RHEUMATOLOGY

Concise report

Work participation is reduced during the development of RA, months before clinical arthritis manifests

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Abstract

Objectives. We investigated whether work participation is affected in patients with arthralgia during transition to RA. Arthralgia patients with symptom resolution and early RA patients at diagnosis were used as a reference.

Methods. Three groups of patients were studied: arthralgia patients converting to RA ($n = 114$), arthralgia patients with spontaneous symptom resolution ($n = 57$), and early RA patients ($n = 617$). Both presenteeism (i.e. working while sick, scale 0–10) and absenteeism (i.e. sick leave) were taken into account. Work ability 1 year prior to clinical arthritis was estimated (in absolute numbers). The course of work restriction over time was studied using linear mixed models (β coefficient; delta per month) within each patient group.

Results. One-year prior to the development of clinical arthritis, mean presenteeism was 7.0 (95% CI 5.8, 8.1) in patients with arthralgia, indicating 30% loss, and further worsened to 6.1 (95% CI 5.3, 6.6) at RA diagnosis, thus indicating 39% loss. In early RA patients, presenteeism improved over time after DMARD initiation (β 0.052 per month 95% CI 0.042, 0.061, $P < 0.0001$). Presenteeism also improved in arthralgia patients who achieved spontaneous symptom resolution (β 0.063 per month, 95% CI 0.024, 0.10, $P = 0.002$). Absenteeism did not change significantly in arthralgia patients, but did improve in RA after DMARD-start. ACPA stratification revealed similar results.

Conclusion. In the months preceding RA, presenteeism was already apparent, and it worsened further during progression to clinical arthritis and diagnosis. This underlines the relevance of the symptomatic pre-RA phase for patients. The observed reversibility in arthralgia patients with symptom resolution may suggest that intervention in pre-RA could improve work participation.

Key words: early RA, patient reported outcome measures, work disability, presenteeism, outcomes research

> **Rheumatology key messages**
> - Reduced work participation (both presenteeism and absenteeism) is already apparent in the phase of arthralgia.
> - Presenteeism tends to worsen during progression to RA, whereas it improves upon symptom resolution.
> - Reversibility in presenteeism may suggest that intervention in pre-RA could improve or prevent permanent work-loss.

Introduction

Work participation is a major issue for patients with RA. As the onset of RA is generally during the midst of working life, this constitutes limitations for patients, as well as an economic burden for society [1–4]. The effect of RA on work participation is reflected in poorer work outcomes and patients being more likely to be forced into early retirement, indicating a partial or even non-reversible effect [4, 5]. It is known that preceding the occurrence of clinical arthritis and RA, patients already experience pain and have functional limitations that can be as serious as in early arthritis [6]. However, the effect of these limitations on work-related outcomes in this pre-RA phase is unknown. Studying work participation during this symptomatic phase is important from the perspective of whether loss of work participation can be prevented by intervening earlier.

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Restrictions in work participation can be distinguished into presenteeism (i.e. impaired productivity at work due to sickness) and absenteeism (i.e. sick leave). A recent retrospective registry showed that RA patients had increased absenteeism in the year preceding initiation of treatment, but presenteeism was not investigated [2, 7].

With the aim of better understanding the evolution of restriction in work participation during RA development, we studied arthralgia patients during progression to rheumatoid arthritis (RA). As a reference for the outcome of arthralgia patients converting to RA, the course of work participation was also studied in arthralgia patients who had the best possible outcome, i.e. symptom resolution. Work restrictions in patients with early RA was studied to put our findings in perspective in relation to what is known from the literature.

Methods

Patients

We studied arthralgia and early RA patients who were included in longitudinal Dutch cohorts. Arthralgia patients converting to RA (i.e. clinical diagnosis of RA plus fulfilment of the 2010/1987 criteria and/or DMARD start) were selected from the Leiden clinically suspect arthralgia (CSA)-cohort (inclusion period between 2012 and 2019) and the Sonographic evaluation of hands, feet and shoulders in patients with inflammatory arthralgia (SONAR) cohort (Rotterdam) (inclusion period between 2011 and 2015) [8, 9]. Both cohorts included a similar study population: patients who were considered as suspected for RA development based on clinical characteristics at presentation. The development of RA was the outcome and marked the end of follow-up in these cohorts. Arthralgia patients who experienced symptom resolution were selected from the Leiden CSA cohort. The patient selection is described previously; this group is now studied for work participation [10]. In the absence of work participation data from the general Dutch population, this group served to evaluate to what extent work-loss is reversible. Finally, patients with early RA (clinical diagnosis plus fulfilment of the 1987/2010 criteria) who were consecutively included in the Leiden Early Arthritis cohort between 2010 and 2016 were also studied [11].

