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Interrelationships Between Heath Utility Measurements, Disease Activity and Psychological Factors in Behçet’s Disease

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Running title: Health utilities, disease activity and psychological factors in Behçet’s disease

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3 Tables, 1 Figure, 2 supplementary tables, text word length 4477, abstract word length 196
Abstract

Objective
To measure the health utilities Time Trade-Off (TTO) and Standard Gamble (SG), that ask to consider sacrifices in terms of length of life (TTO) or risk of death (SG) for improvements in quality of life in Behcet’s disease (BD), and explore the interrelationships with disease activity, depression, anxiety and fatigue.

Method
TTO, SG, EQ-5D-5L, EQ VAS, depression (PHQ-9), anxiety (GAD-7) and fatigue (MAF) questionnaires were administered to 103 adult BD patients. Disease activity was assessed using the Behçet’s Disease Activity Index (BDAI).

Results
Mean TTO was 0.72 ± SD 0.27 and mean SG 0.70 ± SD 0.34. Moderate/severe depression was identified in 55.2%, moderate/severe anxiety in 35.1% and moderate/high fatigue in 97.7% patients. TTO negatively correlated with depression (p<0.01), anxiety (p<0.01) and fatigue (p<0.01) but did not correlate with BDAI. Cluster analysis revealed one cluster where psychological factors rather than disease activity may have influenced TTO and SG scores.

Conclusions
TTO and SG show that BD patients would on average forgo 28% of their remaining life or run a 30% risk of death to avoid the condition. Complex interrelationships with depression, anxiety and fatigue may be more influential than disease activity in treatment decision making.

Keywords: Behçet’s disease; Healthcare Quality Indicators; Disease Activity; Depression; Anxiety; Fatigue.
1. Introduction

Behçet’s disease (BD) is a chronic, relapsing, systemic inflammatory disease with a wide range of clinical manifestations, most commonly oro-genital ulcers, skin lesions and potentially blinding intraocular inflammation (uveitis). BD also has a profound effect on quality of life (QoL) including the psychological wellbeing of patients. [1,2] Many patients require systemic immunomodulatory therapy, such as corticosteroid, immunosuppressants and biologics.

Understanding how patients make treatment decisions is important and the personal impact of illness can influence patients’ willingness to take risks. Health-related quality of life (HRQoL) is a key factor in decision making about treatment and is widely recognised as one of the major health outcome indices in clinical studies, health services research and health policy formation.

A 'utility' is the measure of value that an individual gives a particular health state and reflects not only the presence, frequency, or intensity of symptoms, abilities, or feelings as measured on psychometric instruments but also a preference for that state. Health utilities will reflect an individual’s preferences for different health outcomes i.e. HRQoL. [3] It is generally a number between 0 (representing death) and 1 (perfect health). The closer the health utility to a score of 1.0, the better the associated QoL state.

Patient-reported health utility scores are important measurements that indicate the overall well-being of patients and increasingly considered among clinical trial endpoints. Patient
choices, clinical decision-making and resource allocation all take survival and HRQoL into consideration simultaneously.

Many different tools have been developed for the measurement of HRQoL, and although they vary widely, it is common that HRQoL is multi-dimensional that captures all the relevant areas of a patient’s life, including physical health, mental health and functioning, social interaction and role functioning, and general well-being. Health-related quality of life outcomes are crucial complementary indicators for monitoring health services and patient-related outcomes, and along with health-economic evaluations, are an important component of assessing the efficiency of treatment interventions.

Health status should ideally be reported directly from patients, and several methods are used to obtain health state preference values (utilities). Direct health utilities are more sensitive, are based on societal preferences using a choice-based method and account for all dimensions that contribute to health utility. These include time trade-off (TTO) that asks the number of years of remaining life a patient would trade off in return for perfect health for the rest of their life, [4] standard gamble (SG) that asks the patient the maximum percentage risk of death, if any, they would be willing to accept if a new treatment was developed that could give them perfect health for the rest of their life, but there was an immediate risk of death if the treatment was unsuccessful, [5] and rating scales, such as the EuroQoL visual analogue scale (EQ VAS) [6] that allow direct comparison, without the need for mapping, of health utilities across different health conditions. TTO and SG are commonly measured utilities and have been studied widely in many health states including cancers, [7-10] osteoporosis, [11] renal transplant, [12] type 1 diabetes [13] stroke, [14] rheumatoid
arthritis,[15,16] asthma,[17] psoriasis[17] and AIDS.[18] Indirect utilities usually comprise a number of domains that patients can use to describe various aspects of their health e.g. limitations in daily activities, mobility, pain and discomfort. These are preference-based measures and map on to the utility scale indirectly via a generic health related QoL questionnaire, such as the EuroQol Five Dimensions Five Level (EQ-5D-5L).[19]

Previous studies have reported a reduction in HRQoL in BD patients using the indirect health utilities EQ-5D-3L,[20,21] EQ-5D-5L[2] and other QoL instruments, such as the Short Form 36 Health Survey (SF-36) and compared them to disease activity.[22-24] Depression, anxiety and fatigue have also been studied in BD and found to have a detrimental effect on QoL.[25-27] To our knowledge measuring direct health utilities TTO and SG in BD has not previously been undertaken.

