**Predictors of presenteeism, absenteeism and job loss in patients commencing methotrexate or biologic therapy for rheumatoid arthritis**

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**Abstract**

**Objectives:** Work is an important health outcome. This study aimed to identify predictors of work loss, absenteeism and presenteeism over one year in rheumatoid arthritis (RA) patients commencing treatment with methotrexate (MTX) or biologics.

**Methods:** Patients aged 18-65 years in full/part-time employment from two UK prospective cohorts were included: MTX-starters = Rheumatoid Arthritis Medication Study, biologic-starters = Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate. Presenteeism/absenteeism were assessed using the RA-specific Work Productivity Survey at baseline, 6 and 12 months. Potential predictors including baseline age, gender, clinical measures (e.g. disability, pain, fatigue), psychological distress, occupation, and EULAR response from baseline-6 months were investigated.

**Results:** 51/463 MTX-starters and 30/260 biologic-starters left work over 12 months. Higher baseline psychological distress in MTX-starters (OR 1.1 [95% CI 1.0, 1.1]) and higher disability in biologic-starters (OR 3.4 [95% CI 1.4, 8.4]) predicted work loss. 16.1% of patients reported sick-leave which was predicted by disability (OR [95% CI], MTX-starters: 1.5 [0.9, 2.3]; biologic-starters: 2.4 [1.1, 5.2]). Median presenteeism scores were very low (minimal interference) in both cohorts. Higher fatigue for MTX starters (IRR 1.2 [95% CI 1.0, 1.4]) and higher disability in biologic-starters (IRR 1.4 [95% CI 1.1, 1.7]) predicted presenteeism. Good EULAR response was associated with lower absenteeism and presenteeism in both cohorts.

**Conclusions:** Patients with RA still face significant limitations regarding their ability to work. Disability and EULAR response were the main predictors of work outcomes, emphasizing the need to control the disease and the importance of function in enabling work participation.

Work is important for quality of life (QoL), economic independence and sense of purpose.(1) Patients with rheumatoid arthritis (RA) consistently report that they want to remain in work, but research has shown that 36-84% of individuals with RA take sickness absence because of their condition (absenteeism), and up to 50% of patients have to stop work altogether over a period of 4.5-22 years.(2) In the United Kingdom (UK), 10% of early RA patients left work over a median of 3 years of follow-up,(3) and 49% of patients starting a biologic were work disabled.(4) This loss of productivity is accompanied by significant socio-economic consequences.(5-7) Attempts made by employers and policy makers to reduce absenteeism and maintain work retention may lead to an increased likelihood of reduced job performance at work (known as presenteeism).(8) Presenteeism is common in all workforces (everybody performs below their peak on occasion because of stress, aches and pains, or mild infections) and is not universally undesirable. For example, a phased return to work after prolonged sickness absence is a desirable form of presenteeism aiming towards total rehabilitation. However, presenteeism can be harmful to the individual and can increase demands on co-workers, and thus the factors associated with presenteeism are receiving increased research attention.(9)

Historically, the majority of research exploring factors associated with work participation in RA has concentrated on job loss (e.g. (10-12)), and to a lesser extent absenteeism and presenteeism. Cross-sectional studies have reported that higher disease activity, higher disability, poorer mental health and lower QoL are associated with presenteeism and absenteeism.(13-15) Longitudinal predictors are less well studied but, amongst patients with early RA, presenteeism was higher in those with physically demanding jobs and those reporting less support from colleagues.(16;17) In patients with established RA, greater disability and poorer mental health predicted presenteeism over one year.(18)

A weakness of existing research on work participation in RA cohorts is the inclusion of a wide range of symptom durations. Therefore, we investigated baseline factors associated with three important work measures: job loss, absenteeism and presenteeism over 12 months of follow-up in two cohorts of patients at fixed points in the disease progression of RA: at the initiation of methotrexate (MTX) and at the initiation of biologic therapy.

**Methods**

***Patients and setting:*** Participants were recruited to one of two UK multicentre one year prospective observational studies: The Rheumatoid Arthritis Medication Study (RAMS) (MTX-starters), or the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGSS) (biologic-starters). Recruiting centres were spread across the UK, including both teaching and non-teaching centres as well as serving both urban and rural populations. The detailed methods of both studies have been published elsewhere.(19;20) In brief, the studies recruited patients with RA starting either MTX or biologics, collecting data at baseline (treatment initiation), six and 12 months. The inclusion criteria for the current analysis were: aged 18-65 years, in paid full- or part-time employment at the start of treatment, and employment data for at least one follow-up. MTX-starters were recruited from 2008; those with >2 years symptom duration were excluded from this analysis. Biologic-starters were limited to those starting their first biologic. Furthermore, work outcomes were only collected since 2012 amongst biologic-starters, therefore only biologic-starters recruited after 2012 were included.

All patients gave written informed consent. Ethical approval for the MTX-starters cohort was obtained from the National Research Ethics Service Central Manchester Research Ethics Committee (ref: 08/H1008/25) and ethical approval for the biologic-starters cohort came from the North West Ethics Committee (ref: 04/Q1403/37).