DMARD treatment was not allowed in arthralgia patients; RA patients were treated with routine care. A description of the cohorts is presented in Supplementary Methods S1, available at *Rheumatology* online.

Ethics

The CSA cohort Leiden and the early arthritis cohort (EAC) were both approved by the medical ethics committee of the Leiden University Medical Center, Leiden, The Netherlands (approval number P10.108). The medical ethics committee of Erasmus Medical Center, Rotterdam, the Netherlands, and each participating centre approved the SONAR study (MEC-2010–353). All patients gave written informed consent before inclusion. The studies comply with the Declaration of Helsinki.

Outcomes

Arthralgia patients completed questionnaires at structured visits (baseline, 4, 12, 24 months for Leiden), (baseline, 6, 12 months for SONAR) or at time of conversion to clinical arthritis. Early RA patients filled out the same questionnaires at baseline and yearly thereafter (4-year follow-up). Presenteeism (impaired productivity at work due to sickness) and absenteeism (sick leave and decrease in working hours per week) were assessed using the Work Productivity and Activity Impairment (WPAI-GH) (Leiden) and Productivity Cost Questionnaire (IPCQ) (Rotterdam) [12, 13]. Presenteeism was measured by the degree to which health problems affected work productivity on a rating scale ranging from 0 to 10, where $0 =$ complete impairment and $10 =$ no impairment. Absenteeism was measured using sick leave (presence *vs* absence), and decrease in the average number of working hours per week (Supplementary Data S1, available at *Rheumatology* online).

Statistical analysis

From all groups, only patients who had paid work at baseline and who were <65 years (i.e. the working population) were studied. Visits of patients turning 65 during follow-up were excluded from analysis, and only data before the age of 65 was used. This age was chosen because the average retirement age in the Netherlands is 65 years. In arthralgia patients converting to RA, the moment of clinical arthritis development was set as time $= 0$ (T0). In arthralgia patients with spontaneous symptom resolution, the final visit was set as T0. For RA patients, the first presentation to the outpatient clinic was set as T0. This was comparable with the original set-up of the cohort. A schematic overview of these adjusted timelines and follow-up can be found in Supplementary Fig. S1, available at *Rheumatology* online.

The three groups—(1) arthralgia patients converting to clinical arthritis; (2) arthralgia patients with symptom resolution; and (3) early RA patients—were analysed as separate groups.

Raw data with imputation were used to estimate the work ability (i.e. productivity, sick leave, working hours) at different points in time for each group. Thereafter, the course of work-loss over time was studied using linear mixed models (LMMs) or a mixed-effect logistic regression model. A beta coefficient with 95% CI (delta per month) was derived from the LMM and presented a change per month.

LMMs with an unstructured covariance matrix were used to assess productivity and working hours. For sick leave (yes/no), a mixed-effect logistic regression model was used with an unstructured covariance matrix, with the regression coefficients on the logit scale. The models were corrected for age, gender and, for the analyses

in CSA, also for the cohort (SONAR/CSA-Leiden). Results were stratified for ACPA status (in arthralgia patients converting to RA, and early RA patients) and for cohort (in arthralgia patients converting to RA). As functional impairment is known to be present in CSA and can contribute to restrictions in work participation [6, 14], an additional LMM analysis also included functional ability [measured with the HAQ disability index (HAQ-DI)], next to gender, age and cohort.

Missing data at baseline and at follow-up were imputed using chained equations ($m = 40$). Imputation regression models were constructed for paid work, productivity, sick leave, and number of working hours. Age, gender, and HAQ-DI were used as auxiliary variables. Subsequent analyses were performed within the imputed databases. No large differences were found between the unimputed dataset (complete cases) and the imputed dataset (Supplementary Table S1, available at *Rheumatology* online). Analyses were performed using STATA 16. *P*-values of <0.05 were considered statistically significant.

Results

Of arthralgia patients who converted to RA, patients with spontaneously resolving arthralgia, or early RA patients, 81, 50 and 291 patients, respectively, were aged <65 and had paid work. Patient characteristics are presented in Supplementary Tables S2/S3, available at *Rheumatology* online. The percentage of females was 79%, 66% and 68%, respectively. The symptom duration at first visit of the three groups was 26, 18 and 16 weeks, respectively, and the median HAQ-DI was 0.8, 0.4 and 0.88.

