Optimizing Rheumatology Referrals

Insights into international practice and the impact of digital support

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Optimalisatie van reumatologische verwijzingen
Inzicht in de internationale praktijk en de impact van digitale ondersteuning

Thesis

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Chapter 1

General Introduction

Challenges in healthcare

In the last decades, advancements in healthcare, particularly among high-income countries, have resulted in lower mortality rates and increased life expectancy [1–3]. In the Netherlands, life expectancy increased in the last ten years from 74.3 years to 80.1 years for males and 80.3 years to 83.1 years for females [4], and is expected to increase up to the age of 85 years for females and 82 years for males by the year 2030 [5]. As a consequence, the proportion of people with chronic diseases will also increase. It is expected that approximately 7 million Dutch citizens (40% of the population) will develop a chronic disease [5]. Simultaneously, the number of patients with multimorbid conditions will increase as well, where two-thirds [6] of 7 million people may develop multimorbidities, leading to increased demand for care with a subsequent rise in healthcare costs. The Netherlands spends in total 51 billion euros on healthcare in 2022; this amount rose with 3 billion euros in 2023 [7], and future increases are anticipated as a result of longer life expectancy and the deployment of new drugs and innovations. This increase is in opposition to the limited financial budgets [8].

Another significant challenge for healthcare in the Netherlands is the need for and scarcity of skilled healthcare professionals [9]. Currently, one in seven working people is deployed within the healthcare sector. However, by 2040, one in three working individuals must be employed in the healthcare sector to fulfill the growing need for care [9]. The mentioned challenges may impact the domains of quality of care [10] as defined by the Institute of medicine, leading to particularly inefficient and untimely care. Therefore, to ensure sustainable healthcare provision today and in the future, it is essential to reevaluate how the healthcare delivery system is currently organized and search for solutions.

Value-based healthcare principle

One of the approaches for improving healthcare delivery is value-based healthcare (VBHC) which has been embraced and applied worldwide [11,12] and in particular in the Netherlands. VBHC replaces volume-based payment with a system that rewards healthcare professionals for the added value they deliver on both outcomes that are relevant to patients and cost over the care path. This approach strives to a more patient-centered healthcare, where healthcare providers provide integrated care with the goal to deliver care at the right time and place.

Following the VBHC principle, healthcare could be improved using Integrated Practice Unit where a multidisciplinary team from primary care and secondary care or tertiary care can work together around a group of patients who have similar care needs. In the VBHC model, outcomes that matter to patients and the associated costs are determined throughout clinical care paths [11,13]. The clinical care path provides insight into how the care around a patient is organized creating integral clinical care paths to steer outcomes and costs across the entire care path. Thereby,

a strong digital support is essential. This is expected to further improve healthcare delivery system [14]. In The Netherlands, this has been formalized in the integral care agreement ("Integraal Zorgakkoord" (IZA)), which focusses on promoting optimal quality of care by centering on accessibility and affordability of healthcare [15] through the delivery of appropriate care ("Passende Zorg") [16]. One of the fundamentals of "appropriate care" is delivering value based care [16,17]. By that, within the Netherlands a digital support between primary and secondary care is strongly emphasized.

Primary care gatekeeping and referral system

Until now, the Dutch health care system is symbolized by the gatekeeping system, where general practitioners (GPs) are the primary point of contact and care is organized in silo's. The aim of the gatekeeping system is to keep care accessible, to advise/guide patients about where and with whom treatment should take place, and, subsequently, to only refer patients who need specialized care, thereby minimizing the costs [18]. Depending on the complexity of health issues, patients are thereafter referred to secondary or tertiary care. The current sub-optimal gatekeeping system within the Netherlands can be improved by means of defragmentation of care through enhancing communication and patient health information exchange between primary care and secondary care specialists. Thereby the integration of digital support tools could be useful.

Rheumatology as user case

Musculoskeletal complaints are the most common cause of primary care visits, which account for up to one-third of GP consultations [19]. These complaints could be explained by inflammatory rheumatic diseases (IRDs). Therefore, patients at risk for IRDs should be timely identified and referred to a rheumatology outpatient clinic. IRDs are a heterogeneous group of chronic disorders occurring in about 3% of adults [20], of which the most common forms include rheumatoid arthritis (RA), axial spondyloarthritis (axSpA), and psoriatic arthritis (PsA) [21-23]. Without treatment, IRDs can lead to disabilities and irreversible damage [24]. Fortunately, knowledge of the disease pathogenesis is growing, and improvements have been made towards early therapy initiation, treat-to-target approaches, and the use of biologicals [25]. Nevertheless, several other challenges remain, such as the early recognition of IRDs and the expected increase in incidence [26–28]. IRDs have a substantial burden on the economy [29]. In the Netherlands, healthcare expenditure for RA only was 292 million euros in the year 2019 [30]. This corresponds to 5.1% of total healthcare expenditure for diseases of the musculoskeletal system and connective tissue and 0.3% of total healthcare expenditure [30]. The healthcare landscape will undoubtedly

be impacted by the increase of non IRD joint complaints [31,32] leading to subsequent more referrals to the rheumatology outpatient clinic.

IRD recognition and referral

Musculoskeletal complaints, such as low back pain or joint complaints, are early symptoms of IRDs [33,34]. Moreover, musculoskeletal complaints occur frequently among patients with inflammatory bowel disease (IBD) and psoriasis [35,36]. The burden of musculoskeletal complaints in patients with IBD is less known. Assessing patient outcomes is relevant in evaluating the experienced burden of disease, as it is not always captured by clinical outcomes [37]. As a result, several programs have been initiated, including the International Consortium for Health Outcomes Measurement (ICHOM), which develops standard sets of outcomes that are relevant for patients for general health and specific diseases [38]. In addition to the outcome of disease, gaining insight into the incidence and/or prevalence of IRD is important with regard to resource availability and budgets.

The prevalence of IRDs among IBD patients is approximately 30% [35]. As all patients with joint complaints might visit either the GP or consequently, the gastroenterologist, both healthcare providers should refer patients at risk for IRDs to a rheumatologist. Unfortunately, it is often difficult for health care providers to detect IRDs among a large number of patients with musculoskeletal disorders, as early symptoms are comparable while the prevalence of IRDs is low [33,39].

Early recognition of IRDs has favorable outcomes for the individual patient and society as it results in less structural damage [40]. A review by Akbari et al. reported that effective referral from primary to secondary care can be enhanced through active local educational initiatives for GPs, clinical triage, and the use of structured referral sheets [41]. One of the initiatives to encourage early diagnosis of IRDs is clinical triage, where medical specialist expertise is provided in primary care. This strategy has the advantages of improving patient referrals, decreasing waiting lists, and cost savings [42-44]. In the last few decades, a major focus has been placed on the use of referral sheets to assist in the early identification of IRDs. As a result several referral strategies have been developed including the Delft rule [45]. However, current referral guidelines for IRDs in primary care are broad, which leads to a large group of patients who are unnecessarily referred to the rheumatology outpatient clinic [46,47]. This induces a high workload for rheumatologists and results in them spending less time with actual IRD patients. The burden for patients is also substantial, as it may cost them time and money to travel to the hospital and ultimately may result in a negative patient experience [48]. This emphasizes the need for referral strategies that are specific in capturing IRDs in daily clinical practice.

Available referral strategies for axSpA

One of the most common forms of IRDs is axSpA [24]. Several referral tools have been developed to identify and timely refer axSpA patients to the rheumatologist [49]. Most of the available referral strategies include sacroiliitis detected by imaging, which is not preferable due to high costs and possible interpretation difficulties by the GP. In the Netherlands, GPs have limited access to MRIs, and funding for X-rays and HLA-B27 testing is limited. Preferably, referral strategies should be developed within a primary care setting and are in preference easy to apply and less costly. Nevertheless, most of the available referral strategies are developed and validated in secondary care [50].

Table 1. The CAFaSpA referral strategy.

Applicable in patients ≥3 months back pain and age at onset <45 years
Inflammatory back pain Inflammatory back pain is considered present if at least four questions are answered with yes - Age at onset <40 years - Insidious onset - Improvement with exercise - No improvement with rest - Pain at night (with improvement upon getting up)
Positive family history A positive family history is considered present if there is a first or second degree family member with axial spondyloarthritis, crohn's disease, psoriasis or uveitis anterior
Good reaction to NSAIDs A good reaction to NSAIDs is present when a patients reports a relieve in pain perception within 48 hours after receiving a non-steroidal anti-inflammatory drug
Chronic low back pain ≥5 years A long low back pain duration is present if the duration of the back pain is 5 years or longer
If at least two out of the four referral parameters is present ⟶ a referral to the rheumatologist is advised

The CAse Finding Axial SpondyloArthritis (CaFaSpA) referral strategy (Table 1) was developed by our research group among the primary care chronic low back pain (CLBP) population. The CaFaSpA referral strategy contains four parameters that are simple and non-invasive [51,52]. If at least two parameters are present, a referral to a rheumatologist is advised. After model development an external validation was

performed where the model was tested in a new study population to assess its accuracy, generalizability, and updated if deemed necessary. Therefore, the CaFaSpA referral strategy was validated among a new primary care CLBP population. The CaFaSpA referral strategy indicated a good discriminative, but an impact analysis is required before its implementation in daily clinical practice [53].

Call for impact analyses

Referral models or prediction models are often developed to assist physicians in decision-making and to inform patients [52]. Showing that a prediction model successfully predicts the outcome of interest is not sufficient to confirm that it is valuable. As prediction models may ultimately have an impact on patients' health outcomes and the cost-effectiveness of healthcare, an impact study must be performed. This may facilitate the implementation of the prediction model leading to providing the right care at the right place and time, which is in line with the value attainment as described by the VBHC principles. An impact study determines whether the developed model will improve patients' health outcomes and/or reduce costs [53]. Determining the impact of health care innovation is also stressed in the Netherlands by the IZA. For example, an impact study to assess if a personalized 10-year cardiovascular disease (CVD) risk estimate can increase physical activity and estimate CVD risk at one month among type 2 diabetes patients found no evidence of a beneficial effect of the personalized risk estimate on physical activity nor did it estimated CVD risk [54].

Impact studies on available digital referral strategies for IRDs are currently lacking. Despite the positive attempts to increase the appropriateness of referrals towards the rheumatology outpatient clinic, the lack of evidence on health effects and cost-effectiveness often hinders its implementation in daily clinical practice.

Thesis objectives

The overarching objective of this thesis was to optimize the referral of patients at risk for IRDs. Therefore, we aimed to quantify the proportion of IRDs among patients referred to the outpatient rheumatology clinic as well as evaluation of the impact of one of the most promising referral strategy (CaFaSpA) on health outcomes, process outcomes, and cost-effectiveness.

Overall, the aims of this thesis are:

1. To investigate the proportion of IRDs among patients referred to the rheumatology outpatient clinic;
2. To assess the burden of musculoskeletal complaints on health out comes in patients at risk for IRDs in a specific IBD population;
3. To evaluate the impact of the CaFaSpA referral strategy for axSpA on pa tient reported outcomes and cost-effectiveness;

Thesis outline

Part I. Occurrence and impact of IRDs in patients with musculoskeletal complaints

To assess how many non-IRD patients are referred to the rheumatology outpatient clinic, we performed a systematic review to quantify the proportion of IRDs among patients referred to the rheumatology outpatient clinic and to gain insight into the magnitude of this phenomenon. In **Chapter 2**, we provided the pooled proportion estimates for RA among patients referred to the rheumatology outpatient clinic and estimated the impact of the introduction of the ACR/EULAR criteria for the definition of RA. In **Chapter 3**, similar analyses were performed with focus on axSpA and PsA taking the introduction of the ASAS and CASPAR classification criteria for axSpA and PsA into account.

As IBD patients with joint complaints are at risk for IRDs, we studied the impact of joint complaints on quality of life (**Chapter 4).** A cross-sectional study was performed among secondary care IBD patients and patients recruited from primary care and patient organization.

Part II. Impact of CaFaSpA strategy

Before implementation of a referral strategy in daily clinical practice, the performance of an impact analysis is crucial. In this thesis, we investigated the impact of the most promising CaFaSpA referral strategy on health outcomes, process outcome and cost-effectiveness. We performed a cluster randomized control trial in which GPs were randomized to either the use of the referral strategy or usual care. The impact of the CaFaSpA strategy on disability after four months of follow-up and the percentage of axSpA diagnoses were investigated in **Chapter 5**. A following economic evaluation of the CaFaSpA strategy from a societal perspective during a 12 month follow-up period was executed, including health outcomes that matter most to the patients **(Chapter 6)**.

The research presented in this thesis is discussed in **Chapter 7**, including methodological considerations, practical implications, and suggestions for future research.

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Part I

Occurrence and impact of IRDs in patients with musculoskeletal complaints

Chapter 2

A systematic review on time trend incidence of rheumatoid arthritis in outpatient rheumatology clinics

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ABSTRACT

Objectives: To classify patients with rheumatoid arthritis (RA) in an earlier stage of the disease, the ACR/EULAR classification criteria were updated in 2010. These criteria might have led to an increased incidence of RA in the rheumatology clinic. Since a higher incidence increases the socio-economic burden of RA, it is worthwhile to evaluate whether there is a time effect.

Materials and methods: A systematic review was conducted using Embase, Medline Ovid, Cochrane Central, and Web of Science from database inception to February 2021. Included were only articles that addressed incidence rates of rheumatoid arthritis from rheumatology outpatient clinics.

Results: Of the 6,289 publications only 243 publications on RA were found eligible for full-text review. Nine studies were included reporting incidence. The pooled incidence for RA was 11% (95% CI 6–16%) per year. Over time the incidence increased after the introduction of the 2010 ACR/EULAR classification criteria. Overall there was a high intragroup heterogeneity (I^2 = 97.93%, $p < 0.001$), caused by geographical area, study design and differences in case definitions.

Conclusion: Although the incidence seems to increase after the introduction of the 2010 ACR/EULAR criteria, no conclusions can be drawn on this time effect due to heterogeneity.

INTRODUCTION

About 5% of the population suffers from chronic inflammatory arthritis (IA) [1] of which rheumatoid arthritis (RA) is the most common form [2]. The main consequences of RA are painful, swollen, and stiff joints, leading to disability [3]. Rheumatoid arthritis has a major impact on socio-economic costs [4], which constitutes a substantial public health issue [5]. In the Netherlands the direct healthcare costs for RA are around 0.74% of the entire expenditure on healthcare [6]. Next to that, RA also has a major impact on indirect costs, generally resulting from lost productivity [4].

The hallmark in RA treatment is to treat in an early stage with intensive regimens to prevent disability on the longer term [7, 8]. Early treatment requires early diagnosis, hence early referral. To facilitate early treatment, updated classification criteria for RA were published in 2010 by a task force of experts from both the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) [9]. Compared to older criteria sets for RA these criteria from 2010 cover a broader spectrum of early disease features [10]. Compared with the 1987 classification criteria for RA, the 2010 criteria have higher sensitivity but lower specificity [10].

Although classification criteria are developed for use in research and not for the purpose of diagnosing, they are widely used as aids for diagnosing RA. Furthermore the 2010 ACR/EULAR criteria are used commonly in teaching hospitals for trainees [9, 11]. Since patients with early arthritis are a very heterogeneous group, the low specificity of the new criteria might cause misclassification when used for diagnosing. Next to that, the criteria also aimed at changing the way professionals look at RA. Therefore, the 2010 ACR/EULAR criteria might have led to an increased reported incidence of RA [12].

Since there is a risk of misclassification due to the use of the 2010 ACR/EULAR criteria, it is of great importance to assess the incidence proportions over time. By conducting a systematic review we aimed to acquire time trends in incidence proportions before and after the introduction of the updated 2010 ACR/EULAR classification criteria within the rheumatology outpatient clinics.

MATERIAL AND METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines [13]. The research question was whether a time trend could be seen in incidence proportions

of RA in rheumatology clinics after introduction of the 2010 ACR/EULAR classification criteria.

Literature search

The search strategy was developed in collaboration with an experienced medical librarian of the Erasmus Medical Center, Rotterdam, Netherlands. The digital databases of Embase, Medline, Cochrane, and Web of science were searched to identify relevant studies published from database inception to February 2021. Keywords, indicated as MeSH terms, included terms and synonyms for inflammatory arthritis, prevalence, incidence, and a setting of specialized outpatient secondary or tertiary healthcare. A broad search strategy was established since terms like arthritis, prevalence and incidence are not always used or interpreted uniformly. Therefore the search strategy covered the entire spectrum of inflammatory arthritis to ensure that no articles on RA are missed. The complete search strategy is available in Supplementary file 1.

Selection criteria

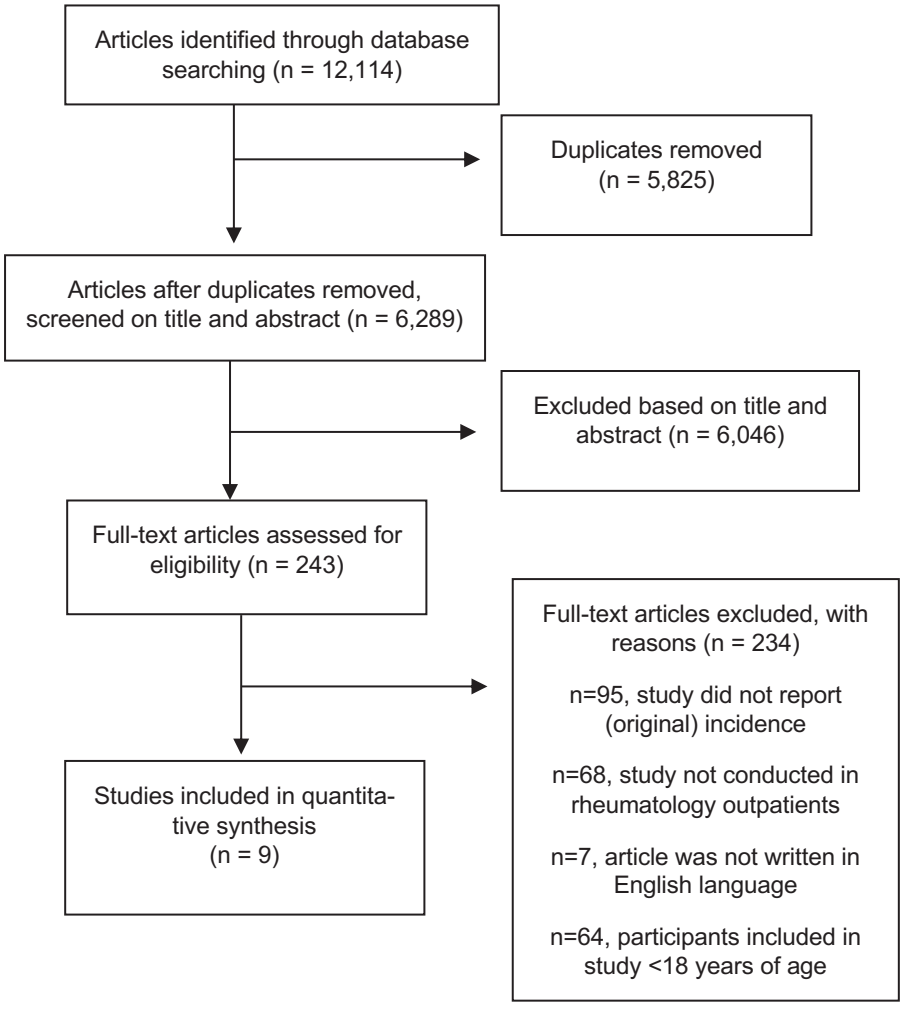
Studies were eligible if they: (i) were written in English language; (ii) included patients aged 18 years or older; (iii) reported the incidence of RA in patients referred to rheumatology outpatient clinics. Studies were excluded if they did not contain original data or had only been published in the form of conference abstracts. There was no restrictive criterion on study design. In case any deviations from the protocol were present, these were clearly reported.

Data extraction

Inclusion of studies was executed in two stages. First, titles and abstracts were screened for eligibility according to the selection criteria described above. Second, the full text of all articles that had passed the first screening was retrieved to further check the same eligibility criteria. Two reviewers [ED and MJ] screened all titles and abstracts independently and in case of disagreement a third reviewer [HB] was consulted. Following the two-stage inclusion process, ED assessed the full text of half of selected articles and MJ and HB each assessed a quarter of these articles for eligibility. Data were extracted by two investigators [ED and MJ] according to a predefined data form. The following information was extracted: country, setting (secondary care and tertiary care), study design (retrospective and prospective follow-up), number of referred patients participating, mean age, percentage of men, case definition of RA, and number of cases with an RA diagnosis. For any missing

information, the authors of the concerning article were contacted to ask for clarification. All data was discussed among the reviewers and disagreements were resolved by consensus after discussion.

Figure 1. Flow diagram of study selection.



Assessment of methodological quality

All included papers were assessed for methods of data collection by a quality assessment tool for prevalence studies [14]. The tool was adjusted for our situation, following the example of Karreman et al. [15]. The final list comprised six yes/no

questions. Response options for individual items were either low or high risk of bias. If there was insufficient information in the article to permit a judgment for a particular item, then the item was deemed to be at high risk of bias [13]. The full quality assessment tool with instructions on how the tool was applied can be found in Supplementary file 2. Agreement between the two raters was assessed using the Kappa statistic. A benefit of using the Kappa statistic is that it takes agreement by chance into account. Kappa values range from -1 to 1, where scores of -1 to 0 indicate poor agreement, 0.01 to 0.20 slight agreements, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 0.99 almost perfect agreement [16].

Analysis

To estimate a time trend incidence, studies were divided into studies before 2010 and 2010, the year in which the ACR/EULAR classification criteria were introduced. Heterogeneity (I^2) was used to address the inconsistency across studies. I^2 describes the proportion of total variation in study estimates that is due to heterogeneity [17]. Recommendations were drawn up based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [18].

RESULTS

Search results

The electronic database search resulted in 12,114 publications (Figure 1). After removal of duplicates and exclusion based on abstract and title, a number of 243 publications were found eligible for full-text review. The majority of studies (n = 234) were excluded because the incidence of RA was not reported, data was not originating from an outpatient rheumatology clinic or due to age or language restrictions. In total nine publications were included for analysis. The characteristics of the included studies are shown in Table 1. The reporting on demographic data was incomplete in some of the studies, as well as the reporting on case definition.

Incidence of rheumatoid arthritis

The incidence of RA in adult patients referred to a rheumatology outpatient clinic was described in nine articles [19–27]. The pooled incidence of RA was estimated to be 11% (95% CI 6–16%) per year. A high intragroup heterogeneity was observed between studies (I2 = 97.93%, $p < 0.001$).

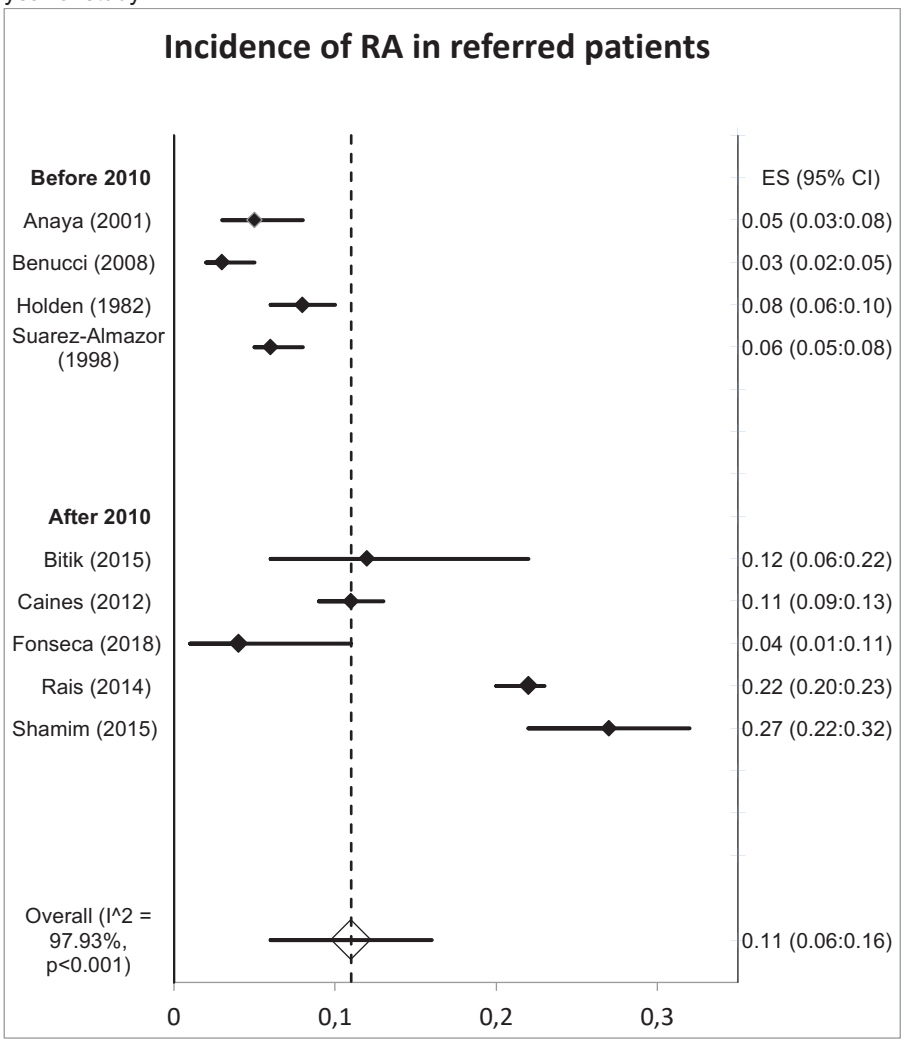
Figure 2 takes into account all nine articles and shows a difference in time trend incidence before and after 2010. Four studies reported on the incidence before and five studies after the introduction of the 2010 ACR/EULAR classification criteria.

Table 1. Study characteristics of included studies.

Article	Year of publication	Country	Study design	Setting	Patients referred (n)	Mean age [years]	% Men	Case definition	Rheumatoid Arthritis n [%]
Anaya, et al[19]	2001	Colombia	RS	TC	321	NA	NA	CR (ACR 1987)	16 [4.98]
Benucci, et al[20]	2008	Italy	PS	TC	920	NA	NA	CR (ACR 1987)	32 [3.48]
Bitik, et al[21]	2015	Turkey	RS	TC	65	56	26	RD	8 [12.30]
Caines, et al[22]	2012	Canada	RS	TC	1101	NA	NA	RD	121 [10.99]
Fonseca, et al[23]	2018	Portugal	PS	SC	78	47	16.8	RD	3 [3.85]
Holden, et al[24]	1982	United Kingdom	PS	SC	814	58.9	NA	NA	65 [8.00]
Rais, et al[25]	2014	Pakistan	RS	SC	2300	40.3 F/ 43.7 M	NA	NA	500 [21.70]
Shamim, et al[26]	2015	Pakistan	PS	TC	316	47.97	26.3	CR (2010 ACR/EULAR)	85 [26.90]
Suarez-Al-mazor, et al[27]	1998	Canada	RS	TC	711	49	39	RD	45 [6.00]

NA, not available; RS, retrospective; PS, prospective; TC, tertiary care; SC, secondary care; F, female; M, male; CR, criteria; RD, rheumatologist diagnosis,

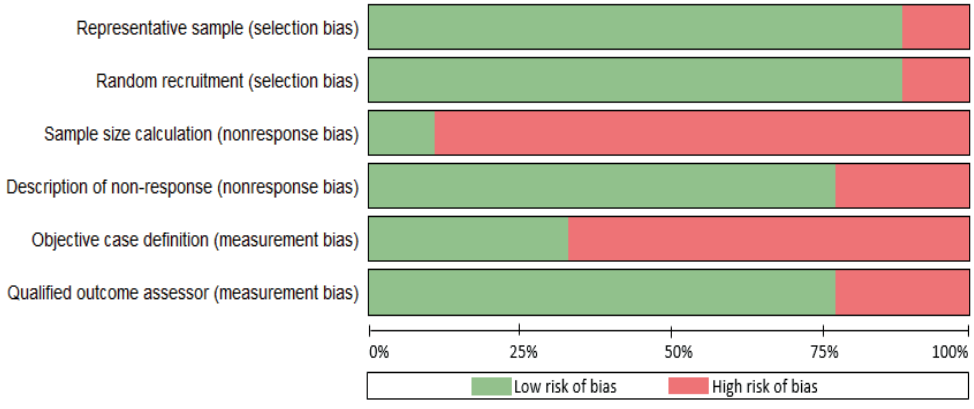
Figure 2. Incidence of rheumatoid arthritis in patients referred to a rheumatologist based on year of study.



