



## King's Research Portal

DOI:

[10.1093/rheumatology/kex528](https://doi.org/10.1093/rheumatology/kex528)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

Matcham, F., Davies, R., Hotopf, M., Hyrich, K. L., Norton, S., Steer, S., & Galloway, J. (2018). The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register. *Rheumatology (Oxford, England)*, 57(5), 835-843. <https://doi.org/10.1093/rheumatology/kex528>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

# **The relationship between depression and biologic treatment response in rheumatoid arthritis: An analysis of the British Society for Rheumatology Biologics Register.**

Faith Matcham, Rebecca Davies<sup>2,3</sup>, Matthew Hotopf<sup>1,4</sup>, Kimme Hyrich<sup>2,3</sup>, Sam Norton<sup>5,6</sup>, Sophia Steer<sup>6</sup>, James Galloway<sup>6</sup>.

1. King's College London, Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, London, UK.
2. Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, the University of Manchester, UK.
3. NIHR Manchester Biomedical Research Centre, Central Manchester Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, UK.
4. South London and Maudsley NHS Foundation Trust, Maudsley Hospital, London, UK.
5. King's College London, Department of Psychology, Institute of Psychiatry, Psychology and Neuroscience, London, UK.
6. King's College London, Department of Academic Rheumatology, London, UK.

## **Correspondence address:**

Dr Faith Matcham,  
Institute of Psychiatry, Psychology & Neuroscience, King's College London,  
Weston Education Centre,  
10 Cutcombe road,  
London SE5 9RJ  
[faith.matcham@kcl.ac.uk](mailto:faith.matcham@kcl.ac.uk)  
(+44) 2078480868

## **ABSTRACT**

### **Objective**

To investigate the relationship between depressive symptoms and treatment response and disease activity over a one-year follow-up.

### **Methods**

Data from the British Society for Rheumatology Biologics Register were used, representing 18,421 RA patients receiving biologic treatment. Depressive symptoms were identified through one of three assessments: reporting a history of depression; the Medical Outcomes Survey 36-item Short Form (SF36); or the EuroQoL (EQ5D). Logistic regression analyses examined the relationship between baseline depressive symptoms and odds of good treatment response by 1-year. Multilevel models addressed the association between baseline depressive symptoms and disease activity outcomes over 1-year follow-up, adjusting for age, gender, disease duration, comorbidities, and baseline disease activity and physical disability.

### **Results**

Depression symptoms at biologic treatment initiation were associated with 20-40% reduced odds of achieving a good treatment response at 1-year. Depressive symptoms at baseline also associated with reduced improvement in disease activity over the course of follow-up. Patients with a history of depression or reporting symptoms of depression according to the EQ5D showed reduced improvement in tender and swollen joints, patient global assessment (PGA) and erythrocyte sedimentation rate (ESR) over 1-year follow-up. Patients with depression symptoms according to the SF36 showed reduced improvement in tender and swollen joints, but not ESR or PGA.

### **Conclusion**

Experiencing symptoms of depression at the start of biologics treatment may reduce the odds of achieving a good treatment response, and reduce improvement in disease activity over time. Depression should be managed as part of routine clinical care to optimise treatment outcomes.

**Keywords:** Rheumatoid Arthritis, Biological therapies, Depression, Epidemiology, Quality of life, Mental health services, Statistics

## INTRODUCTION

Depression is prevalent in RA, with meta-analysis evidence suggesting a 17% point prevalence according to diagnostic interview [1]. Recent evidence has highlighted depression symptoms as a prognostic psychomarker for poor rheumatological outcomes, with symptoms of depression and anxiety associated with worsened disease activity, physical function, and reduced response to Disease Modifying Anti-Rheumatic Drug (DMARD) and glucocorticoid treatments [2,3]. Depression is rarely measured in rheumatological research [4]; assessment of mental health is usually limited to assessment of mental health domains on health-related quality-of-life (HRQoL) questionnaires such as the Medical Outcomes Survey 36-item Short-Form (SF36) [5] or the EQ5D [6].

The development of biologic treatments for RA have revolutionised the management of RA; in comparison to conventional DMARDs, biologics contribute to increased likelihood of disease remission, and significantly improve physical function [7,8]. There is, however, a dearth of research examining the relationship between depression and long-term disease outcomes in RA [3]. The impact of comorbid depression on biologic treatment response has previously been investigated in a United States register; the authors reported an association between depressive symptomatology and likelihood of remission at 6-month follow-up, purported to be driven by an association between depression and subjective experiences of disease [9]. Their assessment was limited to a one-item depression comorbidity tick-box, which may result in high false-positive rates due to poor specificity [10]. Analysis of the Norwegian Disease-Modifying Anti-Rheumatic Drug (NOR-DMARD) database identified an association between depressive symptoms at the start of treatment with biological or synthetic DMARDs, and reduced risk of remission and higher pain and global assessment at 3- and 6- month follow-up [11]. To date, there is stronger evidence for a relationship between depressive symptoms and subjective experiences of disease such a patient global assessment (PGA) and pain [2,11–13], contributing to a growing focus on re-defining remission in RA [14].

The present study seeks to examine the longitudinal association between depressive symptoms and treatment response in a UK national register of RA patients starting their first biologic. In comparison to previous research [9], this study utilises three measures of depression symptoms: history of depression comorbidity tick-box, the

## Depression and biologic treatment response

mental health domain of the SF36, and the depression/anxiety item of the EQ5D, providing an opportunity to investigate the differential relationships between depression symptoms and treatment outcomes based on mental health assessment strategy. The aims are: 1) to examine the relationship between baseline depression symptoms and biologic treatment response over 1-year follow-up; 2) to evaluate the relationship between baseline depression symptoms and disease activity over 1-year.

## **METHODS**

### **Participants**

This study presents an analysis of the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA; [15]). The BSRBR-RA is a national prospective register of RA patients starting a new biologic, and contains data from 18,421 patients enrolled since its inception in 2001. To be eligible for inclusion in the BSRBR-RA, patients must meet UK guidelines for commencing a biologics: sustained active RA (defined as scoring  $>5.1$  on the DAS28 at two timepoints a month apart); and failure to respond to  $\geq$  conventional Disease modifying Anti-Rheumatic Drugs (DMARDs) including methotrexate over a  $\geq 6$  month timeframe [16]. A range of clinical, demographic and psychological assessments are taken at baseline, 6-monthly intervals for the first 3-years of follow-up, and yearly thereafter. We limited our analysis to first biologic exposure only.

