Title: Identification and validation of clinically relevant clusters of severe fatigue in rheumatoid arthritis.

Running head: Clusters of severe fatigue in RA

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Abstract:

Objectives: The considerable heterogeneity of rheumatoid arthritis (RA) related fatigue is the greatest challenge to determining pathogenesis. The identification of homogenous sub-types of severe fatigue would inform the design and analysis of experiments seeking to characterise the likely numerous causal pathways which underpin the symptom. This study aimed to identify and validate such fatigue sub-types in patients with RA.

*Methods***:** Data were obtained from patients recruited to the British Society for Rheumatology Biologics register for RA, as either receiving traditional Disease Modifying Anti-Rheumatic Drugs (DMARD cohort, n=522) or commencing anti-TNF therapy (anti-TNF cohort, n=3909). In those reporting severe fatigue (SF36 vitality≤12.5), this cross-sectional analysis applied hierarchical clustering with weighted-average linkage identified clusters of pain, fatigue, mental health (all SF36), disability (HAQ) and inflammation (ESR) in the DMARD cohort. K-means clustering sought to validate the solution in the anti-TNF cohort. Clusters were characterised using *a priori* generated symptom definitions and between-cluster comparisons.

*Results***:** Four severe fatigue clusters, labelled as *basic (46%), affective (40%), inflammatory (4.5%)* and *global* (8.9%) were identified in the DMARD cohort. All clusters had severe levels of pain and disability, and were distinguished by the presence/absence of poor mental health and high inflammation. The same symptom clusters were present in the anti-TNF cohort, though the proportion of participants in each cluster differed (basic:28.7%, affective:30.2%, global:24.1%, inflammatory:16.9%).

*Conclusions***:** Among RA patients with severe fatigue, recruited to two diverse RA cohorts, clinically relevant clusters were identified and validated. These may provide the basis for future mechanistic studies and ultimately support a stratified approach to fatigue management.

Key words: Fatigue, Pain, Disability, Cluster, Rheumatoid arthritis

Running head: Identifying severe RA-fatigue sub-types

Abbreviations: RA: Rheumatoid Arthritis, BSRBR-RA: British Society for Rheumatology Biologics Register for RA, ACR: American College of Rheumatology, DMARDs: Disease Modifying Anti-Rheumatic Drugs, anti-TNF: anti-tumor necrosis factor, EMS: early morning stiffness, COPD: chronic obstructive pulmonary disorder DAS28: Disease Activity Score for 28-joints, SF36: Short Form 36, ESR: erythrocyte sedimentation rate, HAQ-DI: Stanford Health Assessment Questionnaire Disability Index, IQR: inter-quartile range, MCID: minimum clinically important difference

Introduction

Severe fatigue is a symptom which is common to many chronic diseases and is especially prevalent and burdensome among several inflammatory conditions such as rheumatoid arthritis (RA) (1-3). The pathogenesis of this problem is poorly understood, a situation which may explain the current dearth of fatigue treatment options. Its considerable heterogeneity represents one of the few certainties in the field.

Qualitative studies have highlighted the symptom's varied presentation, reported both as a constant weariness and as a sudden wipe-out (4). Epidemiological studies have identified numerous putative determinants (5) and clinical trials reveal response to both pharmacological and non-pharmacological treatments (6, 7) in selected patients only. Taken together, the results from these studies all support the existence of multiple causal pathways and subsequent fatigue sub-types which have yet to be elucidated.

It is such heterogeneity which presents the greatest challenge to researchers seeking to delineate the symptom's mechanisms. Previous biological investigations of RA-related fatigue aetiology have been largely negative ((8)). However, any true signals may have been masked by methodological artefacts generated from studying fatigue as a single entity rather than focusing upon potentially mechanistically distinct sub-types. Thus, the identification of severe fatigue sub-types should be considered a crucial first step towards the discovery of aetiological pathways and much needed therapies (9).

