


The assessment of presenteeism and activity impairment in Behçet's syndrome and recurrent aphthous stomatitis: a multicentre study

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Abstract

Objective. To evaluate key factors for presenteeism and activity impairment in multinational patients with Behçet's syndrome (BS) and recurrent aphthous stomatitis (RAS).

Methods. In this cross-sectional study, 364 BS patients from Jordan, Brazil, the United Kingdom and Turkey and 143 RAS patients from the United Kingdom and Turkey were included. The Work Productivity Activity Impairment (WPAI) scale was used for presenteeism and activity impairment. Mediation analyses were performed to evaluate both direct and indirect causal effects.

Results. Presenteeism score was higher in active patients with genital ulcers and eye involvement as well as patients with comorbidities and current smokers than the others in BS ($P < 0.05$). In RAS, presenteeism score was elevated by oral ulcer activity in the direct path ($P = 0.0073$) and long disease duration as a mediator in the indirect path ($P = 0.0191$). Patients with active joint involvement had poor scores in absenteeism, presenteeism, overall impairment and activity impairment compared with those of inactive patients ($P < 0.05$). Using mediation analysis, the activity impairment score was directly mediated by joint activity ($P = 0.0001$) and indirectly mediated through oral ulcer-related pain in BS ($P = 0.0309$).

Conclusion. In BS, presenteeism was associated with disease activity, presence of comorbidities and being a current smoker, whereas in RAS, presenteeism was associated with oral ulcer activity and increased length of the disease. Moreover, activity impairment was adversely affected by joint activity and oral ulcer related pain in BS. Patients need to be empowered by using appropriate treatment strategies in their working environment and daily life.

Key words: Behçet's syndrome, aphthous stomatitis, presenteeism, daily activity, mediation analysis

Rheumatology key messages

- Presenteeism was associated with genital ulcer, joint involvement and eye involvement.
- Activity impairment was mediated by oral ulcer-related pain indirectly and joint activity directly in Behçet's syndrome.
- Oral ulcer was a risk factor for productivity loss and activity impairment in recurrent aphthous stomatitis.

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Introduction

Productivity loss is an important condition not only for employees with chronic disease but also organizations in a working environment. The fundamental characteristics of productivity loss cause a decrease in income level and economic independence, as well as a rise in the risk of poverty in employees with chronic disease. Furthermore, productivity loss as an indirect cost element may have a greater effect than direct costs in the setting of any health policy directive. The absence from work, with effects on presenteeism results in underperformance in the working environment and consequent early retirement of employees, which may have deleterious effects on organizations [1–3]. There is a relationship between employability, maintenance of work, disease burden and interventions in chronic diseases [4–6].

The clinical presentation of Behçet's syndrome (BS) is one of unpredictable relapsing and remitting episodes of disease activity. Mucocutaneous manifestations such as oral, genital ulcers and joint involvement adversely affect the patient's quality of life. In addition, blindness, arterial aneurysms, deep venous thrombosis, disability, mortality and morbidity are seen in the severe clinical spectrum [7–13]. Direct and indirect cost elements are associated with the severe disease spectrum [14]. Furthermore, the presence of major organ involvement of ocular [15] and vascular [16] involvement, male gender, being a smoker, the early period of disease and immunosuppressive treatment are associated with productivity loss in BS [16]. From this perspective, the assessment of relationships between productivity loss, daily activity impairment and disease activity would be helpful when performing clinical trials targeting therapies of patient-focused unmet needs in multinational BS patients. Because oral ulcer activity is common in BS, the study is designed to address whether it has a mediator role in activity impairment and loss of productivity. The mediator explains the occurrence of the relationship that occurs between dependent and independent variables [17, 18]. Another essential point is that productivity loss is an underestimated problem for patients with recurrent aphthous stomatitis (RAS) even though different patient-reported outcome measures are used in oral medicine [12, 19, 20].

The primary aim of the study was to evaluate key factors for presenteeism and daily activity impairment in a multinational cohort of BS patients. The secondary aim was to analyse the relationship between the oral ulcer pattern, productivity loss and daily activity impairment in RAS and compared with BS.

Methods

Patients and controls

In this cross-sectional multinational study, 364 patients with BS [F/M: 185/179; 40.8 (11.04) years] diagnosed according to ISG criteria [21] in tertiary outpatient clinics

from Jordan, Brazil, the United Kingdom and Turkey were included (Table 1). The study was performed according to the principles of the Declaration of Helsinki and was approved by the Ethical Committee of Marmara University Medical School (09.2017.497). Patients gave written informed consent.

Patients with RAS [F/M: 71/72, 40.4 (14.16) years] in oral medicine clinics from the United Kingdom and Turkey were an age and gender-matched control group. The inclusion criteria were being adult patients (≥ 18 years of age) and under medical supervision for BS and RAS. The presence of rheumatic diseases and other chronic conditions that were the cause of oral ulcers, productivity loss and activity impairment were exclusion criteria. Data were collected from February 2018 to September 2019. The data is available from the corresponding author.

Organ involvement, disease duration, treatment protocols, oral and genital ulcer-related factors regarding pain, number and healing time of ulcers were recorded in BS. Almost two-thirds of BS patients were treated with immunosuppressive medication (IS; $n = 227$, 62.36%). These are azathioprine, high dose corticosteroids, interferon- α and anti-TNF- α in the severe disease course. One-third of the group were using non-immunosuppressive (non-IS) medication including colchicine, sulfasalazine, NSAIDs and antibiotics ($n = 121$, 33.24%). In addition, 16 patients (4.4%) were not taking any medication in the BS group.

In the study, 90 patients (24.7%) presented with a mild clinical course (mucocutaneous and joint involvement), while 274 (75.3%) patients had a more severe clinical course (major organ involvement).

