Work participation and health in rheumatic and musculoskeletal diseases

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SUMMARY AND GENERAL DISCUSSION

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The work presented in this thesis aimed to contribute to our understanding of the complex relationships between health, context and work participation in persons with rheumatic and musculoskeletal diseases (RMDs). In addition, approaches to improve early detection and treatment of adverse work outcomes in persons with RMDs have been described.

First, we explored the risk of developing cardiovascular co-morbidities in working persons with RMDs and its impact on mortality during working life. Secondly, we explored the additional impact of cardiovascular co-morbidities on work outcomes, i.e. sick leave and long-term work disability, in the same population of working persons with RMDs. Next, we were interested whether the high impact of axial spondyloarthritis (SpA) on presenteeism, sick leave and work disability would be attenuated by innovative treatment with biological disease modifying drugs (biological therapies). As long-term sickness absence and work disability in RMDs remain substantial despite earlier diagnosis and improved treatment, we aimed to identify working persons at risk for future long-term sickness absence. Lastly, to improve work outcome measurement, we directly compared the construct validity and characteristics of three presenteeism measurement instruments in RMDs.

Two large, prospective observational studies have been used to address the abovementioned research questions: the Maastricht Cohort Study for Chapters 2 and 3 and the Study on Transitions in Employment, Ability and Motivation (STREAM) for Chapters 5 and 6.[1,2] In addition, published data were used to summarize the available knowledge about the effects of biological therapies on work outcomes in axial SpA in Chapter 4. The Maastricht Cohort Study was a prospective study starting in 1998 among 12,140 persons employed by 45 different companies located in the south of the Netherlands. It consisted of persons from all working-age categories, working in 678 different professions in many different sectors and trades. Participants were followed for more than a decade at the time of our studies, using extensive self-administered questionnaires on topics such as demographics, work-related factors, domestic and social factors, and health issues.[1,3] The STREAM cohort is an ongoing prospective cohort study starting in 2010 among 15,118 persons aged 45 to 64 years in the Netherlands and working in many different sectors and trades. Participants were included from an online panel and complete online questionnaires on a yearly basis on topics addressing work characteristics, personal factors (e.g. coping, job satisfaction), health factors, employment status and transitions in employment, work-ability and productivity.[2]

In this final chapter, a summary of our main results is reported and these results are discussed in a broader scientific context. The possible implications of our findings for future research and methodological considerations are discussed, and suggestions for future studies are presented.

Cardiovascular and rheumatic diseases in working persons

The pathophysiologic link between systemic inflammation and cardiovascular diseases in the general population has been studied extensively in the past,[4,5] and has been confirmed in clinical samples of patients with inflammatory RMDs in more recent years.[6] However, such clinical samples usually include patients with more severe disease (i.e. higher disease activity at the start of therapy) and might not provide a realistic picture of the role of cardiovascular diseases on relevant clinical outcomes such as work participation.[7,8] Knowledge about the presence of cardiovascular co-morbidities in a population of working persons with inflammatory RMDs is interesting for two reasons; 1) cardiovascular co-morbidities can lead to cardiovascular mortality during working life and result in premature exit from the work force, which makes cardiovascular morbidity an independent epidemiological contributor to reduced work participation, and 2) cardiovascular co-morbidities may lead to additional long-term restrictions in work participation across the entire continuum of work, more specifically sick leave and work disability, increasing the indirect costs of inflammatory RMDs for society.[9,10]

In the Maastricht Cohort Study, half of the baseline population lived in the south of the Netherlands, which allowed us to verify self-reported RMDs and cardiovascular diseases in the medical charts of surrounding hospitals. We were able to confirm 35 diagnoses of inflammatory RMDs, i.e. rheumatoid arthritis, psoriatic arthritis and axial SpA, and 31 diagnoses of gout at baseline or during follow-up. This allowed us to describe work participation in these persons and follow the course of their working career for the next decade in Chapters 2 and 3. In **Chapter 2** we used the verified diagnoses of inflammatory RMDs and gout at baseline to study the risk of developing cardiovascular diseases over the next ten years, as compared to persons without these diseases. This risk was increased more than twofold for inflammatory RMDs, though it did not reach statistical significance, probably due to low numbers. The presence of gout significantly increased the risk of developing cardiovascular diseases more than threefold during follow-up. By linking the Maastricht Cohort Study to the Dutch National Death registry, we were able to show this did not lead to increased cardiovascular-specific mortality during the course of this study. We concluded that the risk of developing cardiovascular morbidity was increased but the impact of cardiovascular mortality on premature exit from the labour force among working persons with inflammatory RMDs was limited in this cohort of relatively young participants (mean age 41.0 years).