### **Assessments**

#### Depression Symptoms

Three measures of depressive symptoms are available in the BSRBR-RA database: upon enrolment, all patients are asked if they have ever had or received treatment for depression, which was used as an indicator of history of depression. The SF36 [5] was used as an assessment of HRQoL between 2001-2008, in the first 11,937 enrolled patients. A threshold of  $\leq 40$  on the normed mental health (nMH) subscale of the SF36 has been shown to have a 92.6% sensitivity and 73.2% specificity for identifying depression in patients with RA [17]. Responses to the SF36 were categorised using this threshold, to represent patients with low HRQoL. The EQ5D [6] was introduced to the BSRBR-RA in 2005 and became the only HRQoL assessment from 2010 onwards. The EQ5D has one item specific to mental health,

## Depression and biologic treatment response

allowing patients to identify whether they are feeling “not depressed/anxious”, “moderately depressed/anxious”, or “extremely depressed/anxious” today. Evidence suggests that one-item mood screeners have 84% sensitivity and 65% specificity [18], and this item has been previously used to predict longitudinal DAS28 and HAQ outcomes, and prednisolone treatment response in RA patients [2].

## Treatment Response

The primary outcome of interest was 1-year treatment response, measured by the European League Against Rheumatism (EULAR) guidelines [19]. Based on their 1-year EULAR response, patients were categorised into those demonstrating a good treatment response and those with a suboptimal treatment response (none/moderate response).

## Disease activity

Secondary outcomes were disease activity (measured via the DAS28), and its composite parts: tender joint count (TJC); swollen joint count (SJC); patient global assessment (PGA); and erythrocyte sedimentation rate (ESR); all measured at 1-year follow-up. TJC and SJC underwent square root transformation and ESR data were log transformed for analysis.

## Statistical Analysis

Although data were available for three years of follow-up, only data until the first year of follow-up were included. This ensured a focus on first biologic exposure, eliminating bias introduced by patients switching biologics due to a lack of treatment response. All analyses were conducted on Stata v14. Clinical and demographic characteristics of patients having a good treatment response by 1-year were compared with those with no/moderate treatment response using means and standard deviations, with statistically significant imbalance determined using t-tests for continuous variables and Chi- squared tests for categorical data.

**Aim 1: The impact of baseline depressive symptoms on 1-year biologic treatment response**

Logistic regression models were performed in 2 stages: unadjusted (model 1), then adjusted for age, gender, disease duration, baseline DAS28, baseline HAQ, and number of comorbidities (model 2). Logistic regression estimates the odds of a binary outcome (i.e. having a good treatment response), based on several predictor

## Depression and biologic treatment response

variables (i.e. baseline depression). In all models, baseline depressive symptomatology was entered as the predictor variable: history of depression (yes/no); SF36 nMH subscale ( $\leq 40$ / $> 40$ ); EQ5D (no/moderate/extreme)). Treatment response at 1-year (none/moderate vs. good) was the outcome variable in primary analyses. Odds ratios (OR), p-values and 95% confidence intervals estimated whether the presence of depressive symptoms at biologic initiation was associated with increased odds of having a good treatment response at 1-year. Multiple imputation was used to address baseline missing data for DAS28, disease duration and HAQ.

Aim 2: Relationship between baseline depressive symptoms and time-course disease activity over 1-year

The relationships between baseline depression and 1-year DAS28, TJC, SJC, PGA and ESR were examined using multilevel longitudinal models, pooling data across the timepoints (baseline, 6-months and 1-year) [20]. Multilevel modelling handles hierarchically nested data, accounting for missing data, and both between- and within- participant variation over time, and multiple imputation was used to address baseline missing data for DAS28, disease duration and HAQ.

Output from multilevel models includes unstandardized maximum likelihood estimates (B coefficients), which estimate the magnitude and direction of change in an outcome variable according to a reference group (no depressive symptoms at baseline). In addition to depressive symptoms as a predictor variable and DAS28 (and its composite parts) as outcome variables, multilevel models included time as a continuous variable coded as 0 at baseline, 1 at 6-months and 2 at 12-months, and the interaction between time and baseline depressive symptoms, to examine whether change over time is different between people with and without symptoms of depression at baseline. A random intercept and random time slope allowed for variation in the baseline level of the outcome and the rate of change in the outcome between individuals. The random effects were allowed to correlate, which means that some control for the baseline level of the outcome is included in the model even though it is not included as a covariate – e.g. a positive correlation would allow for increasing variability in the outcome variable over time [21]. Multilevel models were created in two stages: 1) including only baseline depression symptoms, time and an interaction between time and depression symptoms, plus random effects;

Depression and biologic treatment response

and 2) additionally adjusting for age, gender, disease duration, comorbidities, and baseline physical activity (measured via the Health Assessment Questionnaire (HAQ) [22]). Covariates were selected based on theoretical relevance.

## **RESULTS**

### Missing data

Figure 1 shows the data available for analysis for the primary outcome (treatment response) and secondary outcome (disease activity), in relation to the different methods of depressive symptom measurement. Missing response status/disease activity outcome data at 1-year was associated with increased BMI, and lower baseline DAS28, TJC, SJC, ESR and HAQ, shown in supplementary table t1. Baseline depression symptoms, according to all three measurements available, was not associated with missing outcome data.

### Participant characteristics

Data from 18,421 patients enrolled in the BSRBR-RA by December 2015 were included in this analysis (figure 1). Table 1 displays baseline demographic, clinical and psychological variables for all patients. The mean age was 56.4 years, 76.4% were female, with a mean disease duration of 12.6 years and mean DAS28 of 6.4. By 6-months, 3,638 patients had achieved a good treatment response. At 1-year, a total of 5,271 (34.3%) of patients having reached a DAS28 of  $\leq 3.2$  and an improvement in DAS28 from baseline of  $>1.2$ .

At 1-year follow-up, 17.9% of patients were identified as switching biologic. Biologic switching was significantly higher in patients reporting a history of depression, and depressive symptoms according to the SF36 and EQ5D at baseline (supplementary table t3).