Presenteeism

In arthralgia patients, 1 year prior to the development of RA, presenteeism was 7.0 (5.8–8.1) relative to the maximum attainable productivity (scale 0–10), thus indicating a 30% loss. A further downward trend was present during progression to clinical arthritis development, in which presenteeism was reduced to 6.1 (5.3–6.6) at diagnosis, indicating 39% loss (Fig. 1A, Table 1A). This corresponds to the findings observed in the LMM: a β of −0.078 per month (Table 1B), which is similar to a 0.9 reduction in productivity per year, as was observed in the raw data with imputations.

Presenteeism improved in arthralgia patients with spontaneous symptom resolution. While presenteeism-loss was 6.9 (6.2–7.7) at first visit, this improved to 8.8 (8.5–9.1) after 2 years (Fig. 1A). This change over time was significant ($P = 0.002$; β 0.063 per month, Table 1B).

Presenteeism in early RA patients was reduced at diagnosis (5.0, 4.7–5.3), and was 7.6 (7.1–8.1) after 4 years. The improvement was significant ($P < 0.0001$, β 0.052 per month, which is similar to 2.5 improvement over 48 months; Fig. 1A, Table 1A/B).

Since the pathophysiology of ACPA-positive and ACPA-negative is somewhat different, and it is unknown whether this affects work participation, analyses were stratified for ACPA status. This yielded similar results (Supplementary Figs S2/S3, available at *Rheumatology* online). In arthralgia patients converting to RA, a stratification on cohort was also performed; both showed presenteeism preceding clinical arthritis (Supplementary Fig. S4, available at *Rheumatology* online). Analyses on the course of HAQ-DI in relation to the course of presenteeism showed that these were significantly associated. In patients converting to clinical arthritis, worsening of functional ability was associated with an increase in presenteeism (β −2.52, $P < 0.0001$), and in patients with early RA, an improvement in HAQ-DI was associated with a decrease in presenteeism (β −2.97, $P < 0.0001$: Supplementary Table S4, available at *Rheumatology* online).

Absenteeism

The results indicated that 19% (95% CI 7%, 34%) of arthralgia patients who progressed to RA reported sick leave 1 year prior to RA development; at RA diagnosis, this was 24% (15%, 35%). The average working hours remained stable over time (Fig. 1B, C). Of the arthralgia patients with symptom resolution, 22% (12%, 36%) had sick leave while presenting with arthralgia; this remained stable over time, as did the working hours (Fig. 1C, Table 1A/B). Early RA patients reported 36% (30%, 41%) sick leave at diagnosis; this improved to 23% (16%, 32%) over time after initiation of treatment (β −0.024, $P < 0.0001$) (Table 1B). While sick leave became less frequent, the working hours per week slightly decreased over time and went from 29 (28, 30) hours per week at baseline to 23 (21, 26) hours after follow-up in early RA patients. This change was statistically significant in the LMM ($P < 0.0001$; β −0.116 −0.160, −0.073) per month, which is a change of 5.6 in 4 years (Fig. 1C, Table 1B). Stratifying for ACPA showed similar results, as did the stratification for cohort (Supplementary Figs S2–S4, available at *Rheumatology* online). Incorporating functional ability showed that a decrease in HAQ-DI over time was associated with a decrease in sick leave (β 0.90, $P < 0.0001$).

Discussion

We showed that arthralgia patients already experience absenteeism and presenteeism. Presenteeism tended to worsen during progression to RA, while it improved in the patients who achieved spontaneous resolution. Although information from the general Dutch population is absent, the results suggest that after symptom resolution the level of presenteeism became within the normal range, implying that these impairments in work productivity are reversible.

Longitudinal data from early RA patients were studied to relate our findings to the literature. The absenteeism