***Clinical data collection:*** Age, gender, symptom duration and smoking status were collected at baseline. The DAS28 and its components (28 swollen and tender joint counts; C-reactive protein (mg/l; assayed at central biocentre); patient global visual analogue scale [100mm VAS]) were assessed at each assessment.(21) EULAR response (good, moderate, no response) from baseline to six months was calculated.(22) Comorbidities were self-reported by patients from a pre-defined list, and were categorised for analysis as: no comorbidities; one comorbidity; ≥2 comorbidities.

Patients completed a questionnaire at each visit measuring pain and fatigue (0-100mm VAS where high scores indicate worse state), functional ability (Health Assessment Questionnaire [British version]; HAQ),(23) QoL (assessed using the EQ-5D with scores calculated using the Time Trade-off valuation technique),(24) and anxiety and depression (Hospital Anxiety and Depression Scale; HADS; higher scores are worse).(25)

***Work measures:*** Patients recorded their current work status (full-time, part-time, work disabled, retired, retired early due to arthritis, unemployed, working full time in the home) at baseline and subsequent assessments. Patients were coded as in work if they reported being in paid work (part-time or full-time) or on temporary sick-leave, and as having left the labour force if they reported any other work status at follow-up. Self-reported occupation was coded using the UK Standard Occupational Classification (SOC).(26;27) These codes were then used to classify jobs into three classes using the National Statistics Socio-Economic Classification (NS-SEC).(28) Absenteeism (sick-leave) was measured as days missed from work in the last month due to RA. Due to the extremely high number of zeros (MTX-starters = 82.4%; biologic-starters = 85.7%) and sparse data for each of the other possible values (1-31 days), absenteeism data were dichotomised into reported any sick-leave, yes or no. Everybody completed an adapted version of the RA-specific Work Productivity Survey (WPS-RA),(9;29-31) which measures presenteeism with the question *‘In the last month, how much has arthritis interfered with your work productivity (paid work) on a scale of 0‐10, where 0=no interference and 10=complete interference’.*

***Statistical analysis:*** Descriptive statistics were used to summarise the baseline and work outcome data for each cohort. Candidate predictors were selected *a priori* to be assessed in univariable analyses as follows: age, gender, smoking status, swollen joint count, HAQ, pain-VAS, fatigue-VAS, HADS-depression, HADS-anxiety, EQ5D, NS-SEC and comorbidities. The baseline EQ5D, pain-VAS and fatigue-VAS were standardised, meaning that these coefficients represent a change in the outcome for a one standard deviation change of the baseline factor. Due to the relatively low number of patients leaving work and taking sick leave, some modelling decisions were made when constructing multivariable models based on univariable analysis and theory, namely: EQ5D was excluded due to high collinearity with other variables, HADS depression and anxiety were combined to produce a psychological distress score (32) and swollen joint count was removed after univariable analysis. Patients who reported having left work at an assessment did not contribute to the absenteeism and presenteeism analyses at that or subsequent assessments, but did contribute to these outcomes at earlier time-points. Predictors of leaving work and absenteeism were assessed using population average logistic regression models – a type of longitudinal model that included data from both time-points and adjusts for within-patient correlation. Odds ratios (OR) are reported. A zero-inflated negative binomial (ZINB) regression model was used to model presenteeism due to excess zeros, with standard errors adjusted for within-patient clustering over the repeated measures. ZINB regression models assume that a zero score and a count score are produced by two separate processes. A logit model is used to predict whether a participant belongs in the zero presenteeism group (i.e. predictors of no presenteeism; ORs reported), and a negative binomial model predicts the count data (i.e. amount of presenteeism if presenteeism occurred; incidence rate ratios (IRR) reported). EULAR response (good, moderate, none) at six months was used to predict work participation over follow-up using population average logistic and negative binomial regression, controlling for age and gender. Those in remission at baseline were excluded from the EULAR response analysis (i.e. DAS28<2.6). Multiple imputation was used to account for missing baseline data (10 imputed datasets created; variables ranged from complete to 15.4% missing (NS-SEC in biologic-starters cohort)). Statistical analyses were performed using Stata 14 (StataCorp, College Station, TX).

**Results**

In total, 463 (43.4%) of 1065 18-65 year old MTX-starters and 260 (20.9%) of 1247 18-65 year old biologic-starters met the inclusion criteria and were available for these analyses. The median age in both cohorts was 52 years (IQR: MTX-starters = 45, 57; biologic-starters = 45.5, 57). There was a higher proportion of women in the biologic-starters compared to MTX-starters (MTX-starters = 315 [68.0%], biologic-starters = 201 [77.3%]). As expected, symptom duration was longer in biologic-starters (median (IQR) months: MTX-starters = 7 (4, 12), biologic-starters = 48 (24, 102)). Biologic-starters also had higher median scores for all disease activity measures and patient reported outcomes compared with MTX-starters (Table 1). Of those with sick-leave data at baseline, 107/350 (30.6%) MTX-starters and 53/208 (25.5%) biologic-starters reported taking sick-leave in the month prior to baseline.

