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Clinical science

The impact of demographics on organ damage in Behçet's syndrome: a cross-sectional analysis of the international PROBE cohort

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Abstract

Objective: To examine the influence of demographics on organ damage in a broad, multiethnic cohort of patients with Behçet's syndrome (BS).

Methods: In this cross-sectional ancillary analysis of the PROBE project, the investigated demographic variables were sex, age, education level and geographic area of residence. Damage was measured by the BS Overall Damage Index (BODI). Multivariate linear (β) and logistic (adjusted odds ratio [adjOR]) regression analyses examined associations between demographics and the extent and prevalence of damage.

Results: A total of 970 patients were enrolled. The median (interquartile range) age was 40 (31–50) years; 56.5% were males; 21.4% had a low level of education. The median BODI score was 1 (0–3), with 65.6% of patients having a BODI ≥1. Males had higher damage (β 0.103) and a higher prevalence of total (adjOR 1.7, per 10 years), ocular (adjOR 1.6), and vascular (adjOR 2.1) damage. Age was associated with greater damage (β 0.104), and a higher prevalence of overall (adjOR 1.4), neuropsychiatric (adjOR 1.2) and miscellaneous (adjOR 2.0) damage. Low education was associated with a greater frequency of overall (adjOR 1.9) and ocular (adjOR 1.6) damage. North African patients experienced greater damage than South European (β 0.400) and Middle Eastern (β 0.314) patients, as well as a higher risk of overall damage (adjOR 13.9 and 10.7, respectively) across all organ domains, except for the reproductive and gastrointestinal systems.

Conclusions: This study demonstrates how the extent, prevalence and characteristics of damage in BS vary with demographic factors, underscoring their importance in research and personalized management.

Keywords: Behçet's syndrome, damage, sex, age, education, geographic variability

Rheumatology key messages

- Organ damage is a crucial outcome to be prevented in Behçet's syndrome (BS)
- In BS, damage is significantly affected by sex, age, education and geographic residence.
- Demographics should be considered to guide future clinical trials design and enhance prevention strategies.

Introduction

Behçet's syndrome (BS) is a multisystem inflammatory disease of unknown aetiology, characterized by a strong genetic predisposition, distinctive geographic distribution and a wide variability in clinical presentation [1]. While oral ulcers, genital ulcers and non-granulomatous uveitis are commonly considered the clinical hallmarks of BS, almost any organ or system can be affected, including the mucocutaneous, musculoskeletal, cardiovascular, neurological and gastrointestinal systems [1].

Demographic factors, such as sex, age, socio-cultural level and geographic area of residence, are widely recognized as significantly influencing the heterogeneity of BS, including its clinical presentation, progression and prognosis [2–10]. Several studies have linked male sex to a more severe disease course, with higher risks of major organ involvement such as uveitis, vascular issues and heart complications, while females more often present with genital ulcers and joint issues [2, 3].

Regarding age, BS is most frequently diagnosed between ages 20 and 40; however, cases in both children and the elderly have been reported, each with distinct features [4]. Paediatric BS is generally considered milder, though it can still be associated with systemic involvement [4]. Late-onset BS has been noted to have a lower prevalence in males and is associated with fewer skin, joint and eye issues compared with classic onset. Young adults, especially those under 25, tend to show higher eye involvement and greater overall disease activity [5].

Socioeconomic factors, particularly educational level, also appear to influence disease presentation. Education, often used as an indicator of socioeconomic status alongside income and access to resources, has been linked to the quality of life related to the disease [11]. Specifically, lower educational attainment is associated with poorer quality of life in BS patients and a higher prevalence of eye involvement [6, 7].

BS is often called the 'Silk Route disease' because its highest prevalence is observed along the historic trade route, closely linked with the distribution of HLA-B*51 across the globe, spanning from the Middle East to Far East Asia, between latitudes 30° and 45° north [12]. Geographic origin not only influences disease incidence but also impacts clinical patterns and progression. Vascular complications are more common in Turkey and other Middle Eastern areas than in East Asia and Europe. Gastrointestinal involvement is more frequently reported in East Asia, particularly in Japan, whereas it is relatively rare in Turkey and the Mediterranean region [8]. Conversely, neurological features are more often seen in European patients compared with those from the Middle East [9]. Patients from non-endemic regions, such as the Americas, usually experience a milder form of the disease [13].

