instance by including participants via social media. All these study-related aspects might affect both engagement with an eHealth monitoring approach and the generalisability of the results. Furthermore, comparisons between studies are inevitably limited because of these differences. Similar reports on the challenges of heterogeneity in eHealth studies also emerged as major conclusions in several recent systematic reviews, focusing on synchronous telemedicine, mobile health interventions and wearable activity trackers in rheumatology(9,48,49). Moreover, this challenge is clearly not limited to the rheumatology field(50). Therefore, future research on the use of eHealth systems should not only assess engagement outcomes, but also report them in a standardised way. Based on our review results, the most suitable measures for this purpose seem to be completion rates and proportional wear time for PRO-based and wearable-based interventions, respectively.

A second challenge faced by the eHealth research field in rheumatology is the limited availability of data from daily clinical practice, as is clear from the studies included in our review. This seems particularly important when considering the issue of disengagement over time reported both in many eHealth studies and for mobile applications outside of the research setting. For instance, an estimated 71% of app users across all industries stop using the app within 3 months(17), and a study of adherence to activity trackers in students showed 75% disengagement within 4 weeks(51). In our review, only 20/45 included studies effectively reported data on attrition, and in most cases these data were collected within a strictly controlled research environment. This is particularly relevant since generally low levels of attrition were primarily reported in studies that were either of shorter duration or included strong incentives to support engagement, such as financial compensation. Similarly, completion rates for the PDA e-diaries did not show any decline over time in the phase III baricitinib trials RA-BEAM and RA-BUILD, again in a setting of close follow-up and targeted participant training(39). By contrast, much higher attrition rates were reported in several "fully digital" studies, with 89% of participants disengaging within less than 3 months in the PARADE study(27), 45% disengaging within 3 months in an ancillary study of the ArthritisPower registry(28), and 41% not completing the 2-week lead-in period in another ArthritisPower study(32). These striking differences in attrition between closely or less closely controlled research settings have also been reported for other chronic diseases, with higher engagement rates in studies that compensated patients for their participation(52). Consequently, there is a clear need for more eHealth engagement data from routine care settings, where higher attrition rates are likely.

Pending such data, the current evidence on eHealth in rheumatology might underestimate the problem of attrition.

However, we should note that some potentially relevant studies from daily practice settings were excluded from our review because they did not report engagement based on data completeness. For instance, in a 12-month, multicentric study from France, patients with RA were randomised to either usual care or additional access to the web-based Sanoia platform, developed to support self-monitoring(53). In this study, no direct incentives to access the platform were provided to optimally mirror daily care. Although satisfaction with the platform was high, 26% of patients never accessed Sanoia, and the number of accesses clearly declined over time.

The phenomenon of attrition has prompted researchers to explore the optimal target population and possible barriers and facilitators for engaging with eHealth systems. Our review identified several demographic and disease-related aspects that might be associated with eHealth engagement. Among these, the finding that older age seems associated with higher engagement is somewhat surprising, given the known barriers of aging on technology use(54). However, since much of the available evidence stems from research populations, it is likely that the most vulnerable elderly patients were either excluded from these studies or did not express an interest to participate. Moreover, older age was associated with lower eHealth engagement in JIA studies, in line with the commonly reported lower treatment adherence in adolescents(55). Interestingly though, the diagnosis did not appear to affect eHealth engagement, either in individual studies or in subgroup meta-analysis, despite the important differences in how different types of chronic arthritis are managed.

Another intriguing finding of our review is that engagement rates do appear to be affected by the approach to outcome collection. For instance, one included study investigated the effect of different pain reporting frequencies on completion rates in JIA patients, using a randomised N-of-1 cross-over design(43). In this study, engagement was higher in less time-intensive schedules, such as weekly rather than daily reporting, even though participants tended to prefer the once-a-day schedule. Similar differences were apparent in an additional four studies(30,32,44,45), while another intervention allowed participants to choose their preferred reporting frequency up-front and found that monthly reporting was chosen most often(34). In contrast, our meta-analysis showed that completion rates were highest in studies requesting daily PRO reporting. This discrepancy might be explained by differences in study or population characteristics. Nevertheless, these findings are particularly interesting in relation to concerns, raised in qualitative research, that more frequent reporting could cause more internal resistance or illness behaviour in patients(16,41). Evidence to support this concern is still limited, however, with one trial indeed showing a negative effect of a gout self-management app on illness perceptions(56), while Lee et al. found no differences in pain interference between reporting schedules in their N-of-1 trial(43). Interestingly, the choice of outcome measure to be collected by the eHealth system might be equally important, with some studies allowing participants to freely select their preferred outcome measure(28,34).

Regardless of the way eHealth tools are implemented, benefiting from their promising potential requires efforts to maximise and maintain participant engagement. To achieve this, previous research has highlighted the importance of co-designing eHealth systems with patients, optimising system usability, minimising workload and time commitment for users, including community-building efforts or personal contact with care providers, and sending automated reminders for data entry(17). Interestingly though, reminders did not appear to have a clear effect on data completeness in both included studies that quantitatively assessed this. Additionally, qualitative results from the studies included in our review suggested that eHealth engagement might be hindered in case of well-controlled symptoms or by system-related

technical issues, lack of digital literacy, interference of other daily activities, and internal resistances like respondent fatigue(24,30,34,41,57,58).
Furthermore, our review showed positive effects on engagement when feedback was provided to participants, either by the physician or by the eHealth system itself(27,46), a finding that is extensively supported by qualitative evidence(16,24,30,34,41). Finally, motivational techniques such as gamification could help users to remain engaged and are generally underused in the existing array of eHealth systems(59,60). Our systematic review adds to this growing body of evidence and could support researchers and system developers in designing and implementing eHealth tools that optimally meet the challenges of attrition and low engagement.
Some limitations of this systematic review should be acknowledged. We focused specifically on remote monitoring in an asynchronous setting, which implies that eHealth tools were not considered if they were intended to facilitate real-time contact between patients and care providers. Consequently, studies based on telehealth interventions like telephone or video consultations were not included. The results of this systematic review can therefore not be extended to any type of eHealth intervention. Additionally, we did not consider purely qualitative studies. Finally, both the conclusions and the generalisability of our review are inherently limited by selection bias in the included studies, the majority of which considered participants only if they had access to digital tools and sufficient experience using them.
However, our review was conducted and reported according to commonly recommended guidelines. The protocol was registered in PROSPERO, the search string was developed in collaboration with biomedical reference librarians, study selection and data extraction were conducted independently by 2 reviewers in both published and “grey” literature, and a third reviewer was consulted to resolve conflicts. Moreover, the search was updated at a later time, and a meta-analysis was performed with subgroup and sensitivity analyses to explore between-study heterogeneity.

Conclusion
Relatively high levels of participant engagement were reported in studies involving eHealth systems for asynchronous remote monitoring in chronic arthritis. However, comparisons were hindered by considerable heterogeneity and a relative lack of data from routine care settings. This is of particular importance given the observed differences in attrition in closely controlled versus less incentivised research settings, as well as the finding that engagement tends to decline with longer study duration. To provide a clear picture of the feasibility of remote monitoring eHealth strategies, future studies should therefore use standardised measures of engagement, such as PRO completion rates or proportional tracker wear time, and assess them with study designs that optimally reflect daily clinical practice

Table 1. Characteristics and engagement data for included eHealth studies.

First author (year)	*Diagnosis*	*N*	*Age, years (SD)*	*Female, %*	*Duration, days*	*Recruitment*	*eHealth tool*	*Monitoring frequency*	*Incentives*	*Engagement (definition)*	*Engagement (%)*
Austin (2020)(61)	RA	20	32-84	75	85	Physical/clinic	Smartphone app	Daily; weekly; monthly	Reminders	Completion rate	86; 85; 58
Bellamy (2010)(62)	OA	12	63 (9)	75	12	Physical/clinic	Smartphone app	Once every 3 days	Reminders	Completion rate	100
Beukenhorst (2020)(30)	OA	26	64	50	90	Advertisements → event	WAT (C)	Continuous + PROs daily; weekly; monthly	Reminders	Proportion of days worn (WAT) + completion rate (PRO)	73 + 66; 69; 89
Bingham III (2019)(39)	RA	1305	53 (12)	77	84	Physical/clinic	PDA e-diary	Daily	Reminders	Completion rate	94
	RA	684	52 (12)	82	84	Physical/clinic	PDA e-diary	Daily	Reminders	Completion rate	93
Broderick (2013)(44)	OA	98	57 (10)	60	28	Online survey → phone call	Web-based	Daily; weekly	Financial; phone calls	Completion rate	96; 100
Bromberg (2014)(23)	JIA	59	13 (3)	45	28	Physical/clinic	Smartphone app	Thrice daily	Reminders; financial; phone calls	Completion rate	66
Christodoulou (2014)(29)	OA	100	57 (10)	60	28	Online survey → phone call	Web-based	Daily	Reminders; financial; phone calls	Completion rate	93
Colls (2021)(40)	RA	78	55 (11)	81	210	Physical/clinic	Smartphone app	Daily	Reminders	Completion rate	79
Connelly (2010)(63)	JIA	9	12 (3)	89	14	Physical/clinic	PDA e-diary	Thrice daily	Reminders	Completion rate	88
Connelly (2012)(64)	JIA	43	13 (3)	86	28	Physical/clinic	Smartphone app	Thrice daily	Reminders; phone calls	Completion rate	69
Connelly (2017)(65)	JIA	66	13 (3)	73	30	Physical/clinic	Smartphone app	Thrice daily	Reminders; financial	Completion rate	81
Costantino (2022)(66)	AxSpA	99	NR	64	356	Online (SPONDY+ platform)	Web-based	Weekly	NR	Completion rate	54
Crouthamel (2018)(27)	RA	388	48 (12)	81	84	Social media	Smartphone app	Weekly; monthly	Reminders	Proportion of active participants (per week)	20-100*
Druce (2017)(31)	RA(19%) SpA(9%) Arthritis(40%) Gout(3%) FMS(24%) Headache(7%) Neuropathic(13%) Other(23%)	6370	49 (13)	81	180	Advertisements; directing to app	Smartphone app	Daily	Reminders	Categorical engagement: - High (15%) - Moderate (22%) - Low (38%) - Tourists (25%). For each group: proportion of days with complete data	High: 70 Moderate: 28 Low: 3 Tourists: 1

Table 1 (cont.). Characteristics and engagement data for included eHealth studies.

First author (year)	*Diagnosis*	*N*	*Age, years (SD)*	*Female, %*	*Duration, days*	*Recruitment*	*eHealth tool*	*Monitoring frequency*	*Incentives*	*Engagement (definition)*	*Engagement (%)*
Elmagboul (2020)(21)	Gout	33/44†	49 (15)	15	183	Physical/clinic	WAT (C) + smartphone app	Continuous + ePROs weekly	Reminders	Proportion of days worn + completion rate	61; 81
Fu (2019)(67)	OA	252	62 (8)	79	90	Online survey → phone call	Web-based	Once every 10 days + in case of flare	Reminders	Completion rate	81
Gilbert (2021)(68)	OA	2127	65 (9)	56	7	Physical/clinic	WAT (R)	Continuous	NR	Proportion wearing WAT ≥4/7 days	91
Harbottle (2018)(35)	JIA	12	14	50	90	Physical/clinic	WAT (R)	Continuous	NR	Proportion of days worn	17
Heale (2018)(36)	JIA	28	15	74	28	Physical/clinic	WAT (C)	Continuous	Reminders	Proportion of days worn	72
Heiberg (2007)(69)	RA	38	58 (13)	66	84	Mail → event	PDA e-diary	Daily; weekly	Phone calls	Completion rate (overall daily/weekly)	85
Jacquemin (2018)(37)	RA & axSpA	177	46 (12)	64	90	Physical/clinic	WAT (C)	Continuous	NR	Proportion of days worn	88
Kempin (2022)(25)	AxSpA	69	42 (11)	42	168	Physical/clinic	Smartphone app	Once every 2 weeks	Reminders (1/2); phone calls	Proportion providing requested data ≥80% of moments by week 12	29 (but 81% exported at least once)
Lalloo (2021)(70)	JIA	60	15 (2)	78	56	Physical/clinic	Smartphone app	Daily	Financial; phone calls	Completion rate	52
Lazaridou (2019)(71)	OA	121	66 (9)	59	7	Physical/clinic	PDA e-diary	Daily	NR	Completion rate	98
Lee (2013)(42)	RA	85	18+ (categorical)	77	60	Physical/clinic	SMS	Monthly	Reminders; financial	Completion rate	75
Lee (2020)(43)	JIA	14	13 (2)	64	56	Physical/clinic	Smartphone app	Twice daily; daily; weekly + in case of pain	Phone calls	Completion rate	51; 63; 38
Martin (2021)(72)	RA	104			Ongoing	SMS	SMS	Monthly	Reminders	Completion rate	69
McBeth (2022)(33)	RA	254	57 (49-64)	81	30	Email → phone call	Smartphone app	Thrice daily; daily; once every 10 days	Reminders	Completion rate (overall thrice daily & daily)	92
Murray (2022)(73)	RA	26	18+ (categorical)	77	56	Mail[l] → phone call	Smartphone app	Daily (alternating cycle)	Reminders	Completion rate	66
Nowell (2020)(32)	RA	278	50 (11)	92	84	Email to ArthritisPower members	WAT (C) + smartphone app	Continuous + PROs daily; weekly	Reminders; financial; phone calls/emails	Proportion providing requested data >70% of days	82 + 57; 87
Nowell (2021)(28)	OA(65%); RA(49%); PsA(26%); AS(16%); FMS(40%); OP(16%); SLE(9%)	253	56 (9)	89	90	Email to ArthritisPower members	Smartphone app	Monthly	Reminders	Proportion completing all ePROs	55

Table 1 (cont.). Characteristics and engagement data for included eHealth studies.

First author (year)	*Diagnosis*	*N*	*Age, years (SD)*	*Female, %*	*Duration, days*	*Recruitment*	*eHealth tool*	*Monitoring frequency*	*Incentives*	*Engagement (definition)*	*Engagement (%)*
Östlind (2021)(38)	OA	74	57 (5)	87	84	Physical/clinic	WAT (C)	Continuous	Emails	Proportion of days worn	88
Pers (2021)(74)	RA	45	18-75	73	183	Physical/clinic	Smartphone app	Weekly	Reminders Phone calls	Completion rate (final 16 weeks)	67
Pouls (2021)(22)	Gout	29	57 (13)	3	90	Physical/clinic	Smartphone app	Daily	Reminders	Completion rate	96
Reade (2017)(57)	RA	20			60	Physical/clinic	Smartphone app	Daily	Reminders	Completion rate	68
Renskers (2020)(34)	RA & SpA	47	57 (11)	57	14-597 (mean 350)	Physical/clinic	Web-based	Free to choose (at baseline)	Reminders	Completion rate	68
Rouzaud-Laborde (2021)(45)	OA	28	73 (6)	70	14	Physical/clinic	WAT-based ePRO-app (C)	Thrice daily; daily	Reminders	Completion rate (adjusted for wear time - technical issues)	81; 93
Seppen (2020)(41)	RA	42	54 (13)	86	28	Physical/clinic	Smartphone app	Weekly	NR	Completion rate	82
	RA	27	52 (11)	78	28	Physical/clinic	Smartphone app	Weekly	NR	Completion rate	70
Seppen (2022)(11)	RA	50	58 (13)	56	356	Physical/clinic	Smartphone app	Weekly	Reminders (only 1 month)	Completion rate	59
Skrepnik (2017)(46)	OA	211	63 (9)	50	90 (+ 90 day follow-up)	Physical/clinic	WAT (C) ± smartphone app (1:1)	Continuous	Reminders (app only)	Proportion providing data >80% of days (first 90 days)	91
Stinson (2008)(58)	JIA	13	13 (3)	85	14	Physical/clinic	PDA e-diary	Thrice daily	Reminders Financial Phone calls	Completion rate	72
Tyrrell (2016)(24)	AS	223	50 (14)	39	84	Email/social media	Web-based	Weekly	Reminders	Completion rate	67
Wilson (2013)(75)	OA	144	66 (10)	57	22	Physical/clinic	PDA e-diary	Daily	NR	Completion rate	92
Yu (2022)(26)	OA	65	61 (6)	46	2x7	Physical/clinic	WAT (C)	Continuous	NR	Proportion wearing WAT ≥6/7 days	99
Zaslavsky (2019)(76)	OA	24	71 (4)	70	133	Physical/clinic	WAT (C)	Continuous	Reminders Financial Phone calls	Proportion of hours worn per day	88

* Proportion of active participants was reported separately for each week, ranging from 100% in week 1 to approximately 20% at week 12.

† ePROs were evaluated in 44 participants, WAT in a subgroup of 33 participants from the same study.

‖ Recruitment letters were mailed to patients who participated in the preceding trial with the same smartphone app (Colls 2021).

RA = rheumatoid arthritis, OA = osteoarthritis, JIA = juvenile idiopathic arthritis, SpA = spondyloarthritis, FMS = fibromyalgia syndrome, OP = osteoporosis, SLE = systemic lupus erythematosus, AS = ankylosing spondylitis, WAT = wearable activity tracker (either consumer-grade (C) or research-grade (R)), PDA = Personal Digital Assistant, SMS = short message service, PROs = patient-reported outcomes

Table 2. Overview of included studies reporting loss of eHealth engagement over time (attrition).

First author (year)	*Duration (days)*	*eHealth tool*	*Monitoring frequency*	*Attrition (definition)*	*Attrition (%)*
Beukenhorst (2020)	90	WAT	Continuous + PROs daily; weekly; monthly	Active participants (WAT) + completion rate (overall PROs): baseline - end	54 + 55
Bingham III (2019)	84	PDA e-diary	Daily	Completion rate: week 1 - week 12	0
Colls (2021)	210	Smartphone app	Daily	Completion rate: first 3 months - final 3 months	26
Connelly (2012)	28	Smartphone app	Thrice daily	Completion rate: first 2 weeks - second 2 weeks	24
Crouthamel (2018)	84	Smartphone app	Weekly; monthly	Active participants: baseline - end	89
Elmagboul (2020)	183	WAT + smartphone app	Continuous + ePROs weekly	Proportion not meeting minimal WAT wear time	18
Jacquemin (2018)	90	WAT	Continuous	Active participants: baseline - end	22
Kempin (2022)	168	Smartphone app	Once every 2 weeks	Proportion providing data ≥80% of moments: week 12 - week 24	10
Lalloo (2021)	56	Smartphone app	Daily	Completion rate: first day - final day	48
Lee (2013)	60	SMS	Monthly	Completion rate: first month - final month	10
Nowell (2021)	90	Smartphone app	Monthly	Active participants: baseline - final month	45
Murray (2022)	56	Smartphone app	Daily (alternating cycle)	Completion rate: first week - final week	16
Östlind (2021)	84	WAT	Continuous	Proportion of days worn: first week - final week	20
Pouls (2021)	90	Smartphone app	Daily	Active participants: baseline - end	0
Renskers (2020)	14-597 (mean 350)	Web-based	Free to choose (at baseline)	Active participants: baseline - end	49
Seppen (2020)	28	Smartphone app	Weekly	Completion rate: first week - final week	39
	28	Smartphone app	Weekly	Completion rate: first week - final week	63
Seppen (2022)	356	Smartphone app	Weekly	Completion rate: first 3 months - final 3 months	4
Skrepnik (2017)	90 (+ 90 day follow-up)	WAT ± smartphone app (1:1)	Continuous	Proportion providing data >80% of days: day 90 - day 180 (app-group)	64
Stinson (2008)	14	PDA e-diary	Thrice daily	Completion rate: week 1 - week 2	10
Zaslavsky (2019)	133	WAT	Continuous	Proportion of hours worn per day: first week - final week	-1 (increase)

WAT = wearable activity tracker, PDA = Personal Digital Assistant, PROs = patient-reported outcomes

Table 3. Factors quantitatively associated with eHealth engagement in included studies.

	Facilitates engagement	*Hinders engagement*	*No apparent influence*	*Reference*
Age: older adults	♦			(25,31,32,40)
Age: children vs. adolescents	♦			(35)
Sex: female	♦			(31)
Disease activity: higher	♦	♦		Facilitates: (25) Hinders: (40)
Treatment: bDMARDs	♦	♦		Facilitates: (32) Hinders: (25)
Employment: full-time		♦		(42)
Employment: non-employed		♦		(32)
Outcomes: less frequent reporting	♦			(30,32,43,44)
Outcomes: morning reporting	♦			(58)
Feedback	♦			(27,46)
Reminders			♦	(11,25)
Habitual use of eHealth tools	♦			(45)

bDMARDs = biological disease-modifying antirheumatic drugs

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Chapter 5

Mobile health to support self-management of rheumatoid arthritis: exploring new options

This chapter is based in part on the following publications:

- Doumen M, De Meyst E, Lefevre C, Pazmino S, Joly J, Bertrand D, Devinck M, Westhovens R, Verschueren P. Effectiveness and feasibility of a mobile health self-management intervention in rheumatoid arthritis: study protocol for a pragmatic multicentre randomised controlled trial (AEGORA). Trials 2023; 24(1):697.

- Manuscript to be submitted as: Doumen M, et al. A mobile health self-management intervention to improve self-efficacy and remotely monitor disease impact in rheumatoid arthritis: results of a randomised controlled trial.

ABSTRACT

Background: Patients with rheumatoid arthritis (RA) should be encouraged in their self-management of the disease. Mobile app interventions could facilitate this but involve challenges like variable user engagement and concerns that apps might induce negative perceptions by increasing patients' vigilance to symptoms. We aimed to study the effectiveness and feasibility of an app-based self-management intervention to improve self-efficacy among patients with RA. Additionally, we aimed to explore if such an intervention is associated with changes in pain catastrophising, as a measure of symptom hypervigilance.

Methods: App-based Education and GOal-setting in RA (AEGORA) was a multicentre, open-label, randomised controlled trial with 1:1-allocation to usual care or an app-based self-management intervention. Patients with RA who had access to a smartphone were included during outpatient clinic visits in two rheumatology centres. The 16-week intervention was accessible via a study version of a commercially available health app and consisted of patient education, goal-setting, lifestyle support and remote reporting of the Rheumatoid Arthritis Impact of Disease (RAID) instrument. The primary endpoint was achieving a clinically important difference in the Arthritis Self-Efficacy Scale (ASES, range 11-110) at the follow-up visit after 4-6 months with the intervention compared to usual care, assessed with analysis of covariance adjusted for baseline values. Secondary endpoints included non-inferiority regarding the Pain Catastrophizing Scale (PCS) and superiority regarding patient-reported physical activity, sleep quality and RAID. Engagement with the app and in-app reported RAID-scores were analysed descriptively.

Results: In total, 122 patients were recruited, 60 of whom were randomised to the intervention. Baseline characteristics reflected a population with well-controlled established RA: mean (SD) disease duration 12 (9) years, mean (SD) age 58(11), 68% female, mean (SD) DAS28-CRP 2.4(0.9), mean (SD) ASES 72(21). The intervention did not result in a statistically significant difference in the ASES over the control group (β: 0.44/110, p = 0.87). Non-inferiority was established for effects on the PCS (β -0.95 [95% CI -3.30 to +1.40] favouring the intervention). No differences were found in other predefined outcomes. App retention steadily declined to 43% by 16 weeks, and 49% of prompted RAIDs were completed. Although the RAID remained stable over time at the group level, 35% of app users reported ≥1 episode of clinically important worsening over 16 weeks.

Conclusion: This app-based self-management intervention was not superior to usual care in the improvement of self-efficacy among patients with RA. Although app-based education was feasible in a diverse patient population, our results are in line with recommendations that self-management interventions should include needs-based rather than standardised education. However, remote symptom monitoring provided valuable additional insight and did not result in more catastrophising perceptions of pain, alleviating concerns regarding the psychological impact of remote monitoring.

INTRODUCTION

Both the so-called treat-to-target strategy and novel disease-modifying antirheumatic drugs (DMARDs) have considerably improved outcomes for people living with rheumatoid arthritis (RA)(1). Nevertheless, many patients still experience ongoing pain and fatigue or suboptimal psychosocial wellbeing(2–4), while others are confronted with comorbidities that complicate the management of their disease(5,6). Consequently, it is becoming increasingly clear that managing RA requires a biopsychosocial approach, including attention for disease burden that is best addressed non-pharmacologically(7). In part, this requires regular assessment of disease impact, for instance via patient-reported outcome (PRO) instruments, to highlight potential targets for additional intervention beyond controlling disease activity.

In this regard, a crucial aspect of care is empowering patients to assume a more active role in the shared decision-making process to manage their disease, which is often termed self-management behaviour(8). The benefits of self-management are clear on both the individual and the societal level. RA is a chronic disease with an often-unpredictable course, characterised by intermittent flares and even day-to-day symptom variation(9,10). Since most patients see their rheumatologist only 3-5 times per year on average(11), people living with RA should be supported in their ability to manage or react to flares, symptoms or other difficulties they encounter in between clinic visits(12,13). Consequently, adequate self-management interventions have shown varying improvements in numerous health outcomes, while on a societal level, improved self-management might also reduce health care utilisation(14,15). A key concept regarding self-management is self-efficacy, or patients' confidence in their ability to control the disease and its consequences, which has been shown to positively affect various aspects of living with RA(16,17). Self-efficacy is endorsed by the European Alliance of Associations for Rheumatology (EULAR) as both an important facilitator and an outcome of self-management interventions for inflammatory arthritis(18). Indeed, several studies have shown that self-efficacy is not a static personality trait, but can be improved with personalised patient education and psychological support(19,20).

EULAR also defined several recommendations for the content of self-management interventions, including patient education and lifestyle advice(18). A healthy lifestyle is not only relevant for the management of RA, but also to prevent and manage comorbidities like cardiovascular disease, which is more prevalent among patients with RA and still the leading cause of death in this population(21). Finally, EULAR highlighted the potential benefits of using digital tools like mobile health (mHealth) applications to facilitate these interventions(18). Mobile applications can be a convenient and accessible way to support self-management in patients' everyday environment, outside of the clinical office(22). In addition, apps can be used to remotely monitor PROs, providing a more accurate and detailed picture of disease activity over time(23). Indeed, studies based on various forms of digitally delivered self-management interventions for RA have shown promising results, for instance decreasing healthcare utilisation and improving empowerment, physical activity and hand functioning(24,25). Similarly, web-based educational programmes have proved effective in supporting self-efficacy among patients with RA in the past(26).

Nevertheless, providing self-management interventions for RA through mHealth raises several challenges. For one, studies have reported large variations in user engagement with mobile apps in clinical practice(27,28). While motivational principles like gamification are often proposed as potential solutions to this problem, most existing mHealth-apps do not include these features(29). Secondly, qualitative studies have suggested that mHealth-apps might induce negative perceptions and anxiety by increasing patients' focus on symptoms(30,31). To date however, research regarding these effects remains scarce and conflicting(27). Finally, the content of self-management interventions differs widely across published studies, most

interventions are insufficiently supported by a theoretical framework, and mHealth remains underrepresented in the literature as an approach to deliver self-management interventions for inflammatory arthritis(32).
Therefore, this randomised controlled trial (RCT) aimed to study the effectiveness and feasibility of an mHealth-based self-management intervention intended to improve self-efficacy for the management of RA-related symptoms. The intervention consisted of education, lifestyle advice and remote monitoring elements supported by motivational features and gamification, and was based on principles of goal-setting, self-efficacy theory and behavioural economics. As a key secondary objective, the trial aimed to assess if such an intervention is associated with changes in pain catastrophising, as a measure of hypervigilance to symptoms.

METHODS

Study setting and population

App-based Education and GOal-setting in Rheumatoid Arthritis (AEGORA) was a pragmatic, multicentre RCT conducted in a superiority setting with 2:1:1 allocation to either usual care or one of two different versions of an mHealth-based self-management intervention for RA. The trial was conducted in two hospitals across Belgium: an academic centre, University Hospitals Leuven, and a non-academic hospital, AZ Sint-Lucas Bruges. Both hospitals have a strong teaching background, ample experience in the management of RA, and a shared electronic medical record (EMR) system. The trial was registered on clinicaltrials.gov (NCT05888181), and the protocol(33) was approved by the Ethics Committee Research of the University Hospitals Leuven (reference S66633) after consultation of the committee at AZ Sint-Lucas Bruges.
Between March and July 2023, consecutive patients were assessed for eligibility by their treating rheumatologist during outpatient clinic visits in the Rheumatology department of both participating centres. Patients were considered eligible if they were able to understand and read Dutch, had access to a smartphone with a recent operating system and felt comfortable using it, were 18 years or older, and were diagnosed with RA by a rheumatologist minimally 16 weeks before. We specifically opted not to include patients within the first 16 weeks from diagnosis based on our prior research, which suggested that these dynamic first weeks are less suitable to assess psychosocial outcomes(2). To include an optimally representative patient population to study feasibility, no additional exclusion criteria were defined. All included participants provided written informed consent.

Trial procedures, randomisation and intervention

Participants had a clinical visit at baseline and a follow-up visit that was scheduled as in routine care but restricted to 4-6 months from baseline. At baseline, participants were randomised 2:1:1 to either a usual care control group or one of two intervention groups (A/B, differing only in Rheumatoid Arthritis Impact of Disease [RAID] questionnaires being prompted either weekly or monthly). Randomisation was performed with a designated module in the web-based platform Research Electronic Data Capture (REDCap)(34), based on (local) randomisation stratified by study centre. The random allocation sequence was computer-generated to ensure allocation concealment. AEGORA was an open-label trial: by necessity, participants were not blinded to their group assignment, and outcomes were patient-reported as described below.
Usual care included informal screening for general wellbeing during outpatient clinic visits, with referral to specific allied health professionals if needed, as well as a standardised educational leaflet about RA. In addition to usual care, the study intervention consisted of a self-management programme accessible via the smartphone application Sidekick, developed by Sidekick Health (Reykjavik, Iceland) and adapted to two different study versions (A/B) in

collaboration with the research team. The study app's content was based on the self-efficacy theory with elements from behavioural economics(16,35). Overall, the programme aimed to improve self-efficacy by providing individuals with RA-specific information and achievable goals to help them build confidence. Moreover, users were provided feedback and encouragement in the form of personalised messages and a points-based gamification system.
The study app's programme comprised several components to support self-management. First, the app contained an RA-specific educational programme consisting of 16 weekly modules. Each module related to a different topic regarding living with RA, presented as sequential videos at prespecified time points. The educational content was co-developed by a panel of rheumatologists and patient research partners (PRPs). Second, the app provided patients with healthy lifestyle advice, both as part of the educational programme and via messages from a certified health coach employed by the app developer. Specifically, general information was provided to all users via the app regarding the benefits of physical activity, a balanced diet and a regular sleeping pattern, while more personalised, non-medical information could be additionally communicated by the health coach based on participants' activity in the app. Third, the study app included remote monitoring features underpinned by goal-setting principles. For instance, participants could use the app to log daily steps, physical activity, diet, sleep, and mental health. Personal goals relating to these aspects, as well as physical and mental challenges and exercises, could then be set up to encourage behavioural change.
For the purpose of this study, several modifications to the app were made. Specifically, interaction with the health coach was limited to one-way communication, from coach to patients, to ensure a more comparable provision of information. Additionally, patient-reported disease impact could be monitored within the app as part of the study via prompted completion of the Rheumatoid Arthritis Impact of Disease (RAID) instrument(36). Based on random allocation to one of both intervention groups, the RAID was prompted either weekly (group A) or monthly (group B), to explore the influence of requested PRO-reporting frequency on specific outcomes as described below. To ensure the protection of participants' personal data, a pseudonymised study account was created for each participant randomised to the intervention. This study account was based on the participant's unique study ID and was used to log into the app. After the follow-up visit, participants in both the control and intervention groups were allowed to start or continue using the Sidekick-application free of cost. Alternatively, if they chose to terminate the account, all personal data connected to it was removed from the application's data cloud.