One way to identify sub-types of severe fatigue is to apply clustering methodologies. Once largely a descriptive strategy used to examine symptom profiles, cluster analysis is increasingly used to inform the mechanisms of symptoms. For example, within the cancer field, cluster analyses have identified symptom sub-sets which were subsequently found to be genetically distinct (9, 10). Employing RA as a prototype for inflammatory chronic disease, this study aimed to be the first to

examine the existence of severe fatigue sub-types in two distinct, large cohorts using cluster analysis methods.

Methods

Design

The data of 16896 participants were obtained from the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), the data collection methods of which are described in detail elsewhere (11, 12). Briefly, UK based patients with RA (physician diagnosed or American College of Rheumatology (ACR) criteria (13) are recruited to two cohorts , one which recruits patients treated with traditional Disease Modifying Anti-Rheumatic Drugs (DMARDs, non-specific immunomodulators) alone. The second cohort enrols those commencing modern anti-tumor necrosis factor (anti-TNF) therapies (specific immunomodulators), including Infliximab, Etanercept or Adalimumab, which are typically limited to patients with moderate to severe disease who have not responded to DMARDs.

For the purposes of this analysis, only participants recruited October 2000 to November 2008 were eligible, as fatigue data were not captured after this date. Eligible participants from the DMARD cohort had fatigue data at enrolment and a score which reflected ‘severe fatigue’. Eligible anti-TNF commencers also had ‘severe fatigue’, reported within 14 days of therapy commencement, and were required to be anti-TNF naïve. No other eligibility criteria were applied.

Data

Demographics

Basic demographic data were recorded on enrolment to the study. Specifically, age, sex, ethnicity and working status were of interest.

Clinical variables

Clinicians reported whether the patient was rheumatoid factor positive (RF positive), had a history of early morning stiffness (EMS)> one hour and had joint erosions. Clinicians also used a check list of potential co-morbidities to report a previous history of depression, hypertension, stroke, chronic obstructive pulmonary disorder (COPD) and renal disease, within the five years prior to enrolment. Disease activity was captured by the routinely measured composite score Disease Activity Score for 28-joints (DAS28), which comprises a continuous scale (0 to 9.4). A DAS28 score ≤3.2 is considered to indicate low disease activity, while DAS28 3.3-5.1 and DAS28 >5.1 reflect moderate and high disease, respectively(14). Finally, the duration of disease in years was recorded.

Clustering variables

Although participants were required to have severe fatigue to be eligible, we included it as a continuous clustering variable to capture any further variation in symptom reports. Other variables selected for the cluster analysis were identified as factors commonly considered to be of potential importance in the aetiology of fatigue, based on existing evidence (1, 5, 15).

Fatigue, Pain and Mental Health

Fatigue was reported using the four-item Short Form 36 (SF36) Vitality domain: a validated measure of RA-fatigue which has good internal consistency, construct validity and sensitivity (16). Measures of pain and mental health were also provided by the SF36, via the bodily pain (2 items) and mental health (5 items) domains respectively. In line with recommendations, missing items for fatigue and pain were imputed with the mean value of completed items, provided 50% of items were populated, but no missing pain items were imputed (17). Full scoring was then completed and transformed into a 0-100 scale, where higher scores reflect less symptoms. The pain (DMARD: Cronbach's alpha (α)=0.83; anti-TNF: α=0.80) and mental health (DMARD:α=0.83; anti-TNF: α=0.80) subscales had good internal consistency.

Inflammation

Inflammation was captured by erythrocyte sedimentation rate (ESR) at the time of enrolment to the BSRBR-RA.

Disability

Disability was measured using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI), which has been well validated for use within this population (18). In keeping with previous analyses, the HAQ-DI was shown to have excellent internal consistency (DMARD:α=0.94; anti-TNF: α=0.93).

Analysis

Only those with severe fatigue were included in these analyses. The enrolment characteristics of the cohorts were compared using median and inter-quartile range (IQR), or proportion and 95% confidence interval (95% CI). Clinically meaningful differences in the median scores of continuous variables were defined using previously defined minimum clinically important difference (MCID).