In this study we have sought to develop a deeper understanding of patients’ perception of the personal impact of BD and its influence on their willingness to take risks associated with treatment. Our aims were to measure the direct health utilities TTO and SG in BD and evaluate the interrelationships with an indirect measure of health utility EQ-5D-5L, disease activity (objectively assessed by a physician), and to explore the associations between health utilities and depression, anxiety and fatigue. These factors are important as long-term morbidity and mortality of BD may differ according to phenotype[28] so individual outcomes may differ significantly along with treatment associated risks that may vary from minimal to potentially life threatening.
2. Methods

2.1 Patients

Adult patients who fulfilled the International Study Group criteria for BD [29] were recruited from the Birmingham National Centre of Excellence for BD, Birmingham, UK. The study was registered as a service evaluation on the Clinical Effectiveness Department Safeguard Audit System with Sandwell and West Birmingham Hospitals NHS Trust (audit #1311).

A national survey from Behçet’s UK (UK patient support group) highlighted problems in delivering care appropriately to BD patients in England. [20] This led to the approval of three National Centres of Excellence for Behçet’s Syndrome in Birmingham, Liverpool and London. These Centres provide an ideal opportunity to capture health information on BD as patients are seen by a Rheumatologist, Ophthalmologist, Oral Medicine Specialist and, if they wish, a Clinical Psychologist. [30]

Using the postcode of each patient we also looked at the Index of Multiple Deprivation (IMD) and its relationship with HRQoL. The IMD are widely used datasets in England to classify the relative deprivation (essentially a measure of poverty) of small areas. [31] Multiple components of deprivation are weighted with different strengths and compiled into a single score of deprivation.

At each clinic visit, as part of their normal clinical care, all patients self-complete the following questionnaires that had been agreed by the three Centres when they were established. The only additional questionnaires used in this study were TTO and SG.
2.2 Health Utility questionnaires

Time Trade-Off and Standard Gamble

The TTO and SG questionnaires were administered by face-to-face interview conducted by a trained interviewer. A standardized script was followed to ensure consistency. Our TTO and SG models, both summarized below, measured HRQoL at the precise time of questioning. Our TTO model first asked patients how many more years they expect to live. They were then asked to consider a hypothetical scenario where a new treatment for BD was developed that was to give them perfect health for the rest of their life, but its side effect was to reduce the number of years of life remaining. They were then asked how many, if any, of those remaining years they would be willing to trade off in return for guaranteed permanent perfect health. For example, a patient expecting to live 40 more years but willing to trade off 5 years in return for permanent perfect health would infer a TTO utility of \((40-5)/40=0.875\). Patients who would not trade off any of their remaining years would score 1. For our SG model patients were asked to consider a hypothetical scenario where a new treatment for BD was developed that could give them perfect health for the rest of their life, but in this instance there was an immediate risk of death if the treatment was unsuccessful. They were then asked what the maximum percentage risk of death, if any, they would be willing to accept. For example, a patient willing to accept a 5% risk of death would infer a SG utility of \(1-0.05=0.950\). Patients unwilling to accept any risk of death would score 1.

EuroQol Five Dimensions Five Level questionnaire (EQ-5D-5L) / EuroQol Visual Analogue Scale (EQ VAS)
The EQ-5D-5L questionnaire includes five domains related to mobility, self-care, usual activities (e.g. work, study, housework, family or leisure activities), pain/discomfort, and anxiety/depression. [19] It includes the EQ VAS where patients rate their health on the day as a score between zero and 100. [32]

2.3 Depression, anxiety and fatigue questionnaires

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a validated questionnaire to diagnose depression and grade severity of symptoms in general, medical and mental health settings. By scoring each of the 9 Diagnostic and Statistical Manual criteria for diagnosis of Major Depressive Disorder (MDD) between 0 and 3, with 0 being ‘not at all’ and 3 being ‘nearly every day’, a score between 0 and 27 is calculated. Question 9 specifically refers to ‘suicide risk’. The scores can be categorised into clinical significance according to the Instruction Manual and recommended by Kroenke et al. A score between 0 and 4 indicates minimal or no depression, 5-9 as mild, 10-14 as moderate, 15-19 as moderately severe and 20-27 as severe depression. [33]

General Anxiety Disorder-7 (GAD-7)