## Depression and biologic treatment response

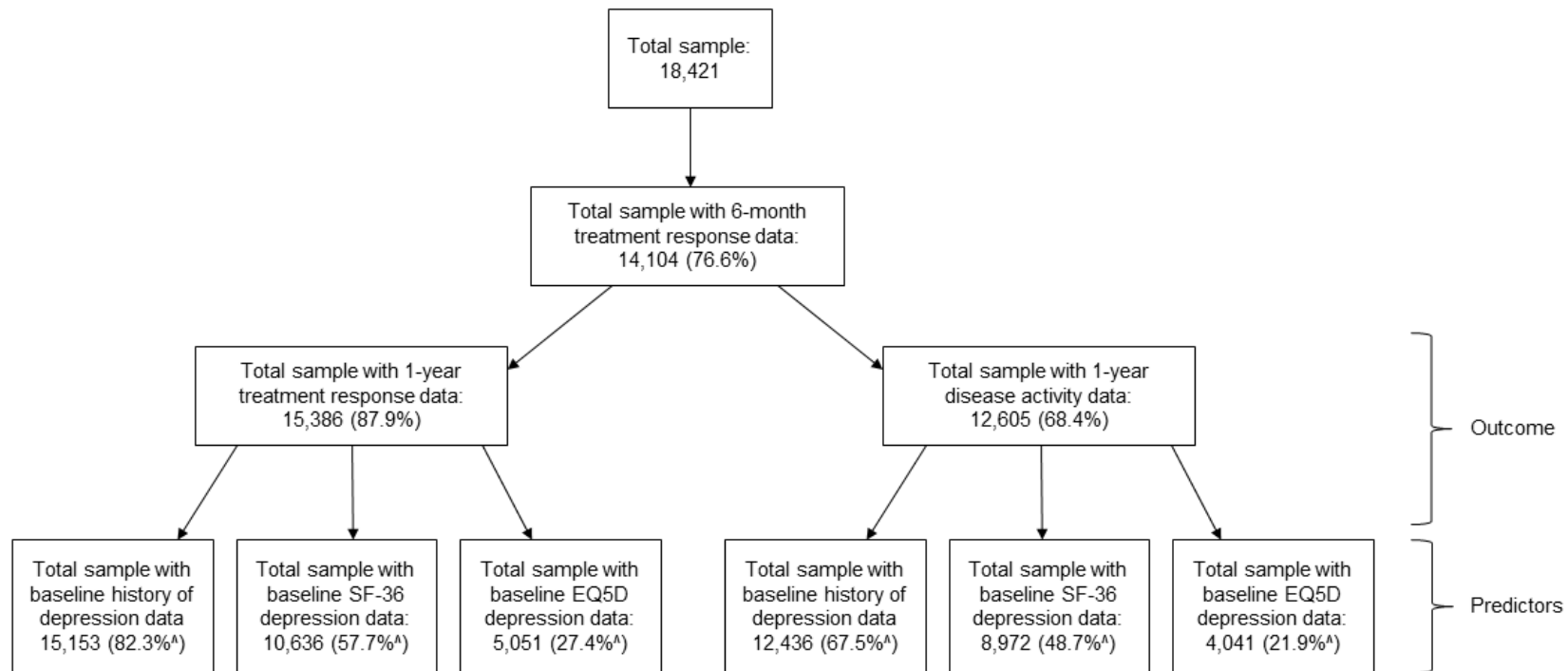


Figure 1. Summary of the number of patients available for each outcome analysis. ^percentages calculated from the total sample.

## Depression and biologic treatment response

Table 1. BSRBR-RA cohort baseline characteristics for total group, and according to baseline depressive symptoms.

	Total Sample (N=18,421)	History of depression		p-value	SF36 nMH depression symptoms			EQ5D depression symptoms			p-value
		No (N=14,426; 73.7%)	Yes (N=3,669; 20.3%)		No (N=5,388 (45.1%))	Yes (N=6,549, 54.9%)	p-value	None (N=2,761 (44.6%))	Moderate (N=2,975 (48.1%))	Extreme (N=453 (N=7.3%))	
<b>Age, M (SD)</b>	56.4 (12.4)	56.6 (12.6)	55.2 (11.4)	<0.0001	55.9 (12.1)	56.1 (12.3)	0.07	57.6 (12.9)	57.1 (12.4)	54.8 (11.5)	<0.0001
<b>Female Gender, N (%)</b>	14,065 (76.4)	10,799 (74.9)	2,999 (81.7)	<0.0001	4,056 (75.3)	5,057 (77.2)	0.01	2,094 (75.8)	2,299 (77.3)	354 (78.2)	0.329
<b>BMI, M(SD)</b>	27.3 (6.6)	27.1 (6.5)	28.1 (6.8)	<0.0001	26.8 (6.4)	27.0 (6.2)	<0.0001	27.7 (7.1)	28.2 (7.3)	29.6 (7.5)	<0.0001
<b>Disease Duration, years, M(SD)</b>	12.6 (9.7)	12.7 (9.8)	12.3 (9.6)	0.001	13.1 (9.5)	12.9 (9.7)	0.007	12.1 (10.0)	11.8 (10.0)	9.8 (9.6)	<0.0001
<b>Smoking, N(%)</b>											
<b>Current</b>	3,733 (20.3)	2,762 (20.2)	922 (27.3)	<0.0001	1,053 (19.7)	1,546 (23.8)	<0.0001	420 (17.9)	593 (23.4)	118 (30.2)	<0.0001
<b>Ex-smoker</b>	6,584 (35.7)	5,176 (37.9)	1,312 (38.9)		2,119 (39.6)	2,415 (37.1)		897 (38.2)	979 (38.6)	135 (34.5)	
<b>Never smoked</b>	6,990 (38.0)	5,736 (42.0)	1,141 (33.8)		2,176 (40.7)	2,546 (39.1)		1,031 (43.9)	967 (38.1)	138 (35.3)	
<b>Comorbidity, N(%)*</b>	9,988 (55.5)	7,565 (53.3)	2,281 (63.5)	<0.0001	2,747 (52.0)	3,561 (55.4)	<0.0001				
<b>N comorbidities, M(SD)*</b>	0.9 (1.0)	0.8 (1.0)	1.1 (1.2)	<0.0001	0.8 (1.0)	0.9 (1.0)	<0.0001	0.9 (1.1)	1.0 (1.1)	1.1 (1.3)	<0.0001
<b>Treatment Type, N(%)</b>											
<b>Etanercept</b>	5,356 (29.1)	4,232 (29.3)	1,039 (28.3)	<0.0001	1,797 (33.5)	2,275 (34.7)	0.001	298 (10.8)	259 (8.7)	39 (8.6)	<0.0001
<b>Infliximab</b>	4,249 (23.1)	3,348 (23.2)	853 (23.3)		1,587 (29.5)	2,062 (31.5)		72 (2.6)	122 (4.1)	19 (4.2)	
<b>Adalimumab</b>	5,024 (27.3)	4,044 (28.0)	904 (24.6)		1,992 (37.0)	2,196 (33.5)		840 (30.4)	993 (33.4)	162 (35.8)	
<b>Rituximab</b>	1,650 (9.0)	1,208 (8.4)	393 (10.7)		12 (0.22)	16 (0.24)		654 (23.7)	813 (27.3)	100 (22.1)	
<b>Tocilizumab</b>	1,008 (5.5)	709 (4.9)	267 (7.3)		-	-		411 (14.9)	378 (12.7)	68 (15.0)	
<b>Certolizumab</b>	1,115 (6.1)	870 (6.0)	210 (5.7)		-	-		478 (17.3)	404 (13.6)	65 (14.4)	
<b>Infliximab Biosimilar</b>	19 (0.1)	15 (0.1)	3 (0.1)		-	-		8 (0.3)	6 (0.2)	0 (0.0)	
<b>Baseline disease status</b>											
<b>DAS28, M(SD)</b>	6.4 (1.1)	6.4 (1.1)	6.4 (1.1)	<0.0001	6.5 (1.0)	6.6 (1.0)	<0.0001	5.9 (1.2)	6.1 (1.1)	6.3 (1.0)	<0.0001
<b>TJC, M(SD)</b>	15.2 (7.5)	15.0 (7.5)	15.9 (7.5)	<0.0001	15.2 (7.3)	15.9 (7.4)	<0.0001	13.6 (7.5)	15.0 (7.5)	16.2 (7.3)	<0.0001