Besides influencing BS symptoms and severity, demographics likely impact irreversible organ damage, a key long-term outcome, since preventing it is crucial [14]. However, the significance of this disease outcome has only recently been acknowledged, and measurement tools have been developed [15, 16]. As a result, evidence concerning determinants and risk factors for damage, including demographic variability, remains limited. Nonetheless, this information is vital for understanding damage in research and implementing prevention strategies.

This study aims to evaluate how demographic factors affect the extent and characteristics of damage in a global multicentre cohort of BS patients, with the overall aim of enhancing our understanding of its risk factors. This knowledge could help guide future clinical trial designs and the development of effective damage prevention strategies for clinical use.

Methods

Population and study design

The present study is an ancillary cross-sectional analysis of baseline data collected from 17 centres participating in the PROBE ('PROspective multiethnic validation of the BEhçet's

syndrome Overall Damage Index') study (NCT07073261). The PROBE study was designed with the primary goal of evaluating the relationship between organ damage accumulation and long-term outcomes, such as mortality, and examining the comprehensiveness and criterion validity of the Behçet's syndrome Overall Damage Index (BODI) in a broad, ethnically varied cohort of BS patients. In each involved centre, consecutive BS patients were recruited between July 2021 and June 2022, according to the following inclusion criteria: (i) age ≥16 years, and (ii) diagnosis of BS meeting the ICBD or ISG classification criteria [17, 18]. The PROBE study was approved by the Local Ethical Committee (PROT. 2021/9952) of the Azienda Ospedaliero-Universitaria of Cagliari. Written informed consent was obtained from all participants.

Data collection

For every enrolled patient, the following data were recorded: sex, age at enrolment, age at the disease onset (the time when first manifestation other than oral ulcers appeared), disease duration, smoking history, level of education, active and cumulative clinical manifestations, previous and ongoing medications, overall disease activity assessed by the Behçet's Disease Current Activity Form (BDCAF), Physician Global Assessment (PGA), and Patient Global Assessment (PtGA) [19].

The demographic variables investigated as factors potentially affecting organ damage in BS were sex, age at enrolment, level of education and geographic area of residence. The level of education was analysed as a dichotomous variable, distinguishing between low level, which comprised illiteracy and primary education, and medium to high level, which included secondary school, college and university education. The evaluated geographic areas were Southern Europe (Italy, Greece, Portugal, Spain), North Africa (Egypt, Morocco), the Middle East (Iran, Turkey), Central Asia (Kazakhstan) and the Americas (USA, Brazil). Ethnicity was collected based on self-declaration, but was not analysed as a demographic factor associated with damage. Geographic area of residence was preferred, as it allowed for a more consistent classification and implicitly accounted for other relevant factors, such as healthcare system type and socioeconomic status. Moreover, stratifying by ethnicity would have required grouping populations that, according to the literature, differ significantly in many aspects of Behçet's disease.

The extent and type of organ damage were assessed using the BODI, which consists of 34 items and 12 subitems, categorized into nine organ/system domains: mucocutaneous, musculoskeletal, ocular, vascular, cardiovascular, neuropsychiatric, gastrointestinal, reproductive system and miscellaneous [16]. Each item and subitem scores 1 point; thus, the total score ranges from 0 to 46 [16]. Supplementary Figs S1 and S2 report the latest version of the BODI form with the list of the individual items of damage and the respective glossary. The extent of damage was evaluated using the total BODI score. The prevalence of damage was determined by the percentage of patients with at least one damage item (BODI ≥ 1). The prevalence of damage to individual organs or systems was assessed based on the presence of at least one damage item in specific BODI domains (e.g. ocular BODI ≥ 1, cardiovascular BODI ≥ 1, etc).

Statistical analysis

Summary statistics were calculated by expressing categorical variables as numbers and frequencies (%), and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), depending on whether they had a normal or non-normal distribution.