Existing estimates of the MCID for domains captured by the SF36 range from 5-10 units (19, 20), thus, for this analysis, a conservative clinically meaningful difference of 10 units was adopted. Established MCIDs for HAQ and DAS28 suggest that differences of 0.22 units (21) and 1.2 units (14, 22), respectively, are of importance.

Cluster analysis is an umbrella-term for a number of analyses, known as hierarchical or non-hierarchical (partitioning), which use variables specified by the researcher, to organise data into subgroups. Groups are identified so as to maximise the similarity (homogeneity) between those within a cluster and the dissimilarity (heterogeneity) to those in other clusters (23).

As we did not know the number of groups likely present in the data, in order to meet our core aim, which was to identify robust clinically relevant clusters of fatigue, it was first necessary to identify an optimal cluster solution using hierarchical clustering.

We applied agglomerative hierarchical cluster analysis to the DMARD cohort, because the cohort had greater generalisability in comparison to the anti-TNF cohort (which comprises patients with active and severe disease). The clustering was performed by applying Euclidean distance measures and weighted-average-linkage to continuous data. The number of clusters present in the data was selected by consultation of the resultant dendrogram and the Duda and Hart Je(2)/Je(1) index(24).

As statistical analysis may produce a cluster solution which lacks face validity, it is important that criteria are used to determine whether statistically derived clusters are clinically relevant. For that reason to characterise the resultant cluster profiles generated using continuous scales, median scores on each clustering variable were calculated and compared to pre-defined cut-offs for severe symptoms.

Severe symptom-cut offs

Severe symptom cut offs for SF36 domains were defined in reference to the 5th percentile of domain scores observed in an age and sex matched general population sample ((25)): 1604 participants randomly selected from health board records, as part of a large scale general population postal survey conducted in the Grampian Region of the UK.

Severe fatigue was defined as a score of less than or equal to 12.5 units on the SF36 Vitality 0-100. Severe pain and poor mental health were also similarly dichotomised such that severe pain was defined as SF36 Bodily pain (0-100) ≤22 units and poor mental health as SF36 mental health (0-100) ≤35 units.

For the purposes of cluster interpretation and reflecting clinical experience, ESR was dichotomised using an *a priori* selected definition where ESR≥50 reflected high inflammation and ESR<50 represented low inflammation (26). The HAQ is scored from 0 (no disability) to 3 (completely disabled) and was dichotomised for cluster characterisation such that a score <2 “no/low disability” and ≥2 “moderate/severe disability” (21).

Between cluster comparisons were conducted in line with the methods used to compare the enrolment characteristics of the cohorts.The resultant clustering solution was then validated through the application of non-hierarchical K-means cluster analysis in the anti-TNF cohort. The profile of each cluster was again characterised by comparing the median score of each clustering variable to the cut-offs for severe symptoms. The resultant cluster solutions from both clusters were compared for consistency. Clusters were considered validated if the same symptom clusters were returned following the application of the cut-offs for severe symptoms.

All analysis was conducted using Stata statistical software: release 13.0 (StataCorp).

RESULTS

Participants

Of the 16896 participants, 3774 were enrolled in the DMARD cohort; 762 had missing fatigue data at enrolment and a further 2460 did not meet the definition of severe fatigue. Thus, 552 participants from the DMARD cohort were eligible for this analysis. Of those eligible from the DMARD cohort, 492 participants provided complete clustering data and could therefore be entered into the clustering analysis (Figure 1).

A total of 13122 participants were enrolled into the anti-TNF cohort, of whom 1234 were missing fatigue data at enrolment, 836 participants were not anti-TNF naïve and 1676 were missing information about SF36 completion date or had completed the questionnaire more than 14 days

after therapy commencement. Of those remaining, 3909 participants from the anti-TNF cohort had severe fatigue and were eligible for this study; 3554 had complete clustering data available.