Depression and biologic treatment response

<b>SJC, M(SD)</b>	10.5 (6.1)	10.6 (6.1)	10.0 (6.1)	0.141	11.2 (6.1)	11.5 (6.2)	<0.0001	8.7 (5.9)	9.0 (5.7)	9.1 (5.9)	<0.0001
<b>PGA, M(SD)</b>	72.0 (20.0)	71.6 (20.1)	73.6 (19.6)	<0.0001	70.5 (20.0)	74.2 (19.3)	<0.0001	68.5 (21.0)	72.5 (18.8)	79.1 (18.5)	<0.0001
<b>ESR, M(SD)</b>	43.2 (28.4)	47.0 (29.1)	35.9 (25.1)	<0.0001	45.2 (12.1)	46.5 (28.6)	<0.0001	36.0 (26.9)	37.8 (27.6)	38.8 (29.0)	<0.0001
<b>HAQ, M(SD)</b>	1.9 (0.6)	1.9 (0.6)	2.1 (0.6)	<0.0001	1.9 (0.6)	2.1 (0.6)	<0.0001	1.5 (0.7)	1.9 (0.6)	2.2 (0.5)	<0.0001
<b>RF+, N(%)</b>	11,275 (64.3)	8,985 (64.1)	2,113 (62.1)	0.002	3,465 (64.4)	4,267 (65.2)	0.324	1,484 (61.5)	1,669 (62.5)	255 (63.9)	0.58
<b>Good 1-year treatment response, N(%)*</b>	5,271 (34.3)	4,293 (35.5)	917 (30.0)	<0.0001	1,665 (34.7)	1,759 (30.1)	<0.0001	997 (44.7)	856 (34.9)	97 (26.4)	<0.0001

\*data available for 15,386 participants.

Table 2. Association between baseline depression and treatment response at 12-months.

		History of depression			SF36 (nMH≤40)			EQ5D		
		OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Unadjusted	Depression symptoms (vs. none)	0.75	0.66, 0.85	<0.0001	0.79	0.69, 0.92	0.002	-	-	-
	Moderate depression symptoms (vs. none)	-	-	-	-	-	-	0.76	0.63, 0.91	0.003
	Extreme depression symptoms (vs. none)	-	-	-	-	-	-	0.51	0.38, 0.69	<0.0001
Adjusted*	Depression symptoms (vs. no depression)	0.80	0.69, 0.92	0.002	0.90	0.77, 1.18	0.177	-	-	-
	Moderate depression symptoms (vs. none)	-	-	-	-	-	-	0.85	0.69, 1.04	0.105
	Extreme depression symptoms (vs. none)	-	-	-	-	-	-	0.62	0.45, 0.87	0.005

\* adjusted for age, gender, disease duration, baseline DAS28, number of comorbidities, baseline HAQ. SF36 Medical Outcomes Survey 36-item Short Form. nMH normed Mental Health subscale. OR odds ratio. CI confidence interval. N Number of participants included in analysis.

## Depression and biologic treatment response

### History of depression

In comparison to patients without a history of depression, logistic regression indicated that patients reporting a history of depression have reduced odds (OR=0.80, 95%CI: 0.69-0.92) of having a good treatment response by 1-year follow-up after adjusting for covariates (table 2).

Using multilevel longitudinal models, patients reporting a history of depression reported significantly lower levels of baseline DAS28 (B=-0.07, 95%CI:-0.12, -0.02) but a significantly lower rate of improvement in DAS28 over time in comparison to patients without a history of depression (table 3). Those without a history of depression reported a total improvement in DAS28 of -0.4 at 1-year, whereas patients with a history of depression reported a decrease in DAS28 score of -0.36 between baseline and 1-year follow-up (table 3). This significant interaction effect is displayed graphically in figure 2.

Supplementary tables t3-t6 show the results of the multilevel longitudinal analyses examining the relationship between history of depression status and TJC, SJC, PGA and ESR outcomes respectively. Patients without a history of depression show significantly reduced improvement in all components over time in comparison to patients with a history of depression.

### SF36 nMH subscale

In comparison to patients scoring  $\leq 40$  on the SF36 nMH subscale, logistic regression analysis revealed that those scoring  $>40$ , had no significant difference in the odds of having a good treatment response at one-year follow-up (table 2).

