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Corresponding Author:	Alla Yankouskaya, Ph.D Liverpool Hope University Faculty of Science Liverpool, UNITED KINGDOM
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Liverpool Hope University Faculty of Science
Corresponding Author's Secondary Institution:	
First Author:	Alla Yankouskaya, Ph.D
First Author Secondary Information:	
Order of Authors:	Alla Yankouskaya, Ph.D
	Alexandra Boughey, M.Sc
	Jane McCagh, Clinical Doctorate
	Alison Neal, B.Sc. (hons)
	Christophe de Bezenac, Ph.D
	Simon J Davies, Ph.D
Order of Authors Secondary Information:	
Manuscript Region of Origin:	UNITED KINGDOM
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Running head**: illness perception**

Illness perception mediates the relationship between the severity of symptoms

and perceived health status in patients with Behcet's disease.

*Corresponding author: Alla Yankouskaya, Ph.D in Cognitive Neuropsychology,
Department of Psychology, Bournemouth University, Fern Barrow, Poole BH12 5BB
Tel: +44710569381, Email: yankoua@hope.ac.uk

Alexandra Boughey, M.Sc. in Cognitive Neuroscience & Neuroimaging

Jane McCagh, PhD in Clinical Psychology

Alison Neal, B.Sc. (hons), Nutritional Science

Christophe de Bezenac, Ph.D. in Psychology

Simon J. Davies, Ph.D. in Psychology

Abstract

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Methods. Using cross-sectional survey design, data on self-administered questionnaires on illness perception, health status, symptoms severity and demographic characteristics were collected from 273 patients with Behçet's Disease (age range 18 – 65+). The data were subjected to mediation analysis to test whether cognitive and emotional components of illness perception mediate the relationship between the severity of symptoms and heath status.

Results. The results support our hypotheses that cognitive components of illness perception (perceived consequences and identity of the illness) mediate the link between symptom activity and pain, whereas emotional components of the illness (emotional representations about the illness) mediate the relationship between disease activity and perceived energy level.

Conclusion. The robustness of these mediation effects suggests potential directions for clinical psychologists and health care practitioners in developing support programmes. We supplement our study with Open Access database containing information about type of medication, comorbid mood disorder, detailed measurement of the severity of BD symptoms for sharing and accumulating multidisciplinary knowledge aiming to support the development of interventions. Addressing psychological aspects of BD will help to manage complex patients effectively.

Key words

Behçet's Disease; illness perception; mediation effect; pain, level of energy; the severity of symptoms

Introduction

Each long-term condition can be characterised by a unique combination of psychological, physical and psychosocial factors. Understanding links between these factors is particularly important when there is no medical cure, and their quality of life heavily relies on self-regulation and coping strategies.

One such long-term condition is Behçet's Disease (BD), also known as Behçet's Syndrome, a multi-system disorder with unclear etiology. Although lower prevalence rates have been reported in a population of European ancestry [1] compared to Middle Eastern and Mediterranean descent [2,3], immigration and awareness among physicians have influenced an increased prevalence and diagnosis of BD in the UK [1]. It is only relatively recently that BD has received focused attention from the biomedical and health sciences, and therefore the psychological aspects of BD are still very poorly understood. The present paper aims to make a step toward understanding the relationship between psychological representations of illness, perceived health status and self-assessment of symptom severity in patients with Behçet's Disease.

One useful framework for considering the mechanisms underlying perceived health outcomes is the Common Sense Model (CSM) [4,5]. Research on the CSM has indicated an emergent pattern of cognitive and emotional components of illness perception and the relationships between them that are specific to a particular illness [6,7].

There are three unique aspects of BD that might shape the patients' interpretive schema(s) of their illness. First, clinical manifestations of BD symptoms are overlapped with a number of chronic conditions such as systemic vasculitis, rheumatoid arthritis, autoimmune disease, recurrent oral ulcers [2]. In the majority of cases, patients are misdiagnosed several times prior to the correct diagnosis of BD being made [8]. Second, Behçet's Disease is classified as a rare disease [2], and as such is affected by a lack of both medical and non-medical information for both patients and practitioners. It

3

is known that as information becomes more widely and easily available, individuals are able to take a more active role in managing their illness [9,10].Third, BD pathogenesis involves profound inflammatory responses which are frequently associated with intense pain and unpredictable dynamics [11-13]. This sporadic pattern of BD activity can affect perceived health status in relation to pain [14]. Indeed, there is evidence that over 80% of patients with BD perceived their health status as having not enough energy [15], and were severely affected by the experience of pain [16].

Research on Behçet's Disease indicates that both perceived energy level and pain significantly relate to the perceived severity of BD symptoms [16,17]. However, there is also evidence that the relationship between them may be mediated by different aspects of illness perception. For example, a number of studies in patients with Behçet's disease link their diminished energy level to a low level of emotional wellbeing, which in turn is related to their health self-assessment [16,18]. Studies on systemic vasculitis – a group of systemic diseases which share common clinical manifestations with Behçet's Disease - suggested that fatigue might be driven by negative emotional representations of the illness, concerns about illness outcomes and individual identification with the illness [18]. These findings, taken together, point to the possibility that emotional representations and concerns about the illness may mediate the relationship between the perceived severity of symptoms and energy level in patients with Behçet's Disease.

There is a large body of research suggesting that patients' attributions and beliefs about pain can modulate the level of perceived pain. For example, patients' beliefs about the consequences of their condition on physical, social and emotional aspects of their life, showed a strong link with both the severity of symptoms and their quality of life [19-21]. Another aspect of BD patients' beliefs may reflect that pain is the core feature (identity) of their illness. Although there is high degree of the variability of manifestations of Behçet's Disease, both between and within patients [22,23], one of the

4

most common features of BD is inflammatory reactions. As BD is characterized by recurrent episodes of acute inflammation, and often in new places, patients may perceive pain as the core identity of their illness.

The findings above highlight the role of an illness perception in Behçet's Disease from the patients' perspective and point at two important features. First, the relationship between the perceived severity of symptoms and perceived health status relating to pain and energy levels can be mediated by different components of illness perception. Second, cognitive representations about the illness (consequences of BD and symptom identification) may mediate the link between BD symptom activity and perceived pain, whereas emotional components of the illness perception (emotional representations and concerns about the illness) may mediate the relationship between the activity of BD and perceived energy level. The objectives of the present study were to test these two assumptions.

Method

Design and study sample

This study adopted a cross-sectional online survey design. The board of trustees of the Behçet's Society in the UK reviewed the design and granted permission for the publication of the Survey Monkey web link to be posted on their social media sites alongside the generic website. This enabled a wider sample of participants to be recruited. Inclusion criteria stated that participants must be aged 18 or over and have a diagnosis of Behçet's Disease confirmed by their GP or Rheumatology Consultant.

Data elements

Using survey design, we collected data on (i) demographic information (age, gender and marital status); (ii) Behçet's Disease related information (Behçet's Disease Current Activity Form (BDCAF) [24]; (iii) self-assessment of the illness perception and heath

5

status (the Nottingham Heath Profile questionnaire [25], and the Brief Illness Perception questionnaire [26].

Although medication and comorbid aspects of BD were not in a focus of this study, we provide open access database containing information about type of medication at the time of survey, comorbid mood disorder, detailed self-report assessment on the Behçet's disease Current Activity Form, the length of the disease duration from clinical diagnosis onset, the time of symptoms occurred prior a medical diagnosis (DOI 10.5281/zenodo.1251563). This information can provide a general picture about Behçet's Syndrome for general practitioners and clinical rheumatologists who are caring for BD patients.

