Context matters in outcome and management of rheumatoid arthritis

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Chapter 9

Summary and general discussion
In this final part of the thesis, first the main results are summarized. Next, we discuss methodological challenges in the conduct of our studies. Finally, we address possible clinical implications of the results and suggest areas for future research.

Summary (of the main findings)

The important role of context in the outcome of chronic diseases is widely acknowledged. It is estimated that up to 80% of the avoidable burden of illness can be found in the context of persons or populations.\(^1\) This thesis addressed the role of two contextual factors that so far have received limited attention in rheumatoid arthritis (RA) care, namely the role of country of residence on outcomes in RA and the role of the healthcare professionals’ (HCPs) preferences in the management of RA. The main findings are summarized in Figure 9.1.
Chapter 9

I. Country of residence as contextual factor in outcome measurement in rheumatoid arthritis
   a. Country of residence has an important influence on variations in outcomes including fatigue, disease activity and physical function
   b. When exploring the influence of specific country characteristics on fatigue, a stronger effect was found for the country’s economic and development status compared to the country’s level of income inequalities, climate and language
   c. A paradox was observed for the relation between the country’s wealth and outcomes: While patients from wealthier and more developed countries had lower objectively assessed disease activity, they perceived a higher impact of the disease (especially fatigue and well-being)

II. The healthcare professionals’ preferences as contextual factor in the management of rheumatoid arthritis
   a. When choosing drug treatments for patients with rheumatoid arthritis, efficacy clearly dominates rheumatologists’ choices across countries
   b. In addition to efficacy, rheumatologists overall account for patients’ preferences and economic aspects when choosing drug treatments
   c. Interestingly, patients’ preferences are in particular influential on rheumatologists’ drug choices when patients express their dislike with a proposed treatment
   d. When considering economic aspects in a drug choice, rheumatologists primarily consider absolute costs. It is estimated that more than half of European rheumatologists even disregard the cost-effectiveness of a drug
   e. Significant heterogeneity in preferences for a drug treatment choice exists among individual rheumatologists: While there is some influence of country of residence, the role of the rheumatologists’ socio-demographic background seems minor
   f. Overall, healthcare professionals agree with patients on priorities in rheumatoid arthritis care as well as key areas of care that need to be improved

Figure 9.1 Summary of key findings
Further, on the following pages, the main findings of the individual studies of the thesis will be summarized in more detail.

Part I: The role of country and socio-cultural context in outcome measurement in rheumatoid arthritis

In chapter 2, we analysed the possible role of country of residence on fatigue, an important outcome for patients with RA. Fatigue is often assessed using a single global measure, the 0-10 visual analogue scale (VAS). In a study among 3920 RA patients from 17 countries from different world regions, we revealed that objective measures of disease activity, namely tender- and swollen joint counts (TJC, SJC) and erythrocyte sedimentation rate (ESR) had only limited contribution to the variation in the level of fatigue or in the likelihood to be severely fatigued (0-10 VAS≥5), while more subjective outcomes (such as self-assessed physical function and overall health) moderately contributed to the observed variations. Of interest, fatigue varied importantly across countries, even after adjustment for individual and disease characteristics. In the Netherlands (NL), the country with the highest level of fatigue, average fatigue was 5.0, which was 3.5 points higher than in the country with the lowest level of fatigue, and the odds to be severely fatigued were 31-fold higher in NL, the country with the highest proportion of severely fatigued patients compared to the one with the lowest proportion (Venezuela). When trying to understand factors that could explain the ‘country effect’ on fatigue, we found that higher economic welfare, measured by gross domestic product per capita adjusted for purchasing power parity (GDP-PPP), and higher development status, measured by human development index (HDI), contributed to higher levels of fatigue and to a larger proportion of patients being severely fatigued, while effects of latitude (a possible surrogate for climate or sunshine), language and income inequality within the country (Gini-index) were negligible.

