

Beyond the straight line: Non-Linear Insights into Fatigue in Rheumatoid Arthritis



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Non-linear form preferred by

MSE (%)

91.80

39.15

23.65

55.30

47.60

100.00

23.20

92 00

100.00

66.35

74.90

83.55

70.70

INTRODUCTION

Patients with rheumatoid arthritis (RA) report fatigue to be a major impairment associated with the disease. Many studies examined risk factors for fatigue in RA $^{(1)}$.

Yet, there are still inconsistent results on the association of various factors with fatigue. This applies in particular to age, disease duration, and seasonal variation⁽¹⁾. One potential explanation for inconclusive results may be the erroneous assumption of linear relationships⁽²⁾.

AIM

This explorative study examined whether non-linear associations with fatigue can be identified.

METHODS

STUDY POPULATION

- 6196 Patients of the German biologics register RABBIT
- Enrolment: 2017 2023
- RA treatment: conventional synthetic, biologic, biosimilar, or targeted synthetic DMARD

MEASURES

- Fatigue
- One item, numerical rating scale (0 10)
- Short form 36 (SF36), four items of vitality subscale
- Continuous covariates: age, c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), DAS28-ESR, tender and swollen joint count (TJC, SJC), pain, morning stiffness, physical function, patient global assessment of health, sleep disturbances, enrolment date, and body mass index (BMI)

STATISTICS

- Restricted cubic splines (or natural splines)
- Resampling (Bootstrap, b = 2000) to compare linear versus nonlinear associations
- Criteria: mean squared error (MSE) in independent data (out-of-bag) and goodness of fit according to Bayesian information criteria (BIC)
 (a)



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Patients of this study population were on average 59.4 years old, 71.9 % (4452) were female, and 84.0 % (5205) were naïve to biologic disease-modifying anti-rheumatic drugs (bDMARDs). The disease duration was 8.4 years at enrolment and the mean DAS28-ESR was 4.5.

The average level of fatigue (NRS: 0-10) was 5.0 in this population and was higher in those with two (5.5) or more (5.9) bDMARD failures.

Covariate

Disease duration

Physical function

Body-Mass-Index

Enrolment date

Swollen joint count (SJO)

Tender joint count (TJC)

Sleeping difficulties (NRS)

NRS: numerical rating scale ranging 0 - 10

Morning stiffness (minutes)

Age

CRP

ESR

DAS28-ESR

Pain (NRS)

Association form with Fatigue

- In one out of three examined characteristics, there
 was evidence against a linear association with fatigue
- Strong evidence was observed for: age, physical function, morning stiffness, and tender joint count
- Weak evidence or inconclusive results were found for: sleep disturbances, pain, and BMI
- No evidence for non-linear association with fatigue was found for: disease duration, CRP, ESR, DAS28-ESR, and SJC
- Although no intra-year seasonal variability was found, results suggested more intense fatigue during the Covid19 pandemic

In sensitivity analyses using items of the SF36 vitality sub scale we found similar results. The only difference observed refers to the average level of fatigue at baseline (SF36 energy: 6.4, SF36 fatigue: 5.5). For interpretation, we transformed SF36 sum scores to a range that is similar to the fatigue NRS.

CONCLUSIONS

The findings of this study can partly explain previous inconsistent results.

For example, the relationship between fatigue and age (Figure, panel A) is not straightforward. There may be some relief in fatigue around the age of retirement, but fatigue is not per se decreasing with age as suggested from linear associations in this study population.

Our results show that the common assumption of linear relationships requires verification for every factor considered. In one out of three characteristics, there was evidence against linearity in this study.

ACKNOWLEDGEMENT

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Table: The study data were resampled 2000 times. In each

iteration we evaluated whether a linear or non-linear form

describes the association with fatique best. The numbers

presented below show the percentage of iterations in which

BIC (%)

94 95

2.90

0.25

0.70

0.45

100.00

0.40

95 40

100.00

12.60

27.70

41.65

6.05

non-linear association was superior.

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Figure: Associational forms between covariates and fatigue. Solid lines correspond to non-linear associations, dashed lines to conventional and inferior linear associations according to this study. * The dot-dash line in panel F describes the association according to the median; all other lines refer to fitted means of fatigue.

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