A univariate analysis using the chi-squared test, Fisher's exact test, Mann–Whitney test or Spearman's coefficient (ρ) was performed to evaluate the association of sex, education and geographic areas with the total BODI score and the prevalence of overall and individual organ/system BODI damage. In the sub-analysis focusing on geographic areas, Central Asia and the Americas were excluded, as each represented <5% of the total sample. Indeed, their inclusion would have resulted in excessive fragmentation of the analysis and a loss of statistical power, thereby limiting the interpretability of the finding.

Multivariate linear regression and logistic regression models were built to confirm the independent association of the investigated demographic variables with, respectively, the total BODI score (a continuous variable) and the total or single organ/system BODI ≥ 1 (a categorical variable). Beta coefficient (β) and adjusted odds ratio (adjOR) with 95% CI were calculated. To identify potential confounders for inclusion in the multivariate analysis models, separate preliminary analyses were conducted to search for other demographic and clinical factors associated with the demographic variables of interest. In particular, the variables investigated as potential confounders were: age at disease onset, smoking history, diagnostic delay, disease duration, major organ involvement (ocular, vascular, neuropsychiatric, or gastrointestinal involvement), treatment with glucocorticoids, conventional and biological immunosuppressants, and the modified BDCAF score. Results of these preliminary analyses are reported in Supplementary Tables S1–S4.

Finally, a decision model based on classification and regression tree (CART) analysis was developed using the SPSS classification module to identify the demographic profile associated with the highest likelihood of damage accrual.

Statistical significance was set at $P < 0.05$. All statistical analyses were performed using SPSS software (version 24, IBM Corp., Armonk, NY, USA).

Results

Population

In total, 970 consecutive BS patients were enrolled, 344 (35.5%) from Southern Europe, 289 (29.8%) from North Africa, 261 (27.0%) from the Middle East, 43 (4.4%) from the Americas, and 33 (3.4%) from Central Asia. In the entire cohort, 548 (56.5%) patients were male, the median age at enrolment was 40 years (31–50) and the disease duration was 9 years (range, 5–17). More details on demographic and clinical features of the study cohort are reported in Table 1. The distribution of different disease manifestations according to gender, level of education and geographic area is reported in Supplementary Table S5.

The median BODI score was 1 (0–3), with 636 (65.6%) patients having a total BODI score of 1 or higher. When evaluating the prevalence of different organ/system BODI damage, 259 (26.7%) had at least one item of damage in the mucocutaneous domain, 22 (2.3%) in the musculoskeletal, 352 (36.3%) in the ocular, 185 (19.8%) in the vascular, 28 (2.9%) in the cardiovascular, 141 (14.5%) in the neuropsychiatric, 9 (0.9%) in the gastrointestinal, 4 (0.4%) in the reproductive, and 58 (6.0%) in the miscellaneous domain. When the prevalence of

Table 1. Demographic and clinical features at baseline

Demographic	Value ($n = 970$)
Males, *n* (%)	548 (56.5)
Age at enrolment, median (IQR), years	40 (31–50)
Age at the disease onset, median (IQR), years	28 (20–36)
Disease duration, median (IQR), years	9 (5–17)
Geographic area, *n* (%)	1 (0–5)
Europe	344 (35.5)
Middle East	261 (27.0)
North Africa	289 (29.8)
Central Asia	33 (3.4)
Americas	43 (4.4)
Ethnicity, *n* (%)	
Caucasian	622 (64.1)
Arab	292 (30.1)
Asian	34 (3.5)
Afro-American	15 (1.5)
Other	7 (0.8)
Smoking history, *n* (%)	374 (38.6)
Level of education, *n* (%)	
Low	173 (21.4)
Illiterate	33 (4.1)
Primary school	140 (17.3)
Medium to high	635 (78.6)
Secondary school	322 (39.9)
University/college	313 (38.7)
Mucocutaneous involvement, *n* (%)	957 (98.7)
Oral aphtosis, *n* (%)	941 (97.0)
Genital aphtosis, *n* (%)	659 (68.1)
Skin lesion, *n* (%)	573 (59.3)
Major organ involvement, *n* (%)	708 (73.0)
Ocular	467 (48.1)
Vascular	241 (24.8)
Neurological	149 (15.4)
Gastrointestinal	76 (7.8)
Ongoing treatment, *n* (%)	
Glucocorticoids	559 (57.6)
Conventional IS	458 (47.2)
Biologic IS	226 (23.3)
BDCAF, median (IQR)	3 (0–5)
PGA, median (IQR)	2 (1–5)
PtGA, median (IQR)	3 (1–6)