In Chapter 3, we then investigated whether the role of country of residence is similar across different outcome domains. The same dataset as in chapter 2 was used. Specifically, this study explored patterns in the role of country of residence when comparing more objective measures that assess disease activity (TJC, SJC, and an adjusted Disease Activity Score 28 (DAS28), consisting of both joint counts and ESR, but without patient global assessment of the disease (PatGA)) or physician global assessment of the disease (PhysGA)) with three more subjective patient-reported outcome (PRO) measures (fatigue, physical function, PatGA). Important country differences were present across all outcomes and persisted after adjusting for individual confounders. When grouping countries by their level of economic wealth (GDP-PPP), we observed opposite results for objective measures (DAS28, PhysGA) and PROs (fatigue,
PatGA and less strongly also physical function). Patients in wealthier (higher GDP) countries had on average 1.0 point better DAS28 compared to poorer countries (lower GDP), but paradoxically worse PROs (e.g. on average, subjective self-reported fatigue was 1 point higher on a 0-10 VAS). Of note, independent of country of residence, patients with poorer education had worse objective- and patient-reported outcomes (PROs).

Chapter 4 introduced a methodological approach to investigate the influence of contextual factors on patient- and physician-reported outcome measures. Specifically, we investigated differential item functioning (DIF) within the item response theory (IRT) framework when measuring the construct 'physical function' captured using the different versions of the Health Assessment Questionnaire (HAQ) in RA. The IRT framework is a widely used approach to explore the psychometric properties of a measurement scale consisting of multiple items. IRT implies that both, the 'person's ability' and the 'item difficulty' are placed along the same single latent dimension, in this study 'physical function'. By exploring DIF, we could show that socio-demographic factors including age, gender, employment status and education cause bias across a substantial but varying number of items of the various HAQ versions. This means these individual items perform differently – assessed through standardized odds ratio in one subgroup compared to another (e.g. lower opposed to higher educated persons, or females opposed to males) at the same level of physical function – and these differences reach 10% or more. However, the effect on the composite HAQ scores after adjusting for DIF was minimal (mean composite scores increased by < 0.1) indicating the overall accuracy of composite HAQs across socio-demographic groups. Further, regressions analyses of the HAQ before and after adjusting for DIF revealed that the association between socio-demographic factors and HAQ remains largely similar confirming the difference in HAQ scores between socio-demographic groups is not simply caused by item bias.

Part II: The healthcare professionals’ preferences as contextual factor in the management of rheumatoid arthritis

In chapters 5 to 7 we studied how rheumatologists trade-off different characteristics of drug treatments. We aimed specifically to understand to what extent patients’ preferences and economic implications of treatments play a role in rheumatologists' treatment choices, in addition to classical aspects such as efficacy and safety. Further, we were interested in understanding whether a) socio-demographic factors (Chapter 5), b) country of residence (Chapter 6) and c) the patient profile (Chapter 7) influence the treatment choice of rheumatologists. To answer this question, a discrete choice
experiment (DCE), a frequently used method to elicit preferences in healthcare, was designed. Rheumatologists were asked to repeatedly choose their preferred drug treatment for the clinical context of a specific patient with clearly defined personal (female, 42 years old, smoking) and disease characteristics (moderate active RA despite two conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs)). In a series of choice tasks, two alternative (hypothetical) treatment options were presented to rheumatologists, differing according to five attributes relevant to our study objective, i.e. efficacy, safety, patients’ preferences, absolute costs and cost-effectiveness.

Chapter 5 shed light into the preferences of 63 Dutch rheumatologists towards drug treatment characteristics. Efficacy had the strongest relative contribution to the drug choice (44%) followed by medication costs (24%), patients’ preferences (17%) and cost-effectiveness (14%). Patients’ preferences were most relevant when patients disliked a proposed treatment. Interestingly, when making economic trade-offs, absolute costs were more important than the weighted cost-effectiveness considerations. The study further showed an important heterogeneity in rheumatologists’ preferences, although not explained by differences in age, gender or work-environment of rheumatologists.