To determine whether the high pooled incidence after 2010 was related to the differences in geographical area and access to specialized medical care we performed an additional analysis excluding the two Asian studies published after 2010. Then, there was still an increasing time trend in incidence of RA after 2010.
Case definition in the included articles showed great variety both before and after 2010. Whereas before 2010 in 50% of the articles criteria were used to establish RA and in 25% rheumatologist diagnosis was used as a golden standard. After 2010 only 20% of articles used criteria to establish RA and 60% used rheumatologist diagnosis. Variability in the participants and types of case definition is causing clinical heterogeneity.

Methodological quality of included studies
The Kappa statistic for the overall interrater agreement was 0.81, indicating a very high level of agreement between the two raters. Most of the studies had a sample representative of the target population (89%) and recruited their patients randomly from an appropriate source (89%) (Figure 3). Hence, for one study the sample was not representative and the recruitment was not random, making it subjective to selection bias [21]. Only one study reported sample size calculation, although seven out of nine studies did conduct data-analysis with sufficient coverage of the identified sample. With regard to measurement bias, in 33% objective standard criteria were used and in 78% of the studies the outcome assessor was qualified to define cases of RA reliably. The variability in study design and quality is causing methodological heterogeneity. A complete overview of the assessment of methodological quality is found in Supplementary file 3.

Figure 3. Risk of bias as percentage across the nine included studies in this review.



DISCUSSION

In this systematic review we provide insight into the time trend in incidence of RA with respect to the introduction of the 2010 ACR/EULAR classification criteria. An increase in the number of referred patients diagnosed with RA after the introduction of the 2010 ACR/EULAR classification criteria is found.

Whether this increase in incidence is due to an increase of overall disease expression is hard to say. Studies on prevalence before 2010, however, have in fact shown that the prevalence of RA on a population and global level remained stable over the past decades up to 2010 [28–30]. Unfortunately not many studies have been performed on the incidence or prevalence of RA after 2010 to compare our findings with. Most likely, the increase in incidence is related to an increased awareness and recognition of RA since rheumatologists and primary care practitioners have better knowledge and diagnostics to detect the disease. The increased use of the 2010 ACR/EULAR criteria in trainee programs might have by implication swayed more primary care physicians to question a diagnosis of RA and lead to more rheumatology referrals [31]. This provides rheumatologists with the opportunity to classify RA more frequently. On top of that, more sensitive diagnostic methods and the availability of the 2010 ACR/EULAR classification criteria might have increased the number of RA patients [32].

While in practice the classification criteria are used as aids in diagnosing, they were not developed for the purpose of being used as diagnostic criteria or as a referral tool for primary care [6]. Classification criteria are primarily intended to create well-defined, relatively homogenous cohorts for clinical research. On the contrary, diagnostic criteria are generally broad and must reflect the heterogeneity of a disease [33]. This makes classification criteria inappropriate for use as aids in diagnosing in daily clinical practice [34] and thus neither as means to determine the incidence of RA. In this review studies are included in which both rheumatologist diagnosis and classification criteria are used to establish RA. Luckily there appears to be a shift toward diagnosing merely based on rheumatologist diagnosis as a golden standard, opposed to using inappropriate classification criteria for diagnosing.

We show that the reported incidence is influenced by a large heterogeneity. However, after excluding the two Asian studies by Rais et al. and Shamim et al. that were conducted in Pakistan after 2010, the incidence is still higher when we compare the incidence before and after 2010. The high incidence in the Shamim study [26] might have been influenced by the use of the 2010 ACR/EULAR criteria. Another influencing factor might have been the difference in access to specialized medical care in Pakistan compared to other countries included in this review. The specialist referral in Pakistan is patient-driven [25, 35], most people access secondary or tertiary care hospitals directly. Whereas in other countries there is a strict referral system in which patients need referral through primary care before visiting a rheumatologist.

The quality assessment of the included studies shows that there is large variety in methodological quality of studies. Most studies score positive on four out of six items

of the quality assessment tool; however there are also studies that score less than three positive items. Additionally, the reporting on demographic data or case definition is incomplete in some of the studies. Unfortunately, not all continents are represented in this study and some demographic data are absent which does not allow for inferences on general population characteristics.
There might be some indication bias due to the fact that referral systems differ across the globe. In this review only articles are included in which diagnoses are made by a rheumatologist, while in some countries RA is already diagnosed in primary care. These methodological issues might have affected the results of studies in the comparison between the occurrence of the disease among different countries or when analyzing the time trends [36]. The results of this review are therefore only generalizable to countries with a similar referral system in which patients are referred from primary care toward a rheumatologist.
Several strengths of the current review should be taken into account. This systematic review is conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analysis (PRISMA) guidelines [13]. An extensive search strategy was set up in collaboration with an experienced librarian in order to identify as many relevant studies as possible. The decision to include terms and synonyms for both prevalence and incidence has enhanced our results, since in literature prevalence and incidence are often used interchangeably. A risk of bias assessment is also included to give an indication of the methodological quality of the included studies. The risk of bias tool that is used was initially developed for prevalence studies only. However, since detailed criteria and examples were given for each item of this tool, we were able to select items that were applicable to incidence studies. Having evaluated the quality of evidence precisely helps strengthen recommendations [37]. The entire selection of studies, data extraction and assessment of methodological quality were conducted by two independent reviewers and every paper was discussed until full consensus was reached. Nevertheless, it is important to note that updating a systematic review periodically is recommended [38].
For future research into incidence of inflammatory rheumatic diseases, we do have some recommendations. To overcome methodological issues, it is of great importance to use an objective case definition to overcome measurement bias. Next to that, the case definition should be clearly reported in the article, as well as crucial data like demographic parameters of the study population. As a final recommendation, we would encourage researchers to clearly look at whether the study investigates the prevalence or the incidence of a certain condition, since both terms are often used interchangeably. Within the era we live in at the moment, with digital revolution happening at high speed, this adequate data registration is not only important for research purposes, but overall to ensure real life hospital data transparency.
A clinical implication following from this review might be to conclude that the workload for rheumatologists increases equivalently with the increasing incidence of RA.

For society this would mean increasing healthcare costs. However, as mentioned the 2010 ACR/EULAR criteria may sway primary care physicians to consciously question a diagnosis of RA and be more cautious on whom to refer [31]. Next to that, numerous initiatives are being conducted at the moment with the aim of improving appropriateness of referrals toward the rheumatologist [39]. It is our experience that around 70% of all patients referred to an outpatient rheumatology clinic is not diagnosed with an inflammatory rheumatic disease. While with a smaller number of inappropriate referrals, rheumatologists can spend more of their time on patients with an inflammatory rheumatic disease. This may outbalance the increasing number of RA patients and allows starting treatment in an early stage of the disease to overcome progression. Next to that the increase of appropriateness of referrals may also have socioeconomic advantages.

In conclusion, an increased incidence of RA in the outpatient rheumatology clinic is seen after 2010 compared to earlier studies. However, due to the large heterogeneity between studies, this increase cannot be fully attributed to the introduction of the 2010 ACR/EULAR classification criteria. Although it is stated that these criteria lead to better and earlier recognition of RA, further research with coherent use of the 2010 ACR/EULAR criteria is needed to establish the diagnostic effects in daily clinical practice worldwide.

SUPPLEMENTARY MATERIAL

1. Supplementary Data S1; Search strategy (2021-02-09).

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('rheumatoid arthritis'/de OR 'spondylarthritis'/de OR 'psoriatic arthritis'/de OR 'ankylosing spondylitis'/de OR 'rheumatic disease'/de OR 'rheumatology'/de OR 'rheumatologist'/de OR (alibert-bazin OR beauvais-disease* OR ((arthrit* OR osteoarthrit*) NEAR/3 (deforman* OR inflammat* OR rheumat* OR vertebr* OR spina* OR psoria*)) OR rheumarthrit* OR spondylarthrit* OR spondyloarthrit* OR (ankylos* NEAR/3 spondylit*) OR (Rheumatic NEAR/3 (disease* OR disorder*)) OR rheumatolog* OR reumatolog* OR ((rheuma* OR arthralgi*) NEAR/3 specialist*)):ab,ti) AND ('incidence'/de OR 'prevalence'/de OR 'statistics'/de OR (incidence* OR prevalence* OR statistic* OR ((spectrum OR pattern* OR occurenc* OR frequenc* OR percent* OR proportion*) NEAR/6 (disease* OR inflammat*)) OR ((spectrum OR pattern* OR distribution) NEAR/3 patient*)):ab,ti) AND ('outpatient'/exp OR 'outpatient department'/exp OR 'secondary health care'/exp OR 'tertiary health care'/exp OR 'ambulatory care'/de OR 'patient referral'/de OR (outpatient* OR out-patient* OR ((secondar* OR tertiar* OR specialist OR public) NEAR/3 (care* OR healthcare OR hospital OR center* OR centre*)) OR ((rheumat* OR reumat* OR Arthrit*) NEAR/3 (clinic OR department* OR centre* OR center* OR institut* OR unit OR units)) OR ((rheumat* OR reumat* OR Arthrit*) NEXT/1 practice*) OR ambulator* OR referr*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

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rheumatologist|reumatologist|"rheumatology|arthralgia specialist |specialists" incidence|prevalence|statistics|spectrum|pattern|frequency inflammation|inflammatory outpatient|"secondary|tertiary|specialist care|healthcare|hospital|center|centre"

2. Supplementary Table S2; Risk of bias assessment instructions.

		YES	NO
1.	Was the sample representative of the target population?	The sample was representative of the target population. Selected patients are representative of a population of patients suspected of RA. No pre-selection took place in selecting the patients based on for example work. The center from which the RA patients were recruited should me mentioned	Sample was not representative.
2.	Were study participants recruited in an appropriate way?	Patients were recruited from an appropriate source and were "randomly" invited for the study (all patients OR consecutive patients OR random patients)	Patients were not recruited from an appropriate source and no random selection was used to recruit patients
3.	Was the sample size adequate / Was sample size calculation performed?	Sample size calculation was performed and it was reported if this target was reached	No sample size calculation
4.	Was the data analysis coducted with sufficient coverage of the identified sample?	Non-response was described **AND** a comparison between the responders and non-responders was performed. If retrospective design, answer is yes	No information about response percentages was given or no comparison between responders and non-responders was made.
5.	Were objective, standard criteria used for the measurement of the condition?	Criteria were used for the diagnosis of RA (for example ACR or EULAR criteria) OR A detailed description of how a case of RA was defined is included in the manuscript. OR In case of use of ICD codes, a validation/check was performed	No criteria were used and no description of how a case was defined is included in the manuscript.
6.	Was the condition measured reliably?	Outcome assessor was qualified to use the case definition criteria (for example; medical specialist, trained research nurse)	Outcome assessor was not qualified to use the case definition criteria or it was not mentioned who defined a case.

3. Supplementary Table S3; Overview of assessment of methodological quality

	Anaya, 2001	Benucci, 2008	Bitik, 2015	Caines, 2012	Fonseca, 2018	Holden, 1982	Rais, 2014	Shamim, 2015	Suarez-Almazor, 1998
Representative sample (selection bias)	+	+	−	+	+	+	+	+	+
Random recruitment (selection bias)	+	+	−	+	+	+	+	+	+
Sample size calculation (nonresponse bias)	−	−	−	−	+	−	−	−	−
Description of non-response (nonresponse bias)	+	−	+	+	+	−	+	+	+
Objective case definition (measurement bias)	+	+	−	−	−	−	−	+	−
Qualified outcome assessor (measurement bias)	+	+	+	+	+	−	−	+	+

+ Low risk of bias

− High risk of bias

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Chapter 3

Increase in axial spondyloarthritis diagnoses after the introduction of the ASAS criteria: a systematic review

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ABSTRACT

Objectives: To explore the proportion of axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) diagnoses within all newly referred patients visiting rheumatology outpatient clinics. And more specifically, to analyze whether there is an effect of the introduction of the ASAS and CASPAR classification criteria for axSpA and PsA.

Methods: We systematically searched Embase, Medline Ovid, Cochrane Central and Web of Science from database inception to November 2022. Articles that investigated new onsets of axSpA and PsA in adults from rheumatology clinics were included.

Results: In total 170 out of 7139 studies were found eligible for full-text review, after which 33 unique studies were included. Seventeen studies reported new onsets of axSpA, and 20 studies of PsA. The pooled proportion of axSpA within all newly referred patients was 19% (95%CI 15-23%) and 18% (95%CI 14-22%) for PsA. The proportion of axSpA before 2009 was 3% (95% CI 0-6%) and increased up to 21% (95% CI 14-28%) after 2009. For PsA limited data was available in order to analyse the proportions of PsA before 2006. Overall, heterogeneity was high (I^2>95%, p<0.001) that was most likely caused by geographical area, study design, setting and use of different referral strategies.

Conclusion: The pooled proportion of axSpA and PsA among patients referred to the rheumatology outpatient clinic was 19 and 18%, respectively. Although the proportion of diagnosed axSpA patients seemed to increase after the introduction of the ASAS criteria, due to the large heterogeneity our findings should be interpreted with caution.

INTRODUCTION

Spondyloarthritis (SpA) represents a group of chronic rheumatic diseases with common clinical and genetic features [1]. Axial SpA (AxSpA) and psoriatic arthritis (PsA) are the most common types of SpA and have major impact on patients' lives [2]. The main consequences are joint damage, pain, and disabilities [3-5]. These disabilities cause high social and medical costs in which medication and productivity loss costs represent the major part of the total costs [6-8].

During the past decades, treatment possibilities in patients with SpA have improved considerably and responses are better when treatment is started as soon as the diagnosis has made. Therefore, early recognition of SpA is crucial to prevent joint damage or disability on the long-term [9-11]. To facilitate early axSpA and PsA classification for research purposes, new classification criteria were introduced: The assessment of spondyloarthritis international society (ASAS) criteria for axSpA and the classification criteria for PsA (CASPAR) [12, 13]. Unlike the previously used classification sets, the new sets cover a broader spectrum of early disease features [14, 15]. Although the new classification criteria have higher sensitivity, the specificity remains low and are therefore not suitable for diagnosis [16]. However, as diagnostic criteria in the rheumatology setting are lacking, these classification criteria are used for training purposes, but are also widely used as diagnostic tools in daily practice [17]. Therefore, the introduction of the new classification criteria might have led to misdiagnosis and may have influenced the reported hospital incidence of SpA. In this line, it is relevant to evaluate the proportion of SpA in a rheumatology outpatient as this may enrich our understanding of the occurrence of the disease and the needs of healthcare systems in terms of availability of healthcare resources and budgets.

In this systematic review we aim to assess the proportions of axSpA and PsA within all newly diagnosed rheumatic diseases among patients referred to the rheumatology outpatient clinic and to investigate whether there is an effect of the introduction of the ASAS and CASPAR classification criteria for axSpA and PsA.

METHODS

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. This study on axSpA and PsA is part of a full review for inflammatory rheumatic diseases including rheumatoid arthritis.

Literature search

In collaboration with an experienced medical librarian [WB and SM] a search strategy was developed. Embase (1964 to present), Medline (1971 to present), Cochrane (1992 to present) and Web of science (1975 to present) were searched to identify relevant

studies published until November 2022. Keywords indicated as MeSH terms included terms and synonyms for SpA, AS, axSpA and PsA, prevalence, incidence and a setting of specialized outpatient secondary or tertiary healthcare. Keywords for both prevalence and incidence were included, because terms like prevalence and incidence are not always used, reported or interpreted uniformly. The full search strategy is provided in supplementary file 1.

Inclusion and exclusion criteria

Eligible studies were identified by three reviewers [MJ, ED and HB], and the inclusion of studies was based on a two-stage process. First, titles and abstracts were screened, followed by retrieval of full-text articles. In case of disagreement a fourth reviewer [DLB] was consulted. Studies were selected for inclusion if: [i] were written in Dutch or English language; [ii] included patients aged 18 years or older; [iii] reported new onsets of axSpA or PsA in patients referred to rheumatology outpatient clinics. Unpublished studies, poster presentations, and conference abstracts were excluded. There was no restrictive criterion on study design.

Data extraction

Data was extracted by one investigator [MJ] using a pre-defined data extraction form. Subsequently, a validation set of the data was drawn and extracted by a second investigator [ED]. The following information was extracted: year of publication, country, setting (secondary care, tertiary care, integrated secondary and tertiary care), study design (retrospective, prospective follow-up, cross-sectional), number of referred patients participating, mean age, percentage of men, case definition of axSpA or PsA, and number of cases with an axSpA or PsA diagnosis. In case of doubt about the data extraction two investigators were consulted (DLB and TMK) and discrepancies between readers were resolved by consensus after discussion.

Primary and secondary outcome

Our primary outcome was the proportion of new onsets of axSpA and PsA among all newly diagnosed rheumatic diseases in patients visiting the rheumatology outpatient clinic.

Secondary outcome was the change in proportion of axSpA and PsA after the introduction of the new classification criteria. To explore the proportion of axSpA and PsA, studies were grouped based on the introduction year of the classification criteria: before and after 2009 (ASAS classification criteria for axSpA) the before and after 2006 (CASPAR criteria for PSA). The choice for selecting the CASPAR criteria for PsA over other classification criteria was because of its wide usage that is mainly due to its simplicity and the high specificity [13].

Table 1. Study characteristics of the included studies.

Article	Year of publication	Country	Study design	Setting	No. of patients referred	Mean age [years]	% Male	Case definition (axSpA)	AxSpA n (%)	Case definition (PsA)	PsA n (%)
Holden, et al [26]	1982	UK	PS	SC	814	58.9	NR	NR	14 (1.7)	NA	NA
Mijiyawa, et al [27]	2000	Togo	RS	SC	3204	44.5	100	CR (Amore)	15 (0.5)	NA	NA
Reich, et al [45]	2008	Germany	PS/CS	SC	432	49.4	NR	NA	NA	CR (Moll & Wright)	266 (61.6)
Bitik, et al [28]	2009	Turkey	RS	TC	65	56	26	RD	3 (4.6)	NA	NA
Hermann, et al [46]	2009	Austria	PS	SC	92	34.7	41.3	RD	27 (33)	CR (McGoNRgle)	0 (0%)
Poddubnyy, et al [33]	2011	Germany	PS	SC	560	38.8	54.3	RD	222 (39.3)	NA	NA
Bonifati, et al [39]	2011	Italy	PS	SC	106	NR	NR	NA	NA	CR (CASPAR)	43 (12.8)
Sieper, et al [32]	2012	Germany	PC	SC	1049	37.1	50.8	RD	397 (37.8)	NA	NA
Deodhar, et al [30]	2012	USA	PS/CS	TC	303	40.7	54	CR (ASAS)	153 (50.5)	NA	NA
De Marco, et al [38]	2012	Italy	CS/PS	SC	277	55.7	47	NA	NA	CR (CASPAR & VASEY)	65 (29.5)
Haroon, et al [47]	2012	Ireland	CS	TC	100	52.3	64	NA	NA	CR (CASPAR)	29 (29)

Article	Year of publicaion	Country	Study Design	Setting	No. of Patients referred	Mean age [years]	% Male	Case definition (axSpA)	AxSpA n (%)	Case definition (PsA)	PsA n (%)
Toloza, et al [48]	2012	Peru	RS	TC	8191	NR	NR	NA	NA	CR (CASPAR)	16 (0.2)
Estebaránz, et al [49]	2014	Spain	CS	SC	375	47.4	57.2	NA	NA	CR (Moll & Wright and CASPAR)	86 (22.9)
Caines, et al [50]	2015	Canada	RS	TC	1101	NR	NR	RD	46 (4.2)	RD	35 (3.2)
Spelman, et al [51]	2015	Australia	PS	TC	424	49.6	53.5	NA	NA	CR (CASPAR)	37 (9)
Moghimi, et al [29]	2016	Iran	PS	SC	118	36.3	NR	NR	29 (24.6)	NR	NA
Urbancek, et al [52]	2016	Slovak Republic	PS	TC	831	NR	50.5	NA	NA	CR (CASPAR)	177 (21.8)
Tant, et al [53]	2017	Belgium	CS	SC	117	36	46	RD	37 (31.6)	NA	NA
De Socio, et al [40]	2017	Italy	RS	SC	409	NR	53	NA	NA	CR (CASPAR)	19 (4.6)
Fonseca, et al [31]	2018	Portugal	PS	SC	29	40.3	32.5	RD	3 (10.3)	NA	NA
Chimenti, et al [37]	2019	Italy	PS	SC	239	51.2	45.6	NA	NA	CR (CASPAR)	120 (50.2)
Hočevar, et al [54]	2019	Slovenia	RS	IC	2130	NR	NR	CR (ASAS)	98 (4.6)	CR (CASPAR)	NA

Article	Year of publication	Country	Study design	Setting	No. of patients referred	Mean age [years]	% Male	Case definition (axSpA)	AxSpA n (%)	Case definition (PsA)	PsA n (%)
Jamal, et al [44]	2020	Holland	PS	SC	75	36.2	36	RD	6 (8)	NA	NA
Elnady, et al [55]	2019	Saudi Arabia	PS	TC	104	41.11	53	NA	NA	CR (CASPAR)	9 (4.3)
Barliakos, et al [56]	2020	Gemany	PS	SC	326	36.0	50.6	RD	46 (14.1)	NA	NA
Proft, et al [57]	2020	Germany	PS	SC	361	37.0	49.3	RD	106 (29.4)	NA	NA
Kiil, et al [58]	2021	Demark	PS	SC	84	32.0	40.5	MDT	25 (29.8)	NA	NA
Liyanage, et al [59]	2021	Sri anka	CS	TC	199	54	54	NA	NA	CR (CAsPAR)	47 (23.6)
Felbo, et al [60]	2021	Denmark	CS	SC	126	57*	46	NA	NA	CR (CASPAR)	11 (8.7)
Pasalent, et al [61]	2022	Canada	PS	SC	405	36.9	45	RD	63 (15.6%)	NA	NA
Hal, et al [62]	2022	Holland	PS	TC	22	56	74	RD	7 (31.8)	NA	NA
Cui, et al [63]	2022	China	CS	SC	482	48.4	70.1	NA	NA	CR (CASPAR)	77 (16)
Sarabia, et al [64]	2022	Canada	PS	SC	203	50.8	43.8	NA	NA	RD	27 (13.3)

NA, not available; RS, retrospective; PS, prospective; TC, tertiary care; SC, secondary care; CR, criteria; RD, rheumatologist diagnosis. MDT, Multi-Disciplinary Team.

Assessment of methodological quality

The methodological quality of all included studies was assessed by a quality assessment tool for prevalence studies [19]. The tool was adjusted for our situation, following the example of Karreman et al. [20]. We included six yes/no questions about [i] representativeness of the sample for the target population, [ii] appropriate recruitment of the study participants, [iii] adequate sample size calculation and [iv] whether the data analysis was conducted with sufficient coverage of the identified sample. In addition, we included a question about [v] case establishment, whether objective (observable and fact based) or standard criteria were used and [vi] whether the condition was measured by a qualified outcome assessor for example a rheumatologist or a trained research nurse. Two reviewers [MJ and ED] assessed whether there was a high or low risk of bias in the studies. Agreement between the two raters was assessed using the Kappa statistic.

Values between 0.01–0.20 indicate none to slight agreement, 0.21–0.40 fair agreement, 0.41– 0.60 moderate agreement, 0.61–0.80 substantial agreement, and ≥0.81 (almost) perfect agreement [21].

Statistical analysis

To assess the change in proportion of axSpA and PsA, studies were grouped based on year of publication before or after the introduction of either the ASAS or CASPAR classification criteria. Between-study heterogeneity was assessed using the I^2 index [22]. In case studies reported a proportion of 0%, we set the nominator to 1 to avoid omission of the study in the pooled analyses.

To explore heterogeneity sensitivity analysis was performed. Studies were grouped and analyzed based on use of referral strategy, study design, access to medical care and case definition.

RESULTS

Literature search results

A total of 14,339 publications were identified from the literature search (Figure 1). After removing duplicates and exclusion based on abstract and title, 170 publications were found eligible for full-text review. A total number of 137 studies were excluded due to age, language, new onsets of axSpA or PsA were not reported, or when new onset was not among referred patients or data not originating from an outpatient rheumatology clinic. Thirty-three unique studies were included in the analysis. Seventeen studies reported the proportion of axSpA and twenty studies reported the proportion of PsA. Four studies reported the proportion of both axSpA and PsA. The characteristics of the included studies are shown in Table 1. The inter-rater reliability between the two reviewers for risk of bias was 0.70.

Proportion new onsets of axSpA

The proportion of new onsets of axSpA in adult patients visiting the rheumatology outpatient clinic during was reported in seventeen studies (Figure 2a). The mean age of the study participants ranged between 32.0 and 58.9 years. Percentage of male patients varied between 26.0 and 100.0 percent. The pooled proportion of axSpA was 19% (95% CI 15-23%) which was accompanied by a large heterogeneity (I^2=99.1%, p-value <0.001).

Change in proportion of axSpA after the introduction of the ASAS criteria

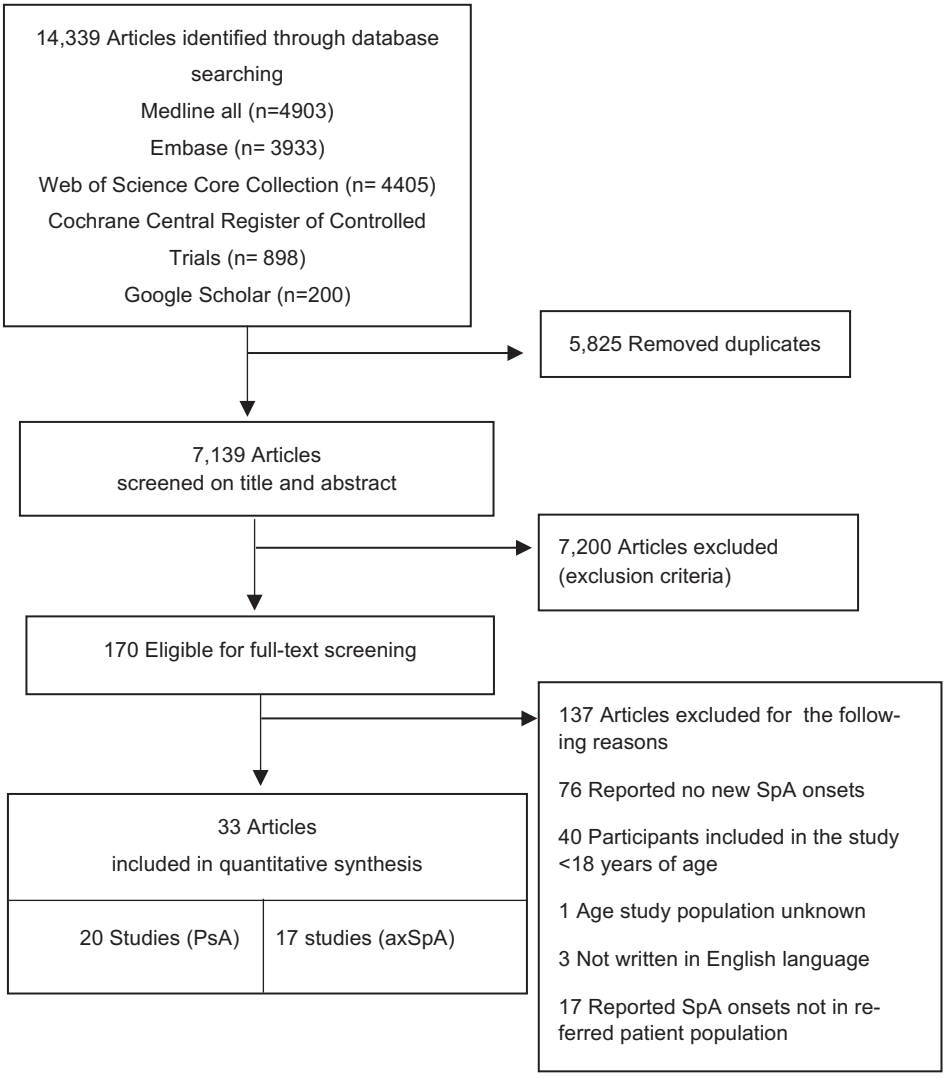
Three studies reported the proportion before, and twelve studies after the introduction of the ASAS classification criteria. The proportion of axSpA before 2009 was 3% (95% CI 0-6%) and increased up to 21% (95% CI 14-28%) after 2009, statistically significant (p-value=0.03).