BDCAF: Behçet's Disease Current Activity Form; BODI: Behçet's syndrome Overall Damage Index; IQR: interquartile range; IS: immunosuppressant; PGA: Physician's Global Assessment of Disease Activity; PtGA: Patient's Global Assessment of Disease Activity.

organ/system damage was analysed within specific patient subgroups with a history of active disease in the same organ/system, the proportion of patients with damage in the mucocutaneous domain was 259/957 (27.1%), in the ocular domain was 352/467 (75.4%), in the vascular domain was 185/241 (76.8%), in the neuropsychiatric domain was 141/149 (94.6%), and in the gastrointestinal domain was 9/76 (11.8%).

Sex and damage

Males had a significantly higher total BODI score (median 2; IQR 1–4]) than females (median 1; IQR 0–2; $\beta = 0.103$, $P = 0.001$) as well as a higher prevalence of overall damage (77.2% *vs* 50.5%, $P < 0.001$). Moreover, males showed a significantly higher rate of damage in the mucocutaneous (30.7% *vs* 21.6%, $P = 0.002$), ocular (46.9% *vs* 22.5%, $P < 0.001$), vascular (27.2% *vs* 8.5%, $P < 0.001$) and cardiovascular (4.2% *vs* 1.2%, $P = 0.005$) BODI domains (Fig. 1A). Logistic regression analysis confirmed male sex to be independently associated with overall damage (adjOR 1.7 [95% CI: 1.1, 2.5], $P = 0.009$), as well as ocular (adjOR 1.6 [95% CI: 1.1, 2.4], $P = 0.014$) and vascular (adjOR 2.1 [95% CI: 1.3, 3.4], $P = 0.002$) damage. A trend toward statistical significance was observed for cardiovascular damage (adjOR 2.7 [95% CI: 0.9, 8.3], $P = 0.077$) (Fig. 2A). Extended data on the multivariate analysis results are provided in Supplementary Table S6.

Age and damage

Age was significantly correlated with the total BODI score, both in univariate ($\rho = 0.07$, $P = 0.03$) and multivariate ($\beta = 0.104$, $P = 0.002$) analysis. Moreover, the median age in patients with BODI ≥ 1 (40.1 years [95% CI: 32.7, 50.6]) was significantly higher than in patients with BODI $= 0$ (37.5 years [95% CI: 29.7, 48.7], $P = 0.004$). When stratified by different types of organ damage, older age was associated with damage in the musculoskeletal (57.2 [95% CI: 57.2, 63.4] *vs* 39.2 [95% CI: 31.3, 49.4] years, $P < 0.001$), neuropsychiatric (42.4 [95% CI: 36.2, 53.4] *vs* 38.8 [95% CI: 31.0, 49.0] years, $P < 0.001$) and miscellaneous (54.8 [95% CI: 44.8, 63.4] *vs* 38.7 [95% CI: 31.0, 48.6], $P < 0.001$) BODI domains (Fig. 1B). In the multivariate analysis, age was confirmed to be independently associated with total BODI (adjOR 1.4 [95% CI: 1.2, 1.6] for 10-year increases, $P < 0.001$), as well as neuropsychiatric (adjOR 1.2 [95% CI: 1.0, 1.5], $P = 0.015$) and miscellaneous (adjOR 2.0 [95% CI: 1.5, 2.5], $P < 0.001$) BODI domains (Fig. 2B). Extended results from the multivariate analysis are reported in Supplementary Table S7.