[Insert Figure 1 here]

Figure 1 – Flow of participant selection from 16896 patients recruited to the BSRBR-RA.

The cohorts were of comparable ages (Median age (IQR) DMARD: 59 (51-67), anti-TNF: 57 (48-64), though the median years of disease duration in the anti-TNF cohort was almost twice that of the DMARD cohort (12 (6-19) vs 7 (2-15). Moreover, those in the anti-TNF cohort had a substantially higher median disease activity (6.81, 6.14-7.48) when compared to those in the DMARD cohort (5.58, 4.63-6.52), indicating that they had greater disease burden. Greater proportions of those in the anti-TNF cohort were also RF positive (64.8%, 95%CI 63.2-66.4 vs 53.9%, 49.5-58.3) and had erosions (62.2%, 60.6-63.8 vs 42.7%, 38.3-47.1). Finally, the differences in pain and disability between the cohorts were clinically relevant, further indicating an increased disease burden in the anti-TNF cohort (Table 1).

[Insert Table 1 here]

Hierarchical clustering solution

Consultation of the resultant dendrogram (Supplementary material) and the Duda and Hart Je(2)/Je(1) index indicated that a four cluster solution was optimal.

Defining the groups

Pre-defined cut-offs for severe symptoms were applied to the resultant clusters and showed that all clusters reported severe pain and disability, and symptom clusters were distinguished based on the presence/absence of poor mental health and high inflammation. The first observed cluster comprised 46% of all those clustered (n=227) and was labelled '*Basic*'. Participants in this cluster had severe pain and disability, as well as fatigue, but low inflammation and good mental health. Cluster 2 was labelled '*Affective'*, as the 199 (40%) participants in this cluster reported severe pain, disability and poor mental health, but low inflammation. Just 22 participants (4.5% of those clustered) were captured by the '*Global*' cluster, in which participants scored poorly on all clustering variables. The final cluster comprised 8.9% of clustered participants (n=44), who reported severe pain, disability and high inflammation, but good mental health. This final cluster was labelled '*Inflammatory*'.

Distinguishing the groups

Between-cluster comparisons of median and inter-quartile ranges (IQR), or proportions and 95% confidence intervals (95% CI), as appropriate sought to distinguish the groups (Table 2). There were no substantial differences in demographic variables; a higher proportion of those in the *Global* cluster were not working due to illness and disability (54.4%), when compared to the other clusters (range: 30.2-34.7%), though the 95% confidence intervals overlapped between the clusters.

The *Affective* cluster was distinguished from the *Basic* and *Inflammatory* clusters, on the basis of clinician reported history of depression, which was more prevalent in the *Affective* group (40.9%,34.1-47.7) than in the other clusters (18.1%, 13.6-22.6 and 6.8%,-0.64-14.2, respectively). Further, along with the *Global* cluster, mental health was the poorest in the *Affective* cluster, (both 30, 20-40), with the difference compared to the *Basic* (60, 50-70) or *Inflammatory* clusters (65, 50-80) in excess of three times the MCID. The *Affective* cluster was distinguished from the *Global* cluster by differences in excess of the MCID in median DAS28 (*Affective:* 5.53, 4.47-6. 38 vs

Global: 7.14, 6.43-8.02) and a difference of more than four-fold in median inflammation (22, 13-42 vs 99.5, 94-115, respectively).

The *Global* cluster had the most severe median pain (0, 0-10), compared to all other clusters (*Basic* and *Affective*: 20, 10-30; *Inflammatory*: 20, 20-30) and the greatest median disability (2.4, 2.2-2.7 vs *Basic*: 2.0, 1.5-2.4; *Affective* 2.0, 1.6-2.4; *Inflammatory* 2.0, 1.5-2.0). This cluster was distinguished from the *Basic* cluster on the basis of DAS28, which was substantially higher amongst participants in the *Global* cluster (7.14, 6.43-8.02 vs 5.40, 4.68-6.37) and level of inflammation (ESR: 99.5, 94-115 vs 31, 18-44). The principal difference between the *Global* and *Inflammatory* clusters was difference in excess of three times the MCID indicating that those in *Global* cluster had poor mental health (30, 20-40 vs 65, 50-80, respectively).