According to multilevel longitudinal analysis, there were no differences in baseline DAS28 levels between those scoring  $\leq 40$  and  $>40$  on the nMH subscale, although patients scoring  $\leq 40$  reported a significantly reduced rate of improvement in DAS28 over time in comparison to those scoring  $>40$ . Whereas patients scoring  $>40$  on the nMH reduce in DAS28 scores by -0.42 at 1-year, patients scoring  $\leq 40$  show an overall improvement in DAS28 of -0.40 by one-year follow-up (table 3). This significant interaction effect is shown graphically in figure 2.

Supplementary tables t3-t6 show the results of the multilevel analyses examining the relationship between nMH status and TJC, SJC, PGA and ESR outcomes

respectively. Depressive symptomatology according to the SF36 nMH subscale was not associated with change in PGA or ESR scores over time, however patients scoring  $\leq 40$  showed reduced improvements in TJC and SJC outcomes in comparison to patients scoring  $>40$ .

### EQ5D

Logistic regression analysis adjusting for covariates, reveals no significant difference in odds of having a good treatment response between patients reporting no depression symptoms and those reported moderate symptoms (OR=0.85, 95%CI: 0.69-1.04). In comparison to patients reporting no depression symptoms, those reporting extreme depression symptoms had a significantly reduced odds of a good treatment response at 1-year follow-up (OR=0.62, 95%CI: 0.45-0.87) (table 2).

Results of longitudinal multilevel analyses reveal no significant difference between depression symptom groups and baseline levels of DAS28, however in comparison to patients with no depression symptoms at baseline, those with moderate and extreme symptoms show significantly reduced rate of improvement over time. In comparison to patients with no symptoms of depression according to the EQ5D, who improve by -0.38 at 1-year follow-up, patients with some symptoms and extreme symptoms report reductions in DAS28 of -0.34 and -0.32 respectively at one-year follow-up (table 3). The significant interaction between depression symptoms and follow-up timepoint is displayed graphically in figure 2.

Supplementary tables t3-t6 show the results of the multilevel analyses examining the relationship between EQ5D status and TJC, SJC, PGA and ESR outcomes respectively. In comparison to patients with no symptoms of depression at baseline, those with moderate symptoms show significantly reduced improvements in TJC, SJC, PGA and ESR over time. In comparison to patients with no symptoms of depression at baseline, those with extreme symptoms show significantly reduced improvements in TJC, SJC and ESR over time.

## Depression and biologic treatment response

Table 3. Association between baseline depression, and DAS28 outcomes over 12-month follow-up.

	History of depression			SF36 (nMH ≤40)			EQ5D		
	B	95%CI	p	B	95%CI	p	B	95%CI	p
<i>Unadjusted</i>									
Depression symptoms (vs. none)	0.03	-0.02, 0.08	0.294	0.14	0.09, 0.19	<0.0001	-	-	-
Moderate depression symptoms (vs. none)	-	-	-	-	-	-	0.25	0.18, 0.32	<0.0001
Extreme depression symptoms (vs. none)	-	-	-	-	-	-	0.50	0.36, 0.64	<0.0001
Follow-up number	-0.20	-0.21, -0.20	<0.0001	-0.21	-0.21, -0.20	<0.0001	-0.19	-0.20, -0.18	<0.0001
Depression*follow-up	0.02	0.02, 0.03	<0.0001	0.01	0.00, 0.01	0.003	-	-	-
Moderate depression (vs. none)	-	-	-	-	-	-	0.02	0.01, 0.03	<0.0001
Extreme depression (vs. none)	-	-	-	-	-	-	0.03	0.01, 0.05	<0.0001
<i>Adjusted<sup>^</sup></i>									
Depression symptoms (vs. none)	-0.07	-0.12, -0.02	0.011	0.03	-0.02, 0.08	0.276	-	-	-
Moderate depression symptoms (vs. none)	-	-	-	-	-	-	0.04	-0.04, 0.11	0.364
Extreme depression symptoms (vs. none)	-	-	-	-	-	-	0.11	-0.04, 0.26	0.144
Follow-up number	-0.20	-0.21, -0.20	<0.0001	-0.21	-0.21, -0.20	<0.0001	-0.19	-0.20, -0.19	<0.0001
Depression symptoms*follow-up	0.02	0.02, 0.03	<0.0001	0.01	0.00, 0.01	0.002	-	-	-
Moderate depression symptoms (vs. none)	-	-	-	-	-	-	0.02	0.01, 0.03	<0.0001
Extreme depression symptoms (vs. none)	-	-	-	-	-	-	0.03	0.01, 0.05	0.001

<sup>^</sup>model adjusted for age, gender, disease duration, comorbidities and baseline HAQ. B unstandardized coefficient. SF36 Medical Outcomes Survey 36-item Short Form. nMH normed Mental Health subscale.