Level of education and damage

The total BODI score was significantly higher in patients with a low level of education (illiteracy or primary school) in univariate analysis ($P = 0.002$), but not in multivariate analysis ($\beta = 0.014$, $P = 0.664$). However, a low level of education was significantly associated with a higher prevalence of overall damage (72.2% *vs* 57.3%, $P < 0.001$) and ocular damage (41.0% *vs* 30.6%, $P = 0.009$) (Fig. 1C). Multivariate analysis confirmed the level of education to be independently associated with overall damage (adjOR 1.9 [95% CI: 1.2, 2.9], $P = 0.003$), as well as ocular damage (adjOR 1.6 [95% CI: 1.1, 2.4], $P = 0.022$) (Fig. 2C). Extended results from the multivariate analysis are reported in Supplementary Table S8.

Geographic area of residence and damage

In univariate and multivariate analyses, North African patients had a higher total BODI score than Southern European ($\beta = 0.400$, $P < 0.001$) and Middle Eastern ($\beta = 0.314$, $P < 0.001$) patients. No significant difference was recorded between the Middle East and Southern Europe (data not shown).

The geographic area was significantly associated with higher prevalence of overall damage ($P < 0.001$), as well as with mucocutaneous ($P < 0.001$), musculoskeletal ($P = 0.029$), ocular ($P < 0.001$), vascular ($P < 0.001$), cardiovascular ($P = 0.009$), neuropsychiatric ($P < 0.001$) and miscellaneous ($P < 0.001$) BODI domains. Details on comparisons between different areas are reported in Table 2 and Fig. 1D. In multivariate analysis, the geographic area was confirmed to be independently associated with total BODI damage, as well as with damage in mucocutaneous, musculoskeletal, ocular, vascular, neuropsychiatric and miscellaneous domains. This was particularly in the primary models using North Africa as a reference (Fig. 2D). In models comparing Middle East *vs* Southern Europe, a higher prevalence of damage was observed in Middle East patients for the total BODI and mucocutaneous