The oral ulcer pattern and oral ulcer-related pain scores were recorded in patients with RAS. These patients without systemic disease were mainly treated with topical medication ($n = 135$, 94.4%).

Patient-reported outcome measures (PROMs)

Work productivity activity impairment (WPAI)

Productivity loss regarding presenteeism, overall work impairment (presenteeism and absenteeism) in the employed group and activity impairment for all patients were evaluated using WPAI to assess both paid and unpaid work during the last seven days prior to the clinic appointment. High scores indicate greater impairment in the scale. Turkish, Arabic, English and Brazilian Portuguese versions are available [22]. The scale was validated in BS patients in our previous study [15].

Behçet's disease current activity form

Disease activity was assessed by Behçet's disease current activity form (BDCAF) during the last 4 weeks. Transformed BDCAF score was used in the analysis [23, 24].

TABLE 1 The profile of patients with Behçet's syndrome and recurrent aphthous stomatitis

	Behçet's syndrome (n = 364)		Recurrent aphthous stomatitis (n = 143)		P
	Mean	S.D.	Mean	S.D.	
Age (years)	40.8	11.04	40.4	14.16	0.666
Education period (years)	10.53	4.29	13.23	2.69	0.000
Working h per day	40.0	12.8	33.84	9.81	0.000
Disease duration (years)	10.78	7.94	15.3	12.5	0.013
Number of medical visits	4.2	3.24	1.07	1.23	0.000
Number of oral ulcers	3.17	2.78	3.26	2.67	0.383
Healing time of oral ulcers	6.69	4.89	11.41	5.58	0.000
Oral ulcer-related pain	2.25	2.45	3.68	1.18	0.000
	n	%	n	%	
Male	179	49.18	72	50.3	0.889
Female	185	50.82	71	49.7	
Total	364	100	143	100	
<i>Organ involvement</i>					
Oral ulcer	364	100.00	143	100	
Genital ulcer	296	81.32			
Cutaneous involvement	293	80.49			
Musculoskeletal involvement	212	58.24			
Eye involvement	181	49.73			
Vascular involvement	86	23.63			
Nervous system involvement	70	19.23			
Gastrointestinal involvement	37	10.16			
Pathergy positivity	238	65.38			

Bold indicate the statistical significance of $P < 0.05$.

Reliability and validation of work productivity and activity impairment

Internal consistency was examined by computing Cronbach's alpha values for the last two items with the same scoring method. These were 0.844 in BS (0.704 in Brazil; 0.722 in Jordan, 0.834 in UK and 0.900 in Turkey) and 0.886 in RAS (0.913 in UK; 0.865 in Turkey). Test-retest results of WPAI were carried out at an interval of 4 weeks in clinically stable patients ($n=10$) in the external reliability. In construct validity, patients with absenteeism (score ≥ 1), presenteeism (score ≥ 1), overall impairment (score ≥ 1) and activity impairment (score ≥ 1) were assessed according to global disease activity by using BDCAF score in BS (0: inactive vs ≥ 1 : active).

The effects of oral ulcer activity in RAS (0: inactive vs ≥ 1 : active) were also examined in this perspective.

Pain status

Pain status was evaluated by using a 5-point Likert type scale (0 point: no pain vs 4 points: the worst pain status) for oral ulcer in BS and RAS and genital ulcers in BS during the last month.

Statistical analysis

Data were analysed by using SPSS 26.0 statistic program (SPSS Inc, Chicago, IL, USA). Non-parametric analysis

regarding Mann-Whitney U test and Spearman correlation test were used due to the non-normal distribution of data. χ^2 tests were used for categorical variables. In the study, $P \leq 0.05$ was accepted as statistically significant.

Mediation analysis

Possible independent and mediator variables were selected for WPAI domains as dependent variables after primary statistical analysis. Then, mediation analyses were performed to evaluate both direct and indirect causal effects among variables in BS and RAS by using PROCESS macro adopted in SPSS [17]. Activity in joint involvement (0: inactive vs 1: active) as an independent variable, oral ulcer-related pain as the mediator (continuous data) and WPAI-activity impairment as a dependent variable (continuous data) were in the mediation model in BS.

Two mediation models were compiled in RAS. Presenteeism in the first model and overall impairment in the second model were used as dependent variables (continuous data). Oral ulcer activity (0: inactive vs 1: active) was an independent variable and disease duration (continuous data) a mediator for both models.

Results

Even though the number of the oral ulcers was found to be similar in BS and RAS ($P = 0.383$), prolonged healing

TABLE 2 Employment, smoking, comorbidities and WPAI subgroups in Behçet's syndrome and recurrent aphthous stomatitis

	BS		RAS		P
	n	%	n	%	
Employment status					
Employed	196	53.8	116	81.1	0.000
Unemployed	168	46.2	27	19.8	
Total	364	100	143	100	
Smoking habits					
Non-smoker/past smoker	289	79.4	101	70.6	0.03
Current smoker	75	20.6	42	29.4	
Total	364	100	143	100	
Comorbidity					
Comorbidity-present	113	31.04	—	—	
Comorbidity-absent	251	68.95	—	—	
Total	364	100	—	—	
		Active patients ^a			
	n	%	n	%	
WPAI subgroups					
Absenteeism (score ≥ 1) ^b	21	87.5	52	98.1	
Presenteeism (score ≥ 1) ^b	105	84	88	90.7	
Overall impairment (score ≥ 1) ^b	108	84.4	88	90.7	
Activity impairment (score ≥ 1) ^b	209	77.1	95	91.3	
	Mean	s.d.	Mean	s.d.	
Scores WPAI subgroups					
• Absenteeism (%)	2.92	9.67	10.73	15.78	0.000
• Presenteeism (%)	29.84	30.81	53.27	35.65	0.000
• Overall impairment (%)	31.43	31.16	55.04	35.91	0.000
• Activity impairment (%)	39.69	32.90	34.05	33.1	0.088