## Depression and biologic treatment response

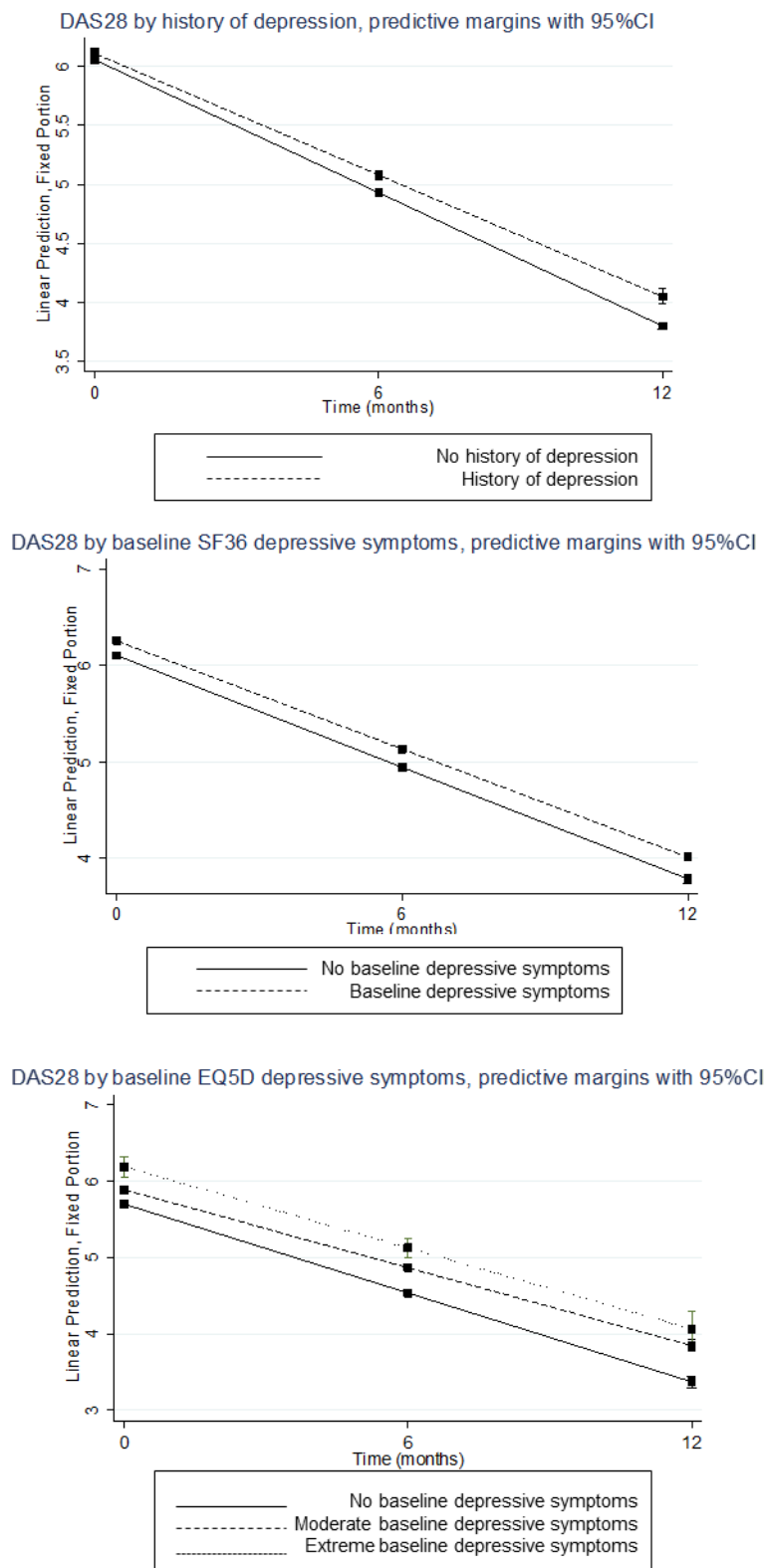


Figure 2. Graphical representation of fully-adjusted interactions between baseline depression symptoms and time on DAS28 outcomes over 12-month follow-up.

## **DISCUSSION**

This study found symptoms of depression at baseline to be associated with reduced long-term odds of reaching clinical remission in patients receiving their first biologic drug. This supports previous evidence from US and Norwegian demonstrating reduced likelihood of reaching remission in patients with symptoms of depression at treatment initiation [9,11]. We also identified prospective associations between baseline depression symptom status and disease activity, with depression symptoms contributing to increased DAS28 over the 12-month follow-up, and impacting change in DAS28 in response to treatment. Examination of the DAS28 components identified associations between depression and both subjective and objective aspects of disease activity; effect sizes did not differ between subjective and objective outcomes, contradicting previous research findings emphasising the relationship between depressive symptoms and subjective experiences of disease [3,11,23].

There are several explanations for this novel finding. Firstly, depression is known to impact health behaviours such as medication adherence [24], and non-adherence to biologics has been shown to reduce DAS28 treatment response [25]. Whilst adherence data is not collected for all contributors to the BSRBR-RA dataset and not available for inclusion in this paper, the role of adherence as a mechanism for this relationship is a valuable area for future research. Secondly, there may be a biological explanation for these findings. Systemic inflammation and elevated cytokines typically associated with RA disease manifestation and disease severity are also identified in people with depressive disorder [26–28]. Finally, the large sample size available for this analysis may have provided sufficient statistical power to identify small effect sizes typically unobservable in smaller datasets.

We identified differential effects of symptoms of depression on rheumatological outcomes, based on the depression assessment method. Whereas a history of depression and EQ5D categories were largely predictive of all assessed outcomes, either showing a main effect or modifying change over time, the SF36 was not associated with ESR or PGA. This may be due to these assessments representing different elements of mental health. Ticking a depression comorbidity tick box may indicate a lifetime history of depression, or exposure to mental health



treatment, however it provides no timeframe or qualifications for endorsement [29]. As the history of depression assessment may include people who have previously received treatment for depression, they may not be experiencing current symptomatology. This measure should be viewed as lifetime depression prevalence, rather than presence of current symptomatology.

The SF36, alternatively, contains multiple items covering a range of psychological symptoms, including happiness, nervousness, calmness, tiredness and participation in social activities [5] and is framed to detect a change from normality within the last month. It may represent a more nuanced perspective of mental health, including positive and negative affect, as well as psychosomatic and behavioural symptoms often associated with chronic illness. We used thresholds based on a validation study [30], but the high prevalence of “depression” measured on the SF-36 suggests a lack of specificity which may have reduced effect sizes due to measurement error [31]. The EQ5D assesses current depressive symptomatology, and although by no means a diagnostic test for depression, representing moderate sensitivity and specificity, the low proportion of patients reporting “extreme depression/anxiety” is lower than typical prevalence estimates of depression in RA [1].

This study has used appropriate longitudinal data analysis methodology to examine the long-term relationship between symptoms of depression and biologic treatment response. There is a shortage of high-quality longitudinal investigation in this field, and the evidence that does exist is limited to studies with highly selected samples, suboptimal depression assessments, inadequate adjustment for confounding variables, and inappropriate analysis methodologies [3]. The current study uses the largest prospective observational biologics registry in the world to examine the impact of depression symptoms on outcomes in real-world patients undergoing biologic treatment. Our results are therefore externally valid, representing patients prescribed biologics across the UK; a diverse population.

There are limitations to consider when interpreting these findings. Although providing several interpretations of depression, none of the measurement tools available for baseline depression are “gold-standard” indicators of the presence of diagnostically ascertained depression. Due to the scarcity with which validated

screening tools or diagnostic interviews are utilised to measure depression in RA research [4], the opportunity to compare three methods in the current paper is helpful, however given the high prevalence and impact of depression on disease outcomes, symptoms of depression should be routinely measured in rheumatological practice.