Next, Chapter 6 revealed the role of country of residence on preferences towards drug treatments. Data from 559 rheumatologists from 12 countries were retrieved using the same DCE. The countries represented different European geographic regions with varying economic and healthcare environment comprising (Belgium (BE), Germany (GE), Hungary (HU), Netherlands (NL), Norway (NO), Sweden (SE), Spain (SP), United Kingdom (UK), France (FR), Italy (IT), Portugal (PT) and Romania (RO). The study confirmed the Dutch findings with a high importance of efficacy, but additional relevance of patients’ preferences and economic aspects in drug treatment choices. The relative contribution of absolute costs was higher than of cost-effectiveness, and this happened across all countries, with the exception of the UK and HU, in which cost-effectiveness was more valued. Cluster analyses of the countries’ mean relative importance weights for the five attributes revealed two clusters of countries. When further exploring the heterogeneity in individual preference profiles of rheumatologists using latent class models, four classes of rheumatologists were identified despite substantial inter-individual variations among clinicians. The majority of rheumatologists (43%) belonged to the first identified class, and accounted for both economic attributes (absolute costs and cost-effectiveness) but largely disregarded safety while rheumatologists belonging to the remaining classes (22.6%, 31.1% and 11.1% respectively) largely disregarded cost-effectiveness. Rheumatologists from FR, IT, PT, RO were significantly more likely to be located in the latter classes, and thus overall disregard cost-effectiveness. Of note,
absolute costs remained a relevant criterion in treatment choices for 77% of individual clinicians.

Finally, the role of the patient’s disease profile in rheumatologists’ drug choice was described in Chapter 7. Rheumatologists from countries with more restricted healthcare settings and thus higher sensitivity to also economic implications of a drug choice, were asked to complete the above described DCE not only for a patient with moderate active RA, but also for a patient with high disease activity. In line with the previous studies, drug efficacy was the driver for treatment choices, irrespective of disease status. Interestingly, the importance of economic considerations was largely independent of disease severity, indicating that individual rheumatologists valued the beneficial effects of medication to lower disease activity and achieve remission similarly in patients with moderate and high disease activity. This findings confirm an indisputable support for a treat-to-target approach in every RA patient. Rheumatologists were however willing to give up some efficacy to account for patients’ preferences when choosing treatments for patients with moderate compared to high disease activity.

As the management of chronic diseases including RA became more holistic in recent years, with evolution towards patient centred care in which patients have a voice in the care they want to receive, we dedicated the last chapter (Chapter 8) to the comparison of the patients’ and HCPs’ perspective on RA care. The study aimed to better understand concordance and discordance when it comes to priorities in daily care and areas that require improvement. For this study, we used the lay version of the 20 European Standards of Care (SOCs) and investigated the level of agreement for two dimensions: a) level of implementation of the SOCs and b) priorities in RA care among 386 patients and 91 HCPs from NL. We found that patients and HCPs agreed that adequate DMARD treatment, access to care in case of emergency and regular re-appraisal of treatment targets in case of treatment failure are among the most important aspects of RA care. Fortunately, these standards were considered as appropriately implemented by both patients and HCPs. However, some relevant care gaps were identified by patients and HCPs, including diagnosis within 6 months of symptom onset and availability of a treatment plan. Patients, to a larger extent than HCPs, suggested in addition improvements in receiving a schedule of regular assessment of disease. While patients and HCPs agreed that limited financial coverage of some recommended health services was a barrier for implementation, patients additionally pointed to the limited time of physicians during consultations.
Methodological considerations

Specific methodological strengths and limitations of the individual studies in this thesis have already been addressed in the discussion sections of the respective chapters. Below, we expand on some overarching issues pertaining to the thesis.

1. Country of residence in outcome research in rheumatoid arthritis

While we highlighted the role of country of residence as a contextual factor in outcome of RA, the mechanisms through which 'country' actually exerts its influence on outcome remain difficult to understand. Possible explanations include underlying factors that characterize country of residence, linguistic issues of the outcome measure, and the design and analyses of multinational data.

1.1 Availability of factors characterizing country of residence in outcome research

Only a limited number of studies available in the literature investigated the influence of 'country' on variations in health outcomes beyond potential biological (often genetic) factors shared within populations. Such studies commonly interpret 'country' as a surrogate for healthcare standards i.e. the quality of a healthcare system and patients’ access to care. In general, higher healthcare standards and better access to care are considered to result in better outcomes. However, only few studies formally tested this assumption. This is not surprising, as variables that allow measurement of 'quality of healthcare' including 'access to healthcare' on the country level are very limited. Even basic factors such as the number of HCPs relative to the population size or availability of reimbursed technologies and treatments for specific diseases and interventions at the population level are difficult to retrieve across countries. In RA, one study was able to show that variation in disease activity between countries was partly explained by difference in gross domestic product per capita (GDP), and further revealed the relation between GPD and disease activity was partly mediated by uptake of biologicals. However, access to high quality healthcare does not explain all country related variations in health outcomes. Our studies suggest that the influence of country is indeed more complex: first, multiple country characteristics contributed to variations in outcomes across countries, and secondly the magnitude and direction of influence can differ across outcome domains.