The GAD-7 is a validated questionnaire that measures severity of anxiety and is used as a screening tool and symptom severity measure in primary care and mental health settings. Similar to PHQ-9, it asks patients whether they have experienced 7 symptoms of the four most common anxiety disorders on a scale from 0 to 3, with 0 being ‘not at all’ and 3 being ‘nearly every day’. The final score then ranges from 0 to 21 and can be categorised. A score between 5 and 9 indicates mild anxiety, 10-14 indicates moderate and greater than 15 indicates severe anxiety.
Multi-Dimensional Assessment of Fatigue (MAF) - that incorporates the Global Fatigue Index

The MAF is a validated, patient self-reported scale to assess fatigue score in the preceding week. It consists of 16 items over four dimensions of fatigue: 1) severity, 2) distress, 3) impact on various activities of daily living e.g. household chores, cooking bathing/washing, dressing, working, visiting or socializing with friends or family, sexual activity, leisure/recreational activities, shopping, walking, and other exercise, 4) timing of fatigue frequency and change during the previous week. The items are used to calculate scores for each of the four dimensions and 15 of the 16 questions are used to calculate the global fatigue index (GFI). A higher score indicates more severe fatigue, fatigue distress, or impact on activities of daily living. The GFI ranges from 1 (no fatigue) to 50 (severe fatigue).

2.4 Behçet’s disease activity

The validated Behçet’s Disease Current Activity Form (BDCAF), [34,35] was completed by a Consultant Rheumatologist. It includes questions that allow the history of headache, orogenital ulceration, skin lesions, joint involvement, gastrointestinal system involvement, eye involvement, nervous system involvement, and major vessel involvement that were present during the four weeks prior to the day of assessment to be scored and used for the evaluation of disease activity. From these scores the Behçet’s Disease Activity Index (BDAI) can be calculated from 0-12 with 0 being no activity.

2.5 Statistical analysis

Clinical data capture was facilitated using REDCap v9.6.3 (© 2020 Vanderbilt University, Nashville, TN, USA) and statistical analysis was undertaken using SPSS v26.0 (IBM
Corpora, New York, USA). As the distribution of the TTO and SG scores were not normally distributed (one-sample Kolmogorov-Smirnov test statistic was 0.150 and 0.222 respectively, \( p=0.000 \) for both), the Kruskal-Wallis test was used to evaluate the relationships between HRQoL scores and categorical measurements. Spearman correlation coefficients (\( r_s \)) were calculated for the relationship between HRQoL scores and continuous measurements. A \( p \) value of 0.05 or less was accepted as indicating statistical significance. Multivariable analysis was used (multiple linear regression) to predict HRQoL scores as the dependent variable based on other variables collected as independent variables. A Bonferroni correction for multiple comparisons was made; a \( p \) value of 0.00625 or less was accepted as indicating statistical significance based on the number of comparisons. K-means clustering analysis was undertaken creating three cluster centres using the variables TTO, SG, BDAI, PHQ-9, Q9 ‘suicide risk’ of PHQ-9, GAD-7, GFI, IMD and age using the option ‘Exclude case pairwise’ for missing data.
3 Results

There was a total of 103 patients, 27 (26.2%) males and 76 (73.8%) females with an age range of 17-71 years (mean 43.3 years ± SD 13.97). Ethnicity, clinical manifestations and disease duration is shown in Table 1. Mean IMD (n = 100 as three patients resided outside England) was 4.76 ± SD 3.16; median 4 (range 1-10 where 1 = most deprived, 10 = least deprived). Disease duration was statistically significantly associated with EQ-5D-5L (p=0.002) and EQ VAS (p=0.000). There was no statistically significant association with TTO, SG, BDAI, PHQ-9, GAD-7 or GFI.

Insert Table 1 here

The immunomodulatory medication the patients were taking is shown in Table 2. There was no statistically significant association with TTO, SG, EQ-5D-5L, EQ VAS, BDAI, PHQ-9, GAD-7 or GFI.

Insert Table 2 here

3.1 Health Utilities

Time Trade-Off

The TTO was completed by 101 (98%) patients. Two questionnaires were only partially completed and excluded. The mean TTO was 0.72 ± SD 0.27 (95% CI 0.667 to 0.773), median 0.75. There were 26/101 (26%) patients who would not trade off any years and scored 1.0. The remaining 75 (74%) patients would trade a mean of 38 years off their remaining years of life in return for perfect health for the rest of their life. There was no statistically significant association with duration of disease or immunomodulatory medication. TTO correlated with SG ($r_s 0.474$, p<0.01), EQ-5D-5L index value ($r_s 0.373$, p<0.01), and negatively correlated with
PHQ-9 ($r_s$ -0.328, p<0.01), GAD-7 ($r_s$ -0.304, p<0.01) and GFI ($r_s$ -0.283, p<0.01). There was no significant correlation with EQ VAS, BDAI, age or IMD (Supplementary Table 1). Multiple linear regression with TTO as the dependent variable and SG, EQ-5D-5L index value, EQ VAS, PHQ-9, GAD-7, GFI and BDAI as independent variables showed that only SG was a predictor of TTO (p=0.002).