We did not adjust our models for treatment type, or previous failure with conventional DMARDs. As all patients are receiving biologics and there is no well-established association between different types of biologic or DMARD on our dependent or independent variables, we chose not to include treatment type as a confounder in our models. No data were available on concurrent mental health treatment, and it is likely that some patients may have been receiving therapy or antidepressant treatments which may reduce our observed effects.

These results contribute to the growing body of literature highlighting the role depression plays in predicting long-term health outcomes and treatment response in RA. These findings have several implications. Repeated screening and management of mental disorder should be undertaken as part of clinical care. Biologics are expensive [32], and poor treatment response can result in switching biologics, which can result in further costs [33]. Depression should therefore be routinely measured in RA clinical trials, and in clinical practice.

In conclusion, experiencing symptoms of depression at the start of biologics treatment is associated with reduced treatment response, impacting change over time in disease activity. The management of symptoms of depression in routine care is NICE recommended [34], and depression is treatable within the context of long-term physical health conditions [35–37]. Future research examining the impact of mental health intervention for physical health outcomes may identify whether effectively managing depression can improve treatment response in RA.

### **Key Messages**

1. Depression at baseline contributes to approximately 30% reduced odds of good biologics treatment response.
2. Depression is associated with reduced change in DAS28 over time in response to biologics.

## Financial Acknowledgement

This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or the British Society for Rheumatology.

The BSRBR-RA is a UK-wide national project to investigate the safety of biologic agents in routine medical practice. This work was supported by the British Society for Rheumatology (BSR), which receives restricted income from UK pharmaceutical companies, presently Abbvie, Celltrion, Hospira, Pfizer, UCB, Samsung and Roche, and in the past Swedish Orphan Biovitrum and MSD. All decisions concerning analyses, interpretation and publication are made autonomously of any industrial contribution.

## Conflict of Interest

The authors disclose no conflict of interest

## REFERENCES

- [1] Matcham, F., Rayner, L., Steer, S. and Hotopf, M. (2013) The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology (Oxford, England)*, **52**, 2136–48. <https://doi.org/10.1093/rheumatology/ket169>
- [2] Matcham, F., Norton, S., Scott, D.L., Steer, S. and Hotopf, M. (2016) Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. *Rheumatology (Oxford, England)*, **55**, 268–78.

<https://doi.org/10.1093/rheumatology/kev306>

- [3] Rathbun, A.M., Reed, G.W. and Harrold, L.R. (2013) The temporal relationship between depression and rheumatoid arthritis disease activity, treatment persistence and response: A systematic review. *Rheumatology (Oxford, England)*, **52**, 1785–94. <https://doi.org/10.1093/rheumatology/kes356>
- [4] Kalyoncu, U., Dougados, M., Daurès, J.-P. and Gossec, L. (2009) Reporting of patient-reported outcomes in recent trials in rheumatoid arthritis: a systematic literature review. *Annals of the Rheumatic Diseases*, **68**, 183–90. <https://doi.org/10.1136/ard.2007.084848>
- [5] Ware, J.E.J. and Sherbourne, C.D. (1992) The MOS 36-Item Short-Form Health Survey (SF-36): I. Conceptual Framework and Item Selection. *Medical Care*, **30**, 473–83.
- [6] Hurst, N.P., Kind, P., Ruta, D., Hunter, M. and Stubbings, A. (1997) Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *Rheumatology*, **36**, 551–9. <https://doi.org/10.1093/rheumatology/36.5.551>
- [7] Callhoff, J., Weiss, A., Zink, A. and Listing, J. (2013) Impact of biologic therapy on functional status in patients with rheumatoid arthritis--a meta-analysis. *Rheumatology (Oxford, England)*, **52**, 2127–35. <https://doi.org/10.1093/rheumatology/ket266>
- [8] Nam, J.L., Ramiro, S., Gaujoux-Viala, C., Takase, K., Leon-Garcia, M., Emery, P. et al. (2014) Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Annals of the*

- Rheumatic Diseases*, **73**, 516–28. <https://doi.org/10.1136/annrheumdis-2013-204577>
- [9] Rathbun, A.M., Harrold, L.R. and Reed, G.W. (2016) A prospective evaluation of the effects of prevalent depressive symptoms on disease activity in rheumatoid arthritis patients treated with biologic response modifiers. *Clinical Therapeutics*, **38**, 1759–72.e3. <https://doi.org/10.1016/j.clinthera.2016.06.007>
- [10] Mitchell, A.J. and Coyne, J.C. (2007) Do ultra-short screening instruments accurately detect depression in primary care?. A pooled analysis and meta-analysis of 22 studies. *British Journal of General Practice*, **57**, 144–51.
- [11] Michelsen, B., Kristianslund, K., Sexton, J., Hammer, H.B., Fagerli, K.M., Lie, E. et al. (2017) Do depression and anxiety reduce the likelihood of remission in rheumatoid arthritis and psoriatic arthritis? Data from the prospective multicentre NOR-DMARD study. *Ann Rheum Dis*, **0**, 1–5. <https://doi.org/10.1136/annrheumdis-2017-211284>
- [12] Overman, C.L., Bossema, E.R., van Middendorp, H., Wijngaards-de Meij, L., Verstappen, S.M.M., Bulder, M. et al. (2012) The prospective association between psychological distress and disease activity in rheumatoid arthritis: a multilevel regression analysis. *Annals of the Rheumatic Diseases*, **71**, 192–7. <https://doi.org/10.1136/annrheumdis-2011-200338>
- [13] Rathbun, A.M., Harrold, L.R. and Reed, G.W. (2015) Temporal effect of depressive symptoms on the longitudinal evolution of rheumatoid arthritis disease activity. *Arthritis Care & Research*, **67**, 765–75. <https://doi.org/10.1002/acr.22515>
- [14] Ferreira, R.J.O., Duarte, C., Ndosi, M., de Wit, M., Gossec, L. and da Silva,