FIG. 1 The course of presenteeism and absenteeism over time in three different patient populations
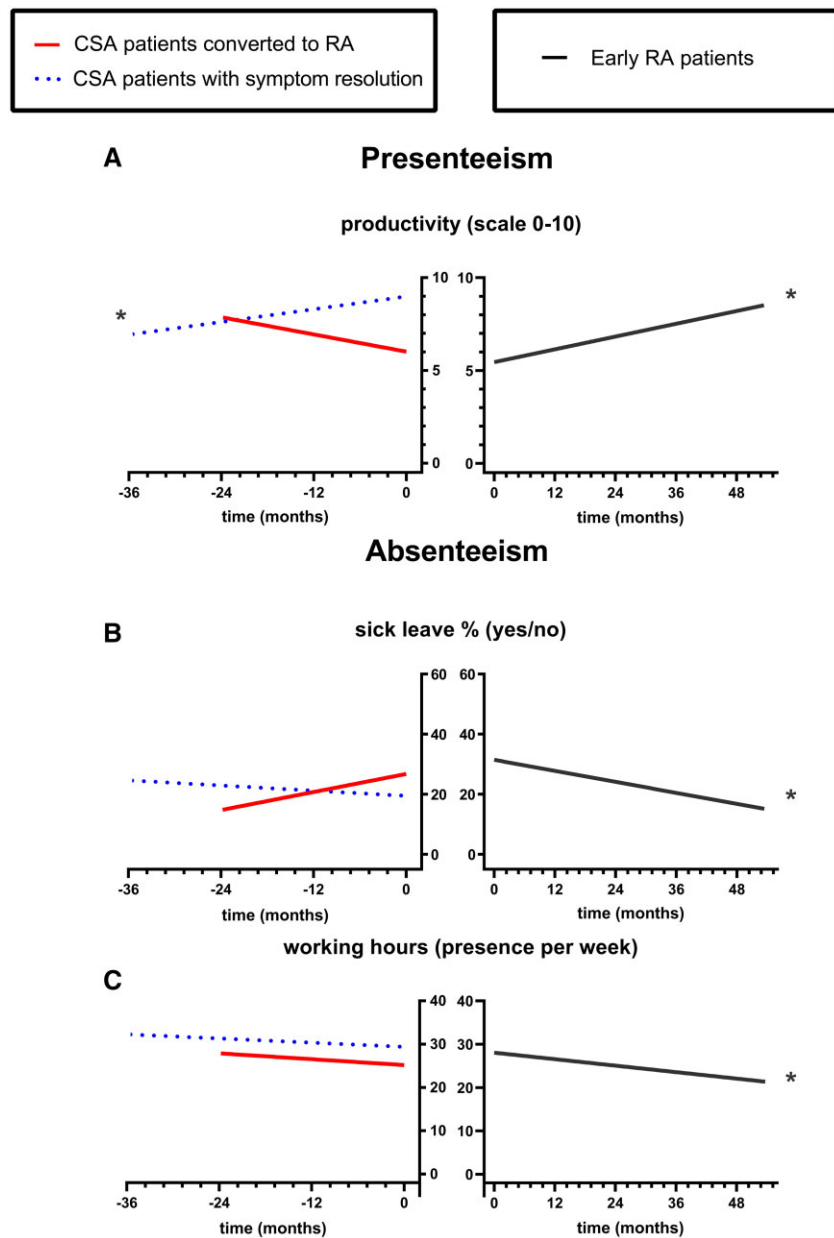
(**A**, **B**, **C**) Red lines: Clinically suspect arthralgia (CSA) patients converting to RA; 0 at x-axis marks the moment clinical arthritis is diagnosed. Blue-dotted lines: CSA patients non-converting with spontaneous symptom resolution; 0 at x-axis marks the final visit at which patients were all symptom-free. Dark grey lines: early RA patients; 0 at x-axis marks the first presentation at the outpatient clinic. Productivity: 0 = complete impairment and 10 = no mpairment. *Indicates a significant change over time.

levels observed in our data are in line with previous literature [15]. Less is known on presenteeism in early RA. Our findings showed that this improved after treatment start. Working hours, in contrast, decreased, which was similar to the findings of previous studies [16]. This reduction may indicate that in order to maintain some level of work participation some patients have to reduce their working hours. This supports our hypothesis that work-loss in early RA is not fully reversible, which corresponds with other long-term work participation outcomes, e.g. sickness and early retirement [5, 17, 18].