***Baseline occupation:*** The occupations of MTX-starters were evenly spread across the three NS-SEC classes, with around a third in each class. There was a slightly higher proportion of biologic-starters in NS-SEC class one, representing higher managerial jobs (Table 2) (Supplementary table 1 for distribution across the nine SOC chapters). At baseline, 87 (19.2%) MTX-starters and 121 (47.8%) biologic-starters reported having made adaptions to their work environment since symptom onset.

***Work status over one year:*** From baseline to six months, 33/423 (7.8%) MTX-starters and 18/240 (7.5%) biologic-starters left work. From six to 12 months, 18/346 (5.2%) MTX-starters and 12/147 (8.2%) biologic-starters left work. Twenty patients became work disabled (MTX-starters = 15, biologic-starters = 5), 17 retired (MTX-starters = 9, biologic-starters = 8), 13 retired early due to arthritis (MTX-starters = 6, biologic-starters =7) and 31 left for other reasons (MTX-starters = 21, biologic-starters = 10). Of those still working, 72/356 (20.2%) and 47/300 (15.6%) MTX-starters took sick-leave the month preceding their six and 12 month assessment respectively. For biologic-starters, the proportions were similar (six months = 33/195 [16.9%], 12 months = 20/121 [16.5%]). For both cohorts, the proportions taking sick-leave at six and 12 months were lower than the proportions at baseline. Low rates of presenteeism were reported by patients at both assessments in both cohorts (six months, median [IQR]: MTX-starters = 2 [0, 5], biologic-starters = 2 [0, 5]; 12 months: MTX-starters = 2 [0, 4], biologic-starters = 1 [0, 5]) (Figures 1 & 2).

***Baseline predictors of work outcomes:*** There were several significant univariable baseline predictors of leaving work in both cohorts (MTX-starters: current smoking, HAQ, HADS depression, HADS anxiety, EQ5D, NS-SEC; biologic-starters: age; Table 3). In multivariable analysis, the odds of leaving work increased by 55% per unit increase in disability (HAQ: OR 1.55, 95% CI 0.85, 2.84) for MTX starters. General psychological distress predicted leaving work amongst MTX-starters (OR 1.05, 95% CI 1.00, 1.10), as did current smoking (vs never smoking: OR 3.47, 95% CI 1.65, 7.31) and people in routine and manual occupations were more likely to leave work compared with those in higher managerial occupations (OR 2.14, 95% CI 1.01, 4.54). For biologic-starters, more functional disability predicted leaving work (OR per unit increase in HAQ: 3.46, 95% CI 1.39, 8.62) (Table 4).

Amongst those remaining in the work-force, there were a number of univariable baseline predictors of absenteeism (MTX-starters: age, HAQ, pain-VAS, fatigue-VAS, HADS depression, HADS anxiety, EQ5D; biologic-starters: HAQ, fatigue-VAS, HADS depression, HADS anxiety, EQ5D; Table 3). In multivariable analysis, more functional disability (OR per unit increase in HAQ: 1.46, 95% CI 0.90, 2.34), more fatigue (OR per standard deviation increase in fatigue-VAS: 1.35, 95% CI 0.97, 1.89) and greater psychological distress (OR per unit increase in HADS psychological distress: 1.04, 95% CI 1.00, 1.08) predicted absenteeism for MTX-starters (Table 4). Amongst biologic-starters, more disability predicted absenteeism (OR per unit increase in HAQ: 2.41, 95% CI 1.12, 5.22) (Table 4).

There were several univariable baseline predictors of reporting no presenteeism from the ZINB analyses (MTX-starters: HAQ, pain-VAS, fatigue-VAS, HADS depression, HADS anxiety, EQ5D; biologic-starters: SJC28, HAQ, HADS depression, HADS anxiety, EQ5D; Table 3). Baseline independent predictors of no presenteeism in MTX-starters were less fatigue (OR per standard deviation increase in fatigue-VAS: 0.54, 95% CI 0.34, 0.86) and less disability (OR per unit increase in HAQ: 0.63, 95% CI 0.34, 1.18). For biologic-starters, less disability (OR per unit increase in HAQ: 0.42, 95% CI 0.21, 0.84), less psychological distress (OR per unit increase in HADS psychological distress: 0.94, 95% CI 0.89, 0.99) and being in routine and manual occupations vs higher managerial, administrative and professional occupations (OR: 2.08, 95% CI 0.90, 4.80) predicted no presenteeism (Table 4). Of the patients with presenteeism, independent baseline predictors of higher presenteeism score in MTX-starters included: female gender (IRR women vs. men: 1.27, 95% CI 1.01, 1.60) and more fatigue (IRR per standard deviation increase in fatigue-VAS: 1.17, 95% CI 1.01, 1.35). For biologic-starters, higher baseline disability (IRR per unit increase in HAQ: 1.40, 95% CI 1.13, 1.74) and higher baseline fatigue (IRR per standard deviation increase in fatigue-VAS: 1.15, 95% CI 0.98, 1.34) predicted more presenteeism over follow-up.