Outcomes
At baseline, patients' demographic and clinical characteristics were collected via an electronic case report form (eCRF) within REDCap. Before both study visits, patients additionally completed the patient's global assessment of disease activity (PGA) on a Visual Analogue Scale (VAS), and the Health Assessment Questionnaire (HAQ)(37). These outcomes were collected as in routine clinical practice, either online via the hospital's EMR companion platform or via a tablet or in pen-and-paper form in the clinic waiting room. Additionally, participants completed the following study-specific outcome measures at both visits:

- Self-efficacy for arthritis-related symptoms, measured with the Arthritis Self-Efficacy Scale (ASES)(38). The ASES is a patient-reported questionnaire consisting of 20 items across 2 subscales: self-efficacy for managing pain (range 5-50) and other symptoms (range 6-60). Both scores can be summed to derive a total ASES-score (range 11-110). Higher scores indicate higher perceived self-efficacy.
- Impact of RA on various aspects of life, measured with the RAID(36). The RAID consists of 7 items on a 0-10 numeric rating scale, enquiring about the impact of RA on

pain, functional limitations, fatigue, sleep, physical wellbeing, emotional wellbeing, and coping. Higher scores indicate more perceived disease impact. A ≥3/10 absolute or ≥50% relative change has previously been proposed as the minimal clinically important difference (MCID), and values <2/10 as an acceptable symptom state(39). The RAID was collected at both study visits and via the study app in between visits on either a weekly or monthly basis (intervention group A and B, respectively).

- Cognitive-affective appraisal of pain, measured with the Pain Catastrophizing Scale (PCS)(40). The PCS comprises 13 items on a 0-4 Likert scale, resulting in a total score of 0-52 with subscales for rumination, magnification, and helplessness. Higher scores indicate more catastrophic perceptions concerning pain.
- Physical activity, measured with the International Physical Activity Questionnaire Short form (IPAQ-S)(41). The IPAQ-S is a 7-item questionnaire regarding physical activities during the last 7 days. An activity score is obtained for different domains, each multiplied with the accompanying metabolic equivalent of task (MET) value, leading to a sum score representing MET minutes of physical activity per week.
- Patient-perceived sleep quality, measured with the Pittsburgh Sleep Quality Index (PSQI)(42). The PSQI measures sleep quality through 19 items across 7 domains, with a resulting total score ranging from 0-21 and higher scores reflecting worse sleep quality.

These study-specific outcome measures were completed by participants within REDCap, using a QR-code or email link. If these questionnaires were not completed, a reminder was sent via email after 3 days, and participants were contacted via telephone after one week.
Upon completion of the study, we additionally recorded participants' overall satisfaction with the intervention on a VAS and enquired if they would like to continue using the app. Finally, participant engagement with the intervention was assessed by passively collecting pseudonymised usage data from the study app, including all logins, activities and questionnaires registered within the app. Based on this information, engagement was defined as the proportion of participants with any ongoing activity in the study app beyond each time point (rolling retention), the number of days participants actively used the app (activity), and the proportion of prompted RAID instruments that were completed in both intervention arms (completion rate).

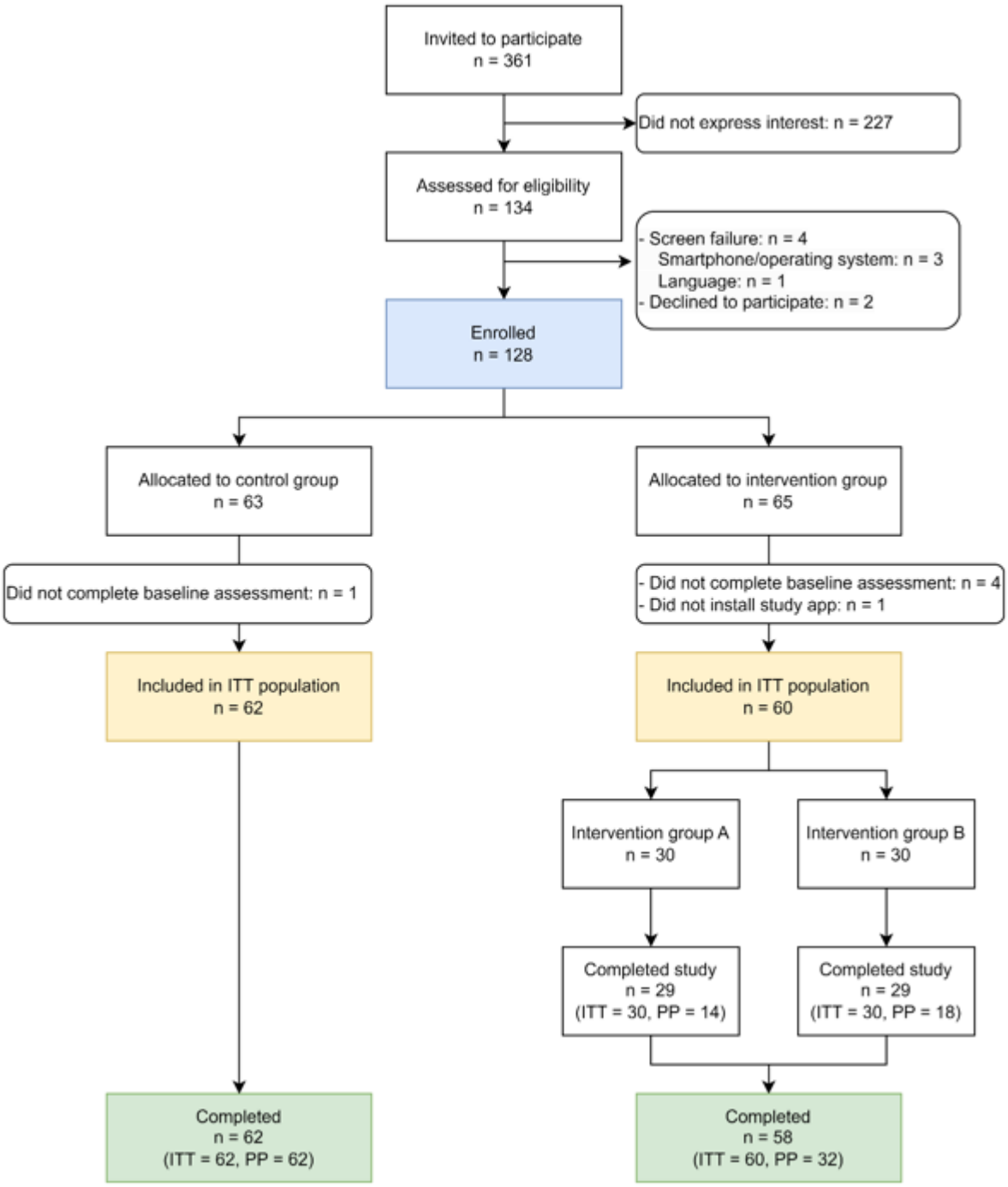
Study endpoints
The primary endpoint was defined as achieving an MCID in the total ASES-score, previously estimated as 5.5(19,43), at the follow-up visit in favour of the intervention group (group A and B combined) when compared to the control group.
As secondary endpoints, we assessed: 1) non-inferiority of the intervention compared with usual care regarding change from baseline in the PCS total score at follow-up, and the influence of PRO-reporting frequency (Group A vs Group B) on this outcome; 2) superiority of the intervention regarding change from baseline in the IPAQ-S sum score, the PSQI total score and the RAID at the follow-up visit; and 3) feasibility of the intervention in terms of user engagement, its predictors and its influence on other outcomes.

Statistical analysis
We hypothesised that the intervention would be superior to usual care with respect to self-efficacy improvement. Sample size calculations, partly based on ASES-score estimates from the Care in early RA (CareRA) trial(44), suggested a target of 47 participants in both the combined intervention and control group to detect the primary endpoint of clinically

meaningful difference on the ASES with 80% power at a significance level of 0.05. Considering an estimated drop-out rate of 10% and a 15% correction for the potential need of non-parametric hypothesis tests, we aimed to include a total of 120 participants. This number would also be sufficient to assess the main secondary outcome of non-inferiority of the intervention regarding change in the PCS-score with 90% power, assuming an MCID of 7.7 on the PCS as the non-inferiority margin(40,45,46).
Following data exploration, missing data were assumed to be missing at random and imputed with multiple imputation by chained equations (m = 20 imputations for total missingness of 3.7%). App usage data and in-app reported RAID questionnaires were not imputed and analysed as-observed.
The primary outcome was assessed via analysis of covariance (ANCOVA) comparing the total ASES-score at the follow-up visit between the control and combined intervention group while adjusting for baseline ASES. As main secondary outcome, we compared in a non-inferiority setting the total PCS-score at the follow-up visit between the control and intervention groups using ANCOVA adjusted for baseline PCS. Other predefined secondary outcomes were compared using similar ANCOVA models in a superiority setting. Outcomes concerning satisfaction and engagement with the intervention, as well as in-app reported RAID questionnaires, were analysed descriptively. Additionally, predictors of engagement were studied with linear regression by modelling as dependent variable the number of weeks participants actively used the app. Finally, the influence of this engagement measure on the primary outcome was assessed with linear regression including the total ASES-score at week 16 as the dependent variable and baseline ASES, age, sex, RF/ACPA-status, comorbidities and within-study DMARD-adaptations as covariates.
All analyses were carried out in the intention-to-treat (ITT) population, consisting of all patients who completed the ASES at baseline and either installed the study app (intervention groups) or were assigned to the control group. Finally, sensitivity analyses were carried out in the per protocol (PP) population, consisting of only those patients who attended the follow-up visit and completed ≥50% of in-app RAID questionnaires (intervention groups). An additional sensitivity analysis was conducted by adjusting the primary outcome for DMARD-adaptations during the study and any randomised imbalances between groups in baseline confounders. All statistical analyses were carried out in R version 4.3.2.

Patient and public involvement
Both the rationale for the trial and the choice of study outcomes were based on previously published qualitative research conducted at the host institution among patients with RA. These studies investigated patient-preferred outcomes of RA treatment and specific barriers and facilitators for mHealth use(30,47). PRPs were involved in both the setup and analysis of these studies, and in the adaptation of the study app's educational content.

Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart.



Participants were randomized 2:1:1 to either a usual care control group or the app-based self-management intervention with either weekly (group A) or monthly (group B) prompts to complete the Rheumatoid Arthritis Impact of Disease (RAID) instrument. *AEGORA = App-based Education and GOal-setting in Rheumatoid Arthritis, ITT = intention-to-treat, PP = per protocol*

RESULTS

Between March and July 2023, 361 patients were invited to participate, 134 (37%) of whom expressed an interest and were subsequently assessed for eligibility (Figure 1). Of those, 128 patients were eventually enrolled in the study and randomised to the usual care control group (n = 63) or the intervention groups (n = 65). One participant in the control group and 4 in the intervention groups did not complete the baseline ASES assessment, while 1 additional participant in the intervention group did not install the study app. Consequently, 122 participants were included in the ITT population (control group: n = 62; intervention group A: n = 30; intervention group B: n = 30). All participants in the control group completed the study and were included in the PP population. In the intervention groups, 58/60 participants attended the follow-up visit, but only 32 participants completed ≥50% of in-app prompted RAID questionnaires and were thus included in the PP population (group A: n = 14/30; group B: n = 18/30).

Overall, clinical and demographic characteristics at baseline were similar between the control and combined intervention groups, except for slightly higher proportions of women and RF/ACPA-seropositivity in the control group (Table 1). Generally, baseline characteristics reflected a population with established RA, with a mean disease duration of 12 (SD 9) years, a mean age of 58 (SD 11), a female majority (n = 83/122; 68%), and a well-controlled disease (28-joint Disease Activity Score with C-reactive protein [DAS28-CRP]: mean 2.4, SD 0.9; total ASES: mean 72/110, SD 21; total RAID: mean 3.7/10, SD 2.4). Among participants in the intervention groups, 33/60 (55%) had attained at least a bachelor's level tertiary education, but only 18/60 (30%) had any prior experience with mHealth.

Effect of the intervention on self-efficacy

The intervention did not result in a statistically significant difference in the total ASES-score at the follow-up visit when compared to the control group, with a non-significant adjusted mean difference β of 0.44/110 (95% CI -4.89 to 5.77, p = 0.87) in favour of the intervention group (Table 2, Figure 2). A sensitivity analysis adjusted for DMARD-adaptations during the study and baseline between-group imbalances in sex and RF/ACPA-status yielded similar results (β +0.59 [95% CI -4.92 to +6.10], p = 0.82). Finally, when including only patients from the PP population, a slightly larger difference was observed in favour of the intervention, but this exceeded neither statistical significance nor the MCID (β +3.73 [95% CI -2.30 to +9.75], p = 0.23).

Effect of the intervention on secondary outcomes

The intervention did not result in worsening on the PCS when compared to the control group (Table 2, Figure 3). Non-inferiority for this outcome was established, with the 95% CI of the adjusted between-group mean difference at follow-up not exceeding the non-inferiority margin of 7.7 (β -0.95 [95% CI -3.30 to +1.40] in favour of the intervention group). In the PP sensitivity analysis, results were similar and non-inferiority was confirmed (β -2.04 [95% CI -4.92 to +0.84] in favour of the intervention group). When comparing intervention groups A and B, a trend was observed towards more improvement in the PCS total score with monthly rather than weekly questionnaire prompts, but this was not statistically significant (β -2.66 [95% CI -5.65 to +0.33] in favour of group B, p = 0.09). Regarding the other secondary outcomes, no statistically significant differences between intervention and control groups were observed in the RAID, PSQI or IPAQ-S sum score (Table 2).

Table 1. Clinical and demographic characteristics of participants at baseline.

	Intervention group (n = 60)	**Control group (n = 62)**
Age, mean (SD)	58 (12)	58 (11)
Female, n(%)	38 (63)	45 (73)
RF/ACPA positive, n(%)	43 (72)	55 (89)
Erosions, n(%)	26 (43)	27 (44)
Disease duration, years, mean (SD)	11.2 (9)	12.6 (10)
BMI, mean (SD)	26 (5)	27 (5)
Smoking ever, n(%)	30 (50)	27 (44)
RDCI (0-9), mean (SD)	1.1 (1.4)	1.5 (1.5)
DAS28-CRP, mean (SD)	2.3 (0.9)	2.4 (1.0)
Patient-reported outcomes:		
- HAQ, mean (SD)	0.67 (0.66)	0.63 (0.62)
- RAID, mean (SD)	3.6 (2.4)	3.7 (2.3)
- ASES pain, mean (SD)	30 (12)	32 (10)
- ASES other symptoms, mean (SD)	42 (12)	40 (12)
- ASES total, mean (SD)	72 (22)	72 (20)
- PCS rumination, mean (SD)	5.2 (3.8)	5.3 (4.5)
- PCS magnification, mean (SD)	2.5 (2.4)	2.6 (2.9)
- PCS helplessness, mean (SD)	5.8 (5.4)	5.9 (5.9)
- PCS total, mean (SD)	13 (11)	14 (13)
Treatment:		
- no DMARD, n(%)	1 (2)	1 (2)
- csDMARD monotherapy, n(%)	23 (38)	17 (27)
- csDMARD combination, n(%)	5 (8)	7 (11)
- b- or tsDMARD, n(%)	31 (52)	37 (60)
Education:		
- Primary	2 (3)	4 (6)
- Secondary	25 (42)	26 (42)
- Bachelor's	23 (38)	21 (34)
- Master's	10 (17)	11 (18)

SD = standard deviation, n = number, RF = rheumatoid factor, ACPA = anti-citrullinated protein antibodies, BMI = body mass index, RDCI = Rheumatic Disease Comorbidity Index, DAS28-CRP = 28-joint Disease Activity Score with C-reactive protein, HAQ = Health Assessment Questionnaire, RAID = Rheumatoid Arthritis Impact of Disease, ASES = Arthritis Self-Efficacy Scale, PCS = Pain Catastrophizing Scale, DMARD = Disease-Modifying Antirheumatic Drug, csDMARD = conventional synthetic DMARD, bDMARD = biologic DMARD, tsDMARD = targeted synthetic DMARD

Table 2. Primary and secondary outcomes.

	Intervention group (I)		Control group (C)		Difference (I vs C) at follow-up*	
	Baseline, mean (SD)	Follow-up, mean (SD)	Baseline, mean (SD)	Follow-up, mean (SD)	Mean (95% CI)	p-value
ASES (11-110)	72 (22)	74 (22)	72 (20)	74 (20)	+0.44 (-4.89 to +5.77)	0.87
PCS (0-52)	13 (11)	11 (8)	14 (13)	13 (10)	-0.95 (-3.30 to +1.40)	NI
RAID (0-10)	3.6 (2.4)	3.6 (2.4)	3.7 (2.3)	3.5 (2.2)	+0.11 (-0.44 to +0.65)	0.70
PSQI (0-21)	7.7 (3.8)	7.5 (3.9)	8.1 (3.5)	8.0 (3.6)	-0.24 (-1.28 to +0.79)	0.65
IPAQ-S (MET minutes / week)	4383 (3760)	5036 (3927)	4430 (4067)	4674 (4046)	+387 (-839 to +1612)	0.54

* Adjusted for baseline values via analysis of covariance (ANCOVA).
For ASES and IPAQ-S, higher scores indicate improved status. For PCS, RAID and PSQI, higher scores indicate worsening status. *SD = standard deviation, CI = confidence interval, NI = non-inferiority, ASES = Arthritis Self-Efficacy Scale, PCS = Pain Catastrophizing Scale, RAID = Rheumatoid Arthritis Impact of Disease, PSQI = Pittsburgh Sleep Quality Index, IPAQ-S = International Physical Activity Questionnaire Short form, MET = Metabolic Equivalent of Task*

Feasibility of the intervention: satisfaction, engagement and PRO completion rate
In the intervention groups, rolling retention steadily declined to 43% by the end of the 16-week intervention, trending towards higher retention in Group A (Figure 4). The median (IQR) number of days participants actively used the app was 19 (65), with 19/60 (32%) participants using the app on ≥ 56/112 days and 13/60 (22%) on ≥ 84/112 days. In total, 292/600 (49%) of prompted RAIDs were completed, with no clear difference between groups A and B (completion rate 47% and 53%, respectively, p = 0.26 in an unpaired t-test).
Overall, participants were moderately satisfied with the intervention, rating it a mean of 6/10 (SD 3) and median 7/10 (IQR 5) on a VAS. Of 58 participants who were randomised to the intervention and completed the trial, 34 (59%) expressed an intention to continue using the app after the study.

Predictors of engagement and influence of engagement on primary outcome
In a multivariate linear regression model, only a higher RAID-score at baseline was associated with more weeks of active app-use, while no significant effect was found for age, sex, RF/ACPA-status, disease duration, comorbidity burden, DAS28-CRP, PCS or ASES at baseline (Supplement 5.1). The number of weeks participants actively used the app was not significantly associated with the ASES-score at week 16 when adjusted for its baseline value and age, sex, RF/ACPA-status, comorbidity burden and within-study DMARD-adaptations as potential confounders: β +0.36 (95% CI -0.42 to +1.13), p = 0.37.

Temporal dynamics of disease impact based on the RAID instrument
RAID-scores reported in the study app remained stable over time at the group level, but with considerable inter- and intra-individual variation (Figure 5). In 22/204 (11%) pairs of consecutively completed questionnaires, intra-individual variations in the RAID-score exceeded both the minimal clinically important deterioration and the threshold value corresponding with an acceptable symptom state. Among patients who completed consecutive questionnaires at least once, 14/40 (35%) experienced ≥1 such episode over the 16-week intervention. When a subsequent score was available, RAID-scores eventually returned to their initial value in only 4/11 (36%) of these patients.

Figure 2. Arthritis Self-Efficacy Scale (mean ± SD) in intervention and control groups.

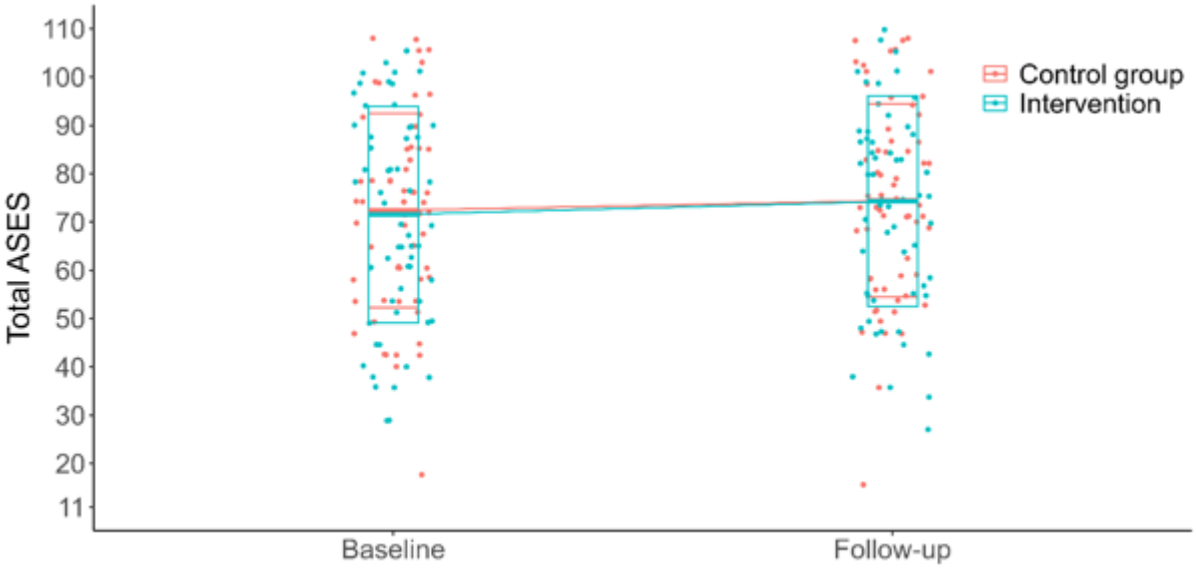


Figure 3. Pain Catastrophizing Scale (mean ± SD) in intervention and control groups.

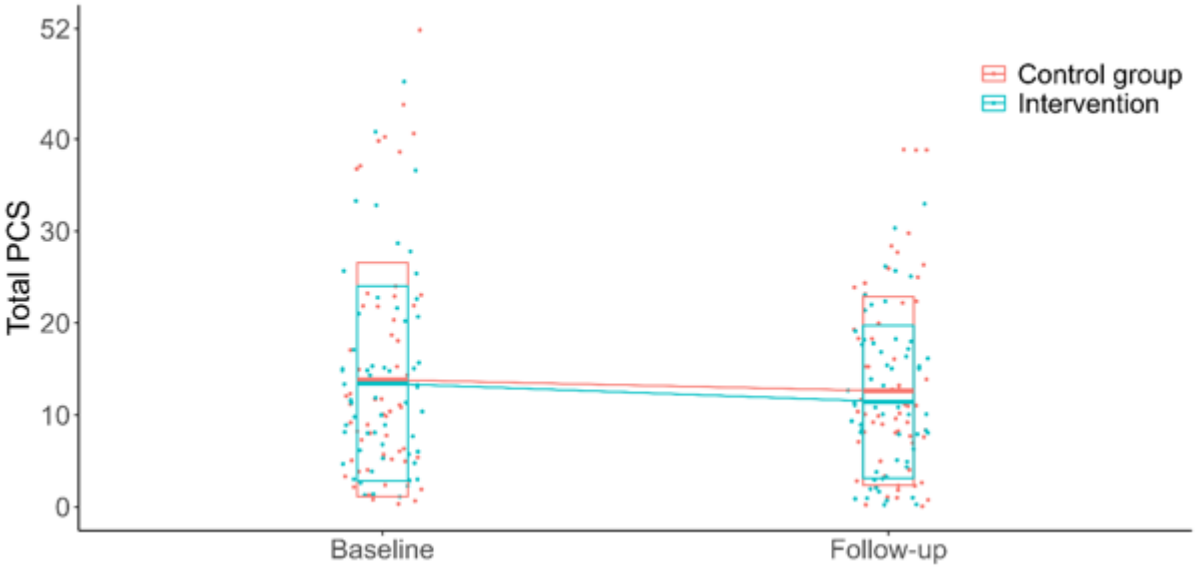


Figure 4. Proportion of participants with ongoing activity in the study app over time (rolling retention) for Group A (weekly questionnaires) and Group B (monthly questionnaires).

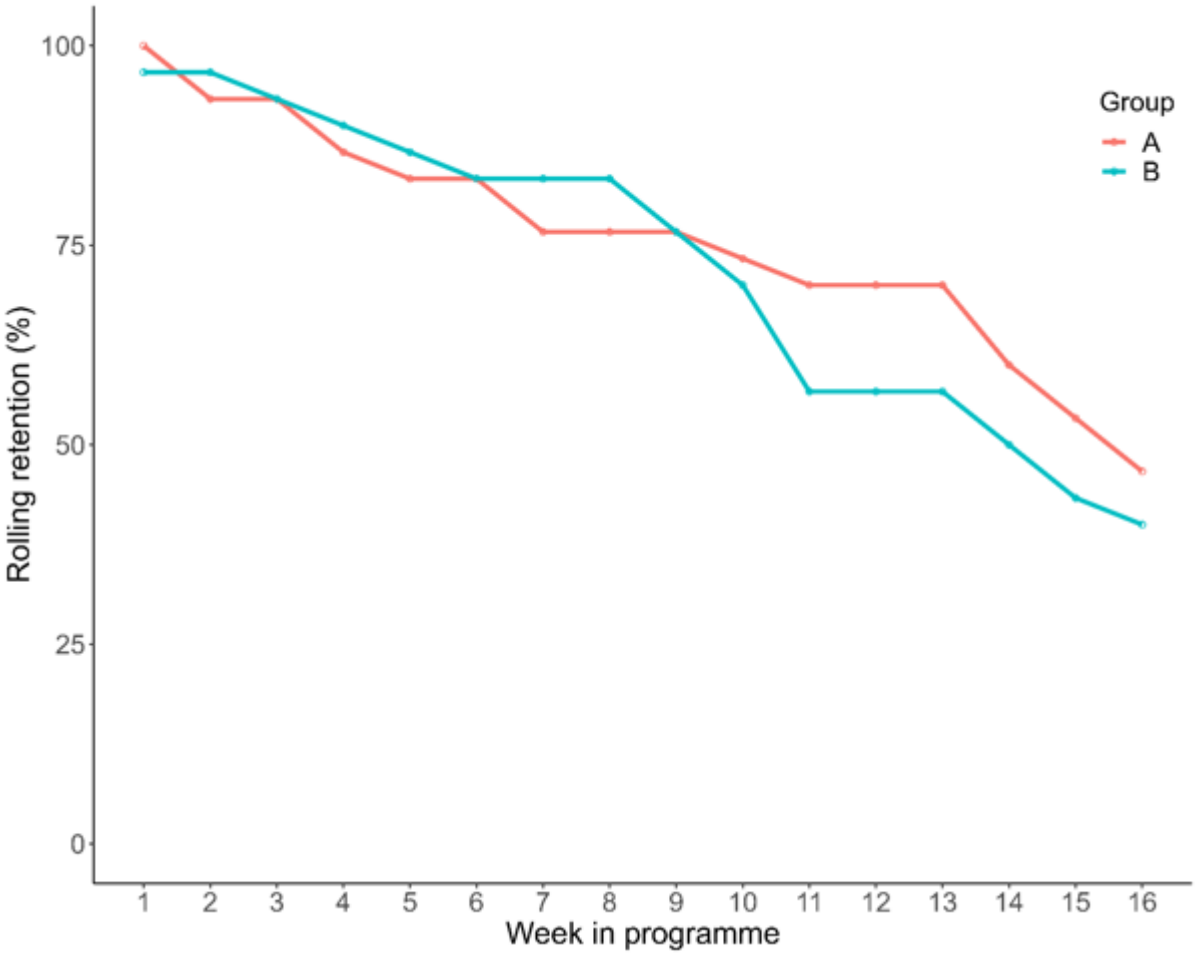
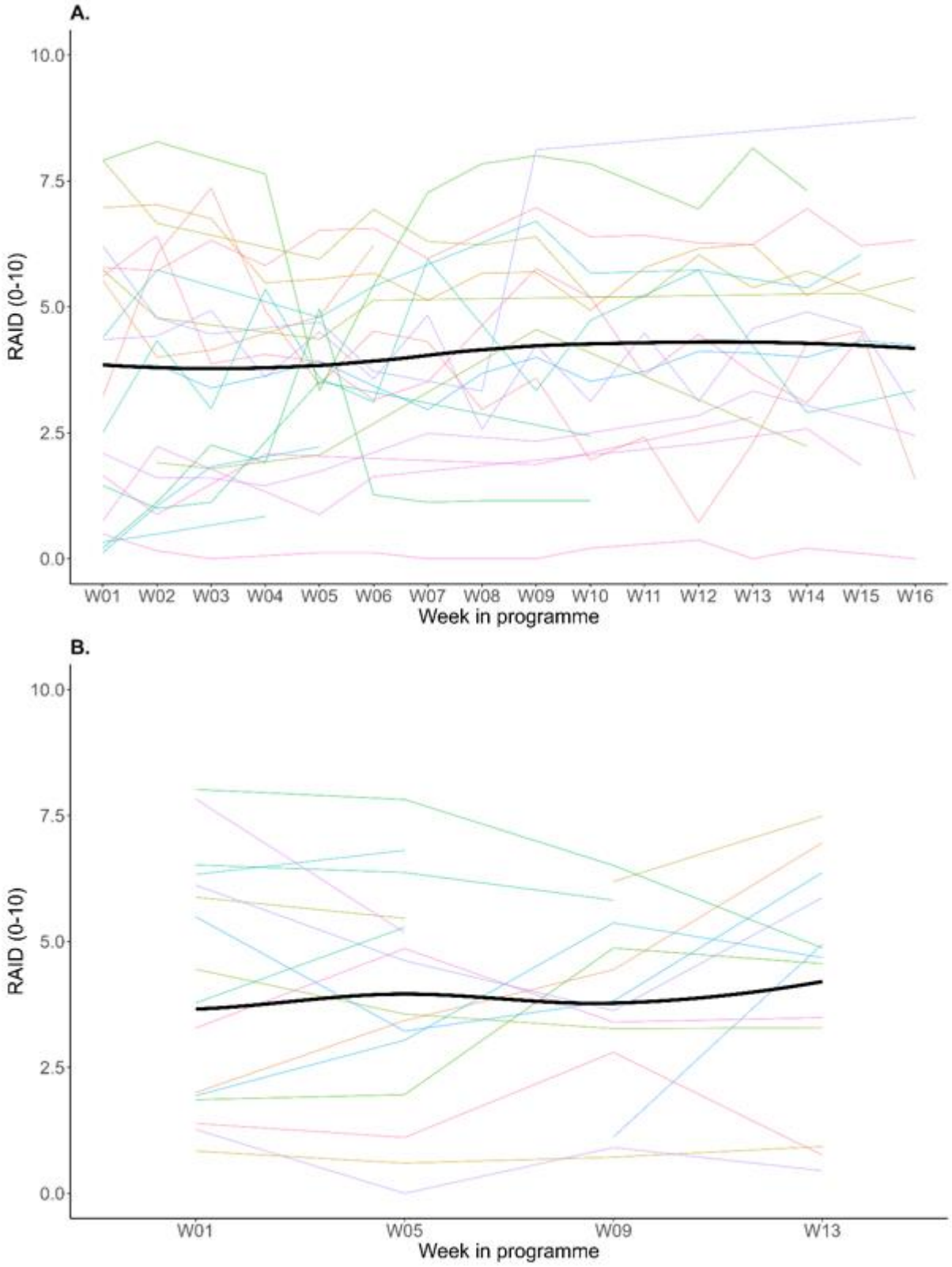


Figure 5. Rheumatoid Arthritis Impact of Disease (RAID) scores reported by participants in the study app for A) Group A (weekly); and B) Group B (monthly).