Bold indicate the statistical significance of $P < 0.05$. ^aBDCAF score ≥ 1 in BS; presence of oral ulcer in RAS. ^bAbsenteeism: $n=24$ in BS, $n=53$ in RAS; presenteeism: $n=125$ in BS, $n=97$ in RAS; overall impairment: $n=128$ in BS, $n=97$ in RAS; activity impairment: $n=271$ in BS, $n=104$ in RAS.

time and elevated pain score were seen in RAS than BS ($P=0.000$ for both). The number of visits in the previous year was higher in BS whereas disease duration was longer in RAS ($P=0.000$; $P=0.013$) (Table 1). The ratio of the current smokers was lower in BS (20.6%) than RAS (29.4%) ($P=0.03$) (Table 2).

Both the employment rate and education period were the lowest in comparison to those of RAS ($P=0.000$ for both) (Tables 1 and 2). Full-time employment was commonly seen in both groups (full-time employment: 86.73% in BS vs 93.96% in RAS; part-time and self-employment: 6.63% for both in BS; vs 2.58%, 3.45% in RAS), respectively. Self-reported unemployment due to health problems ($n=48$, 13.18%) was associated with major organ involvement ($n=38$; 79.2%), with mucocutaneous and joint involvement ($n=10$, 20.8%) in BS.

In the employed group, the scores for absenteeism, presenteeism and overall impairment were lower in BS than those of RAS ($P=0.000$ for all). Activity impairment was similar in BS and RAS ($P=0.088$) (Table 2). No significant association was observed in WPAI

domains in relation to the gender in BS and RAS ($P > 0.05$). In BS, disease duration and education period were not associated with WPAI domains ($P > 0.05$) whereas education period was weakly correlated with scores of presenteeism and overall impairment in RAS ($r: 0.2$ $P=0.032$; $r: 0.2$ $P=0.034$).

Scores of activity impairment and BDCAF were significantly higher in females [41.70 (32.95); 4.96 (3.57)] than males [24.87 (27.42); 3.46 (2.91)] in mucocutaneous and joint involvement ($P=0.020$, $P=0.047$).

Self-reported working hours and gender

In the employed group ($n=196$ in BS vs $n=116$ in RAS), the ratio of males was higher (66.8%) than females (33.2%) in BS than in RAS (55.2% vs 44.8%, respectively) ($P=0.000$; $P=0.019$, respectively). The working hours per week was higher in BS [40.0 (12.8)] than RAS [33.84 (9.81)] ($P=0.000$). Male patients worked longer hours than females in BS [41.98 (12.18) vs 36.25 (13.19)] and RAS [36.53 (5.92) vs 30.57 (12.35)] ($P=0.005$; $P=0.000$, respectively).

In isolated eye involvement, weekly working hours were also higher in males [45.33(13.6)] than females in BS [34.21(10.11)] ($P = 0.002$).

Treatment protocol, comorbidity, smoking habit and WPAI in Behçet's disease

IS medications regarding azathioprine, high dose corticosteroids, interferon- α and anti-TNF- α ($n = 91$) were associated with elevated WPAI scores, except absenteeism in BS ($P < 0.05$). The scores for presenteeism and overall impairment were higher in current smokers ($n = 45$) and patients with comorbidities ($n = 52$) than patients without comorbidities and smoking habits ($P < 0.05$). Similarly, comorbidity and IS use were also associated with activity impairment ($P < 0.05$) (Table 3).

Disease activity, disease course and WPAI in Behçet's disease

Increases in the scores of presenteeism and overall impairment were found in patients with active genital ulcers ($n = 38$) ($P = 0.033$; $P = 0.025$), as well as in patients with active eye involvement ($n = 10$) ($P = 0.020$;

$P = 0.021$) compared inactive patients with no genital ulcer involvement and eye involvement. Patients with joint activity ($n = 47$) had higher scores of absenteeism, presenteeism and overall impairment than inactive patients ($P < 0.05$) (Table 3) (Fig. 1a). However, no significant relationship was observed in patients with cutaneous activity in relation to folliculitis and erythema nodosum ($P > 0.05$).

Scores of activity impairment were elevated in active clinical features of oral ulcers ($n = 226$; 62.1%), genital ulcers and joint involvement ($P = 0.032$; $P = 0.008$; $P = 0.000$) (Table 3). The pain score for oral ulcers [2.25(2.45)] correlated with the activity impairment score in mucocutaneous and joint involvement ($\rho: 0.3$; $P = 0.004$).

Mediation analysis was performed as patients with active oral ulcers could also have both joint activity ($n = 73$) and genital ulcer activity together ($n = 47$) ($P = 0.001$; $P = 0.003$). The score of activity impairment was directly mediated by joint activity ($B = 17.2897$; $P = 0.0001$) and indirectly mediated by oral ulcer-related pain ($B = 1.7005$; $P = 0.0309$) (Fig. 1b) (Table 4).