***EULAR response over the first six months and work outcomes:*** In total, 121 (31.4%) MTX-starters and 89 (57.8%) biologic-starters had a good response and 99 (25.7%) MTX-starters and 49 (31.8%) biologic-starters had moderate response over the first six months. EULAR response was not significantly associated with leaving the labour force over follow-up in MTX-starters (moderate vs no response: OR 1.30, 95% CI 0.60, 2.85; good vs. no response: OR 0.90, 95% CI 0.41, 1.93) or biologic-starters (moderate vs. no response: OR 0.88, 95% CI 0.23, 3.36; good vs. no response: OR 0.57, 95% CI 0.16, 2.09). However amongst MTX-starters, both moderate and good response were associated with lower odds of absenteeism (MTX-starters: moderate vs. no response: OR 0.36, 95% CI 0.19, 0.67; good vs. no response: OR 0.23, 95% CI 0.12, 0.42) and less presenteeism (MTX-starters: moderate vs. no response: IRR 0.71, 95% CI 0.50, 1.00; good vs. no response: IRR 0.38, 95% CI 0.27, 0.52) compared with no response. For biologic-starters, good response was associated with lower odds of absenteeism (biologic-starters: moderate vs. no response: OR 0.44, 95% CI 0.14, 1.34; good vs. no response: OR 0.36, 95% CI 0.13, 1.04) and less presenteeism compared with no response (biologic-starters: moderate vs. no response: IRR 0.72, 95% CI 0.41, 1.26; good vs. no response: IRR 0.44, 95% CI 0.27, 0.71); the effect sizes of the moderate vs. no response comparisons also indicated an association in favour of moderate response, but the confidence interval overlapped one in both analyses.

**Discussion**

These analyses of over 700 people with RA in paid employment when starting either MTX or a biologic have allowed us to explore the prevalence of and risk factors for job loss, sickness absence and presenteeism over 12 months of follow-up. Overall, 11% of the MTX-starters and 11.5% of biologic-starters left work during the study period. On average, 16.6% of MTX-starters and 14.9% of biologic-starters took sickness absence in the month prior to each follow-up, a reduction from baseline. The reported rates of presenteeism were low in this study. Higher ratings of disability at baseline predicted poorer work outcomes, highlighting the importance of function in enabling work participation. Fatigue, psychological distress and job type also significantly predicted different work outcomes. Furthermore, good treatment response was associated with lower odds of absenteeism and lower presenteeism scores. Therefore a holistic approach combining both good control of disease activity and interventions aiming to address the other salient predictors including reducing physical demands and increasing support at work, and improving disability and fatigue may be required to further improve the work participation of patients with RA.

Over 10% of patients with RA starting MTX left work over the first year, rates similar to those in another UK cohort recruited in the 2000s.(3) Whilst these are lower than those reported in a UK study of early RA patients recruited in the 1990s,(33) this represents significant loss to the work force and a major negative impact on these patients’ lives. Disability, current smoking and psychological distress predicted leaving work for MTX-starters, as did manual occupations.(3;4;10;34-39). Biologic treatment has been shown to have positive effects on work participation in the past,(40) and a similar proportion of biologic-starters left work compared to MTX-starters. In the current study, biologic-starters differ from MTX-starters as they have remained in work for longer since the onset of RA. Patients at high risk of leaving work may have done so prior to starting a biologic. This attrition affect may explain why psychological distress and smoking no longer predict leaving work in biologic-starters. However, disability still predicted leaving work in biologic-starters, indicating the importance of monitoring and responding to other aspects of RA symptomology beyond disease activity. Interestingly, lower baseline pain also predicted biologic-starters leaving work and we found an interaction in this group between pain and age, whereby lower pain predicted leaving work in older patients only, although low number of events meant that this interaction was not statistically significant and may be a chance finding (data not shown).

Of those remaining in work after starting MTX, around 20% of patients reported taking sick-leave in the months preceding each assessment. These levels of absenteeism are similar to those found in other observational studies, although comparisons are difficult since methods for collecting absenteeism data are not standardised.(41) Higher fatigue, psychological distress and disability predicted taking sick-leave for MTX-starters. Fatigue has been reported elsewhere as a key factor affecting the ability to remain in work with RA.(42;43) Similar proportions of biologic-starters reported taking sick leave. In these patients, disability was the only significant predictor of taking sick-leave.(38) The HAQ assesses difficulties performing activities of daily living and is clearly pointing to the importance of function in work participation.

Presenteeism scores were low in both cohorts, as found elsewhere.(41) Whilst this may suggest that productivity is not affected by arthritis when patients are able to attend work, there are concerns regarding the utility of a 10 point scale in detecting presenteeism accurately. In both cohorts, fatigue, psychological distress and disability predicted presenteeism;(38;41;44;45) for biologic-starters, presenteeism was less likely amongst those with fewer comorbidities.