Next, in **Chapter 3** we linked company records to the Maastricht Cohort Study, providing individual sick leave data for the first two and a half years of follow-up, to study the additional impact of cardiovascular diseases on sick leave. Our results showed that in working persons with self-reported RMDs the percentage of sick leave days (i.e. proportional to the total number of expected work days) in 2.5 years more than doubled, as compared to participants without self-reported RMDs. Self-reported cardiovascular diseases also increased the mean percentage of sick leave days almost twofold. The number of sick leave days increased further when self-reported RMDs and cardiovascular disease were both present by more than 2.5-fold, as compared to participants without these diseases. In the sample verified by clinical review, the percentage of sick leave days was increased more than twofold in those with confirmed inflammatory RMDs. No participants with confirmed inflammatory RMDs and co-existing cardiovascular diseases were present at baseline in the Maastricht Cohort Study. Similarly, we used self-reported data on work disability benefits from the entire length of follow-up to study the additional impact of cardiovascular diseases on the risk of work disability. Self-reported RMDs and cardiovascular disease increased the risk of work disability after ten years by more than 6.5-fold and 4-fold, respectively. Additive or synergistic effects were not found when both diseases were present. Similarly, the risk of work disability after ten years was increased for confirmed inflammatory RMDs more than eightfold and cardiovascular diseases almost fivefold. Confirmed gout also increased this risk fivefold, although this was not statistically significant, probably due to low numbers. Our results also show that working persons with confirmed osteoarthritis and fibromyalgia are especially at risk of work disability in the next ten years. The burden of the latter diseases on society may have been underestimated up until now. Given the high prevalence of osteoarthritis in the world, we believe extra attention should be directed towards prevention and treatment of adverse work outcomes resulting from osteoarthritis.[11,12]

A few considerations need to be taken into account to correctly interpret our findings presented in Chapters 2 and 3. First of all, we studied the additional impact of cardiovascular diseases on adverse work outcomes (i.e. sick leave, work disability), including mortality during working life, because of the direct pathophysiological link between systemic inflammation and cardiovascular diseases.[4,5] Cardiovascular diseases frequently occur and are relevant co-morbidities in inflammatory RMDs. Therefore, cardiovascular risk management has become part of European League Against Rheumatism (EULAR) recommendations.[13] Other co-occurring diseases (e.g. mental diseases) or multi-morbidity may be present but do not share the same pathophysiological link. Yet, these may be more detrimental for work participation in persons already suffering from RMDs. In the limited number of studies available in the literature, multi-morbidity has been shown to have important adverse effects on work outcomes.[10,14] This seems especially important for

co-existing mental diseases.[15-17] The cross-sectional Dutch population study by *Van der Zee et al.* reported that the specific combination of RMDs and mental diseases had one of the strongest associations with each of the four work outcomes studied: work disability, dependence on a living allowance, economic unemployment and sick leave.[10] This study also showed an almost linear relation between each additional co-morbidity and the presence of work disability, dependence on living allowances and sick leave, but not with economic unemployment. The additional impact of cardiovascular co-morbidities on the risk of work disability in persons with RMDs was increased as compared to persons with only RMDs, but not for dependence on living allowances and economic unemployment.[10] In other studies, the large impact of RMDs on increased sick leave, especially in those with mental diseases and RMDs, had already been identified.[18,19] From a societal point of view, RMDs account for a major part of the expenditures for sick leave and work disability in absolute terms due to the high prevalence, while the relative impact of mental disease on adverse work outcomes is considerably higher.[10] It is important to keep in mind that with aging of the population, multimorbidity will become the rule rather than the exception, and special attention should be paid to preventing (the consequences of) multi-morbidity. Unfortunately, multi-morbidity is still poorly understood and should be better integrated into clinical practice and research.[20]