Standard Gamble
The SG was completed by 103 (100%) patients. The mean SG was 0.70 ± 0.34 (95% CI 0.634 to 0.766), median 0.8. There were 31/103 (30%) patients who would not take any risk and scored 1. Of the 72/103 (70%) patients willing to take a risk their mean SG was 0.57 i.e. a 43% risk of immediate death if the treatment was unsuccessful. There was no statistically significant association with duration of disease or immunomodulatory medication. SG correlated with TTO ($r_s$ 0.474, p<0.01) and EQ-5D-5L index value ($r_s$ 0.265, p<0.01). There was no significant correlation with EQ VAS, BDAI, PHQ-9, GAD-7, GFI, age or IMD (Supplementary Table 1).

EQ-5D-5L
The EQ-5D-5L was completed by 103 (100%) patients with a mean index value of 0.519 ± 0.315 where the index value was calculated using the UK standard EQ-5D-5L value set that gives a score between -0.285 (worst possible health status) and 1 (perfect health). [36] The EQ-5D-5L frequencies and proportions were also reported by dimension and level with approximately 50% of patients stating they had slight or moderate problems in all 5 domains (Table 3). There was a statistically significant association with disease duration (p=0.002) but not immunomodulatory medication. EQ-5D-5L index value correlated with
TTO ($r_s 0.373, p<0.01$), SG ($r_s 0.265, p<0.01$), EQ VAS ($r_s 0.763, p<0.01$), IMD ($r_s 0.205$, $p<0.05$) and negatively correlated with PHQ-9 ($r_s -0.758, p<0.01$), GAD-7 ($r_s -0.638, p<0.01$), GFI ($r_s -0.668, p<0.01$) and age ($r_s -0.198, p<0.05$) (Supplementary Table 1). Multiple linear regression showed that only EQ VAS was a predictor of EQ-5D-5L ($p=0.001$).

**EQ VAS**

The EQ VAS was completed by 103 (100%) patients. The EQ VAS ranged from 10-100, mean 59.04 ± SD 23.8, (95% CI 54.8 to 64), median 60. There was a statistically significantly association with disease duration ($p=0.000$) but not immunomodulatory medication. EQ VAS correlated with EQ-5D-5L ($r_s 0.763, p<0.01$), and negatively correlated with PHQ-9 ($r_s -0.680, p<0.01$), GAD-7 ($r_s -0.497, p<0.01$), and GFI ($r_s -0.498, p<0.01$). There was no significant correlation with TTO, SG, BDAI, age or IMD (Supplementary Table 1).

### 3.2 Depression, anxiety and fatigue

**Patient Health Questionnaire-9 (PHQ-9)**

A total of 96/103 (93.2%) patients completed the PHQ-9 with a mean score of 10.89 ± SD 7.23 (range 0-27, median 10). According to their scores, patients were categorised as minimal or no depression ($n=26$, 26.1%), mild depression ($n=17$, 17.7%), moderate depression ($n=19$, 19.8%), moderately severe depression ($n=19$, 19.8%) and severe depression ($n=15$, 15.6%). There was no statistically significant association with disease duration or immunomodulatory medication. PHQ-9 correlated with GAD-7 ($r_s 0.838, p<0.01$) and GFI ($r_s 0.680, p<0.01$), and negatively correlated with TTO ($r_s -0.328, p<0.01$), EQ-5D-5L index value ($r_s -0.758, p<0.01$), EQ VAS ($r_s -0.680, p<0.01$) and IMD ($r_s -0.211, p<0.05$). There
was no significant correlation with SG, BDAI or age (Supplementary Table 1). From the answers to Question 9 (suicide risk) we identified 68 (70.8%) patients who scored 0 (Not at all), 12 (12.5%) who scored 1 (Several days), 11 (11.5%) who scored 2 (More than half the days), and 5 (5.2%) who scored 3 (Nearly every day). The only statistically significant correlation of ‘suicide risk’ was inversely with TTO (rs -0.253, p<0.05).