Materials

The *Behçet's Disease Current Activity Form (BDCAF)* was developed and validated [27] to assess the severity of BD symptomology over the last four weeks. Summed scores on 12 items measure only disease activity (range 0-12). Previous research on the BDCAF has found good inter-observer reliability for assessing general disease activity in British patients.

The Brief Illness Perception Questionnaire (Brief-IPQ) is a 9-item questionnaire designed to rapidly assess cognitive and emotional representations of illness. The Brief-IPQ showed good test-retest reliability (0.24-0.73) across a wide range of chronic diseases, including vasculitis and rheumatoid arthritis. The discriminant validity of the questionnaire was supported by its ability to distinguish between different illnesses including different types of vasculitis, and has advantages in terms of brevity and lower participant burden [28].

The Nottingham Health Profile Questionnaire (NHP) contains 38 items included in Part I and seven optional items that comprise Part II. For statistical analyses, we used

only Part I. Internal consistencies (Cronbach's α) for the NHP (Part I) were reported as following: .63 for Energy level, .81 for Pain, .81 for Emotional Reactions, .76 for Sleep, .65 for Social Isolation, and .80 for Physical Abilities [29].

Procedure

An information sheet explaining the purpose, content, data use, withdrawal from the study, consent page and details about the researchers preceded the survey. After a participant's agreement was received, they were taken into the survey.
During recruitment, the randomness of participants' age, gender, and duration of the disease was assumed, but it was not under control due to the small population of people suffering from BD.

Data Analysis

Three analyses were performed in this study. First, we analysed the demographic characteristics of the sample and the type and number of BD symptoms. Secondly, we analysed concerns with characteristics of the illness perception and perceived health status in our sample. In the third analysis, we modelled the relationship between BD symptom severity (independent variable), illness perception (mediator) and the NHP (the outcome variable) using a mediation approach. All statistical analyses were done using the computing environment **R** (**R** Development Core Team, 2005), *lavaan* package [30].

Participants

In total, 273 adults with a confirmed Behçet's Disease diagnosis participated in the present study. After inspection of the data, 23 participants were removed due to an incomplete or partly completed survey. The data from the remaining 250 participants were selected for the analyses.

For analysis of demographic characteristics of the sample, the data were collapsed across four age categories: 18-29, 30-44, 45-59 and over 60 years old. Table 1 summarises the sample characteristics with respect to age and sex.

The distribution of sample by age category, disease duration and symptom onset before medical diagnosis of BD and discussion are reported in the Supplementary Material, Section 1.

<div align="center">Results</div>

Behçet's Disease Current Activity

The average BDCAF score for the sample was 6.29, SD = 2.4. Symptoms assessed by BDCAF and the number of respondents who experienced these symptoms are presented in Table 2.

Illness perception and Health Profile

Previous research demonstrated that beliefs about an illness's etiology might affect patients' emotional responses, particularly in illnesses in which the etiology is unclear [31]. To identify the most common factors that BD patients attribute to their illness, we analysed individual responses for an open question requesting participants to indicate three factors that they believe caused their illness. The results are displayed in Figure 1.

The average profile of illness perception and perceived health status in BD patients are displayed in Figure 2.

An additional analysis assessing whether illness perception in BD patients differs from other people suffering from chronic conditions and discussion are reported in the Supplementary Material, Section 2. It has to be noted that the pattern of illness perception and health status were consistent across age and the different length of BD (Supplementary Material, Section 3).

Modelling the relationship between BD symptom severity, illness perception and the NHP

To answer the question of whether illness perception mediates the relationship between the severity of BD symptoms and perceived health status we first assessed associations between the symptom severity, and the NHP. The severity of BD symptoms and the NHP showed significant correlations with Consequences, Identity, Concerns and Emotional Representation subscales of the Brief IPQ (Table 3). These subscales of illness perception were entered as potential mediators in the mediation models with the severity of BD symptoms as the independent variable, and two subscales of perceived health status (Pain and Energy level) as the dependent variables.

Two modelling procedures were carried out: Model 1 and Model 2 (Figure 3). In Model 1, we tested an assumption that the relationship between the severity of BD symptoms and perceived Pain is mediated by Consequences and Identity of illness perception (cognitive components of illness perception), but not by Emotional Representation and Concerns (emotional components of illness perception). In Model 2, we tested the assumption that the association between symptom severity and perceived Energy level in BD patients is mediated by emotional components of illness perception (Emotional Representation and Concerns), but not by cognitive components (Consequences and Identity) of illness perception. Including both cognitive and emotional components of illness perception in initial models allow us to compare the effects of all mediators while accounting for covariance between them [32].

The modelling was performed in two steps. First, we specified all possible relationships between estimated parameters in each model and ran the models. The variances for each variable and all covariance terms between each pair of variables were added to the models. After inspecting the parameters of these initial models, we

tested final models. To examine the indirect effects, we used the product-of-coefficients tests (see for details in Supplementary Material, Section 4).

Models fit. There were no missing data. To estimate fitting parameters, we chose weighted least squares (WLS) because the data were not distributed normally. The initial models which included all possible covariation terms between the mediators showed bad fit. After an inspection of the covariance matrices and removing non-significant ones (covariance between Consequences and Concerns, and Identity and Concerns), the hypothesized models appear to be a good fit to the data. Fit parameters for Model1 were: ($\chi2$ = 1.968, p($\chi2$) = .161; the comparative fit index (CFI) = 0.992; the RMSEA (Root Mean Square Error of Approximation) = 0.062, 90%CI [0.000, 0.193]; the SRMR (Standardized Root Mean Square Residual) = 0.011. Fit parameters for Model 2 were: ($\chi2$ = 1.968, p($\chi2$) = 0.161; CFI = 0.988; the RMSEA = 0.062, 90%CI [0.000, 0.193]; the SRMR = 0.012.

Mediation models. Mediation is said to occur if an indirect effect contributes significantly to the model estimation (defined by subtracting the direct effect from the total effect) [33]. Therefore, mediation is present if the confidence interval of the indirect path does not contain zero. The results of mediation analyses are summarized in Table 4.

The results of mediation analyses (Table 4) indicate that in both models only indirect effects reached a significance level. For substantive interpretation of the results, we next report the unstandardized regression coefficients a, b, and c. In Model 1, the indirect path BDCAD -> Consequences -> Pain (a1xb1 in Figure 3, Model 1) indicates that a unit increase in the severity of BD symptoms increases 0.4 units of perception of illness consequences, which leads to increasing perceived pain by 4.9 units. In the indirect path BDCAD -> Identity -> Pain (a2xb2 in Figure 3, Model 1), a unit increase in the severity of BD symptoms increases identification with the disease by 0.3 units,

which elevates the level of perceived pain by 4.5 units. Notably, no significant direct effect (BDCAF -> Pain) was observed here (Table 4), suggesting the mediating role of illness perception.

In Model 2, the indirect path BDCAD -> Emotional representation -> Energy (a4xb4 in Figure 3, Model 2), indicates that a unit increases in BD symptom severity facilitates emotional representations of illness by 0.3 units, which leads to perceived tiredness increasing by 3.1 units. Similar to Model 1, the direct effect (BDCAF -> Energy) was non-significant, suggesting the mediating effect of emotional representations between the severity of symptoms and reported energy level in BD patients.