Interventions to improve work outcomes have been developed which examine work schedules and environments, and barriers to work,(46-48) although with uncertain efficacy.(49) Targeted referral to interventions aiming to address important areas influencing patients’ personal ability to work (e.g. disability, fatigue, psychological distress) for patients at high risk of job loss may be the next step towards improving work participation amongst patients with RA.

This analysis has a number of strengths. This study combines two large cohorts with similar methods and assessments but recruiting patients at different stages of disease progression, allowing comparison of prognostic factors across RA disease progression. Limitations of the study include the fact that productivity loss is self-reported, meaning we are unable to assess objective reductions in productivity. Furthermore, the measure used to detect presenteeism may not be a sensitive tool for measuring this multi-dimensional concept, although the tool has been shown to have good validity and reliability in the past.(30;31) There were also missing data for presenteeism scores in both cohorts, with some differences in baseline factors. However, analysis using imputed presenteeism scores did not differ substantially from the unimputed outcome analysis (see Supplementary tables 2 and 3).

In conclusion, there are a number of important baseline factors that predict different work-related outcomes. These factors may be useful in identifying patients who are at increased risk of having poor work-related outcomes. This indicates that a holistic approach towards disease management is necessary, alongside good control of disease activity, to improve the work-related outcomes of patients with RA.

**KEY MESSAGES**

* Patients with RA still face significant work limitation in the modern treatment era.
* Disability predicts a majority of work-outcomes, highlighting the importance of function in enabling work participation.
* Holistic approach to disease management, alongside good disease control, may be necessary to improve work-outcomes.

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**CONTRIBUTORS**

Review of manuscript: JMG, SL, ML, AB, KLH, KWB, SMMV; Study concept and design: KWB, SMMV; Acquisition of data: AB, KLH, SMMV; Analysis and interpretation of data: JMG, SL, ML, SMMV

**COMPETING INTERESTS**

None

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|  |  |  |
| --- | --- | --- |
|  | Total Cohort | Patients included in work analyses |
|  | **MTX-starters** |  | **Biologic-starters** | **MTX-starters** |  | **Biologic-starters** |
| Variable | **N (%)** | **Median (IQR)** | **N (%)** | **Median (IQR)** | **N (%)** | **Median (IQR)** | **N (%)** | **Median (IQR)** |
| Age at baseline, years | 1065 | 52 (44, 59) | 1247 | 54 (47, 59) | 463 | 52 (45, 57) | 260 | 52 (45.5, 57) |
| Female (% of total cohort) | 742 (69.7) |  | 970 (77.9) |  | 315 (68.0) |  | 201 (77.3) |  |
| Symptom duration, months | 1065 | 7 (4, 12) | 1233 | 60 (24, 120) | 463 | 7 (4, 12) | 256 | 48 (24, 102) |
| Smoking status*Never**Former**Current* | 407 (38.5)374 (35.4)276 (26.1) |  | 452 (36.6)504 (40.8)280 (22.7) |  | 190 (41.1)175 (37.9)97 (21.0) |  | 102 (36.2)113 (43.5)45 (17.3) |  |
| Swollen joint count (28 joints) | 1020 | 4 (2, 9) | 1190 | 8 (5, 11) | 448 | 4 (1, 8) | 250 | 8 (5, 12) |
| Tender joint count (28 joints) | 1019 | 6 (2, 13) | 1190 | 15 (10, 21) | 449 | 5 (2, 11) | 249 | 14 (9, 20) |
| CRP (mg/l) | 1056 | 5 (2, 14) | 1027 | 9 (4, 22) | 461 | 5 (2, 12) | 227 | 8 (4, 17) |
| DAS28-CRP | 1000 | 4.3 (3.2, 5.2) | 995 | 5.8 (5.2, 6.3) | 442 | 4.0 (3.1, 4.9) | 219 | 5.6 (5.2, 6.2) |
| HAQ | 957 | 1.00 (0.38, 1.50) | 944 | 1.63 (1.13, 2.13) | 461 | 0.88 (0.38, 1.38) | 258 | 1.38 (0.88, 1.75) |
| RF status*Total measured**Positive* | 818553 (67.6) |  | 1058691 (65.3) |  | 384277 (72.1) |  | 224154 (68.8) |  |
| Pain-VAS | 946 | 51 (28, 72) | 929 | 70 (54, 81) | 459 | 48 (25, 68) | 256 | 67 (49, 78) |
| Fatigue-VAS | 945 | 57 (29, 76) | 927 | 76 (60, 88) | 458 | 53 (25, 73) | 256 | 72 (52, 85) |
| Patient global VAS | 1056 | 43 (22, 64) | 1177 | 80 (65, 90) | 459 | 35 (20, 60) | 244 | 78 (65, 86) |
| HADS depression | 953 | 6 (2, 9) | 920 | 7.5 (5, 11) | 461 | 5 (2, 8) | 256 | 6 (3, 9) |
| HADS anxiety | 952 | 6.5 (4, 10) | 914 | 8 (5, 12) | 460 | 6 (3, 9) | 256 | 8 (5, 11) |
| EQ-5D  | 935 | 0.66 (0.52, 0.76) | 911 | 0.52 (-0.02, 0.66) | 453 | 0.69 (0.52, 0.76) | 254 | 0.59 (0.19, 0.69) |
| Comorbidity*No comorbidity**One comorbid condition**≥2 comorbid conditions* | 501 (47.0)355 (33.3)209 (19.6) |  | 418 (39.9)369 (35.2)261 (24.9) |  | 236 (51.0)155 (33.5)72 (15.6) |  | 128 (53.3)77 (32.1)35 (14.6) |  |