When searching for the availability of indices to operationalize possible candidate country characteristics in our study on variation in fatigue across countries, we faced a number of challenges. Several available country characteristics were associated with patients' reported fatigue, with strong (negative) influence of the country’s economic
and development status (GDP and HDI) and smaller influences of prevailing income inequalities (Gini-index), climate or language. However, when exploring whether more sunshine results in less fatigue, we used latitude of the country’s capital, recognizing that latitude rather reflects hours of daylight than sunshine, and further ignores variation between regions in large countries. Also, although GDP can be a helpful proxy to describe the country’s overall wealth, important differences may be present in economic prosperity within the country (e.g. urban vs rural regions). Further, available indices were not always calculated similarly across countries and were often not available for comparable periods in time. As an example, availability of the Gini-index, which we explored as a possible surrogate for inequality in access to healthcare, spanned 15 years, a period in which income inequalities may have substantially changed in selected countries. Finally, there is large overlap between some country-indices (e.g. HDI and GDP are strongly correlated) making it difficult to draw clear conclusions on their individual contribution.

1.2 Country of residence as possible surrogate for the socio-cultural environment

Importantly, a large part of the influence of country of residence on outcome remained unexplained and raised the question what this 'unexplained' variation actually represents. Much insight was obtained from the observed paradox with patients from wealthier countries overall scoring worse on PROs despite lower disease activity, reflected by lower TJC, SJC and ESR. PROs primarily assess how patients feel (e.g. fatigue, PatGA), and thus reflect the patients’ appraisal of disease in the context of their personal believes and living environment. The reverse relationship between GDP and disease activity measures as opposed to fatigue, strengthened the idea that also intangible factors such as the socio-cultural environment play a role in the patients’ individual disease experience. When interpreting the finding of higher fatigue and worse wellbeing in wealthy countries, we speculated that hectic and stressful lifestyle in higher income countries may play an important role. Possibly, in richer countries the society demands more from patients, eventually because it offers them better healthcare. In return, patients may be expected to keep up with the fast-paced lifestyle and high work productivity, an expectation patients may not always manage to cope with. In this context, it would have been interesting to also understand how the general population scores on the same scales (e.g. fatigue or general health) and compare the data with patients’ responses across countries.

Understanding and measuring the construct of 'socio-cultural values' or 'socio-cultural environment' however is a challenge. The term 'culture' is a quite intangible notion that lacks clear definition. In the literature, multiple definitions for culture exist. Culture can be considered as a set of guidelines (explicit and implicit) that individuals inherit as
members of a society and that tells them how to view the world, how to experience it emotionally and how to behave in it in relation to other people, supernatural forces (e.g. God) and to their natural environment. In a shorter definition, culture can be described in its broadest sense as a ‘cultivated behavior’; that is the totality of what a person has learnt, accumulated experience which is socially transmitted, or more briefly, behavior through social learning. Both definitions reveal the multidimensional nature of culture and indicate the difficulty to transform it into a single, unambiguous, variable for research.

1.3 Linguistic aspects, scale interpretation and item bias of outcome measures

Multi-national studies on diseases outcome assume that measurement instruments are culture-proof, i.e. assess the same construct across countries. Over the last decades, much attention has been paid to correct linguistic and cultural validation when translating PROs into other languages. Notwithstanding, it cannot be excluded that some questions or even whole questionnaires had different meanings in different countries. Specific for our study on fatigue, the distinction in meaning between the words ‘tiredness’, ‘fatigue’ and ‘exhaustion’ does not exist in all languages. This suggests that linguistic aspects require continuous attention and add complexity to cross-country comparisons.