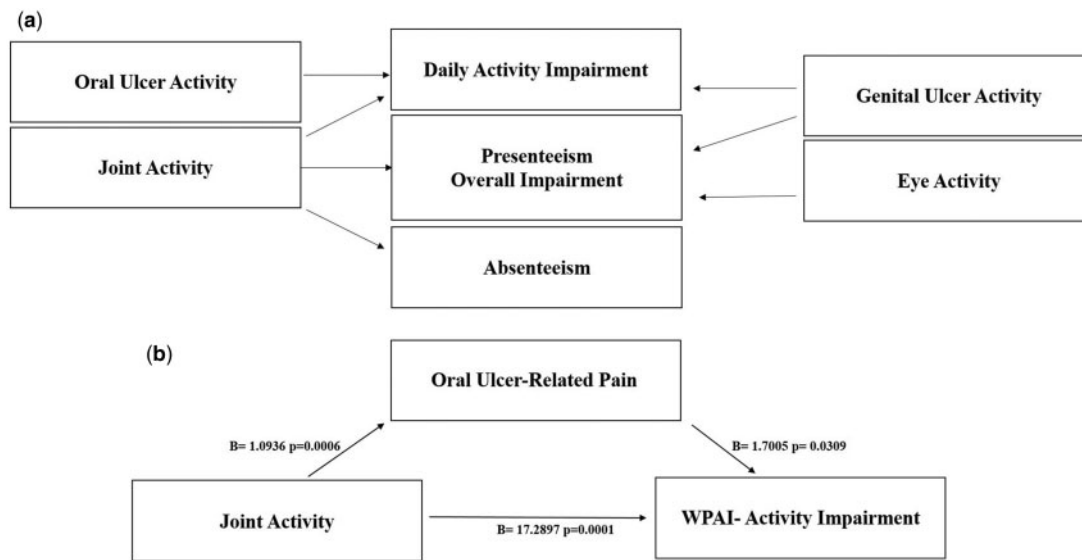
Bootstrap analysis with 5000 replications were applied to estimate mediation effects and to generate 95% CI.

TABLE 3 Percentages of WPAI subgroups and related factors in Behçet's syndrome and recurrent aphthous stomatitis

Behçet's syndrome	Absenteeism (%)	Presenteeism (%)	Overall impairment (%)	Activity impairment (%)
	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)	Mean (s.d.)
Oral ulcer-active ($n = 226$)	3.44 (10.66)	30.11 (30.73)	32.02 (31.34)	42.63 (34.01)
Oral ulcer-inactive ($n = 138$)	1.91 (7.33)	29.32 (30.11)	30.28 (31.01)	34.85 (30.51)
P	0.337	0.742	0.655	0.032
Genital ulcer-active ($n = 54$)	4.91 (10.25)	40.0 (33.11)	42.23 (32.71)	49.25 (33.46)
Genital ulcer-inactive ($n = 242$)	2.95 (9.57)	26.05 (28.68)	27.67 (29.15)	36.28 (32.28)
P	0.201	0.033	0.025	0.008
Joint involvement-active ($n = 96$)	5.42 (11.28)	39.04 (30.31)	41.95 (30.53)	53.33 (33.44)
Joint involvement-inactive ($n = 116$)	1.58 (7.67)	25.0 (30.34)	26.06 (30.71)	34.80 (32.01)
P	0.000	0.002	0.001	0.000
Eye involvement-active ($n = 17$)	4.04 (9.79)	48.0 (26.85)	49.72 (27.39)	36.47 (29.77)
Eye involvement-inactive ($n = 164$)	2.11 (8.91)	26.04 (29.66)	27.74 (29.75)	38.48 (31.57)
P	0.182	0.020	0.021	0.798
Comorbidity-absent ($n = 251$)	2.17 (8.14)	25.27 (26.4)	26.56 (27.1)	32.32 (27.7)
Comorbidity-present ($n = 113$)	4.94 (12.82)	41.63 (38.54)	44.01 (38.01)	55.78 (37.46)
P	0.110	0.01	0.004	0.000
Non-smoker/past smoker ($n = 289$)	2.44 (9.01)	26.62 (29.93)	28.24 (30.18)	37.96 (32.64)
Current smoker ($n = 75$)	4.44 (11.48)	39.55 (31.95)	40.94 (32.80)	46.33 (33.29)
P	0.143	0.021	0.025	0.06
Non-IS ($n = 121$)	2.5 (7.33)	20.70 (25.5)	22.38 (25.95)	31.76 (31.63)
IS ($n = 227$)	3.40 (10.85)	34.84 (32.3)	36.45 (32.64)	45.0 (32.78)
P	0.695	0.005	0.005	0.000
Recurrent aphthous stomatitis				
Oral ulcer active ($n = 117$)	11.68 (13.86)	57.95 (33.78)	60.05 (33.83)	39.48 (33.62)
Oral ulcer inactive ($n = 26$)	5.55 (23.57)	27.77 (35.57)	27.77 (35.57)	9.61 (21.25)
P	0.001	0.001	0.001	0.000

Bold indicate the statistical significance of $P < 0.05$.

Fig. 1 Mediation analysis for WPAI-daily activity impairment, disease activity and WPAI subgroups in Behçet's syndrome



(A) Productivity loss and activity impairment according to disease activity in Behçet's syndrome; **(B)** Mediation analysis for WPAI-daily activity impairment in patients with Behçet's syndrome.

TABLE 4 Mediation analyses for subgroups of WPAI in Behçet's syndrome and recurrent aphthous stomatitis

	B	S.E.	t	P	LLCI	ULCI
Behçet's syndrome						
Daily activity impairment						
• Constant	30.5274	2.8178	10.8338	0.0000	24.9805	36.0742
• Musculoskeletal activity (0: inactive 1: active)	17.2897	4.2443	4.0736	0.0001	8.9347	25.6447
• Oral ulcer related pain	1.7005	0.7837	2.1697	0.0309	0.1577	3.2433
Recurrent aphthous stomatitis						
Presenteeism						
• Constant	21.7822	8.2659	2.6352	0.0096	5.4061	38.1584
• Oral ulcer activity (0: inactive 1: active)	24.3289	8.9111	2.7302	0.0073	6.6744	41.9833
• Disease duration	0.6501	0.2734	2.3782	0.0191	0.1085	1.1917
Overall impairment						
• Constant	21.3633	8.2416	2.5921	0.0108	5.0351	37.6916
• Oral ulcer activity (0: inactive 1: active)	26.0118	8.8849	2.9276	0.0041	8.4091	43.6145
• Disease duration	0.6955	0.2726	2.5518	0.0121	0.1555	1.2355

B: coefficient; LLCI: lower-level confidence interval; ULCI: upper-level confidence interval. Bold indicate the statistical significance of $P < 0.05$.