Coloured lines show scores of completed RAID instruments (no imputation) from individual participants. The black line shows their overall group-level evolution. Group A received weekly prompts to complete the RAID in the study app. Participants in Group B received these monthly (at weeks 1, 5, 9 and 13).

DISCUSSION

In this randomised controlled trial, access to a mobile app to provide patient education, remote symptom monitoring and self-management support did not significantly improve self-efficacy, disease impact, sleep quality or physical activity among people living with RA when compared to usual care and educational leaflets. However, in response to concerns raised in qualitative studies, app use and remote monitoring did not result in hypervigilance to symptoms, with non-inferiority of the intervention being established for effects on pain catastrophising. In addition, our results support the added value of remote symptom monitoring in RA, with more than one-in-three patients reporting at least one episode of significant worsening of disease impact over the 16-week intervention period despite having well-controlled disease activity overall.

Several factors may contribute to the absence of an observed improvement with the intervention in self-efficacy or other predefined outcomes. For one, the study app's educational content was designed based on a more generalisable approach rather than being tailored to individual patient needs, and the intervention did not include face-to-face education by healthcare professionals. In fact, the option for interactive communication with a health coach via the app was disabled for this study for both regulatory reasons and to maintain reasonable comparability of the intervention's content between participants in the RCT context. While these choices were intentional to assess the feasibility of digital self-management support as well as its potential benefits, they may have limited the intervention's effectiveness. Indeed, our observation that a "one-size-fits-all" approach to digital self-management support does not appear to improve self-efficacy substantiates the EULAR recommendations regarding patient education and self-management interventions in inflammatory arthritis, which advocate for needs-based and individually tailored education and suggest that digital or multimedia material should supplement and not replace personal interaction(18,48). This need for tailored education was elegantly shown by Ndosi and colleagues, who observed significant improvements in self-efficacy among patients with RA who received personalised education based on the Educational Needs Assessment Tool (ENAT), while no improvements were found among patients randomised to standard education(19). Similarly, several recent RCTs showed no benefit of standardised web-based or video-supported education over usual care or paper-format education regarding self-efficacy among patients with RA, osteoarthritis and osteoporosis(49–52). A second factor that could explain the absence of observed benefit in our trial was the inclusion of a patient population with a predominantly established and well-controlled disease, as a result of our aim to include a study population reflecting routine clinical practice. As supported by their relatively high self-efficacy scores at baseline, included participants consequently had limited educational needs on average, and thus little room for improvement with additional education. This is in contrast to studies like the RAHelp trial, which showed major improvements in RA-related self-efficacy with web-based education but recruited participants predominantly via online advertisements to contact the research team if interested(26). Presumably, this will have attracted participants with unmet educational needs, who are more likely to experience benefit from additional patient education. A third potential contributor to the absence of clear benefit of our intervention is the moderate engagement with the app, with only 43% of participants still using it by the end of the 16-week intervention. However, app retention was generally in line with previous mHealth studies(27). Furthermore, since per protocol and post-hoc analyses did not show a clear correlation between app usage and outcomes, engagement is unlikely to have had a major impact on the trial endpoints.

An important finding of our trial is the observation that the use of a mobile app for remote symptom monitoring did not increase catastrophising perceptions of pain, as an indicator of symptom hypervigilance. Results from several qualitative studies have indicated that both patients with RA and healthcare providers are concerned that recording their symptoms on a

regular basis might prompt patients to become overly attentive to their symptoms, in turn affecting their mental health(30,31). To date, quantitative evidence regarding this concern has been conflicting, with one study among patients with gout showing stronger negative beliefs about the impact and severity of the disease after using a gout self-management app(53), while no such effect was observed among young people with juvenile idiopathic arthritis who used an app to report pain at various different sampling intervals(54). To our knowledge, ours is the first study to specifically address this question as a predefined non-inferiority outcome with appropriate statistical power. Specifically, non-inferiority of the intervention regarding change in the PCS score was established in both the ITT and PP population and no differences were observed between weekly and monthly PRO-reporting intervals. Although we cannot exclude that participants who experienced feelings of hypervigilance might have disengaged with the app early, these data provide reassurance concerning the potential negative effects of remote symptom monitoring in RA.

Furthermore, our study highlights the potential benefits of remote monitoring, particularly to capture patient-reported flares between clinic visits. Over one-in-three patients randomised to the app group reported at least one episode of clinically important worsening on the in-app RAID-questionnaire over 16 weeks. Moreover, RAID-scores eventually returned to their initial value in only 36% of these patients. These findings are particularly relevant since the RAID has recently been shown to have excellent discriminative accuracy to detect RA flares(55). Using other PROs, several app-based remote monitoring studies have previously shown similar results. For instance, a Swiss study reported that 47% of patients with RA experienced at least one episode of relevant worsening in weekly Routine Assessment of Patient Index Data 3 (RAPID3) scores over 3 months, and even 75% of patients in the Remote Monitoring of RA (REMORA) study reported at least one flare week over a 12-week period(10,13). Even though patient-reported flares do not always correlate with composite disease activity scores, they have a considerable impact on patients' lives and might certainly influence treatment decisions(9). Our findings again illustrate the potential added value of digital tools to help recognise these flares and their influence on patients' experienced disease impact.

Several limitations of this trial should be acknowledged. As stated above, the absence of personally tailored and interactive patient education, as well as the inclusion of a patient population with relatively limited educational needs, is likely to have negatively affected the intervention's ability to improve patients' self-efficacy. Nevertheless, a standardised educational approach and a patient population reflecting daily practice were intentionally chosen to assess feasibility and generalisability of digital education and self-management support in routine care. Second, app retention was moderate, reflecting the ongoing challenge of ensuring lasting engagement with mobile apps in practice. Finally, since the follow-up visit took place after 4-6 months, potential shorter-term effects of the intervention might have been missed. All of these considerations underscore the complexity of implementing digital interventions in real-world settings and highlight avenues for future research to optimise their efficacy. On the other hand, this was a randomised controlled trial that met its predefined statistical power with minimal missingness of data, adding robustness to our findings. Moreover, the intervention was underpinned by the self-efficacy theory and gamification principles, and the educational content was co-developed by PRPs.

Conclusion

This pragmatic, open-label RCT did not show superiority of a mobile app-based education and self-management intervention to improve self-efficacy among patients with RA over usual care and educational leaflets. Although app-based education was feasible in a diverse group of patients, our results confirm those of previous studies and support the EULAR recommendation that educational and self-management interventions should include interactive and needs-based rather than standardised educational content. However, remote symptom monitoring via the app provided valuable additional insight into the evolution of disease impact over time and did not result in more catastrophising perceptions of pain, alleviating concerns raised in qualitative studies regarding the psychological impact of remote symptom monitoring.

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GENERAL DISCUSSION

This chapter is based in part on content from the following publications:

- Doumen M, Pazmino S, Verschueren P, Westhovens R. Viewpoint: supporting mental health in the current management of rheumatoid arthritis: Time to act! Rheumatology (Oxford) 2023; 62(SI3):SI274-SI281.

- Doumen M, Pazmino S, Bertrand D, Westhovens R, Verschueren P. Glucocorticoids in rheumatoid arthritis: Balancing benefits and harm by leveraging the therapeutic window of opportunity. Joint Bone Spine 2023; 90(3):105491.

- Doumen M, Stouten V, Pazmino S, De Meyst E, Bertrand D, Joly J, Westhovens R, Verschueren P. Patient-physician discordance impairs outcomes in early rheumatoid arthritis through less consistent treat-to-target implementation. Rheumatology (Oxford) 2023; kead694.

"The good physician treats the disease, the great physician treats the patient who has the disease."

Sir William Osler

PART I - A psychosocial window of opportunity to improve disease impact

I.1 - Unmet patient needs in the modern age of treating RA

The findings outlined in Part I of this thesis shed new light on some of the challenges that persist when treating RA in the modern age. The therapeutic landscape for this chronic disease has changed dramatically in recent years, allowing clinicians to offer a vastly more positive outlook to patients when compared to decades ago. However, in spite of this, there is still much room for improvement. Even today, the impact of RA on patients' lives is clear. Recent evidence indicates that, although disease activity is more effectively managed than before the era of advanced therapies, pain, fatigue, disability and mental health generally do not improve to the same extent(1). Specifically, results from several prospective cohorts and trials have shown that at least 20-30% of patients with RA continue to experience such symptoms despite achieving inflammatory disease control(2,3), or fail to achieve remission solely because of an elevated patient global assessment (PGA)(4). The same is true for the psychological impact of RA, with a recent systematic review showing that improvement of mental health with DMARD therapy alone was limited even for biologic DMARDs, while over 50% of otherwise eligible trials did not even measure mental health and another 24% provided no estimates of treatment effect on these outcomes(5). This is all the more striking because addressing mental health and the ability to return to a "normal life" are acknowledged by patients as priorities in the management of their disease(6).

These conclusions are mirrored by our findings from Chapter 1, where we showed that 20% of patients who were in DAS28-CRP-remission at week 16 in the CareRA trial could nonetheless be distinguished by more negative illness perceptions and suboptimal psychosocial wellbeing. Moreover, this subgroup of patients was also less likely to sustain their remission status over time. Similarly, as outlined in Chapter 2, less than one-in-four patients included in CareRA achieved a sustained improvement in fatigue despite intensive DMARD therapy. Interestingly though, the relationship between disease activity and disease impact appears to work both ways, as illustrated by the cross-lagged analyses from Chapter 1, as well as by the ever-recurring predictive association of early patient-reported outcomes (PROs) with long-term outcomes like sustained remission (Chapter 1), fatigue (Chapter 2) and self-efficacy (Chapter 3).

This raises the question what patients with RA and their healthcare providers could do to mitigate or even prevent persistent disease impact.

I.2 - The psychosocial impact of living with RA

According to the World Health Organisation (WHO), wellbeing encompasses quality of life and "the ability of people and societies to contribute to the world with a sense of meaning and purpose"(7). An important part of this is psychosocial or mental health, which WHO in turn defines as a "state of mental wellbeing that enables people to cope with the stresses of life", existing on a "complex continuum that is experienced differently from one person to the next"(8). It is perhaps unsurprising that this equilibrium comes under threat when confronted with a diagnosis of RA. Living with RA involves having to adopt new ways of coping with the specific challenges this illness brings about(9). Our findings from Chapter 1 provide additional insight into the psychological mechanisms that might play a role in this process. For instance, illness perceptions appeared to contribute more to psychosocial wellbeing after a few months of treatment than at baseline, and also became more reliable predictors of long-term remission with time. This might reflect that patients indeed need time to find a place for the diagnosis in their life, or even in their identity, to eventually shape their perspective on it.

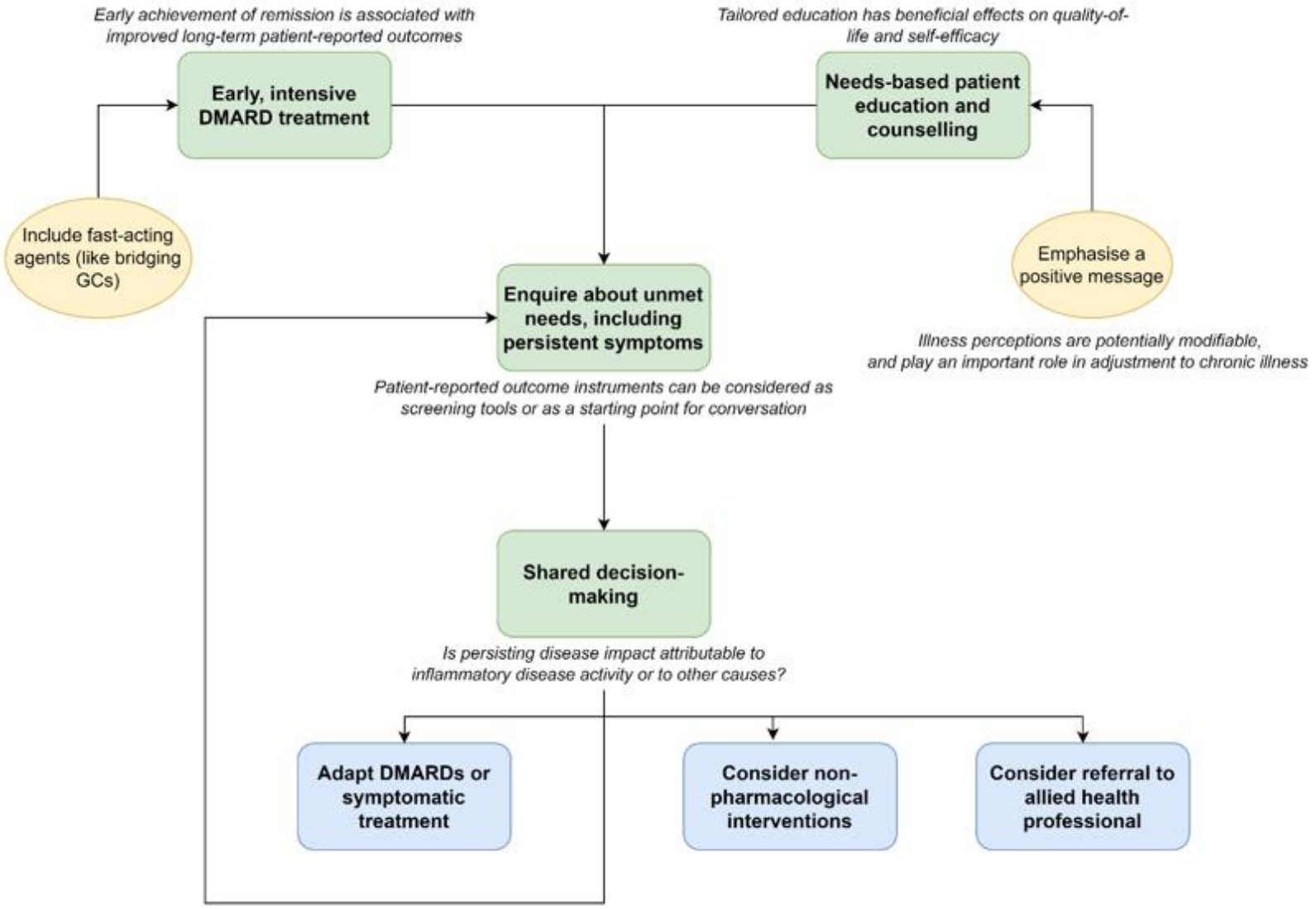
The complex link between RA and mental health likely involves several physical, cognitive, behavioural and emotional mechanisms. On a biological level, ample evidence suggests that chronic physical stress, circulating pro-inflammatory cytokines and abnormal hypothalamic-pituitary-adrenal axis signalling might affect psychological states in patients with RA(10). For

instance, chronic inflammation in RA contributes to alterations in central pain processing and mood disorders, with an important role in this process for pro-inflammatory cytokines such as tumour necrosis factor (TNF) alpha. Interestingly, based on functional MRI studies, anti-TNF therapy seems to rapidly attenuate these pathways(11). Similarly, a large Swedish registry study found decreased use of psychotropic drugs among patients with autoimmune disorders after initiating either anti-TNF therapy or non-biological drugs(12).
Beyond biology and the impact that physical symptoms like pain and fatigue can have on mental health(13), RA also affects patients' ability to participate in activities of everyday life. Given how social support may act as a "buffer" against the adverse effects of stressors(14), impaired social participation is an additional contributor to RA-related disability(15). Moreover, the patient's cognitive appraisal of the disease and its symptoms has an important influence on how it affects their life(16). For example, pain catastrophising, an overall negative cognitive-affective response to pain, is associated with poor physical and psychological outcomes in patients with RA(17), while improved quality of life is seen in individuals who report higher self-efficacy, or confidence in their ability to control the disease's symptoms(18). In other words, numerous adaptation mechanisms come into play when a patient transitions to a life with RA, illustrating that psychosocial wellbeing in this context is best approached from a holistic perspective.

I.3 - What can be done to prevent or improve the psychosocial impact of RA?
Based on the findings from Part I of this thesis, we propose a possible framework to practically approach prevention and management of the psychosocial impact of RA (Figure 1).

I.3.A - Prioritise prompt control of disease activity with adequate pharmacotherapy: leveraging the psychosocial window of opportunity
In the care for patients with RA, the healthcare provider's first priority should arguably be the timely initiation of effective DMARD therapy. This concept has come to be known as the "window of opportunity", a crucial time in early disease during which its progression might be more effectively modified by DMARDs(19). More recently though, evidence is emerging to suggest that our interpretation of the window of opportunity could be extended to a crucial time frame where treatment should not only be started, but during which this should also result in a clinically meaningful treatment response. Indeed, it has long been recognised that early achievement of remission is associated with more favourable long-term clinical outcomes. Specifically, patients who achieve remission early in the disease course are more likely to sustain remission and experience less radiographic progression over time(20–22). In recent years, it is becoming increasingly clear that a favourable treatment response within this early time frame is also associated with improved long-term patient-reported outcomes. For instance, 5-year scores on the Health Assessment Questionnaire (HAQ) were lower for patients who achieved early remission in the IMPROVED trial(20), and early responders in the ARCTIC trial experienced less fatigue over 2 years of follow-up(23). Notably though, the beneficial effects of early disease control are likely not unique to RA. Similar findings were recently reported for patients with psoriatic arthritis, in whom attaining minimal disease activity (MDA) within the first year was associated with improved quality of life and lower levels of pain, fatigue, anxiety and depression during follow-up(24).

Figure 1. Practical framework to support prevention and management of the psychosocial impact of RA.



Our analyses of the CareRA trial, partly replicated in the CareRA2020 cohort (Part I – Epilogue), illustrate that these benefits seem to extend even further, with early remission being associated with improved psychosocial wellbeing and self-efficacy for up to 2 years, and less fatigue over even 5 years of follow-up (Chapters 1-3). Moreover, mediation analyses of these associations suggested that prompt control of disease activity mainly improved self-efficacy via beneficial effects on psychological aspects, including more positive illness perceptions, rather than through (peripheral) inflammatory pathways (Chapter 3). Stated differently, there might also be a "psychosocial window of opportunity" during which the achievement of early disease control leads to a more positive long-term outlook for patients regarding their disease.
Prioritising prompt control of disease activity with appropriate pharmacotherapy, aiming to achieve remission within this time window, thus seems an important first step to prevent persistent disease impact in patients with RA. According to the most recent recommendations from the European Alliance of Associations for Rheumatology (EULAR), this first-line treatment for early RA should consist of a csDMARD like methotrexate in combination with a bridging step-down scheme of glucocorticoids that should be tapered towards discontinuation whenever and as soon as possible(25). These recommendations were based on numerous early RA strategy trials, including the pivotal COBRA trial from 1997(26) and more recent examples like BeST(27), tREACH(28), IMPROVED(29), IDEA(30), COBRA-light(31), NORD-STAR(32), ARCTIC(33), and our own CareRA(34).
Our findings from Part I provide additional support for the use of bridging glucocorticoids in the first-line treatment of RA. Specifically, a key advantage of glucocorticoids is their rapid effect, making them a particularly attractive treatment option when prompt inflammatory disease control is warranted. By including fast-acting agents like glucocorticoids in their first-line treatment, clinicians can maximise the probability of favourably affecting disease activity within the therapeutic window of opportunity, leading to long-term benefits in disease control and overall patient wellbeing. These benefits even extend to a societal level, with a noteworthy example again coming from CareRA: patients who were treated with methotrexate and bridging glucocorticoids, rather than methotrexate alone, had a significantly lower risk of chronic analgesic consumption(35), and cost-effectiveness analyses also favoured the bridging approach(36). Whatever the choice of treatment though, it seems clear that to prevent persistent disease impact, early remission should be the rheumatologist's first priority when treating patients with RA.

I.3.B - Optimise patient education and counselling, building towards self-efficacy
Owing to its nature as a chronic disease that may affect all aspects of life, a diagnosis of RA implies having to learn how to live with this disease until eventually, patients become experts in what RA means for their lives and in how they can adapt to its impact(37). However, adjustment is an active process that involves more than mere acceptance. Care providers should encourage patients to assume a shared responsibility for the management of their disease, and support patients' confidence in their ability to do so. An important role in this process is reserved for illness perceptions, a patient's cognitive representations or beliefs about the disease. According to conceptual models like Leventhal's Common-Sense Model, illness perceptions guide a person's preferred coping strategies, eventually influencing how the disease's symptoms and the success or failure of treatment are perceived(38).
In the context of RA, accumulating evidence suggests that illness perceptions are not static personality traits, but can evolve over time(39), as we also showed in Chapter 1. This has important implications for patient education and counselling and illustrates the need to emphasise a positive message whenever possible, particularly early in the disease course and when discussing treatment success. Ample evidence supports the beneficial effects of patient

education on quality of life and self-efficacy among patients with RA, particularly when tailored to a person's individual needs(40). Interestingly, these benefits are apparently particularly clear when educational interventions include behavioural skills rather than the mere provision of information(41). Moreover, novel ways to approach patient education have gained increasing popularity in recent years, including peer mentoring and online support groups(42,43). This diversity in content and format of educational interventions also has implications on a broader scale. For instance, professional societies like EULAR could provide guidance for education and counselling in collaboration with the allied health professionals and patients in their midst. Ideally, such guidance should be adapted to local health care systems, and funding for its implementation should likely be organised locally as well. Stated differently, reimbursement discussions should move beyond drug pricing and aim to additionally integrate funding for patient education and counselling.

I.3.C - Expand the scope of treating-to-target

Shared decision-making and treating-to-target are recognised as overarching principles in current RA treatment guidelines(25). However, treatment decisions can only be truly shared when patients and rheumatologists agree on what the goals of treating-to-target should be(44). For patients, the ultimate goal of treatment is arguably to improve on all aspects of disease, be they directly or indirectly related to disease activity, whereas rheumatologists tend to base pharmacological treatment decisions on objective signs of inflammation(45). Although controlling disease activity is often a necessary prerequisite for maintaining or improving psychosocial disease impact, this is often not sufficient by itself, and psychosocial problems may be a reason why disease activity-related treatment targets are not met, through their influence on the PGA(4,46). It is thus up to a shared decision between patient and rheumatologist to recognise which aspects of disease impact might be ameliorated with pharmacotherapy, and which aspects require adjuvant non-pharmacological care.

Naturally, making this distinction implies a need to screen for symptoms and repercussions of RA that patients perceive as unmet needs, even when disease activity appears well-controlled. Numerous patient-reported outcome instruments could be suitable tools for this purpose, including the EULAR-endorsed RA Impact of Disease (RAID) questionnaire or generic instruments like the Short Form-36 (SF-36)(47,48). Alternatively, the discordance score (DS) has recently been proposed by our research group as a tool to screen for patient-perceived unmet needs(49). The DS is a weighted difference between commonly used patient-reported outcomes (pain, fatigue, the PGA and the HAQ) and clinical/laboratory outcomes. The score ranges from -1 to +1, with positive values reflecting more patient-perceived disease impact than would be expected based on clinical and laboratory measures. Higher values on the DS are not only a potential indicator for current patient-perceived unmet needs but are also predictive of lower self-efficacy and quality of life after up to 2 years of follow-up, a particularly helpful property when considering patients' psychosocial wellbeing. Furthermore, we recently showed in analyses from the CareRA trial that higher values on the DS are associated with a lower probability that the rheumatologist will apply treat-to-target principles to control disease activity, in turn impairing remission and functional outcomes(50). We aim to further validate the DS in the future for use in daily practice. The first step will be to specify the unmet needs reflected by the DS, which could include but are not limited to educational, counselling, physical, psychosocial or self-management needs. In a second step, a prospective trial will be needed to explore the benefits of adding these additional targets to our current treat-to-target approach in a so-called "dual target" strategy(51).

In parallel with the DS, myriad validated questionnaires are available to further investigate the broader or psychosocial impact of RA. However, regardless of the chosen instrument, these

questionnaires should not replace true patient-care provider dialogue and could for instance be used primarily as a tool to aid further discussion. When instruments like these indicate a "red flag" for patients' overall or psychosocial wellbeing, this might then be used as a means to initiate a more open dialogue, or as a motivation for referral to a specific allied health professional.
Finally, to improve disease impact, several non-pharmacological interventions might then be considered in addition to tailored patient education, including cognitive behavioural therapy, mindfulness-based stress reduction, self-management interventions and physical exercise interventions(52–55). Given their potential to facilitate access to such interventions, digital tools like mobile apps are particularly attractive options and warrant further investigation in this context. Although some of these approaches might be more effective in the early stages of RA(56), a continued relationship of trust and open communication between patient and rheumatologist is key to ensuring every patient receives the care they require. Naturally though, enabling early access to appropriate non-pharmacological interventions, including digitally supported ones, will likely require a certain reallocation of societal resources. Further research focusing on the benefits, feasibility and cost-effectiveness of adjuvant care in RA should therefore be encouraged to help motivate these organisational shifts. This rationale became the foundation for the analyses outlined in Part II of this thesis.

PART II - Mobile apps in rheumatology: the perfect sidekick… or perhaps not always?

II.1 - How preparatory studies informed the design of an app-based intervention trial

In part II, we aimed to study if and how smartphone apps could help to provide more detailed insight into the impact of RA on patients' lives, and potentially to support patients in their management of this impact. Although this eventually resulted in the design of an RCT to study the effects of an app-based self-management intervention on self-efficacy, this was not the primary intention from the outset of this PhD. Originally, we intended to set up an observational cohort study with a focus on app-based remote symptom monitoring to facilitate patient-initiated follow-up. However, the preparatory work for this study had a profound impact on these plans and dates back to early 2020, several months before the official start of this PhD. Between January and March 2020, while I was drafting the grant proposal for this PhD project, the research team conducted the focus group interviews that I would eventually process into the basis for Chapter 4.1 of this thesis.
In this qualitative study, which investigated the opinions of patients, rheumatologists and rheumatology nurses concerning the use of smartphone apps to support the management of RA, we found that although the various stakeholders were certainly open to the idea of apps in healthcare, there was much to consider first. Overall, participants believed that mobile apps could make healthcare more efficient, both by facilitating communication between patients and care providers and by aiding in the signposting of patients in need of urgent care. Importantly though, our participants also highlighted how apps could be used to empower patients to assume a more active role in their healthcare, for instance by providing education and insight into the evolution of their personal health. At the same time, this focus group study made clear that several important barriers need to be considered when designing an app or app-based study. Aside from the clear legal and organisational barriers that currently still exist, the study illustrated the uncertainty surrounding the ideal target population for a mobile health app, with some participants suggesting a focus on patients with sufficient "disease experience" and others

proposing the opposite: an emphasis on those people with a recent diagnosis. Furthermore, care providers were convinced that patients would need training in the use of the app, and all parties expressed a concern that asking patients to regularly report their symptoms might have an unwanted psychological impact. Finally, the challenge of motivating patients to continue using any app for an extended period of time was clear to all stakeholders. Overall, these findings were in line with existing literature at the time, and other studies that have more recently been published also support this(57). For instance, in a recent survey study from the UK, which investigated the opinions of patients with RA and clinicians on digital technologies in the RA care pathway, both parties highlighted access to care and patient education as potential opportunities and organisational challenges as the greatest barriers(58).

In addition to a qualitative study, we also conducted a systematic review, as outlined in Chapter 4.2, to gain more insight into the level of patient engagement with an app that could realistically be expected. Although this review showed that previous studies had reported relatively high levels of engagement with electronic health (eHealth) tools in chronic arthritis populations, it also made clear that evidence from "real-world", routine care settings was underrepresented. Specifically, most available data came from strictly controlled research environments, often with considerable incentives to stimulate lasting patient engagement, while our findings suggested that attrition may be more pronounced in daily practice. Moreover, our systematic review indicated a need for more standardisation and transparency in the way studies report engagement and attrition with apps, with clear retention estimates often not being reported. For this purpose, PRO completion rate, or the proportion of prompted questionnaires that were effectively completed by users in the eHealth tool, emerged as a candidate outcome. Finally, we found inconsistent results regarding the influence of PRO-reporting frequency and demographic or disease-related predictors on engagement outcomes.