*Anti-CCP = anti-cyclic citrullinated peptide antibody, BRAGGSS = Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate, CRP = C-reactive protein, DAS28-CRP = Disease Activity Score (28) using CRP, HADS = Hospital Anxiety and Depression Scales, HAQ = Health Assessment Questionnaire, IQR = interquartile range, N = number, RAMS = Rheumatoid Arthritis Medication Study, RF = rheumatoid factor, VAS = visual analogue scale*

*Table 1 – Baseline characteristics of the two cohorts*

*Table 2 – The NS-SEC classes of the two cohorts*

|  |  |  |
| --- | --- | --- |
| NS-SEC - Three classes | MTX-starters, N (%) | Biologic-starters, N (%) |
| 1. Higher managerial, administrative and professional occupations | 160 (34.6) | 81 (31.2) |
| 2. Intermediate occupations | 144 (31.1) | 70 (26.9) |
| 3. Routine and manual occupations | 143 (30.9) | 69 (26.5) |
| Uncoded §*§ Patients who did not provide enough information on their occupation to be coded using SOC**N = number, NS-SEC = The National Statistics Socio-Economic Classification* | 16 (3.5) | 40 (15.4) |

*Figure 1 – Flowchart and work-outcomes [MTX-starters]*

*Figure 2 – Flowchart and work-outcomes [biologic-starters]*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Left work, OR (95% CI) | Sick-leave, OR (95% CI) | No presenteeism, OR (95% CI) | Presenteeism Score, IRR (95% CI) |
| Baseline Predictor | **MTX-starters****(N=463)** | **Biologic-starters****(N=260)** | **MTX-starters (N=404)** | **Biologic-starters (N=217)** | **MTX-starters (N=325)** | **Biologic-starters (N=207)** | **MTX-starters****(N=325)** | **Biologic-starters (N=207)** |
| Age | 1.01 (0.97, 1.04) | 1.05 (1.00, 1.11) | 0.98 (0.96, 1.00) | 1.00 (0.97, 1.04) | 1.01 (0.98, 1.05) | 1.01 (0.99, 1.04) | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.01) |
| Women vs men | 1.18 (0.63, 2.19) | 0.76 (0.32, 1.77) | 1.57 (0.95, 2.61) | 0.94 (0.43, 2.05) | 1.00 (0.56, 1.79) | 0.97 (0.52, 1.80) | 1.43 (1.16, 1.77) | 1.10 (0.85, 1.41) |
| Smoking*Ex vs never**Current vs never* | 1.10 (0.51, 2.35)3.78 (1.88, 7.60) | 0.94 (0.41, 2.16)1.25 (0.45, 3.49) | 0.84 (0.51, 1.37)1.09 (0.59, 1.99) | 1.32 (0.64, 2.69)1.58 (0.64, 3.91) | 0.76 (0.42, 1.35)0.48 (0.20, 1.15) | 1.45 (0.80, 2.64)1.19 (0.53, 2.68) | 0.93 (0.74, 1.21)0.94 (0.74, 1.21) | 1.15 (0.92, 1.42)1.21 (0.91, 1.63) |
| SJC28 | 1.02 (0.97, 1.07) | 1.02 (0.94, 1.10) | 1.01 (0.97, 1.05) | 1.00 (0.94, 1.07) | 1.00 (0.95, 1.06) | 1.09 (1.03, 1.16) | 1.01 (0.99, 1.03) | 1.01 (0.99, 1.03) |
| HAQ | 1.63 (1.08, 2.46) | 1.83 (0.96, 3.49) | 2.08 (1.50, 2.89) | 2.86 (1.63, 5.05) | 0.43 (0.28, 0.68) | 0.47 (0.29, 0.76) | 1.37 (1.22, 1.54) | 1.55 (1.30, 1.86) |
| Pain-VAS *Natural scale**Standardised scale* | 1.01 (0.995, 1.02)1.18 (0.88, 1.57) | 0.99 (0.98, 1.01)0.83 (0.58, 1.18) | 1.02 (1.01, 1.03)1.53 (1.22, 1.93) | 1.01 (0.998, 1.03)1.38 (0.97, 1.95) | 0.98 (0.97, 1.00)0.65 (0.47, 0.90) | 0.99 (0.98, 1.01)0.88 (0.66, 1.17) | 1.01 (1.00, 1.01)1.23 (1.11, 1.36) | 1.01 (1.00, 1.01)1.16 (1.03, 1.30) |
| Fatigue-VAS*Natural scale**Standardised scale* | 1.01 (0.997, 1.02)1.22 (0.91, 1.64) | 1.00 (0.98, 1.01)0.90 (0.63, 1.30) | 1.02 (1.01, 1.03)1.80 (1.41, 2.31) | 1.02 (1.00, 1.03)1.50 (1.03, 2.19) | 0.97 (0.96, 0.98)0.46 (0.34, 0.63) | 0.99 (0.98, 1.00)0.83 (0.63, 1.10) | 1.01 (1.01, 1.01)1.31 (1.19, 1.45) | 1.01 (1.00, 1.02)1.26 (1.10, 1.45) |
| HADS Depression | 1.11 (1.03, 1.19) | 1.05 (0.95, 1.15) | 1.13 (1.07, 1.19) | 1.14 (1.05, 1.23) | 0.83 (0.75, 0.92) | 0.89 (0.82, 0.96) | 1.06 (1.03, 1.08) | 1.04 (1.02, 1.06) |
| HADS Anxiety | 1.12 (1.05, 1.19) | 1.04 (0.95, 1.14) | 1.12 (1.06, 1.18) | 1.09 (1.01, 1.18) | 0.85 (0.78, 0.93) | 0.88 (0.82, 0.95) | 1.04 (1.02, 1.06) | 1.03 (1.01, 1.05) |
| EQ5D (standardised) | 0.74 (0.58, 0.96) | 0.82 (0.57, 1.17) | 0.61 (0.50, 0.75) | 0.61 (0.45, 0.83) | 1.94 (1.24, 3.02) | 1.46 (1.08, 1.98) | 0.80 (0.74, 0.87) | 0.88 (0.80, 0.96) |
| NS-SEC*Class 2 vs. Class 1**Class 3 vs. Class 1* | 1.22 (0.55, 2.71)2.22 (1.05, 4.70) | 0.79 (0.30, 2.06)0.62 (0.24, 1.64) | 0.68 (0.38, 1.22)1.32 (0.78, 2.23) | 1.89 (0.84, 4.29)1.89 (0.84, 4.28) | 1.32 (0.70, 2.51)0.93 (0.48, 1.80) | 0.94 (0.44, 2.02)1.45 (0.72, 2.90) | 0.79 (0.62, 0.99)0.99 (0.80, 1.21) | 1.31 (1.03, 1.67)1.31 (1.02, 1.69) |
| Comorbidity*1 comorbidity vs 0**≥2 comorbidities vs 0* | 0.81 (0.41, 1.60)1.62 (0.79, 3.35) | 1.45 (0.61, 3.42)1.81 (0.64, 5.16) | 1.19 (0.73, 1.94)1.33 (0.71, 2.49) | 1.25 (0.60, 2.59)1.51 (0.58, 3.94) | 0.79 (0.44, 1.42)0.66 (0.27, 1.62) | 0.72 (0.38, 1.35)0.37 (0.16, 0.86) | 1.11 (0.91, 1.36)1.17 (0.91, 1.50) | 1.03 (0.81, 1.31)1.18 (0.88, 1.56) |