A second consideration are the 'healthy worker effect' and other modifying effects (i.e. confounding, effect modification) which may have masked some of the increased risks in our studies. The healthy worker effect is a type of selection bias in occupational cohorts occurring because less healthy individuals are more likely to be unemployed than healthy individuals.[21] Most studies indicate that the healthy worker effect will reduce the association between exposure and outcome by an average of 20-30%.[22] The healthy worker effect may indeed play a role in the Maastricht Cohort Study, as indicated by the lower prevalence of RMDs and cardiovascular diseases, lower excess mortality, and the lack of (significant) additive or synergistic effects by cardiovascular co-morbidities on sick leave and work disability, as opposed to what we expected based on prevalence data. On the other hand, attenuation of studied associations by contextual factors (e.g. gender, age, type of job) seems especially important when interpreting work outcome studies.[23,24] We were able to adjust for some confounders in our analyses in Chapters 2 and 3, but were limited in number and range of confounders (i.e. independent variables) that could be included in our analyses due to the small numbers of verified RMDs and cardiovascular diseases, i.e. small number of events per independent variable.[25] We also cannot rule out that some unmeasured confounders may have attenuated our results. Lastly, certain subgroups may be especially at risk of adverse work outcomes (i.e. effect modification), such as persons working in physically demanding jobs or blue collar workers.[26-28] These modifying effects should be explored further in complementary studies.

Prevention of adverse work outcomes

Early interventions to prevent long-term adverse work outcomes are essential, because having work is associated with higher levels of a persons' health and wellbeing, and a reduced burden of disease on societal expenditures.[29-31] This can be achieved by more intensive treatment strategies of the underlying disease to reduce disease activity and improve work outcomes.[32] Another intervention is early detection of risk factors for adverse work outcomes, amongst other options not presented in this thesis.[19,33]

In **Chapter 4** we report the results of a systematic literature review showing that biological therapies have promising beneficial effects on work outcomes in patients with axial SpA.[34] We included two randomized clinical trials (RCTs) and seven observational cohorts, reporting on 39 comparisons in before-after or between-group comparisons and including a total of 961 patients (*n* = 851 (89%) in cohort studies and *n* = 110 (11%) in RCTs). These patients were treated with three different tumour necrosis factor alpha inhibitors (TNFi, i.e. etanercept, infliximab and adalimumab). Most comparisons suggested a numerical positive change in work outcome (32/39 comparisons), but were often not tested for significance (14/32 comparisons) or proved not statistically significant (7/32 comparisons).

Presenteeism was studied by three uncontrolled cohort studies and both RCTs, all showing a numerical improvement in favour of biological therapies. However, not all comparisons were statistically significant or tested, and usually pertained to before-after analyses without between-group comparisons. For example, one open-label study showed a significant decrease in impairment in work productivity of 2.9 points on the Work Productivity and Activity Impairment - Specific Health Problem questionnaire (WPAI-SHP, score range 0-10) after 28 weeks of follow-up and compared with baseline.[35]

Absence from paid work (i.e. sick leave) was the outcome most often studied. Six out of seven cohorts and both RCTs reported on this outcome, and all cohorts and one RCT showed an improvement, although this was not always statistically tested. For example, one population-controlled cohort showed a significant within-patient reduction in sick leave after 52 weeks, expressed as the percentage of full-time at work and compared with treatment start.[36] One RCT actually showed a deterioration in absenteeism, but this was not statistically significant.[37]

Changes in work status were reported in five cohort studies and by none of the RCTs. The results for work status were less often positive, but it should be noted that included studies dealt with patients with longstanding axial SpA (10.6-16.4 years since diagnosis), lacked power and had a relatively short follow-up to detect changes in employment (28

to 156 weeks). The average age of patients in the cohort studies ranged from 39.5 to 49.9 years and in the RCTs this was 40.3 years. This suggests that the negative impact of the disease on employment status had already occurred before the start of TNFi, leaving limited opportunity for improvement by pharmacological interventions. Unfortunately, methodological limitations such as a lack of standardization of outcomes used and the limited number of studies included precluded a meta-analysis, but trends towards beneficial effects of biological therapies in longstanding axial SpA were seen on all work outcomes.