Discussion

In the present study, we make a step toward understanding the relationship between psychological representations of illness, perceived health status and self-assessment of symptom severity in patients with Behçet's Disease.

The CSM suggests that acting as a scientist, a patient may use the unexplained causality in BD as a heuristic for reducing the level of frustration [4]. Over 16% of BD respondents in our study linked the cause of their illness to unsuccessful surgical procedures, pregnancy, abused parenteral behavior in their childhood, "bad luck" and "fate", and medical negligence. It is well known that causal illness attributions influence emotional reactions, physical self-concept, coping strategies, illness behavior and comorbid mood disorders [34]. Addressing these issues by facilitating information awareness in BD patients about causes of the illness may help to reduce the number of misattributions to the causes of Behçet's Disease.

We hypothesized that the relationship between the severity of Bechet's Disease symptoms and health status related to pain and energy level is influenced by different

11

components of illness perception and tested this assumption by using a mediation approach. Two important findings emerged from our analyses. The first is that we confirmed our hypothesis and provided evidence that cognitive components of illness perception mediated the relationship between perceived pain and the severity of BD symptoms. The relationship between energy level and the severity of BD symptoms was mediated by emotional, but not cognitive components of illness perception.

Our correlation analysis showed significant positive association between the BDCAF scores and either Pain and Energy scores of the NHP, indicating that with increasing symptom severity, the levels of perceived pain and tiredness also increase. These results point to the presence of a direct effect between symptom severity and perceived health status. However, this direct effect disappeared once we modelled the relationship between these variables as indirect paths via illness perception (the total effects in Model 1 and Model 2 remained significant while the direct effects were not), suggesting an indirect-only mediation [35], which is considered as the strongest demonstration of mediation occurring [36].

Importantly, both perception of illness consequences and representation of illness identity mediate the relationship between the severity of BD symptoms and perceived pain, and we found no significant difference in the 'strength' of the mediation effect between them. Furthermore, neither the control-related dimensions, including representations of the length of the disease and understanding the illness, nor emotional-related dimensions showed mediation effects. This finding may have practical implications. For example, knowing that perception of consequences and identification of illness symptoms in patients with Behçet's Disease mediate perceived pain, interventions may focus on changing these mediating variables to affect behavior and perceived quality of life.

Mediation analysis in the present study demonstrated that emotional representations but not concerns about the illness mediate the relationship between BDCAF scores and perceived energy level. Only indirect effect 'BDCAF – emotional representations – energy' was significant. This finding suggests that negative emotional representations about the illness may facilitate feelings of tiredness and lack of energy. In contrast to our assumption, there was no mediation effect of concerns about the illness on energy level (Model 2) or pain (Model 1). This finding may indicate that illness-related concerns in BD patients are not a function of the emotional component of illness perception but emerged as a function of the perceived severity of the disease and are associated with energy level directly or via other dimensions of illness perception.

Our study provides findings of mediation effects of illness perception on perceived health status, which can be used by heath providers for the development of interventions to help people suffering from Behçet's Disease. Considering that Behçet's Disease is classified as a rare disease, and there were 1,221 patients registered in the UK by December 2015 [37], the study sample is representative of the general population.

Directions for practical implications of the results and further research are outlined in Supplementary Material, Section 5.

Limitations of the present study

First, our data are based on self-reported diagnosis. However, demographic characteristics, the disease symptoms, types of medications, perceived health status and symptom severity were consistent with previous papers on Behçet's Disease. Furthermore, we provide raw data in the Open Access Repository which includes all variables and additional information about the sample in our study. By providing the raw data, we encourage other researchers to create a database which could be useful for

accumulating existing knowledge about psychological, medical and socio-demographic

aspects of Behçet's Disease, and supporting the development of interventions.

Second, all variables in the present study were measured using validated (and

accepted by the NHS) measurements of perceived health status, illness perception and

the severity of Behçet's Disease. However, due to the majority of the data being

collected using an online survey, there was a chance of residual confounding.

Third, a prevalence of female respondents over males in our study was 5.4 : 1.

Although the previous study in the UK with a larger sample size reported similar sample

characteristics (22), it may not be representative for groups of BD patients in other

countries.

Fourth, the design of our study is cross-sectional and therefore, possesses the

limitations of this design. However, due to the nature of the variables that were taken

into mediation analyses, it is unlikely that our findings reflect any 'time-limited'

relationship between the variables.

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Figure 1. Patients' beliefs of the causes of their illness

Figure 2. Illness perception (CQ – consequences of illness, TL- timeline of illness, PC - personal control, TR – treatment control, ID – identity of illness, CS – concerns, UN – understanding illness, ER – emotional representations). Health status (P – pain, SL – sleep, ER – emotional reactions, MB – mobility, SI – social isolation, EN – energy). Error bars represent +/-SEM

Figure 3. Models tested in the present study. BDCAF – severity of BD symptoms - independent variable; Illness perception (Consequence, Identity, Emotional Representation, Concerns) are mediators; the NHP (Pain and Energy level) are dependent variables; a1-a4 in each model represent the effects of the independent variable on the mediators; b1-b4 represent the effects of the mediators on the dependent variables; c represents the direct effect of the independent variable on the dependent variables. Plain lines outline the main hypothesis tested in each model.

Table legends

Table 1. *Distribution of the sample by age category and sex*

Table 2. *BDCAF symptoms (N = 250, fem = 211).*

Table 3. Associations[1] between BD symptom severity (BDCAF), illness perception CQ – consequences of illness, TL- timeline of illness, PC - personal control, TR – treatment control, ID – identity of illness, UN – understanding illness, CS – concerns, ER – emotional representations) and health status (P – Pain, SL – sleep, ER – Emotional Reactions, MB – Mobility, SI – Social Isolation, EN – Energy)

Table 4. Summary of mediation analyses for Model 1 and Model 2. IV-independent variable; DV - dependent variables; BDCAF - severity of BD symptoms; P-Pain, EN = Energy level, CQ = Consequences, ID - Identity, ER - Emotional Representation, CS - Concerns

Supplementary Material

Illness perception mediates the relationship between the severity of symptoms and perceived health status in patients with Behcet's disease

Yankouskaya A, Boughey A, McCagh J, Neal A, de Bezenac C, Davies SJ

Section 1. Distribution of sample by age category and symptom onset before medical diagnosis of BD

Table S1. *Distribution of sample by age category and symptom onset before medical diagnosis of BD*

	Disease duration				
Age	1 - 5 years	6 - 10 years	11 - 15 years	15 + years	Total
18-29	29	14	2	1	46
30 - 44	59	21	12	14	106
45 - 59	35	17	8	21	81
60+	5	2	1	9	17
Total	128	54	23	45	250

Table S2. *Distribution of sample by age category and disease duration (after receiving the diagnosis)*

	Disease duration				
Age	1 - 5 years	6 - 10 years	11 - 15 years	15 + years	Total
18-29	22	12	8	4	46
30 - 44	29	14	15	48	106
45 - 59	12	14	12	43	81
60+	0	0	1	16	17
Total	63	40	36	111	250

It has to be noted that the majority of existing research on BD focuses on medical aspects of its symptomology and reports a duration of disease from the time of medical diagnosis. However, our data indicate that symptom onset occurs much earlier (Tables S1 and S2), almost doubling the time of its impact on well-being. Although progress has been made in clarifying diagnostic criteria for BD, medical decisions are mainly based on specific patterns of symptoms. In the case of

incomplete patterns, the diagnosis and therefore, an appropriate treatment, is delayed
to rule out any other causes of these symptoms. This fact needs to be taken into
account when assessing a patient's health profile and the impact of BD on well-being.