Percentile bootstraps of the mediators were found to be effective in BS.

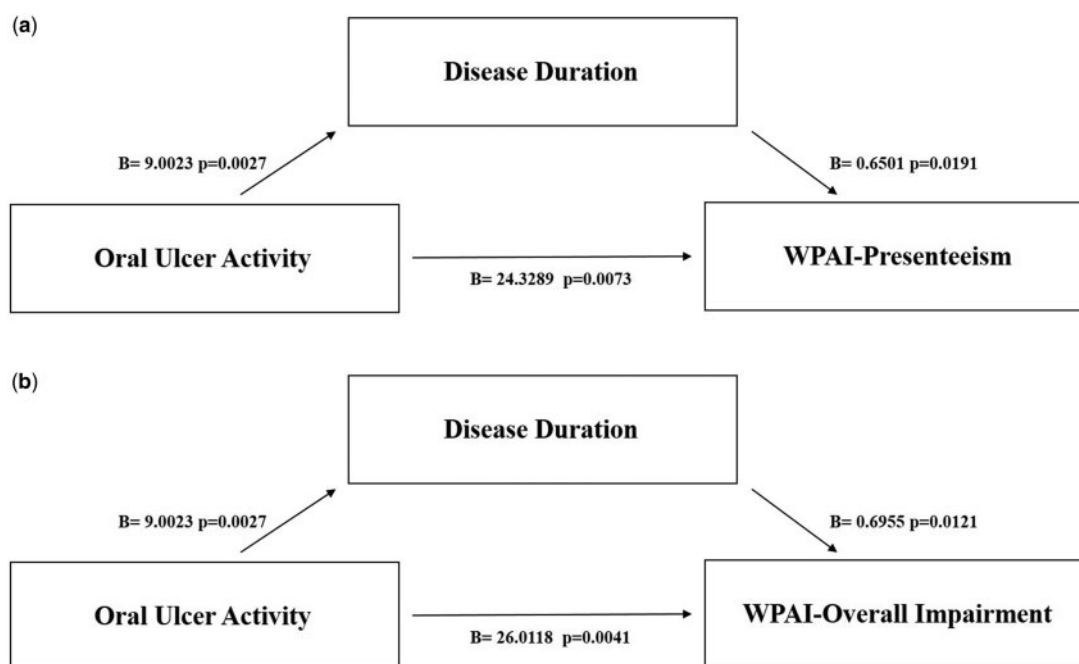
In isolated vascular involvement, the number of clinic visits during the previous year [4.1 (2.75)] was correlated with percentages of WPAI subgroups regarding presenteeism ($\rho: 0.4; P = 0.027$), overall impairment ($\rho: 0.4; P = 0.027$) and activity impairment ($\rho: 0.5; P = 0.007$).

Activity impairment score was higher in those with nervous system involvement [49,61 (37,22)] than eye

involvement [33.03 (30.88)] ($P = 0.034$). Moreover, the elevated score was also observed in patients with gastrointestinal involvement [50.0 (39.0)] in isolated major organ involvement.

Recurrent aphthous stomatitis

Employed patients with active oral ulcers ($n=98$) had poor WPAI scores compared with those of inactive

Fig. 2 Mediation analyses for WPAI-presenteeism and WPAI-overall impairment in patients with recurrent aphthous stomatitis**(A)** Mediation analysis for WPAI-presenteeism in patients with recurrent aphthous stomatitis; **(B)** Mediation analysis for WPAI-overall impairment in patients with recurrent aphthous stomatitis.

ulcers ($n=18$) ($P < 0.05$). Significant correlations were shown between WPAI domains and the oral ulcer healing time ($\rho: 0.39-0.63$; $P < 0.05$), oral ulcer related pain score ($\rho: 0.56-0.73$; $P < 0.05$), the number of oral ulcer ($\rho: 0.25-0.32$; $P < 0.05$, except absenteeism) and disease duration ($\rho: 0.21-0.29$; $P > 0.05$) (Table 3). However, no significant relation was observed in WPAI subgroup scores in relation to the patients' smoking status in RAS ($P > 0.05$).

In addition, two simple mediation models were carried out. In the first model, oral ulcer activity increased presenteeism ($B=24.3289$; $P=0.0073$) in the direct path. Disease duration as a mediator for increased presenteeism in the indirect path ($B=0.6501$; $P=0.0191$) (Table 4) (Fig. 2a).

In the second model, overall impairment was directly mediated by oral ulcer activity as the independent variable ($B=26.0118$; $P=0.0041$) and indirectly mediated by disease duration as a mediator in RAS ($B=0.6955$; $P=0.0121$) (Fig. 2b) (Table 4). Bootstrap analyses with 5000 replications were also applied in RAS. Percentile bootstraps of the mediators in both models for RAS were significant mediators.

Behçet's disease current activity form, oral ulcer activity and WPAI

Construct validity was used to assess the relationships between disease activity using the BDCAF (active: ≥ 1 vs 0: inactive) and presence of productivity loss and

activity impairment of the WPAI domains (presence: ≥ 1 vs absence: 0).