The linguistic and cultural validity of PROs further expands to clinimetric properties such as minimal important difference or cut-offs to categorize severity of symptoms. As part of our analyses, we explored the risk for patients to be severely fatigued across countries and used a score equal or above 5 on the numeric rating scale/ VAS as threshold for severe fatigue. This threshold was proposed in a study conducted in UK, Western Europe. However, it can be questioned whether this threshold is equally applicable across countries and cultures. Persons from different cultural background might have different perception on the level of fatigue that actually constitutes ‘severe fatigue’. An interesting approach to further understand whether a country effect in a multi-item outcome measure is true or results from an instrument bias, is the exploration of DIF in the context of IRT. In the present work, we investigated DIF for all the items contained in different HAQ versions across several socio-demographic patient characteristics. We showed that socio-demographic factors caused bias in the majority of the individual HAQ items, but the effect on the composite HAQ scores was minimal. Importantly, even after adjustment of HAQ scores for DIF, the socio-demographic factors contributed to variance in HAQ, indicating differences in HAQ between these subgroups cannot be attributed to item bias only. Investigation of DIF on country level involved technical complexities, and therefore these analyses were not yet part of the present thesis. Preliminary data revealed that composite HAQs overall have good psychometric
properties across countries, the use of M-HAQ may however be favoured when comparing physical function across countries. Important DIF on country level was in particular found for Serbia, Egypt, Russia, Morocco. For that reason, these countries were also removed from our study investigating DIF across socio-demographic variables (chapter 4). It should be reminded that IRT models are only applicable to multi-item questionnaires. Moreover, while DIF can reveal whether a contextual factor causes item bias, it cannot identify the underlying reason. Finally, when DIF for some items across countries is detected, the key question is actually whether these items should be deleted to ensure clinimetric comparability in outcome measures, or whether these items have high face validity. In the latter situation, different instruments across countries should be used, limiting direct comparability of scores.

1.4. Datasets, study design and analyses of multinational observational studies

When investigating the influence of country on outcomes and management of RA, we faced several challenges related to availability of multinational data, the study design and analysis of the data.

Setting up new studies/cohorts is complex, expensive and particularly involves a long period of time, therefore we used existing studies to the extent possible. To our knowledge COMORA and QUEST-RA are the two largest international observational studies in RA. In order to explore the complex relationship between individual and country-level determinants, it is essential that such databases are rich in individual level factors related to the disease, personal characteristics and personal environment. Unfortunately, none of the available datasets included variables such as personal/household income or level of health insurance (as proxy for uptake of care), coping style or level of self-efficacy. These person-level determinants can vary importantly between countries and thus would help to interpret independent differences between countries. On the other hand, collecting more background information increases length and complexity of questionnaires and increases risk of non-participation and selection bias.

Efforts to collect new data in the setting of multinational research should not be underestimated. The preference studies among rheumatologists (chapter 5 to 7) and the audit-study of European SOCs in RA as an international study (chapter 8 describes only the Dutch results) posed clear challenges. First, translation and adaptation of questionnaires to the varying local realities was a work intensive step that often restrained local principal investigators to support study conduct. Second, different regulations had to be followed with regard to ethical approval of clinical studies among patients and even professionals. Even on the level of participating centers within a country, important differences in the need, procedures and costs for study approvals
existed. Last, when collecting new data in an international setting, ensuring generalizability of data remains a challenge as some approaches for recruitment might not be possible or feasible in all countries (e.g. differences in availability and accessibility of registries). Also, the preparedness of patients or professionals to participate in a study might differ between countries. Studies that aim to explore country of residence (or country level determinants of health) should give additional attention to sampling strategies and ensure proper phenotyping for country-relevant factors.

Of note, the data used in the present work include cross sectional data only. Notwithstanding, longitudinal data have additional value as they can, opposed to cross-sectional studies, shed light into causal relationships and are further informative when studying changes over time (e.g. innovations in (cost of) technologies, regulations of healthcare systems, etc.).