Those in *Inflammatory* cluster had the least median fatigue (12.5 units), compared to all other clusters (6.25 units), but this difference was not clinically meaningful. They also had a substantially lower prevalence of COPD 2.3% (-2.1-6.7), than in the *Basic* (11.0 (7.3-14.7) and *Affective* clusters (13.1 (8.4-17.8) and fewer had erosions (29.5% vs range: 40.7-45.4%), though the 95% confidence intervals overlapped with those of the other clusters.

K-means validation

Following the identification of the optimal cluster solution in the DMARD cohort, K-means clustering, proposing the existence of four clusters was applied. Following the application of pre-defined cut-offs for severe symptoms, the same symptom cluster solution was observed in the anti-TNF cohort to that observed in the DMARD cohort (Figure 2), though the proportion of participants in each cluster differed. . The first cluster, labelled as a '*Basic*' cluster, contained 1021 participants (28.7% of all those clustered) who reported severe levels of pain and disability, but low median levels of inflammation and few mental health problems.

[Insert Figure 2 here]

Figure 2 – Cluster solution identified following the application of severe symptom cut-offs; Pain SF36 (0-100) ≤22, Mental Health (MH) SF36 (0-100) ≤35, Disability (HAQ) Stanford HAQ≥2, Inflammation (ESR)≥50.

The '*Affective*' cluster produced in the anti-TNF cohort comprised 1074 participants (30.2% of those clustered) who reported severe median reports of pain, disability and poor mental health, but with an absence of inflammation (Table 3). The third cohort represented a comparable '*Global'* cluster, identified by median scores on all clustering variables which reflected severe symptom burden and containing 857 participants (24.1% of those clustered). Finally, the '*Inflammatory*' cluster was replicated as the smallest cluster, with 16.9% of all those clustered (n=602), reporting severe pain, disability and high inflammation, but few median mental health complaints.

[Insert Table 3 here]

DISCUSSION

We present the first known study to investigate the existence of severe fatigue sub-types in chronic inflammatory disease. In two large distinct cohorts of RA, four fatigue sub-types (*Basic, Affective, Inflammatory* and *Global*) have been identified and validated.

A number of potential limitations should be considered before interpreting these results. First, we conducted our analyses in highly selected participants with severe fatigue from two cohorts, of which neither may be fully generalizable to 'real life' RA populations. However, that the identified clusters appear to be stable, albeit in different proportions, across two clinically disparate cohorts suggests that these conclusions may be applicable across many population samples. Moreover, given the pervasive nature of fatigue across inflammatory rheumatic diseases and the evidence shared with idiopathic chronic fatigue populations, that mood characterises distinct clusters (27,

28), it would be interesting to examine whether these fatigue sub-types also exist within other inflammatory disorders.

As this analysis used secondary data, there was no control over what data were collected (e.g. not all co-morbidities which may influence ESR were available) and the measures by which they were assessed.(e.g.the SF36 Mental Health domain represents a broad assessment of psychological distress and wellbeing and cannot be considered comprehensive or specific to any underlying mental health complaint). We also acknowledge that although validated to measure fatigue in RA, the vitality subscale of the SF36 was not originally developed to directly capture 'fatigue' and so future studies are needed to confirm the present clusters using questionnaires which have been specifically designed to assess fatigue.

Nevertheless, the variables used to capture all clustering variables represent those commonly used in clinic, and/or those which have been validated for use in RA populations(14, 16, 18, 29). Furthermore, we selected those factors for our cluster analysis that are most commonly referenced as putative aetiologies. However, a number of potentially important discriminators, such as sleep problems and physical activity(30), were not captured by the original study and therefore could not be included in this analysis. It is clear that additional data may have further aided the interpretation of clusters. For example, information on fibromyalgia status may have informed an improved understanding of the *Affective* cluster, for whom the high prevalence of depression history and sero-negativity, along with other characteristics may have better identified them as patients with co-existing fibromyalgia (or indeed primary fibromyalgia mis-classified as RA). Clearly, future investigations should incorporate more clinical data such as this as well as harnessing new biological correlates (e.g. cytokines) as they emerge.