Since the publication of our review at least six new longitudinal studies have been published on this topic; 5 RCTs some including long-term extensions, and 1 observational cohort, all showing a positive influence of biological therapies on work-related outcomes in axial SpA.[38-43] Some of these studies have recently been reviewed narratively by *Nikiphorou et al.*[44] The study by *Shim et al.* is of particular interest because it provides real-life observational data investigating the impact of biological therapies on presenteeism and sick leave in the longer-term.[38] They used the large British Society for Rheumatology Biologics Register (BSRBR, n = 577) to show that axial SpA patients starting biological therapy at the time of recruitment experienced significantly greater improvements in work outcomes as compared to matched controls not treated with a biological. After twelve months, biological therapies had improved presenteeism, overall work impairment and overall activity impairment but did not improve absenteeism all measured on the WPAI. All analyses only included patients if they were employed at baseline and after twelve months, making it impossible to show changes in employment status. The positive effect on work productivity was further supported by pooled estimates from a meta-analysis of BSRBR data combined with four RCTs also measuring the WPAI. They showed a statistically significant improvement in favour of biological therapies for presenteeism and overall work impairment and concluded there is consistent evidence, across different study designs, that treatment with biological therapies significantly and meaningfully improves presenteeism in patients with axial SpA.[38] In line with most of the more recent clinical trial data, the meta-analysis by *Shim et al.* did not show significant improvements in absenteeism with the use of biologics, despite improvements in presenteeism, work impairment and activity impairment.[44] This is in contrast to our findings in Chapter 4, which were mainly based on observational studies and showed positive effects with the use of biological therapies, although not always statistically tested. Future real-life observational data from controlled cohort studies are necessary to clarify these conflicting results. In addition, there remains a substantial gap between axial SpA patients and the general population in terms of work participation, suggesting that pharmacological interventions alone are not enough and other (multidisciplinary) approaches are needed.[31]

In **Chapter 5** we presented the results of the development and validation of a multivariable risk prediction model, discriminating between workers with high- and low-risk for long-term sickness absence in the coming year. We used data from 11,221 working persons in the STREAM cohort to develop this multivariable risk prediction model for long-term sickness absence lasting ≥28 accumulated working days in the coming year. Logistic regression analysis using backward stepwise elimination was used to reduce the full statistical model including 27 pre-selected predictors to a more practical model including 11 predictors. This final model showed good discrimination (Area Under the Curve: 0.76) and good calibration (Hosmer-Lemeshow test: p = 0.41) in a second validation cohort of 5,604 newly recruited working persons. Multivariable regression coefficients of the predictors in the final model of the development cohort revealed that poor self-rated physical health (measured with the Short Form-12 [SF-12] physical component score), poor self-rated work-ability (measured with one item from the Work Ability Index (WAI)) and a high number sickness absence days in the previous year showed the strongest associations with future long-term sickness absence. The level of perceived limitations in physical functioning predicted future long-term sickness absence better than the health condition possibly underlying these limitations, such as musculoskeletal disease or multimorbidity. These variables were eliminated from the full model that included self-reported physical health and physical job load. Mental health was not included as a predictor in our final model, but may be more important in specific working populations or sectors (e.g. younger persons, white collar workers). The importance of mental health problems for predicting long-term sickness absence was confirmed by other studies reporting on multifactorial risk prediction models.[45-47] Other previously identified risk factors for future long-term sickness absence (i.e. social and financial factors, emotional job demands and autonomy) were excluded during statistical analyses using backward stepwise elimination to obtain a more practical model for clinical practice.[45-47] Future studies validating and updating this prediction model are encouraged to determine if these factors add to the predictive validity of our model in other settings and populations where a more practical model is of less priority.