Sensitivity analyses

To explore the high heterogeneity that was probably caused by variety in study population, a sensitivity analysis was performed. The case definition differed slightly in the included studies. Using a diagnosis that was made by a rheumatologist resulted in a pooled axSpA proportion of 21% (95% CI 11-29%), whereas using classification criteria as a case definition resulted in a pooled axSpA proportion of 17% (95% CI 9-24%). In one study case definition was performed through a multidiscipline team conference whereas two studies did not report how case definition was performed.

The pooled proportion of axSpA was 19% (95% CI 15-23%). To explore whether heterogeneity was caused by differences in access to medical care, three studies performed in Asia and Africa were excluded. The pooled proportion of axSpA was 19% (95% CI 15-23%). Use of referral strategies and study design differed in the included studies as the goal of the included studies was diverse. Eleven studies (65%) used a referral strategy. One study (33%) that was reported before the introduction of the ASAS criteria used a referral strategy, while this was the case in ten studies (71%) that were reported after the introduction of the ASAS criteria. Thirteen (76%) of the included studies used a prospective design. One study (33%) before the introduction of the ASAS criteria had a retrospective design, while this was the case in in three studies (21%) after the introduction of the ASAS criteria.

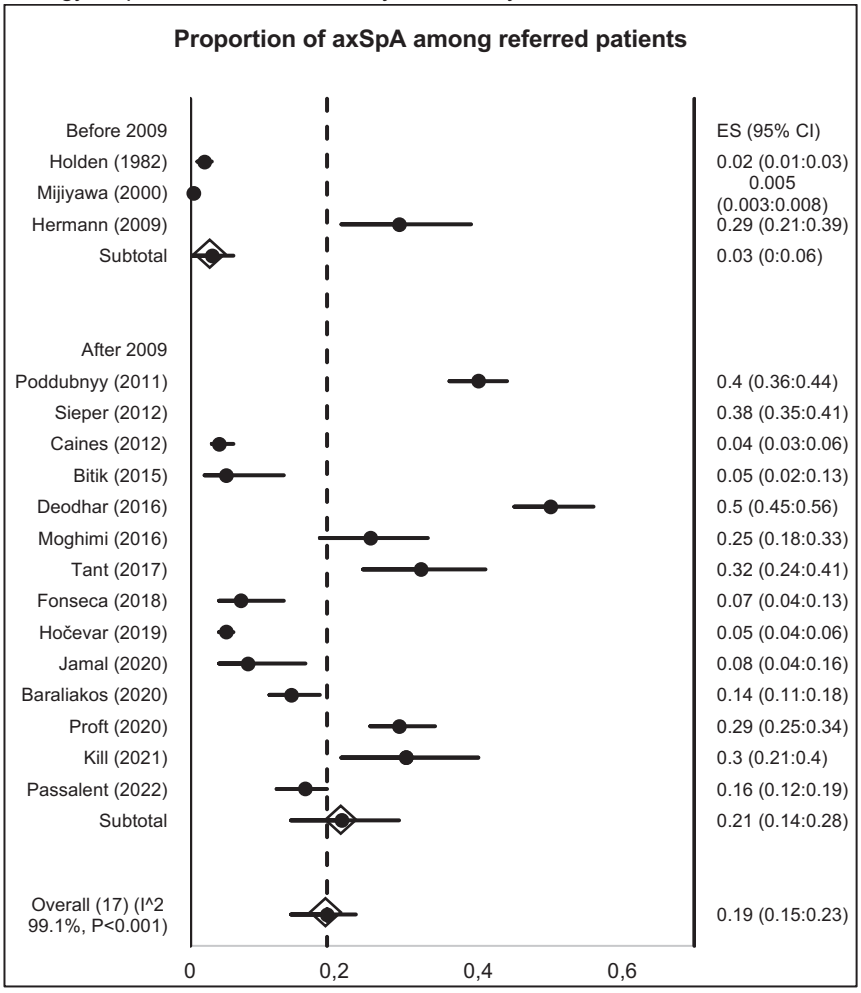
Figure 1. Flow diagram of study population.



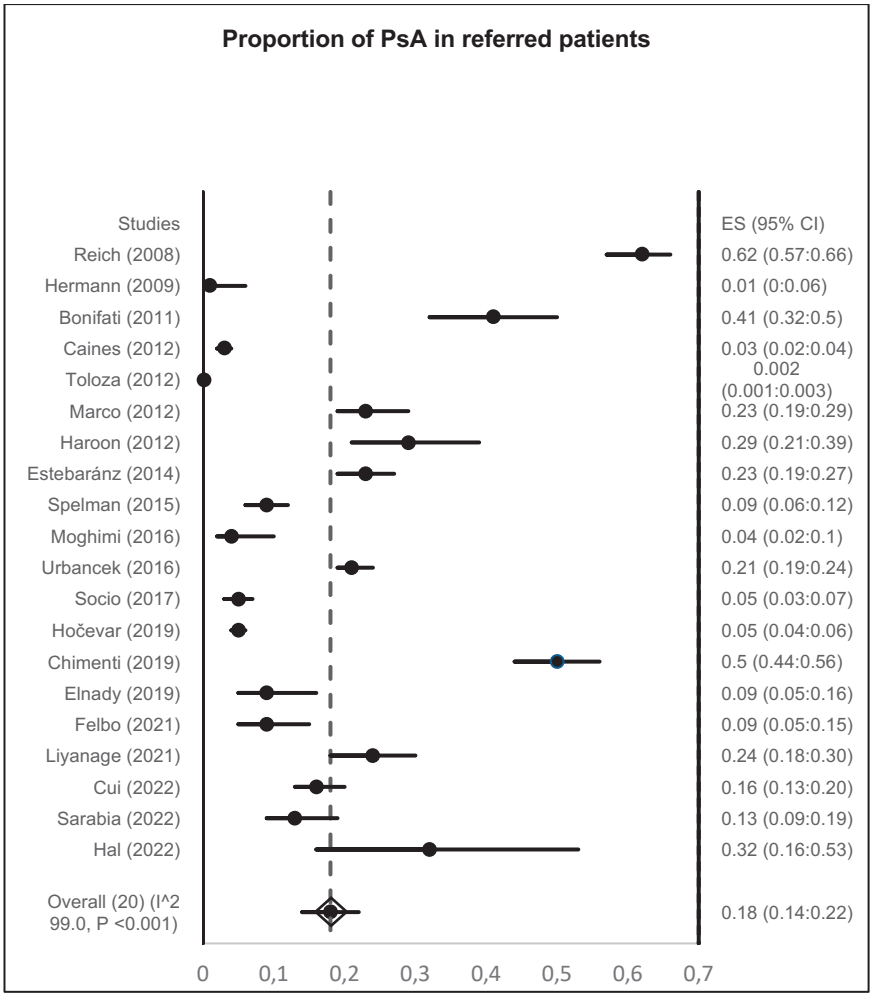
Proportion new onsets of PsA

The proportion of PsA in adult patients referred to a rheumatology outpatient clinic was reported in twenty studies. The mean age of study participants varied between 34.7 and 56.0 years and the percentage of male patients varied between 34.8% and 73%. All eligible studies were published after the introduction of the CASPAR criteria therefore we could not investigate the change proportion

Figure 2. Reported proportion of axSpA (2a) and PsA (2b) in newly diagnosed patients visiting rheumatology outpatient clinics based on year of study. ES; effect estimate.



2a



2b

of patients after the introduction of this criteria.The pooled proportion of PsA was estimated to be 18% (95% CI 14-22%) (Figure 2b) that was accompanied by a large heterogeneity between studies (I^2 99.2%, P<0.001). Study design varied between the included studies, four studies (20%) used a retrospective design, five studies (25%) had a cross-sectional design, nine studies (45%) had a prospective design and two studies (10%) had a prospective cross-sectional design.

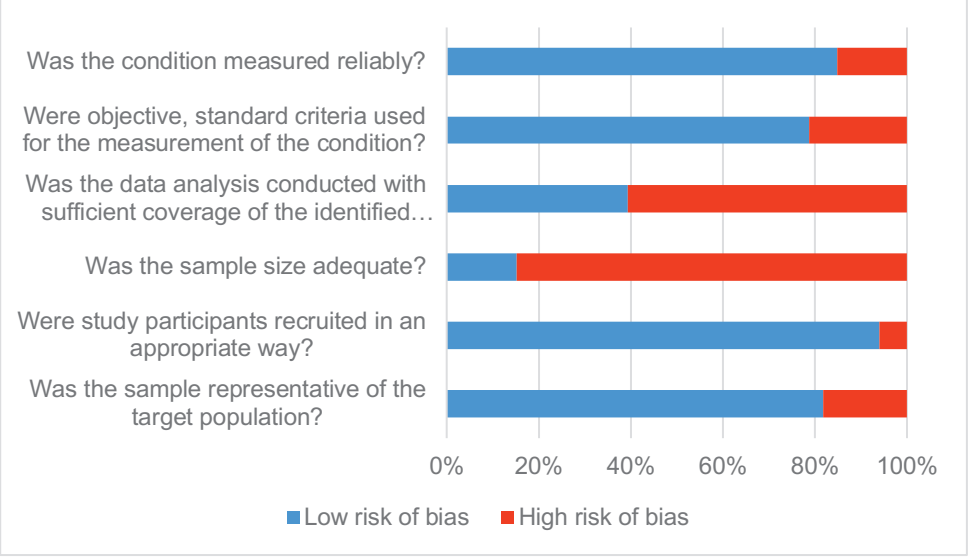
Methodological risk of bias assessment

A complete overview of the assessment of methodological quality can be found in supplementary file S2 and S3.

Figure 3 shows the percentage of the studies that scored positive on the quality list. The majority of studies had a sample representative of the target population (82%) and most studies recruited their patients in a random way (94%).

Sample size calculation was reported in only 15% of the studies, while 39% conducted the analysis with sufficient coverage of the identified sample. Objective standard criteria for case-ascertainment were used in 79% of studies and SpA was measured reliably in 85% of the studies.

Figure 3. Risk of bias as percentages across the 33 included studies in this review.



DISCUSSION

We performed a literature review to assess the proportion of new onsets of axSpA and PsA in patients referred to the outpatient rheumatology clinic. The accompanied pooled proportion were found to be 19% (95% CI 15-23) for axSpA and 18% (95% CI 14-22) for PsA.

Overall, use of classification criteria led to a lower proportion of axSpA diagnoses when compared to case definition by a rheumatologist. The proportion of axSpA increased by 18% among the referred patients after the introduction of the ASAS classification criteria. The increase in proportion could be due to the introduction of the new criteria. However, heterogeneity was large in this study where geographic area, study design, and use of referral strategy seemed to contribute to its magnitude in the proportion of new onset estimates.

Classification criteria have originally been developed to assist in enrolling patients with axSpA or PsA in clinical trials [23]. However, as diagnostic criteria or definitive diagnostic tests are lacking, classification criteria are widely used as aids in making the diagnosis [24]. Moreover, classification criteria were originally developed in populations where a diagnosis was made therefore there is a strong link between classification and diagnostic criteria. In addition, diagnosis is nothing different than classification in the individual patient. Previous classification criteria for axSpA focused on classifying AS only and thus did not capture patients in the early stages of the disease, which is currently defined as non-radiographic axSpA [15]. The 2009 ASAS classification criteria allows to classify non-radiographic axSpA in addition to AS [12]. This could also have led to an increase in the number of diagnosed axSpA patients. Furthermore, in this review ten out of fourteen studies that were published on axSpA after 2009 used the diagnosis made by the rheumatologist as reference standard. The proportion of axSpA was higher in studies where case definition was made by a rheumatologist rather than classification criteria. Although it is fortunate to witness that no major shift took place towards using the ASAS criteria for diagnosing unfortunately, it is difficult to verify whether the rheumatologists based their diagnose on the classification criteria.

With regard to the new onsets of PsA, we could not analyze the change in proportion since all reported studies were published after the introduction of the CASPAR criteria. Remarkably, among the sixteen studies that used some form of classification criteria to report the proportion of PsA, fourteen studies used the CASPAR criteria to classify patients as PsA. Interestingly, even in two studies where case definition was made by a rheumatologist patients were evaluated whether they met the CASPAR criteria. Although a number of classification criteria have been proposed for PsA over the years, none of them have been widely used in clinical research nor in epidemiological studies [14]. It seems that the CASPAR criteria are widely accepted classification criteria for PsA worldwide [13].

It is worth mentioning that all studies included in this systematic review were published after the introduction of the CASPAR criteria. This suggests that there was hardly any adoption of the PsA classification criteria's before the CASPAR criteria.

Our study is unique as it the first systematic review aimed to assess new onsets of PsA before/after the introduction of CASPAR criteria.

AxSpA is strongly associated with HLA-B27 which accounts for almost 20% of its heritability. Geographical distribution of axSpA is affected by HLA-B27 positivity among different geographical population [25]. Unfortunately, HLA-B27 positivity was not often reported in the studies [26-29]. Interestingly, when it was reported this was usually as part of the studies that used referral strategy towards a rheumatologist [30-33]. HLA-B27 is highly prevalent in Europe, followed by the US population and is nearly absent in African countries [34]. Another possible explanation for the low proportion in the studies performed in Africa could be the low access to medical care in Africa, especially access to secondary or tertiary care [35].
The use of a referral strategy might also have contributed to the presence of a higher proportion of axSpA. Since there is a long diagnostic delay between symptom onset and diagnosis of axSpA several referral strategies have been developed to assist early recognition of axSpA [16]. Selective referral of patients towards a rheumatologist by using a referral strategy indicated an increasing tendency in proportion when compared to studies that did not use a referral strategy. In general, the increased proportion could be related to an increased awareness and (timely) recognition of axSpA among primary care physicians. In addition, recently more sensitive diagnostic tools such as MRI are available to aid earlier detection of inflammation of the SI joints [36]. This could have enhanced the proportion of axSpA diagnoses. A wide variation in the proportion of PsA was observed, even studies from the same country report different proportion estimates. Four of the fifteen studies performed in Italy reported proportion estimates that range between 4.6 and 50.2% [37-40] most likely due to difference in study design and study population.
This systematic review that was conducted in accordance with the PRISMA guidelines has several strengths and limitations. The search strategy for this systematic review was set-up in collaboration with an experienced librarian and covered the entire spectrum of rheumatic diseases. Additionally, we assessed the risk of bias with regard to methodological quality by means of a situational adjusted tool.

Regarding the limitations, the proportion of axSpA or PsA was assessed in a rheumatology outpatient clinic while in some countries across the globe SpA is diagnosed and treated in primary care. Therefore, results of this study are only generalizable to countries with the same referral system in which patients are referred from primary care to the rheumatology outpatient clinic.

As established in our study the increased trend in axSpA proportion since the introduction of the ASAS criteria might imply a major impact on the healthcare costs and the health care system. The workload for rheumatologists is expected to increase and more rheumatologists may be needed. In addition, our findings indicate that over 80% of referred patients towards the rheumatologist were diagnosed with neither axSpA nor PsA.

This entails that there is still an unmet need for selective referral of patients at risk towards the rheumatologist. However, currently, in the field of SpA more studies are performed on developing, validating and optimizing referral strategies to identify patients at risk for SpA [41-44]. This could result in appropriate, timely referral of patients towards a rheumatologist which will on the other hand balance or reduce the healthcare costs and the workload for the rheumatologists.
Future studies with consistent methodology, i.e., objective case definition, are needed to estimate the proportion of axSpA. Although as seen in our study, many studies used the CASPAR criteria to classify patients with PsA, future agreement on which classification for PsA should be used is warranted. In addition, complete sufficient data including demographic data as well as HLA-B27 positivity should be reported in future studies. In addition, more studies from low income countries are needed to investigate the global proportion of SpA. Finally, we hope that our recommendations for researchers on data reportage improves future research where more accurate proportion estimates for SpA patients are facilitated.

In conclusion, the pooled proportion of newly diagnosed axSpA and PsA patients visiting the rheumatology outpatient clinic were 19% and 18%, respectively. The proportion of axSpA increased by 18% after the introduction of the ASAS criteria. Due to the large heterogeneity between studies, this increase in proportion cannot be attributed with certain to the introduction of the ASAS criteria.

SUPPLEMENTARY MATERIAL

1. Supplementary Data S1; Search strategy (2022-11-01)

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('rheumatoid arthritis'/de OR 'spondylarthritis'/de OR 'psoriatic arthritis'/de OR 'ankylosing spondylitis'/de OR 'rheumatic disease'/de OR 'rheumatology'/de OR 'rheumatologist'/de OR (alibert-bazin OR beauvais-disease* OR ((arthrit* OR osteoarthrit*) NEAR/3 (deforman* OR inflammat* OR rheumat* OR vertebr* OR spina* OR psoria*)) OR rheumarthrit* OR spondylarthrit* OR spondyloarthrit* OR (ankylos* NEAR/3 spondylit*) OR (Rheumatic NEAR/3 (disease* OR disorder*)) OR rheumatolog* OR reumatolog* OR ((rheuma* OR arthralgi*) NEAR/3 specialist*)):ab,ti) AND ('incidence'/de OR 'prevalence'/de OR 'statistics'/de OR (incidence* OR prevalence* OR statistic* OR ((spectrum OR pattern* OR occurenc* OR frequenc* OR percent* OR proportion*) NEAR/6 (disease* OR inflammat*)) OR ((spectrum OR pattern* OR distribution) NEAR/3 patient*)):ab,ti) AND ('outpatient'/exp OR 'outpatient department'/exp OR 'secondary health care'/exp OR 'tertiary health care'/exp OR 'ambulatory care'/de OR 'patient referral'/de OR (outpatient* OR out-patient* OR ((secondar* OR tertiar* OR specialist OR public) NEAR/3 (care* OR healthcare OR hospital OR center* OR centre*)) OR ((rheumat* OR reumat* OR Arthrit*) NEAR/3 (clinic OR department* OR centre* OR center* OR institut* OR unit OR units)) OR ((rheumat* OR reumat* OR Arthrit*) NEXT/1 practice*) OR ambulator* OR referr*):ab,ti) NOT ([Conference Abstract]/lim OR [Letter]/lim OR [Note]/lim OR [Editorial]/lim) AND [english]/lim

Medline Ovid

(Arthritis, Rheumatoid/ OR Spondylarthritis/ OR Arthritis, Psoriatic/ OR Spondylitis, Ankylosing/ OR Rheumatic Diseases/ OR Rheumatology/ OR Rheumatologists/ OR (alibert-bazin OR beauvais-disease* OR ((arthrit* OR osteoarthrit*) ADJ3 (deforman* OR inflammat* OR rheumat* OR vertebr* OR spina* OR psoria*)) OR rheumarthrit* OR spondylarthrit* OR spondyloarthrit* OR (ankylos* ADJ3 spondylit*) OR (Rheumatic ADJ3 (disease* OR disorder*)) OR rheumatolog* OR reumatolog* OR ((rheuma* OR arthralgi*) ADJ3 specialist*)).ab,ti.) AND (incidence/ OR prevalence/ OR (incidence* OR prevalence* OR statistic* OR ((spectrum OR pattern* OR occurenc* OR frequenc* OR percent* OR proportion*) ADJ6 (disease* OR inflammat*)) OR ((spectrum OR pattern* OR distribution) ADJ3 patient*)).ab,ti.) AND (Outpatients/ OR Outpatient Clinics, Hospital/ OR Secondary Care/ OR Tertiary Healthcare/ OR Ambulatory Care/ OR " Referral and Consultation "/ OR (outpatient* OR outpatient* OR ((secondar* OR tertiar* OR specialist OR public) ADJ3 (care* OR healthcare OR hospital OR center* OR centre*)) OR ((rheumat* OR reumat* OR Arthrit*) ADJ3 (clinic OR department* OR centre* OR center* OR institut* OR unit OR units)) OR ((rheumat* OR reumat* OR Arthrit*) ADJ practice*) OR ambulator*

OR referr*).ab,ti.) NOT (letter* OR news OR comment* OR editorial* OR congres* OR abstract* OR book* OR chapter* OR dissertation abstract*).pt. AND english.la.

Cochrane CENTRAL
((alibert-bazin OR beauvais-disease* OR ((arthrit* OR osteoarthrit*) NEAR/3 (deforman* OR inflammat* OR rheumat* OR vertebr* OR spina* OR psoria*)) OR rheumarthrit* OR spondylarthrit* OR spondyloarthrit* OR (ankylos* NEAR/3 spondylit*) OR (Rheumatic NEAR/3 (disease* OR disorder*)) OR rheumatolog* OR reumatolog* OR ((rheuma* OR arthralgi*) NEAR/3 specialist*)):ab,ti) AND ((incidence* OR prevalence* OR statistic* OR ((spectrum OR pattern* OR occurenc* OR frequenc* OR percent* OR proportion*) NEAR/6 (disease* OR inflammat*)) OR ((spectrum OR pattern* OR distribution) NEAR/3 patient*)):ab,ti) AND ((outpatient* OR out-patient* OR ((secondar* OR tertiar* OR specialist OR public) NEAR/3 (care* OR healthcare OR hospital OR center* OR centre*)) OR ((rheumat* OR reumat* OR Arthrit*) NEAR/3 (clinic OR department* OR centre* OR center* OR institut* OR unit OR units)) OR ((rheumat* OR reumat* OR Arthrit*) NEXT/1 practice*) OR ambulator* OR referr*):ab,ti)

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TS=(((alibert-bazin OR beauvais-disease* OR ((arthrit* OR osteoarthrit*) NEAR/2 (deforman* OR inflammat* OR rheumat* OR vertebr* OR spina* OR psoria*)) OR rheumarthrit* OR spondylarthrit* OR spondyloarthrit* OR (ankylos* NEAR/2 spondylit*) OR (Rheumatic NEAR/2 (disease* OR disorder*)) OR rheumatolog* OR reumatolog* OR ((rheuma* OR arthralgi*) NEAR/2 specialist*))) AND ((incidence* OR prevalence* OR statistic* OR ((spectrum OR pattern* OR occurenc* OR frequenc* OR percent* OR proportion*) NEAR/5 (disease* OR inflammat*)) OR ((spectrum OR pattern* OR distribution) NEAR/2 patient*))) AND ((outpatient* OR out-patient* OR ((secondar* OR tertiar* OR specialist OR public) NEAR/2 (care* OR healthcare OR hospital OR center* OR centre*)) OR ((rheumat* OR reumat* OR Arthrit*) NEAR/2 (clinic OR department* OR centre* OR center* OR institut* OR unit OR units)) OR ((rheumat* OR reumat* OR Arthrit*) NEAR/1 practice*) OR ambulator* OR referr*))) AND DT=(article) AND LA=(english)

Google scholar
Rheumatologist|reumatologist|"rheumatology|arthralgia specialist |specialists"incidence|prevalence|statistics|spectrum|pattern|frequency
inflammation|inflammatoryoutpatient|"secondary|tertiary|specialist
care|healthcare|hospital|center|centre"

2. Supplementary Table S2; Risk of bias assessment instructions

		YES	NO
1.	Was the sample representative of the target population?	The sample was representative of the target population. Selected patients are representative of a population of patients suspected of RA. No pre-selection took place in selecting the patients based on for example work. The center from which the RA patients were recruited should me mentioned	Sample was not representative.
2.	Were study participants recruited in an appropriate way?	Patients were recruited from an appropriate source and were "randomly" invited for the study (all patients OR consecutive patients OR random patients)	Patients were not recruited from an appropriate source and no random selection was used to recruit patients
3.	Was the sample size adequate / Was sample size calculation performed?	Sample size calculation was performed and it was reported if this target was reached	No sample size calculation
4.	Was the data analysis conducted with sufficient coverage of the identified sample?	Non-response was described **AND** a comparison between the responders and non-responders was performed. If retrospective design, answer is yes	No information about response percentages was given or no comparison between responders and non-responders was made.
5.	Were objective, standard criteria used for the measurement of the condition?	Criteria were used for the diagnosis of RA (for example ACR or EULAR criteria) OR A detailed description of how a case of RA was defined is included in the manuscript. OR In case of use of ICD codes, a validation/check was performed	No criteria were used and no description of how a case was defined is included in the manuscript.
6.	Was the condition measured reliably?	Outcome assessor was qualified to use the case definition criteria (for example; medical specialist, trained research nurse)	Outcome assessor was not qualified to use the case definition criteria or it was not mentioned who defined a case.

3. Supplementary Table S3; Overview of assessment of methodological quality

	Representative sample (selection bias)	Random recruitment (selection bias)	Sample size calculation (non-rsponse bias)	Description of non-response (nonresponse bias)	Objective case definition (measurement bias)	Qualified outcome assessor (measurement bias)
Toloza, 2012	−	+	−	−	+	+
Estebaránz, 2014	−	+	−	−	+	+
Chimenti, 2019	+	+	−	−	+	+
Marco, 2012	−	+	−	−	+	−
Spelman, 2015	+	+	−	+	+	+
Urbancek, 2016	+	+	−	−	+	+
Elnady, 2019	+	+	−	−	+	+
Socio, 2017	+	+	−	−	+	+
Reich, 2008	+	+	−	+	+	+
Haroon, 2012	+	+	−	−	+	−
Bonifiati, 2009	−	+	−	−	+	+
Holden, 1982	+	+	−	−	−	−
Mijiyawa, 2000	+	+	−	+	+	−

Hermann, 2009						
Bitik, 2015						
Caines, 2012						
Deodhar, 2016						
Hočevar , 2019						
Moghimi, 2016						
Fonseca, 2018						
Jamal, 2020						
Sieper, 2012						
Poddunyy, 2011						
Tant, 2017						
Baraliakos, 2020						
Proft, 2020						
Passalent, 2022						
Kiil, 2021						
Cui, 2022						

Sarabia, 2022						
Felbo, 2021						
Liyanage, 2021						
Hal, 2022						

 Low risk of bias  High risk of bias

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Chapter 4

Impact of musculoskeletal joint complaints on quality of life in patients with inflammatory bowel disease

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ABSTRACT

Background: Musculoskeletal joint complaints (MSC) are the most common extra-intestinal manifestation of inflammatory bowel disease (IBD). We aimed to investigate the effect of MSC on the health-related quality of life (QoL) in patients with IBD.

Design: A survey-based cross-sectional study among adult Dutch IBD patients.
Setting: Primary care, secondary care, and patient association.
Participants: In total, 635 IBD patients were included. The mean age was 46.3 (SD 14.2) years, and 35% were male.
Outcome: MSC was defined as suffering from any joint complaints. QoL was measured using the Inflammatory Bowel Disease Questionnaire (IBDQ) and a 36-item Short Form Health Survey questionnaire.

Methods: A univariate analysis was performed to estimate the impact of various factors such as demographic characteristics, setting, type of IBD and fatigue, which was followed by a multiple regression analysis to adjust for the confounding factors.

Results: Of the 635 IBD patients, 332 suffered from crohn's disease (CD) and 303 from ulcerative colitis (UC). After adjusting for confounding factors, MSC was independently associated with reduced QoL among IBD patients (β = -10.6, 95%CI: -15.2--6.1), both in CD (β = -8.3, 95%CI: -14.6--2.1) and UC (β = -13.9, 95%CI: -20.5--7.3). Eleven percent of the IBD patients had a rheumatological diagnosis. QoL in these patients was significantly lower compared to IBD patients with non-rheumatological MSC.