**General Anxiety Disorder-7 (GAD-7)**

A total of 94/103 (91.3%) patients completed the GAD-7 with a mean score of 7.43 ± SD 6.16 (range 0-21, median 6). According to their scores, patients were categorised as normal (n=38, 40.4%), mild anxiety (n=23, 24.5%), moderate anxiety (n=16, 17%) and severe anxiety (n=17, 18.1%). There was no statistically significant association with disease duration or immunomodulatory medication. GAD-7 correlated with PHQ-9 (rs 0.838, p<0.01) and GFI (rs 0.602, p<0.01), and negatively correlated with TTO (rs -0.304, p<0.01), EQ-5D-5L index value (rs -0.638, p<0.01) and EQ VAS (rs -0.497, p<0.01). There was no significant correlation with SG, BDAI, age or IMD (Supplementary Table 1).

**Global Fatigue Index (GFI)**

The GFI is the score derived from the MAF questionnaire. A total of 87/103 (91.3%) patients completed the MAF with a mean GFI of 31.2 ± SD 11.48 (range 0-49.36, median 33). There was no statistically significant association with disease duration or immunomodulatory medication. GFI correlated with BDAI (rs 0.277, p<0.05), PHQ-9 (rs 0.680, p<0.01) and GAD-7 (rs 0.602, p<0.01), and negatively correlated with TTO (rs -0.283, p<0.01), EQ-5D-5L index value (rs -0.668, p<0.01) and EQ VAS (rs -0.498, p<0.01). There was no significant correlation
with SG, age or IMD (Supplementary Table 1). Multiple linear regression showed that none of the 8 variables were statistically significant predictors of GFI.

### 3.3 Disease activity

**Behçet’s Disease Activity Index (BDAI)**

The BDAI was documented in 73/103 (72.9%) patients with a mean of 3.12 ± SD 1.90 (range 0-9, median 3). There was no statistically significant association with disease duration or immunomodulatory medication. BDAI negatively correlated with EQ-5D-5L index value ($r_s$ -0.281, $p<0.05$) and GFI ($r_s$ 0.277, $p<0.05$). There was no significant correlation with TTO, SG, EQ VAS, PHQ-9, GAD-7, age or IMD (Supplementary Table 1). Multiple linear regression showed that none of the 8 variables were statistically significant predictors of BDAI.

### 3.4 K-means clustering analysis

Three final cluster centres were defined using the variables TTO, SG, BDAI, PHQ-9, the ‘suicide risk’ Q9 of the PHQ-9, GAD-7, GFI, IMD and age. These are graphically represented in Figure 1.

*Insert Figure 1 here*
4 Discussion

In our cohort, we found a mean TTO of 0.72 and mean SG of 0.70 i.e. patients would trade off a mean of 28 years of their life and accept a 30% risk of immediate death, respectively to have perfect health for the rest of their life. Our TTO and SG values are comparable to that of a number of other health conditions (Supplementary Table 2). Neither TTO or SG were associated with longer disease duration, immunomodulatory medication or IMD and multiple linear regression revealed that only SG was a predictor of TTO. Our major finding was disease activity did not correlate with TTO or SG, but that factors, such as depression, anxiety and fatigue could materially influence patients' willingness to take risks with their treatment to gain benefit.

Our patients 53/96 (55.2%) were moderately to severely depressed and 33/94 (35.1%) had moderate to severe anxiety. The high levels of depression, anxiety and fatigue identified adds to the growing literature that the psychological effect on QoL in BD patients is immense. We found that PHQ-9, GAD-7 and GFI all showed a statistically significant negative correlation with TTO, EQ VAS, EQ-5D-5L. This implies that a reduction in HRQoL is associated with higher degrees of depression, anxiety and fatigue and vice versa. The ‘suicide risk’ Question 9 of the PHQ-9 also showed a statistically significant negative correlation only with TTO. Yet, disease activity (BDAI) was not correlated with TTO, SG, PHQ-9 (depression) or HAD-7 (anxiety). Only GFI showed a weak statistically significant correlation with BDAI.

Therefore, we undertook cluster analysis to see if distinct populations of patients could be identified to explain our findings. Of the three final cluster centres, Cluster 1 showed what one might reasonably expect with lower depression (PHQ-9 and ‘suicide risk’), anxiety (GAD-
7), fatigue (GFI) and disease activity (BDAl) scores being reflected in higher TTO and SG scores i.e. better HRQoL, and patients were from slightly more deprived areas. Cluster 2 appeared the most interesting as it contained patients who were slightly older and from slightly less deprived areas with lower TTO and SG scores i.e. worse HRQoL and more likely to trade years or risk immediate death, with worse depression (including ‘suicide risk’), anxiety and fatigue scores. Yet these patients had much lower disease activity scores thus identifying a cluster of patients where psychological factors rather than their disease activity could play a major influence in determining their TTO and SG scores i.e. HRQoL. Cluster 3 included slightly younger patients and more deprived. There was a slight discrepancy between TTO and SG values i.e. slightly more likely to trade years than risk immediate death, moderate depression (including moderate ‘suicide risk’), anxiety and fatigue but more active disease.