Both our findings from these preparatory studies, presented in Chapter 4, and the insights from Part I of this thesis informed the eventual design of the App-based Education and GOal-setting in Rheumatoid Arthritis (AEGORA) trial in several crucial ways. For one, we decided to expand the scope of the study beyond its initial remote monitoring purpose by including patient education and self-management support in an attempt to improve patient outcomes. Second, we concluded that we would aim to include as diverse a population of patients with RA as possible, training them in the use of the app up-front, with a view to gaining more insight into the feasibility and ideal target population of such an intervention. Third, we set up AEGORA as a pragmatic trial without financial or other external incentives for app use and with transparent reporting of PRO completion rate and app retention. We also concluded that a candidate study app should include some form of motivational features or gamification elements, which was often missing in apps reported in the literature. Finally, we decided to include pain catastrophising as a trial outcome to study if app use and remote monitoring could indeed have deleterious psychological consequences.

II.2 – Engagement with mobile apps in rheumatology practice: lessons from AEGORA

When the commercially available app Sidekick Health was brought to our attention, it emerged as an attractive option within the context of AEGORA for several reasons. For one, the app included specific features to motivate engagement, such as a points-based gamification system and direct messages from a certified health coach. Additionally, it provided access to an RA-specific educational programme, whose content was co-developed with rheumatologists and

patient experts and covered numerous aspects of living with RA, including modules related to psychosocial wellbeing, fatigue and other topics that Part I of this thesis had clearly indicated to be particularly relevant. Finally, the app developers were open to making some adjustments for the purpose of our study, so that we could incorporate remote monitoring of disease impact via the Rheumatoid Arthritis Impact of Disease (RAID) instrument, which could then be prompted at varying intervals at our request to study the impact of PRO-reporting frequency on specific outcomes. Unfortunately, it should be noted that integration of these results into the electronic medical record (EMR) was not possible due to legal and practical reasons.

The AEGORA trial was thus set up as a pragmatic, multicentre RCT where people living with RA were randomly allocated to either a usual care control group or the additional access to a study version of the Sidekick Health app with either weekly (Group A) or monthly (Group B) prompts to complete the RAID.

In terms of user engagement, there are several lessons to be learned from this trial. As we also concluded from our systematic review, loss of engagement with apps remains an important challenge, even when specific motivational app features are included. Overall, the observed 43% 16-week retention, which we defined as the proportion of app users with ongoing activity beyond each time point, was largely in line with estimates from previous studies, although these were highly variable and often not even reported(59). However, when considering PRO completion rate, which was 49% of prompted RAIDs in our study, engagement was lower than most studies have previously reported. Most likely, an important reason for this is the pragmatic nature of the AEGORA trial, which was intentionally kept close to daily practice. When considering other recent studies conducted in a comparable setting, engagement results are strikingly similar(60–62). As we concluded from Chapter 4, the relative lack of evidence from a "real-world" setting implies that the available literature probably underestimates the problem of attrition with apps in daily rheumatology practice.

Our findings from AEGORA suggest that this is indeed the case, and investigators and healthcare providers should be wary that long-term engagement with any mobile health app will most likely be moderate at best without direct incentives to continue using it, like financial compensation or regular follow-up of the app's usage. With this in mind, it may be worthwhile to further explore how passively collected data from wearable devices or even from general smartphone use could "fill in the blanks", with recent proof-of-concept studies suggesting that this may be feasible(63,64).

Another important finding from AEGORA is that the target group of patients with RA who are most likely to benefit from app-based follow-up and self-management support remains undefined. As was already the case in previous mobile health studies, which reported inconsistent results regarding predictors of engagement with apps(59,61,63), we found no association of engagement with demographic factors like age and sex or with disease-related factors like disease activity and disease duration. By contrast, as was also suggested in our qualitative study, several AEGORA participants informally commented during the study that they assumed such an intervention would have been more helpful to them during the early stages of disease, when their need for educational support was greater. Regrettably though, a qualitative follow-up study was not included in the protocol and these remarks could thus not formally be registered. However, we did find that patients who reported more disease impact on the RAID instrument at baseline tended to access the study app more often. This might be an indication of more need for support. For instance, in a recent focus group study, patients

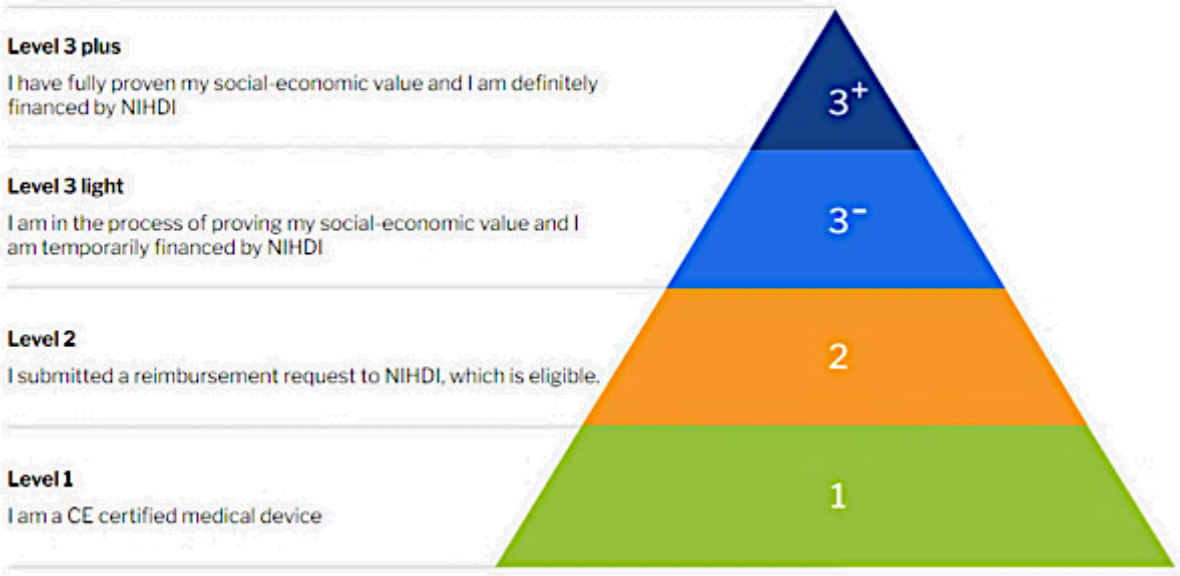
with inflammatory arthritis who had previously participated in a telemonitoring study indicated that they were more inclined to complete remote PROs when they were experiencing a more fluctuating disease activity(65).

Ultimately though, the target population for any mobile health intervention will inevitably be limited to those patients who have access to a smartphone or other digital tools and feel comfortable using them. As an illustration, a recent study from the UK estimated that 20% of patients suffering from inflammatory rheumatic diseases do not have access to an internet-enabled device(66). This also implies that mobile health studies, including AEGORA, are inherently limited by a certain degree of selection bias, even though we attempted to minimise this by limiting exclusion criteria.

When considering user engagement, a third important finding from AEGORA is that we found no effect of PRO-reporting frequency on either the number of days participants used the app or on the PRO completion rate. As stated before, this research question was inspired by both our own and previous qualitative studies, which had suggested that the interval at which patients would be asked to complete a questionnaire might affect engagement. To date however, this has scarcely been studied quantitatively. Specifically, most remote monitoring studies included in our systematic review prompted PRO completion either at only one specific interval or made no randomised comparison between different intervals(59). To our knowledge, only one study to date has specifically addressed the latter question, showing a higher completion rate among children and young people with juvenile idiopathic arthritis during periods where remote PROs were requested less frequently(67). Our results add to this by comparing engagement outcomes in a randomised fashion between patients with RA who received either weekly or monthly prompts to complete a questionnaire, suggesting that this does not affect engagement with an app to a significant extent.

In the end though, the feasibility of using mobile apps in rheumatology practice will inevitably come down to the legal, contextual and organisational factors that are at play in each individual local setting. Among others, this includes legal considerations regarding the responsibility of healthcare professionals to track remotely registered data and act upon them in a timely manner when necessary. It is important to emphasise that the AEGORA trial was conducted in the Belgian context, where there is currently no system in place to allow for the remuneration of processing asynchronously collected remote health data and where physicians are compensated on a per-consultation basis. Evidently, as long as this is the case, the support base for an app-based patient-initiated follow-up system will undoubtedly be limited. This stands in contrast to for instance the Dutch setting, where specific characteristics of the healthcare system encourage physicians to see patients in clinic less often when possible. It is therefore perhaps unsurprising that several successful studies based on remote monitoring with patient-initiated follow-up have been conducted in the Netherlands(68,69). If this approach is to become more widely implemented, far-reaching legal and organisational shifts will have to take place in countries like Belgium, and there seems to be a long way to go in this regard. However, an important first step has recently been taken with the establishment of a “validation pyramid” allowing for the reimbursement of apps within specific care processes with proven added value (Figure 2)(70). Then again, this system is intended to compensate patients for the costs of acquiring the app, and not for the remuneration of healthcare practitioners’ activities.

Figure 2. The mHealthBelgium "validation pyramid" for reimbursement of software applications with a medical purpose.



II.3 – What AEGORA teaches us about using mobile apps to further explore RA's impact and support its self-management

As outlined in Chapter 5, the AEGORA trial did not show a significant improvement in self-efficacy with access to the app-based education and self-management intervention when compared to usual care. Similarly, no differences were seen between intervention and control groups concerning the other predefined outcomes of physical activity, sleep quality and disease impact. As previously discussed in Chapter 5, potential reasons for this lack of observed benefit include the study population, which had on average a well-controlled and established disease and seemingly limited support needs, as well as the emphasis on generalised rather than personally tailored educational content, thus supporting EULAR's recommendations to adapt education to patients' individual needs(71). However, the absence of significant improvements in self-efficacy or other study outcomes should not imply that mobile apps serve no purpose at all in the care for people living with RA.

For one, even without an observable effect on self-efficacy, the AEGORA trial did confirm that providing patient education via a mobile app is feasible. As one of the potential advantages of mobile apps according to patients participating in our focus group study, it was important to study this approach in practice. Considering the trial's results, we should however conclude that standardised patient education in digital form should be seen as supplementary rather than as a replacement of personalised, face-to-face education. For instance, in a recent RCT from Canada, improvements in self-management ability, fatigue and depression were seen among patients with RA who were given access to a self-monitoring smartphone app and wearable activity tracker, but this was part of a multicomponent intervention with remote physical therapy counselling and group education(72). Our findings also suggest that educational or self-management efforts should maximally target those scenarios where patients experience the most need for additional support, for example during early disease or with changes in treatment.

Again, these conclusions substantiate EULAR's recommendations for patient education in inflammatory arthritis and suggest that patients' educational needs should be specifically assessed and periodically re-evaluated(71).

Second, it should also be noted that several potentially relevant outcomes of patient education were not studied in the AEGORA trial. In hindsight, it would have been particularly interesting to include a measure of efficient communication between patients and care providers, given how participants of our focus group study suggested that mobile health apps could facilitate interaction between both parties. Some examples from the literature suggest that this can indeed be the case, but results have generally been inconclusive. For example, patients with RA who were given access to the web-based self-monitoring platform Sanoia as part of a French multicentre RCT experienced a modest but significant improvement on the Perceived Efficacy in Patient-Physician Interactions (PEPPI-5) questionnaire when compared to the control group(73), while no effects on the same outcome were seen with several other eHealth interventions(68,74,75). On the other hand, a Swiss cohort study showed that patients with RA or spondyloarthropathies who used a remote monitoring app rated their rheumatologist more favourably in shared decision-making and physician awareness of disease fluctuations, but only when they actually discussed the remote monitoring results with their rheumatologist(76). Considering the role of shared decision-making in the T2T-paradigm as addressed above, more research is needed to identify potential strategies to help align treatment goals between patients and healthcare providers. Although evidence is now mounting that digital tools are perhaps not the perfect solution to this problem when used in isolation, the rheumatology community will have to figure out how these tools can be most efficiently deployed in a supporting role. As supported by previous studies and our qualitative work, integrating remote monitoring results into the EMR and encouraging discussions about them with the treating rheumatologist appear to be important in this regard.

Third, although the AEGORA trial was not able to show a benefit from app-based patient education and self-management support, it did illustrate the added value of remote symptom monitoring even for patients with well-controlled RA. As has been amply reported in the literature, many people living with RA frequently experience flares or episodes of increased symptoms, and these have a major impact on their quality of life(77). When flares occur often, they contribute to worse functional outcomes and even to more radiographic disease progression(78,79). Digital tools like mobile apps have shown promising capabilities to detect these flares outside the clinical office, mostly in the form of worsening PROs(80). In addition, studies based on wearable activity trackers have shown that patient-reported flares are often associated with decreasing step counts, reflecting the impact that flares have on patients' daily functioning(81). However, as discussed above and in Chapter 4.1, the commonly mentioned shadow side to remote monitoring is that recording one's health status on a regular basis might induce feelings of anxiety and an overemphasis on symptoms. It was thus important to study these potential negative effects in detail, particularly since this has rarely been investigated to date and results have been conflicting(67,82).

In this regard, our findings from the AEGORA trial provide some reassurance. As, to our knowledge, the first study to specifically assess non-inferiority of a remote monitoring intervention regarding negative illness perceptions, AEGORA did not show an increase in pain catastrophising after the intervention. At the same time, the trial again confirmed that patient-reported flares are more common than one might expect, even among patients with generally

well-controlled RA, with 35% of app users reporting at least one episode of clinically important worsening on the RAID over the 16-week intervention period. Even though patient-reported flares do not always correlate with clinical or imaging findings of active disease and should thus not necessarily imply therapeutic action(83), flares do play a major role in the patient's perspective of disease control(84). As such, strategies that provide more insight into the frequency, timing and impact of flares can surely facilitate the shared decision-making process and should be encouraged. Taken together, our findings from Part II of this thesis support the notion that remote symptom monitoring using mobile health applications can be a feasible and safe way to approach this.

CONCLUSION - Looking beyond the horizon

In summary, the analyses outlined in this thesis aimed to provide more insight into the various ways in which RA affects patients' lives and intended to explore how this impact can be prevented or addressed. First, we focused on patient-reported outcomes during the early stages of disease, and found that a considerable proportion of patients with RA continue to experience a psychosocial impact of the disease, including symptoms like fatigue, despite early and intensive DMARD therapy and even when inflammatory disease activity is well-controlled. Further investigation into this illustrated that prompt control of disease activity is crucial, with patients who attained remission early on experiencing less fatigue, more positive illness perceptions and more confidence in their self-management abilities over several years of follow-up. This suggests that striving for early control of RA within the so-called window of opportunity has even broader implications than commonly believed, a concept we have come to call the "psychosocial window of opportunity". In any case, it is clear that rheumatologists' first priority in the care for patients with RA should be to strive for control of inflammatory disease activity as early as possible, preferably within the first 2-4 months from diagnosis.
Our results also underline the need to regularly reassess whether patients experience unmet needs or persistent symptoms, even when disease activity targets are met. For instance, we found that indicators of psychosocial wellbeing are closely and bidirectionally intertwined with disease activity metrics. Moreover, over one-in-three patients included in our AEGORA trial experienced at least one episode of worsening symptoms over a 16-week period despite having well-controlled disease overall. Based on the results of Part II of this thesis, remote symptom monitoring via mobile apps is one possible approach to gain more insight into the impact of RA experienced by patients. Unfortunately though, we were not able to show that a mobile app intervention could also effectively reduce this impact, suggesting that apps are potentially more suitable for a supplementary rather than a standalone role in needs-based, personally tailored patient education and self-management support.
Despite the considerable progress that has been made in the management of RA over the past few decades, our results illustrate that there is still some way to go. Research has made clear that patients' ultimate goal is to be able to lead a normal life despite living with RA. If we are to achieve this goal, our findings highlight several areas where further research would be welcome. First, the existence of a psychosocial window of opportunity emphasises that optimising early RA treatment is paramount. Even with timely first-line treatment following the international guidelines, at least one-in-three patients in most cohorts do not achieve treatment targets within the first few months. The rheumatology community should continue

to investigate both new pharmacological treatment options and the optimal approach to using the existing ones. Investigations into the latter could include the search for prognostic (bio)markers to facilitate personalised medicine as well as treatment strategy trials that take into account matters of cost-effectiveness. Secondly though, our results illustrate that achieving the goal of normality is unlikely to be possible with pharmacological treatment alone. Future research should aim to optimise the approach to patient education, self-management support and non-pharmacological care for patients with RA. This includes the ideal timing, format and target population for these interventions as well as the positioning of digital and other innovative tools in this context. To make this possible, efforts will also have to be made to address issues of digital illiteracy, which still exist in a substantial proportion of our patient population.

In a world where treating-to-target has become the norm, it is perhaps time to expand the scope of this approach by considering how we can prevent and manage the repercussions of RA, including those perhaps not directly related to disease activity or inflammation, from a holistic perspective. Only then can we hope to maintain and improve our patients' overall and psychosocial wellbeing in a time when this is becoming ever more important.

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SUMMARY/SAMENVATTING

The work outlined in this PhD thesis focused on the impact of rheumatoid arthritis (RA) on patients' lives. The management of RA has improved considerably in the past few decades, with the advent of both novel disease-modifying antirheumatic drugs (DMARDs) and a more structured approach to the use of the existing drugs, or the "treat-to-target" strategy. Nevertheless, research indicates that the impact of this disease on patients' lives continues to be considerable even in the modern age. The increasing adoption of patient-reported outcomes (PROs) in both research and clinical care has resulted in a growing recognition that managing the impact of RA may require a therapeutic approach extending beyond the control of inflammatory disease activity. For instance, many people suffering from RA continue to experience symptoms like pain and fatigue even when the treatment target of controlled disease activity, or "remission", is achieved. In parallel with these emerging insights, a digital revolution has taken place in recent years. Smartphone apps, for example, have become ubiquitous throughout society. Although apps show clear promise in a healthcare context, for instance as tools to monitor symptoms from a distance or to provide education and self-management support to patients, more research was needed to study if and how apps could be used to explore and improve the disease impact experienced by patients with RA.
The **objective** of this PhD research was therefore to further explore in which ways RA affects patients' lives, how this impact relates to disease activity, and which potential strategies, including the use of mobile apps, could be considered to prevent or mitigate this impact.

In **Part I**, consisting of Chapters 1 to 3, this thesis first delved deeper into the various ways that living with RA affects patients' wellbeing. All analyses in Chapters 1 to 3 were based on data from the 2-year Care in early RA (CareRA) trial and its 3-year observational extension CareRA-plus. CareRA was a multicentre, pragmatic randomised controlled trial conducted in 13 Belgian rheumatology centres between 2009-2013. This trial was designed to compare the effectiveness of different remission-induction treatment regimens, all consisting of methotrexate with/without additional conventional synthetic DMARDs and bridging step-down glucocorticoids, among patients with recently diagnosed RA. During the trial, whose primary results were published prior to this PhD research, several PROs were collected that allowed us to strive for a more accurate picture of the disease impact experienced by patients and its relationship with disease activity during the early phase of RA.
First, in **Chapter 1**, we used data from CareRA to gain more insight into patients' psychosocial wellbeing during the early stages of disease. We found that early indicators of suboptimal psychosocial wellbeing were associated with a lower probability of achieving and maintaining remission, despite intensive treat-to-target therapy. Based on these analyses, temporal relationships between disease activity and psychosocial wellbeing appeared to be complex, bidirectional and disease-phase dependent. Crucially, 20% of patients included in CareRA still exhibited worse psychosocial outcomes and more negative perceptions on their disease despite being in early clinical remission, and these patients tended to lose remission earlier than patients with more "positive" psychosocial profiles.
Chapter 2 focused on fatigue, one of the most common and debilitating symptoms of RA. Based on several outcome measures for fatigue that were collected during CareRA, we showed that this is a dynamic but persistent symptom in early RA. Less than 25% of included patients made lasting improvements in fatigue despite intensive DMARD-treatment, and one-in-five patients even experienced worsening fatigue during the first months. Additionally, the association between disease activity and fatigue was mainly explained by its effect on pain, mental health, and sleep quality, and higher fatigue over time was seen in patients who at baseline had more perceived disease impact and fewer swollen joints. Most importantly though,

achieving early remission improved fatigue over 5 years of follow-up, even when disease activity temporarily relapsed later on.
To conclude Part I, **Chapter 3** explored the outcome of self-efficacy, or patients' confidence in their ability to control RA and its consequences with their own means. In line with the preceding results, our findings from this chapter suggested that the long-term self-efficacy beliefs of patients with RA are strongly influenced by psychosocial characteristics, even starting from the early stages of disease, and by the timely achievement of remission with treatment. Importantly, additional analyses showed that this relationship between early treatment response and stronger long-term self-efficacy beliefs was explained by positive effects on illness perceptions, fatigue and quality of life, and not by better control of the markers of inflammation.
These results prompted some important overarching conclusions. It has been clear for some time that the early initiation of DMARD therapy for RA, ideally leading to early remission, is associated with improved long-term clinical outcomes. This concept has been called the "window of opportunity". Taken together and further corroborated by a smaller-scale validation study in the recent CareRA2020 cohort (**Part I - Epilogue)**, the results of Chapters 1 to 3 suggest that this concept could be expanded to a "psychosocial window of opportunity". In other words, the achievement of early disease control within this window seemingly also leads to improved patient-reported outcomes and a more positive long-term outlook for patients regarding their disease. Based on Part I of this thesis, prioritising prompt control of disease activity with appropriate pharmacotherapy, aiming to achieve remission as early as possible, thus seems an important first step to prevent persistent disease impact for patients with RA.
Following up on these findings, **Part II** focused on how smartphone applications could be used to further explore and possibly mitigate the patient-reported impact of RA.
In **Chapter 4.1**, we described the results of a focus group study conducted among patients with RA, rheumatologists and rheumatology nurses. Participants were generally open to the use of apps in a healthcare setting, with potential advantages like facilitating communication between patients and care providers, aiding in the identification of patients requiring urgent care, and educating and empowering patients to assume a more active role in their healthcare. However, this study also made clear that several important barriers need to be considered when designing an app or app-based intervention. In addition to underlining several legal and organisational barriers, participants had reservations over the challenge of motivating patients to continue using an app, were uncertain about what the ideal target population for a mobile health app would look like, and expressed a concern that asking patients to regularly report their symptoms might have an unwanted psychological impact.
In **Chapter 4.2,** we presented a systematic review and meta-analysis which attempted to gain more insight into the level of patient engagement with digital tools that could realistically be expected in a chronic arthritis population. Although this review showed relatively high reported levels of engagement, it also made clear that evidence from "real-world", routine care settings was underrepresented, suggesting that attrition may be more pronounced in daily practice. Moreover, our systematic review indicated a need for more standardisation and transparency in the way studies report engagement and attrition with apps, with clear retention estimates often not being reported.
Based on our insights from Chapter 4 and Part I of this thesis, we set up the App-based Education and GOal-setting in RA (AEGORA) trial that became the focus of **Chapter 5**. AEGORA was a 16-week multicentre, pragmatic, open-label randomised controlled trial studying the effectiveness and feasibility of an app-based education and self-management intervention to improve self-efficacy and disease impact among patients with RA. In summary, this intervention was not superior to usual care regarding improvement of self-efficacy or the

secondary outcomes of disease impact, physical activity and sleep quality. Most likely, this was due in part to the inclusion of a patient population with well-controlled, established RA and generally limited educational needs. In turn, this was a direct result of our intentional choice for lenient inclusion criteria to allow for a realistic evaluation of feasibility. A second likely explanation for the lack of observed benefit was that the app's educational content, while co-developed with patient experts and rheumatologists, was generalised rather than needs-based and interactive. In this respect, the results of AEGORA are in line with those of previous studies and international recommendations for patient education in inflammatory arthritis, which suggest that apps should be used primarily in a supplementary role while providing personalised, needs-based education. Finally, despite AEGORA's negative primary outcome, we did find that remote symptom monitoring via the app provided valuable additional insight into the evolution of disease impact over time, with over one-in-three included patients experiencing at least one episode of worsening symptoms over a 16-week period despite having well-controlled disease overall. Furthermore, the intervention did not result in more catastrophising perceptions of pain, and we were able to formally establish non-inferiority for this outcome. This might alleviate some of the concern raised in our own and other qualitative studies regarding the psychological impact of remote symptom monitoring.

In conclusion, the analyses outlined in this thesis aimed to provide more insight into the various ways in which RA affects patients' lives and intended to explore how this impact can be prevented or addressed. First, we found that a considerable proportion of patients with RA continue to experience a psychosocial impact of the disease, including symptoms like fatigue, despite early and intensive DMARD therapy and even when inflammatory disease activity is well-controlled. Further investigation into this illustrated that prompt control of disease activity is crucial, with patients who attained remission early on experiencing less fatigue, more positive illness perceptions and more confidence in their self-management abilities over several years of follow-up. This suggests that striving for early control of RA within the so-called window of opportunity has even broader implications than commonly believed, a concept we have come to call the "psychosocial window of opportunity".

Our results also underline the need to regularly reassess whether patients experience unmet needs or persistent symptoms, even when disease activity targets are met. Based on the results of Part II of this thesis, remote symptom monitoring via mobile apps is one possible approach to gain more insight into the impact of RA experienced by patients. Unfortunately though, we were not able to show that a mobile app intervention could also effectively reduce this impact, suggesting that apps are potentially more suitable for a supplementary rather than a standalone role in needs-based, personally tailored patient education and self-management support.

Despite the considerable progress that has been made in the management of RA over the past few decades, our results illustrate that there is still some way to go. Research has made clear that patients' ultimate goal is to be able to lead a normal life despite living with RA. If we are to achieve this goal, our findings highlight several areas where further research would be welcome. First, the existence of a psychosocial window of opportunity emphasises that optimising early RA treatment is paramount. Secondly though, our results illustrate that achieving the goal of normality is unlikely to be possible with pharmacological treatment alone. Future research should aim to optimise the approach to patient education, self-management support and non-pharmacological care for patients with RA. In a world where treating-to-target has become the norm, it is perhaps time to expand the scope of this approach by considering how we can prevent and manage the repercussions of RA, including those perhaps not directly related to disease activity or inflammation, from a holistic perspective.

Het werk in dit proefschrift richtte zich op de impact van reumatoïde artritis (RA) op het leven van patiënten. De behandeling van RA is de afgelopen decennia aanzienlijk verbeterd, met de komst van zowel nieuwe ziektemodificerende antireumatische geneesmiddelen (DMARD's) als een meer gestructureerde aanpak van het gebruik van de bestaande geneesmiddelen, of de "treat-to-target"-strategie. Desondanks geeft onderzoek aan dat de impact van deze ziekte op het leven van patiënten zelfs in het moderne tijdperk nog steeds aanzienlijk is. Dankzij de toenemende toepassing van patiëntgerapporteerde uitkomsten (PRO's) in zowel onderzoek als de klinische praktijk groeit het besef dat het verbeteren van de impact van RA een therapeutische aanpak vereist die verder gaat dan de zuivere controle van de inflammatoire ziekteactiviteit. Zo blijven veel mensen die lijden aan RA symptomen ervaren zoals pijn en vermoeidheid, zelfs wanneer het therapeutische doel van gecontroleerde ziekteactiviteit, of "remissie", is bereikt. Parallel aan deze nieuwe inzichten heeft er de afgelopen jaren een digitale revolutie plaatsgevonden. Smartphone apps zijn bijvoorbeeld alomtegenwoordig geworden in de samenleving. Hoewel apps duidelijk veelbelovend zijn in een gezondheidszorgcontext, bijvoorbeeld als hulpmiddel om symptomen op afstand te monitoren of om patiënten educatie en zelfmanagementondersteuning te bieden, was er meer onderzoek nodig om te bestuderen of en hoe apps kunnen worden gebruikt om de patiëntgerapporteerde ziekte-impact van RA te verkennen en te verbeteren.
Het **doel** van dit doctoraatsonderzoek was daarom om verder te onderzoeken op welke manieren RA het leven van patiënten beïnvloedt, hoe deze impact gerelateerd is aan ziekteactiviteit en welke mogelijke strategieën, waaronder het gebruik van mobiele apps, overwogen kunnen worden om deze impact te voorkomen of te reduceren.