In the present work we were naturally interested in true effects and not in spurious relationships. Therefore, we performed linear and logistic regression analyses to investigate the effect of a given country (compared to a reference country) on the outcomes. Following the Outcome Measures in Rheumatology (OMERACT) definition that effect modification would add to the importance of a factor as a real contextual factor, also interactions between individual and country socio-economic characteristics were tested. However, not all analytical methodological challenges could be solved following the selected approach. When a model is not corrected for the appropriate confounders, spurious relationships might be detected. In the case of the analysis of PROs (e.g. fatigue or PatGA), some additional factors could be relevant like level of illness beliefs or coping mechanisms or even genetic effects, relevant individual level confounders, that may cluster in countries and thus explain some of the observed impact of country of residence. Furthermore, by adding country or country characteristics as a factor variable to the models, we ignored the dependency in observations, as patients are nested within countries. This could have been taken into account by using a multilevel model. However, this is turn, is also limited in terms of power, as the power to detect country level predictors is driven largely by the number of countries. The number of countries included in multinational studies, though impressive in what concerns the logistic challenges they represent, is usually relatively small in statistical terms when analysing country-level variables. Nevertheless, this represent more elegant solutions to analyse multinational studies. Last but not the least, our analyses on country effects have been limited to observational studies. Also, an interesting question would be whether interventions have different effects across countries, in other words, whether effect sizes are country dependent.20
2. Assessing preferences of healthcare professionals

Few studies in health research addressed beliefs or behaviours of HCPs and their influence on management decisions and/or disease outcomes.\textsuperscript{21-24} Several well established methodological approaches are available. The selection primarily depends on the specific study question, and both qualitative as well as quantitative methods can be useful. For our research question, a DCE seemed an appropriate study design, as we were especially interested in how rheumatologists trade-off specific treatment characteristics when choosing a drug. Also, the DCE setting allows the use of a single and clearly defined ‘paper patient profile’ that eliminates heterogeneity in preferences related to variations in patient characteristics, likely a major source of heterogeneity in physicians’ behavior in a real life clinical setting. Of interest, our study comparing clinicians’ preferences for two different patient profiles confirmed an influence of the patient’s disease severity on preference patterns of rheumatologists, suggesting the need for a clear definition of a patient profile in preference research.

When interpreting the findings of our preference studies, the principles of a DCE should be acknowledged. In a DCE, the number of attributes and levels that can be tested is limited, i.e. individuals can only account for a limited number of choice characteristics, generally a maximum of about eight, that describe a choice option. On that line, we carefully selected the attributes and levels while keeping in mind the main study question. Further, it is essential to understand that a DCE can only provide insights into \textit{stated} preferences while \textit{revealed} preferences may differ in several aspects and thus partly limit conclusions for clinical practice. While in some situations the choices in real life are equally or even more important, stated preferences can also be important to understand what respondent would wish to choose in hypothetical situation. When such hypothetical choices do not exist, DCE might indicate how reality would preferably be adjusted.

With regard to the results, the high heterogeneity in preferences among individual rheumatologists was striking. Interestingly, available factors characterizing physicians (e.g. age, gender or work environment) could not explain the observed high inter-individual heterogeneity, leaving the question ‘how/why’ physicians make their choices partly unanswered. It may have been additionally insightful to study the influence of factors such as affiliation with research or believe in authority. However, no data were collected in the present study that would allow for such analyses.

From the outset of the study, it was our intention to compare preferences of rheumatologists across countries. This posed additional methodological challenges. First, we computed the relative importance weights of the attributes for each country separately. However, results did not allow for statistical conclusion on differences between countries. As a second step in the approach to assess the potential effect of
country on preferences, we aimed to include country as a covariate in the latent class model to assess if the probability to belong to a class differs between countries. However, given the limited sample size, it was not possible to add all individual countries as covariates. When trying to group countries into smaller, but theoretically meaningful groups, such as geographic regions, clinical criteria for drug reimbursement, type of insurance system or the country’s wealth and development status, no clear patterns could be found. We therefore explored the data statistically and applied cluster analyses that grouped countries based on similarity in mean relative importance weights across the five attributes resulting in two clusters. To understand whether country and individual characteristics could further explain heterogeneity, we continued our analyses with a latent class model. This analysis revealed four different response patterns that could be primarily described by the rheumatologists’ attitude towards economic treatment characteristics and safety while attitude towards efficacy and patients’ preferences did not determine affiliation with a class. Last we included the cluster as a covariate in the latent class model. We observed that countries from one cluster (FR, IT, PT, RO) have a higher probability to disregard cost-effectiveness considerations.