In our earlier publication we also showed that a large proportion of changes in psychological status in BD could not be explained by changes in disease activity alone and that intra-individual variation appeared to play an important role. [2] Evidently, factors that influence one’s health utility are complex and multifactorial.

Looking at the range of health utilities studied, TTO or SG was not significantly correlated with EQ VAS, yet the EQ VAS significantly correlated with EQ-5D-5L and multiple linear regression showed that only EQ-5D-5L was a predictor of EQ VAS (p=0.001). There is debate as to the ideal TTO methodology as some studies use a 10-year time horizon, [37] but a clear-cut answer does not exist. [38] As BD is a chronic disease with the likelihood of relapses over many years, using a longer time frame appeared appropriate. It is possible
that younger patients may have higher TTO valuations than older patients as they will perceive their life expectancy and quality differently, but we did not find any significant correlation between TTO and age (rs=-0.107, p=0.287).

Previous studies have also examined QoL, depression, anxiety, and fatigue in BD patients. In 2009 Behçet’s UK surveyed their members assessing QoL using cross sectional postal surveys.[20] Their mean EQ-5D-3L was 0.47 and BD affected all the five domains of the EQ-5D descriptive system. They repeated the survey a few years later [21] with a mean EQ-5D-3L of 0.63 and almost half their cohort suffered from anxiety and depression. We found a mean EQ-5D-5L of 0.519 and 39% of our patients had moderate to extreme problems in the anxiety and depression dimension. The studies are not directly comparable as Behçet’s UK used the EQ-5D-3L that has only three options for each of the 5 domains. Using a previously described classification of GFI scores, [25] 2/87 (2.3%) of our patients had no fatigue, 17/87 (19.5%) moderate fatigue and 68/87 (78.2%) high fatigue. In their series of 123 BD patients Ilhan et al. reported a mean GFI score of 20.6 despite 70% of their patients perceived to have active disease, [26] compared with our mean GFI score of 31.2. They identified that 40.6% of their patients had depression and 28.5% had anxiety but used different validated questionnaires, HADS-Depression and HADS-Anxiety. Can Sandikci et al. also found a lower mean GFI of 25.0 in their 155 BD patients. Although they perceived 76.8% of patients to have active disease their mean BDAI was only 2.7, lower than our mean of 3.12. They identified that 43.9% of BD patients had depression and 43.2% had anxiety but also used the HADS-Depression and HADS-Anxiety questionnaires. [27]
In the Behçet Centres the Rheumatologist, Ophthalmologist, and Oral Medicine specialist will have knowledge of disease activity, damage and clinical phenotype but not necessarily the skills to assess other factors, such as psychological status (that from this study appears very important). Therefore, the addition of a Clinical Psychologist as part of the multidisciplinary team has been invaluable. Yet, there are some patients whose range of problems, such as self-harm, adjustment to illness (particularly with a chronic disease) and physical and psychological co-morbidities who require further professional input. This could be achieved by having access to a Liaison Psychiatrist who would provide an important role.

Our case-mix of patients reflects a slightly older and predominantly female population compared with other published BD cohorts but mirrors two previous publications from our Centre. [2,39] Recently our group reported a prevalence of BD in the UK of 14.61 (95% CI 13.35–15.88) per 100,000 population for 2017. The mean age was 42.33 (± SD 14.51) years with a predominantly female cohort (817 patients, 63.78%). [28]

The main strength of this study is that we have undertaken a large number of health utility and psychological questionnaires on a deeply phenotyped cohort of patients. The potential limitations were that we could not identify if patients’ TTO and SG responses were influenced by their symptoms over the preceding four weeks, and that the BDAI had only been documented in 73/103 (72.9%) patients that may have a bearing on some of the results. Although we could confirm a BDAI score had been calculated in those patients, responses on individual system involvement were not always recorded, making a more comprehensive examination of the relationships with disease features unfeasible.
In BD with the acknowledged distinctive personality traits that have been previously reported as materialistic, self-contained, self-confident, cold, detached and reserved, [40] and with intra-individual variation playing a large role in the relationship between psychological status and disease activity, [2] plus the characteristics of the patients described in cluster 2 (above) then TTO and SG may not always be the most appropriate utilities to measure in routine clinical practice. Nevertheless, they could have a role pre and post the introduction of a new treatment modality to detect improvement as has been shown in many conditions including rheumatoid arthritis, [41] suggesting applicability to clinical trials. To achieve this future work should be directed towards a better understanding of the factors that influence TTO/SG in patients with BD. These include the disease subtype/phenotype and the timing of assessment of TTO/SG in relation to mood and anxiety as they may have important implications in treatment discussions and decision making with patients.
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Conflicts of interest