In **deel I**, bestaande uit de hoofdstukken 1 tot en met 3, ging dit proefschrift dieper in op de verschillende manieren waarop RA het leven en welzijn van patiënten beïnvloedt. Alle analyses in de hoofdstukken 1 tot en met 3 waren gebaseerd op gegevens van de 2-jarige Care in early RA (CareRA) trial en de 3-jarige observationele uitbreiding hiervan, CareRA-plus. CareRA was een multicentrische, pragmatische, gerandomiseerde gecontroleerde studie die tussen 2009-2013 werd uitgevoerd in 13 Belgische reumatologische centra. Deze studie was ontworpen om de effectiviteit te vergelijken van verschillende remissie-inductie behandelingsschema's, allemaal bestaande uit methotrexaat met/zonder aanvullende conventionele synthetische DMARD's en overbruggende afbouwschema’s van corticosteroïden, bij patiënten met recent gediagnosticeerde RA. Tijdens deze studie, waarvan de primaire resultaten werden gepubliceerd voorafgaand aan dit promotieonderzoek, werden verschillende PRO's verzameld die ons in staat stelden om te streven naar een nauwkeuriger beeld van de ziekte-impact ervaren door patiënten en de relatie met ziekteactiviteit tijdens de vroege fase van RA.
Ten eerste gebruikten we in **hoofdstuk 1** gegevens van CareRA om meer inzicht te krijgen in het psychosociale welzijn van patiënten tijdens de vroege stadia van de ziekte. We ontdekten dat vroege indicatoren van suboptimaal psychosociaal welzijn samenhingen met een lagere kans op het bereiken en behouden van remissie, ondanks intensieve behandeling. Op basis van deze analyses bleken tijdsgebonden relaties tussen ziekteactiviteit en psychosociaal welzijn complex, wederkerig en ziektefase-afhankelijk te zijn. Cruciaal is dat 20% van de patiënten die deelnamen aan CareRA nog steeds slechtere psychosociale uitkomsten en negatievere percepties rond hun ziekte vertoonden ondanks het feit dat ze in vroege klinische remissie

waren, en deze patiënten verloren hun remissiestatus algemeen ook eerder dan diegenen met "gunstigere" psychosociale profielen.
Hoofdstuk 2 richtte zich op vermoeidheid, een van de meest voorkomende en invaliderende symptomen van RA. Op basis van verschillende uitkomstmaten voor vermoeidheid die werden verzameld tijdens de CareRA studie toonden we aan dat dit een dynamisch maar hardnekkig symptoom is in een vroege fase van RA. In minder dan 25% van de geïncludeerde patiënten was er een blijvende verbetering in vermoeidheid ondanks intensieve DMARD-behandeling, en bij één op de vijf patiënten was er zelfs een verslechtering van de vermoeidheid tijdens de eerste maanden. Bovendien werd de relatie tussen ziekteactiviteit en vermoeidheid voornamelijk verklaard door pijn, mentale gezondheid en slaapkwaliteit, en we zagen ook een hogere vermoeidheid doorheen de tijd bij patiënten die bij de start van de studie meer ziekte-impact en minder gezwollen gewrichten hadden. De belangrijkste bevinding van hoofdstuk 2 was echter dat het bereiken van vroegtijdige remissie klachten van vermoeidheid verbeterde gedurende 5 jaar opvolging, zelfs wanneer de ziekteactiviteit later tijdelijk weer opflakkerde.
Ter afsluiting van deel I onderzocht **hoofdstuk 3** het begrip zelfeffectiviteit, of het vertrouwen van patiënten in hun vermogen om RA en de gevolgen ervan te beheersen met hun eigen middelen. In lijn met de voorgaande resultaten suggereerden onze bevindingen uit dit hoofdstuk dat de zelfeffectiviteitsovertuigingen van patiënten met RA op de lange termijn sterk beïnvloed worden door psychosociale kenmerken, zelfs vanaf de vroege stadia van de ziekte, en door het tijdig bereiken van remissie via behandeling. Belangrijk is dat aanvullende analyses aantoonden dat deze relatie tussen vroege behandelrespons en sterkere zelfeffectiviteitsovertuigingen op de lange termijn werd verklaard door positieve effecten op ziektepercepties, vermoeidheid en kwaliteit van leven, en niet door een betere controle van de ontstekingsparameters uit bloedonderzoek.
Deze resultaten leidden tot enkele belangrijke overkoepelende conclusies. Het is al enige tijd duidelijk dat de vroege start van DMARD-therapie voor RA, idealiter leidend tot vroege remissie, geassocieerd is met verbeterde klinische resultaten op lange termijn. Dit concept wordt ook wel het "window of opportunity" genoemd. Samengevoegd en verder bevestigd door een kleinschaligere validatiestudie in de recente CareRA2020-cohorte (**Deel I - Epiloog**), suggereren de resultaten van de hoofdstukken 1 tot 3 van dit proefschrift dat dit concept kan worden uitgebreid tot een "psychosociaal window of opportunity". Met andere woorden lijkt het bereiken van vroegtijdige ziektecontrole binnen dit tijdsvenster ook te leiden tot betere PRO's en een positievere kijk voor patiënten op hun ziekte op de lange termijn. Gebaseerd op deel I van dit proefschrift, lijkt het prioriteren van snelle controle van ziekteactiviteit met geschikte farmacotherapie, gericht op het zo vroeg mogelijk bereiken van remissie, dus een belangrijke eerste stap om aanhoudende ziekte-impact voor patiënten met RA te voorkomen.
In vervolg op deze bevindingen richtte **Deel II** zich op hoe smartphone-applicaties gebruikt zouden kunnen worden om de door patiënten gerapporteerde impact van RA verder te onderzoeken en mogelijk te verminderen.
In **hoofdstuk 4.1** beschreven we de resultaten van een focusgroepstudie uitgevoerd bij patiënten met RA, reumatologen en reumaverpleegkundigen. Deelnemers stonden over het algemeen open voor het gebruik van apps in de gezondheidszorg, met potentiële voordelen zoals het vergemakkelijken van de communicatie tussen patiënten en zorgverleners, het helpen bij de identificatie van patiënten die dringende zorg nodig hebben en het bieden van educatie en ondersteuning om patiënten te helpen een actievere rol aan te nemen in hun

gezondheidszorg. Deze studie maakte echter ook duidelijk dat er rekening moet worden gehouden met een aantal belangrijke barrières bij het ontwerpen van een app of een app-gebaseerde interventie. Naast het benadrukken van verschillende juridische en organisatorische barrières, hadden de deelnemers bedenkingen bij de uitdaging om patiënten te motiveren om een app te blijven gebruiken, waren ze onzeker over hoe de ideale doelgroep voor een mobiele gezondheidsapp eruit zou zien, en toonden ze zich bezorgd dat het vragen van patiënten om regelmatig hun symptomen te rapporteren een ongewenste psychologische impact zou kunnen hebben.

In **hoofdstuk 4.2** presenteerden we een systematische review en meta-analyse van de wetenschappelijke literatuur. Deze trachtte meer inzicht te geven in welke mate patiënten met chronische artritis langdurig gebruik blijven maken van digitale hulpmiddelen. Hoewel deze review relatief hoge gerapporteerde niveaus van activiteit met digitale hulpmiddelen aantoonde, maakte ze ook duidelijk dat evidentie uit de dagelijkse praktijk ondervertegenwoordigd is in de literatuur. Dit suggereert dat de afname van app-gebruik over de tijd in de praktijk meer uitgesproken zou kunnen zijn dan de literatuur doet vermoeden. Bovendien gaf onze systematische review aan dat er behoefte is aan meer standaardisatie en transparantie in de manier waarop studies het gebruik van apps rapporteren, gezien duidelijke schattingen van retentie vaak niet werden gerapporteerd.

Op basis van onze inzichten uit hoofdstuk 4 en deel I van dit proefschrift ontwierpen we de App-based Education and GOal-setting in RA (AEGORA) studie, die het onderwerp werd van **hoofdstuk 5**. AEGORA was een 16 weken durende multicentrische, pragmatische, open-label gerandomiseerde gecontroleerde trial. De focus van deze studie was het onderzoeken van de effectiviteit en praktische haalbaarheid van een app-gebaseerde educatie- en zelfmanagementinterventie om de zelfeffectiviteit en ziekte-impact bij patiënten met RA te verbeteren. Samenvattend was deze interventie jammer genoeg niet superieur aan gebruikelijke zorg wat betreft verbetering van zelfeffectiviteit of de secundaire uitkomsten van ziekte-impact, fysieke activiteit en slaapkwaliteit. Vermoedelijk was dit deels te wijten aan de inclusie van een patiëntenpopulatie met goed gecontroleerde, lang bestaande RA en over het algemeen beperkte educatieve noden. Op zijn beurt was dit een direct gevolg van onze bewuste keuze voor soepele inclusiecriteria om een realistische evaluatie van de praktische haalbaarheid mogelijk te maken. Een tweede waarschijnlijke verklaring voor het gebrek aan geobserveerde verbetering was dat de educatieve inhoud van de app, hoewel mede ontwikkeld met patiëntdeskundigen en reumatologen, eerder algemeen was dan behoeftegericht en interactief. In dit opzicht zijn de resultaten van AEGORA in lijn met die van eerdere studies en internationale aanbevelingen voor patiënteducatie bij inflammatoire artritis, die suggereren dat apps voornamelijk in een aanvullende rol moeten worden gebruikt, bovenop gepersonaliseerde, behoeftegerichte educatie. Tot slot, ondanks de negatieve primaire uitkomst van AEGORA, stelden we vast dat het monitoren van symptomen op afstand via de app een waardevol aanvullend inzicht gaf in de evolutie van de ziekte-impact doorheen de tijd. Zo zagen we dat meer dan één op de drie geïncludeerde patiënten ten minste één episode van toenemende symptomen ervoer over een periode van 16 weken, ondanks het feit dat de ziekte over het algemeen goed onder controle was. Bovendien resulteerde de interventie niet in meer negatieve percepties van pijn en konden we formeel non-inferioriteit voor deze uitkomst vaststellen. Dit resultaat biedt enige geruststelling rond de bezorgdheden over de psychologische impact van symptoomregistratie via apps, wat uit onze eigen en andere kwalitatieve studies naar voren was gekomen.

Concluderend hadden de analyses in dit proefschrift tot doel meer inzicht te verschaffen in de verschillende manieren waarop RA het leven van patiënten beïnvloedt en te onderzoeken hoe deze impact kan worden voorkomen of aangepakt. Ten eerste vonden we dat een aanzienlijk deel van de patiënten met RA een psychosociale impact van de ziekte blijft ervaren, inclusief symptomen zoals vermoeidheid, ondanks vroege en intensieve DMARD-therapie en zelfs wanneer de inflammatoire ziekteactiviteit goed onder controle is. Verder onderzoek hiernaar toonde aan dat snelle controle van de ziekteactiviteit cruciaal is, waarbij patiënten die vroeg remissie bereikten minder vermoeidheid, positievere ziektepercepties en meer vertrouwen in hun zelfmanagementcapaciteiten ervoeren gedurende meerdere jaren. Dit suggereert dat het streven naar vroege controle van RA binnen het zogenaamde "window of opportunity" nog bredere implicaties heeft dan algemeen wordt aangenomen, een concept dat we het "psychosocial window of opportunity" hebben genoemd.

Onze resultaten onderstrepen ook de noodzaak om regelmatig opnieuw te beoordelen of patiënten onvervulde behoeften of aanhoudende symptomen ervaren, zelfs wanneer de doelen voor ziekteactiviteit worden gehaald. Op basis van de resultaten van deel II van dit proefschrift is symptoommonitoring op afstand via mobiele apps een mogelijke aanpak om meer inzicht te krijgen in de impact van RA die patiënten ervaren. Helaas konden we echter niet aantonen dat een interventie via een mobiele app deze impact ook effectief kon verminderen, wat suggereert dat apps mogelijk meer geschikt zijn voor een aanvullende dan een op zichzelf staande rol in behoeftegerichte, persoonlijk afgestemde patiënteducatie en zelfmanagementondersteuning.

Ondanks de aanzienlijke vooruitgang die de afgelopen decennia is geboekt in de behandeling van RA, illustreren onze resultaten dat er nog een lange weg te gaan is. Onderzoek heeft duidelijk gemaakt dat het uiteindelijke doel van patiënten is om een normaal leven te kunnen leiden ondanks de aandoening RA. Als we dit doel willen bereiken, wijzen onze bevindingen op verschillende gebieden waar verder onderzoek welkom zou zijn. Ten eerste benadrukt het bestaan van een psychosociaal "window of opportunity" dat het optimaliseren van RA-behandeling in een vroeg stadium van het grootste belang is. Ten tweede illustreren onze resultaten echter dat het bereiken van het doel van “normaliteit” waarschijnlijk niet mogelijk is met alleen medicamenteuze behandeling. Toekomstig onderzoek dient zich te richten op het optimaliseren van de aanpak van patiënteducatie, zelfmanagementondersteuning en niet-farmacologische zorg voor patiënten met RA. In een wereld waar “treating-to-target” de norm is geworden, is het misschien tijd om de reikwijdte van deze benadering uit te breiden door na te denken over hoe we vanuit een holistisch perspectief de repercussies van RA kunnen voorkomen en verminderen, inclusief deze die misschien niet direct gerelateerd zijn aan ziekteactiviteit of ontsteking.

SUPPLEMENTAL MATERIALS

Chapter 1

Supplement 1.1

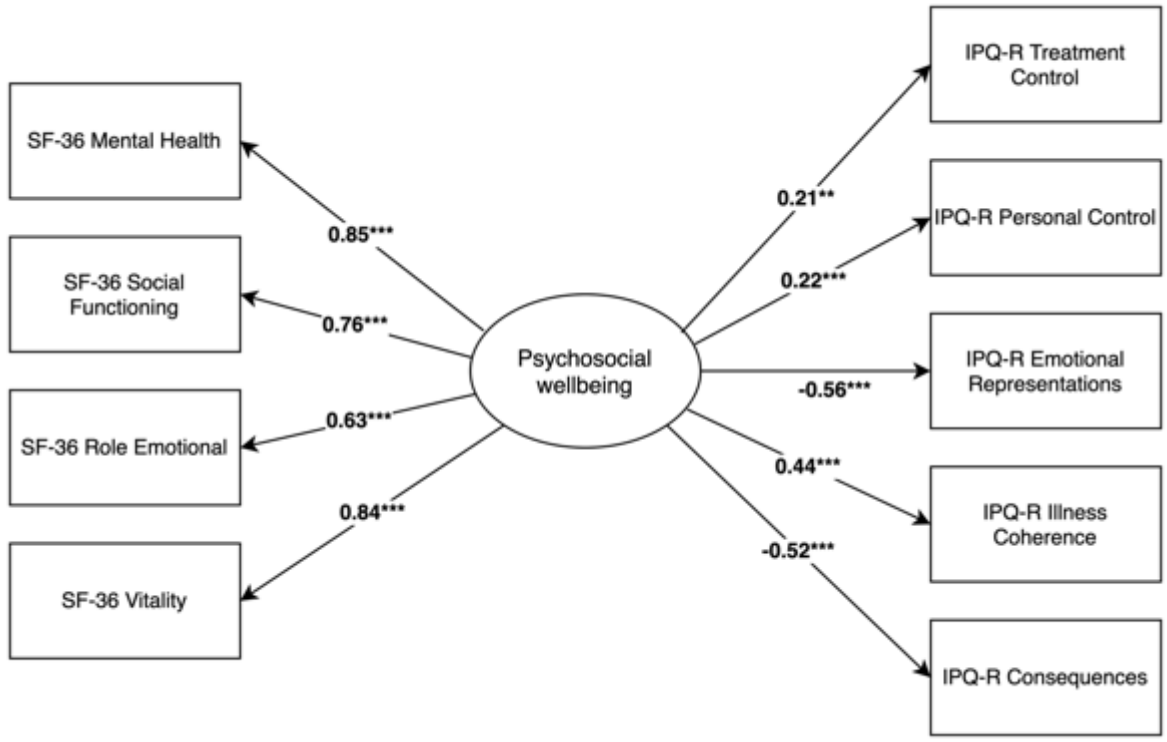
A. Detailed methods for confirmatory factor analysis (CFA) and measurement invariance

To further examine the directionality of associations between indicators of psychosocial wellbeing and disease activity, one option are cross-lagged panel models (CLPMs).
However, an intermediary step is recommended for our data to reduce measurement error due to the repeated observation of 9 different variables (the SF-36 mental components and the 5 available IPQ-R dimensions). To this end, we first performed a confirmatory factor analysis (CFA) defining psychosocial wellbeing as a latent construct loaded upon by these 9 psychosocial factors as observed variables, normalized to the same scale (see Supplement 1.1B and 1.1C). Factor loadings for all observed variables represent how strongly each variable is related to its underlying latent construct.

Second, to ensure that comparisons can be made between different points in time, it should first be established that the construct of psychosocial wellbeing is measured consistently over time. Establishing this so-called measurement invariance (MI) requires the construction of a series of nested CFA-models with increasing levels of constraint on equality across timepoints, before selecting the best-fitting model based on model fit statistics.
Supplement 1.1D presents a relevant selection of model fit indices for all 4 nested models: the configural model, which imposes the same factor structure across time points but allows factor loadings and the intercepts and residual variances of the observed variables to vary; the metric model, which constrains factor loadings to equality across time; the scalar model, which additionally constrains the intercepts to remain equal; and the full uniqueness model, which sets the residual variances to equality in addition to the aforementioned constraints.
All nested models showed acceptable and generally comparable model fit. Based on a lower Akaike Information Criterion (AIC) and conceptual reasons, the configural model was finally chosen. This model implies that, although psychosocial wellbeing remains defined by the same variables at each timepoint, the relative contribution of these variables may vary.

Finally, the configural model was extended to a cross-lagged panel model studying the association between psychosocial wellbeing and disease activity (DAS28-CRP). For this association, psychosocial wellbeing was treated as a continuous latent construct and DAS28-CRP as a continuous observed variable. As per the lavaan *sem*-function's default settings, paths were estimated with a maximum likelihood estimator (Supplement 1.1E).

B. Confirmatory factor analysis at baseline



Rectangles represent observed variables; circles represent latent constructs. Numbers displayed are factor loadings and represent how strongly each variable is related to its underlying latent construct. Variables were first normalized to the same scale for comparability.
** = p < 0.05, ** = p < 0.01, *** = p < 0.001; SF-36 = Short-Form 36; IPQ-R = Revised Illness Perception Questionnaire*

C. Factor loadings for confirmatory factor analysis at all time points

Variable	Baseline	W16	W52	W104
SF-36				
Mental Health	0.85	0.79	0.79	0.80
Social Functioning	0.76	0.77	0.83	0.81
Role Emotional	0.63	0.65	0.69	0.70
Vitality	0.84	0.77	0.83	0.83
IPQ-R				
Illness coherence	0.44	0.57	0.57	0.56
Treatment control	0.21	0.44	0.49	0.59
Personal control	0.22	0.27	0.25	0.22
Emotional representations	-0.56	-0.66	-0.68	-0.72
Consequences	-0.52	-0.59	-0.68	-0.62

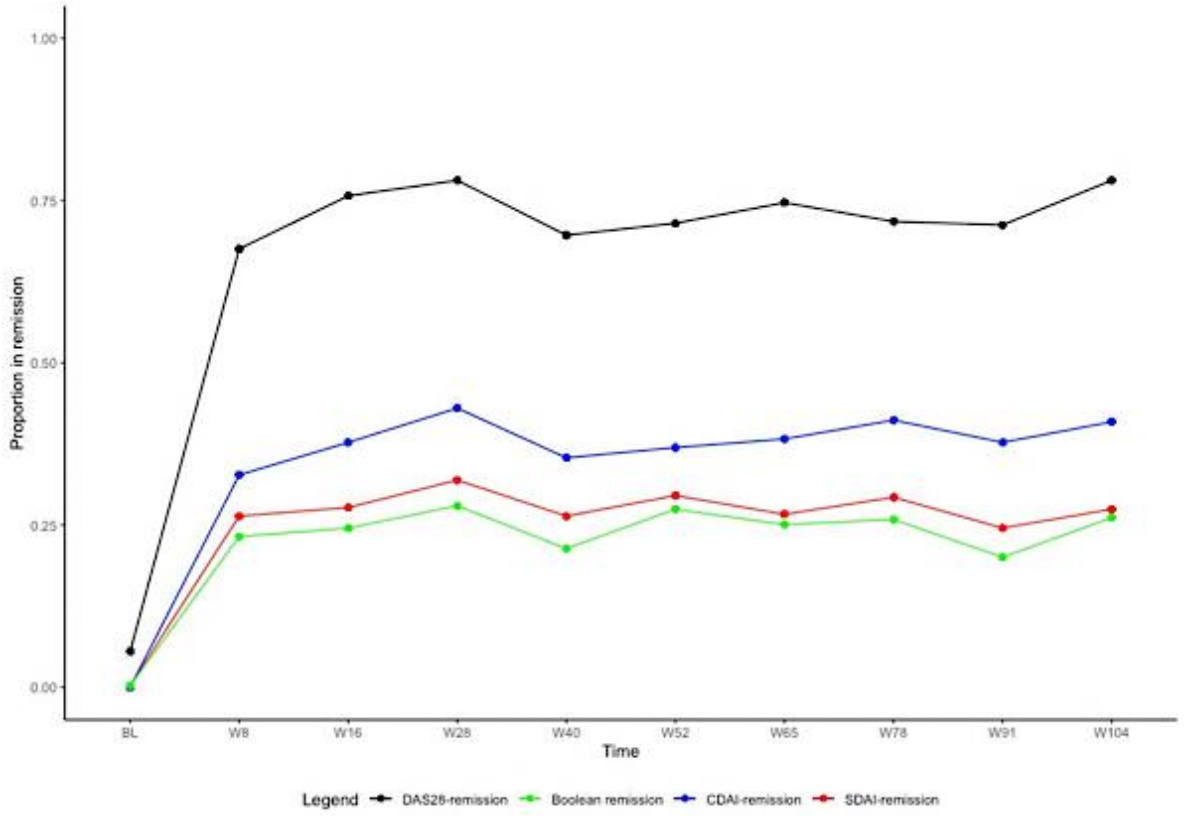
Numbers displayed are factor loadings and represent how strongly each variable is related to its underlying latent construct. Variables were first normalized to the same scale for comparability.
SF-36 = Short-Form 36; IPQ-R = Revised Illness Perception Questionnaire

D. Model fit indices for nested CFA-models

Model	TLI	CFI	RMSEA	SRMR	AIC	BIC
Configural	0.89	0.90	0.065	0.074	30489	30832
Metric	0.89	0.90	0.065	0.083	30504	30740
Scalar	0.90	0.90	0.062	0.081	30522	30794
Full uniqueness	0.89	0.89	0.064	0.082	30598	30763

Model fit is considered acceptable when TLI and CFI are >0.90 and RMSEA and SRMR are <0.08. Fit indices implied acceptable and comparable model fit for all nested models. The configural model was chosen based on a lower AIC-value and for conceptual reasons.
TLI = Tucker-Lewis Index; CFI = Comparative Fit Index; RMSEA = Root Mean Square Error of Approximation; SRMR = Standardized Root Mean Squared Residual; AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

Supplement 1.2. Proportion of patients in remission across time.



Supplement 1.3. Baseline clinical predictors of sustained remission.

Variable	Coefficient	SD	OR (95% CI)	Z-value	P-value
DAS28-CRP	-0.44	0.10	0.64 (0.53-0.78)	-4.36	**<0.001**
TJC28	-0.08	0.02	0.92 (0.88-0.96)	-3.75	**<0.001**
SJC28	-0.08	0.02	0.93 (0.89-0.97)	-3.19	**0.001**
PGA	-0.16	0.05	0.86 (0.78-0.94)	-3.32	**<0.001**
PhGA	-0.22	0.06	0.80 (0.71-0.91)	-3.54	**<0.001**
VAS pain	-0.16	0.05	0.85 (0.78-0.93)	-3.41	**<0.001**
VAS fatigue	-0.22	0.05	0.80 (0.73-0.88)	-4.41	**<0.001**
HAQ	-0.71	0.18	0.49 (0.35-0.69)	-4.02	**<0.001**
BMI	-0.05	0.03	0.95 (0.90-1.00)	-1.93	0.055

Results of multivariate logistic regression with the specified variables as individual predictors and the odds of sustained DAS28-CRP-remission as dependent variable. All models contained age, sex, treatment arm, and the presence of autoantibodies as covariates. *OR = odds ratio, CI = confidence interval, DAS28-CRP = Disease Activity Score in 28 joints using C-reactive protein, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, VAS = visual analogue scale, HAQ = Health Assessment Questionnaire, BMI = body mass index*

Supplement 1.4. Model fit statistics for LPA of patients in DAS28-CRP-remission at week 16.

	Week 16 remission	
Number of classes	**AIC**	**BIC**
1	6539	6736
2	**6326**	**6560**
3	6332	6603

The optimal number of classes was chosen based on lower values for both AIC and BIC, representing better model fit. The lowest AIC/BIC before the first increase was chosen as the optimal cut-off. Therefore, the 2-class model was chosen. All model fit statistics correspond to an LPA-model of equal variances and equal covariances. *LPA = latent profile analysis, AIC = Akaike's Information Criterion, BIC = Bayesian Information Criterion*

Supplement 1.5A. Kaplan-Meier event table for survival of DAS28-CRP-remission by week 16 psychosocial profile.

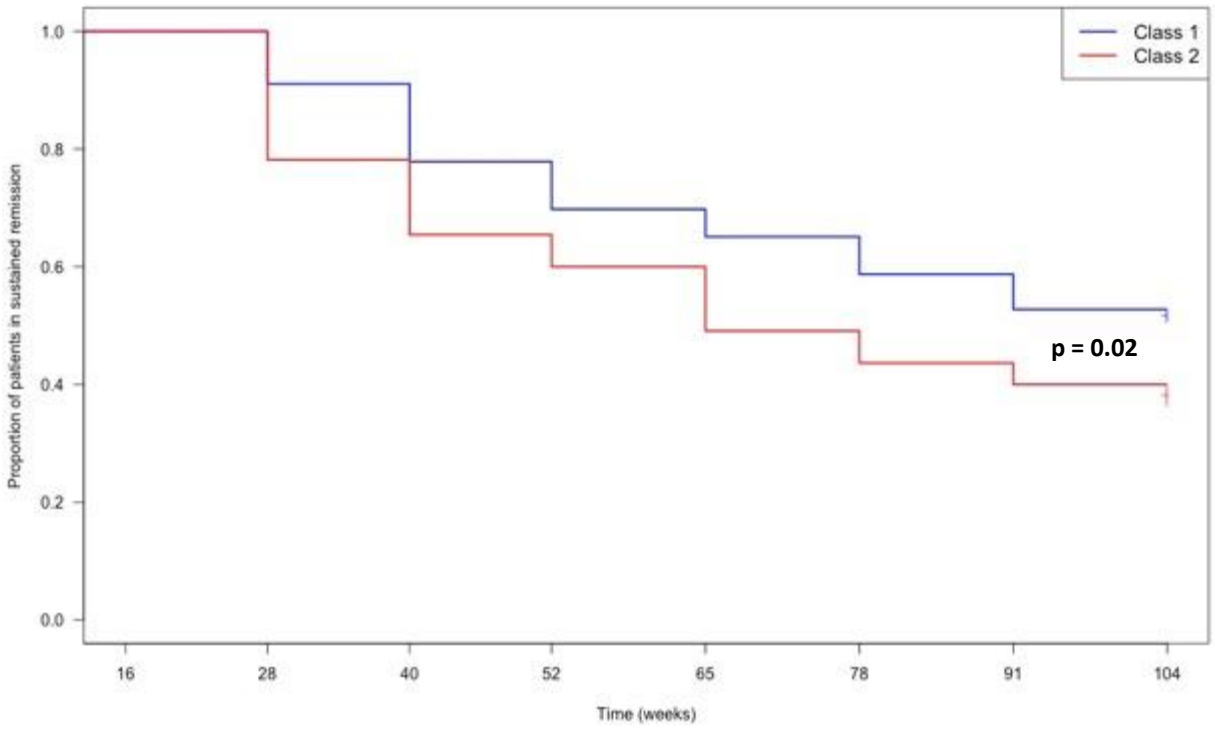
Low burden			
Week	**No at risk**	**No of events**	**Survival**
28	231	20	0.913
40	211	31	0.779
52	180	19	0.697
65	161	12	0.645
78	149	15	0.580
91	134	6	0.554
104	128	7	0.524
High burden			
Week	**No at risk**	**No of events**	**Survival**
28	56	12	0.786
40	44	13	0.554
52	31	7	0.429
65	24	3	0.375
78	21	3	0.321
91	18	1	0.304
104	17	1	0.286

Supplement 1.5B. Kaplan-Meier event table for survival of CDAI-remission by week 16 psychosocial profile.

Low burden			
Week	**No at risk**	**No of events**	**Survival**
28	121	28	0.769
40	93	19	0.612
52	74	8	0.545
65	66	8	0.479
78	58	4	0.446
91	54	9	0.372
104	45	3	0.347
High burden			
Week	**No at risk**	**No of events**	**Survival**
28	25	11	0.56
40	14	2	0.48
52	12	5	0.28
78	7	2	0.20
91	5	1	0.16

No at risk = number at risk, No of events = number of events, DAS28 = Disease Activity Score in 28 joints, CDAI = Clinical Disease Activity Index

Supplement 1.6. Kaplan-Meier curves for retention of SDAI-LDA by psychosocial profile of patients in SDAI-remission or LDA at week 16.



Profiles resulted from Latent Profile Analysis of patients in remission or LDA at week 16 based on SDAI. Class 1 (low psychosocial burden) consisted of 235/290 patients (81%), class 2 (high psychosocial burden) of 55 patients (19%). Significance was assessed by Cox-proportional hazards regression adjusting for age, sex, treatment arm, and autoantibody status.
SDAI = Simplified Disease Activity Index, LDA = low disease activity

Chapter 2

Supplement 2.1A: Exclusion criteria and stratification scheme of the CareRA study protocol.

Exclusion criteria:
Previous treatment with methotrexate, leflunomide, cyclophosphamide, azathioprine, cyclosporine, sulfasalazine for more than three weeks, hydroxychloroquine for more than six weeks

Oral glucocorticoids at a dosage of more than 10 mg prednisone or dosage equivalent within four weeks before baseline

Oral glucocorticoids at a dosage equal to or less than 10 mg prednisone or dosage equivalent within two weeks before baseline, oral glucocorticoids for more than four weeks, intra-articular glucocorticoids within four weeks before baseline or an investigational drug for the treatment or prevention of RA

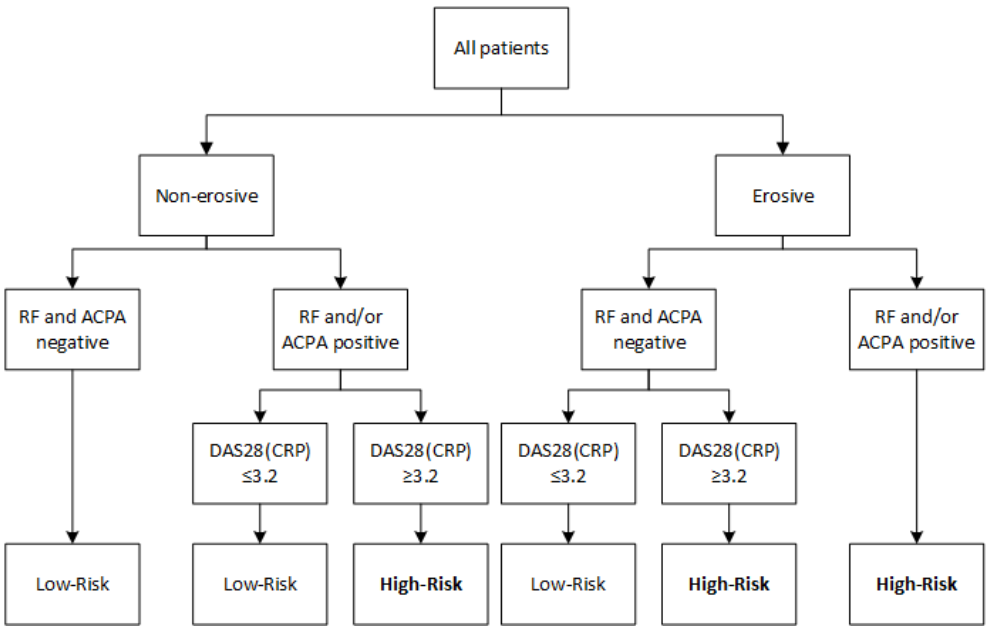
Contra indications for glucocorticoids

Contra indication for methotrexate, sulfasalazine or leflunomide at the discretion of the investigator: chronic hepatic diseases, pulmonary interstitial disease or fibrosis, chronic renal failure, history of malignant neoplasm within five years, hematologic problems

Patients with psoriatic arthritis

Underlying cardiac, pulmonary, metabolic, renal or gastrointestinal conditions, chronic or latent infectious diseases or immune deficiency which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study

Pregnancy; Breastfeeding; No use of a reliable method of contraception



Stratification scheme: Classification of patients in high or low-risk according to classical prognostic factors. RF= Rheumatoid Factor; ACPA= Anti-Citrullinated Protein Antibody; DAS28 (CRP) = 28 joint disease activity score calculated with C-reactive protein.