Clinical implications & future research

1. Influence of country on outcomes in rheumatoid arthritis

Although evidence on the influence of 'country' on outcomes might not have immediate impact on daily clinical care, we feel our findings are useful when supporting patients to self-manage the disease, and also to get further insight into outcome determinants.

It is important that patients understand that outcomes experienced by patients (such as fatigue) are complex and multifactorial. Patients’ experiences of impairments and limitations are not only related to the biology of the disease and its treatments, but are also influenced by context including personal appraisal. Specifically for fatigue, patients can be informed that, although (severe) fatigue is a common symptom among patients with RA, no clear relationship has been shown between disease activity and fatigue. In addition, it might be informative to share the results of our paradox and thus stimulate patients’ self-reflection on internal and external stressors in their life, including personal expectations, pressure at work or pressure to fulfil multiple social roles. Of interest, recent studies exploring fatigue over time suggest that despite significant advances in RA care during the past decade as reflected in lower SJC and lower ESR, patients express more fatigue and worse pain. This further strengthened our hypothesis that ‘context’, likely internal and external stressors, contribute importantly to a patient’s individual disease experience.
With regard to future research on fatigue, it could be interesting to apply multidimensional fatigue questionnaires in multinational studies. Multidimensional questionnaires aim to explore several types of fatigue and often distinguish physical, emotional, mental and cognitive fatigue.\textsuperscript{27} Such studies might be helpful to understand whether also types of fatigue indeed differ across countries. We hypothesize a more dominant role of emotional and cognitive fatigue in Western high income countries. As part of such a study, exploring DIF related to country might help to understand whether some items related to subdomains of fatigue have indeed a different position in the latent scale ‘fatigue’ in some countries. Moreover, future research projects may explore the role of stress on PROs (and specifically on fatigue) in RA. Extensive literature can be found on measures to assess levels of (perceived) stress\textsuperscript{28-30} that can be helpful to address the role of stressors such as self-expectations, social or economic pressure on the individual disease experience. It may be further interesting to investigate not only whether stress relates to fatigue, but also to explore how this relates to other individual personal contextual factors such as coping strategies or self-efficacy, and whether such relationships are different across countries. Currently, there is limited evidence on the role of these personal factors in relation to e.g. fatigue.\textsuperscript{32} Moreover, insight into country level differences in perceived stress and its impact on the patient’s disease experience can fuel discussions on Western lifestyle and start initiatives on the public health level to adopt a lifestyle that is less prone to stress, anxiety and pressure.

The paradox in our study also raises the question whether priorities in patient goals would be different across countries. Existing studies on patients’ needs and priorities commonly provide information from highly developed countries in Europe or North America.\textsuperscript{32-35} It may therefore be interesting to understand how patients from different world regions prioritize the core outcome domains as identified by international initiatives such as the International Classification of Functioning, Disability and Health (ICF)\textsuperscript{36} and OMERACT.\textsuperscript{37} Of interest, our study investigating treatment priorities and gaps related to the European SOCs, collects data from rheumatologists and patients in more than 40 European countries to understand differences in priorities in care across countries and regions. However, data collection is still ongoing in some countries, therefore data are not part of the present work.

This thesis made clear that a sound methodological framework is needed when further investigating the role of country of residence in relation to outcomes. In addition to the theoretical framework and classification of personal and environmental contextual factors, the approach to select patient-level and country level factors for studies should be clarified, valid and reliable instruments to measure such factors should be developed and appropriate statistical approaches to understand relationships should be applied. As indicated in the paragraph on methodological challenges, to really understand whether
country of residence plays a role independent of possible individual level factors, there is a need to better understand how the personal factors interact with system level factors. Structural equation modeling and multilevel analyses will become the rule and not the exception in such study questions. Last but not least, we have to acknowledge that our studies addressed observational and cross-sectional data. Even more relevant to understand whether the effect of interventions would be different across countries and/or across different outcomes.  