**Section 2. Whether illness perception in BD patients differs other people suffering
from chronic conditions**

Previous research indicated that illness perceptions are purported to be disease-
specific. To examine whether illness perception in BD patients differs from other people
suffering from chronic conditions, we performed analysis of variance (ANOVA) using
summary data (N – sample size, M – mean, and SD – standard deviation) from
published studies (Table S3). One of the studies was selected based on symptoms
shared with BD patients (rheumatoid arthritis) [1]. The second study had patients with
life-threatening conditions (cardiovascular and ischemic heart diseases) [2]. Both
studies had similar sample characteristics.

Table S3. *Average profile of illness perception in BD patients in the present study*
(Group 1, N=250) and two groups of patients with long-term conditions from previous
studies: Rheumatoid arthritis patients (RA, Group 2, N=292) and cardiovascular disease
(CVD/IHD, Group 3, N=235).

Illness* perception	Group 1	Group 2	Group 3	ANOVA F(2,774)	**Tukey HSD Post-hoc Test D=difference CI =99%confidence interval
CQ	7.62 (2.2)	7.14 (2.3)	7.68 (2.4)	4.51 p=.01	Group 1 vs Group 2: D=0.48, CI [-0.1; 1.1], p= .04 Group 1 vs Group 3: D=-0.06, CI [-0.67; 0.55], p=.9
TL	8.81 (2.3)	8.27 (2.6)	6.21 (2.2)	80.7 p<.001	Group 1 vs Group 2: D=0.54, CI [-0.06; 1.4], p=.02 Group 1 vs Group 3: D=2.6, CI [1.9; 3.2], p<.001
PC	3.22 (2.2)	7.25 (2.0)	3.76 (1.5)	350.6 p<.001	Group 1 vs Group 2: D=-4.03, CI [-4.5; 3.5], p<.001 Group 1 vs Group 3: D=-0.54, CI [-1.1;0.03], p=.006

TR	4.43 (2.8)	8.21 (1.8)	6.26 (0.9)	242.3 p<.001	Group 1 vs Group 2: D=-3.8, CI [-4.28;3.27], p<.001 Group 1 vs Group 3: D=-1.8, CI [-2.4; -1.3], p<.001
ID	7.57 (1.9)	5.92 (2.2)	4.39 (0.9)	190.2 p<.001	Group 1 vs Group 2: D=1.65, CI [1.19; 2.1], p<.001 Group 1 vs Group 3: D=3.2, CI [2.7;3.65], p<.001
UN	6.56 (2.8)	5.89 (2.7)	3.7 (1.5)	91.2 p<.001	Group 1 vs Group 2: D=0.7, CI [0.05; 1.3], p=.004 Group 1 vs Group 3: D=2.9, CI [2.2;3.5], p<.001;
CS	7.9 (2.2)	7.86 (2.6)	7.38 (2.6)	3.5 p=.03	Group 1 vs Group 2: D=-0.01, CI [-0.6; 0.6], p=.9; Group 1 vs Group 3: D=-0.5, CI [-1.2; 0.14], p=.06
ER	7.5 (2.4)	6.27 (3.1)	4.27 (0.9)	112.4 p<.001	Group 1 vs Group 2: D=-1.2, CI [-1.8; -0.6], p<.001 Group 1 vs Group 3: D=-3.2, CI [-3.8; -2.6], p<.001

*CQ – consequences of illness, TL- timeline of illness, PC - personal control, TR – treatment control, ID – identity of illness, UN – understanding illness, CS – concerns, ER – emotional representations
**Tukey's HSD Post Hoc test (with the harmonic mean of n-sizes as n to compare groups with unequal sample sizes) was used to maintains alpha levels for multiple tests

Table S2 indicates that illness perception in BD patients differs from patients suffering from RA and CVD/IHD. BD people showed significantly lower personal control over the illness and treatment, higher emotional response, identification with the illness and understanding. The most striking differences reflect emotional representations about the illness and perception of illness identity. Patients with BD are significantly more emotionally distressed compared to patients with rheumatoid arthritis and vascular diseases. This negative emotional perception of illness is noteworthy, as it has been shown to negatively influence emotional adjustment, health-related outcomes and non-adherence to treatment across other severe [3] and chronic illness populations [4,5]. Previous research linked patients' beliefs about the impact of their illness on emotional wellbeing to negative interpretations of the situation (catastrophizing), illness threats, perceived availability of support from close people, and economic and family problems attributed to illness [6]. To date, no studies have looked specifically at core factors

triggering negative emotional reactions in BD patients that limits the development of health care provision, and psychological and social care services.

One of the cognitive mechanisms underlying developing coping strategies in patients with a long-term condition is determining psychological ownership of the illness. It was suggested that the epiphanic moment of diagnosis is a significant life event that led down the path of identity reconstruction, interpretation, and acceptance of the reality of living with a long-term condition which are important prerequisites in coping with the consequences of a disease on a daily basis [7]. As an individual reflexively interprets a long-term condition as a part of 'the self', the identification with a long-term illness is fixed as an idea of control over the illness [8] and responsibility towards the disease state, resulting in an enhanced sense in maintaining or protecting one's identity.

The results of our study suggest that illness perception in BD patients is associated with low personal control over the illness[1]. The level of personal control in our BD patients (3.22 +/-2.2) is significantly lower compared to groups of patients with other long-term condition (7.25+/-2.0; 3.76+/-1.5). However, the perception of the illness identity showed the opposite pattern (7.57+/-1.9 in BD patients compared to 5.92+/-2.2 and 4.39+/-0.9 in RA and CVD patients respectively). Moreover, we found a weak but significant negative correlation between the level of personal control and illness identity (r=-0.23, p<.001, BCa 95% CI [-0.353, -0.114]). This finding indicates that the more symptoms BD patients attribute to the illness, the less control they feel over the illness, and, as a result, decreasing the development of coping mechanisms. Although the low level of perceived personal control in BD patients may, partly, stem from medical issues (such as the delayed diagnosis, unclear causes of the disease and triggering factors), the role of clinical psychologists in facilitating CBT and online guided self-help

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[1] Similar result is reported in Grayson et al., 2013

programmes on developing adaptive coping strategies in patients with BD will be invaluable.

Section 3.

3.1 The effects of illness duration on illness perception in BD patients

Separate analyses of variance were performed to test the effect of illness duration on cognitive and emotional aspects of illness perception. Participants were divided into 4 groups based on the duration of BD (after medical diagnosis): up to 5 years, from 6-10 years, from 11-15 years, and over 15 years. The average scores of illness perception in each group are displayed in Figure S1
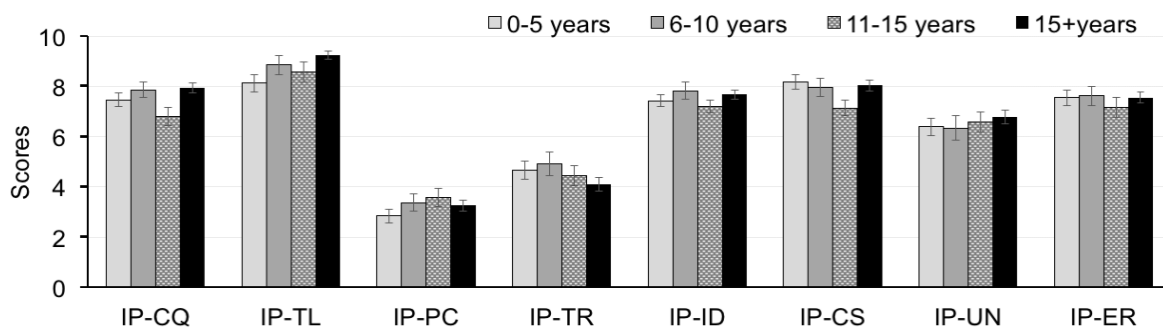

Figure S1. Average scores of illness perception in four groups BD participants. Error bars represent +/- SEM

The results of eight between-subject ANOVAs are summarized in Table S3.