Conclusions: IBD patients with MSC are associated with a lower QoL, explicitly in patients with a rheumatological diagnosis. Prospective research is necessary to evaluate the causality and suitable interventions to increase QoL in these multimorbid patients.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a collective term given to multiple chronic inflammatory diseases of the digestive tract, such as crohn's disease (CD) and ulcerative colitis (UC). Worldwide, 6.8 million IBD cases were identified in the year 2017 [1]. In the Netherlands, the prevalence of IBD is estimated to be 432 per 100,000 patients [2]. Musculoskeletal complaints (MSC) are the most common extra-intestinal manifestation and can, in up to 30% of IBD patients, be explained by the rheumatologic diagnosis spondyloarthritis (SpA) [3-5]. Timely detection of SpA within IBD is important as early treatment, can reduce the burden of the disease.
In both IBD and SpA, the burden of disease is high, which is expressed by a lower quality of life (QoL) [6,7]. QoL is an important health outcome to monitor in patients with IBD and SpA as recommended by the International Consortium for Health Outcomes Measurement (ICHOM) [8,9]. However, it is less known whether the QoL of IBD patients is affected by SpA itself or via MSC since this disorder also negatively affects QoL [10]. As approximately 70% of all IBD patients with MSC do not develop SpA, we therefore aimed to investigate the impact of MSC with and without SpA on QoL in patients with IBD.

METHODS

Study design, participants and settings

We used existing data from the AppSpA study (primary care and patient association population) and a cross-sectional study performed in secondary care hospital to evaluate QoL in IBD patients. This enabled the integration of different care settings and avoided duplicate data generating efforts. A survey-based cross-sectional design was performed on Dutch IBD patients aged ≥ 18 years from secondary care, primary care, and the national IBD patient association (Crohn & Colitis Ulcerosa NL). Patients with IBD from secondary care who were under routine control by the gastroenterologist at the Maasstad Hospital, a large trainee hospital in Rotterdam, the Netherlands, were invited to participate. Patients were selected from the electronic patient file system based on having a CU or CD. Thereafter, all IBD patients received a letter explaining the purpose of the study, informed consent, and a set of questionnaires by mail. Patients were included from March 2013 until August 2013.
To explore the relation between MSC and QoL, not only in more complex secondary care IBD patients, we additionally included patients from the AppSpA study [11], which recruited IBD patients from primary care and patient association in almost the same period. This study was approved by the medical ethical committee of the Erasmus University Medical Center (MEC-2014-269). All patients signed an informant consent when they agreed to participate.

The AppSpA study was designed to gain insight into GPs' knowledge about early recognition of SpA and to create more awareness for SpA. Between December 2014 and August 2015, 81 general practitioners (GPs) from the Southwest of the Netherlands were recruited to participate in the AppSpA study. GPs selected all IBD patients aged 18 to 55 years from their databases using ICPC code D94 (International Classification of Primary Care code for IBD, including CD, UC, and undifferentiated IBD). ICPC is the standard for coding and classification of signs and symptoms in general practice in the Netherlands [12].
Patients from patient association were invited to participate by e-mail.

Characteristics of study population

Demographic data for all settings were patient-reported and included age, gender, diagnosis (CD or UC), disease duration, bowel surgery (yes/no), working status (employed, non-employed, and retired), education (low; ≥12 years, intermediate; professional education, and high; bachelor's or master's degree), rheumatological diagnoses (reflects any kind of rheumatological condition), and medications (IBD and non-IBD).

Measures

Musculoskeletal complaints

MSC complaints were defined as suffering from any joint complaints. Patients recruited from secondary care were asked if they suffered from joint complaints (yes or no), while this data was extracted from the arthralgia questionnaire (Table S1) for patients recruited from the AppSpA study, which included patients from primary care and patient association. Data on rheumatology visits was available for patients in the AppSpA study. Patients were asked if they visited the rheumatologist, and if so which diagnosis was made.

Health related quality of life questionnaires

Short form-36 (SF-36)

The SF-36 is a 36-item, patient-reported survey of patient health with high validity and reliability [13]. It consists of eight domains: Vitality, physical functioning, bodily pain, general health perception, physical role functioning, emotional role functioning, social role functioning, and mental health. The scales are individually made into a 0–100-point scale. A higher score indicates a higher QoL. The score on all eight separate domains was compared with the scores of the reference population in the Netherlands [14]. Patients from the AppSpA study (primary care and patient association) filled out the SF-36v1, whereas patients from secondary care filled out the SF-

36v2. It has been demonstrated that the norm-based scores of the SF-36v2 and SF-36v1 versions are comparable [15]. To evaluate whether the difference in SF-36 domains between patients with MSC and patients without MSC is clinically relevant, values for the minimal clinically important difference from Coteur et al. were used [16]. These values ranged from 3.4 to 8.9 for different domains and were obtained using distribution-based estimates.

Inflammatory Bowel Disease Questionnaire (IBDQ)

Both the AppSpA study and secondary care study used IBDQ. The IBDQ is a widely used questionnaire for quality of life assessments in patients with IBD [17,18]. The IBDQ consists of 32 questions and can be divided into four domains: Bowel fatigue (10 questions, score 0-70), systemic fatigue (5 questions, score 0-35), social function (5 questions, score 0-35), and emotional function (12 questions, score 0-84). The answers to the questions range from 1 (worst) to 7 (best). A total score can be calculated as the sum of all 32 items (with a total score range between 0 and 224). The higher the score, the better the QoL. For IBDQ, a clinically meaningful difference was estimated at 16 points [19].

Statistical analysis

The baseline characteristics of all patients were described using simple descriptive statistics and were stratified by setting and type IBD. Patients who had missing items responses on the IBDQ or SF-36 questionnaire were not included in the analysis. As data on disease activity were not available, we used IBD medications as a proxy. This is a useful alternative in adult non-elderly patients.

To investigate whether the impact of MSC on QoL differs among patients with CD and UC, QoL (IBDQ) was assessed in these patient groups separately. To validate the results, the same analysis was performed using the SF-36 questionnaire as a QoL measure.

A linear regression analysis (adjusted for setting) was used to estimate the association of each variable, i.e., MSC, age, gender, type of IBD, disease duration, education, working status, medications (IBD and non-IBD) and fatigue, with IBDQ scores. Variables were chosen based on available literature [20,21]. Then, variables that were statistically significant were added as a covariate and adjusted for in the multiple regression analysis. The results are presented as beta estimates with 95% confidence intervals (CI). The adjusted R-square was extracted from the model. Statistical analysis was performed using STATA (version 15.2). A p-value < 0.05 was considered statistically significant.

Patient and public involvement

There was no direct involvement of patients and the public in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Participants

In total, 6807 patients were invited: 872 from secondary care, 535 from primary care, and 5400 from patient association (Figure 1). Of the 872 invited IBD patients in secondary care, 391 agreed to participate (44.8%). Of those, 32 patients (8%) were excluded for returning the questionnaires without signing the informed consent. Nineteen patients (5%) were excluded on the grounds of disease other than IBD (irritable bowel syndrome and unclassified colitis) or due to follow-up with their general practitioner. Finally, 340 secondary care IBD patients were included. From the 535 primary care patients selected by the GP, 215 (40%) were willing to participate, of whom finally 194 patients (36%) were included. Via the patient association, from the 5400 patients invited, another 110 (2%) IBD patients wanted to participate, of whom finally 101 (2%) were included.

Characteristics study population

Table 1 shows the characteristics of all 635 included IBD patients, with a mean age of 46.3 (SD 14.2) years and n = 225 (35%) being male. In 11% of the IBD patients, rheumatological diagnoses were present.

Among the total 635 patients 332 (52%) patients suffered from CD, and 303 (48%) patients suffered from UC. Patients differed significantly in characteristics between settings and types.

Musculoskeletal complaints

MSC was present in 56% of the patients with IBD. The demographic characteristics of the patients with or without MSC are presented in Table S2. The percentage of patients with MSC was significantly higher in CD (62%) compared with UC (50%) (p-value = 0.002). Characteristics of patients with CD were comparable between patients with and without MSC, except that MSC was more prevalent among males. In UC, patients with MSC were older and less educated compared to patients with no MSC.

Figure 1. Flow chart of patients with inflammatory bowel disease (IBD) included from secondary care (a), primary care (b), patient association (c). CD, crohn's disease. UC, ulcerative colitis.

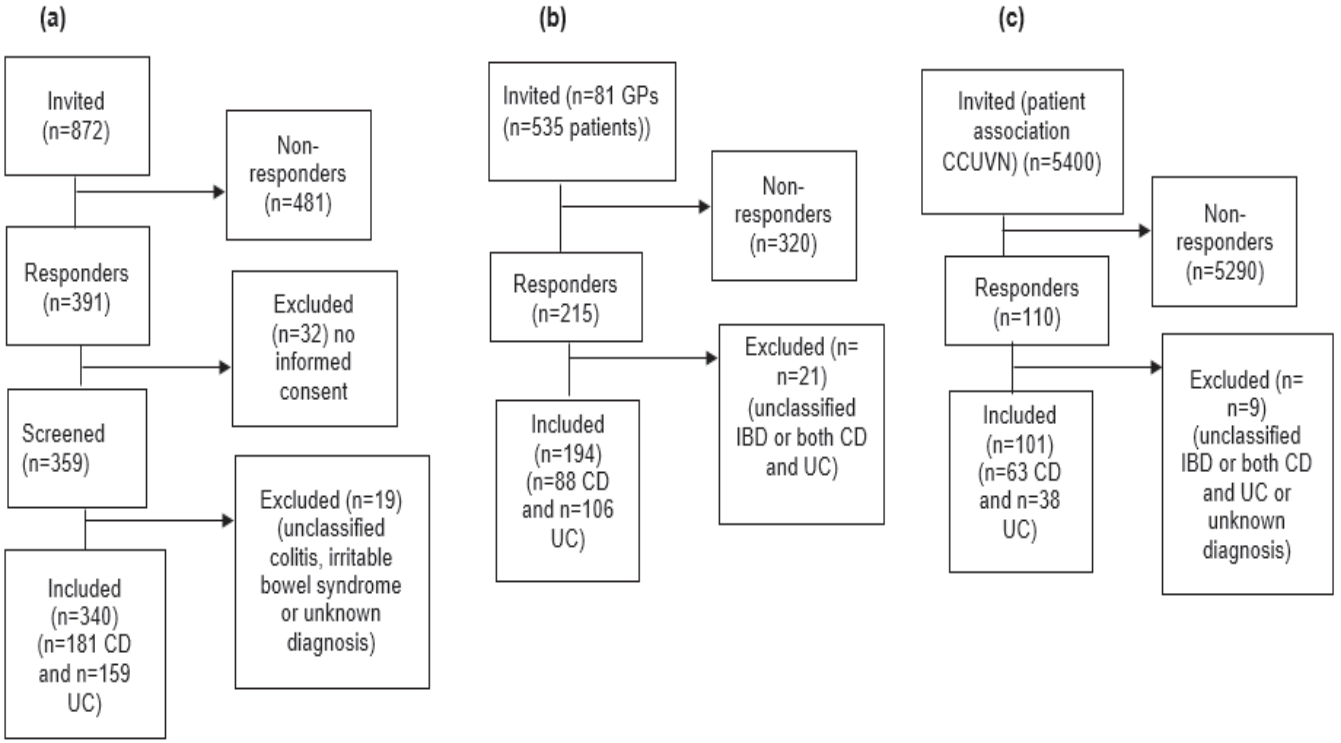


Table 1. Baseline characteristics.

	All IBD	Primary care	Patient association	Secondary care	P-value	Crohn's disease	Ulcerative colitis	P-value
	n=635	n=194 (31%)	n=101 (16%)	n=340 (53%)		n=332 (52.3%)	n=303 (47.7%)	
Age (years), mean (SD)	46.3 (14.2)	42.4 (9.5)	41.9 (9.2)	49.8 (16.6)	<0.001	45.1 (14.1)	47.6 (14.3)	0.028
Male gender,n (%)	225 (35.4)	56 (28.9)	19 (18.8)	150 (44.1)	<0.001	225 (35.4)	410 (64.6)	0.009
Disease duration (years), n (%)					0.043			0.266
Short (0-2)	113 (17.8)	37 (19.1)	8 (7.9)	68 (20.0)		55 (16.6)	58 (19.1)	
Intermediate (3-10)	203 (32.0)	55 (28.4)	40 (39.6)	108 (31.8)		100 (30.1)	103 (34.0)	
Long (>10)	319 (50.2)	102 (52.6)	53 (52.5)	164 (48.2)		177 (53.3)	142 (46.9)	
Bowel surgery, n (%)	158 (24.9)	53 (27.3)	35 (34.7)	70 (20.6)	0.010	134 (40.4)	24 (7.9)	<0.001
Reumatological diagnoses, n (%)*	33/295 (11.2%)	15 (7.7%)	18 (17.8%)	NA	0.008	23/151* (15.2)	10/144 * (6.9)	0.025
Work status, n (%)					<0.001			0.613
Non-employed	154 (25.2)	41 (22.2)	34 (34)	79 (24.2)		83 (25.9)	71 (24.4)	
Employed	434 (71.0)	144 (77.8)	66 (66)	224 (68.7)		223 (69.7)	211 (72.5)	
Retired	23 (3.8)	NA	NA	23 (7.1)		14 (4.4)	9 (3.1)	

	All IBD	Primary care	Patient association	Secondary care	P-value	Crohn's disease	Ulcerative colitis	P-value
	n=635	n=194 (31%)	n=101 (16%)	n=340 (53%)		n=332 (52.3%)	n=303 (47.7%)	
Level of education, n (%)					<0.001			0.424
Low	187 (29.9)	46 (24.7)	6 (6)	135 (39.8)		92 (28.2)	95 (31.8)	
Intermediate	246 (39.4)	77 (41.4)	48 (48)	121 (36.7)		136 (41.7)	110 (36.8)	
High	192 (30.7)	63 (33.9)	46 (46)	83 (24.5)		98 (30.1)	94 (31.4)	
Medication IBD, n (%)					<0.001			<0.001
None	126 (19.8)	58 (29.9)	16 (15.8)	52 (15.3)		68 (20.5)	58 (19.1)	
Mesalazine	214 (33.7)	65 (33.5)	34 (33.7)	115 (33.8)		52 (15.7)	162 (53.5)	
Corticosteroids	88 (13.9)	14 (7.2)	13 (12.9)	61 (17.9)		55 (16.6)	33 (10.9)	
Immunosuppressants	178 (28.0)	52 (26.8)	33 (32.7)	93 (27.4)		115 (34.6)	63 (20.8)	
Anti-TNF	104 (16.4)	29 (15.0)	25 (24.8)	50 (14.7)		72 (21.7)	32 (10.6)	
Other (non-IBD)	73 (11.5)	30 (15.5)	18 (17.8)	25 (7.3)		46 (13.9)		

*Data only available for primary care and patient association. TNF, tumor necrosis factor.

Quality of life

Table 2 shows QoL as measured by IBDQ. In total, 623 out of 635 patients were analyzed, as 12 patients had missing outcomes on IBDQ. The mean IBDQ score, bowel symptoms, systemic symptoms, and social and emotional function were significantly lower in patients with MSC in both CD and UC.

Figure 2a shows that the SF-36 was significantly lower on every domain between IBD patients with and without MSC. A minimal clinically important difference was reached for all domains except for the emotional role limitation and the mental health domain.

Patients with no MSC experienced lower QoL in most domains when compared to the Dutch reference population (Figure 2a). Figure 2b/c shows QoL

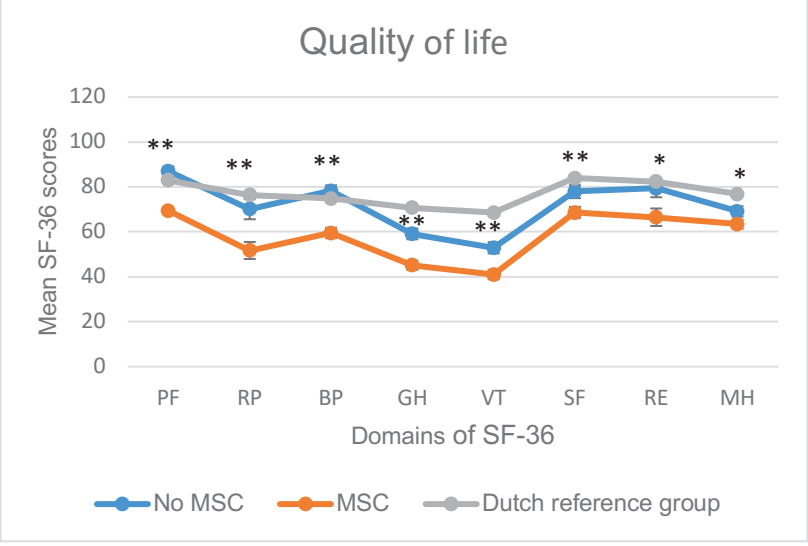
Table 2. Mean scores of the IBDQ questionnaire among crohn's disease and ulcerative colitis patients with and without musculoskeletal complaints.

	Crohn's disease			**Ulcerative colitis**		
	MSC n=203 (62.9%)	No MSC n=120 (37.2%)	P-value	MSC n=147 (49.7%)	No MSC n=149 (50.3%)	P-value
Total score IBD	144.8 (32.4)	155.9 (31.0)	0.003	150.2 (6.3)	169.0 (29.9)	<0.001
Bowel symptoms	46.4 (10.2)	49.6 (10.1)	0.008	48.3 (11.7)	52.6 (10.1)	0.001
Systemic symptoms	18.2 (6.1)	21.4 (6.5)	<0.001	19.5 (6.2)	24.0 (5.6)	<0.001
Social function	24.8 (7.1)	26.5 (6.0)	0.023	26.7 (7.7)	29.4 (5.2)	<0.001
Emotional function	51.6 (12.4)	54.4 (11.2)	0.040	52.0 (13.5)	58.7 (11.4)	<0.001

Variables are presented as means (standard deviation). MSC, musculoskeletal complaints.

measured with the SF-36 questionnaire for subtypes of IBD with and without MSC. Patients with CD and MSC had lower QoL in all domains (p-value < 0.05) except for the mental health domain (Figure 2b). A minimal clinically important difference was reached for the domains of physical functioning, bodily pain, and general health perception. Figure 2c shows that UC patients with MSC scored lower on all SF-36 domains (p-value < 0.05) compared to patients without MSC. A minimal clinically important difference was reached for all domains except emotional role functioning, despite the observed statistical difference.

Figure 2. Mean scores of the SF-36 questionnaire in IBD with/without musculoskeletal joint complaints (MSC) and the Dutch reference population (2a), Crohn's disease (CD) with/without MSC (2b), and Ulcerative colitis (UC) with/without MSC (2c). Error bars indicate the 95% CI. PF, physical function; RP, physical role limitation; BP, bodily pain; GH, general health; VT, vitality; SF, social function; RE, emotional role limitation; MH, mental health). *P-value<0.05. **Minimal clinical important difference.



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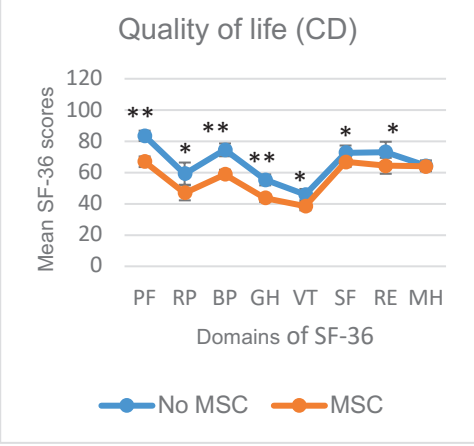

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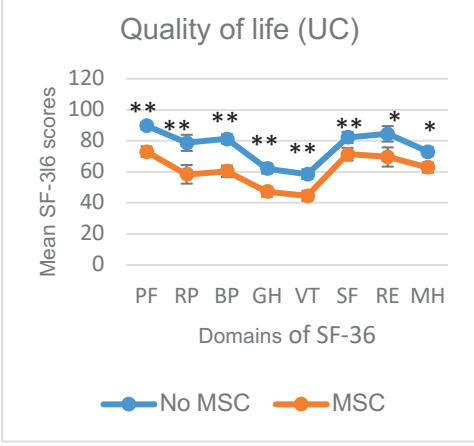


2c

Table 3. Results of the multivariable analysis with the IBDQ score as the dependent factor and all variables that were significant in the univariate analyses as independent factors (adjusted for setting) for all IBD patients and patients with crohn's disease and ulcerative colitis.

	All IBD			Crohn's disease			Ulcerative colitis		
	β	95% CI	P-value	β	95% CI	P-value	β	95% CI	P-value
MSC	-10.5	-15.0--6.0	<0.001	-8.3	-14.6--2.1	0.009	-13.9	-20.5--7.3	<0.001
Age in years	0.28	0.09-0.46	0.003	0.34	0.09-0.60	0.008	0.20	-0.07-0.47	0.149
Gender (female)	-4.6	-9.2--0.06	0.047	-6.0	-12.5-0.57	0.073	-3.5	-9.9-3.0	0.291
Type of IBD (UC)	2.3	-2.3-6.9	0.320	NA	NA	NA	NA	NA	NA
Fatigue	-27.5	-33.6--21.4	<0.001	-29.4	-39.2--19.6	<0.001	-24.4	-32.2--16.5	<0.001
Medications									
Mesalazine	3.4	-1.4-8.2	0.164	1.2	-6.9-9.3	0.767	4.2	-1.9-10.3	0.178
Corticosteroids	-5.3	-11.3-0.75	0.086	-1.8	-9.8-6.1	0.648	-11.4	-20.9--2.1	0.017
Other (non-IBD)	-7.9	-14.3--1.4	<0.001	-5.0	-13.4-3.4	0.247	-10.8	-21.2--0.55	0.039
Employment									
Employed	9.6	4.5-14.7	<0.001	8.1	1.0-15.3	0.026	9.1	1.6-16.6	0.017
Retired	10.6	-2.11-23.2	0.102	12.2	-3.8-28.2	0.135	1.3	-20.6-23.2	0.906
Education									
Intermediate	4.3	-1.4-9.9	0.137	9.5	1.5-17.5	0.020	-3.7	-12.0-4.6	0.385
High	6.8	0.63-13.0	0.031	10.6	1.7-19.5	0.020	1.7	-7.1-10.5	0.707

β, beta-coefficient. NA, not applicable. MSC, musculoskeletal complaints. UC, unlcerative colitis.

Additional analysis was performed in IBD patients with rheumatological diagnosis. Patients with rheumatological diagnosis had a mean score of 153.2 (SD 29.6), whereas patients with MSC and no rheumatological diagnoses had a mean total IBDQ score of 164.3 (SD 27.0). The mean difference in QoL between both groups was statistically significant (p = 0.037). However, clinical relevance was inconclusive.

Adjusted analysis

The univariate analysis (adjusted for setting) showed that MSC was associated with a statistically significant and clinically meaningful decrease in QoL (β = -17.9, 95% CI: -22.6- -13.1). Fatigue, corticosteroid use, and other non-IBD specific medications were associated with reduced QoL, whereas age, higher education, employment, disease type UC, and mesalazine use were positively associated with QoL. Disease duration was not associated with QoL (Table S3).

After adjusting for significant factors from the univariate analysis, MSC (β = -10.5 (95%CI: -15.2- -6.1) remained statistically significant (Table 3).

Similar results were found for patients with CD (β = -8.3 (95%CI: -14.6- -2.1) and UC (β = -13.9 (95%CI: -20.5- -7.3). Twenty-six percent of the variation in IBDQ was explained by MSC, whereas in total, 42% of the variation was explained by MSC, age, gender, fatigue, education, work status, type of IBD, and medications.

DISCUSSION

Our study shows that MSC had an independent reduced effect on QoL irrespective of type IBD patients or setting. This was demonstrated by both the SF-36 and IBD questionnaires. Both the physical and mental domains of the SF-36 was affected in patients with MSC compared to patients without MSC. Eleven percent of the IBD patients received rheumatological diagnoses and QoL in these patients were lower compared to IBD patients with MSC.

Several studies have been performed to evaluate QoL in patients with IBD. However, most studies do not make the distinction between IBD with and without MSC nor for different setting. A study from the Netherlands reported an arthropathy prevalence of 60.1% in IBD patients [22], and demonstrated that MSC has a negative impact on the QoL of IBD patients, which is comparable to our study findings. The added value of our study in comparison to the study by van der Have *et al.* is that we investigated and controlled for a broader set of factors such as age, level of education, work status and type of IBD that may impact the QoL or MSC of IBD patients. In addition, we analyzed its impact by setting.

Palm et al. reported a low prevalence (16%) of non-inflammatory joint pain although they only analyzed non-inflammatory joint pain among IBD patients who had a shorter disease duration than our study population. Their study reported reduced SF-36 and IBDQ scores [23]. Within the same cohort, after a follow-up of twenty years, 40% arthralgia of was reported, which was associated with poorer QoL [24]. Unlike our study SpA was not associated with poor QoL. Both studies did not include other disturbing factors that are important in the relation between MSC and QoL such as work status and education.

Rheumatological diagnosis among IBD patients was reported by the study of van Erp *et al.* [25]. Similar to our study rheumatological diagnosis were made in 12% of the IBD patients.
In this study, only one case of osteoarthritis was reported. Presumably as the inclusion criteria for patients from primary care and patient association were <45 years and the average age of our study population in all setting was <50 years.
The present study has several strengths: First, our study evaluated the relation between MSC and QoL in several settings. The added value of including patients from a primary care setting is important in evaluating the impact of MSC in IBD patients, because based on results this patient population also suffer from MSC associated with a reduced QoL. Therefore, extra attention should be paid for MSC by the GP. Second, we included both the SF36 and IBDQ to evaluate QoL. Therefore, we were able to confirm the impact of MSC on QoL on both the generic and disease specific questionnaires. This may have impact for its use in daily care. Third, this is the first study that investigated multimorbidity in relation to QoL in different settings. This study indicates that assessing the effect of morbidities and setting is crucial for the interpretation of outcomes on QoL.
Finally, we had a large sample size where the degree of missing data was minor, resulting in a patient exclusion rate of less than two percent. Moreover, we selected IBD patients from various GP databases, resulting in an adequate representation of the general IBD population from various regions of the Netherlands, which may have increased the accuracy of our data.
This study also has some limitations. First, we performed a cross-sectional study, which limited the interpretation of a causal relation between MSC and QoL. However, since other studies show the same associations, our findings do underline the need for MSC management of IBD patients in both primary and secondary care. Second, we could not verify whether primary care and patient association were seen by secondary care specialist therefore the impact of MSC on QoL might have been an underestimation. Third, information on IBD disease activity was not available. Therefore, we could not investigate whether disease activity is a confounding variable in the relationship between MSC and QoL. However, as in previous studies, medications were used as a proxy for disease activity [26,27] for which we controlled for in the analyses. We believe that in adult non-elderly patients, as in our study population, the use of medication as a proxy for disease activity is a useful alternative. However, in elderly patients, this could be misleading due to polypharmacy and multimorbidities [27]. Fourth, data on comorbidities other than rheumatological diagnosis was not collected explicitly. However, this was controlled for in the analysis by adjusting for non-IBD medication use. Finely, although we did not performed sample size calculation however, our sample size was large and representative of the population, which makes our findings valuable.

CONCLUSIONS

MSC has a significant independent negative impact on the QoL of patients irrespective of type of IBD or setting. This was most obvious in patients having both IBD and a rheumatological disease. This might have clinical consequences for the gastroenterologists, GPs and rheumatologists. We therefore recommend routinely administering a questionnaire investigating MSC such as the one used by van Erp *et al.* [25] prior or during hospital or GP visit, as this is currently often not performed in clinical practice In addition, we suggest to incorporate referral strategies in international guidelines for gastroenterologists, and GPs for patients at risk for inflammatory rheumatic diseases.

SUPPLEMENTARY MATERIAL

Table S1. Musculoskeletal complaints among patients with crohn's disease and ulcerative colitis.