One of the most important limitations of cluster analysis pertains to the number of techniques available and the paucity of guidelines as to which should be used in any given context ((23)). For that reason, other methods of analyses, such as latent class analysis (LCA) were considered for

this study. However, LCA is particularly useful when it is assumed that a latent (unobserved) variable is responsible for the relationships between observed symptoms. Here, we suggested that fatigue persons would differ on the basis of the absence or presence of observed variables. In this way, cluster analysis is the most suitable method for our descriptive analysis of symptom clusters.

Nevertheless this largely exploratory approach may be sensitive to experimenter bias, where the expectancies of the researcher inform the identification of an optimal solution. To alleviate these concerns, we pre-specified a) our clustering variables based their relevance shown in existing literature and b) the hierarchical method by which we clustered our variables in the DMARD cohort and our rules to determine the number of clusters present. In particular, we selected weighted-average-linkage because this technique assumes that the common characteristics of the cluster are more representative of their true type than any single data-point. This may be especially pertinent for subjectively-influenced symptoms such as pain and fatigue where it may be more important to be similar to an existing typology of symptoms, than to the symptoms reported by a specific individual. Finally, weighted-average-linkage is particularly suitable when there is no reason to assume group sizes would be equal ((31)), as other methods such as Ward's method are known to try and force identification of similarly sized clusters.

Cluster analysis represents an increasingly useful set of techniques to identify patient subgroups between which the aetiology of symptoms may differ. For example, work in cancer has identified the existence of genetic and hormonal variations between symptom clusters(9, 32, 33). In rheumatology, these techniques have underscored the heterogeneity of fibromyalgia, identifying physiologically distinct sub-groups (34, 35). They have also been employed in RA populations, though to the best of our knowledge, no studies have specifically deconstructed severe fatigue in RA, rather their application has been limited to the investigation of psychosocial risk profiles(36), pain behaviours(37), or general symptom profiles(38).

The identification of distinct severe RA-fatigue subtypes may explain why previous experiments seeking to understand the biology of this problem have been unfruitful and why existing interventions have been shown to have only modest effects on fatigue(7, 39). We propose that such studies could adapt their sample inclusion criteria in line with these subtypes. For example, it seems plausible that any specific cytokine mediators of fatigue would be more optimally identified within powered samples of patients fulfilling the characteristics of 'inflammatory fatigue' (as defined here) rather than the inclusive approach to sampling which has been commonly applied in other populations(40). More immediate clinical benefits may be derived from longitudinal inspection of these clusters to test their stability (recognising that they may change with therapy) and prognostic capacities. We, for example, would hypothesise that membership of the global fatigue cluster confers poorer prognosis in comparison to membership of the basic fatigue cluster. Moreover the subtypes may inform stratified treatment approaches. Fatigue is not only a significant predictor of disability, poor quality of life and reduced well-being but also of medical costs and employment loss(3, 41-44) and its alleviation is clearly important for patients. Future studies should be conducted to test the predictive value of these sub-types within the context of trials, for example testing the efficacy of cognitive behavioural therapy on 'affective fatigue' or more aggressive immunomodulation for 'inflammatory fatigue' may ultimately lead to a personalised approach to fatigue management.

In conclusion, among RA patients with severe fatigue, our results validate the impression given by patients, clinicians and existing evidence as to the heterogeneity of this disabling symptom. Clinically relevant severe fatigue sub-types were identified and validated in two diverse RA cohorts and may now provide a crucial platform to launch enriched mechanistic investigations through the selection of more homogenous samples. In the future, these may also inform steps towards sub-phenotyping fatigue across the chronic inflammatory disease spectrum and beyond.