Supplement 2.1B: Treatment regimens and adaptation steps of the CareRA study protocol.

Treatment regimens in the induction phase (Year 1)
COBRA Classic:
MTX 15 mg with SSZ 2g and a step-down scheme of steroids (60-40-25-20-15-10-7,5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks). At week 40, patients will continue MTX (min. 15 mg/week) in mono therapy if disease activity is acceptable low (DAS 28 CRP ≤ 3,2)

COBRA Slim:
MTX 15 mg with a step-down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks).

COBRA Avant-Garde:
MTX 15 mg with Leflunomide 10 mg and a step-down scheme of steroids (30-20-12,5-10-7,5-5 mg prednisone, each for 7 days except for the lowest dose, this will be maintained until w28 and then tapered over 6 weeks). At week 40, patients will be randomly assigned to maintenance therapy with either MTX (≥15 mg/week) or leflunomide (20 mg daily) if disease activity is acceptable low (DAS 28 CRP ≤ 3,2).

Tight Step Up:
MTX 15 mg and no additional oral steroids allowed

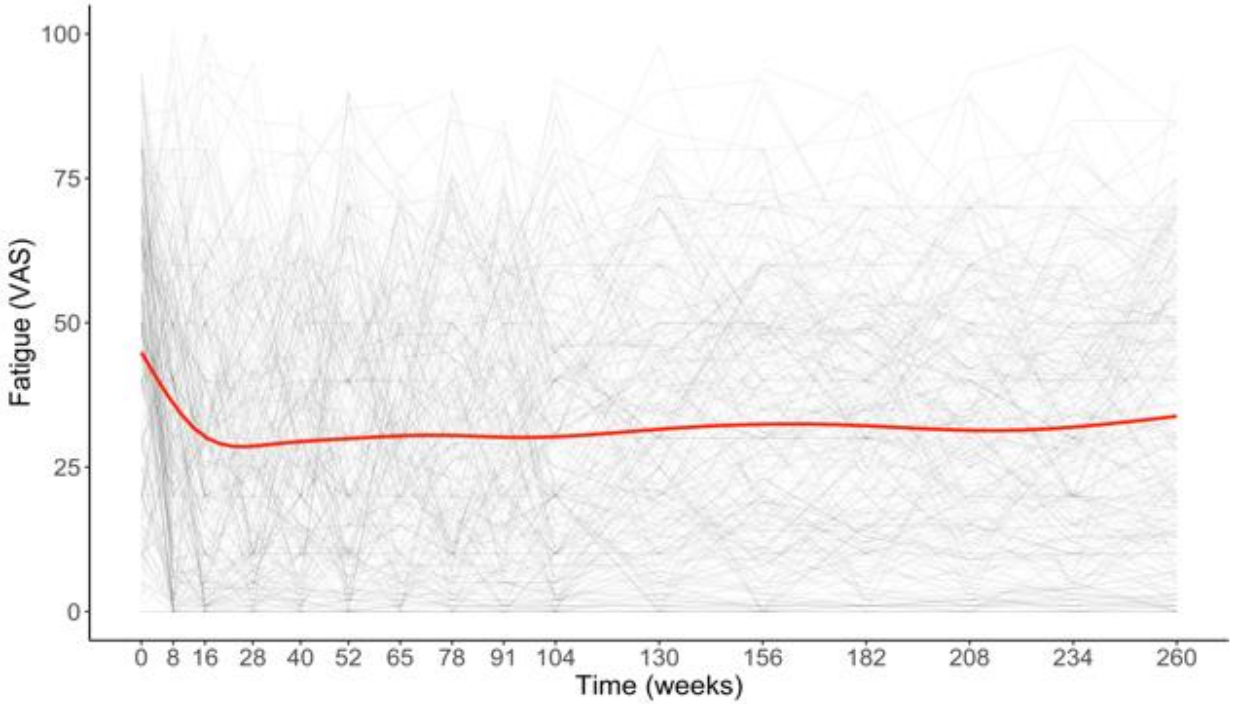
Predefined adaptation steps in the induction phase (Year 1)
If patients fail to respond (DAS28-CRP > 3.2), treatment adjustments will be made from 8 weeks of treatment onwards, if desirable and feasible.
First step: methotrexate dose increase to 20 mg per week in all groups
Second step: COBRA-Classic: sulfasalazine dose increase to 3 g
COBRA-Slim and Tight Step Up: add leflunomide 10 mg
COBRA-Avant-Garde: leflunomide dose increase to 20 mg
An intramuscular depot-corticoid injection is allowed together with these treatment adjustments, but not within 4 weeks preceding week 16, 28, 40 and week 52 visits. As an alternative an oral bridging scheme could be considered, after discussion with the principal investigator
Intra-articular corticosteroids are allowed maximally once every 8 weeks but not within 4 weeks preceding week 16, 28, 40 and week 52 visits
Further DMARD treatment adjustments are only allowed from 8 weeks after prior treatment adjustments onwards.

Treatment regimen in the maintenance phase (Year 2)
Treatment adjustments during the maintenance phase from week 52 onwards will be at the discretion of the local physician according to good clinical practice.

Supplement 2.2A. Linear mixed model (LMM) analysis of the group-level fatigue evolution over time.

Before investigating distinct fatigue trajectories, we first studied the group-level evolution of fatigue (VAS) over time with linear mixed models (LMMs) including only participants with available 5-year data (n = 244). Four timeframes were studied: baseline to year 5, week 16 to year 5, year 1 to year 5, and year 2 to year 5. For each timeframe, three LMMs were constructed: 1) unconditional means model, which included a random intercept for each individual participant but no independent variable, implying that mean fatigue (VAS) varied between participants but did not change over time at the group level; 2) unconditional growth model, which additionally included time as an independent variable to reflect change over time in group-level mean fatigue (VAS); and 3) unconditional growth model with a random slope for time, allowing the rate of this change to vary between individual participants. The best-fitting model was chosen based on lower values for Akaike and Bayesian Information Criterion (AIC/BIC).

Supplement 2.2B. Group-level evolution of fatigue (VAS) over 5 years in CareRA (n = 244).



Supplement 2.2C. Model fit statistics for linear mixed models (LMM) predicting group-level and interindividual change in fatigue (VAS) over time (n = 244).

	Baseline – year 5			**W16 - year 5**			**Year 1 - year 5**			**Year 2 - year 5**		
Model	**Log-L**	**AIC**	**BIC**	**Log-L**	**AIC**	**BIC**	**Log-L**	**AIC**	**BIC**	**Log-L**	**AIC**	**BIC**
Unconditional means model	-16723	33452	33471	-14415	28836	28855	-11281	22568	22586	**-7136**	**14278**	**14294**
Unconditional growth model	-16725	33459	33484	-14410	28828	28852	-11278	22565	22589	-7136	14280	14302
Unconditional growth model with random slope	**-16640**	**33292**	**33330**	**-14314**	**28641**	**28677**	**-11226**	**22464**	**22500**	-7130	14273	14306

All models are LMM with fatigue (VAS) as the dependent variable. The unconditional means model includes a random intercept for all individual participants, but no independent variable. In this model, mean fatigue (VAS) varies between individual participants but does not change over time at the group level. By contrast, the unconditional growth model additionally includes time (weeks) as an independent variable to reflect change over time in mean fatigue (VAS) at the group level. Finally, including a random slope for time allows the rate of this change to vary between individual participants. For both Log-L, AIC and BIC, lower numbers indicate better model fit. *VAS = Visual Analog Scale, Log-L = log-likelihood, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion*

Supplement 2.3A. Model fit statistics for multivariate growth mixture models to detect trajectories of fatigue evolution over the first 2 years of CareRA with increasing number of classes (n = 356).

	Log-L	AIC	BIC	Class 1, n (%)	Class 2, n (%)	Class 3, n (%)	Class 4, n (%)	Class 5, n (%)
1	-40560	81196	81344	100.00	NA	NA	NA	NA
2	-40103	80291	80458	26.40	73.60	NA	NA	NA
3	-39978	80053	80239	62.64	17.98	19.38	NA	NA
4	**-39859**	**79825**	**80030**	**55.62**	**10.39**	**14.04**	**19.94**	**NA**
5	-39798	79712	79936	5.06	17.13	12.64	55.62	9.55

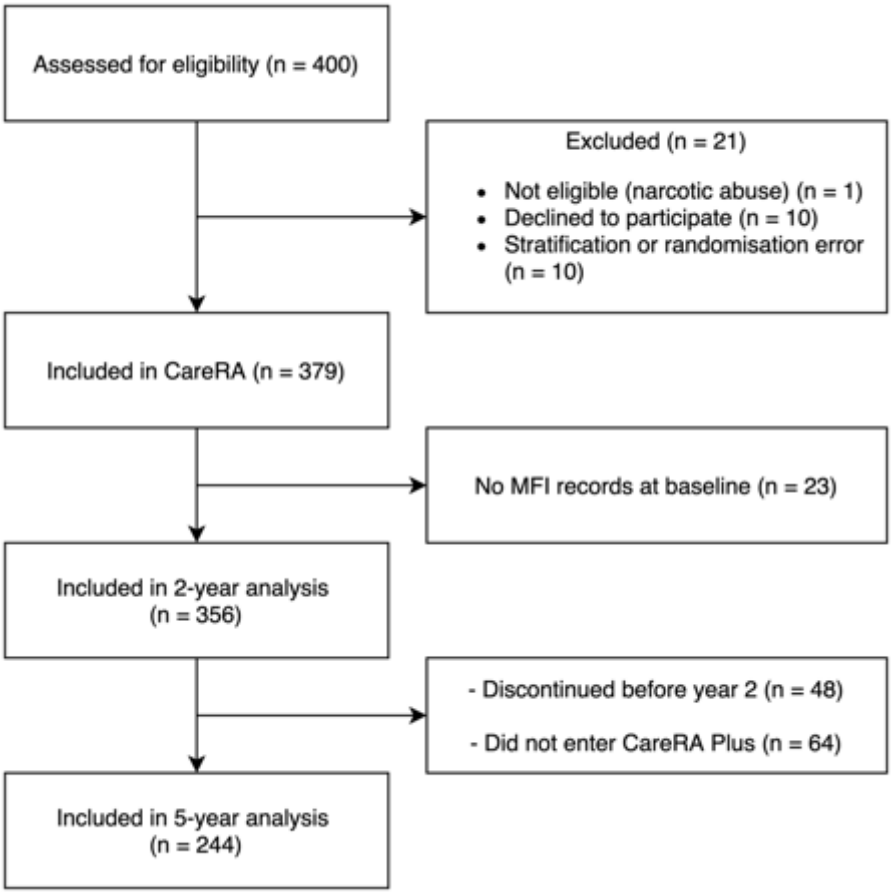
For both Log-L, AIC and BIC, lower numbers indicate better model fit. The 5-class model was deemed at risk of overfitting, because it derived two trajectories of <10% of participants. Moreover, model fit statistics were largely comparable with the 4-class model. Consequently, the 4-class model was chosen as the optimal representation of the data, based on both fit statistics and distribution among classes. *Log-L = log-likelihood, AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion*

Supplement 2.3B. Mean of posterior probabilities for each class in the 4-class model.

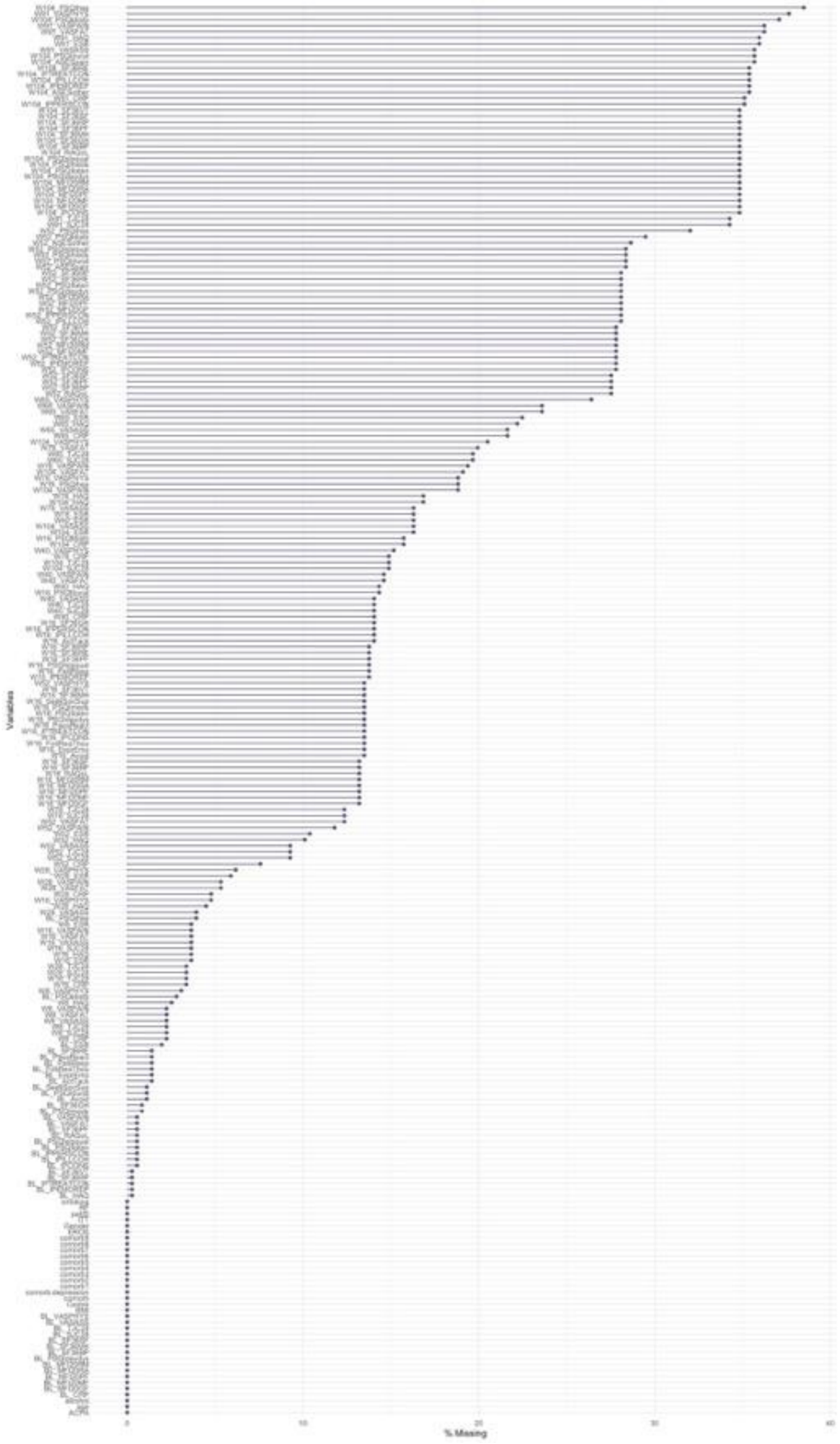
	Class 1	Class 2	Class 3	Class 4
Class 1	**0.93**	0.01	0.03	0.04
Class 2	0.02	**0.96**	0.02	0.00
Class 3	0.08	0.04	**0.87**	0.00
Class 4	0.11	0.00	0.01	**0.88**

Reported are the mean posterior probabilities of participants being correctly assigned to the corresponding latent trajectory class. Lower posterior probabilities indicate a higher degree of uncertainty in the model, and thus more overlap between classes.

Supplement 2.4A. Flow chart of participants included in analyses of 2-year and 5-year CareRA results.



Supplement 2.4B. Overview of missing data per variable.



Supplement 2.5. Spearman coefficients for the correlation between different measures of fatigue at baseline for patients included in CareRA (n = 356).

	VAS	**MFI GF**	**MFI PF**	**MFI RA**	**MFI MF**	**MFI RM**	**SF-36 VT**
VAS	**1.00**	0.60	0.47	0.39	0.33	0.36	-0.56
MFI GF	0.60	**1.00**	0.74	0.65	0.46	0.58	-0.72
MFI PF	0.47	0.74	**1.00**	0.78	0.39	0.58	-0.60
MFI RA	0.39	0.65	0.78	**1.00**	0.48	0.68	-0.61
MFI MF	0.33	0.46	0.39	0.48	**1.00**	0.53	-0.52
MFI RM	0.36	0.58	0.58	0.68	0.53	**1.00**	-0.59
SF-36 VT	-0.56	-0.72	-0.60	-0.61	-0.52	-0.59	**1.00**

VAS = Visual Analog Scale, MFI = Multidimensional Fatigue Inventory, GF = General Fatigue, PF = Physical Fatigue, MF = Mental Fatigue, RA = Reduced Activity, RM = Reduced Motivation, SF-36 = Short Form-36, VT = Vitality

Supplement 2.6A. Initial, full multivariable models for candidate baseline predictors of fatigue (VAS) over time.

	Baseline – year 2 (n = 356)		**Baseline – year 5 (n = 244)**	
Baseline predictors	**ß (95% CI)**	**p-value**	**ß (95% CI)**	**p-value**
Age at inclusion (y)	-0.14 (-0.30 to 0.02)	0.07	-0.07 (-0.25 to 0.11)	0.44
Sex (male)	-2.48 (-6.24 to 1.28)	0.20	-3.98 (-8.35 to 0.39)	0.08
Autoantibodies (+)	-2.73 (-8.41 to 2.95)	0.35	-2.00 (-8.68 to 4.68)	0.56
Treatment type*				
LR: Tight-Step Up	4.10 (-2.98 to 11.18)	0.26	8.04 (-1.03 to 17.11)	0.09
HR: COBRA classic	-2.25 (-7.01 to 2.51)	0.35	-2.28 (-7.77 to 3.21)	0.42
HR: COBRA avant-garde	-1.55 (-6.27 to 3.17)	0.52	0.18 (-5.39 to 5.75)	0.95
RDCI (0-9)	0.97 (-0.70 to 2.64)	0.25	-0.26 (-2.24 to 1.72)	0.80
Symptom duration (days)	0.00 (0.00 to 0.00)	0.89	0.00 (0.00 to 0.00)	0.06
Erosive disease (+)	-1.42 (-5.71 to 2.87)	0.52	1.40 (-3.56 to 6.36)	0.58
BMI (kg/m²)	0.38 (-0.03 to 0.79)	0.06	0.40 (-0.09 to 0.89)	0.11
PGA (VAS)	0.23 (0.15 to 0.31)	**<0.001**	0.14 (0.04 to 0.24)	**0.008**
PhGA (VAS)	0.16 (0.04 to 0.28)	**0.014**	0.09 (-0.07 to 0.25)	0.22
TJC28 (0-28)	0.17 (-0.26 to 0.60)	0.46	0.56 (0.01 to 1.11)	0.05
SJC28 (0-28)	-0.68 (-1.17 to -0.19)	**0.007**	-0.91 (-1.56 to -0.26)	**0.007**
CRP (mg/dL)	0.02 (-0.05 to 0.09)	0.59	0.01 (-0.07 to 0.09)	0.74
Pain (VAS)	0.22 (0.14 to 0.30)	**<0.001**	0.15 (0.05 to 0.25)	**0.003**
HAQ (0-3)	5.36 (2.26 to 8.46)	**0.001**	4.18 (0.50 to 7.86)	**0.027**
SF-36 MCS (0-100)	-0.34 (-0.49 to -0.19)	**<0.001**	-0.42 (-0.60 to -0.24)	**<0.001**

Results were obtained from multivariable linear mixed models with fatigue (VAS) as the dependent variable and the reported candidate predictors as the independent variables, adjusted for time and with participant-specific random intercepts. Starting from these initial models, candidate predictors were backwards-stepwise excluded based on p-values, model fit statistics, and conceptual reasons, to obtain the final models presented in Table 3.
* During the CareRA trial, participants were first stratified into either high-risk or low-risk groups according to autoantibody status, baseline disease activity and radiographic damage. For these analyses, the COBRA slim regimen was coded as the reference category in both groups.
LR = low-risk stratification group, HR = high-risk stratification group, RDCI = Rheumatic Diseases Comorbidity Index, BMI = Body Mass Index, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, TJC28 = tender joint count in 28 joints, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein, VAS = Visual Analog Scale, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, MCS = Mental Component Score

Supplement 2.6B. Model fit statistics for each backwards variable selection step.

Baseline – year 2 (n = 356)	**AIC**	**BIC**
Initial, full model	30698	30821
- symptom duration	30686	30803
- RDCI	30687	30798
- erosive disease	30688	30793
- autoantibodies	30691	30790
Baseline – year 5 (n = 244)	**AIC**	**BIC**
Initial, full model	33423	33548
- RDCI	33423	33542
- erosive disease	33425	33538
- autoantibodies	33428	33534
- BMI	33427	33527
- symptom duration	33418	33512

AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion. In both cases, lower values represent better model fit.

Supplement 2.7. Variables associated with fatigue (VAS) over time.

	Baseline – year 2 (n = 356)		**Baseline – year 5 (n = 244)**	
Time-varying predictor	**ß (95% CI)**	**p-value (*)**	**ß (95% CI)**	**p-value (*)**
SDAI	0.01 (-0.05 to 0.07)	0.83 (1.00)	0.01 (-0.03 to 0.05)	0.98 (0.98)
Pain (VAS)	0.45 (0.39 to 0.51)	**<0.001 (<0.001)**	0.46 (0.44 to 0.48)	**<0.001 (<0.001)**
HAQ	2.97 (0.17 to 5.77)	***0.039 (0.35)***	5.67 (4.22 to 7.12)	**<0.001 (<0.001)**
PSQI global score	0.55 (0.22 to 0.88)	**<0.001 (0.01)**		
SF-36				
Mental health	-0.15 (-0.23 to -0.07)	**<0.001 (<0.001)**		
Emotional role functioning	0.02 (-0.02 to 0.06)	0.18 (1.00)		
Social functioning	-0.05 (-0.11 to 0.01)	0.16 (1.00)		
IPQ-R				
Treatment control	-0.04 (-0.49 to 0.41)	0.88 (1.00)		
Personal control	-0.08 (-0.39 to 0.23)	0.61 (1.00)		
Consequences	0.04 (-0.31 to 0.39)	0.84 (1.00)		
Emotional representations	0.07 (-0.18 to 0.32)	0.61 (1.00)		
Illness coherence	-0.27 (-0.60 to 0.06)	0.12 (0.96)		

Results were obtained from multivariable linear mixed models (LMMs) with fatigue (VAS) as the dependent variable, the reported variables as time-varying predictors and a participant-specific random intercept. SF-36 Vitality was not studied as a predictor since it is considered a measure of fatigue. The 2-year model contained data from baseline, week 16, 52 and 104, while the 5-year model contained data from every available visit but no PSQI, SF-36 or IPQ-R outcomes, since these were only collected between baseline and year 2. Both models were adjusted for age, sex, treatment type, and time as confounders.
* P-value adjusted for multiple comparisons with Bonferroni-Holm-correction. Since correction was applied separately for 2 and 5-year outcomes, up to 12 p-values were considered in these adjustments.
SDAI = Simple Disease Activity Index, VAS = Visual Analog Scale, HAQ = Health Assessment Questionnaire, PSQI = Pittsburgh Sleep Quality Index, SF-36 = Short Form-36, IPQ-R = Revised Illness Perception Questionnaire

Supplement 2.8. Standardized regression coefficients for multilevel mediation analysis of the association between SDAI and fatigue (VAS) over time.

	ß (95% CI)	**RE (%)**	**p-value**
Direct effect	-0.03 (-0.25 to 0.19)	-8	0.82
Indirect: PGA (VAS)	0.19 (0.10 to 0.28)	**49**	**<0.001**
Indirect: PhGA (VAS)	0.00 (-0.06 to 0.05)	-1	0.87
Indirect: SJC28	-0.05 (-0.12 to 0.02)	-13	0.16
Indirect: TJC28	0.00 (-0.07 to 0.07)	0	1.00
Indirect: CRP	0.02 (-0.10 to 0.14)	5	0.76
Indirect: Pain (VAS)	0.18 (0.11 to 0.26)	**47**	**<0.001**
Indirect: HAQ	0.01 (-0.03 to 0.06)	3	0.65
Indirect: SF-36 Mental health	0.04 (0.02 to 0.06)	**9**	**<0.001**
Indirect: SF-36 Emotional role functioning	-0.01 (-0.02 to 0.00)	-2	0.22
Indirect: SF-36 Social functioning	0.01 (-0.02 to 0.04)	3	0.41
Indirect: IPQ-R Illness coherence	0.00 (-0.01 to 0.01)	0	0.76
Indirect: IPQ-R Consequences	0.00 (-0.01 to 0.02)	1	0.67
Indirect: IPQ-R Emotional representations	0.00 (-0.01 to 0.01)	1	0.76
Indirect: IPQ-R Treatment control	0.00 (0.00 to 0.00)	0	0.95
Indirect: IPQ-R Personal control	0.00 (0.00 to 0.00)	0	0.91
Indirect: PSQI global score	0.02 (0.00 to 0.04)	**5**	**0.036**
Total effect	0.39 (0.31 to 0.46)	**100**	**<0.001**

Results were obtained from multilevel mediation analysis studying the association between SDAI and fatigue (VAS) across baseline, week 16, 52 and 104, with participant-specific random intercepts (n = 356). Reported are the standardized regression coefficients (ß) for the direct effect of SDAI on fatigue (VAS) and the indirect effects that act through the reported mediators. For both direct and indirect paths, relative effect (RE) was defined as ß / (ß of total effect).

SDAI = Simple Disease Activity Index, VAS = Visual Analog Scale, RE = relative effect, PGA = patient's global assessment of disease activity, PhGA = physician's global assessment of disease activity, SJC28 = swollen joint count in 28 joints, TJC28 = tender joint count in 28 joints, CRP = C-reactive protein, HAQ = Health Assessment Questionnaire, SF-36 = Short Form-36, IPQ-R = Revised Illness Perception Questionnaire, PSQI = Pittsburgh Sleep Quality Index

Chapter 3

Supplement 3.1. Standardised coefficients and bootstrapped CIs for direct and indirect effects of treatment response on self-efficacy.

Mediators	**Coefficient (95% CI)**	**P-value**
Direct effect	0.01 (-0.08, 0.11)	0.79
Indirect: SF-36 MCS	-0.02 (-0.05, 0.01)	0.13
Indirect: IPQ-R Illness coherence	-0.01 (-0.03, 0.01)	0.33
Indirect: IPQ-R Emotional representations	-0.03 (-0.07, 0.00)	0.08
Indirect: IPQ-R Consequences	-0.18 (-0.24, -0.12)	**<0.001**
Indirect: IPQ-R Treatment control	-0.01 (-0.04, 0.02)	0.36
Indirect: IPQ-R Personal control	-0.03 (-0.05, -0.01)	**0.01**
Indirect: VAS Pain	-0.03 (-0.10, 0.03)	0.33
Indirect: VAS Fatigue	-0.04 (-0.08, 0.00)	**0.04**
Indirect: HAQ	-0.03 (-0.09, 0.04)	0.39
Indirect: RAQoL	-0.12 (-0.20, -0.04)	**0.01**
Indirect: PGA	-0.04 (-0.10, 0.02)	0.21
Indirect: SJC28	-0.01 (-0.02, 0.01)	0.45
Indirect: CRP	0.00 (-0.02, 0.01)	0.94
Total effect	**-0.54 (-0.65, -0.43)**	**<0.001**

Results were obtained from a mediation analysis of the effect of treatment response on total ASES-scores at week 52 and week 104. Reported coefficients for the indirect effects were obtained by multiplying the coefficients within each pathway. Treatment response was treated as an ordinal variable with lower values representing earlier and more persistent response.

ASES = Arthritis Self-Efficacy Scale, SF-36 = Short-Form 36, MCS = mental component score, IPQ-R = Revised Illness Perception Questionnaire, VAS = Visual Analogue Scale, HAQ = Health Assessment Questionnaire, PGA = patient's global assessment of disease activity, SJC28 = swollen joint count in 28 joints, CRP = C-reactive protein

Chapter 4

Supplement 4.1. Search string.