 *CI = confidence interval, DAS28 = Disease Activity Score, HADS = Hospital Anxiety and Depression Scale, HAQ = Health Assessment Questionnaire, IRR = incidence rate ratio, NS-SEC = The National Statistics Socio-Economic Classification (see table 2 for definition of classes), OR = odds ratio, SJC = swollen joint count, VAS = visual analogue scale*

*Natural scale = the unadjusted scores from the visual analogue scales ranging from 0-100. The ORs and IRRs are interpreted as the change in odds or the relative change in the outcome per unit increase in the predictor. For the natural scale, a 1 unit change is very small. Hence, the results are also given on a standardised scale. Here, a 1 unit increase in the scale corresponds to 1 standard deviation change in the visual analogue scale score (approx. 20 unit change in this case).*

*Interpretation of zero-inflated negative binomial (ZINB) regression output used to model presenteeism scores: ZINB models data with a high number of zeros (i.e. presenteeism) by splitting the data into two portions: the zero scores and the non-zero scores. Then the model predicts whether or not a patient had zero presenteeism or more than zero using a logistic regression model, and gives an odds ratio for no presenteeism (with a score <1 indicating that, as the variable increases, patients are less likely to have no presenteeism). After this, the model predicts the non-zero scores in all the people that scored greater than zero, using a negative binomial regression model and gives incidence rate ratios (with a score >1 indicating that as the predictor increases, presenteeism score increases – for example, an IRR of 1.55 for HAQ scores of biologic-starters indicates that, for each unit increase in HAQ score, the average presenteeism score increases by 55%).*