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at
References


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</tr>
<tr>
<td>Oral ulceration</td>
<td>103 (100)</td>
</tr>
<tr>
<td>Genital ulceration</td>
<td>83 (80.6)</td>
</tr>
<tr>
<td>Skin lesions</td>
<td>79 (76.7)</td>
</tr>
<tr>
<td>Arthritis/arthralgia</td>
<td>63 (61.2)</td>
</tr>
<tr>
<td>Uveitis</td>
<td>49 (47.6)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>45 (43.7)</td>
</tr>
<tr>
<td>Neurological</td>
<td>28 (27.2)</td>
</tr>
<tr>
<td>Vascular</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td><strong>Duration of disease</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 1 year</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>26 (25.2)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>32 (31.1)</td>
</tr>
<tr>
<td>11-20 years</td>
<td>19 (18.4)</td>
</tr>
<tr>
<td>Greater than 20 years</td>
<td>21 (20.4)</td>
</tr>
</tbody>
</table>
Table 2
Immunomodulatory medication in 103 patients with Behçet’s disease

<table>
<thead>
<tr>
<th>Medication</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral prednisolone only</td>
<td>11 (10.7)</td>
</tr>
<tr>
<td>Disease Modifying Antirheumatic Drugs (DMARD)(^a) only</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Biologic/Biosimilar(^b) only</td>
<td>5 (4.8)</td>
</tr>
<tr>
<td>Prednisolone and DMARD</td>
<td>15 (14.6)</td>
</tr>
<tr>
<td>Prednisolone and Biologic/Biosimilar</td>
<td>11 (10.7)</td>
</tr>
<tr>
<td>Prednisolone, DMARD and Biologic/Biosimilar</td>
<td>15 (14.6)</td>
</tr>
<tr>
<td>DMARD and Biologic/Biosimilar</td>
<td>12 (11.6)</td>
</tr>
<tr>
<td>No treatment</td>
<td>26 (25.2)</td>
</tr>
</tbody>
</table>

\(^a\) DMARD included azathioprine, ciclosporin A, cyclophosphamide, methotrexate, mycophenolate mofetil.

\(^b\) Biologic/Biosimilar included adalimumab, certolizumab pegol, etanercept, infliximab, interferon 2-alpha, rituximab, ustekinumab.
Table 3
EQ-5D-5L frequencies and proportions reported by dimension and level in 103 patients with Behçet’s disease

<table>
<thead>
<tr>
<th>Level</th>
<th>Mobility N (%)</th>
<th>Self-Care N (%)</th>
<th>Usual Activities N (%)</th>
<th>Pain / Discomfort N (%)</th>
<th>Anxiety / Depression N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 (No problem)</td>
<td>36 (35)</td>
<td>47 (46)</td>
<td>24 (23)</td>
<td>13 (13)</td>
<td>34 (33)</td>
</tr>
<tr>
<td>Level 2 (Slight problems)</td>
<td>19 (18)</td>
<td>26 (25)</td>
<td>27 (26)</td>
<td>21 (20)</td>
<td>29 (28)</td>
</tr>
<tr>
<td>Level 3 (Moderate problems)</td>
<td>34 (33)</td>
<td>22 (21)</td>
<td>32 (31)</td>
<td>39 (38)</td>
<td>24 (23)</td>
</tr>
<tr>
<td>Level 4 (Severe problems)</td>
<td>13 (13)</td>
<td>8 (8)</td>
<td>13 (13)</td>
<td>25 (24)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Level 5 (Extreme problems / unable to do)</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>7 (7)</td>
<td>5 (5)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>
Fig. 1. K-means cluster analysis of 103 Behçet patients showing three final cluster centres
**Supplementary Table 1**  
Spearman Correlation Coefficients ($r_s$) in 103 patients with Behçet’s Disease