PUBMED

CONCEPT 1: "chronic arthritis"

("Ankylosis"[Mesh] OR "Arthritis, Juvenile"[Mesh] OR "Arthritis, Psoriatic"[Mesh] OR "Arthritis, Rheumatoid"[Mesh] OR "Gout"[Mesh] OR "Osteoarthritis"[Mesh] OR "Spondylarthritis"[Mesh] OR "ankylosis"[tiab] OR "juvenile arthritis"[tiab] OR "juvenile rheumatoid arthritis"[tiab] OR "juvenile chronic arthritis"[tiab] OR "Still's disease"[tiab] OR "Still disease"[tiab] OR "juvenile oligoarthritis"[tiab] OR "juvenile psoriatic arthritis"[tiab] OR "psoriatic arthropathy"[tiab] OR "gout*"[tiab] OR "degenerative arthritis"[tiab] OR "spinal arthritis"[tiab] OR "spondyl*"[tiab] OR "rheumatoid arthritis"[tiab] OR "osteoarthritis"[tiab] OR "psoriatic arthritis"[tiab])

CONCEPT 2: "eHealth"

("Telemedicine"[MeSH Terms] OR "Telenursing"[MeSH Terms] OR "User-Computer Interface"[MeSH Terms] OR "Mobile Applications"[MeSH Terms] OR "Cell phone"[MeSH Terms] OR "Cell Phone Use"[MeSH Terms] OR "computers, handheld"[MeSH Terms] OR "Wearable Electronic Devices"[MeSH Terms] OR "Microcomputers"[Mesh] OR "Internet"[Mesh] OR "ehealth*"[Title/Abstract] OR "e health*"[Title/Abstract] OR "mhealth*"[Title/Abstract] OR "m health*"[Title/Abstract] OR "mobile health*"[Title/Abstract] OR "digital health"[Title/Abstract] OR "remote consult*"[tiab] OR "tele consult*"[tiab] OR "remote monitoring"[tiab] OR "app"[Title/Abstract] OR "apps"[Title/Abstract] OR "smartphone*"[Title/Abstract] OR "smart phone*"[Title/Abstract] OR "smartwatch*"[Title/Abstract] OR "smart watch*"[Title/Abstract] OR "phone application*"[Title/Abstract] OR "telephone application*"[Title/Abstract] OR "watch application*"[Title/Abstract] OR "mobile application*"[Title/Abstract] OR "mobile technolog*"[Title/Abstract] OR "mobile device*"[Title/Abstract] OR "smart device*"[Title/Abstract] OR "health application*"[Title/Abstract] OR "ipad"[Title/Abstract] OR "ipads"[Title/Abstract] OR "iphone*"[Title/Abstract] OR "I pad"[Title/Abstract] OR "I pads"[Title/Abstract] OR "I phone*"[Title/Abstract] OR "wearable*"[Title/Abstract] OR "cell phone*"[Title/Abstract] OR "cellular phone*"[Title/Abstract] OR "mobile phone*"[Title/Abstract] OR "computer tablet*"[Title/Abstract] OR "tablet computer*"[Title/Abstract] OR "tablet device*"[Title/Abstract] OR "electronic device*"[Title/Abstract] OR "telemonitor*"[Title/Abstract] OR "tele monitor*"[Title/Abstract] OR "telemedicine"[tiab] OR "tele nursing"[tiab] OR "telenursing"[tiab] OR "internet"[tiab] OR "web-based"[tiab] OR "world wide web"[tiab])

CONCEPT 1 AND 2: 3357 hits

CINAHL (Via EBSCO)

Concept 1: "chronic arthritis"

(MH "Arthritis, Rheumatoid+") OR (MH "Arthritis, Psoriatic") OR (MH "Spondylarthritis") OR (MH "Arthritis, Juvenile Rheumatoid")

AB ("ankylosis" OR "juvenile arthritis" OR "juvenile rheumatoid arthritis" OR "juvenile chronic arthritis" OR "Still's disease" OR "Still disease" OR "juvenile oligoarthritis" OR "juvenile psoriatic arthritis" OR "psoriatic arthropathy" OR "gout*" OR "degenerative arthritis" OR "spinal arthritis" OR "spondyl*" OR "rheumatoid arthritis" OR "osteoarthritis" OR "psoriatic arthritis")

TI ("ankylosis" OR "juvenile arthritis" OR "juvenile rheumatoid arthritis" OR "juvenile chronic arthritis" OR "Still's disease" OR "Still disease" OR "juvenile oligoarthritis" OR "juvenile psoriatic arthritis" OR "psoriatic arthropathy" OR "gout*" OR "degenerative arthritis" OR "spinal arthritis" OR "spondyl*" OR "rheumatoid arthritis" OR "osteoarthritis" OR "psoriatic arthritis")

Concept 2: "eHealth"

(MH "Telehealth") OR (MH "Telemedicine+") OR (MH "Telenursing") OR

AB ("ehealth*" OR "e health*" OR "mhealth*" OR "m health*" OR "mobile health*" OR "digital health" OR "remote consult*" OR "tele consult*" OR "remote monitoring" OR "app" OR "apps" OR "smartphone*" OR "smart phone*" OR "smartwatch*" OR "smart watch*" OR "phone application*" OR "telephone application*" OR "watch application*" OR "mobile application*" OR "mobile technolog*" OR "mobile device*" OR "smart device*" OR "health application*" OR "ipad" OR "ipads" OR "iphone*" OR "I pad" OR "I pads" OR "I phone*" OR "wearable*" OR "cell phone*" OR "cellular phone*" OR "mobile phone*" OR "computer tablet*" OR "tablet computer*" OR "tablet device*" OR "electronic device*" OR "telemonitor*" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR internet OR web-based)

TI ("ehealth*" OR "e health*" OR "mhealth*" OR "m health*" OR "mobile health*" OR "digital health" OR "remote consult*" OR "tele consult*" OR "remote monitoring" OR "app" OR "apps" OR "smartphone*" OR "smart phone*" OR "smartwatch*" OR "smart watch*" OR "phone application*" OR "telephone application*" OR "watch

application*" OR "mobile application*" OR "mobile technolog*" OR "mobile device*" OR "smart device*" OR "health application*" OR "ipad" OR "ipads" OR "iphone*" OR "I pad" OR "I pads" OR "I phone*" OR "wearable*" OR "cell phone*" OR "cellular phone*" OR "mobile phone*" OR "computer tablet*" OR "tablet computer*" OR "tablet device*" OR "electronic device*" OR "telemonitor*" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR internet OR web-based)
CONCEPT 1 AND 2: 520 hits

Web of Science Core Collection
Concept 1: "chronic arthritis"
TI=("rheumatic disease*" OR "rheumatism" OR "spondyl*" OR "osteoarthritis" OR "Stills Disease" OR "still di sease" OR "still s disease" OR "ankylosis"OR "polyarthritis" OR "degenerative arthritis")
AB=("rheumatic disease*" OR "rheumatism" OR "spondyl*" OR "osteoarthritis" OR "Stills Disease" OR "still d isease" OR "still s disease" OR "ankylosis"OR "polyarthritis" OR "degenerative arthritis")
Concept 2: "eHealth"
AB=("ehealth*" OR "e health*" OR "mhealth*" OR "m health*" OR "mobile health*" OR "digital health" OR "remote consult*" OR "tele consult*" OR "remote monitoring" OR "app" OR "apps" OR "smartphone*" OR "smart phone*" OR "smartwatch*" OR "smart watch*" OR "phone application*" OR "telephone application*" OR "watch application*" OR "mobile application*" OR "mobile technolog*" OR "mobile device*" OR "smart device*" OR "health application*" OR "ipad" OR "ipads" OR "iphone*" OR "I pad" OR "I pads" OR "I phone*" OR "wearable*" OR "cell phone*" OR "cellular phone*" OR "mobile phone*" OR "computer tablet*" OR "tablet computer*" OR "tablet device*" OR "electronic device*" OR "telemonitor*" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR internet OR web-based)
TI=("ehealth*" OR "e health*" OR "mhealth*" OR "m health*" OR "mobile health*" OR "digital health" OR "remote consult*" OR "tele consult*" OR "remote monitoring" OR "app" OR "apps" OR "smartphone*" OR "smart phone*" OR "smartwatch*" OR "smart watch*" OR "phone application*" OR "telephone application*" OR "watch application*" OR "mobile application*" OR "mobile technolog*" OR "mobile device*" OR "smart device*" OR "health application*" OR "ipad" OR "ipads" OR "iphone*" OR "I pad" OR "I pads" OR "I phone*" OR "wearable*" OR "cell phone*" OR "cellular phone*" OR "mobile phone*" OR "computer tablet*" OR "tablet computer*" OR "tablet device*" OR "electronic device*" OR "telemonitor*" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR internet OR web-based)
CONCEPT 1 AND 2: 744 hits

Cochrane CENTRAL
Concept 1: "chronic arthritis"
"Ankylosis" OR "juvenile arthritis" OR "Psoriatic arthritis" OR "rheumatoid arthritis" OR "Gout*" OR "Osteoarthritis" OR "Spondylarthritis" OR "juvenile arthritis" OR "juvenile rheumatoid arthritis" OR "juvenile chronic arthritis" OR "Still disease" OR "juvenile oligoarthritis" OR "juvenile psoriatic arthritis" OR "psoriatic arthropathy" OR "degenerative arthritis" OR "spinal arthritis"
Concept 2: "eHealth"
"ehealth*" OR "e health*" OR "mhealth*" OR "m health*" OR "mobile health*" OR "digital health" OR "remote consult*" OR "tele consult*" OR "remote monitoring" OR "app" OR "apps" OR "smartphone*" OR "smart phone*" OR "smartwatch*" OR "smart watch*" OR "phone application*" OR "telephone application*" OR "watch application*" OR "mobile application*" OR "mobile technolog*" OR "mobile device*" OR "smart device*" OR "health application*" OR "ipad" OR "ipads" OR "iphone*" OR "I pad" OR "I pads" OR "I phone*" OR "wearable*" OR "cell phone*" OR "cellular phone*" OR "mobile phone*" OR "computer tablet*" OR "tablet computer*" OR "tablet device*" OR "electronic device*" OR "telemonitor*" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR "internet" OR "web-based"
CONCEPT 1 AND 2: 495 hits

Embase
Concept 1: "chronic arthritis"
'ankylosis'/exp OR 'psoriatic arthritis'/exp OR 'rheumatoid arthritis'/exp OR 'gout'/exp OR 'spondylarthritis'/exp OR 'juvenile arthritis'/exp OR 'juvenile rheumatoid arthritis'/exp OR 'juvenile chronic arthritis'/exp OR 'systemic juvenile idiopathic arthritis'/exp OR 'juvenile oligoarthritis' OR 'juvenile psoriatic arthritis'/exp OR 'psoriatic arthropathy'/exp OR 'osteoarthritis'/exp OR 'spinal arthritis' OR 'still disease'/exp OR 'ankylosis':ti,ab,kw OR 'psoriatic arthritis':ti,ab,kw OR 'rheumatoid arthritis':ti,ab,kw OR 'gout*':ti,ab,kw OR 'spondylarthritis':ti,ab,kw OR 'juvenile arthritis':ti,ab,kw OR 'juvenile rheumatoid arthritis':ti,ab,kw OR 'juvenile chronic arthritis':ti,ab,kw OR 'systemic juvenile idiopathic arthritis':ti,ab,kw OR 'juvenile

oligoarthritis':ti,ab,kw OR 'juvenile psoriatic arthritis':ti,ab,kw OR 'psoriatic arthropathy':ti,ab,kw OR 'osteoarthritis':ti,ab,kw OR 'spinal arthritis':ti,ab,kw OR 'still disease':ti,ab,kw

Concept 2: "eHealth"

'telemedicine'/exp OR 'telemedicine' OR 'telenursing'/exp OR 'telenursing' OR 'user-computer interface'/exp OR 'user-computer interface' OR 'mobile applications'/exp OR 'mobile applications' OR 'mobile phone'/exp OR 'mobile phone' OR 'cell phone use'/exp OR 'cell phone use' OR 'computers, handheld'/exp OR 'computers, handheld' OR 'wearable electronic devices'/exp OR 'wearable electronic devices' OR 'microcomputers'/exp OR 'microcomputers' OR 'ehealth*' OR 'e health*' OR 'mhealth*' OR 'm health*' OR 'mobile health'/exp OR 'mobile health' OR 'digital health'/exp OR 'digital health' OR 'remote consult*' OR 'tele consult*' OR 'remote monitoring'/exp OR 'remote monitoring' OR 'app' OR 'apps' OR 'smartphone'/exp OR 'smartphone' OR 'smart phone*' OR 'smartwatch'/exp OR 'smartwatch' OR 'smart watch*' OR 'phone application*' OR 'telephone application*' OR 'watch application*' OR 'mobile application*' OR 'mobile technolog*' OR 'mobile device'/exp OR 'mobile device' OR 'smart device'/exp OR 'smart device' OR 'health application*' OR 'ipad'/exp OR 'ipad' OR 'ipads' OR 'iphone*' OR 'i pad' OR 'i pads' OR 'i phone*' OR 'wearable*' OR 'cell phone*' OR 'cellular phone*' OR 'mobile phone*' OR 'computer tablet*' OR 'tablet computer'/exp OR 'tablet computer' OR 'tablet device*' OR 'electronic device*' OR 'telemonitor*' OR 'tele monitor*' OR 'internet'/exp OR 'internet' OR 'web-based' OR 'world wide web'/exp OR 'world wide web' OR 'telemedicine':ti,ab,kw OR 'telenursing':ti,ab,kw OR 'user-computer interface':ti,ab,kw OR 'mobile applications':ti,ab,kw OR 'mobile phone':ti,ab,kw OR 'cell phone use':ti,ab,kw OR 'computers, handheld':ti,ab,kw OR 'wearable electronic devices':ti,ab,kw OR 'microcomputers':ti,ab,kw OR 'ehealth*':ti,ab,kw OR 'e health*':ti,ab,kw OR 'mhealth*':ti,ab,kw OR 'm health*':ti,ab,kw OR 'mobile health':ti,ab,kw OR 'digital health':ti,ab,kw OR 'remote consult*':ti,ab,kw OR 'tele consult*':ti,ab,kw OR 'remote monitoring':ti,ab,kw OR 'smartphone':ti,ab,kw OR 'smart phone*':ti,ab,kw OR 'smartwatch':ti,ab,kw OR 'smart watch*':ti,ab,kw OR 'phone application*':ti,ab,kw OR 'telephone application*':ti,ab,kw OR 'watch application*':ti,ab,kw OR 'mobile application*':ti,ab,kw OR 'mobile technolog*':ti,ab,kw OR 'mobile device':ti,ab,kw OR 'smart device':ti,ab,kw OR 'health application*':ti,ab,kw OR 'ipad*':ti,ab,kw OR 'iphone*':ti,ab,kw OR 'i pad*':ti,ab,kw OR 'i phone*':ti,ab,kw OR 'wearable*':ti,ab,kw OR 'cell phone*':ti,ab,kw OR 'cellular phone*':ti,ab,kw OR 'mobile phone*':ti,ab,kw OR 'computer tablet*':ti,ab,kw OR 'tablet computer':ti,ab,kw OR 'tablet device*':ti,ab,kw OR 'electronic device*':ti,ab,kw OR 'telemonitor*':ti,ab,kw OR 'tele monitor*':ti,ab,kw OR 'internet':ti,ab,kw OR 'web-based':ti,ab,kw OR 'world wide web':ti,ab,kw

Concept 1 AND 2: 3341 hits

<u>Clinicaltrials.gov</u>

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232 hits

<u>ICTRP</u>

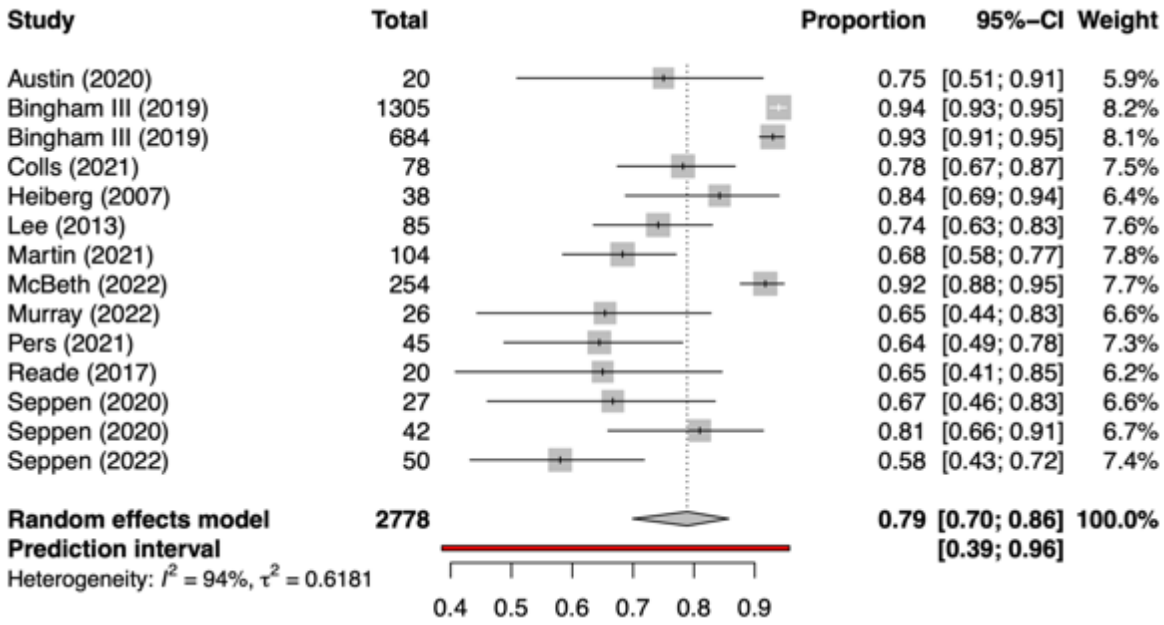
("ankylosis" OR "juvenile arthritis" OR "juvenile rheumatoid arthritis" OR "juvenile chronic arthritis" OR "Still's disease" OR "Still disease" OR "juvenile oligoarthritis" OR "juvenile psoriatic arthritis" OR "psoriatic arthropathy" OR "gout" OR "degenerative arthritis" OR "spinal arthritis" OR "spondyl" OR "rheumatoid arthritis" OR "osteoarthritis" OR "psoriatic arthritis") AND ("ehealth" OR "e health" OR "mhealth" OR "m health" OR "mobile health" OR "digital health" OR "remote consult" OR "tele consult" OR "remote monitoring" OR "app" OR "apps" OR "smartphone" OR "smart phone" OR "smartwatch" OR "smart watch" OR "phone application" OR "telephone application" OR "watch application" OR "mobile application" OR "mobile technology" OR "mobile device" OR "smart device" OR "health application" OR "ipad" OR "ipads" OR "iphone" OR "I pad" OR "I pads" OR "I phone" OR "wearable" OR "cell phone" OR "cellular phone" OR "mobile phone" OR "computer tablet" OR "tablet computer" OR "tablet device" OR "electronic device" OR "telemonitor" OR "tele monitor*" OR "telemedicine" OR "tele nursing" OR "telenursing" OR internet OR web-based)

152 hits

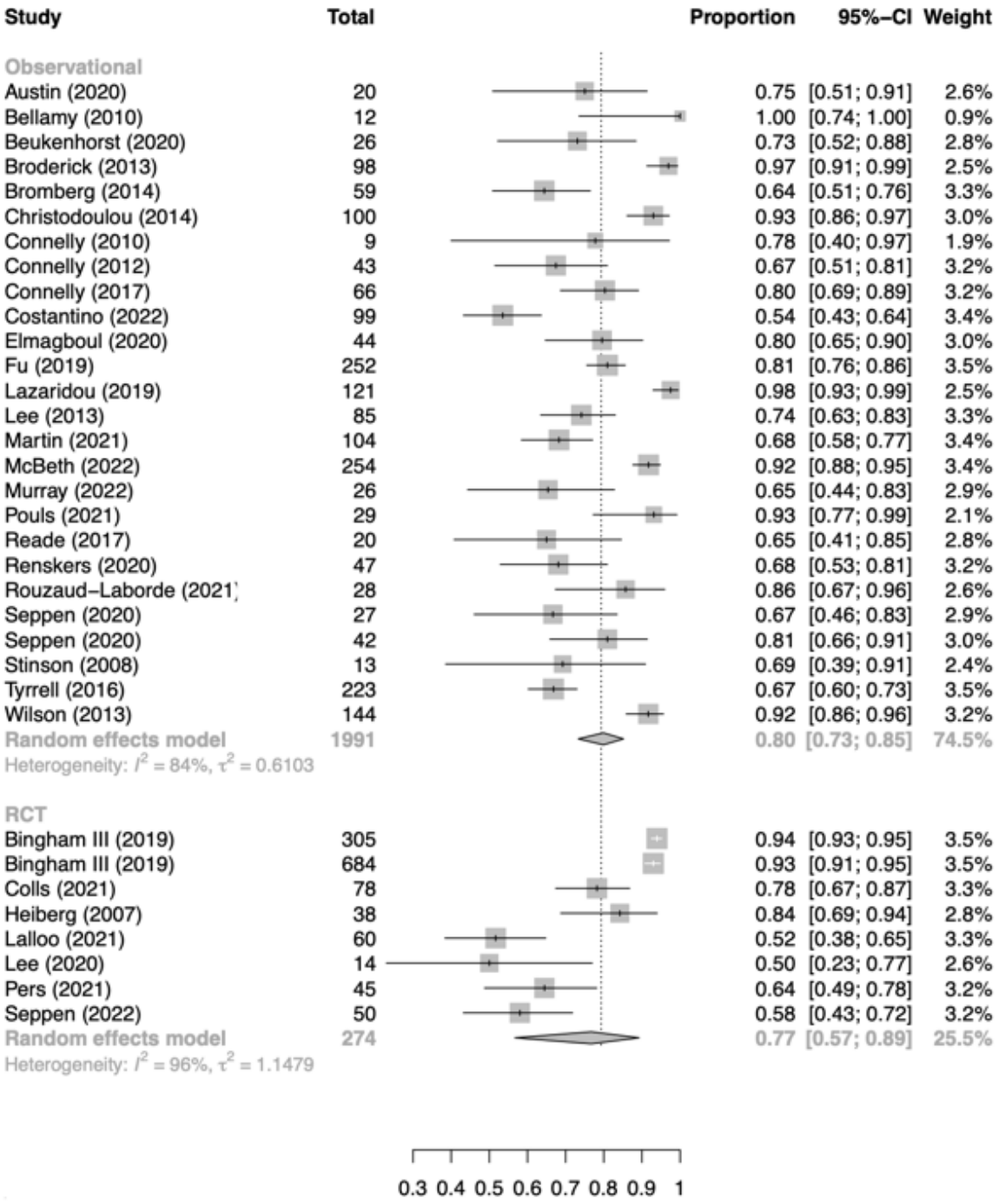
Supplement 4.2. Risk-of-bias assessment for included full-text studies, based on Newcastle-Ottawa Scale (NOS) for cohort or case-control (CC) studies or on PEDro scale for randomised controlled studies.

Study	*Scale*	*Assessment*		
Austin (2020)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆
Bellamy (2010)	NOS	Selection ☆☆☆☆	Comparability ☆	Outcome ☆☆
Beukenhorst (2020)	NOS	Selection ☆☆☆	Comparability	Outcome ☆☆
Bingham III (2019)	PEDro	8/11		
Broderick (2013)	NOS (CC)	Selection ☆☆☆☆	Comparability ☆☆	Exposure ☆☆
Bromberg (2014)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Christodoulou (2014)	NOS (CC)	Selection ☆	Comparability ☆☆	Exposure ☆☆
Colls (2021)	PEDro	8/11		
Connelly (2010)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Connelly (2012)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Connelly (2017)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Crouthamel (2018)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆
Druce (2017)	NOS	Selection ☆☆☆	Comparability	Outcome ☆☆☆
Elmagboul (2020)	NOS	Selection ☆☆☆	Comparability	Outcome ☆☆
Fu (2019)	NOS	Selection ☆☆☆	Comparability	Outcome ☆☆
Heale (2018)	NOS	Selection ☆☆☆	Comparability ☆☆	Outcome ☆☆
Heiberg (2007)	PEDro	5/11		
Jacquemin (2018)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆
Lalloo (2021)	PEDro	9/11		
Lazaridou (2019)	NOS	Selection ☆☆☆	Comparability ☆☆	Outcome ☆
Lee (2013)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Lee (2020)	PEDro	7/11		
Nowell (2021)	NOS	Selection ☆☆☆	Comparability	Outcome ☆☆
Östlind (2021)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆
Pers (2021)	PEDro	8/11		
Reade (2017)	NOS	Selection ☆☆☆	Comparability ☆☆	Outcome ☆☆
Renskers (2020)	NOS	Selection ☆☆☆	Comparability ☆☆	Outcome ☆☆
Seppen (2020)	NOS	Selection ☆☆☆	Comparability	Outcome ☆
Skrepnik (2017)	PEDro	9/11		
Stinson (2008)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Tyrrell (2016)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆
Wilson (2013)	NOS	Selection ☆☆	Comparability ☆	Outcome ☆☆
Zaslavsky (2019)	NOS	Selection ☆☆☆	Comparability ☆	Outcome ☆☆

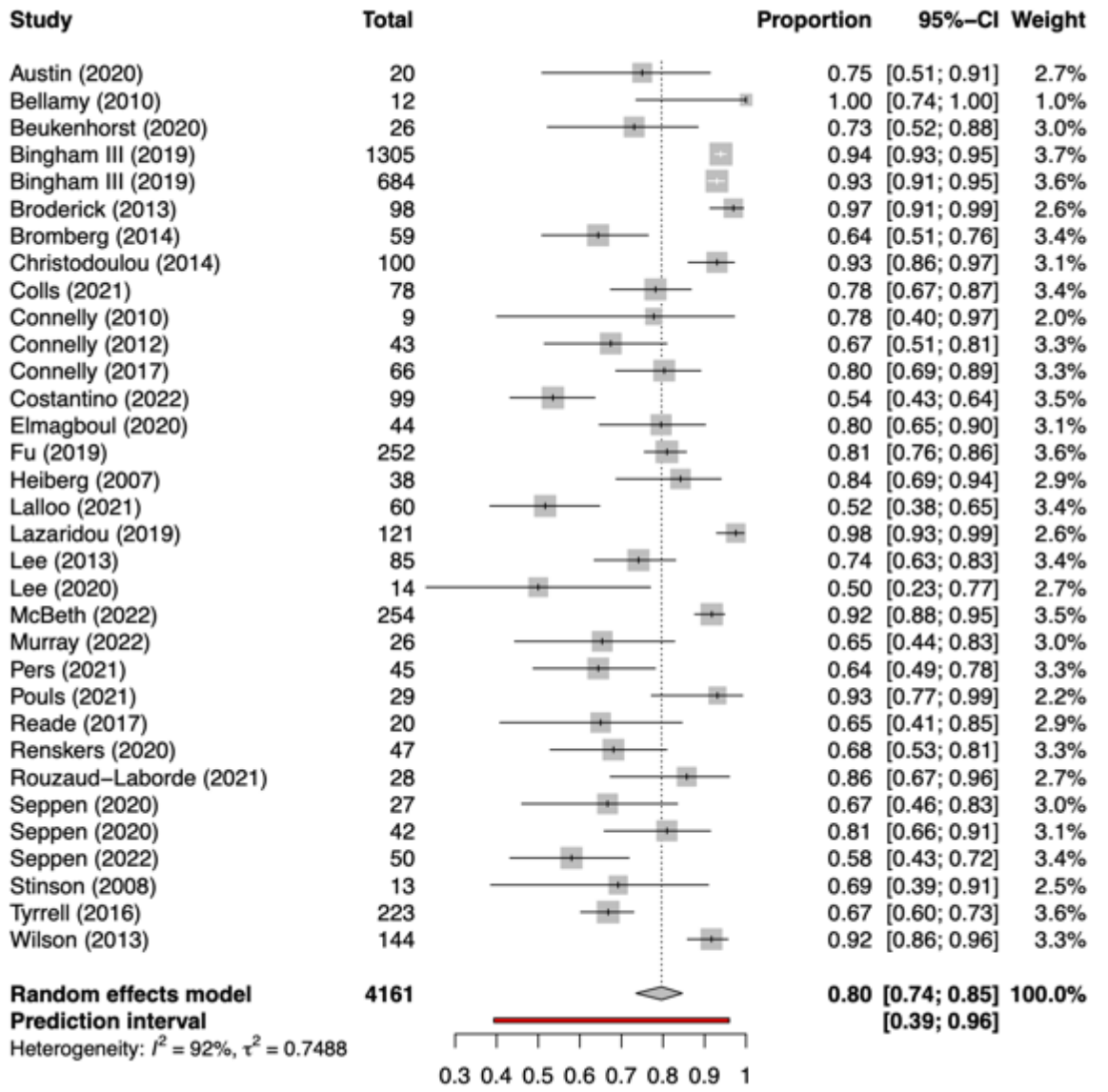
Supplement 4.3A. Forest plot of pooled completion rates for eHealth studies in an RA population.



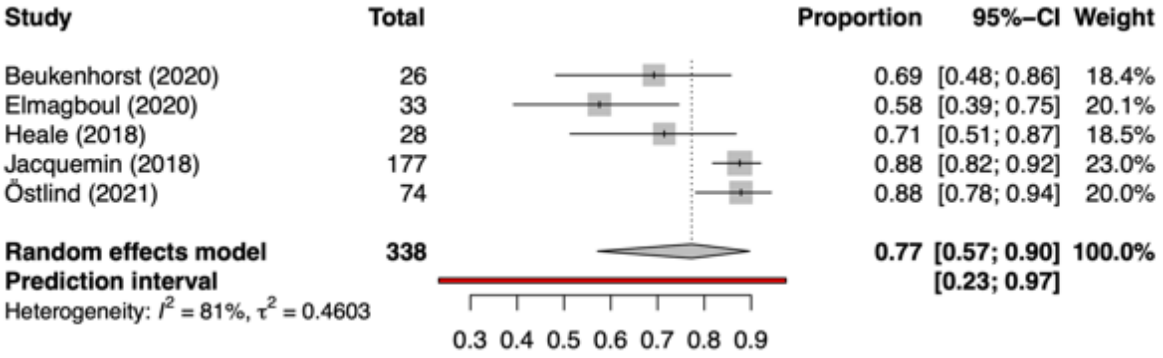
Supplement 4.3B. Forest plot of pooled completion rates according to eHealth study design.