*Table 3 –Predictors of work outcomes from univariable models*

*Table 4 – Independent predictors of work outcomes from multivariable models*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Left work, OR (95% CI) | Sick-leave, OR (95% CI ) | No presenteeism, OR (95% CI) | Presenteeism Score, IRR (95% CI) |
| Baseline Predictor | **MTX-starters (N=463)** | **Biologic-starters****(N=260)** | **MTX-starters (N=404)** | **Biologic-starters (N=217)** | **MTX-starters (N=325)** | **Biologic-starters (N=207)** | **MTX-starters (N=325)** | **Biologic-starters (N=207)** |
| Age | 1.00 (0.96, 1.03) | 1.04 (0.99, 1.11) | 0.98 (0.96, 1.01) | 1.00 (0.96, 1.04) | 1.02 (0.98, 1.06) | 1.02 (0.99, 1.05) | 1.00 (0.99, 1.01) | 1.00 (0.99, 1.02) |
| Women vs men |  1.31 (0.66, 2.63) | 0.79 (0.32, 2.00) | 1.21 (0.71, 2.08) | 0.68 (0.30, 1.56) | 1.40 (0.63, 3.08) | 1.45 (0.76, 2.78) | 1.27 (1.01, 1.60) | 1.03 (0.79, 1.34) |
| Smoking status vs never*Former**Current* | 1.01 (0.45, 2.24)3.47 (1.65, 7.31) | 0.66 (0.27, 1.63)0.84 (0.28, 2.54) | 0.83 (0.49, 1.40)1.01 (0.53, 1.93) | 1.08 (0.51, 2.28)1.02 (0.38, 2.70) | 0.66 (0.34 (1.27)0.44 (0.16, 1.21) | 1.74 (0.89, 3.42)1.58 (0.63, 3.95) | 0.94 (0.78, 1.13)0.96 (0.77, 1.20) | 1.10 (0.89, 1.36)0.95 (0.70, 1.28) |
| HAQ |  1.55 (0.85, 2.84) | 3.46 (1.39, 8.62) | 1.46 (0.90, 2.34) | 2.41 (1.12, 5.22) | 0.63 (0.34, 1.18) | 0.42 (0.21, 0.84) | 1.08 (0.92, 1.28) | 1.40 (1.13, 1.74) |
| Pain-VAS*Natural scale**Standardised scale* |  1.00 (0.98, 1.01)0.90 (0.58, 1.39) | 0.98 (0.96, 1.00)0.65 (0.41, 1.04) | 1.00 (0.99, 1.01)0.96 (0.68, 1.35) | 1.00 (0.98, 1.01)0.90 (0.59, 1.38) | 1.01 (0.99, 1.03)1.33 (0.83, 2.11) | 1.01 (0.99, 1.03)1.28 (0.85, 1.93) | 1.00 (0.997, 1.01)1.05 (0.92, 1.20) | 1.00 (0.99, 1.00)0.99 (0.88, 1.12) |
| Fatigue-VAS*Natural scale**Standardised scale* | 1.00 (0.98, 1.01)0.88 (0.56, 1.35) | 0.99 (0.97, 1.01)0.71 (0.42, 1.19) | 1.01 (0.999, 1.02)1.35 (0.97, 1.89) | 1.00 (0.98, 1.02)1.05 (0.66, 1.69) | 0.98 (0.96, 1.00)0.54 (0.34, 0.86) | 1.01 (0.99, 1.02)1.20 (0.81, 1.78) | 1.01 (1.00, 1.01)1.17 (1.01, 1.35) | 1.01 (0.999, 1.01)1.15 (0.98, 1.34) |
| HADS General Distress | 1.05 (1.00, 1.10) | 1.04 (0.97, 1.11) | 1.04 (1.00, 1.08) | 1.04 (0.98, 1.09) | 0.95 (0.88, 1.02) | 0.94 (0.89, 0.99) | 1.01 (0.99, 1.02) | 1.00 (0.99, 1.02) |
| NS-SEC*Class 2 vs. Class 1**Class 3 vs. Class 1* | 1.28 (0.56, 2.92)2.14 (1.01, 4.54) | 0.57 (0.20, 1.65)0.46 (0.15, 1.37) | 0.67 (0.37, 1.21)1.39 (0.80, 2.40) | 1.58 (0.66, 3.80)1.54 (0.65, 3.65) | 1.11 (0.53, 2.36)0.92 (0.45, 1.87) | 1.12 (0.48, 2.63)2.08 (0.90, 4.80) | 0.85 (0.69, 1.05)1.07 (0.89, 1.29) | 1.22 (0.97, 1.55)1.20 (0.94, 1.53) |
| Comorbidity*1 comorbidity vs 0**≥2 comorbidities vs 0* | 0.81 (0.40, 1.66)1.58 (0.72, 3.48) | 0.89 (0.34, 2.29)1.12 (0.33, 3.76) | 1.16 (0.70, 1.92)1.06 (0.55, 2.07) | 0.97 (0.43, 2.16)0.92 (0.32, 2.66) | 0.92 (0.49, 1.73)0.99 (0.37, 2.68) | 0.82 (0.39, 1.71)0.36 (0.13, 0.98) | 1.03 (0.85, 1.23)1.01 (0.79, 1.28) | 1.05 (0.83, 1.33)1.01 (0.77, 1.33) |

*See table 3 for definitions of abbreviations*