The majority of BS patients with productivity loss and activity impairment had active clinical manifestations (Table 2). Similarly, almost all of RAS patients with productivity loss and activity impairment had active oral ulcers (Table 2). Disease activity was significantly associated with the presence of presenteeism ($P=0.003$ in BS vs $P=0.000$ in RAS), overall impairment ($P=0.001$ vs $P=0.000$, respectively) and daily activity impairment ($P=0.009$ vs $P=0.000$, respectively). Almost all patients with absenteeism ($n=24$ in BS and $n=53$ in RAS) had active clinical manifestations in BS ($n=21$) and RAS ($n=52$) (Table 2).

Discussion

Productivity loss and activity impairment as PROMs reflect the gap between the influence of the patients' management and the impact of chronic conditions on an individual level [2, 15, 16]. In this study, these topics were evaluated by a large sample size including 364 BS patients from four countries and 143 RAS patients from two countries.

In BS, the employment rate was found to be low, with a small number of patients unemployed due to their health problems, mainly major organ involvement. Having a severe disease course and its consequences have been found to be risk factors for productivity loss

in BD [14–16], employment rate may reflect how health care affects patient's work performance [25, 26].

The decrease in the absenteeism score and education years as well as longer working hours, particularly in males were observed in BS. Weekly working hours were in accordance with the legal regulations (48 h or less) according to International Labour Organization standards [27]. Similarly, absenteeism is observed in a very limited number of BS patients in our previous study. The reason for this is that patients who have significant impairment at work are fearful of losing their jobs. This is probably the result of the lower education profile of BS patients [28] with less secure employment, and a cultural structure where men provide the main household income [15].

In isolated eye involvement, the working hours per week were higher in males than females. A small number of patients had active clinical manifestations with poor scores of presenteeism, and overall impairment compared with inactive patients. Untreated ocular attacks cause a decrease in visual acuity or blindness [29]. In addition, a decrease in weekly working hours was also seen in BD patients with eye involvement [15].

Activity associated with joint involvement had a direct effect on both productivity loss and daily life impairment. In this BS cohort, this is not unexpected as previous studies demonstrated that joint involvement presents as oligoarthritic pain in the large joints without tissue damage in BS [29, 30] and influence the patient's ability to work [31] and the patient's quality of life [32, 33].

Activity impairment was affected by active oral ulcers in this study. A reduction of oral ulcers did not occur [34, 35], especially younger female patients [36]. Because oral ulcers as an activity marker [35] lead to difficulties in oral functions and poor oral health-related quality of life [8, 20, 34, 37–40], the effects are commonly evaluated by PROMs [20, 34, 39, 41]. Treatment of oral ulceration is imperative and topical mouthwashes are a good option for the elimination of oral ulcers in BS [37] with added immunosuppressives in severe systemic BS cases [29, 41].

Active genital ulcers also contributed to work impairment regarding presenteeism and overall impairment in BS. Genital ulcers cause severe pain, difficulty with urination, mobility including sitting and walking [42, 43]. Topical medication and colchicine are helpful and effective additions to BS treatment protocols for genital ulcers [7, 29].

In addition, elevated scores in BDCAF and activity impairment were observed in females with mucocutaneous and joint involvement. Our results indicate that patients with a less aggressive clinical course where strong treatment protocols in this spectrum are lacking so that effectively control of disease activity was less than to those with major organ involvement [7, 29].

Because both mucocutaneous manifestations and joint involvement are commonly co-existing features in the heterogeneous spectrum of the BS [8, 9, 30, 44] that affects the patient's quality of life with unpredictable

relapses and remitting course [44], mediation analysis was performed, which assists the clinician in choosing the best therapeutic approaches, tailoring them to a patient's specific needs in this disease spectrum [12, 33, 38–41]. This indicates that activity impairment was directly mediated by joint activity, directly and indirectly by oral ulcer-related pain. The pain of mucocutaneous lesions is a mandatory domain of OMERACT core set for BS [44]. This analysis brings a new perspective in evaluating the effects of both involvements in these domains, and understanding of concomitant symptoms in BS.

In the study group, scores of WPAI domains, except absenteeism were elevated in BS patients treated with IS. These results are not unexpected in view of the effects of a severe disease course [29, 30, 45, 46]. The work-day loss during the previous year is also found to be high in patients treated with IS [16].

In isolated major organ involvement, activity impairment was poorly affected by both nervous system and gastrointestinal involvement. In addition, patients with nervous system involvement had higher activity impairment than eye involvement. These results indicate that the clinical profile of both nervous system [13, 33, 45] and gastrointestinal activity [13] have a detrimental effect on the quality of life.

In isolated vascular involvement, increased need for medical care was associated with activity impairment, presenteeism and overall impairment. In BS patients, the frequency of face-to-face appointments may provide evidence of the disease course [16, 29], especially when more than four visits per work-day loss occurs during the previous year [16].

Poor presenteeism and overall impairment were observed in patients with comorbidities and current smokers, which leads to poorer overall work productivity. Productivity loss is a robust measurement in patient-centred healthcare. Effective treatment plans for controlling the impact of comorbidities could stabilize family income levels in these patients by reducing sick leave days and early retirement [47]. Smoking is not only a risk factor for productivity loss [16, 48, 49] but is also a predictor for poor health status [50]. Consequently, suitable follow-up protocols and health education programs may be helpful for the improvement of work performance to obviate the occurrence of new health problems.

In RAS, both greater productivity loss and activity impairment were associated with oral ulcer activity. Using mediation analyses with the disease duration as a mediator, presenteeism and overall impairment scores were shown to be related to oral ulcer activity. RAS patients were mainly treated with topical medication. This approach is a first-line treatment protocol, except for resistant cases. Yet, the elimination of active flares and shortened healing time of oral ulcers were not achieved by the older traditional topical medications. Newer, more effective topical treatments should be rigorously used together with patient education on oral health. Furthermore, long-term disability due to disease duration

could modify patients' lives, as shown previously in BS [36]. In addition to clinical indicators [20, 39, 40], the evaluation of work performance could be beneficial and to enhance patient-centred care in oral medicine clinics.