The strength of the STREAM cohort is that it collected a comprehensive set of potential predictors for long-term sickness absence, including variables not previously studied. We have found new factors which were important predictors of future long-term sickness absence, such as knowledge/skills matching the current job, the number of major life events in the previous year and self-employment. While our prediction model allows for the calculation of a risk-score by giving "statistical weight" to each risk factor, an optimal cutoff still needs to be determined. Such thresholds should balance between over- and underdiagnoses. This threshold may be different in RMD populations as compared to a general working population, because the *a priori* risk for long-term sickness absence

is probably higher. We, however, believe that implicit use of the reported risk factors in clinical reasoning would perhaps be more desirable. The results from our prediction model have the potential to support healthcare professionals in determining which working persons should be targeted for tailored preventive interventions, but could also serve to identify new and potentially modifiable risk factors at the level of companies or workplaces (e.g. physical fitness).[47,48] Unfortunately, work participation most often is of second-order priority to healthcare professionals in primary and secondary care and is not regarded as a clinical outcome. A simple and practical tool to predict long-term sick leave may increase the attention for work participation as an outcome in clinical practice. Yet, we also require high-quality work outcome measurements to reliably measure other aspects of work participation in clinical practice and research.

Presenteeism – an outcome in clinical practice and research

During the last decades, substantial work has been performed by the Outcome Measures in Rheumatology (OMERACT) initiative to identify and evaluate instruments for outcome measurement in rheumatology clinical trials. A measure is endorsed if it passes through the OMERACT Filter, which evaluates three component criteria: 'truth' (i.e. face, content, construct and criterion validity), discrimination (i.e. reliability and sensitivity to change) and feasibility (i.e. pragmatic reality of the use of the measure).[50] The OMERACT Worker Productivity working group identified and evaluated several worker productivity (i.e. presenteeism) outcome measures in more recent years.[23] One limitation they identified was that direct comparisons between different instruments in longitudinal studies were lacking.

Therefore, in **Chapter 6** we used data from 4,523 working persons with musculoskeletal complaints in the prospective STREAM cohort to compare the construct validity of three presenteeism instruments.[51] One presenteeism measurement instrument concerned a single item global rating of work-ability as part of the WAI, and two measurement instruments addressing at-work productivity, measured using the Quality and Quantity (QQ)-method and the Osterhaus-method. The longitudinal associations of the three presenteeism instruments with external measures of health and sick leave were assessed using Generalised Estimating Equation (GEE) models over a 6-year follow-up period with one-year intervals. Predictive validity is part of the construct validity of an instrument and is used to determine whether the instrument measures what it is intended to measure when the outcome occurs in the future. Overall, the WAI ('the ability to work') showed stronger longitudinal associations with different health variables as compared to the other two measures operationalizing presenteeism as 'productivity while at work'. For example, the SF-12 physical component score was more strongly longitudinally associated with an increase on the WAI in the subsequent year, as compared to the QQ-method and

Osterhaus-method. Similar differences between the three instruments in favour of the WAI were found for the longitudinal associations with mental health (SF-12 mental component score) and vitality (SF-36 vitality index). Sick leave days in the subsequent year were also more strongly associated with the WAI, as compared to the QQ-method and Osterhaus-method. Differences between the three instruments were also reflected in the weak inter-correlations at each timepoint, confirming that self-rated work-ability and work productivity are truly different consequences of disease on work. Work-ability showed higher construct validity against health and economic outcomes as compared to at-work productivity and is clearly more relevant to identify working persons at risk of subsequent sick leave, as for use in the prediction model we constructed in Chapter 5. On the other hand, the Osterhaus-method has (theoretically) higher face validity to estimate costs associated with presenteeism and seems more relevant from an economic perspective, although validation with an objective productivity outcome is still lacking. Clearly, the preferred construct (and thus instrument) selected in future studies to measure the concept presenteeism is dependent on the study type and objectives.