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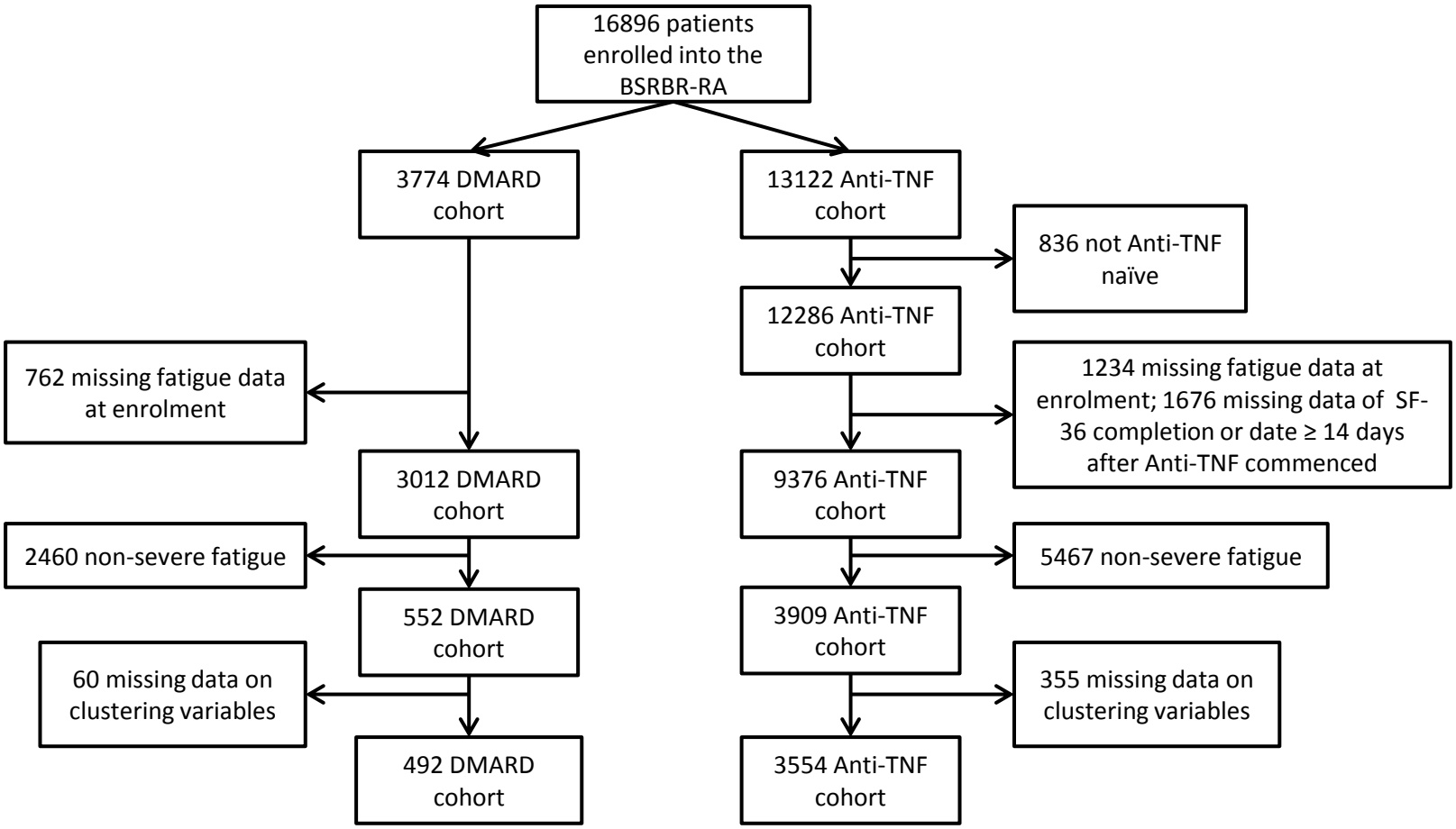
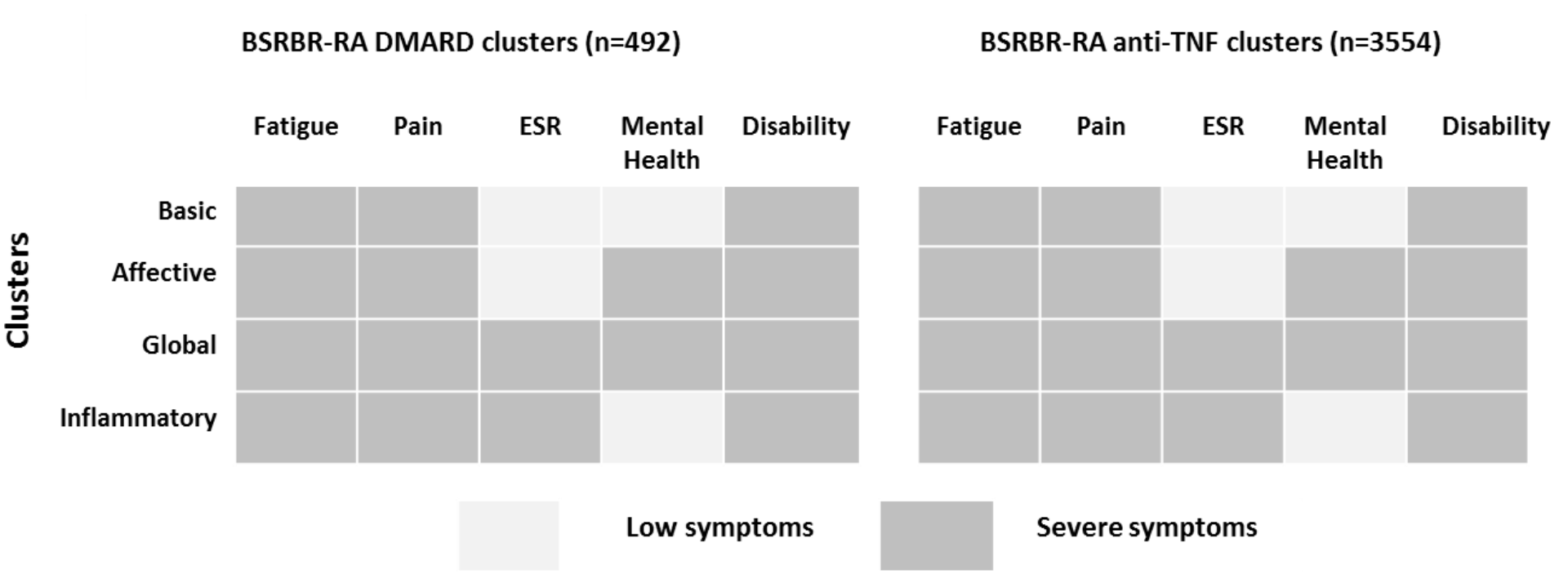

16896 patients enrolled into the BSRBR-RA
3774 DMARD cohort
13122 Anti-TNF cohort
836 not Anti-TNF naïve
12286 Anti-TNF cohort
762 missing fatigue data at enrolment
1234 missing fatigue data at enrolment; 1676 missing data of SF-36 completion or date ≥ 14 days after Anti-TNF commenced
3012 DMARD cohort
9376 Anti-TNF cohort
2460 non-severe fatigue
5467 non-severe fatigue
552 DMARD cohort
3909 Anti-TNF cohort
60 missing data on clustering variables
355 missing data on clustering variables
492 DMARD cohort
3554 Anti-TNF cohort


BSRBR-RA DMARD clusters (n=492)
BSRBR-RA anti-TNF clusters (n=3554)
Fatigue
Pain
ESR
Mental Health
Disability
Clusters
Basic
Affective
Global
Inflammatory
Low symptoms
Severe symptoms