In the study, the WPAI scale using six items [22, 31] was also found to be a valid and reliable tool [15] in clinical practice and trials in the multicentre study. This allowed the short-term effects of diseases to be easily assessed by the scale in the study.

Firstly, a strength of the study is the inclusion of the large BS patient population with participants from four countries being included. Secondly, we performed mediation analysis to reflect the direct and indirect effects of variables on dependent variables. Thirdly, our evaluation of RAS demonstrated that the effect of productivity loss was an indirect cost element, which may be underestimated in oral medicine care.

Despite these advantages, the study had some limitations. Firstly, that the patients from the four countries included in the study were all from tertiary clinics. A more diverse patient cohort from primary and secondary care could be included in the study. Secondly, the study design was cross-sectional, although follow-up studies are necessary to regularly monitor the economic burden on BS of employment in both the mid-term and long-term.

In conclusion, multiple disease activity factors, including the presence of comorbidities and smoking habits were associated with productivity loss related to presenteeism, overall impairment and daily activity impairment. These results emphasize the importance of using suitable treatment strategies to enable them to work and improve daily activity [34]. Furthermore, patients with RAS should be targeted to improve their productivity. In addition, WPAI could be utilized in both clinical practice and trials as a valid and reliable tool for patients with BS and RAS.

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References

- Zhang W, Gignac MA, Beaton D, Tang K, Anis AH. Canadian Arthritis Network Work Productivity G. Productivity loss due to presenteeism among patients with arthritis: estimates from 4 instruments. *J Rheumatol* 2010;37:1805-14.
- Zhang W, Anis AH. Health-related productivity loss: NICE to recognize soon, good to discuss now. *Pharmacoeconomics* 2014;32:425-7.
- Zhang W, McLeod C, Koehoorn M. The relationship between chronic conditions and absenteeism and associated costs in Canada. *Scand J Work Environ Health* 2016;42:413-22.
- CHRODIS PLUS Joint Action EU. CHRODIS PLUS Joint Action, European Union, in the framework of the Health Programme. 2020. <http://chrodiseu/> (16 September 2021, date last accessed).
- Gwinnutt JM, Leggett S, Lunt M *et al.* Predictors of presenteeism, absenteeism and job loss in patients commencing methotrexate or biologic therapy for rheumatoid arthritis. *Rheumatology* 2020;59:2908-19.
- Chun BY, Song CS. A moderated mediation analysis of occupational stress, presenteeism, and turnover intention among occupational therapists in Korea. *J Occup Health* 2020;62:e12153.
- Leccese P, Ozguler Y, Christensen R *et al.* Management of skin, mucosa and joint involvement of Behcet's syndrome: a systematic review for update of the EULAR recommendations for the management of Behcet's syndrome. *Semin Arthritis Rheum* 2019;48:752-62.
- Bettiol A, Hatemi G, Vannozzi L *et al.* Treating the different phenotypes of Behcet's syndrome. *Front Immunol* 2019;10:2830.
- Bettiol A, Prisco D, Emmi G. Behcet: the syndrome. *Rheumatology* 2020;59:iii101-iii107.
- Merkel PA, Aydin SZ, Boers M *et al.* Current status of outcome measure development in vasculitis. *J Rheumatol* 2014;41:593-8.
- Ozguler Y, Leccese P, Christensen R *et al.* Management of major organ involvement of Behcet's syndrome: a systematic review for update of the EULAR recommendations. *Rheumatology* 2018;57:2200-12.
- Senusi AA, Ola D, Mather J, Mather J, Fortune F. Behcet's syndrome and health-related quality of life: influence of symptoms, lifestyle and employment status. *Clin Exp Rheumatol* 2017;35 Suppl 108:43-50.
- Yazici Y, Hatemi G, Seyahi E, Yazici H, eds. Behçet syndrome. Switzerland: Springer Nature, 2020.
- Sut N, Seyahi E, Yurdakul S, Senocak M, Yazici H. A cost analysis of Behcet's syndrome in Turkey. *Rheumatology* 2007;46:678-82.
- Mumcu G, Lehimci F, Fidan O *et al.* The assessment of work productivity and activity impairment in Behcet's disease. *Turk J Med Sci* 2017;47:535-41.
- Mumcu G, Yay M, Aksoy A *et al.* Predictive factors for work-day loss in Behcet's syndrome: a multi-center study. *Int J Rheum Dis* 2020;23:240-6.
- Hayes AF. Introduction to mediation, moderation, and conditional process analysis: a regression-based approach. New York, USA: Guilford Publications, 2017.
- Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: observations, recommendations, and implementation. *Behav Res Ther* 2017;98:39-57.
- Wiryakijja P, Fedele S, Porter S, Mercadante V, Ni Riordain R. Patient-reported outcome measures in recurrent aphthous stomatitis: a critical assessment of quality properties. *Oral Dis* 2017;23:1168-79.