In Chapter 6 we also explored the impact of groups of contextual factors on the associations between health factors, presenteeism instruments and sick leave by testing changes in explained variability of the outcome by the model. This was expressed as relative Quasi-likelihood under the Independence model Criterion (QIC) and compared to a basic model without any contextual factors included, with lower QICs reflecting better data fit. We demonstrated that personal contextual factors (i.e. mastery, coping and self-efficacy) had the most substantial impact on the associations between health factors and the WAI and the QQ-method, but this effect was negligible for the Osterhaus-method. Demographic, lifestyle and work-related contextual factors had a much smaller impact on the associations between health factors and the three presenteeism instruments. The impact of all groups of contextual factors on the associations between the three presenteeism instruments and sick leave was small, possibly because context was already implicitly included in these presenteeism instruments. Personal factors are not routinely collected in occupational studies in RMD populations, but our results indicate that this should be encouraged to correctly interpret work outcome data. In the field of rheumatology, the OMERACT Contextual Factors working group performed significant work to provide guidance on addressing contextual factors in clinical trials and has published provisional generic contextual factor domains.[52,53] We believe that context is highly dependent on the setting it is intended for (e.g. clinical vs. occupational setting) and is outcome-specific (e.g. quality of life vs. pain). Personal factors may indeed prove to be more relevant for the interpretation of work participation data. Future studies should identify and characterize contextual factors specific to occupational settings and work outcomes.

Longitudinal analysis of work participation data

This thesis is primarily based on work participation data from two prospective, occupational cohort studies in the Netherlands and methods used to address our research questions are mainly based on longitudinal data analyses. The key advantage of longitudinal over cross-sectional studies is the ability to show patterns of a variable over time. This knowledge is especially relevant for promoting sustainable employability where insight is needed in determinants of transitions in employment, productivity, and health. However, longitudinal studies are associated with high temporal and financial demands on the one hand. On the other hand, attrition or loss-to-follow-up are important methodological problems in longitudinal studies, resulting in missing data and biased estimates.[54] Fortunately, two accepted methods to deal with missing data in longitudinal studies are available, which have been used for this thesis: multiple imputation techniques and GEE models.[55] The way missing data is handled is different between these two methods.

The first step in multiple imputation is to create multiple copies of the dataset, with the missing values replaced by imputed values which are sampled from their predictive distribution based on the observed data.[56] Appropriate variability is inserted into the multiple imputed values to account for the uncertainty in predicting the missing values. In the second step, standard statistical methods to fit the model of interest to each of the imputed datasets are used and averaged together to give overall estimated associations, including standard errors calculated using Rubin's rules.[57]

On the other hand, GEE models are considered fairly robust with regard to missing data. Previous simulation studies have shown that it is not necessary to impute missing data using multiple imputations before performing a GEE model analysis on longitudinal data.[55,58] Apart from dealing with missingness, GEE models can take into account within-subject correlations over time and other clustered data. It is important to take this correlation into account, otherwise the standard errors of the parameter estimates will not be valid and hypothesis testing results will be non-replicable.

While both methods will give quite similar precise results and make all available data accessible for statistical modelling, the estimates may still be biased and lead to erroneous conclusions if missingness is caused by systematic mechanisms (and not completely at random). Therefore, before such statistical approaches are used, reasons for missingness should be explored.

The two cohorts used in this thesis have been designed with a broad questioning to allow different viewpoints on general working populations, but were not specifically intended for studies in RMD populations. If we would design a new study addressing

(transitions in) work participation, effects of multi-morbidity and the role contextual factors specifically in RMD populations, how should this study be designed? Perhaps the STREAM cohort, used in Chapters 5 and 6, is a good example. The advantage of this cohort is that it is positioned in a large population of employed, self-employed and non-employed persons, who are prospectively followed over a long period of time, allowing the study of transitions in work participation. In addition, it collects a substantial number of contextual factors, morbidities and other health factors, by means of extensive self-administered questionnaires. It would be interesting to enrich a new cohort with a younger population and enroll all subjects within a restricted time period after inception (inception-type prospective cohort), before persons have lost employment. Ideally, this new cohort will eventually be linked to other datasets, such hospital records or social security data. In this thesis we have used different RMD populations, ranging from general working populations which can be found in general practice up till patients with axial SpA found at the out-patient clinic of rheumatologists. The setting from which participants are recruited for this new cohort importantly affects study results and generalizability and should therefore be chosen carefully.

Final conclusions

In conclusion, this thesis contributes to our understanding of the complex relationships between health, contextual factors and restrictions in work participation in persons with rheumatic and musculoskeletal diseases. It specifically adds to the body of evidence showing the impact of multi-morbidity and contextual factors on work outcomes, confirms the beneficial effects of biological therapies on work participation in axial spondyloarthritis and provides new opportunities to improve early detection and outcome measurement in rheumatic and musculoskeletal diseases.