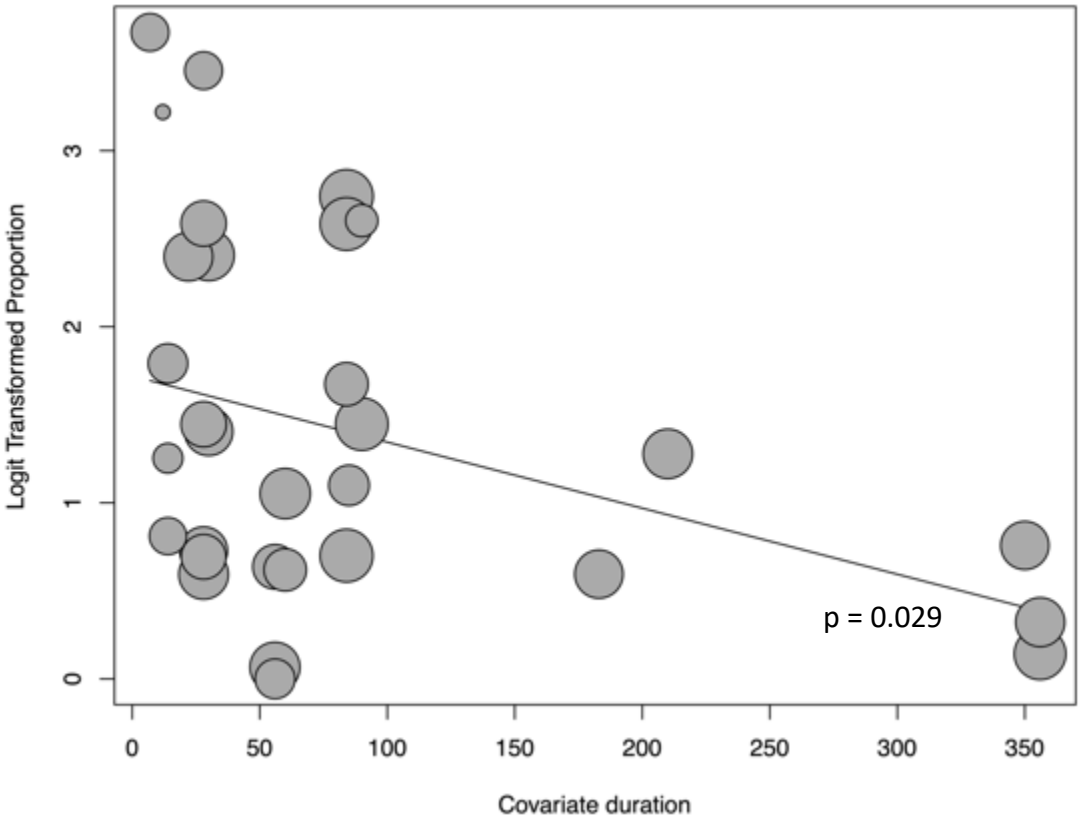
Supplement 4.4A. Sensitivity analysis, excluding abstracts, of pooled completion rates for patient-reported outcomes collected with eHealth tools.



Supplement 4.4B. Sensitivity analysis, excluding abstracts, of pooled proportion of study days a wearable activity tracker was actively worn.



Supplement 4.5: Bubble plot for the association between completion rate (as logit transformed proportion) and study duration in days.



Chapter 5

Supplement 5.1. Predictors of engagement with study app (weeks of active app-use).

	ß (95% CI)	**p-value**
Age (years)	0.05 (-0.09 to 0.19)	0.45
Sex (male)	- 0.75 (-3.87 to 2.37)	0.64
RF (+)	-3.79 (-7.67 to 0.09)	0.06
ACPA (+)	2.67 (-1.35 to 6.69)	0.20
Disease duration (years)	0.00 (-0.18 to 0.18)	0.99
RDCI (0-9)	-0.38 (-1.71 to 0.95)	0.58
DAS28-CRP	-2.13 (-4.62 to 0.36)	0.10
RAID (0-10)	1.16 (0.20 to 2.12)	**0.02**
PCS (0-52)	0.05 (-0.14 to 0.23)	0.64
ASES (11-110)	-0.03 (-0.13 to 0.07)	0.57

Results were derived using linear regression with the number of weeks participants actively used the app as the dependent variable and the listed predictors as independent variables/covariates. *RF = Rheumatoid factor, ACPA = anti-citrullinated protein antibodies, RDCI = Rheumatic Disease Comorbidity Index, DAS28-CRP = 28-joint Disease Activity Score with C-reactive protein, RAID = Rheumatoid Arthritis Impact of Disease, PCS = Pain Catastrophizing Scale, ASES = Arthritis Self-Efficacy Scale*

PERSONAL CONTRIBUTION, SCIENTIFIC ACKNOWLEDGEMENT AND CONFLICTS OF INTEREST

PERSONAL CONTRIBUTION

Prior to the start of this PhD project, I conceived the general **objectives** of the research together with Patrick Verschueren, and drafted the grant proposal for my FWO fellowship based on these objectives.

I wrote all **chapters** in this dissertation and revised them after feedback from Patrick Verschueren and René Westhovens.

Chapters 1, 2 and 3: These chapters were based on post-hoc analyses of data from the CareRA trial. These data were available at the start of this PhD research. I was thus not involved in clinical data collection or the design of the trial these data were derived from.
For the post-hoc analyses each of these chapters were based on, I was primarily responsible for study conception and data analysis. I interpreted the results of the analyses together with Patrick Verschueren, René Westhovens and all co-authors, and drafted and revised the manuscripts based on their feedback and that of anonymous peer reviewers.
Part I – Epilogue: This chapter was based on a post-hoc analysis of data from the CareRA2020 trial. CareRA2020 data became available for analysis in late 2023 and were prepared by co-author Delphine Bertrand. I was thus not involved in clinical data collection or the design of the trial these data were derived from. For this post-hoc analysis, I was primarily responsible for study conception and data analysis. I interpreted the results of the analyses together with Patrick Verschueren, René Westhovens, Delphine Bertrand and all co-authors, and drafted and revised the abstract based on their feedback.

Chapter 4.1: This chapter was based on data that were available at the start of this PhD research. I was thus not involved in study conception, study design or data collection and transcription. For this chapter, I was primarily responsible for data analysis. I interpreted the results together with Patrick Verschueren, René Westhovens and all co-authors, and drafted and revised the manuscript based on their feedback and that of anonymous peer reviewers.
Chapter 4.2: I was primarily responsible for conception and design of this systematic review. I drafted the protocol and collected the data together with co-author Caroline Van Lierde. I analysed the data together with co-author Albrecht Betrains. I interpreted the results of the analyses together with Patrick Verschueren, René Westhovens, and all co-authors, and drafted and revised the manuscript based on their feedback and that of anonymous peer reviewers.
Chapter 5: I was primarily responsible for study conception and design. I drafted the protocol together with co-author Cedric Lefevre. I was involved in clinical data collection and primarily responsible for preparation and analysis of the data. I interpreted the results of the analyses together with Patrick Verschueren, René Westhovens and all co-authors, and drafted and revised the manuscript based on their feedback.

SCIENTIFIC ACKNOWLEDGEMENT
Patrick Verschueren coordinated all studies, was involved in the design and clinical data collection and provided feedback on all manuscripts and chapters of this dissertation.

René Westhovens co-coordinated all studies, was involved in the design and provided feedback on all manuscripts and chapters of this dissertation.

Delphine Bertrand prepared all study data for the Part I – Epilogue chapter as part of her PhD project, and contributed to interpretation of the results and drafting of the abstract. As a co-author on all other manuscripts in this dissertation, she was involved in the interpretation of study results and provided feedback on the final manuscripts.

Sofia Pazmino provided methodological guidance on data analysis, was involved in the interpretation of study results and provided feedback on the final manuscripts for all chapters.

Diederik De Cock was involved in data collection and preparation for Chapters 1, 2, 3 and 4.1. For Chapters 1, 2, 3, 4.1 and 4.2, he was also involved in the interpretation of study results and provided feedback on the final manuscripts.

Johan Joly was involved in clinical data collection and data preparation for Chapters 1, 2, 3 and Part I – Epilogue and provided feedback on the final manuscripts.

Elias De Meyst was involved in clinical data collection and the interpretation of study results for Chapter 5 and provided feedback on the final manuscript. As a co-author on one of the manuscripts included in the General Discussion, he was involved in the interpretation of study results and provided feedback on the final manuscript.

Veerle Stouten was involved in data preparation for Chapters 1, 2, 3 and 4.1, and for one of the manuscripts included in the General Discussion. She provided feedback on the latter manuscript and the publication of Chapter 4.1.

Caroline Van Lierde was involved in data collection and analysis for Chapter 4.2 as second reviewer and provided feedback on the final manuscript.

Albrecht Betrains was involved in the meta-analyses in Chapter 4.2 and provided feedback on the final manuscript.

Marine Piessens was involved in clinical data collection for Chapter 5.

Cedric Lefevre was involved in study design and clinical data collection for Chapter 5 and provided feedback on the protocol manuscript.

Mieke Devinck was involved in clinical data collection for Chapter 5 and provided feedback on the protocol manuscript.

Nelly Creten, Claudia Neys and *Els Van Laeken* provided feedback on the interview guide, the interpretation of the study results and the final manuscript for Chapter 4.1 as patient experts.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.

For this PhD research, Michaël Doumen was supported by a Strategic Basic Research Fellowship grant from the Belgian Fonds Wetenschappelijk Onderzoek (FWO) [grant number 1S85521N].

The CareRA trial was supported by a grant from the Flemish Government Agency for Innovation by Science and Technology (IWT) and by grants from the Fund for Scientific Research in Rheumatology (FWRO) and the Academic Foundation of Leuven.

The CareRA2020 trial was supported by a grant from the Belgian Health Care Knowledge Centre (KCE project CB-1602; Biologicals for early untreated rheumatoid arthritis, the CareRA2020 study).

For the AEGORA trial, licensed access to the study app was provided to participants by the developer (Sidekick Health, Reykjavik, Iceland) via support in kind. No other funding was received for the trial itself, aside from the FWO grant for Michaël Doumen as outlined above.

DANKWOORD

Zij die mij een beetje kennen zullen beamen dat ik soms wat veel over de dingen durf te piekeren. Ze zullen ook bevestigen dat ik een voorliefde heb voor de veilige opties. Ik heb nu eenmaal, zoals ik zelf zo graag zeg, “geen zin in gedoe”. De keuze om te starten aan een doctoraat was dan ook geen evidente, en ik verontschuldig mij postfactum graag nog eens bij Sarah voor de eindeloze monologen met pro’s en contra’s die ze hier destijds over heeft moeten aanhoren. Maar intussen, 4 jaar later, kan ik met overtuiging zeggen dat dit de juiste keuze was. Want wat is dit een mooi avontuur geweest. Een avontuur dat me zo veel geleerd heeft over wat het betekent om wetenschapper te zijn, me een beter arts heeft gemaakt en als mens heeft verrijkt, of toch figuurlijk. Ik ben trots dat ik dit verhaal tot een goed einde heb kunnen brengen, maar besef dat dit onmogelijk was geweest zonder de steun en inspanningen van een heleboel mensen. Ik zou dan ook graag mijn rondje bedankingen bij deze aanvatten.

Ik start daarvoor graag bij de jury. Professors Gossec, Ndosi and Taylor, thank you for agreeing to serve as members of my jury. I thoroughly admire all three of you and it is truly an honour to have you here today. Professor Van Calster, professor Ferrante, bedankt voor jullie heldere inzichten en de interessante discussies, zowel tijdens de tussentijdse evaluatiemomenten als vandaag. Bedankt ook aan de voorzitter van de examencommissie, professor Mieke Verstuyf, en aan professor Lories om vandaag het voorzitterschap op zich te nemen.
Dit project was heel wat moeilijker geweest zonder het vertrouwen van het Fonds Wetenschappelijk Onderzoek, dat ik daarvoor nogmaals wil bedanken. Ook een bijzondere dank aan alle mensen die als studieparticipant of als medewerker hebben deelgenomen aan de verschillende studies waar mijn onderzoek op heeft kunnen bouwen.

Heel veel dank ben ik uiteraard verschuldigd aan professor Verschueren. Patrick, ik wil je oprecht bedanken, niet alleen om me deze kans te bieden, maar ook om de rol van promotor met zo veel verve in te vullen. Bedankt voor je enthousiasme, de vele brainstormmomenten, de inspirerende spreekwoorden en metaforen, maar vooral de uitstekende begeleiding. Ik vergeet nooit hoe je bij één van onze eerste vergaderingen vroeg of ik graag vaste afspraken maakte of liever op indicatie wou samenzitten, omdat iedereen daarin nu eenmaal anders is. Al lijkt dit misschien een kleinigheid, indirect gaf je zo meteen aan dat ik altijd welkom zou zijn bij nood aan meer ondersteuning, maar ook dat het oké was om mijn eigen pad te zoeken en dat je erin vertrouwde dat mij dat wel zou lukken. Vertrouwen is hierin een sleutelwoord, en dat heb ik van jou altijd mogen voelen. Je beheerst als promotor de zeldzame kunst om je teamleden, die inderdaad allemaal verschillend zijn, voldoende zelfstandigheid te geven en toch telkens de vinger aan de pols te houden. Het is een delicate balans die wat mij betreft vanaf het prille begin helemaal juist zat, en ik wil je daarvoor heel graag ook een pluim op de spreekwoordelijke hoed steken.
Professor Westhovens, Rene, bedankt om zelfs tijdens je verdiende emeritaat altijd als eerste klaar te staan voor feedback, bemoedigende woorden en wijze adviezen. Zoals zovelen kijk ik heel erg naar je op, als arts, wetenschapper én mens, en ik ben vereerd om je mijn copromotor te mogen noemen.

Al mijn lieve collega’s, dit hele traject was letterlijk onmogelijk geweest zonder jullie. Sofia, when it comes to this PhD, there is probably no single person I am as indebted to as I am to you. You have inspired and kickstarted my quest for statistical knowledge on so many occasions I have lost count long ago. A thousandfold thank you. Delphine, je eeuwige lach en enthousiasme zijn meer dan eens een licht in de duisternis geweest. Ik zal onze vele gesprekken over Blind Getrouwd, De Mol en andere belangrijke dingen des levens blijven koesteren. Blijf alsjeblieft altijd jezelf. Elias, in de anderhalf jaar dat ik je ken hebben we al heel wat mooie

herinneringen mogen verzamelen. Dat er nog vele mogen volgen, en dat de grens tussen collegialiteit en vriendschap verder mag vervagen. Marlies, het was een plezier om het bureau met jou te mogen delen, en ik hoop dat we in de toekomst nog veel met elkaar mogen samenwerken. Anne-Catherine, Jonas, Marie, Diederik, Jo, Anke, Marine, bedankt om er te zijn, in plezante en in serieuze tijden. Ook bedankt aan alle collega-ASO's en de medische, ondersteunende en verpleegkundige staf reumatologie van het UZ Leuven. Jullie zorgen samen voor een omgeving waarin ik graag ga werken, zodat ik helemaal niet hoef op te kijken tegen die eerste dag terug in de kliniek.

Bijzonder veel dank gaat uit naar mijn geweldige vrienden. Akke, Bokke, Jerre, Kest, Pj, Se'ke, en alle madammen. Wat is het intussen, 15 jaar and counting? Wanneer het werk tegenvalt is het jullie liefde en gezelschap die altijd het verschil zullen maken, en daar ben ik ongelooflijk dankbaar voor. Zeker als ik zie dat er na generatie '93 al een generatie 2023 klaar staat. Als Joppe, Fran, Lua en Vik even veel aan elkaar gaan hebben als wij, dan zit het goed. Kest, dat de cover van mijn thesis van uw hand is maakt mij onwaarschijnlijk trots, dat pakken ze mij niet meer af. Dre, Peach, Sikes en Yannick, merci voor de muzikale connectie, nog altijd mijn grootste passie. Eric, Julie, Joa, Stijn en Victoria, bedankt om al jarenlang de ideale uitlaatklep te zijn voor werkgerelateerde frustraties. Bedankt ook aan Jerre Van Pelt, voor de sportieve uitlaatkleppen en de zakenlunches, en aan Maarten, om mijn ongebreidelde fantasie te delen.
Eindelijk ben ik aanbeland bij mijn allerliefste familie. Mama, papa, jullie hebben me het mooist denkbare cadeau gegeven door jullie liefdevolle opvoeding. Dankzij jullie onvoorwaardelijke steun en liefde kan ik hier vandaag voor jullie staan en deze mijlpaal behalen. Na al die keren dat ik als kind lange monologen tegen jullie afstak over mijn grootse ideeën en wat ik allemaal in mijn boek ging schrijven, kon ik dat de voorbije jaren nog steeds doen. Eigenlijk is er in al die tijd niet zo veel veranderd, toch? Ik ben nog altijd jullie kleinste, en ik zie jullie nog altijd even graag.
Lau, grote zus, bedankt om altijd trots op mij te zijn. Ook al snap je er geen bal van, zoals je zelf zou zeggen, weet ik dat ik altijd bij jou terecht kan en dat betekent veel. Ook bedankt aan Pieter-Paul, low-key het beste luisterend oor van het hele gezin. Julian, grote vriend, bedankt om mij een trotse peter te maken en met je oneindige energie elke slechte dag weer goed te maken. Bedankt aan Jackje om dat nog eens dunnetjes over te doen.
Naast mijn eigen familie wil ik toch ook een woordje van dank uiten voor mijn lieve schoonfamilie. Joke, Luc, Pieter-Jan, bedankt om mij in jullie warme gezin op te nemen. Na meer dan 11 jaar voel ik mij bij jullie helemaal thuis, maar zo lang heeft dat dankzij jullie helemaal niet nodig gehad.
En mijn schoonfamilie brengt me naadloos bij jou, Sarah. Zoals je 3 jaar geleden in je eigen dankwoord schreef: "hoe kan ik jou ooit bedanken?" Al meer dan een derde van ons leven delen we lief en leed, en dat mag gerust letterlijk genomen worden. Ook de voorbije 4 jaar heb ik elk idee, elk hersenspinsel, elke overwinning en elke tegenslag met jou mogen delen, en nooit voelde dit ongewenst. Zo veel naar mij luisteren moet een absolute kwelling zijn, waarvoor je eigenlijk een dikke gouden medaille verdient. Er is dan ook niemand op deze aardbol die me zo kent als jij, en al zal je het zelf ontkennen, zonder jou had ik dit doctoraat nooit tot een goed einde kunnen brengen. Bedankt voor alle knuffels, liefde en steun. Bedankt om er altijd te zijn, en om van mij de voorbije 4 jaar zowel echtgenoot als vader te hebben gemaakt.
Fran, ik ben zo trots om jouw papa te zijn. Het cliché wil dat niets zo belangrijk is als familie. Als ik daar ooit aan twijfel, hoef ik maar naar jou te kijken om te beseffen dat dit doctoraat niet mijn belangrijkste verwezenlijking van de voorbije 4 jaar is.

CURRICULUM VITAE



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EDUCATION

2011 - 2014
BACHELOR OF MEDICINE, KU LEUVEN
Summa cum laude (86.13%, ranked 14th/346 graduates)

2014 - 2018
MASTER OF MEDICINE, KU LEUVEN
Magna cum laude (83.92%, ranked 16th/380 graduates)

2018 - PRESENT
MASTER OF SPECIALIZED MEDICINE (INTERNAL MEDICINE / RHEUMATOLOGY), KU LEUVEN

2020 - PRESENT
PHD CANDIDATE RHEUMATOLOGY, KU LEUVEN

2021 - 2023
EULAR ONLINE COURSE ON RHEUMATIC DISEASES, EULAR

PROFESSIONAL CAREER

2018 – PRESENT
MEDICAL DOCTOR, RESIDENT RHEUMATOLOGY,
UNIVERSITY HOSPITALS LEUVEN
Clinical residency in Internal Medicine including experience in Cardiology, Pulmonology, Gastro-enterology, Geriatrics, General Internal Medicine, Hematology, Nephrology, Emergency Medicine, Medical Intensive Care and Rheumatology.

OCTOBER 2020 – PRESENT
PHD CANDIDATE RHEUMATOLOGY, KU LEUVEN
Clinical research with a focus on rheumatoid arthritis. Specific interests in patient-reported outcomes reflecting current unmet patient needs and in (non-)pharmacological interventions and digital tools to improve these unmet needs.

2024 – PRESENT
GUEST EDITOR BMC RHEUMATOLOGY

2024 – PRESENT
EULAR TASKFORCE "UPDATING THE EULAR RECOMMENDATIONS FOR PATIENT EDUCATION IN INFLAMMATORY ARTHRITIS"

EXTRACURRICULAR TRAINING

- 2015-2016: Medical English course (ILT Leuven)
- 2017-2018: Electrocardiography course (KU Leuven)
- 2020: Cochrane systematic review course (CEBAM)
- 2020: Writing course on qualitative research (FLAMES)
- 2020-2021: Writing course for biomedical researchers (ILT Leuven)
- 2021: Introduction to AI and machine learning for biomedical research (VAIA)
- 2022-2023: Royal Belgian Society of Rheumatology courses on ultrasound and capillaroscopy
- 2023-2024: Interuniversity Certificate basic musculoskeletal ultrasound course for the rheumatologist (Université Liège & Ghent University)

MEMBERSHIP OF PROFESSIONAL ORGANISATIONS

- Orde der Artsen: 2018 – present
- Emerging EULAR Network (EMEUNET): 2020 – present
- Koninklijke Belgische Vereniging voor Reumatologie (KBVR): 2022 – present

GRANTS OR AWARDS RECEIVED

- **2020-present: FWO fellowship grant Strategic Basic Research**

- 2014: Finalist Student Researcher of the Year – Faculty of Medicine, KU Leuven
- 2018: International Foundations of Medicine (IFOM) exam top score of 800, corresponding with >99.5th percentile of candidates
- 2021: Winner Rheumatology Advances in Practice Trainee Publishing Program
- 2021: Runner-up PhD Cup at Lage-Landen Reumatop, Sint-Michielsgestel, NL
- 2022: Travel Bursary for EULAR Conference 2022, Copenhagen

PRESENTATIONS

- 2021:
  - EULAR congress (online) – guided poster tour
  - BCR congress (Brussels) – oral presentation
  - ACR congress (online) – 2x poster presentation
- 2022:
  - EULAR congress (Copenhagen) – 1x guided poster tour, 1x poster presentation
  - BCR congress (Mons) – 2x poster presentation
- 2023:
  - EULAR congress (Milan) – poster presentation
  - BCR congress (Ghent) – oral presentation
- 2024:
  - EULAR congress (Vienna) – oral presentation

PUBLICATIONS

Peer-reviewed publications as first author, included in this thesis

- Doumen M, Stouten V, Pazmino S, De Meyst E, Bertrand D, Joly J, Westhovens R, Verschueren P. Patient-physician discordance impairs outcomes in early rheumatoid arthritis through less consistent treat-to-target implementation. Rheumatology (Oxford) 2023; kead694.
- Doumen M, De Meyst E, Lefevre C, Pazmino S, Joly J, Bertrand D, Devinck M, Westhovens R, Verschueren P. Effectiveness and feasibility of a mobile health self-management intervention in rheumatoid arthritis: study protocol for a pragmatic multicentre randomised controlled trial (AEGORA). Trials 2023; 24(1):697.
- Doumen M, Pazmino S, Verschueren P, Westhovens R. Viewpoint: Supporting mental health in the current management of rheumatoid arthritis: Time to act! Rheumatology (Oxford) 2023; 62(SI3):SI274-SI281.
- Doumen M, Pazmino S, Bertrand D, Westhovens R, Verschueren P. Glucocorticoids in rheumatoid arthritis: Balancing benefits and harm by leveraging the therapeutic window of opportunity. Joint Bone Spine 2023; 90(3):105491.
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- Doumen M, De Cock D, Pazmino S, Bertrand D, Joly J, Westhovens R, Verschueren P. Treatment response and several patient-reported outcomes are early determinants of future self-efficacy in rheumatoid arthritis. Arthritis Res Ther 2021; 23(1):269.
- Doumen M, Westhovens R, Pazmino S, Bertrand D, Stouten V, Neys C, Creten N, Van Laeken E, Verschueren P, De Cock D. The ideal mHealth-application for rheumatoid arthritis: qualitative findings from stakeholder focus groups. BMC Musculoskelet Disord 2021; 22(1):746.

Peer-reviewed publications as first author, not included in this thesis

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- Doumen M, Bertrand D, Pazmino S, De Cock D, Stouten V, Joly J, Westhovens R, Verschueren P. Response to: comment on "validation and predictive capacity of a dutch version of the FLARE-RA questionnaire within the context of a TNFi-tapering trial". Clin Rheumatol 2024;43(2):827-829.
- Doumen M, Bertrand D, Pazmino S, De Cock D, Stouten V, Joly J, de Wergifosse I, Moeyersoons A, Westhovens R, Verschueren P. Validation and predictive capacity of a Dutch version of the FLARE-RA questionnaire within the context of a TNFi-tapering trial. Clin Rheumatol 2023; 42(1):39-45.
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- Doumen M, Vankelecom B, Westhovens R, Michiels S. Pericarditis as a manifestation of IgG4-related disease. Rheumatol Int 2022; 42(7):1287-1295.
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Peer-reviewed publications as co-author, not included in this thesis

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- Pazmino S, Westhovens R, Doumen M, Bertrand D, Verschueren P. Undifferentiated arthritis, not just another early manifestation of rheumatoid arthritis. Rheumatology (Oxford) 2022; 61(8):3101-3103.
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- Doumen, M., Stouten, V., Pazmino, S., De Meyst, E., De Cock, D., Bertrand, D., Joly, J., Westhovens, R., Verschueren, P. (2023). POS0483 PATIENT-PHYSICIAN DISCORDANCE IN DISEASE ACTIVITY ASSESSMENT IS ASSOCIATED WITH LESS CONSISTENT TREAT-TO-TARGET IMPLEMENTATION, IMPAIRING REMISSION OUTCOMES IN EARLY RA: A POST-HOC MEDIATION ANALYSIS OF THE CARERA TRIAL. Presented at the EULAR Conference 2023, Milan.

- Bertrand, D., Joly, J., Neerinckx, B., Durez, P., Lenaerts, JL., Joos, R., Thevissen, K., Zwaenepoel, T., Geusens, P., Méric De Bellefon, L., Taelman, V., Van Essche, E., Corluy, L., Malaise, M., Vanden Berghe, M., Devinck, M., Ajeganova, S., Anne, D., Boutsen, Y., Margaux, J., Peene, I., Van Offel, J., Doumen, M., Pazmino, S., De Meyst, E., Westhovens, R., Verschueren, P. (2023). OP0129 EFFECTIVENESS OF COBRA-SLIM WITH OR WITHOUT EARLY ACCESS TO A TEMPORARY 6-MONTH COURSE OF ETANERCEPT IN EARLY RA: PRIMARY OUTCOME OF THE 2-YEAR, PRAGMATIC, RANDOMISED CARERA2020 TRIAL. Presented at the EULAR Conference 2023, Milan.
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- Doumen, M., Pazmino, S., Bertrand, D., De Cock, D., Joly, J., Westhovens, R., Verschueren, P. (2022). POS0523 FATIGUE TRAJECTORIES IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS: A LONGITUDINAL ANALYSIS OF DATA FROM THE CareRA TRIAL. Presented at the EULAR Conference 2022, Copenhagen.
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- Doumen, M., De Cock, D., Pazmino, S., Bertrand, D., Westhovens, R., Verschueren, P. (2021). Treatment Response and Several Patient-reported Outcomes Are Early Determinants of Future Self-efficacy in Patients with Rheumatoid Arthritis. Presented at the ACR Convergence 2021, Online.
- De Cock, D., Verhavert, G., Pazmino, S., Bertrand, D., Doumen, M., Westhovens, R., Verschueren, P. (2021). The Patient as Assessor of Disease Status: A Graphical Evaluation of Relations Between Patient-Reported Outcomes in Early Rheumatoid Arthritis. Presented at the ACR Convergence 2021, Online.
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- Pazmino, S., Lovik, A., De Cock, D., Stouten, V., Bertrand, D., Joly, J., Doumen, M., Westhovens, R., Verschueren, P. (2021). AB0109 VALIDATION OF SEPARATE PATIENT-REPORTED, CLINICAL AND LABORATORY FACTOR SCORES AS REPRESENTATION OF DISEASE BURDEN IN A POPULATION WITH ESTABLISHED RHEUMATOID ARTHRITIS. In: Annals Of The Rheumatic Diseases, (Abstract No. AB0109). Presented at the EULAR Conference 2021, Online.
- Doumen, M., Pazmino, S., Bertrand, D., De Cock, D., Joly, J., Westhovens, R., Verschueren, P. (2021). POS0266-HPR PATIENTPERCEIVED ASPECTS OF RA FLARE EVOLVE OVER TIME, AS REFLECTED BY THE FLARE-RA QUESTIONNAIRE: POST-HOC ANALYSIS OF TAPERA. In: Annals of the Rheumatic Diseases: vol. 80, (Abstract No. POS0266-HPR). Presented at the EULAR Conference 2021, Online.
- Vervloesem, C., De Cock, D., Van Breda, A., Bertrand, D., Doumen, M., Pazmino, S., Westhovens, R., Verschueren, P. (2021). POS1433 IMPACT OF RHEUMATOID ARTHRITIS ON STRESS: A SYSTEMATIC SCOPING REVIEW. In: Annals Of The Rheumatic Diseases. Presented at the EULAR Conference 2021, Online.
- Van Breda, A., De Cock, D., Vervloesem, C., Doumen, M., Bertrand, D., Pazmino, S., Westhovens, R., Verschueren, P. (2021). POS0300 DOES COGNITIVE BEHAVIORAL THERAPY IMPROVE

PSYCHOSOCIAL OUTCOME IN RHEUMATOID ARTHRITIS: A SYSTEMATIC LITERATURE REVIEW. In: Annals Of The Rheumatic Diseases. Presented at the EULAR Conference 2021, Online.

- Pazmino, S., Lovik, A., Boonen, A., De Cock, D., Stouten, V., Bertrand, D., Doumen, M., Joly, J., Westhovens, R., Verschueren, P. (2021). POS0503 THE DISCORDANCE BETWEEN PATIENT-REPORTED AND CLINICAL/BIOLOGICAL OUTCOMES COULD HELP IN PREDICTING FUTURE DISEASE IMPACT IN PATIENTS WITH RHEUMATOID ARTHRITIS. In: Annals Of The Rheumatic Diseases. Presented at the EULAR Conference 2021, Online.
- Bertrand, D., Pype, N., Conings, T., De Cock, D., Pazmino, S., Doumen, M., Joly, J., Neerinckx, B., Westhovens, R., Verschueren, P. (2021). POS0616 LONG-TERM EFFECTIVENESS AFTER MULTIPLE CYCLES WITH RITUXIMAB FOLLOWING AN ON-FLARE RETREATMENT STRATEGY IN PATIENTS WITH RHEUMATOID ARTHRITIS. In: Annals Of The Rheumatic Diseases. Presented at the EULAR Conference 2021, Online.
- De Cock, D., Vandeputte, M., Van Melder, R., Doumen, M., Bertrand, D., Stouten, V., Pazmino, S., Westhovens, R., Verschueren, P. (2020). The Ideal Mhealth Application for Rheumatoid Arthritis: Qualitative Findings from Stakeholder Focus Groups. Presented at the ACR Convergence 2020, Online.

“There is nothing like looking, if you want to find something. You certainly usually find something, if you look, but it is not always quite the something you were after.”

J.R.R. Tolkien