	Crohn's disease			Ulcerative colitis		
	MSC n=204 (62.4%)	No MSC n=123 (37.6%)	P-value	MSC n=150 (49.8%)	No MSC n=151 (50.2%)	P-value
Age (years), mean (SD)	45.5 (12.7)	44.3 (16.0)	0.453	50.1 (14.7)	45.1 (13.5)	0.002
Male gender, n (%)	150 (73.5)	76 (61.8)	0.026	91 (60.7)	88 (58.3)	0.673
Disease duration (years), n (%)						
Short (0-2)	35 (17.2)	20 (16.3)	0.834	32 (21.3)	26 (17.2)	0.365
Intermediate (3-10)	57 (27.9)	41 (33.3)	0.303	51 (34.0)	52 (34.4)	0.936
Long (>10)	112 (54.9)	62 (50.4)	0.430	67 (44.7)	73 (48.3)	0.522
Work status, n (%)						
Non-employed	62 (31.2)	21 (17.4)	0.006	45 (30.6)	26 (18.1)	0.013
Employed	131 (65.8)	92 (76.0)	0.054	96 (65.3)	115 (79.9)	0.005
Retired	6 (3.0)	8 (6.6)	0.127	6 (4.1)	3 (2.1)	0.351
Level of education, n (%)						
Low	60 (29.6)	31 (25.4)	0.420	57 (38.0)	38 (25.5)	0.020
Intermediate	87 (42.9)	49 (40.2)	0.634	56 (37.3)	54 (36.2)	0.845
High	56 (27.6)	42 (34.4)	0.193	37 (24.7)	57 (38.3)	0.011
Medication IBD, n (%)						
None	40 (19.6)	27 (22.0)	0.611	31 (20.7)	26 (17.2)	0.445
Mesalazine	34 (16.7)	17(13.8)	0.492	79 (52.7)	82 (54.3)	0.776
Corticosteroids	36 (17.7)	18 (14.6)	0.477	18 (12.0)	15 (9.9)	0.566
Immunosuppressants	64 (31.4)	48 (39.0)	0.158	29 (19.3)	34 (22.5)	0.497
Anti-TNF	44 (21.6)	27 (22.0)	0.935	16 (10.7)	16 (10.6)	0.984
Other (non-IBD)	32 (15.7)	14 (11.4)	0.278	13 (8.7)	14 (9.3)	0.854

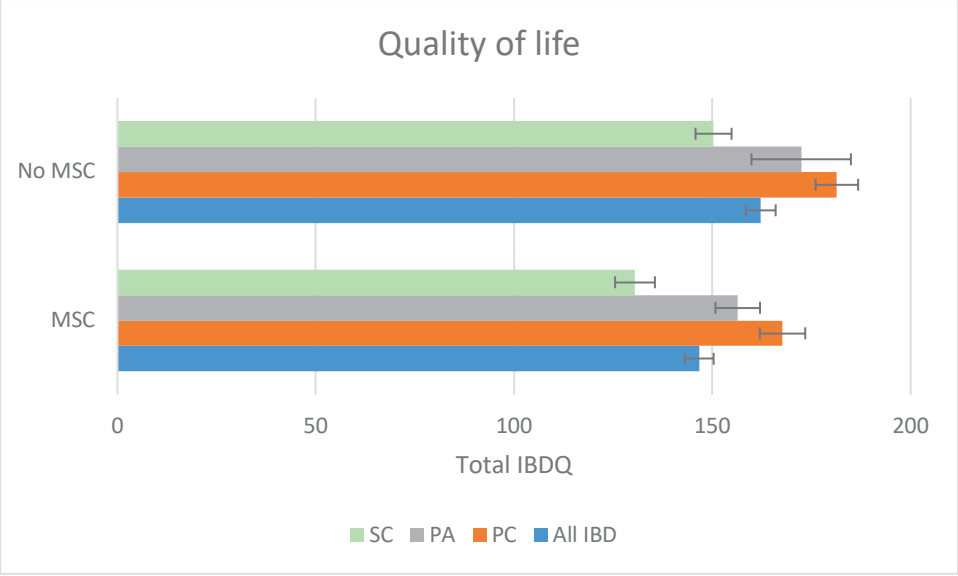
MSC, Musculoskeletal complaints. TNF, tumor necrosis factor.

Table S2. Results of the univariate analysis between the IBDQ and variables analyzed (adjusted for setting).

	β	95% CI	P-value
Musculoskeletal joint complaints	-17.9	-22.6--13.1	<0.001
IBD duration in years	0.197	-0.037-0.430	0.099
Age in years	0.25	0.076-0.428	0.005
Gender (female)	-12.2	-17.2--7.2	<0.001
Type of IBD (ulcerative colitis)	9.0	4.2-13.7	<0.001
Fatigue	-35.6	-41.6--29.6	<0.001
Employment			
Employment (yes)	14.2	8.8-19.7	<0.001
Retired (yes)	24.9	11.3-38.5	<0.001
Education			
Education (intermediate)	2.95	-3.0-9.9	0.329
Education (high)	10.0	3.7-16.3	0.002
Medications			
None	3.9	-2.2-10.1	0.207
Mesalazine	9.6	4.7-14.6	<0.001
Corticosteroids	-9.4	-16.2--2.5	0.008
Immunosuppressants	-0.74	-6.0-4.5	0.784
Anti-TNF	-3.7	-10.1-2.72	0.261
Other (non-IBD)	-12.8	-20.3--5.4	0.001

β, beta- coefiecient. TNF, tumor necrosis factor.

Figure S1. Mean scores of the total IBDQ score among IBD with/without MSC stratified by setting. Error bars indicate the 95% CI. SC, secondary care. PA, patient association. PC, primary care. Error bars indicate the 95% CI. Within all settings a statistical significant difference was present between MSC and no MSC ($p<0.05$). Within settings minimally clinically important difference was reached between MSC and no MSC except for primary care which was inconclusive.



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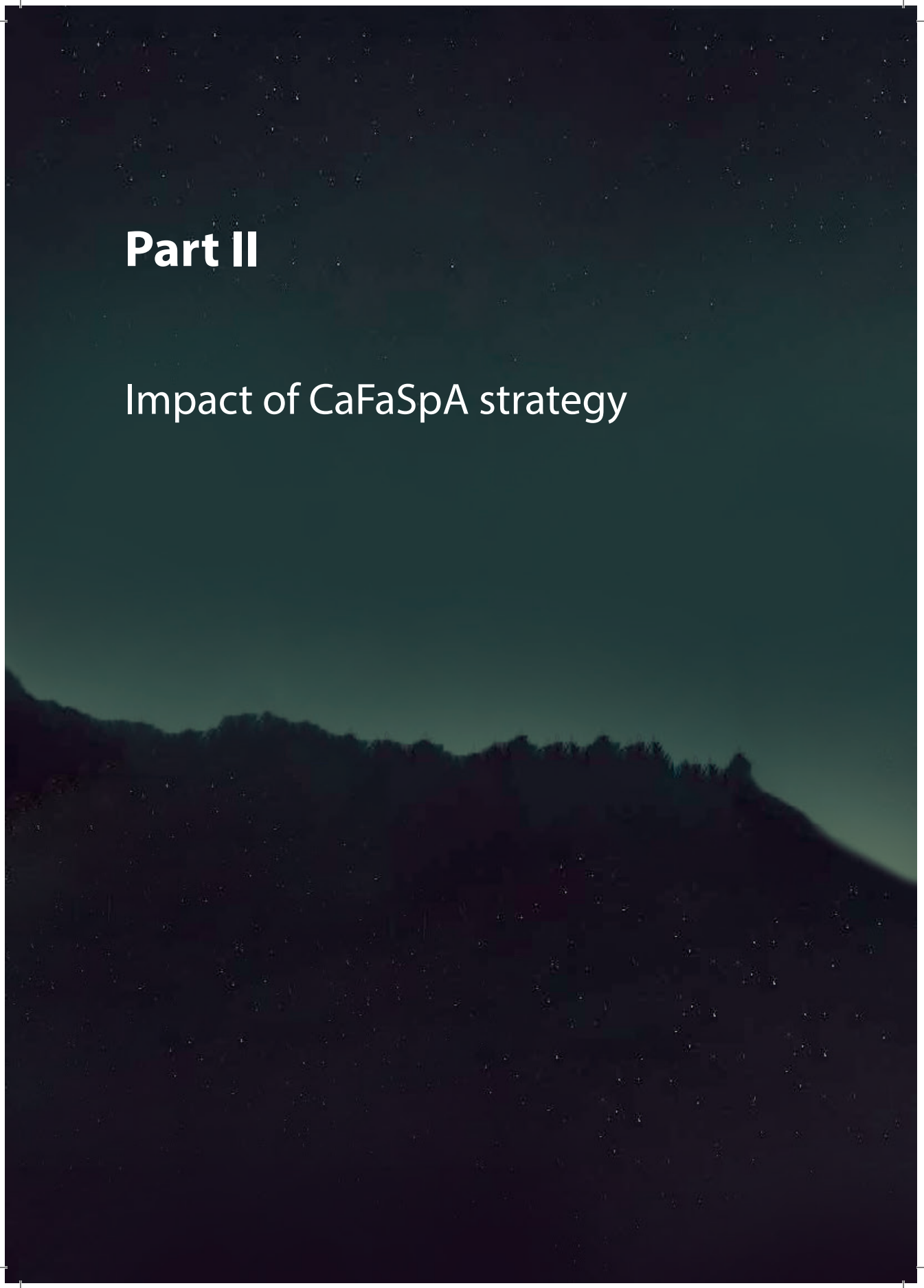

Part II

Impact of CaFaSpA strategy

Chapter 5

The IMPACT study: A clustered randomized controlled trial to assess the effect of a referral algorithm for axial spondyloarthritis

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ABSTRACT

Background: A substantial number of patients with chronic low back pain (CLBP) have axial spondyloarthritis (axSpA), but early recognition of these patients is difficult for general practitioners (GPs). The Case Finding Axial Spondyloarthritis (CaFaSpA) referral strategy has shown to be able to identify patients with CLBP at risk for axSpA, but its impact on clinical daily practice is yet unknown.

Objective: To assess the effect of the CaFaSpA referral strategy on pain caused by disability in primary care patients with CLBP.

Methods: Within this clustered randomized controlled trial 93 general practices were randomized to either the CaFaSpA referral model (intervention) or usual primary care (control). In each group primary care patients between 18 and 45 years with CLBP were included.
The primary outcome was disability caused by CLBP, measured with the Roland Morris Disability Questionnaire (RMDQ) at baseline and four months. Secondary outcome was the frequency of new axSpA diagnosis. Descriptive analyses were performed, and a linear mixed-effects model was used.

Results: In total 679 CLBP patients were included of which 333 patients were allocated to the intervention group and 346 to the control group. Sixty-four percent were female and mean age was 36.2 years. The mean RMDQ score at baseline was 8.39 in the intervention group and 8.61 in the control group. At four months mean RMDQ score was 7.65 in the intervention group and 8.15 in the control group. This difference was not statistically significant (p=0.50). Six (8%) out of the 75 finally referred patients, were diagnosed with axSpA by their rheumatologist.

Conclusions: The CaFaSpA referral strategy for axSpA did not have an effect on disability after four months caused by CLBP. However, the strategy is able to detect the axSpA patient within the large CLBP population sufficiently.

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic disabling rheumatic disease for which the leading symptom is chronic low back pain (CLBP) [1]. The prevalence of axSpA among CLBP patients varies between 5 to 71% depending on the setting where these studies have been performed. AxSpA prevalence is 5-24% in primary care [2-4] and 32-71% in secondary care [5-8]. Previous research has shown that early diagnosis and treatment of axSpA leads to better treatment outcomes [9]. The time between disease onset and diagnosis of axSpA however, is estimated to be around 8-10 years [9,10]. This delay may cause disabilities, a reduced quality of life and affect work participation [11]. Therefore, early recognition of axSpA patients from all CLBP is crucial [12,13]. In most countries CLBP patients are first seen and managed by general practitioners (GPs) or physical therapists [14]. Therefore, GPs should be able to recognize the 'red flags' for axSpA. Early recognition seems difficult in primary care (PC) since the prevalence of CLBP is high and GPs' awareness of SpA features are low. Worldwide 19% of patients (age 20 - 59 years) suffer from CLBP [15]. As a result, several referral strategies have been developed to help physicians identify patients at risk for axSpA within these CLBP patients [16-19]. Most referral strategies however, were developed in secondary care patients and have not been externally validated. Moreover, the effect of implementing these algorithms on outcomes from a patient's perspective are scarce, but is an essential step before implementing these algorithms as digital filters in the referral process of GPs [20-21]. In this study we assessed the effect of implementing a referral algorithm in primary care on disability caused by CLBP by using the Case Finding Axial Spondyloarthritis (CaFaSpA) algorithm: a validated and easy to use, non-invasive algorithm for the PC setting [3,4].

METHODS

Study design

The IMPACT study followed a cluster randomized controlled trial design (trial registration number: NCT01944163, Clinicaltrials.gov), which was carried out in the PC setting in The Netherlands. Each cluster contained the GPs from a single PC practice and their included patients [22].

This study was approved by the medical ethics committee of the Maasstad Hospital in Rotterdam, The Netherlands (Trial registration number: 201340).

Participants

Dutch rheumatologists, widely spread over The Netherlands (Rotterdam, Breda, Groningen and Nijmegen), were invited to participate. General practices in the surrounding areas of participating Dutch rheumatologists were invited to participate by letter or personally. The exclusion criterion for general practices was lack of usage of the International Classification of Primary Care (ICPC) coding system for their patients [23].

Patients between 18-45 years who had current low back pain (LBP) for more than 12 weeks, and were registered by means of the ICPC code L03 (LBP without radiation) were invited to participate by a research assistant. Patients willing to participate signed an informed consent form and were contacted to check in- and exclusion criteria and to register the result of the CaFaSpA referral strategy for referral to a rheumatologist. Patients' exclusion criteria were having a clear medical explanation for the back pain (e.g. trauma, hernia nuclei pulposi), being mentally incompetent or having insufficient understanding of the Dutch language (written). The recruitment period of patients was between 10 September 2014 and 6 November 2015. Depending on the recruitment date patients were followed for four months. Follow-up period ranged between 10 January 2015 and 6 March 2016.

Cluster randomization

The block randomization schedule was computer generated and conducted by an independent person, who was not involved in patient care. Randomization was stratified for the number of GPs working in the general practices (one or two vs. more than two) to ensure a similar number of patients in both groups. Patients and GPs were unblinded, because of the nature of the intervention.

Intervention

The intervention was the use of the digital CaFaSpA referral strategy. In the control group usual primary care was based on the Dutch guideline for LBP [24]. The CaFaSpA referral strategy consists of four parameters: inflammatory back pain (IBP), a positive family history of axSpA, a positive response to treatment with NSAID's and a duration of back pain for more than 5 years [3,4]. IBP is a questionnaire and all other three variables are questions that a GP can apply when a CLBP patient visits their practice units [4]. If at least two out of four referral items are present, referral to a rheumatologist is advised in the intervention group (Table 1). In an external validation study, the CaFaSpA referral strategy had a sensitivity of 75% and specificity of 58%.

In the usual care group, GPs took care of their patients as usual. Due to ethical reasons the score of the CaFaSpA referral strategy was given to both the GP and patient at the end of the 4 months follow-up period.

Outcome measures

Our primary outcome was disability caused by CLBP, measured with the Roland Morris Disability Questionnaire (RMDQ) at baseline and 4 months. In the developmental phase of this study the RMDQ is regarded as a clinically relevant outcome measure for low back pain patients and used in clinical trials within this population.
The RMDQ consists of 24 statements about disability caused by LBP and has a scale of 0 to 24 [25]. A higher score indicates a more severe disability [26]. The RMDQ was captured via questionnaires that were sent by email or post.
Secondary outcome was axSpA diagnosis made by a rheumatologist in the intervention group. The number of referrals to a rheumatologist was also assessed. Rheumatologists in this study performed their usual daily clinical practice. If patients did not seek a rheumatologist, despite of our referral advice, we registered the reasons for not visiting the rheumatologist as much as possible.

Sample size

For the power calculation we assumed a minimal clinical difference of 2.5 points in the RMDQ score after 4 months [27-29]. A value of 6.0 was assumed for the standard deviation, as found in the previous CaFaSpA study [4]. Without clustering, we estimated 180 patients (90 per arm) would be required to detect a minimal difference of 2.5 RMDQ; with 80% power, using a 2-sided 2 sample t-test at a 0.05 significance level. The effect of the referral strategy can only be assessed in patients with a positive result of the referral strategy. As in the previous CaFaSpA studies about 50% of patients scored positive on the referral strategy [3,4], a total number of 180 patients per arm would be required. Initially, an average cluster size of 16 patients was expected, while the intra-cluster correlation coefficient was assumed to be 0.05 [30]. Hence, to account for clustering, the design effect was calculated as 1 + (16-1) * 0.05 = 1.75. Multiplying 180 patients per arm by 1.75 implied that a total number of 315 patients per arm should be included. When also assuming a lost-to-follow-up rate of 25% a total number of 840 patients (420 per arm) was initially calculated as the target for inclusion [22]. However, during the inclusion period of the study the average cluster size [7] was found to be substantially smaller than was initially expected [16]. Therefore a small adjustment to the required sample size was applied. The new design effect was recalculated as 1 + (7-1) * 0.05 = 1.3. This yielded a total sample size of 624 patients after applying the updated design effect and accounting for 25% lost-to-follow-up.

Statistical analysis

STATA/SE 14.2 was used for data analyses. Descriptive statistics were performed to describe the baseline characteristics. The difference over time between the two groups were analyzed by a linear mixed-effects model using maximum likelihood

estimation. Fixed effects included allocation group, result of the referral strategy (positive or negative referral strategy) and their interaction. A random intercept was included for general practice to take clustered randomization into account. This random intercept stand for the effect of different PC practices (i.e. clusters). This random intercept parameter can be interpreted as the variance of the deviances of the cluster-specific intercepts to the overall mean (the intercept estimated in the fixed effects). Hence one random intercept term may account for an arbitrary number of clusters. Repeated measures within patients (outcome measured at baseline and after 4 months) were modeled by an unstructured covariance structure.
The linear mixed model allows for patients to have a missing outcome at either baseline visit or after 4 months (but not all (both) visits) and yields unbiased estimates. A sub-analysis within the intervention group was performed to investigate the effect of our model on RMDQ scores in patients who received a positive or negative referral advice. Finally, a sensitivity analysis was solely performed within patients who responded positively to NSAIDs in order to examine a potential effect among the intervention and usual care group. In all analyses, a p-value < 0.05 was considered statistically significant.

Table 1. The CaFaSpA referral strategy.

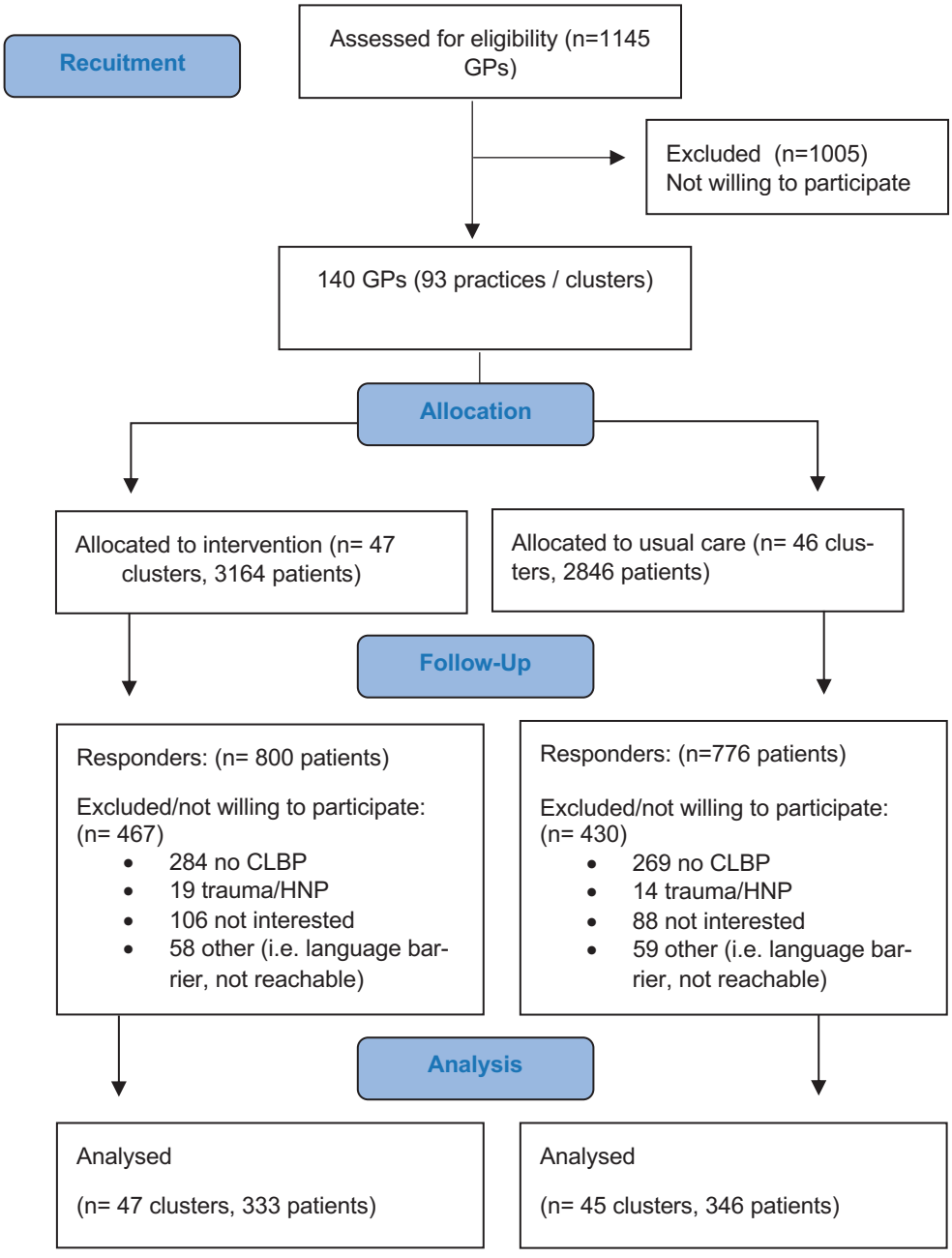
The CaFaSpA referral strategy
Positive ASAS IBP questionnaire
Positive family history for spondyloarthritis
Good reaction to NSAIDs
LBP >5years

If at least two out of the four referral parameters are present a referral to the rheumatologist is advised.

RESULTS

A total of 140 GPs (93 general practices) out of 1145 invited GPs were willing to participate (Figure 1). Following randomization of these 93 clusters, 47 general practices were assigned to the intervention group and 46 to the control group. Within these 93 clusters a total of 6010 patients were invited to participate, and 1576 responded to our invitation (intervention group n=800 patients (25%), control group n=776 patients (27%)). After checking the inclusion criteria by a research assistant, informed consent was obtained from 333 patients in the intervention group and from 346 patients in the control group. One cluster in the usual care group fell out because patients were either (1) not willing to participate (2) has no CLBP, (3) has trauma/HNP, (4) language barrier. This has led to a cluster size of 45 in the usual

Figure 1. Recruitment flowchart impact study.



care group and a total of 679 patients and finally 92 clusters. The overall mean cluster size was 7.4 patients (SD 5.2).

Baseline characteristics

The baseline characteristics of patients are shown in Table 2. Overall, our study population consisted of 64% women. The mean age was 36.2 years (SD 7.5) and the median duration of LBP was 10 years (interquartile range (IQR) 4-15 years). Approximately sixty percent of the patients had a positive outcome of the CaFaSpA referral strategy. The median RMDQ score at baseline was 8 (IQR 4-12) in both groups. In a sensitivity analysis we checked whether positive NSAIDs responders could have influenced our results. However, from our comparative analyses in baseline characteristics including age, gender, LBP duration, and NSAIDs use and dosage no significant differences were present between the intervention and usual care group (data not shown).

Primary endpoint

In total, 577 patients (85%) completed the RMDQ at baseline and 484 (84%) patients completed the RMDQ after 4 months. At baseline the mean RMDQ score was 8.39 (7.59-9.18) in the intervention group and 8.61 (7.83-9.39) in the control group. At four months the mean RMDQ score for the intervention and control group was 7.65 (6.79-8.50) and 8.15 (7.34-8.96) respectively.

A linear mixed-effects regression model was performed on 597 individual patients (47% intervention, 53% control), with at least one available RMDQ score (Figure 2). The mean difference of 0.28 between the groups was not statistically significant (p-value 0.50). Figure 3 shows the sub-analysis of the intervention group. The absolute mean decreases in RMDQ scores between the patients who received either a positive or negative referral advice was similar.

Secondary endpoint

In total, 192 (58%) of the 333 patients in the intervention group received a positive referral advice based on the CaFaSpA rule. Of those finally 103 patients (54%) visited a rheumatologist. Out of the 103 patients we could only verify visits of 75 (73%) patients by receiving their hospital records. Six patients out of these 75 (8%) received the diagnosis axSpA from the rheumatologist. Among those patients one patient was treated with anti-TNF (Humira) and five patients received NSAIDs. The median RMDQ score among patients who visited the rheumatologist decreased from 8 to 5 after four months (p-value 0.17) (Figure 4).

Table 2. Baseline patient characteristics.

	Use of referral strategy (n=333)	Usual care (n=346)
Number of clusters	47	45
Cluster size, mean ± SD	7.1 ± 4.9	7.7 ± 5.5
Age, year mean ± SD	36.7 ± 7.1	35.8 ± 7.8
Male sex, n (%)	115 (35)	130 (38)
CLBP duration, year median (IQR)	10 (4-15)	9 (4-15)
RMDQ, median (IQR)	8 (4-12)	8 (4-12)
VAS pain, median (IQR)	5 (3-7)	6 (3-7)
QoL mean ± SD	0.69 ± 0.26	0.70 ± 0.26
NSAID use, n (%)	88 (53)	87 (49)
Individual components of referral model		
Inflammatory back pain, n (%)	115 (35)	128 (37)
Positive family history, n (%)	82 (25)	71 (21)
Positive response to NSAIDs*, n (%)	154 (46)	192 (55)
CLBP ≥ 5 years	233 (70)	249 (72)
Positive referral model, n (%)	192 (58)	216 (62)

LBP, low back pain. CLBP, chronic low back pain. IQR, interquartile range. RMDQ, Roland Morris Disability Questionnaire. VAS, visual analog scale. Cluster size = number of patients. QoL, Quality of life measured with the EQ-5D. *Positive NSAIDs response according to patients.

Figure 2. Estimated mean RMDQ scores over time for the overall intervention and usual care group. Bars indicate 95% confidence intervals for the mean estimates.

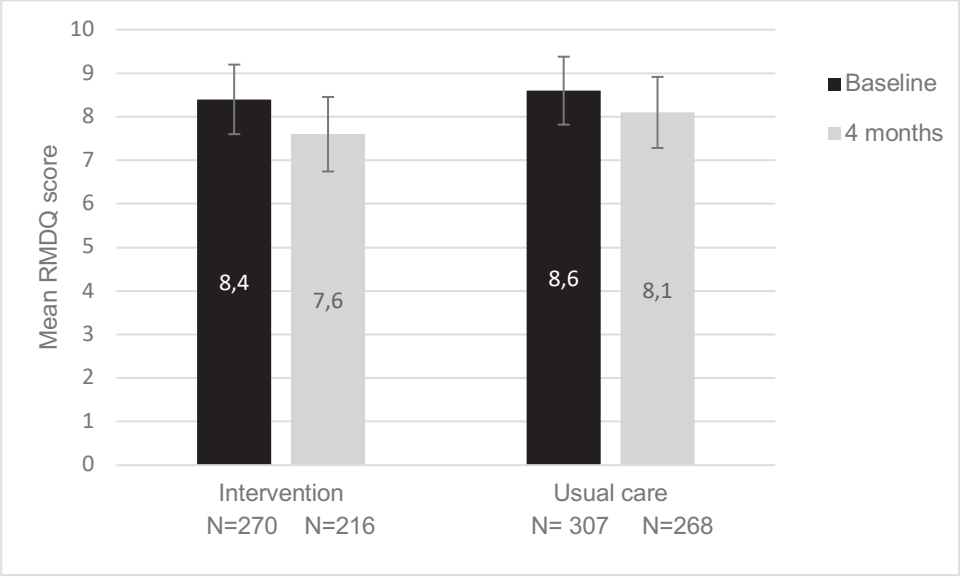


Figure 3. Difference in mean RMDQ scores over time within the intervention group, for patients receiving positive and negative referral strategy. Bars indicate 95% confidence intervals for the mean estimates.