Post Hoc tests using Bonferroni adjustment for multiple comparisons revealed that there was a significant difference between 11-15 years duration and 15+ years (p=.005) for consequence (CQ) and between 0-5 years and 15+ years (p=.009) for timeline (TL). No other significant terms were found here.

Table S3. *The results of between-subject ANOVAs comparing the difference in eight dimensions of illness perception between four groups of participants (with 0-5 years of BD disease, 6-10 years, 11-15 years and over 15 years)*

	Sum of Squares	*df*	Mean Square	F	Sig	*Post Hoc analysis

IP_CQ	38.37	3	12.79	2.81	0.04	11-15 vs 15+ years, p=.005
IP_TL	53.01	3	17.67	3.61	0.014	0-5 vs 15+ years, p=.009
IP_PC	15.03	3	5.01	1.02	0.39	n.s
IP_TR	25.33	3	8.44	1.09	0.35	n.s
IP_ID	10.39	3	3.47	0.95	0.42	n.s
IP_CS	27.63	3	9.21	2.0	0.11	n.s
IP_UN	8.82	3	2.94	0.36	0.78	n.s
IP_ER	5.16	3	1.72	0.3	0.82	n.s

*p-values are adjusted using Bonferroni correction

3.2. The effects of illness duration on perceived heath status (measured by the NHP) in BD patients
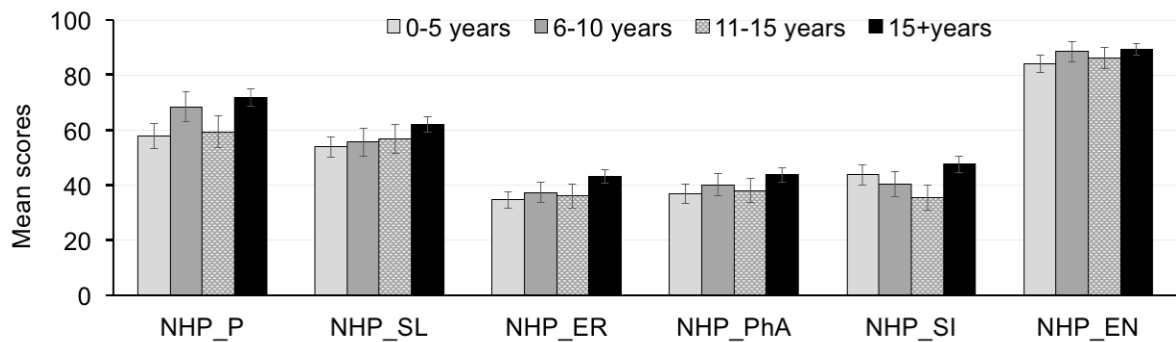

Figure S2. Average scores of perceived health status in four groups BD participants with different length of BD duration. Error bars represent +/- SEM

Separate ANOVAs were carried out to test the effect of the disease duration on the NHP dimensions. These analyses are summarized in Table S4.

Table S4. *The results of between-subject ANOVAs comparing the difference in six subscales of perceived health status in BD patients (with 0-5 years of BD disease, 6-10 years, 11-15 years and over 15 years)*

	Sum of Squares	*df*	Mean Square	F	Sig
NHP_P	9833.63	3	3277.86	2.79	0.041
NHP_SL	3046.84	3	1015.61	1.1	0.35
NHP_ER	3530.55	3	1176.85	1.85	0.139
NHP_PhA	2212.55	3	737.52	0.982	0.402
NHP_SI	4701.65	3	1567.22	1.73	0.162
NHP_EN	1202.37	3	400.79	0.757	0.519

Post Hoc test with Bonferroni correction for multiple comparisons showed no significant difference across the disease duration for each NHP subscales.

Section 4

Prior to the modelling of data, we assessed multicollinearity between the outcome variables by estimating variance inflation factors (VIF). The VIF estimates how much variance of the estimated regression coefficient is "inflated" by the existence of correlation amongst the independent variables in the model:

$$VIF=1/(1-R^2),$$

where the denominator is the percent of variance in the predictor that cannot be accounted for by other predictors.

A VIF of 1 means that there are no correlations among an $X(i)$ predictor and the remaining predictor variables, and hence the variance of the regression coefficient is not inflated. If a VIF exceeds 4, a further investigation of multicollinearity is needed.

4.1 Assessing the assumption of multivariate normality for mediation analyses

Assessing the assumption of multivariate normality was performed using the MVN package in R (version 4.0.2). We report here Mardia's test to compute multivariate skewness and kurtosis coefficients as well as their corresponding statistical significance.

Table S5. Summary of multivariate normality test MVN

g1p	: 34.42962
chi.skew	: 1434.568
p.value.skew	: 4.651011e-56
g2p	: 271.1246
z.kurtosis	: 5.644752
p.value.kurt	: 1.654193e-08
chi.small.skew	: 1453.955
p.value.small	: 2.684789e-58

Table S5 indicates that the skewnwss (denoted as g1p) and kurtosis (denoted as z.kurtosis) do not indicate multivariate normality. To inspect the data, we created Chi-Square Q-Q plot (Figure S3).
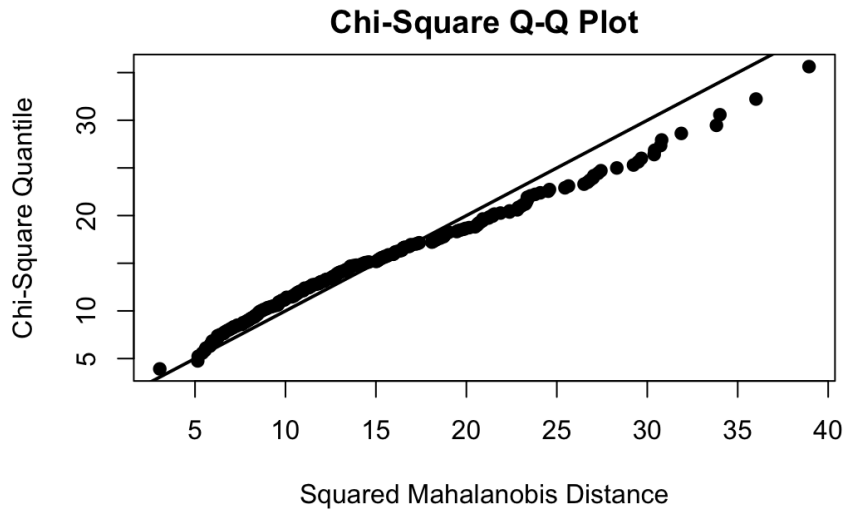
Chi-Square Q-Q Plot

Figure S3. Chi-Square Q-Q plot for mediation data set.