2. The role of healthcare professionals’ preferences in management (and outcome) of rheumatoid arthritis

In clinical care, patient outcomes are much dependent on the choices, attitudes and behaviours of HCPs. Within the limitation that data from our DCE are retrieved from a hypothetical experiment and not from observation in real life, the findings show that all over Europe most rheumatologists consider patients’ preferences and make economic trade-offs when choosing treatments for their patients. The prominent role of patients’ preferences and economic implications in addition to dug efficacy, can be seen as a paradigm shift in clinical decision making. Awareness of the values and beliefs of patients and the need to spend money wisely, seem to affect today’s treatment choices. While these evolutions are necessary in the context of our dynamic society, we revealed important variations in the clinical decision making among individual rheumatologists. Of note, a recent DCE investigating treatment decisions on de-escalation of DMARDs confirms heterogeneity in decisions around drug treatment. The high heterogeneity is of some concern as it jeopardizes equality in care, a common principle that can be found in all European healthcare systems. In simple words, it should not be the lucky incidence of a patient to be treated by a doctor who is more open to patients’ preferences, or who is less cost-sensitive when proposing a treatment. Certainly, some variations in attitudes between clinicians are acceptable but our data suggest that the variations are significant and concerning. Medical doctors are often expected to fulfil two contradicting roles, as gatekeepers for increasing healthcare costs on the one hand and provider of best available healthcare accounting for the patients believes and values on the other hand. Resolving this decisional conflict that likely contributes to observed heterogeneities is not straightforward as the personality of the clinician as well as environmental factors may influence the clinical decision making process. A first step towards reducing heterogeneity likely includes raising awareness on an existing problem and open discussions among rheumatologists about their views on benefits and pitfalls of shared decision making and economic trade-offs in daily life. Existing studies already identified potential difficulties clinicians face in an increasingly
complex decisional process.\textsuperscript{40, 41} However little is known about how these challenges actually impact treatment choices. To feed such discussions, more qualitative research on physicians' behavior might certainly be additionally supportive. In particular, it would be helpful to understand why negative preferences of patients receive more attention compared to positive preferences and how clinicians balance relative cost-effectiveness considerations and absolute budget impact.

However, neither stated preferences analyses nor additional qualitative research reveals what rheumatologists actually do in varying contexts. On this line, it is additionally important to collect data on individual level and system level factors that actually influence treatment decisions in real life. In line with one of the study objectives of this thesis, comparison across countries and regions with varying healthcare setting will be further insightful.

While increased insight into heterogeneity is a first step, it will not solve the question which heterogeneity is acceptable and justified. This requires a discussion among rheumatologists on their actual view on 'value based healthcare' in the consultation room. Although access to technologies is to a large extent regulated though reimbursement criteria, HCPs of many countries still have large autonomy when choosing among diagnostic procedures and treatments. The high heterogeneity indicates that making trade-offs in clinical care is not straightforward. Value based healthcare, a term that can increasingly be found in this context, has the potential to resolve parts of the decisional conflict between value and costs. Perhaps this movement will empower rheumatologists to emphasize 'added value' compared to the widely established budget driven approach. On this line it is essential that physicians agree on 'which value', thus 'what health' they want to improve. Are we willing to e.g. pay for satisfaction of patients or do we want keep a more limited view on health? Importantly, cost reduction without considering the outcomes is dangerous and self-defeating, leading to false savings and potentially limiting effective care. But expenditure without any benefit in patient outcomes are an absolutely unacceptable waste. It is clear that these complex questions on preferences in relation to costs and budget are difficult. Respect for different opinions is needed but also transparency as this will feed discussions. Healthcare providers need to take their position in public debates on how they view 'value based healthcare' for individual patients and emphasize the continuing conflict that can exist between group level evidence of decision and the decisions for the individual. In this era, shared decision making, trade-offs between health effects and costs could be made more explicit in each important clinical decision.
Conclusion

The studies presented in this thesis explored the role of country of residence and physicians’ preferences in outcome and/or management of RA. We provide evidence that in the 21st century, choices of rheumatologists are not only driven by drug efficacy, but also by patients’ preferences and by economic considerations. We also revealed that (country-) wealth is important for ‘objective’ health but not necessarily for patient’s experienced disease impact. Caring for patients is more than only providing the best possible treatment.
References

Summary and general discussion

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