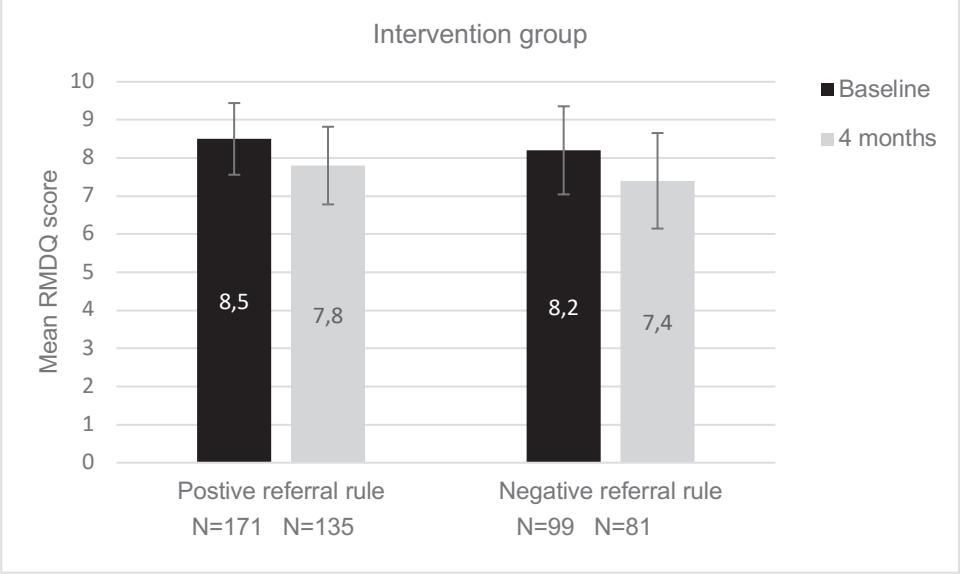
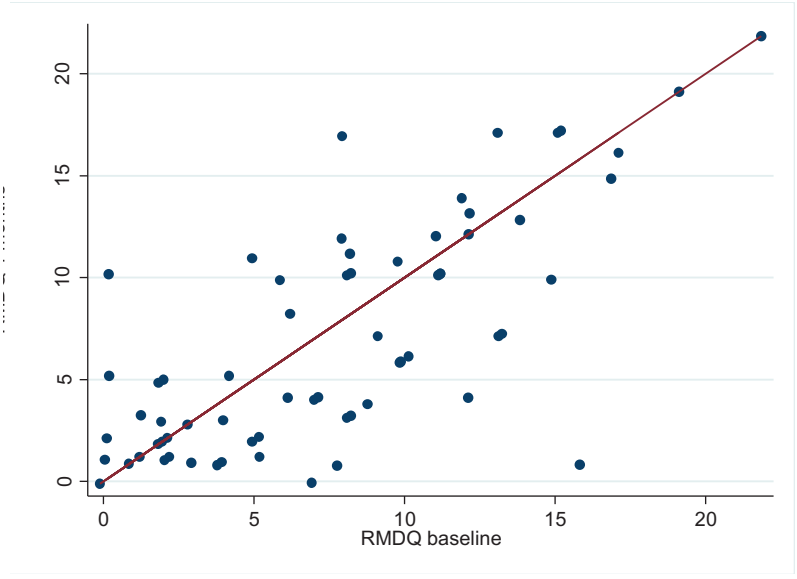


Figure 4. Scatter plot of the RMDQ scores at baseline and after 4 months in the intervention group in patients with a positive referral advice.



DISCUSSION

In a previous prospective study the CaFaSpA referral strategy showed to be potentially efficient and discriminative for the identification of axSpA patients in a CLBP population. Therefore, we performed the current impact analysis, which is an essential step before implementation in daily practice. In this clustered randomized study, the CaFaSpA referral strategy did not have an effect on disabilities caused by CLBP compared to usual primary care after 4 months follow-up period. Although a small decrease in RMDQ scores was detected after 4 months, none of the patient groups reached a clinically meaningful decrease in RMDQ score of 2.5-5 points as described by previous studies [27,28]. To our knowledge this is the first study that examined the effect of a referral strategy for CLBP and for axSpA in daily clinical practice.

The lack of differences between the intervention and usual care groups might have been induced by a considerable short follow-up time as detectable treatment effects may take longer than 4 months. The first step in treatment is using at least two types of highly dosed NSAIDs for at least 4 weeks. When both treatments fail then anti-TNF alpha can be considered. It is expected that the difference between the two groups will be more obvious after a longer follow-up period of 12 months. In addition, we may have created awareness amongst GPs for axSpA or LBP complaints, even

in the usual care group. Patients in the usual care group could have possibly received education, physiotherapy and advice in lifestyle to improve their CLBP, which might have positively influenced their RMDQ score.
Fortunately, the CaFaSpA referral strategy was able to identify newly diagnosed axSpA patients (8%), who had otherwise never been diagnosed and treated as described according to the international guideline [31]. This percentage is comparable to the minimally reported prevalence of axSpA among CLBP patients [2]. The lack of overall difference between the referred and usual care group might have been induced by the low prevalence of axSpA. The axSpA diagnosis in our study is lower than in the previously reported CaFaSpA studies (16% and 24%) [3,4].
In this study axSpA diagnose was made by a rheumatologist which reflects daily clinical practice. Currently we only have a classification criteria (ASAS) for axSpA and diagnostic criteria are still lacking.

The present study has some strengths and limitations. The strengths of our study are multifold. First, an impact analysis of a referral strategy for axSpA in PC has not been performed previously. Secondly, the design of this study as a clustered randomized trial is considered as the most suitable design to address this research question. Thirdly, we were able to include clusters with an equal number of participating patients in both groups (intervention and usual care). The statistical analyses, by using a linear mixed-effects regression model, take the cluster randomized nature of the study into account and is able to handle missing outcomes. Fourthly, in the present study we investigated the impact of the CaFaSpA referral strategy by means of patient relevant health outcomes (disability caused by CLBP). Overall, by using the CaFaSpA referral strategy, 42% of patients received a negative referral advice, who would otherwise be seen by a rheumatologist when the ASAS recommendation for CLBP was followed [16]. The ASAS referral strategy recommends that all CLBP patients with one axSpA feature should be referred to the rheumatologist. This would mean that almost all CLBP patients should be referred to a rheumatologist. Therefore, the CaFaSpA model can be used as an easy to use, non-expensive screening model in PC to identify young CLBP patients at risk for axSpA.
Finely, results of this study are generalizable since our baseline characteristics (including age, gender and LBP duration) and RMDQ scores are comparable with other Dutch studies in PC setting in patients with CLBP, where scores between 6 and 7 have been reported [4,29].
Some limitations must also be addressed. First, NSAIDs use at baseline may have affected our estimates as NSAID's are an over the counter medication in The Netherlands. However, our sensitivity analysis did not reveal any difference with regard to patient characteristics or clinically relevant parameters in those who had a good response to NSAIDs. Second, decisions not to seek a rheumatologist were made both at the patient's and GP level. Despite fulfillment of the CaFaSpA referral advise,

39% of the patients either chose not to visit the rheumatologist due to financial reasons or because they personally did not suspect that their back pain was caused by axSpA. On the other hand, patients were advised by their GP not to seek the rheumatologist because the GP does not suspect an axSpA diagnose. Moreover, in those who had been referred to rheumatologist, the advised diagnostic workup of axSpA was not fully followed. This approach could have influenced our results. For example, only 89% of the patients had a conventional X-ray of the sacroiliac joints and in all patients at least two features were present. Therefore, HLA-B27 positivity or sacroiliitis on MRI should have been tested [32]. Finally, we want to highlight that the expected changes of disability would be much higher if treatment with TNF blockers would have been started.

However, four months follow-up is too short period for a patient to visit a rheumatologist, fail on two different NSAIDs and start biologicals.

In conclusion, the CaFaSpA referral strategy for axSpA did not have an impact on disability after four months caused by CLBP. However, it might still be used as a screening model for primary care to identify CLBP patients at risk for axSpA. We finally want to emphasize that impact studies on outcomes that really matter to patients should be performed before implementing these referral models in daily practice.

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Chapter 6

A trial-based economic evaluation of the CaFaSpA referral strategy for axial spondyloarthritis

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ABSTRACT

Objectives: To assess the cost-utility from healthcare and societal perspective of the digital CaFaSpA referral strategy (CS) for axial spondyloarthritis (axSpA) in primary care patients with chronic low back pain.

Methods: A cluster randomized controlled trial was performed in the Netherlands with general practitioners (GP) as clusters. Clusters of general practice units were randomized into CS or usual care (UC). Economic evaluation was performed from the healthcare and societal perspective within a 12-month time horizon. Outcome measures encompassed disability (RMDQ) and health-related quality of life (EQ-5D-3L). Direct medical (iMCQ) and indirect (iPCQ) costs including productivity loss were evaluated. Incremental cost-utility ratios (ICUR) were calculated.

Results: In total 90 GP clusters included 563 patients (CS_{group}, n=260 and UC_{group}, n=303) with a mean age of 36.3 (SD 7.5) years of which 66% were female. After 12 months no minimal important differences in outcomes were observed for RMDQ: -0.21 (95% CI:-1.52; 1.13) and EQ5D: -0.02 (95% CI:-0.08; 0.05). However, total cost were significantly lower in the CS group due to lower productivity loss costs. The ICUR for RMDQ was €18,059 per point decrease and €220,457 per QALY increase.

Conclusions: Digital referral did not decrease the overall healthcare status of patients after 1 year of follow-up and appears to be more cost-effective compared to UC. Therefore the CS can be used as an appropriate primary care referral model for CLBP patients at risk for axSpA. This will accelerate provision of care at the right time by the right caregiver.

INTRODUCTION

The prevalence of axial spondyloarthritis (axSpA) among chronic low back pain (CLBP) ranges between 5 and 24% [1-5]. Despite the high prevalence, early recognition of axSpA patients within CLBP is difficult for general practitioners (GPs) [3,4]. The diagnostic delay of axSpA is reported to be around 8-10 years [6,7]. This diagnostic delay causes an increase in disability, a reduced quality of life (QoL) and affects work participation, all leading to increased healthcare costs (8). As early diagnose and treatment can reduce the clinical burden of axSpA and reduce healthcare costs on the long-term, this raised the need for the development of referral strategies for CLBP patients at risk for axSpA [7,9,10]. Several referral strategies have been developed to assist GPs to identify axSpA [11]. However, the majority of referral strategies have a low specificity and/or are expensive as they require imaging and HLA-B27 status [11-13]. The CaFaSpA referral strategy (CS) has been

developed and validated in a primary care setting for CLBP patients. This referral strategy uses a simple algorithm in patients with low back pain (LBP) lasting for more than 3 months and age at onset under 45 years, with a sensitivity of 75% and specificity of 58% [3, 4]. Furthermore, the impact of implementing the referral algorithm in daily practice on functionality has been analyzed [5]. Since there is no international consensus yet on which referral strategy should be used, the Assessment of SpondyloArthritis international Society (ASAS) recommends to refer CLBP patients who have at least one axSpA feature [12]. In daily practice, this might result in the inappropriate referral of the majority of CLBP patients from primary to secondary care [13]. Since healthcare resources are limited, the balance between innovative healthcare interventions and costs is crucial. Furthermore cost-effectiveness or cost-utility studies of referral strategies for axSpA are necessary for decision making before implementation in daily clinical practice [14]. Therefore, our aim was to assess the cost-utility of the CS for axSpA in primary care patients with CLBP.

METHODS

Within the Dutch healthcare system each individual can consult a GP in case of any health issue. The GP acts as gatekeeper in referring patients to secondary care. Rheumatology care is delivered within secondary or tertiary care through public hospitals or academic medical centers. Referrals to the rheumatologist are based on the knowledge and experience of the individual GP (usual care). Referrals are in 95% digital and there are no standardized referral sheets incorporated in the Dutch College of General Practitioners.

Study design and population

We used data of the IMPACT study [5], and performed a trial-based economic evaluation. The IMPACT study was a cluster randomized controlled trial in the Dutch primary care setting in patients at risk for axSpA. Randomization took place at the level of the general practice. Each cluster consisted of GPs from a single primary care practice and their included patients. In total 93 practices were randomized either to CS or usual care (UC). The block randomization schedule was computer generated and controlled by an independent person. Stratification on the number of GPs working per practice was performed to ensure an equal number of patients in both study groups. GPs in the surrounding areas of participating Dutch rheumatologists using the International Classification of Primary Care (ICPC) coding system were invited to participate. Patients of the participating GPs were recruited between September 2014 and November 2015. Patients with LBP for more than 12 weeks and aged between 18 and 45 years were recruited from participating practices using the ICPC L03 code [15]. Exclusion criteria were: a clear medical explanation for back

pain (e.g. trauma, hernia nuclei pulposi), mental incompetence or an insufficient understanding of the Dutch language (written).
Informed consent was obtained at the research center before the start of the study. This study was approved by the medical ethics committee of the Maasstad Ziekenhuis, the Netherlands (Trial registration: NCT01944163 (Clinicaltrials.gov)).

Intervention and control group
The intervention was the use of the CS by the GP during the consultation when a patient presented with LBP complaints. The CS consists of four parameters: inflammatory back pain (IBP), a positive family history of axSpA, a positive reaction to treatment with NSAIDs and a duration of back pain for more than 5 years [3]. Referral to a rheumatologist is advised if at least two out of four referral variables are present in the CS. A positive or negative scoring outcome of the CS for referral to a rheumatologist was assessed and registered by a trained research assistant.
In the control group, care as usual was performed in primary care based on the Dutch guideline for LBP [16]. Results of the CS were provided to the UC group after 4 months. In the design phase of the IMPACT study, we aimed to provide results of CS to the UC group after 12 months in order to increase our study window. However, the medical ethical committee advised to provide the CS results after 4 months as patients might benefit from early treatment.

Estimates of effectiveness and utility
Outcome measures were disability and QoL during 12 months of follow-up. Disability is an important patient outcome measure in patients with LBP and has previously been used in cost analysis [17]. Therefore it was included in our cost utility analysis as well. Disability was measured by the Roland-Morris disability questionnaire (RMDQ) [18]. The score ranges from zero (no disability) to 24 (max. disability). QoL was measured with the EuroQol (EQ-5D-3L) [19]. The EQ-5D scores were transformed into utilities using the Dutch values and time trade-off methods [20]. The utilities were then multiplied by the amount of time a patient spent in this particular health state. This resulted in Quality-Adjusted Life Years (QALYs) that range between 1.0 (full health) and 0 (death). Both disability and QoL were assessed at baseline and after four and twelve months.

Estimates of cost
The economic evaluation was performed from a societal and healthcare perspective. Cost estimates were assessed at baseline and after four and twelve months of follow-up. Direct costs are costs of all medical consumption (inside and outside hospital

costs) and medications. Indirect costs are costs due to productivity loss (PL) (absenteeism and presenteeism). Medical consumption was measured with the iMTA Medical Consumption Questionnaire (iMCQ) [21]. The iMCQ is a non-disease specific questionnaire which gathers information in a consistent and standardized way for medical consumption through self-reporting. This questionnaire contains information about contacts with healthcare providers, hospitalizations and medication use. The cost guideline by van Roijen et al. was followed including the mentioned reference prices [22]. Medication costs were calculated from dosages reported in the iMCQ and prices were estimated using unit prices from the Dutch care institute pharmacy database [23].
Indirect costs are costs due to sick leave, unpaid work and reduction in work time which was measured with the Productivity Cost Questionnaire (iPCQ) [24]. We applied the friction cost method to estimate indirect costs due to PL (25). All prices were adjusted to the year 2019 using consumer price indices and calculated in Euros (€) [26]. Since the time horizon of this study was 1 year, discounting of costs and effects was not required.

Secondary outcome axSpA diagnosis
Secondary outcome was axSpA diagnosis made by a rheumatologist. After 12 months of follow-up all patients were asked to fill a questionnaire whether they were under control in the rheumatology setting and for which condition. The self-reported diagnoses were verified by retrieving hospital records after given informed consent by the patient. When hospital records could not be verified, the self-reported diagnosis was reported as proxy.

Statistical analysis
Descriptive statistics were used to describe the patient characteristics. Clinical outcomes and total costs were analyzed for the CS and UC group. We performed an intention-to-treat (ITT) analysis. As mentioned above, due to the advice of the medical ethical committee, after 4 months of follow-up patients in the control group might have had a delayed referral advice. In the ITT analysis they were analyzed as they remained in the control group. This might give an underestimation of the intervention effect.

Incremental Cost-Utility Ratios (ICUR) were calculated in which the mean difference in total costs (CS minus UC) was divided by the mean difference in improvement on the RMDQ and per QALY.
To account for uncertainties in ICUR estimates we used a two stage bootstrapping approach, combined with single imputation to account for missing data [27]. In this

approach, a bootstrap sample is taken from the clusters first, after which bootstrap samples of the individual patients within each bootstrapped cluster are taken. Subsequently, missing data are completed by performing a single imputation on the doubly bootstrapped sample after which the estimates of interest are calculated by taking the means over the imputed bootstrap sample. This process was repeated until 1000 bootstrap estimates were obtained, which were used to construct a cost-utility plane.

Cost-effectiveness acceptability curves (CEAC) were derived for different willingness-to-pay thresholds. The required threshold in the Netherlands for a screening approach for LBP is ≤ €20,000/QALY [28]. CEAC were constructed by plotting the proportion of the incremental cost-effect pairs that lay in the south and east of a ray in the cost-effectiveness plane through the origin with a slope equivalent to the x-axis (i.e., $\lambda = 0$). This was repeated until the slope of the line was equivalent to the y-axis [29]. Sensitivity analyses were performed comparing complete case data and imputed data.

To explore the group of patients with missing data we investigated differences in case mix between responders and non-responders by patient characteristics and clinical outcomes. Additional sensitivity analyses were performed excluding patients who reported absenteeism at baseline in both the CS and UC group to rule out potential effects due to baseline imbalance. All statistical analyses were carried out using STATA version 14.2. A two-sided p-value <0.05 was considered statistically significant.

RESULTS

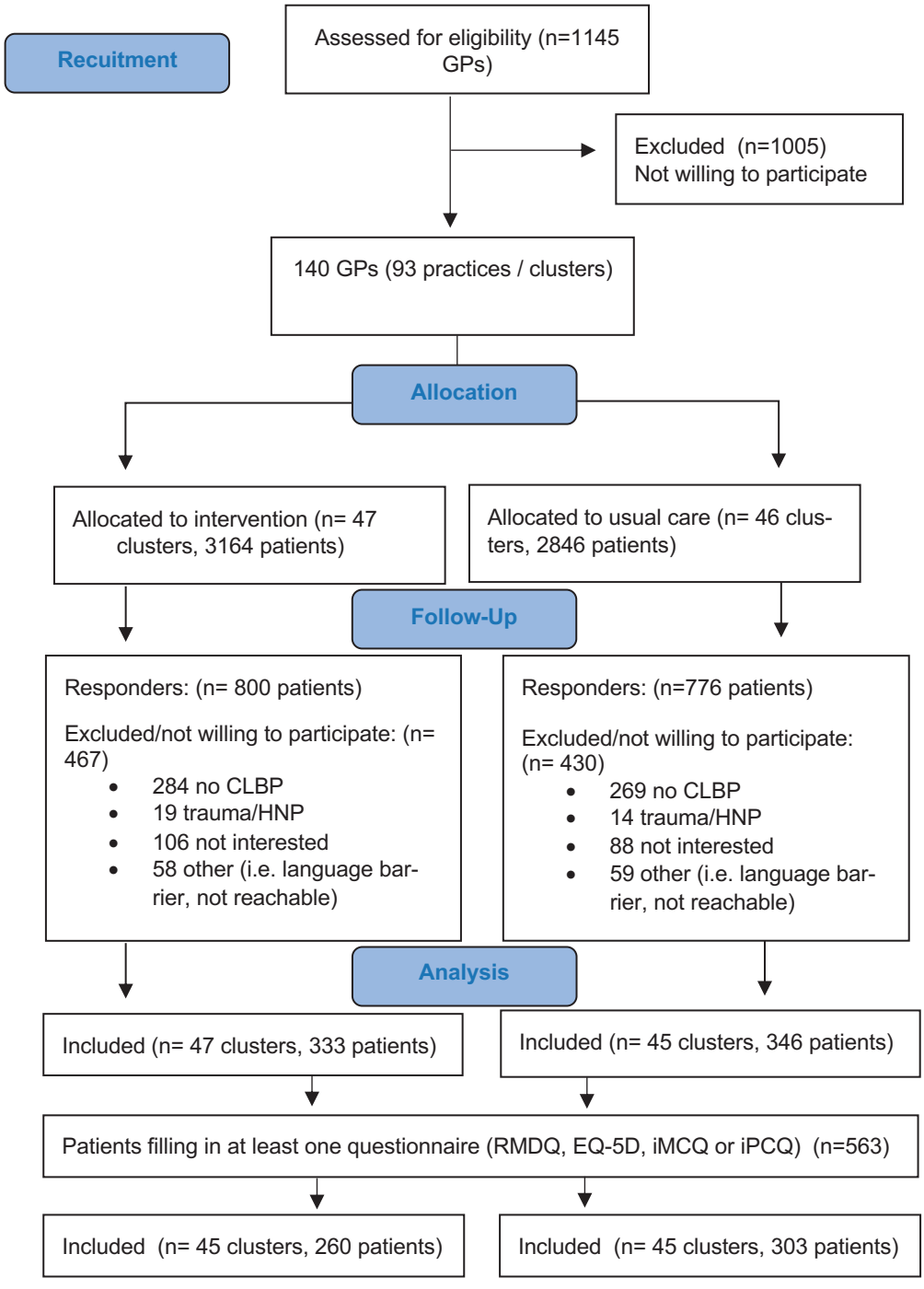
In total, 679 patients were included (Figure 1). Five-hundred-and-sixty-three patients filled in at least one questionnaire (RMDQ, EQ-5D, iMCQ or iPCQ) at any visit and were included in the analyses. Of these, 260 patients were in the CS group and 303 patients in the UC group (Figure 1).

Baseline characteristics

Baseline patient characteristics of both groups are shown in Table 1.

The average response rate of all questionnaires at 12 months was 55%. Complete data on all costs at baseline and after 4 and 12 months were available for 35.5% in both groups. Missing values occurred due to patients not filling in the questionnaires. The percentage of missing values at 12 months was comparable between both the CS and UC groups (p=0.14). At baseline, QoL, disability score and duration of CLBP was comparable between responders and non-responders (p-value>0.05).

Figure 1. Patients flow chart.



Healthcare resources

Table 2 lists the mean resource utilization per patient at 12 months. Percentage healthcare utilization was not statistically different between groups.

Table 1. Baseline patient characteristics. All data are presented as mean and standard deviations unless stated otherwise.

	CS (n=260)	**UC** (n=303)
Number of clusters	45	45
Cluster size, median (IQR)	6 (3-6)	5 (3-8)
Age, year	36.7 (7.2)	35.9 (7.6)
Male sex, n (%)	85 (32.7)	107 (35.3)
CLBP duration, year	10.5 (7.5)	10.2 (7.4)
RMDQ	8.4 (5.8)	8.2 (5.6)
VAS fatigue	5.2 (2.5)	5.3 (2.4)
VAS pain	5.2 (2.3)	5.1 (2.5)
EQ-5D	0.68 (0.26)	0.72 (0.24)
Positive referral advice, n (%)	157 (60.4)	192 (63.4)
Educational level, n (%)		
Primary	7 (2.5)	10 (3.4)
Secondary	61 (25.4)	62 (22.2)
Vocational university	99 (41.3)	117 (41.9)
University	70 (29.2)	84 (30.1)
Work status, n (%)		
Paid job	179 (74.9)	226 (81.6)
Sick leave	20 (11.8)	41 (19.0)

CS, CaFaSpA strategy. UC, usual care. LBP, low back pain. CLBP, chronic low back pain. IQR, interquartile range. RMDQ, Roland Morris Disability Questionnaire. VAS, visual analog scale. Cluster size, number of patients. QoL, quality of Life measured with the EQ-5D. SD, standard deviation. Positive referral advice, percentage of patients who scored ≥2 out of the 4 items of the CS.

Associated costs

Mean difference in total costs during the 12-months follow-up was €5866 (p-value <0.05) favoring the CS (supplementary file Table S1). Mean total costs at baseline, 4 and 12 months are shown in the supplementary file Table S2.

Excluding patients who reported absenteeism at baseline still showed higher absenteeism costs in the UC group at 4 months (mean difference €194,-, p=0.03) and 12 months (mean difference €245,-, p=0.03).

Table 2: Health care consumption in the CS and UC group at 12-months of follow-up.

	CS (n=145)		UC (n=156)	
	Percentage	Mean (SD)	Percentage	Mean (SD)
General practitioner[a]	42.1%	2.6 (2.4)	50.6%	2.2 (1.7)
Social worker[a]	5.5%	2.6 (2.4)	3.2%	4.4 (2.6)
Physiotherapy[b]	33.1%	6.0 (4.8)	32.1%	7.1 (5.9)
Ergotherapy[b]		NA	0.6%	5.0 (-)
Speech therapist[b]	0.0%	NA	0.0%	NA
Dietitian[a]	6.2%	3.3 (1.7)	3.9%	5.5 (6.3)
Homeopath	3.5%	1.8 (1.1)	1.9%	2.3 (0.6)
Psychologist[b]	10.3%	4.2 (2.6)	13.5%	4.1 (5.3)
Occupational physician[b]	5.2%	2.0 (0.8)	8.3%	1.5 (0.7)
Medication	57.9%	1.3 (0.5)	51.3%	
Emergency	4.1%	1.5 (0.7)	3.9%	1.0 (0.0)
Ambulance ride	1.4%	2.0 (1.6)	0.6%	1.0 (.)
Outpatient visits	16.6%	0.0 (0.1)	23.7%	2.6 (2.3)
Day treatment outpatient clinic	2.1%		5.8%	0.1 (0.6)
Day treatment elsewhere				
Living / care center	0.0%	NA	0.0%	NA
Rehabilitation center	0.0%	NA	0.6%	3.5 (2.1)
Psychiatric institution	0.0%	NA	0.0%	NA
Elsewhere	1.4%		0.6%	
Hospitalizations outpatient clinic[d]	2.1%	2.0 (1.0)	2.4%	5.5 (7.7)
Hospitalizations elsewhere[d]				
Living / care center	0.0%	NA	0.0%	NA
Rehabilitation center	0.0%	NA	0.6%	26.0
Psychiatric institution	0.0%	NA	0.6%	42.0

CS, CaFaSpA strategy. UC, usual care. [a] consultation. [b] treatment session. [C] per hour. [d] days.

Cost-utility analysis

Following the combined cluster bootstrap and single imputation procedure, all n=563 participants were included in the base-case analysis. No significant differences nor minimal clinical differences in adjusted (for clustering effect) mean difference were found between the CS and UC group for RMDQ (−0.21, 95% CI: −1.52 to 1.13) and EQ5D (−0.02, 95% CI: −0.08 to 0.05) (Table 3). Total costs (direct and indirect) were significantly higher in the UC group, mean difference: €-3,867 (95% CI: €-7,074 to €-765). Ninety-nine percent of the imputed bootstrapped ICURs were located in the two southern quadrants of the cost-effectiveness planes (Figure 2a and 2b), indicating that costs of the CS are lower.

The ICUR for RMDQ was €25,716 indicating that per point improvement on the RMDQ the CS saved €25,716. The difference in QALY's between the CS and UC was very small resulting in a large ICUR of €220,457.