- J.A.P. (2017) Suppressing inflammation in rheumatoid arthritis: Does patient global assessment blur the target? A practice-based call for a paradigm change. *Arthritis Care & Research*,. <https://doi.org/10.1002/acr.23284>
- [15] Hyrich, K.L., Watson, K.D., Lunt, M., Symmons, D.P.M. and British Society for Rheumatology Biologics Register (BSRBR). (2011) Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. *Rheumatology (Oxford, England)*, **50**, 117–23. <https://doi.org/10.1093/rheumatology/keq209>
- [16] Deighton, C., Hyrich, K., Ding, T., Ledingham, J., Lunt, M., Luqmani, R. et al. (2010) BSR and BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy. *Rheumatology*, **49**, 1197–9. <https://doi.org/10.1093/rheumatology/keq006b>
- [17] Matcham, F., Norton, S., Steer, S. and Hotopf, M. (2016) Usefulness of the SF-36 Health Survey in screening for depressive and anxiety disorders in rheumatoid arthritis. *BMC Musculoskeletal Disorders*, **17**, 224. <https://doi.org/10.1186/s12891-016-1083-y>
- [18] National Institute for Health and Care Excellence. (2009) Depression in adults with a chronic physical health problem: recognition and management (clinical guideline CG91) [Internet]. NICE, <http://www.nice.org.uk/guidance/cg91>.
- [19] Fransen, J. and van Riel, P.L.C.M. (2005) The Disease Activity Score and the EULAR response criteria. *Clinical and Experimental Rheumatology*, **23**, S93–9.
- [20] Kwok O, Underhill, A., Berry, J., Luo, W., Elliott, T. and Yoon, M. (2008)

- Analyzing longitudinal data with multilevel models: An example with individuals living with lower extremity intra-articular fractures. *Rehabilitation Psychology*, **53**, 370–86. <https://doi.org/10.1037/a0012765>
- [21] Twisk, J.W. (2013) Applied longitudinal data analysis for epidemiology: a practical guide. Cambridge University Press.
- [22] Bruce, B. and Fries, J.F. (2005) The Health Assessment Questionnaire (HAQ). *Clinical and Experimental Rheumatology*, **23**, 14–8.
- [23] Matcham, F., Ali, S., Irving, K., Hotopf, M. and Chalder, T. (2016) Are depression and anxiety associated with disease activity in rheumatoid arthritis? A prospective study. *BMC Musculoskeletal Disorders*, **17**. <https://doi.org/10.1186/s12891-016-1011-1>
- [24] DiMatteo, M.R., Lepper, H.S. and Croghan, T.W. (2000) Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. *Archives of Internal Medicine*, **160**, 2101–7. <https://doi.org/10.1001/archint.160.16.2101> [pii]
- [25] Bluett, J., Morgan, C., Thurston, L., Plant, D., Hyrich, K.L., Morgan, A.W. et al. (2015) Impact of inadequate adherence on response to subcutaneously administered anti-tumour necrosis factor drugs: results from the Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate cohort. *Rheumatology*, Oxford University Press. **54**, 494–9. <https://doi.org/10.1093/rheumatology/keu358>
- [26] Liu, Y., Ho, R.C.-M. and Mak, A. (2012) Interleukin (IL)-6, tumour necrosis factor alpha (TNF- $\alpha$ ) and soluble interleukin-2 receptors (sIL-2R) are elevated in patients with major depressive disorder: a meta-analysis and meta-

- regression. *Journal of Affective Disorders*, **139**, 230–9.  
<https://doi.org/10.1016/j.jad.2011.08.003>
- [27] Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K. et al. (2010) A meta-analysis of cytokines in major depression. *Biological Psychiatry*, **67**, 446–57. <https://doi.org/10.1016/j.biopsych.2009.09.033>
- [28] Cutolo, M., Kitas, G.D. and LCM van Riel, P. (2014) Burden of disease in treated rheumatoid arthritis patients: Going beyond the joint. *Seminars in Arthritis and Rheumatism*, **43**, 479–88.  
<https://doi.org/10.1016/j.semarthrit.2013.08.004>
- [29] Buck, H.G., Akbar, J.A., Zhang, S.J., Bettger, J.A.P., Buck, H.G., Akbar, J.A. et al. (2013) Measuring comorbidity in cardiovascular research: A systematic review. *Nursing Research and Practice*, **2013**, 1–11.  
<https://doi.org/10.1155/2013/563246>
- [30] Matcham, F., Norton, S., Steer, S. and Hotopf, M. (2016) Usefulness of the SF-36 Health Survey in screening for depressive and anxiety disorders in rheumatoid arthritis. *BMC Musculoskeletal Disorders*, **17**.  
<https://doi.org/10.1186/s12891-016-1083-y>
- [31] Hotopf, M., Chidgey, J., Addington-Hall, J. and Ly, K.L. (2002) Depression in advanced disease: a systematic review Part 1. Prevalence and case finding. *Palliative Medicine*, **16**, 81–97. <https://doi.org/10.1191/0269216302pm507oa>
- [32] The British Society for Rheumatology. (2016) Biologic drugs. [Internet]. [http://www.rheumatology.org.uk/patient\\_information/patient\\_information/biologic\\_drugs.aspx](http://www.rheumatology.org.uk/patient_information/patient_information/biologic_drugs.aspx).



- [33] Sullivan, S.D., Alfonso-Cristancho, R., Carlson, J., Mallya, U. and Ringold, S. (2013) Economic consequences of sequencing biologics in rheumatoid arthritis: a systematic review. *Journal of Medical Economics*, **16**, 391–6. <https://doi.org/10.3111/13696998.2013.763812>
- [34] National Collaborating Centre for Mental Health. (2010) Depression in adults with a chronic physical health problem: treatment and management [Internet]. <https://www.nice.org.uk/guidance/cg91/evidence/full-guideline-243876061>.
- [35] Matcham, F., Rayner, L., Hutton, J., Monk, A., Steel, C. and Hotopf, M. (2014) Self-help interventions for symptoms of depression, anxiety and psychological distress in patients with physical illnesses: A systematic review and meta-analysis. *Clin. Psychol. Rev.* p. 141–57. <https://doi.org/10.1016/j.cpr.2014.01.005>
- [36] Fiest, K.M., Hitchon, C.A., Bernstein, C.N., Peschken, C.A., Walker, J.R., Graff, L.A. et al. (2017) Systematic review and meta-analysis of interventions for depression and anxiety in persons with rheumatoid arthritis. *Journal of Clinical Rheumatology*, **1**. <https://doi.org/10.1097/RHU.0000000000000489>
- [37] Rayner, L., Price, A., Evans, A., Valsraj, K., Higginson, I.J. and Hotopf, M. (2010) Antidepressants for depression in physically ill people. *Cochrane Database Syst. Rev.* p. CD007503. <https://doi.org/10.1002/14651858.CD007503.pub2>.