Figure S3 indicates some deviations from the straight line suggesting possible departures from a multivariate normal distribution. Taken together, we can conclude that our data do not satisfy MVN assumption of multivariate normality.

4.2 Modelling mediation effects

To examine the indirect effects, we used the product-of-coefficients tests, where the estimates of the indirect effects are divided by its standard error. The estimates of the individual mediated effects can then be summed to form an estimate of the total mediated effect. The main limitation of the product-of-coefficients tests is that the resulting statistics are compared with a normal distribution to test for significance. The sampling in our study violates the assumption of multivariate normality (Table S5, Figure S3), and therefore, leaving the chance that the product of two non-normally distributed variables will also violate the assumption of normality. To overcome this

issue, we used bootstrapping, a nonparametric method that does not assume that the distribution of the product is normal.

Section 5

Directions for practical implications of the results and further research:

1. Consequences are cognitive representations of illness reflecting patient's beliefs of how much the illness affects his/her life. A number of studies have demonstrated that greater *perception of an illness* influence is associated with dysfunctional *coping strategies* in response to illness-related stressors [9], avoidance coping strategies [10], diminished help-seeking behavior [11], and mental and behavioural disengagement [12]. Interventions aiming to adapt the perception of consequences to be more realistic and, possibly, separating them from emotional representations, may help to enhance adaptive coping mechanisms in patients with BD.

2. Advances in current medical and health care practice have made progress in terms of the diagnosis, pathogenesis and etiology of BD. However, there are still no specific diagnostic tests. Furthermore, various diagnostic criteria have been proposed around the world. As the clinical expressions of **Behçet's** Disease are heterogeneous, there is a chance to misrepresent symptoms of the disease as either comorbid or a short-term illness unrelated to BD (e.g., mouth ulcers caused by a number of other conditions). These misrepresentations may lead to misidentification of the disease symptoms resulting in the elevated perception of BD identity. This may explain high scores on the perception of illness identity in BD patients (7.57) compared to other long-term conditions (5.93, 4.39) in our study.

3. Our data showed a strong positive correlation between perception of the illness consequences and perception of illness identity (r=.61, p <.001, 95% BCa CI [.49, .69]) and both dimensions showed a mediation effect on perceived pain. This relationship,

potentially, may be considered as a target for CBT for BD patients. Targeting perception of the disease identity and perception of the anticipated consequences of **Behçet's** Disease may reduce sporadic pain-related psychological and physical functions, both alone and as an adjunct to other treatment.

4. Mediation analysis in the present study demonstrated that in contrast to our hypothesis that both concerns and emotional representations about the illness mediate the relationship between BDCAF scores and perceived energy level, only indirect effect 'BDCAF – emotional representations – energy' was significant. This finding suggests that negative emotional representations about the illness may facilitate feelings of tiredness and lack of energy. The importance of this finding reflects a strong relationship between emotional representations of illness and coping strategies which may be used in planning Cognitive Behavioural (CB) Interventions with a BD cohort. Of potential interest for the CB interventions may be specific emotions underlying these emotional representations about **Behçet's** Disease (e.g., embarrassment, guilt, sadness). Such emotions are easily assessed and likely to have different antecedents, although no studies have sought to examine the cognitive antecedents of these emotions in BD patients yet. Further studies may aim to address this gap.

5. **The relationship between variables in our study reflects a patients' perspective, which can be different from a health providers perspective. Performing research where both perspectives can be compared or taken into account will provide better understanding between patients with Behçet's Disease and health providers, and as a result, better treatment outcomes.**

6. **Behçet's Disease is a long-term condition with unclear etiology, disease pattern, treatment outcomes and life expectancy. People who live with this disease need support from partners, family, friends, and relatives. At this time we have a limited understanding of the role of close social support in alleviating**

the impact of negative emotional appraisal in BD patients. Research linking the effects of social support, negative emotional appraisal, and life satisfaction will help to facilitate programmes for both patients to enable them to do the things that are important to them and their *families,* **and their close support network to develop skills necessary to provide support for individuals with BD.**

7. Longitudinal work is needed to assess the dynamics of illness perception, quality of life and symptom severity to design interventions for the improvement of psychological health among people with **Behçet's** Disease.