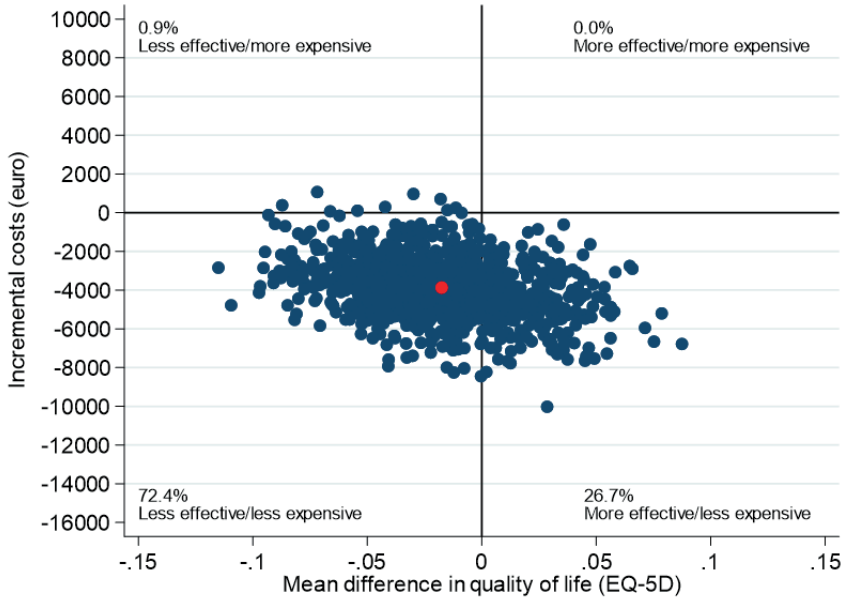
The sensitivity analysis of complete cases showed similar results, where in all estimated bootstrap samples the ICURs were located in the southern hemisphere, indicating that CS is associated with lower costs (supplementary file Figure S1a and 1b). Excluding patients who reported absenteeism at baseline in both the CS and UC group also showed that in approximately 97% of the bootstrap samples of complete case data and imputed data, the ICURs were located in the southern quadrant (supplementary file Figure S2a and S2b).

Table 3: Incremental cost-utility ratios for disability and health-related quality of life adjusted for the clustering.

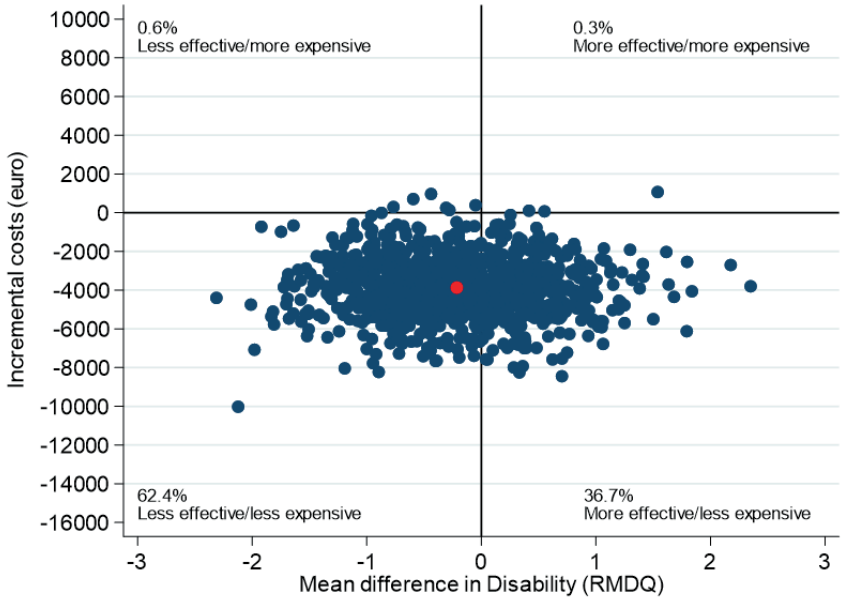
	CS		UC		CS versus UC
Outcome measure	**Costs**	**Effects**	**Costs**	**Effects**	**ICUR**
Disability (RMDQ)	€10,380	1.40[a]	€14,247	1.19[a]	€25,716
Quality of life (EQ-5D)	€10,380	0.70[b]	€14,247	0.72[b]	€220,457

CS, CaFaSpA strategy. UC, usual care. [a] Change score between baseline and 12 months follow-up. [b] Score over 12 months follow-up. ICUR, incremental cost-utility ratio.

Figure 2. Cost-utility plane for quality of life (2a) and disability (2b). Blue dots indicate the estimated ICERs for each bootstrap sample. The red dot indicates the overall mean ICUR over all bootstrap samples.



2a



2b

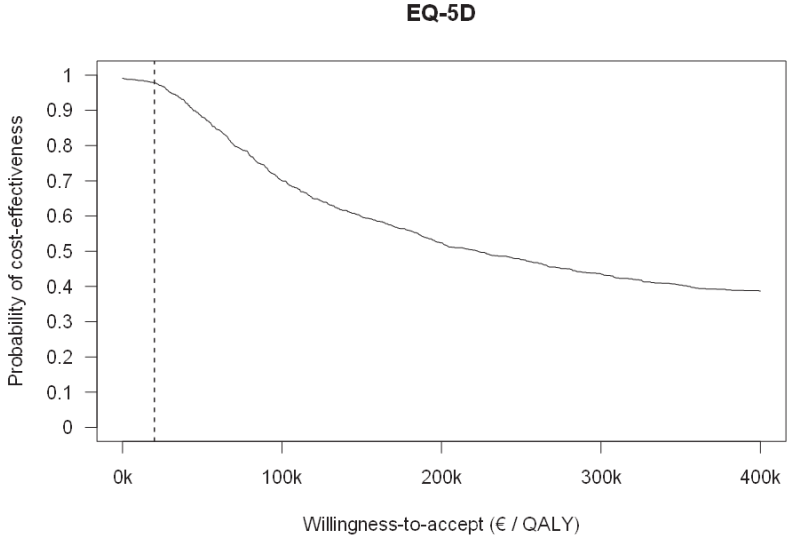
Cost effectiveness acceptability curves

At willingness to pay level of ≤ €20,000, CS had a probability of being cost-effective in comparison with UC of approximately 98% per QALY gained (Figure 3a).
And per reduction of 1 score on the RMDQ, the CS had a probability of being cost-effective in comparison with UC of approximately 48% at willingness to pay level of ≤ €20,000 (Figure 3b).

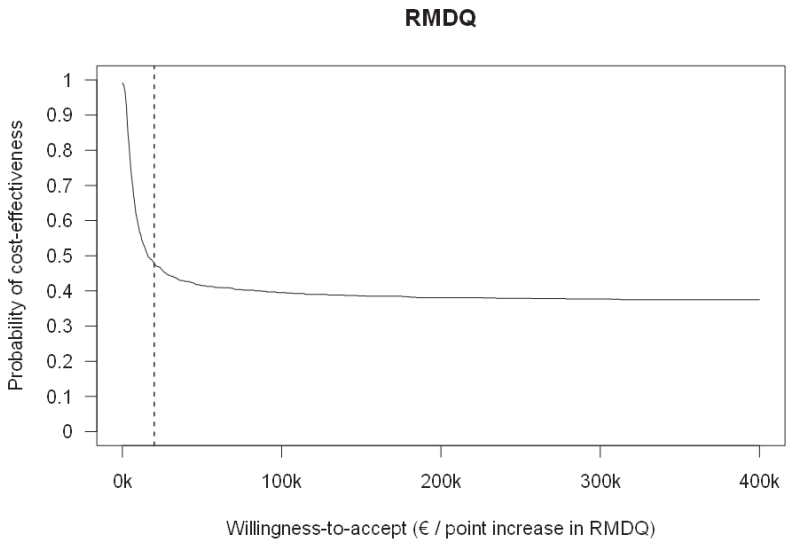
Secondary outcome axSpA diagnosis

The number self-reported axSpA diagnosis during 12 months follow-up was 4.6 %, 12/260 in the CS group and 4.6%, 14/303 in the UC group. Due to a low response rate of hospitals for giving information on the diagnosis, we only could verify the diagnosis of 8 out of the 32 referred patients in the US group compared 59 of the 68 referred patients the CS group. The verified number of axSpA diagnoses was finally 3 in the UC group and 4 in the CS group. For details, see supplementary file Figure S3.

Figure 3. Cost-effectiveness acceptability curve for quality of life (3a) and disability (3b).



3a



3b

DISCUSSION

Our economic evaluation showed no difference in cost from the healthcare perspective but a significant difference in costs from the societal perspective, which was in favor of the CS. After 1 year of follow-up total costs were higher in the UC group despite similarity on disability and quality of life between the CS and UC group. Costs were mainly driven by lower costs due to PL in the CS group at 4 and 12 months irrespectively of baseline differences in costs. This could possibly be explained by rheumatologists offering CLBP patients in the CS lifestyle advice, education or physiotherapy to improve their CLBP complaints and therefore resulted in less PL costs. To the best of our knowledge, this is the first study to investigate cost-effectiveness of a referral strategy for axSpA in patients with CLBP. Total cost for patients having CLBP during 1 year of follow-up were higher in our study compared to a study by the group of Jellema et al. [17]. This difference in costs may be explained by how the data were collected. We used the widely adopted iMCQ questionnaire, while the study by Jellema et al. used cost diaries to document the consumption of healthcare resources. The main difference between both approaches is that the iMCQ covers visits to all healthcare providers as well as other health issues besides CLBP. Moreover, an advantage of the iMCQ is that it reflects real life, as total costs of LBP patients including their comorbidities and mental healthcare are taken into account. Nevertheless, both the iMCQ and cost diaries are self-reported methods to measure healthcare utilizations. Although self-reported questionnaires are reliable [30] actual costs is best captured by medical records and disease registries.

PL costs were significantly higher in the UC group. However, it could not be verified whether the reported sick leave occurred because of CLBP complaints since the iPCQ is a standardized instrument for measuring overall PL. Therefore, the costs of illness for CLBP patients in this study could be overestimated. A study performed in The Netherlands also showed lower PL costs due to LBP [31].

Current economic evaluation showed no difference in outcomes on effectiveness (i.e. disability and health related quality of life) between the CS and UC group after 1 year of follow-up. This lack of difference could be a consequence of the low prevalence of axSpA compared to the previous CaFaSpA 1 and CaFaSpA 2 studies [3,4,14]. The axSpA diagnosis in this study however was made by the workup of a rheumatologist, which reflects daily clinical practice and not by a predefined research protocol as was performed in the published CaFaSpA studies. This could partly explain the low prevalence of axSpA as not all rheumatologists might have performed the advised diagnostic work-up in all cases. Also, many patients in the CS group, despite a positive referral advice, did not visit a rheumatologist. This is unfortunate and could have underestimated the observed effect of the CS as we expect a higher quality of life and less disability in the CS group who receive an axSpA diagnose and receive appropriate treatment. Also participation in the study may have led to increased awareness among GPs for axSpA or LBP complains in the UC group.

Furthermore, although current economic evaluation showed no difference in effectiveness, incremental cost–utility planes indicated lower costs in the CS group and therefor of added value in terms of Value Based Health Care [32], the reforming strategy of Dutch healthcare [33]. Moreover CEAC showed that the CS is cost-effective. The likelihood that the CS is cost-effective exceeds 90% at willingness-to-pay thresholds of ≤€20.000 per additional QALY. Although additional research is required we could speculate that the introduction of the fit for work platforms may have encouraged rheumatologists in the CS group to provide advice regarding productivity, which resulted in lower PL costs. Fit for work programs have been developed to improve healthcare provider's knowledge and skills to support work related challenges [34]. In this way, more people with a chronic condition can continue to work.

This study has several strengths and limitations that are worth mentioning. A first strength is that we assessed the impact of an innovative referral strategy in terms of health effects and costs, as a crucial step before implementation in daily clinical practice. Unfortunately, these types of analyses are generally lacking in the majority of implemented disease management strategies, whilst health resources are scarce and can only be spent once. Second, we used a clustered randomized trial to assess cost-effectiveness of the CS versus UC from a societal and healthcare perspective. Third, we used disability in addition to quality of life to investigate the cost-utility of the CS, as disability is an important patient reported outcome among CLBP patients [35]. Although EQ-5D is less sensitive to evaluate the change in score over time on patient's level it is useful for benchmark between disease indications and countries.

Fourth, generalizability of our study. Our baseline characteristics including age, gender and LBP duration and RMDQ scores are comparable with other studies performed in the Dutch primary care setting [4,36].
Finally, we included presenteeism costs and informal care costs to give a more accurate representation of the true costs related to PL [37].
Study limitations should be noted as well. First, as in most cost-effectiveness trials, sample size calculations were not based on demonstrating cost-effectiveness, but rather on demonstrating a clinically relevant difference of 2.5 points on the RMDQ, which was the primary end-point of the original trial [5]. The required sample size for the cost-effectiveness analysis is therefore expected to be higher than the clinical effectiveness study [38]. Second, missing data was high. However, in addition to a complete case analysis, we performed bootstrap sampling combined with imputation to evaluate the main outcomes of this study. Third, we used the friction cost method instead of the human-capital method to value productivity. The human-capital method takes the patient's perspective and counts any hour not worked as an hour lost. By contrast, the friction-cost method takes the employer's perspective, and only counts as lost those hours not worked until another employee takes over the patient's work. Productivity costs have the potential to compensate for the costs of expensive biological agents, but only in early-onset disease when patients still have jobs and if productivity is given full weight by using the human-capital method. If productivity is given less weight by excluding productivity costs or by using the friction-cost method, biological agents are probably too expensive. Although the friction-cost and the human-capital method can produce widely different results we believe that this would not lead to a different conclusion, since despite the use of the friction-cost method PL costs were still lower in the CS.

With respect to generalizability, results of this study are likely representative for the Dutch situation, since our RMDQ scores and baseline characteristics are comparable with other studies performed in the Dutch primary care setting. Although we do not expect great variability in EQ-5D and RMDQ scores among young primary care CLBP patients in other countries, differences in healthcare systems, the volume and costs of resource use can be expected to be different.

In conclusion, the digital CS referral algorithm did not decrease the overall healthcare status of the patients after 1 year of follow-up but appears to be more cost-effective compared to usual GP referral. Therefore the digital CS can be used as an appropriate primary care referral model for CLBP patients at risk for axSpA. This will accelerate in giving care at the right time by the right caregiver. For the future we recommend to investigate cost-effectiveness of referral strategies as a crucial step before implementation in daily clinical practice. Relevant patient reported outcome measures should be included when investigating the cost-effectiveness of a referral strategy.

SUPPLEMENTARY MATERIAL

Table S1. Mean resource use in Euros per patient among the CS and UC group during the 12-months follow-up (complete case).

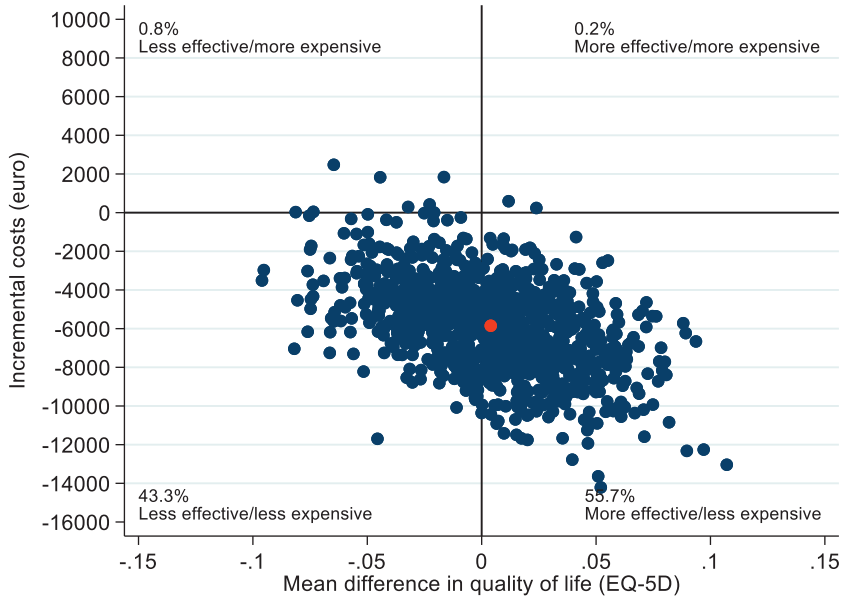
	CS		UC		
	n	Mean (SD)	*n*	Mean (SD)	Mean difference (95% CI)
Primary care	127	795.5 (1135.4)	137	789.5 (964.0)	6.0 (-248.7-260.6)
Home care	127	9.0 (78.3)	137	0.0 (0.0)	9.6(-3.5-22.8)
Secondary care	133	1658.8 (2444.7)	140	1920.4 (4628.7)	-261.6 (-1150.4-627.2)
Medication	127	46.9 (109.7)	137	153.7 (1118.7)	-106.8 (-303.2-89.5)
Total direct costs	127	2533 (3123.7)	137	2884.1 (5262.6	-350.2 (-1409.3-709.0)
Presenteeism	94	4271.1 (5076.8)	111	6589.8 (7018.7)	-2318.7 (-4033.6—603.8)*
Absenteeism	57	4178.0 (6635.2)	176	8038.2 (13770.7)	-3860.2 (-635.7—1484.7)*
Total indirect costs	94	7152.3 (8991.3)	111	12912.5 (14118.7)	-5760.2 (-9088.8—2431.6)*
Total costs	93	9589.6 (10613.8)	110	15455.5 (16380.7)	-5866.0 (-9765.3—1966.6) *

CS, CaFaSpA strategy. UC, usual care. *p-value ≤0.01.

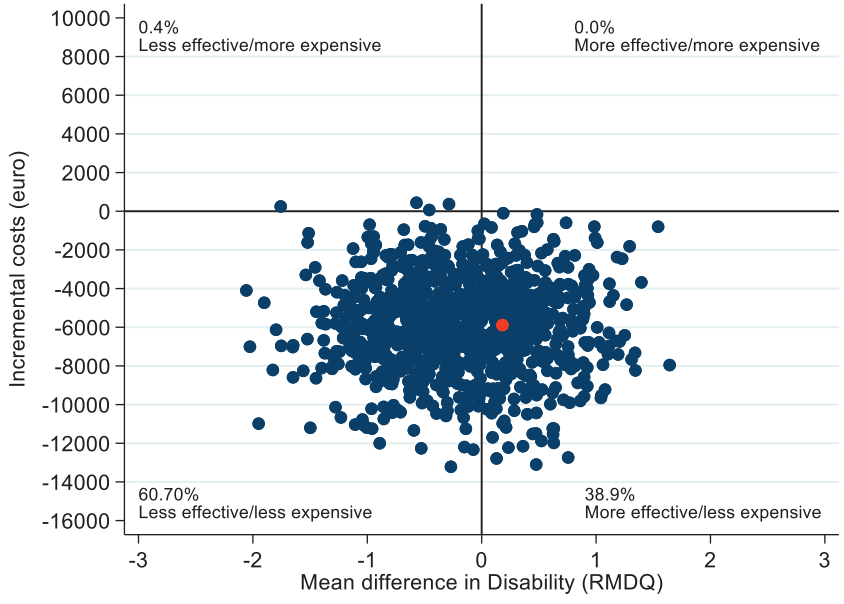
Table S1. Mean resource use in Euros per patient among the CaFaSpA strategy (CS) and usual care (UC) group over time.

	Baseline					After 4 months					After 12 months				
	CS		UC			CS		UC			CS		UC		
	n	Mean (SD)	n	Mean (SD)	P-value	n	Mean (SD)	n	Mean (SD)	P-value	n	Mean (SD)	n	Mean (SD)	P-value
Primary care	237	299.8 (339.3)	273	243.0 (379.7)	0.68	186	187.0 (326.3)	238	186.7 (303.2)	0.99	145	183.5 (270.2)	156	206.5 (299.9)	0.49
Home care	237	35.3 (350.4)	273	4.8 (56.3)	0.16	186	0 (0)	238	13.2 (165.0)	0.28	145	0 (0)	156	0 (0)	-
Secondary care	238	140.7 (425.6)	274	242.3 (935.5)	0.12	198	489.6 (781.1)	244	292.4 (1075.8)	0.03	151	253.0 (772.2)	157	568.0 (1934.0)	0.06
Medications	237	23.9 (173.6)	273	33.6 (244.1)	0.61	186	22.3 (181.9)	238	30.1 (219.5)	0.69	145	11.7 (29.6)	156	33.5 (262.9)	0.32
Total direct costs	237	429.2 (777.8)	273	521.4 (1213.9)	0.32	186	702.7 (1024.2)	238	529.9 (1255.3)	0.13	145	451.5 (832.1)	156	811.7 (2058.5)	0.05
Presenteeism	177	439.8 (747.5)	227	436.1 (709.9)	0.96	143	320.5 (498.7)	201	479.6 (645.5)	0.01	118	323.1 (541.9)	133	522.7 (819.1)	0.03
Absenteeism	237	233.0 (493.7)	273	455.3 (1112.0)	0.005	200	272.1 (504.5)	247	512.8 (1141.5)	0.006	175	367.9 (788.7)	191	639.1 (1237.1)	0.01
Total indirect costs	177	628.1 (923.1)	226	850.4 (1437.8)	0.07	143	530.4 (765.3)	200	974.0 (1445.3)	0.001	118	638.7 (1144.4)	133	1045.7 (1352.3)	0.01
Total costs	175	973.1 (1201.8)	223	1324.4 (1956.7)	0.04	139	1191.3 (1276.1)	199	1482.3 (2247.6)	0.18	117	1067.8 (1552.1)	132	1748.7 (2531.2)	0.01

Figure S1. Cost-effectiveness plane for quality of life (1a) and disability (1b) (complete case).



1a



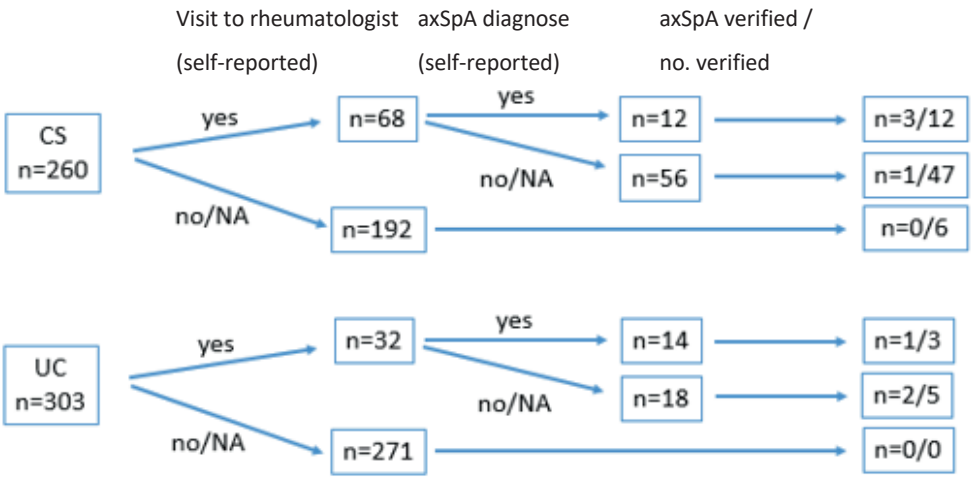
1b

Figure S2. Cost-effectiveness plane for quality of life (complete case 2a and imputed sample 2b), (patients who reported absenteeism at baseline were excluded in both the CS and UC group).

2a

2b

Figure S3. Flow chart of rheumatology visits and SpA diagnoses.



CS, CaFaSpA strategy. UC, usual care. NA, not applicable.

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Chapter 7

Discussion

Within this thesis we aimed at improving referral of patients at risk for inflammatory rheumatic diseases (IRDs). The available referral strategies for IRDs are broad and lack impact analyzes, where health outcomes and costs are taken into account before implementation in daily clinical practice. Therefore, we first aimed to get insights on the proportion of new IRD onsets among patients referred to the rheumatology outpatient clinic and evaluate the burden of disease. Second, we aimed to investigate the impact of the most promising referral strategy for IRD on health outcomes, process outcomes and cost-effectiveness.
This chapter discusses the main findings presented in this thesis and puts these results into a broader perspective. Reflections on the main findings are presented by discussing the following themes: usefulness and necessity of referral strategies, burden of musculoskeletal complaints on quality of life, using an algorithm for referral improvement, applying IMPACT analysis for digital algorithms; the reflection of outcome data and the evaluation of healthcare costs. Next, some methodological considerations are discussed. Finally, implications and recommendations are provided for clinical practice, policy and research.

Part 1. Occurrence and impact of IRDs in patients with musculoskeletal complaints

In Chapter 2 and 3, we gained insights into the number of IRD and non-IRD diagnoses among patients referred to the rheumatology outpatient clinic by performing a systematic review. Results have shown that the actual proportion of axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), and rheumatoid arthritis (RA) within all newly referred patients is 19%, 18%, and 11%, respectively. This finding provides evidence that approximately 80% of patients are referred to a rheumatology outpatient clinic with non-IRD, while these patients could have been remained and treated in primary care. This “overreferral” leads to an increased workload for secondary care lines that is accompanied by unnecessary healthcare costs for all stakeholders. Despite the high heterogeneity between studies, we observed a rising tendency for IRDs over the years indicating improvements in the referral of patients towards rheumatology clinic. Furthermore, our findings suggest that the gatekeeping system should be optimized in the field of rheumatological referral. Gatekeeping varies between nations due to variations in their healthcare systems. In low- and middle-income nations there is often no gatekeeping. Patients frequently go straight to secondary and tertiary hospitals instead of primary care clinics [1]. Interestingly, gatekeeping also differs among high income countries. In the Netherlands, patients require a referral from a GP to visit specialist care, whereas in other European countries such as Germany and France, direct access to specialist care is common [2,3]. The prevalence of IRD is anticipated to be greater in countries that have gatekeeping.

The main goals of gatekeeping were to strengthen healthcare, improve the quality of care, and reduce costs by avoiding unnecessary specialist care visits [4]. While the aforementioned incentives for gatekeeping are valid, they appear not to be fulfilled currently. A potential rationale for this might be that the GP refers patients for other reasons than ruling out a disease. This could be to reassure patients or the GP himself or herself, to obtain an additional opinion, or to pass on care [5,6]. Therefore, to optimize gatekeeping, GPs should be assisted in making referral decisions. A review by Akbari et al. reported that effective referral from primary to secondary care can be enhanced through active local educational initiatives for GPs, clinical triage, and the use of structured referral sheets [7]. In current practice, educational initiatives for GPs are not leading to better IRD detection.
The adoption of referral strategies could be an effective tool to support adequate patient referral. However, referral strategies should first be supported by performing impact studies, where their value is evaluated on relevant health outcomes and cost-effectiveness (Chapter 5 and 6).

Effect of musculoskeletal complaints on quality of life in patients at risk for IRD

In addition to the frequency of IRD, insight into the outcome of disease in patients at risk is important for health decision-makers to provide the right care at the right time and the right place. MSC and IRDs occur frequently among patients with IBD therefore it is important to assess its impact by means of the quality of life in patients with inflammatory bowel disease (IBD). This was assessed in Chapter 4. From these analyses, it appeared that MSC has a significant independent negative impact on the quality of life of patients with IBD (Chapter 4). This was confirmed using both generic and disease-specific questionnaires. Although some overlap may exist, generic patient-reported outcomes (PROs) assess the general aspects of health, while disease-specific PROs assess a specific aspect of health for a particular disease. IBD patients with a rheumatological diagnosis were associated with a significantly reduced quality of life compared to IBD patients with MSC.
A literature by Felice et al. suggests that IBD patients with chronic low back pain or pain/swelling in peripheral joints should be referred to a rheumatologist, as this could be caused by IRDs [8]. However, in case of efficiencies only patients at risk of IRDs should be referred. Therefore, we suggest routinely assessing MSC using a patient self-reported questionnaire such as the one used by van Erp et al. prior to hospital visits, as its importance is currently often ignored [9]. Although some referral strategies have been proposed for IBD patients at risk for IRDs, they lack either validation or an impact study [9-11].