<table>
<thead>
<tr>
<th></th>
<th>TTO</th>
<th>SG</th>
<th>EQ-5D-5L</th>
<th>EQ VAS</th>
<th>BDAI</th>
<th>PHQ-9</th>
<th>GAD-7</th>
<th>GFI</th>
<th>Age</th>
<th>IMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTO</td>
<td>0.474</td>
<td>0.373</td>
<td>0.176</td>
<td>-0.129</td>
<td>-0.328</td>
<td>-0.304</td>
<td>-0.283</td>
<td>-0.107</td>
<td>0.089</td>
<td></td>
</tr>
<tr>
<td>SG</td>
<td>0.474</td>
<td>0.265</td>
<td>0.192</td>
<td>0.091</td>
<td>-0.145</td>
<td>-0.055</td>
<td>-0.198</td>
<td>-0.136</td>
<td>0.033</td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>0.373</td>
<td>0.265</td>
<td>0.763</td>
<td>-0.281</td>
<td>-0.758</td>
<td>-0.638</td>
<td>-0.668</td>
<td>-0.198</td>
<td>0.205</td>
<td></td>
</tr>
<tr>
<td>EQ VAS</td>
<td>0.176</td>
<td>0.192</td>
<td>0.763</td>
<td>-0.193</td>
<td>-0.680</td>
<td>-0.497</td>
<td>-0.498</td>
<td>-0.139</td>
<td>0.131</td>
<td></td>
</tr>
<tr>
<td>BDAI</td>
<td>-0.129</td>
<td>0.091</td>
<td>-0.281</td>
<td>-0.193</td>
<td>0.100</td>
<td>0.171</td>
<td>0.277</td>
<td>-0.046</td>
<td>-0.107</td>
<td></td>
</tr>
<tr>
<td>PHQ-9</td>
<td>-0.328</td>
<td>-0.145</td>
<td>-0.758</td>
<td>-0.680</td>
<td>0.100</td>
<td>0.838</td>
<td>0.680</td>
<td>0.046</td>
<td>-0.211</td>
<td></td>
</tr>
<tr>
<td>GAD-7</td>
<td>-0.304</td>
<td>-0.055</td>
<td>-0.638</td>
<td>-0.497</td>
<td>0.171</td>
<td>0.838</td>
<td>0.602</td>
<td>-0.010</td>
<td>-0.140</td>
<td></td>
</tr>
<tr>
<td>GFI</td>
<td>-0.283</td>
<td>-0.198</td>
<td>-0.668</td>
<td>-0.498</td>
<td>0.277</td>
<td>0.680</td>
<td>0.602</td>
<td>-0.071</td>
<td>-0.173</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.107</td>
<td>-0.136</td>
<td>-0.198</td>
<td>-0.139</td>
<td>-0.046</td>
<td>0.046</td>
<td>-0.010</td>
<td>-0.071</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>IMD</td>
<td>0.089</td>
<td>0.033</td>
<td>0.205</td>
<td>0.131</td>
<td>-0.107</td>
<td>-0.211</td>
<td>-0.140</td>
<td>-0.173</td>
<td>0.04</td>
<td></td>
</tr>
</tbody>
</table>

*Correlation is significant at the 0.01 level.

bCorrelation is significant at the 0.05 level.

Abbreviations: TTO, Time Trade-Off; SG, Standard Gamble; EQ-5D-5L, EuroQol Five Dimensions Five Level questionnaire; EQ VAS, EuroQol Visual Analogue Scale; BDAI, Behçet’s Disease Activity Index; PHQ-9, Patient Health Questionnaire-9; GAD-7, General Anxiety Disorder-7; GFI, Global Fatigue Index; IMD, Index of Multiple Deprivation.
**Supplementary Table 2**
Mean Time Trade-Off and Standard Gamble Values in Behçet’s Disease (this study) and Other Health States

<table>
<thead>
<tr>
<th>Health State</th>
<th>TTO</th>
<th>SG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behçet’s disease (this study)</td>
<td>0.72</td>
<td>0.70</td>
</tr>
<tr>
<td>Psoriasis [17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(10-30% surface involvement)</td>
<td>0.79</td>
<td>0.78</td>
</tr>
<tr>
<td>Asthma [17]</td>
<td>0.81</td>
<td>0.91</td>
</tr>
<tr>
<td>Renal transplant [12]</td>
<td>0.72</td>
<td>0.57</td>
</tr>
<tr>
<td>AIDS [18]</td>
<td>0.81</td>
<td>0.80</td>
</tr>
<tr>
<td>Metastatic breast carcinoma [7]</td>
<td>0.82</td>
<td>NR</td>
</tr>
<tr>
<td>Metastatic prostate cancer [10]</td>
<td>0.71</td>
<td>NR</td>
</tr>
<tr>
<td>(high-risk metastatic prostate cancer who is currently receiving androgen deprivation therapy and is not yet castrate-resistant)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis [11]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(one or more vertebral fractures)</td>
<td>0.82</td>
<td>NR</td>
</tr>
<tr>
<td>(hip fracture)</td>
<td>0.63</td>
<td>NR</td>
</tr>
<tr>
<td>Type 1 Diabetes [13]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(amputation, mean duration of diabetes 22 years)</td>
<td>0.73</td>
<td>NR</td>
</tr>
<tr>
<td>(dialysis, mean duration of diabetes 14 years)</td>
<td>NR</td>
<td>0.70</td>
</tr>
<tr>
<td>Stroke [14]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(moderate severity)</td>
<td>0.69</td>
<td>NR</td>
</tr>
<tr>
<td>(minor severity)</td>
<td>0.73</td>
<td>NR</td>
</tr>
<tr>
<td>Rheumatoid arthritis [15,16]</td>
<td>0.77-0.81</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: TTO, Time Trade-Off; SG, Standard Gamble; NR, Not Reported.