- 20 Mumcu G, Sur H, Inanc N *et al.* A composite index for determining the impact of oral ulcer activity in Behcet's disease and recurrent aphthous stomatitis. *J Oral Pathol Med* 2009;38:785–91.
- 21 International Study Group for Behcet's Disease. Criteria for diagnosis of Behcet's disease. *Lancet* 1990;335:1078–80.
- 22 WPAI. http://www.reillyassociatesnet/WPAI_General.html (16 September 2021, date last accessed).
- 23 Behcet's Disease Current Activity Form. www.behcetdiseasesociety.org/behcetwsData/Uploads/files/BehcetsDiseaseActivityForm (16 September 2021, date last accessed).
- 24 Lee J, Kim SS, Jeong HJ *et al.* Association of sleep quality in Behcet disease with disease activity, depression, and quality of life in Korean population. *Korean J Intern Med* 2017;32:352–9.
- 25 Amick BC, 3rd, Lerner D, Rogers WH, Rooney T, Katz JN. A review of health-related work outcome measures and their uses, and recommended measures. *Spine (Phila Pa 1976)* 2000;25:3152–60.
- 26 Xiang L, Low AHL, Leung YY *et al.* Work disability in rheumatic diseases: baseline results from an inception cohort. *Int J Rheum Dis* 2020;23:1040–9.
- 27 (ILO) ILO. Busines and Working Time. https://www.wilo.org/empent/areas/business-helpdesk/WCMS_DOC_ENT_HLP_TIM_EN/lang-en/index.htm (16 September 2021, date last accessed).
- 28 Pehlivan M, Kurtuncu M, Tuzun E *et al.* The comparison of socio-economic conditions and personal hygiene habits of neuro-Behcet's disease and multiple sclerosis patients. *Int J Hyg Environ Health* 2011;214:335–7.
- 29 Hatemi G, Christensen R, Bang D *et al.* 2018 update of the EULAR recommendations for the management of Behcet's syndrome. *Ann Rheum Dis* 2018;77:808–18.
- 30 Kone-Paut I, Barete S, Bodaghi B *et al.* French recommendations for the management of Behcet's disease. *Orphanet J Rare Dis* 2021;16:352.
- 31 Beaton DE, Dyer S, Boonen A *et al.* OMERACT filter evidence supporting the measurement of at-work productivity loss as an outcome measure in rheumatology research. *J Rheumatol* 2016;43:214–22.
- 32 Karadag O, Bolek EC. Management of Behcet's syndrome. *Rheumatology* 2020;59:iii108–17.
- 33 Bernabe E, Marcenes W, Mather J, Phillips C, Fortune F. Impact of Behcet's syndrome on health-related quality of life: influence of the type and number of symptoms. *Rheumatology* 2010;49:2165–71.
- 34 Senusi A, Higgins S, Fortune F. The influence of oral health and psycho-social well-being on clinical outcomes in Behcet's disease. *Rheumatol Int* 2018;38:1873–83.
- 35 Alibaz-Oner F, Mumcu G, Kubilay Z *et al.* Unmet need in Behcet's disease: most patients in routine follow-up continue to have oral ulcers. *Clin Rheumatol* 2014;33:1773–6.
- 36 Mumcu G, Yay M, Karacayli U *et al.* Moderation analysis exploring associations between age and mucocutaneous activity in Behcet's syndrome: a multicenter study from Turkey. *J Dermatol* 2020;47:1403–10.
- 37 Senusi A, Kang A, Buchanan JAG *et al.* New mouthwash: an efficacious intervention for oral ulceration associated with Behcet's disease. *Br J Oral Maxillofac Surg* 2020;58:1034–9.
- 38 Mumcu G, Niazi S, Stewart J *et al.* Oral health and related quality of life status in patients from UK and Turkey: a comparative study in Behcet's disease. *J Oral Pathol Med* 2009;38:406–9.
- 39 Mumcu G, Hayran O, Ozalp DO *et al.* The assessment of oral health-related quality of life by factor analysis in patients with Behcet's disease and recurrent aphthous stomatitis. *J Oral Pathol Med* 2007;36:147–52.
- 40 Mumcu G, Inanc N, Ergun T *et al.* Oral health related quality of life is affected by disease activity in Behcet's disease. *Oral Dis* 2006;12:145–51.
- 41 Mumcu G, Karacayli U, Yay M *et al.* Oral ulcer activity assessment with the composite index according to different treatment modalities in Behcet's syndrome: a multicentre study. *Clin Exp Rheumatol* 2019;37(Suppl 121):98–104.
- 42 Senusi A, Seoudi N, Bergmeier LA, Fortune F. Genital ulcer severity score and genital health quality of life in Behcet's disease. *Orphanet J Rare Dis* 2015;10:117.
- 43 Mumcu G, Inanc N, Taze A, Ergun T, Direskeneli H. A new mucocutaneous activity index for Behcet's disease. *Clin Exp Rheumatol* 2014;32(4 Suppl 84):S80–6.
- 44 Hatemi G, Meara A, Ozguler Y *et al.* The OMERACT core set of domains for outcome measures in Behcet syndrome. *Arthritis Care Res* 2020;doi: 10.1002/acr.24511. [Online ahead of print]
- 45 Siva A, Kantarci OH, Saip S *et al.* Behcet's disease: diagnostic and prognostic aspects of neurological involvement. *J Neurol* 2001;248:95–103.
- 46 Aksoy A, Yazici A, Omma A *et al.* Efficacy of TNFalpha inhibitors for refractory vascular Behcet's disease: a multicenter observational study of 27 patients and a review of the literature. *Int J Rheum Dis* 2020;23:256–61.
- 47 Sum G, Ishida M, Koh GC *et al.* Implications of multimorbidity on healthcare utilisation and work productivity by socioeconomic groups: cross-sectional analyses of Australia and Japan. *PLoS One* 2020;15:e0232281.
- 48 Suwa K, Flores NM, Yoshikawa R *et al.* Examining the association of smoking with work productivity and associated costs in Japan. *J Med Econ* 2017;20:938–44.
- 49 Troelstra SA, Coenen P, Boot CR *et al.* Smoking and sickness absence: a systematic review and meta-analysis. *Scand J Work Environ Health* 2020;46:5–18.
- 50 Gallucci G, Tartarone A, Lerosé R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation. *J Thorac Dis* 2020;12:3866–76.