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Figure1

Figure2

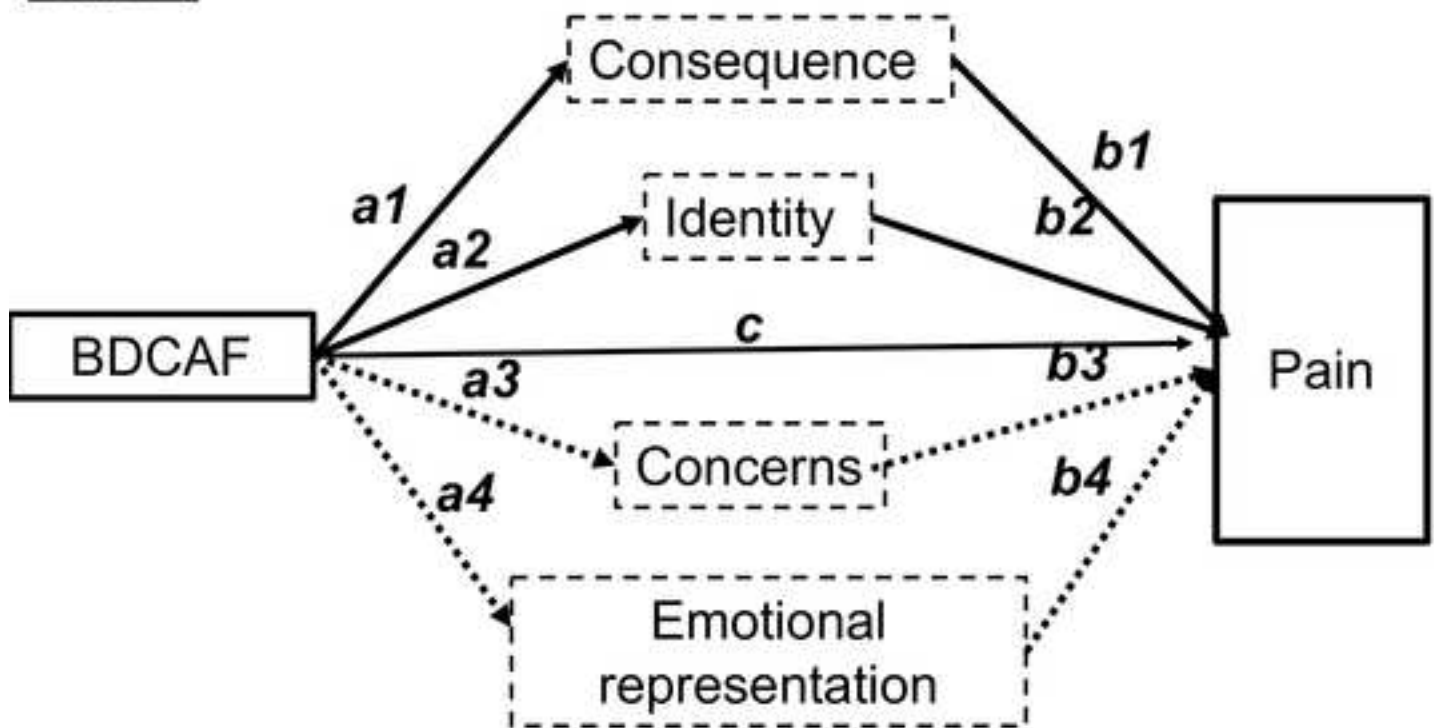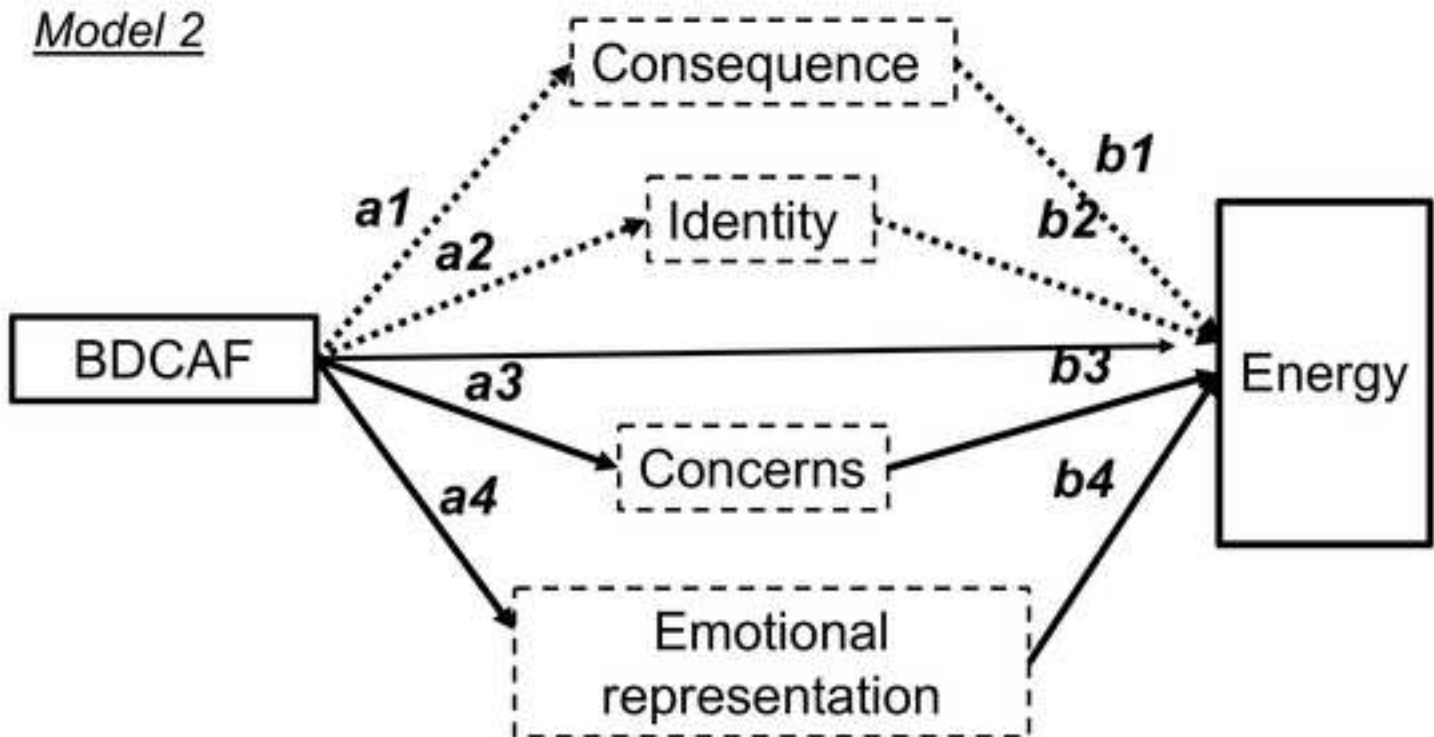Figure3   Click here to download Figure Figure3.tiff ⬇
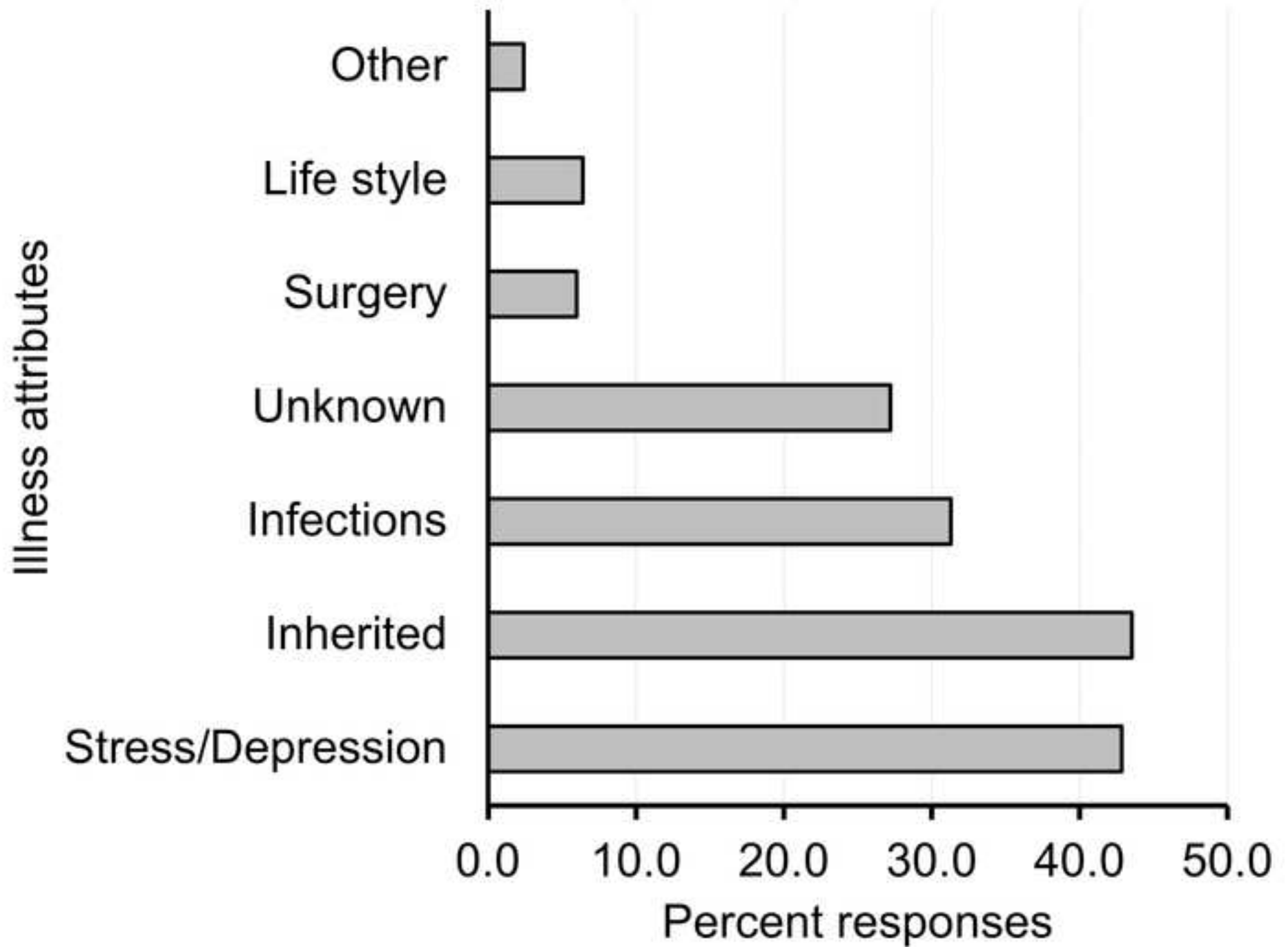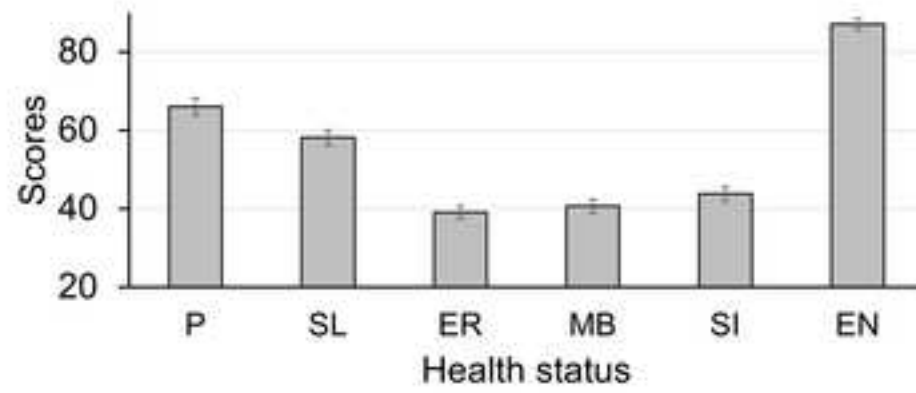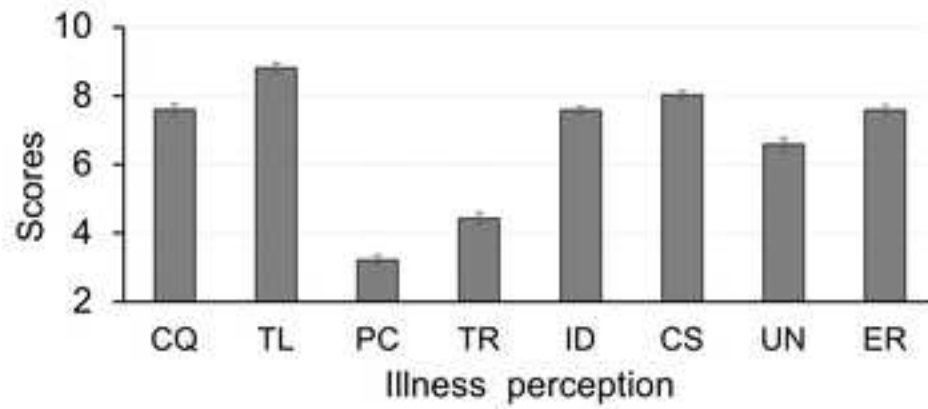
Symptoms severity (IV) — Illness perception (M) — NHP (DV)