Data on work participation in the symptomatic phase preceding clinical arthritis and RA is sparse. Though the populations may not be exactly similar, our results are in

TABLE 1 Outcomes for the course of work restriction over time

Absolute estimates[a]		
Arthralgia patients converting to RA	**1-year before RA (95% CI)**	**T0 (95% CI)[e]**
Productivity at work (scale 0–10)	7.0 (5.8, 8.1)	6.1 (5.3, 6.6)
Sick leave; yes/no (%)	19 (7, 34)	24 (15, 35)
Working hours per week	25 (17, 33)	24 (21, 27)
Arthralgia patients with spontaneous symptom relief	**2 years before symptom resolution (95% CI)**	**T0 (95% CI)[f]**
Productivity at work (scale 0%–100%)	6.9 (6.2, 7.7)	8.8 (8.5, 9.1)
Sick leave; yes/no (%)	21 (11, 35)	22 (12, 36)
Working hours per week	32 (30, 34)	30 (27, 32)
Early RA patients	**T0 (95% CI)[g] comparable to the other two**	**4-year follow-up (95% CI)**
Productivity at work	5.0 (4.7, 5.3)	7.6 (7.1–8.1)
Sick leave; yes/no (%)	36 (30, 41)	23 (16, 32)
Working hours per week	29 (28, 30)	23 (21, 26)
LMM	**Beta coefficients (95% CI)[b]**	**_P_-value**
Arthralgia patients converting to RA		
Productivity at work[c]	−0.078 (−0.178, 0.021)	0.12
Sick leave (yes/no)[d]	0.030 (−0.058, 0.118)	0.51
Working hours per week[c]	−0.208 (−0.578, 0.161)	0.27
Arthralgia patients with spontaneous symptom relief		
Productivity at work[c]	0.063 (0.024, 0.102)	**0.002**
Sick leave (yes/no)[d]	0.008 (−0.029, 0.044)	0.68
Working hours per week[c]	−0.087 (−0.224, 0.050)	0.21
Early RA patients		
Productivity at work[c]	0.052 (0.042, 0.061)	**<0.0001**
Sick leave (yes/no)[d]	−0.024 (−0.034, −0.013)	**<0.0001**
Working hours per week[c]	−0.116 (−0.160, −0.073)	**<0.0001**

[a]Absolute estimates based on raw data with imputations. [b]Beta coefficients (95% CI) refer to the delta per month in productivity at work, sick leave and working hours per week, for patients with: (1) arthralgia converting to RA; (2) arthralgia and spontaneous symptom resolution; and (3) early RA. The models were corrected for age, gender and, for the analyses in CSA, also for the cohort (SONAR/CSA-Leiden). [c]Linear mixed models for continuous variables. [d]Mixed Effects Logistic Regression model for binary variables; beta coefficient are on the logit scale. [e]T0: in arthralgia patients converting to RA: diagnosis of clinical arthritis (RA) (Supplementary Fig. S1). [f]T0: in arthralgia patients with spontaneous symptom resolution: symptom resolution at final visit (Supplementary Fig. S1). [g]T0: in early RA patients: first presentation at outpatient clinic (Supplementary Fig. S1). LMM: linear mixed models.

line with results from a Swedish registry, for which it was retrospectively observed that sick leave started to increase 6 months before diagnosis [14].

Our study is the first to include results on presenteeism. While absenteeism and presenteeism are related, conceptually presenteeism may be more sensitive to change in early disease phases. Presenteeism and changes therein may, therefore, be important to monitor in arthralgia patients. In addition, this is important from an economic perspective, because presenteeism has shown to be responsible for up to 70% of the societal costs in RA patients [19].

In arthralgia-patients that developed RA, both the classification criteria (2010 or 1987) and the clinical diagnosis with DMARD-start were used for defining RA. This was done because patients had easy access, allowing early identification of arthritis and subsequent early DMARD-start may have hampered fulfillment of classification criteria. Exclusion of patients who did not fulfil classification criteria ($n = 29$) did not yield different results (data not shown).

Although we used validated questionnaires, no norm scores exist for presenteeism. Also, work participation levels may differ from country to country due to variations in social security, healthcare systems and economic circumstances [18, 20]. We studied patients longitudinally, in the same region, with the same questionnaires. Although the absolute levels are reflective of the Dutch setting, the trends over time are presumably generalizable to other countries. A limitation is that different questionnaires were used in the SONAR and the Leiden CSA cohorts, including a difference in recall period for sickness. Although stratification for cohort showed similar trends, a longer recall period was not paralleled with higher sickness absence [3].

In conclusion, we showed that presenteeism in the symptomatic pre-RA phase is already evident. This underlines the relevance of the symptomatic pre-RA

phase for patients and society. The observed reversibility in presenteeism may suggest that interventions in the phase preceding clinical arthritis (for instance initiating DMARD treatment) could improve work participation and prevent permanent work-loss, and hence diminish the burden of RA. This should be learnt from intervention studies in arthralgia.

Data availability statement

Data available on request. The data underlying this article will be shared on reasonable request to the corresponding author.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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