Part II. Impact of CaFaSpA strategy

Several (pre)-screening and/or referral strategies have been developed and suggested for patients at risk for IRDs, with more referral strategies generated than implemented or used in clinical practice [12]. This is due to the fact that validation studies are not quite often performed for newly developed prediction models, leading to the existence of many models for one specific disease. In practice, this leads to confusion about which model to use. This is partly due to disappointing validation results, which often result in the development of new models instead of updating or adjusting existing models [13,14]. One of the most promising referral strategies for patients at risk for IRDs is the CaFaSpA strategy. This strategy is externally validated and has shown good performance. However, before implementation in daily practice, impact analysis on outcome and cost is required [15]. Therefore, we aimed to assess the impact of one of the most promising referral strategy (CaFaSpA) for axSpA on patient outcomes and cost-effectiveness. From a short-term perspective, the digital CaFaSpA referral strategy did not lead to significant improvement with regard to the disability of patients (Chapter 5). After 12 months, these results remained the same. The economic evaluation was based on classical health technology assessment (HTA) methodology, using the EQ-5D as a generic outcome as well as the more disease-specific outcome (RMDQ). In these analyses, the digital CaFaSpA referral strategy appeared to be more cost-effective when compared to usual care irrespective of the type of health outcome (Chapter 6). However, in these analyses, we did not apply conversion equations for RMDQ, which was recently suggested in the literature [16]. The study by Koster et al. shows that disease-specific outcome measures yield similar results in terms of incremental cost-effectiveness ratios [16]. One of the added values of the CaFaSpA referral strategy for the patient is the decreased work productivity loss. Also, more attention should be given to returns from patient, organizational, and societal perspectives. Furthermore, as the CaFaSpA leads to approximately 40% less referral of patients to the rheumatologist, this may decrease the workload for rheumatologists. In addition, the implementation of a digital referral strategy may also aid GPs in delivering appropriate care for patients with no IRDs. Therefore, the CaFaSpA strategy can be regarded as an appropriate primary care referral model for CLBP patients at risk for axSpA. Implementation of this strategy could lead to the accelerated provision of care at the right time by the right caregiver. This is in line with the VBHC principles [17].

Another point of attention is that in the impact study, approximately 39% of the patients, despite our positive referral advice, did not visit the rheumatologist. Clinicians and/or patients may not always follow the referral rule for various reasons [18]. A recent report from the Dutch patient federation showed that twenty-percent of patients avoided or postponed healthcare, because they could not afford the mandatory deductible [19].

Methodological considerations

Methodological considerations regarding the studies performed in this thesis are discussed below.

A systematic review is the highest level of evidence when well defined and conducted [20].
For our reviews, a broad search strategy was set up, including prospective, cross-sectional, and retrospective studies. The latter is more prone to information, confounding, and selection bias. In our study, we minimized the risk of bias with regard to methodological by assessing the quality by means of a situational-adjusted tool and reported it.

Regarding the observational study: By carrying out a cross-sectional study that included several settings and studies, we showed that the re-use ability of data can accelerate answering integral research questions and is time and cost-efficient.

With regard to the clustered randomized controlled trial (cRCT): Assessing the impact of a referral strategy requires a comparative approach and is preferably performed using a cRCT in a new study population [12]. Randomization at a cluster level prevents experience contamination between health care providers. Taking this into account, a clustered randomized controlled trial was performed including intention-to-treat analyses. This approach minimizes biased estimates and increases the generalizability of our results. The lack of clusters and patient blinding to their allocation status may have jeopardized the internal validity of the study and introduced bias [21]. However, blinding of clusters (general practices) was not possible as GPs had to use the referral strategy. In addition, blinding of patients was also not possible as patients with a positive referral recommendation had to visit the rheumatologist.
To minimize selection bias, patient selection was based on the ICPC code. ICPC is the standard for coding and classification of signs and symptoms in general practice in the Netherlands [22]. As the incidence of axSpA above 45 years is rare, the inclusion criteria for age were set up to 45 years. A second measure to prevent selective inclusion of patients was asking a broad range of general practices to participate in this study. As no inclusion or exclusion criteria were set for GPs, selection bias at this level was not expected. The exclusion criteria for patients were limited including contraindications for MRI, no understanding of the Dutch language and an explainable cause for the back pain, such as trauma. The broad inclusion criteria for patients and the limited exclusion criteria encourage the generalizability of our results.
Non-participating bias was examined by performing sensitivity analyses between responders and non-responders, which indicated that demographic factors and health outcomes were comparable. In addition, to assess whether there was a selection of patients who participated in the impact study, patient characteristics were evaluated. In line with previous studies, the female gender was more dominant in our study, as

more than 60% of the participants were female [23-27]. Also, the baseline disability score in our study was comparable with other studies performed in Dutch primary care [26]. Therefore, it can be assumed that no selection bias occurred, and our sample was representative of the targeted population, which strengthened the generalizability of the thesis results.

Implications and recommendations for clinical practice and policy

The results of this thesis provide evidence for the magnitude of inappropriate referrals of patients towards a rheumatology outpatient clinic and a call for action. This has implications for the daily practice of GPs and gastroenterologists. To support the GPs, we recommend the implementation of the CaFaSpA strategy in Dutch primary care as well as its uptake in primary care guidelines. For gastroenterologists we suggest routine assessment of MSC via self-reported questionnaires such as the van Erp [9] questionnaire prior to hospital visits, as this is currently often not performed in clinical practice. As many IBD patients are unfamiliar with the link between IBD and IRDs, the awareness of IRDs among gastroenterologists, GPs, and IBD patients should be increased. Finally, a call for action is needed to incorporate referral strategies in international guidelines for rheumatologists, gastroenterologists, and GPs. In addition, policymakers should stimulate the communications and patient information exchange between primary care and secondary care specialists. Thereby incorporating an integrated digital platform could be useful. This may prevent health care defragmentation [28] and improve health care quality, health outcomes and reduce costs.

Recommendation for future research

This thesis has taken a first step towards the implementation of a referral strategy for axSpA by performing an impact study. The next step would be to evaluate factors that may influence implementation, such as acceptance of the referral strategy by GPs and patients. Qualitative studies could provide us with more knowledge about facilitators and barriers such as awareness, accessibility, usability, and acceptance for implementation. This could be evaluated by organizing focus groups with patients and GPs or through the distribution of surveys.

As a triage by a rheumatologist has also been shown to improve patient referral from primary care to a rheumatologist by 30% compared to usual care [29], we recommend evaluating a triage by a rheumatologist among CLBP patients who score positive on the CaFaSpA strategy. Using the CaFaSpA strategy as a pre-screening tool could decrease the workload of the rheumatologists in clinical triage. Combining the CaFaSpA and clinical triage in a two-step referral strategy may lead to more appropriate care and reduced costs. A head-to-head trial could be used as study

design to evaluate the effect of the two-step referral strategy (CaFaSpA plus clinical triage) by comparing the CaFaSpA plus clinical triage to solely the CaFaSpA strategy.

At last, as despite the advice of the CaFaSpA strategy, 39% of the patients did not visit the rheumatologist, we could speculate that the mandatory deductible that is part of the Dutch basic health insurance structure plays a role. Therefore, as the mandatory deductible can result in the accumulation of healthcare delivery leading to high costs [19], we recommend evaluating the impact of the mandatory deductible on health care utilization, health status and outcomes that are relevant for patients, and cost outcomes. With a large government funding, a randomized controlled trial would be the ideal design to evaluate the impact of the mandatory deductible in health care, where patients are randomized to the mandatory deductible, no mandatory deductible, and a low percentage of the mandatory deductible.
In the absence of funding, micro-simulation models [30] on proprietary healthcare claim data of the Dutch population could be used to compare health care expenditure before the introduction of the mandatory deductible (before 2008) and the years after the introduction of the mandatory deductible where the percentage of the mandatory deductible has increased over the years.

With regard to IBD patients with MSC, we recommend that future studies should focus on implementing referral guidelines in primary care and the gastroenterology unit for patients at risk for IRDs. Cohort studies could be used to validate available referral or screening strategies. Next, impact studies should be done. The impact of the referral strategy on health, process, and cost-effectiveness should be evaluated using cRCT.

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Addendum

Summary
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Dankwoord

SUMMARY

To improve quality of care and health outcomes for patients with musculoskeletal complaints that is patient-centered, allocating the right patients to the right care settings is crucial. In primary care, patients with inflammatory rheumatic diseases (IRDs) need to be timely recognized and referred to the rheumatology outpatient clinic as early treatment leads to better outcomes. This involves minimizing the number of patients with non-IRDs from receiving inappropriate referrals to the rheumatology outpatient clinic. Currently, patients with IRD are not adequately recognized in primary care, leading to inappropriate referrals to a rheumatologist. Along with rising healthcare costs and a shrinking healthcare budget, the way referrals are established requires optimization. This thesis provides insights into potential causes, offers solutions, and suggests recommendations for clinical practice.
The first part of this thesis describes the proportion of IRDs among patients referred to the rheumatology outpatient clinic and provides insights on the burden of musculoskeletal complaints among patients at risk for IRDs. The second part evaluates the impact of the most promising referral strategy i.e. CaFaSpA for axial spondyloarthritis (axSpA) on patients' outcomes and cost-effectiveness.

Part I. Occurrence and impact of IRDs in patients with musculoskeletal complaints

In **Chapter 2**, the proportion of rheumatoid arthritis as one of the most common forms of IRDs, among patients referred to the rheumatology outpatient clinic was assessed. A systematic review was performed and the impact of the introduction of ACR/EULAR classification criteria was estimated. In total, nine studies were included indicating a pooled proportion of 11% for rheumatoid arthritis. This proportion seemed to increase after the introduction of the ACR/EULAR classification criteria however, as the heterogeneity between studies was large, this rise could be due to other factors. A similar comprehensive systematic review was performed for other common forms of IRDs i.e. axSpA and psoriatic arthritis, taking the introduction of the ASAS and CASPAR classification criteria for axSpA and psoriatic arthritis into account (**Chapter 3**). Seventeen studies reported new onsets of axSpA, and 20 studies of psoriatic arthritis. The pooled proportion of axSpA within all newly referred patients was 19% and 18% for psoriatic arthritis. The proportion of axSpA before the introduction of the ASAS criteria was 3% and increased up to 21% after the introduction of the ASAS criteria. Similar to the systematic IRD review a wide-ranging heterogeneity was present, indicatin that these findings should be interpreted with caution as well. For psoriatic arthritis, the proportions of psoriatic arthritis before the CASPAR criteria could not be provided due to the limited available data. From the meta-analyses performed in chapter 2 and 3, the proportion of disproportional referrals in the rheumatology outpatient clinic exceeds 80%. This poses a major impact on healthcare systems, outcomes and costs, especially considering the expected

rise in IRD/musculoskeletal complaints incidence along with staffing shortages. Therefore, these results demonstrate an unmet need for selective referral of patients at risk for IRDs.

Next, as musculoskeletal joint complaints (MSC) and IRDs occur frequently among patients with inflammatory bowel disease (IBD), we quantified the burden of MSC on the quality of life of patients with IBD **(Chapter 4)**. A cross-sectional study was performed among secondary care Dutch IBD population and our study was enriched with data from Dutch IBD patients from primary care and a national patient association. MSC was independently associated with reduced quality of life among IBD patients (IBDQ: β = -10.6, 95%CI: -15.2--6.1). Eleven percent of the IBD patients had a rheumatological diagnosis and quality of life in these patients was significantly lower compared to IBD patients with non-rheumatological MSC. Administering a questionnaire to investigate MSC routinely prior to a hospital or GP visit could be a beneficial multidisciplinary disease management strategy that consequently has the potential to enhance the quality of life for IBD patients with MSC in the long run. Moreover, as MSC in IBD patients might be explained by IRDs, the use of a referral strategy to refer IBD patients at risk might be an effective approach to timely allocate the patients to the right care site, and consequently optimize the care delivery for this patient population.

Part II. Impact of a referral strategy

Several referral strategies have been developed for patients at risk for IRDs. However, the lack of evidence on the outcomes and cost-effectiveness of innovative referral strategies introduces challenges for decision-makers regarding the necessity and readiness for implementation. Therefore, the aim was to assess the impact of the most promising referral strategy for axSpA on patient outcomes and cost-effectiveness. The CaFaSpA referral strategy was developed and validated by our research group among the primary care chronic low back pain and contains four parameters that are simple and non-invasive. If at least two parameters are present, a referral to a rheumatologist is advised. The CaFaSpA referral strategy indicated a good discriminative, however before its implementation in daily clinical practice an impact analysis is required. A cluster-randomized controlled trial was performed to compare the use of the CaFaSpA strategy with usual care. In **Chapter 5,** the impact of the CaFaSpA referral strategy on patient-reported disability after 4 months of follow-up was described. The CaFaSpA digital referral strategy was able to identify axSpA patients, and its use did not lead to a decrease in the overall health status of patients. The mean difference in disability score was 0.28, as measured with Roland Morris Disability Questionnaire between both groups, which was not statistically significant nor clinically relevant after four months. As the balance between costs and effects of an intervention is crucial for decision makers, a cost-utility analysis of the CaFaSpA strategy was performed consequently from the healthcare and societal

perspective within a 12-month time horizon **(Chapter 6)**. Both disability and quality of life were used in the cost-utility analysis. After 12 months, the digital referral did not decrease the overall healthcare status of patients however, total costs were significantly lower (€-3,867) in the CaFaSpA strategy group, mainly due to lower productivity loss costs. Therefore, the CaFaSpA appears to be cost-effective when compared to usual care. This indicates that the CaFaSpA can be used as an appropriate primary care referral strategy for chronic low back pain patients at risk for axSpA. This contributes to the acceleration of providing care at the right time by the right caregiver.

In **Chapter 7**, the overall findings are outlined and discussed. Methodological considerations including generalizability of our results are also discussed. Finally, implications and recommendations for clinical practice as well as for future research are provided.

SAMENVATTING

Om de kwaliteit van zorg en de gezondheidsuitkomsten van patiënten met musculoskeletale klachten patiëntgericht te verbeteren, is het van belang dat de benodigde zorg wordt toegewezen aan de juiste patiënt door de juiste zorginstelling. In de eerstelijnszorg moeten patiënten met inflammatoire reumatische aandoeningen (IRD's) tijdig worden herkend en doorverwezen naar de polikliniek reumatologie. Vroegtijdige behandeling leidt immers tot betere gezondheidsuitkomsten. Dit houdt in dat het aantal onnodige doorverwijzingen van patiënten met niet-IRD's naar de reumapolikliniek geminimaliseerd moet worden. De realiteit is echter dat de herkenning van het ziektebeeld en de daaraan gekoppelde doorverwijzing niet optimaal verlopen. Gezien de stijgende zorgkosten en de steeds beperktere zorgbudget, is het belangrijk om de optimalisatiemogelijkheden van het doorverwijzingsproces nader te bekijken. Door de onderzoekingen in dit proefschrift is er inzicht verkregen in het verwijzingspercentage naar de reumatologische praktijk, is er een veelbelovende verwijsstrategie onderzocht en zijn er tot slot aanbevelingen geformuleerd voor de klinische praktijk.

Het eerste deel van dit proefschrift beschrijft de proporties van IRD's onder patiënten die worden verwezen naar de polikliniek reumatologie en geeft inzicht in de impact van musculoskeletale klachten bij patiënten met een risico op IRD's. Het tweede deel evalueert de impact van de CaFaSpA verwijsstrategie voor axiale spondyloartritis (axSpA), ten aanzien van relevante patiëntuitkomsten en kosteneffectiviteit.

Deel I. Aandeel en impact van IRDs bij patiënten met musculoskeletale gewrichtsklachten

In **hoofdstuk 2** is de proportie van reumatoïde artritis als een van de meest voorkomende vormen van IRD, geëvalueerd bij patiënten die naar de polikliniek reumatologie werden verwezen,. Hiervoor is een systematische review uitgevoerd waarin de impact van de introductie van de ACR/EULAR classificatiecriteria werd onderzocht. Negen studies zijn er in totaal geïncludeerd die een gepoolde proportie van 11% voor reumatoïde artritis rapporteerden. Deze proportie leek toe te nemen na de introductie van de ACR/EULAR classificatiecriteria. Door de grote heterogeniteit tussen de studies kan deze toename echter het gevolg zijn van andere factoren die mogelijk een rol spelen in deze geobserveerde toename. Daarnaast is in **hoofdstuk 3** een soortgelijke uitgebreide systematische review uitgevoerd voor andere veelvoorkomende vormen van IRD, namelijk axSpA en artritis psoriatica. Hierbij is de introductie van de ASAS en CASPAR classificatiecriteria respectievelijk voor axSpA en artritis psoriatica geëvalueerd. Voor axSpA zijn er zeventien studies gepooled en voor artritis psoriatica 20 studies. De proportie van axSpA binnen alle nieuw verwezen patiënten was 19% en voor artritis psoriatica bedroeg dit percentage 18%.

De proportie axSpA vóór de invoering van de ASAS-criteria was 3% en steeg naar 21% na de introductie van de ASAS-criteria. Bij deze systematische review was er eveneens sprake van een grote heterogeniteit, wat betekent dat deze bevindingen met voorzichtigheid moeten worden geïnterpreteerd. Voor artritis psoriatica geldt dat de proporties artritis psoriatica vóór de CASPAR-criteria niet geëvalueerd zijn vanwege beperkt beschikbare data.
Uit de meta-analyses in hoofdstuk 2 en 3 is gebleken dat het aandeel onnodige verwijzingen in de polikliniek reumatologie meer dan 80% van de totale verwijzingen bedraagt. Dit heeft aanzienlijke gevolgen voor de gezondheidszorgsystemen, patiëntuitkomsten en kosten. De verwachting is dat deze impact, gelet op de verwachte toename van IRD/musculoskeletale klachten in combinatie met de personeelstekorten, in de toekomst groter zal zijn. De resultaten van deze analyses wijzen op een onvervulde behoefte aan selectieve verwijzing van patiënten met een risico op IRD's.

Aangezien gewrichtsklachten en IRDs vaak voorkomen bij patiënten met inflammatoire darmziekten (IBD) is de impact van musculoskeletale gewrichtsklachten (MSC) op de kwaliteit van leven van IBD patiënten gekwantificeerd **(hoofdstuk 4)**. Hiervoor is een cross-sectionele studie uitgevoerd onder de Nederlandse IBD-populatie in de tweedelijnszorg inclusief IBD-patiënten uit de eerstelijnszorg en de nationale patiëntenvereniging. Het resultaat toont aan dat MSC onafhankelijk geassocieerd is met een lage kwaliteit van leven onder IBD-patiënten (IBDQ: β = -10,6, 95%CI: -15,2--6,1). Elf procent van de IBD-patiënten had een reumatologische diagnose bij wie de kwaliteit van leven significant lager was in vergelijking met IBD-patiënten met een niet-reumatologische MSC.
Het routinematig afnemen van een vragenlijst om MSC te onderzoeken voorafgaand aan een ziekenhuis- of huisartsenbezoek kan een nuttige multidisciplinaire strategie zijn voor ziektemanagement en heeft mogelijk de potentie om de kwaliteit van leven voor IBD-patiënten met MSC op de lange termijn te verbeteren.
Omdat MSC bij IBD-patiënten bovendien verklaard kan worden door IRD's, zou het gebruik van een verwijzingsstrategie waarbij IBD-patiënten met een verhoogd risico op IRDs doorverwezen worden naar een reumatoloog een effectief en gunstig effect kunnen hebben op de praktijk. Hierdoor wordt de IBD-patiënt tijdig aan de juiste medische specialist toegewezen, waardoor de zorgverlening voor deze patiëntenpopulatie optimaliseert kan worden.

Deel II. Impact van de CaFaSpA verwijsstrategie
Meerdere verwijsstrategieën zijn ontwikkeld voor patiënten met een risico op IRD. Het gebrek aan bewijs voor gezondheidsuitkomsten en kosteneffectiviteit van de innovatieve verwijsstrategieën vormt echter een uitdaging voor besluitvormers, omdat de noodzaak voor implementatie niet bekend dan wel niet voldoende onderbouwd is. Het tweede deel van dit proefschrift was daarom gefocust op het beoordelen van

de impact van de meest veelbelovende verwijsstrategie voor axSpA op patiëntuitkomsten en kosteneffectiviteit. Derhalve is de CaFaSpA verwijzingsstrategie ontwikkeld en gevalideerd door onze onderzoeksgroep. Deze strategie richt zich op de eerstelijnszorg voor patiënten met chronische lage rugklachten en bevat vier te beantwoorden parameters die eenvoudig en non-invasief zijn. Als tenminste twee parameters aanwezig zijn, wordt een verwijzing naar een reumatoloog geadviseerd. De CaFaSpA-verwijzingsstrategie bleek een goed onderscheid te kunnen maken tussen axSpA patiënten en patiënten met chronische lage rugklachten. Een impactanalyse is echter vereist, alvorens deze verwijsstrategie geïmplementeerd wordt in de dagelijkse klinische praktijk. Om die reden is een cluster gerandomiseerd gecontroleerd onderzoek uitgevoerd om het gebruik van de CaFaSpA-strategie te vergelijken met de huidige standaard zorg.
In **hoofdstuk 5** is de impact van de CaFaSpA verwijzingsstrategie- na vier maanden follow- up-beschreven met betrekking tot de door patiënten-gerapporteerde fysieke beperkingen en kwaliteit van leven. De digitale verwijsstrategie van CaFaSpA is in staat om axSpA-patiënten te identificeren, waarbij het gebruik ervan niet heeft geleid tot een afname van de algehele gezondheidsstatus van patiënten. Het gemiddelde verschil in fysieke beperkingen score was, zoals gemeten met de Roland Morris Disability Questionnaire, tussen beide groepen 0,28 punten. Echter, was dit resultaat na vier maanden onderzoek niet statistisch significant en/of klinisch relevant.
Daarnaast is een kosten-batenanalyse van de CaFaSpA-strategie uitgevoerd, waarbij rekening gehouden is met een evenwichtige verdeling van baten en kostenverdeling voor besluitvormers. Deze analyse is uitgevoerd vanuit het perspectief van de gezondheidszorg en de maatschappij binnen een tijdshorizon van 12 maanden en wordt in **hoofdstuk 6** beschreven. Bij het maken van de kosten- en batenanalyse zijn zowel de fysieke beperkingen als de kwaliteit van leven meegenomen. In de CaFaSpA-strategiegroep verminderde het aantal digitale verwijzingen de algemene gezondheidsstatus van patiënten niet na afloop van 12 maanden, terwijl de totale kosten significant afnamen (€-3.867). Deze afname is te verklaren door een lagere productiviteitsverlies. Hieruit blijkt dat de CaFaSpA kosteneffectief is, in vergelijking met de standaard zorg. Wij concluderen dan ook dat de CaFaSpA een geschikte verwijzingsstrategie is voor de eerstelijnsgezondheidszorg voor patiënten met chronische lage rugklachten met risico op het ontwikkelen van axSpA. De CaFaSpA-strategie draagt namelijk bij aan het aanbieden van zorg op het juiste moment door de juiste zorgverlener.
In het laatste hoofdstuk, **hoofdstuk 7**, worden de algemene bevindingen beschreven en bediscussieerd inclusief methodologische overwegingen, waaronder de generaliseerbaarheid van de resultaten uit dit proefschrift. Tot slot worden implicaties en aanbevelingen voor de klinische praktijk en toekomstig onderzoek beschreven.

PhD portfolio

Name: Maha Jamal

PhD period: 2017-2024

Promotors: Prof. Dr. A.E.A.M. Weel-Koenders

Prof. Dr. J.M.W. Hazes

Co-promotor: Dr. D. Lopes Barreto

PhD Training (ECTS)	Year	Workload
General academic skills		
Workshop 'Met subsidie meer mogelijk'	2018	0.3
Master class logframe	2018	0.3
Writing in English for publication	2018	2.0
CPO course	2019	0.3
Student Coaching training	2019	0.2
In-depth courses		
Basic principles in Epidemiology	2017	1.0
STATA	2018	0.3
Cost-effectiveness analysis	2019	1.1
Mixed models	2020	1.1
Bio-statistics	2020	2.0
Systematic review and meta-analysis	2020	0.5
National and international conferences		
Nederlandse vereniging voor reumatologie (NVR) (oral presentation)	2017	2.0
Wetenschaps lunch (attendance)	2017	0.1
Nederlandse vereniging voor reumatologie (NVR) (attendance)	2018	1.0
European League Against Rheumatism (EULAR) (attendance)	2018	1.0
Wetenschapsdag (poster presentation)	2019	1.0

Nederlandse vereniging voor reumatologie (NVR) (attendance)	2019	1.0
International Consortium for Health Outcomes Measurement (ICHOM) (poster presentation)	2019	3.0
International congress on low back and pelvic pain (oral presentation)	2019	2.0
European League Against Rheumatism (EULAR) (2x oral presentation)	2020	2.0
Wetenschapsdag (attendance)	2020	0.2
Nederlandse vereniging voor reumatologie (NVR) (attendance)	2020	0.3
International Consortium for Health Outcomes Measurement (ICHOM) (2x poster)	2020	3.0

Teaching activities

Supervising student in data entry	2017-2019	1.0
Coaching 2nd and 3rd year medical students	2019-2021	0.5
Supervising student in bachelor thesis research	2020-2021	1.5

Seminars

Department Research Meetings Erasmus MC	2017-2021	1.0
Journal club	2017	0.5
Department Research meetings Maasstad Hospital	2019-2021	1.0

LIST OF PUBLICATIONS

This thesis

van Delft ETAM, **Jamal M**, den Braanker H, Kuijper TM, Hazes JMW, Lopes Barreto D, Weel-Koenders AEAM. A systematic review on time trend incidence of rheumatoid arthritis in outpatient rheumatology clinics. *Front Med* 2022;9:933884. doi: 10.3389/fmed.2022.933884.

Jamal M, van Delft ETAM, den Braanker H, Kuijper TM, Hazes JMW, Lopes Barreto D, Weel AEAM. Increase in axial spondyloarthritis diagnoses after the introduction of the ASAS criteria: a systematic review. *Rheumatol Int* 2023;43(4):639-649. doi: 10.1007/s00296-022-05262-6.

Jamal M, Korver AM, Kuijper M, Lopes Barreto D, Appels CWY, Spoorenberg APL, Koes BW, Hazes JMW, Hoeven LV, Weel AEAM. The IMPACT study: A clustered randomized controlled trial to assess the effect of a referral algorithm for axial spondyloarthritis. *PLoS One* 2020;15(1):e0227025. doi: 10.1371/journal.pone.0227025.

Jamal M, Kuijper TM, Hazes J, Lopes Barreto D, Weel A. A trial-based economic evaluation of the CaFaSpA referral strategy for axial spondyloarthritis. *Scand J Rheumatol* 2024;53(1):1-9. doi: 10.1080/03009742.2023.2243081.

Jamal M, Karreman M, de Bruijne F, Kuijper TM, Hazes JMW, Lopes Barreto D, Weel AEAM. Impact of musculoskeletal joint complaints on quality of life in patients with inflammatory bowel disease. BMJ Open 2024;14:e088350. doi: 10.1136/bmjopen-2024-088350

ABOUT THE AUTHOR

Maha Jamal was born on November 10, 1987, in Kassala, Soedan. She followed her elementary school in Al Taka, in Kassala, Sudan, and pursued her high school at the Al Echoa Wa Salam school, in Kartoem, Sudan. In 2003, far away from home, she started a new life in the Netherlands. In the year 2003/2004, she started an extensive one-year program to master the Dutch language. After that, she followed a bridge class (colloquium doctum) for people with prior non-Dutch education. To pursue her dream of working in the lab and inventing new medicines, in 2011, she obtained her master's degree in biopharmaceutical science at the University of Leiden. Nevertheless, conducting research at the epidemiology department of the Julius Center provided her with a new career perspective that she found more satisfying than working in the lab, leading her to pursue a master's program in epidemiology at the University of Utrecht. To advance her knowledge and expertise, she decided to pursue a PhD program. In 2017, she started her PhD in the department of rheumatology and clinical immunology at the Maasstad hospital. The main objective of her PhD was to optimize the referral of patients at risk for inflammatory rheumatic diseases. Her work focused on reviewing the amount of (inappropriate) referrals at the rheumatology outpatient clinic. And investigating the impact of an innovative referral strategy on health outcomes and costs.

DANKWOORD

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Daarnaast wil ik mijn zusjes en broertje bedanken voor hun steun tijdens mijn PhD. Eindelijk kan ik dan de vraag 'wanneer ben je nou klaar met je PhD?' beantwoorden. Het antwoord is: nu! Houd de camera's maar gereed voor jullie lang geanticipeerde foto's.

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