Model 1

Model 2

Table 1. *Distribution of the sample by age category and sex*

| | Sex | | |
Age	Female	Male	Total
18-29	39	7	46
30 - 44	87	19	106
45 - 59	72	9	81
60+	13	4	17
Total	211	39	250

Table 2. *BDCAF symptoms (N = 250, fem = 211).*

Symptom	Symptom presence	Females	Males	Total	Missing responses
Headache	no	69	18	87	1
	yes	141	21	162	0
Mouth ulcer	no	59	21	80	0
	yes	152	18	170	0
Genital ulcer	no	100	31	141	0
	yes	101	8	109	0
Erythema	no	144	30	174	0
	yes	67	9	76	0
Pustules	no	98	19	117	0
	yes	113	20	133	0
Joints Arthralgia	no	87	20	107	0
	yes	124	19	143	0
Nausea/ Abdominal pain	no	74	26	100	0
	yes	137	13	150	0
Diarrhoea	no	127	26	153	0
	yes	84	13	97	0

Table 3. Associations[1] between BD symptom severity (BDCAF), illness perception CQ – consequences of illness, TL- timeline of illness, PC - personal control, TR – treatment control, ID – identity of illness, UN – understanding illness, CS – concerns, ER – emotional representations) and health status (P – Pain, SL – sleep, ER – Emotional Reactions, MB – Mobility, SI – Social Isolation, EN – Energy)

	P	SL	ER	MB	SI	EN	BDCAF
ICQ	[2].53**	.26*	.22	.43**	.27*	.42**	.41**
TL	.10	-.01	.11	-.02	.11	.13	.21
PC	-.08	-.08	-.13	-.06	-.24	-.15	-.23
TR	-.03	-.11	-.22	-.00	-.14	-.06	.05
ID	.50**	.25*	.23	.43**	.22	.37*	.41**
CS	.28*	.20	.21	.30*	.21	.44*	.23*
UN	.05	-.12	-.19	.02	-.12	.01	.03
ER	.28*	.24	.38**	.26*	.35**	.49**	.36**
BDCAF	.33*	.19	.18	.22	.19	.28*	

[1] Pearson correlation coefficient with Bonferroni correction of alpha .05/N of tests (=.00093)

[2] correlations significant at the adjusted alpha (two tailed): *$p<0.05$; **$p<0.01$;

Table 4. Summary of mediation analyses for Model 1 and Model 2. IV-independent variable; DV - dependent variables; BDCAF - severity of BD symptoms; P-Pain, EN = Energy level, CQ = Consequences, ID - Identity, ER - Emotional Representation, CS - Concerns

IV	a-paths $(IV \rightarrow M)$	M	b-paths $(M \rightarrow DV)$	DV	Indirect effect $a_n \times b_n$	95 % CI of indirect effect
Model 1						
BDCAF	a1=0.40***	CQ	b1=0.33***	P	a1xb1=0.13**	^{nz}0.009, 0.32
BDCAF	a2=0.41***	ID	b2=0.26***	P	a2xb2=0.11**	^{nz}0.06,0.26
BDCAF	a3=-0.15	CS	b3=0.02	P	a3xb3=-0.001	-0.04,0.03
BDCAF	a4=0.37***	ER	b4=-0.09	P	a4xb4=-0.008	-0.09,0.07
c=0.091, p=.11						
Total effect := c+a1xb1+a2xb2+a3xb3+a4xb4 = 0.32, p<.001, CI [0.28, 0.64]						
Contrast :=a2xb2 – a1xb1 = 0.026, p = .69						
Model 2						
BDCAF	a1=0.40***	CQ	b1=0.12	EN	a1xb1=0.05	-0.001,0.11
BDCAF	a2=0.41***	ID	b2=0.06	EN	a2xb2=0.02	-0.03,0.09
BDCAF	a3=-0.15	CS	b3=0.21*	EN	a3xb3=-0.03	-0.01,0.03
BDCAF	a4=0.37***	ER	b4=0.29***	EN	a4xb4=0.11**	^{nz}0.05,0.18
c=0.045, p=.45						
Total effect := c+a1xb1+a2xb2+a3xb3+a4xb4 = 0.19, p=.005, CI [0.06,0.32]						
Contrast :=a4xb4 – a3xb3 = 0.139, p = .003						

a-paths, b-paths – standardized estimates

95% CI – confidence intervals (bias-corrected, based on 1,000 bootstrap re-samples)

^{nz} 95 % CI does not include zero

*p<0.05; **p<0.01; ***p<0.001