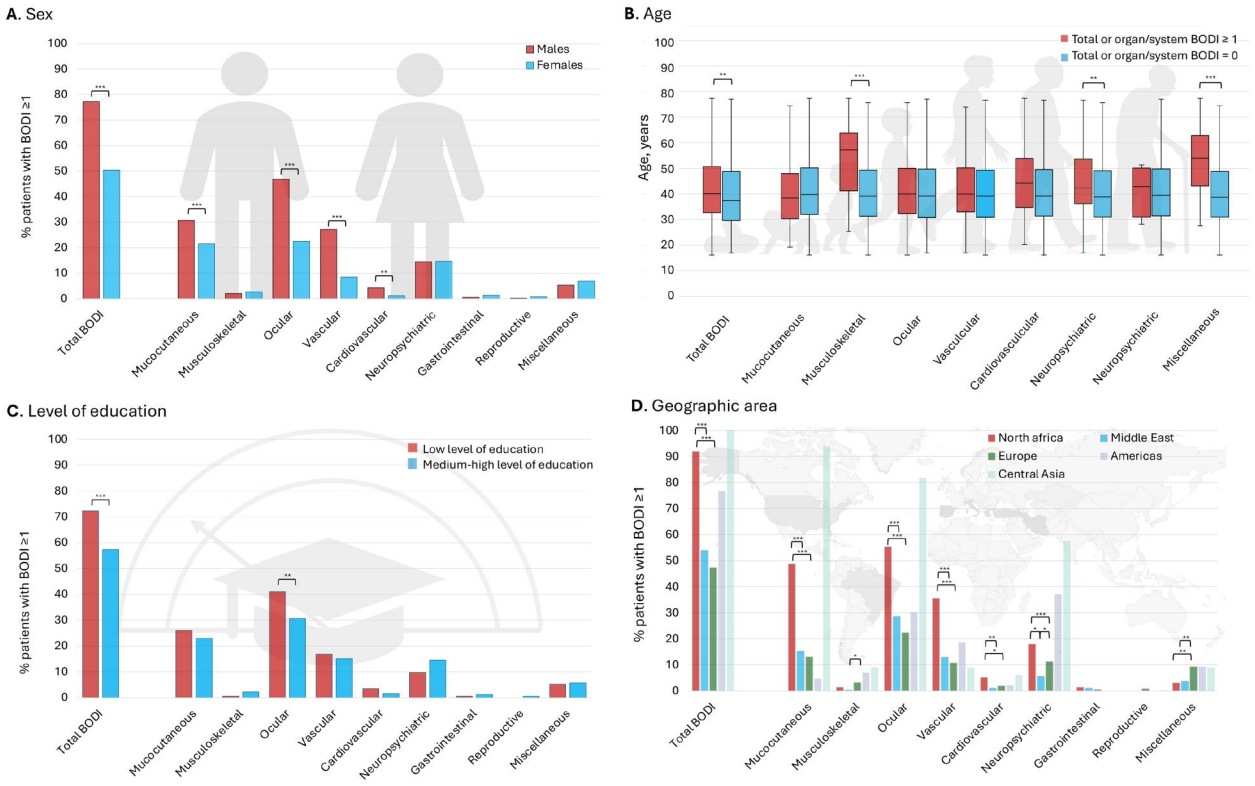

Figure 1. Univariate analysis of the relationship between sex, age, education and geographic region with damage. (**A**) Male sex was associated with a higher prevalence of overall damage (total BODI ≥ 1) as well as mucocutaneous, ocular, vascular and cardiovascular damage (specific organ/system BODI ≥ 1). (**B**) The median age was significantly higher in patients with any damage (BODI ≥ 1), and particularly in the musculoskeletal, neuropsychiatric and miscellaneous BODI domains. (**C**) A low level of education was significantly associated with overall and ocular damage. (**D**) The geographic area of origin significantly affected the prevalence of overall, mucocutaneous, musculoskeletal, ocular, vascular, cardiovascular, neuropsychiatric and miscellaneous damage, with, in most of cases, higher rates observed in North African patients compared with those from Southern Europe and the Middle East (Central Asia and Americas were excluded from the statistical analysis because of the limited sample size). The box and whisker plots in (**B**) represent the median age, the interquartile range and 95% CI. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$. BODI, Behçet's syndrome Overall Damage Index

and cardiovascular organ/system BODI domains; however, the results were not statistically significant (data not shown). Extended data from the multivariate analysis are reported in Supplementary Table S9.

Demographic profile associated with the highest likelihood of damage

The CART analysis, performed to develop a prediction model for damage accrual in BS based on demographics, identified the highest likelihood of overall damage accrual in North African male patients aged older than 32 years (97.5% prevalence of BODI ≥ 1). In contrast, the group with the lowest prevalence of BODI damage consisted of Southern European females, younger than 37 years (37.1% prevalence of BODI ≥ 1).

Discussion

This study provides unique and valuable insights into how demographic factors impact organ damage, which is crucial since preventing damage is a key goal in BS treatment [14]. Notably, the study highlights how sex, age, educational level and geographic area are mutually interrelated, yet each appears to play an independent role in increasing the risk of damage (Fig. 3).

In this study, a significantly greater extent and prevalence of damage was observed in male patients, both overall and specifically in the mucocutaneous, ocular and cardiovascular domains. This correlation aligns with previous data indicating that male patients tend to have a more severe disease course [10], with increased ocular and vascular involvement [2, 3], and experience more damage than females [17]. Furthermore, our study examined how sex interacts with other demographic and clinical factors that are, in turn, influenced by sex and may impact damage development. These factors include a higher rate of major organ involvement, older age at diagnosis and a greater prevalence in specific geographic regions. However, our findings show that even after adjusting for these factors, male sex still independently confers a higher risk of damage, with a 1.5 times greater likelihood than females, supporting the existence of true gender-related traits in BS that are associated with more severe disease and increased damage.

Along with these observations, older patients exhibited a significantly greater extent and prevalence of damage. This association was also confirmed after adjusting the analysis for other factors associated with older age, such as longer disease duration. This finding is highly relevant from a clinical perspective and not entirely expected. Previous studies have shown that older age is often associated with milder disease manifestations and a longer disease course, during which long-term disease activity and severity tend to decrease over time [20, 21]. This supports the earlier observation in the 2-year prospective preliminary BODI validation cohort, where the damage accumulation rate remained steady over time,

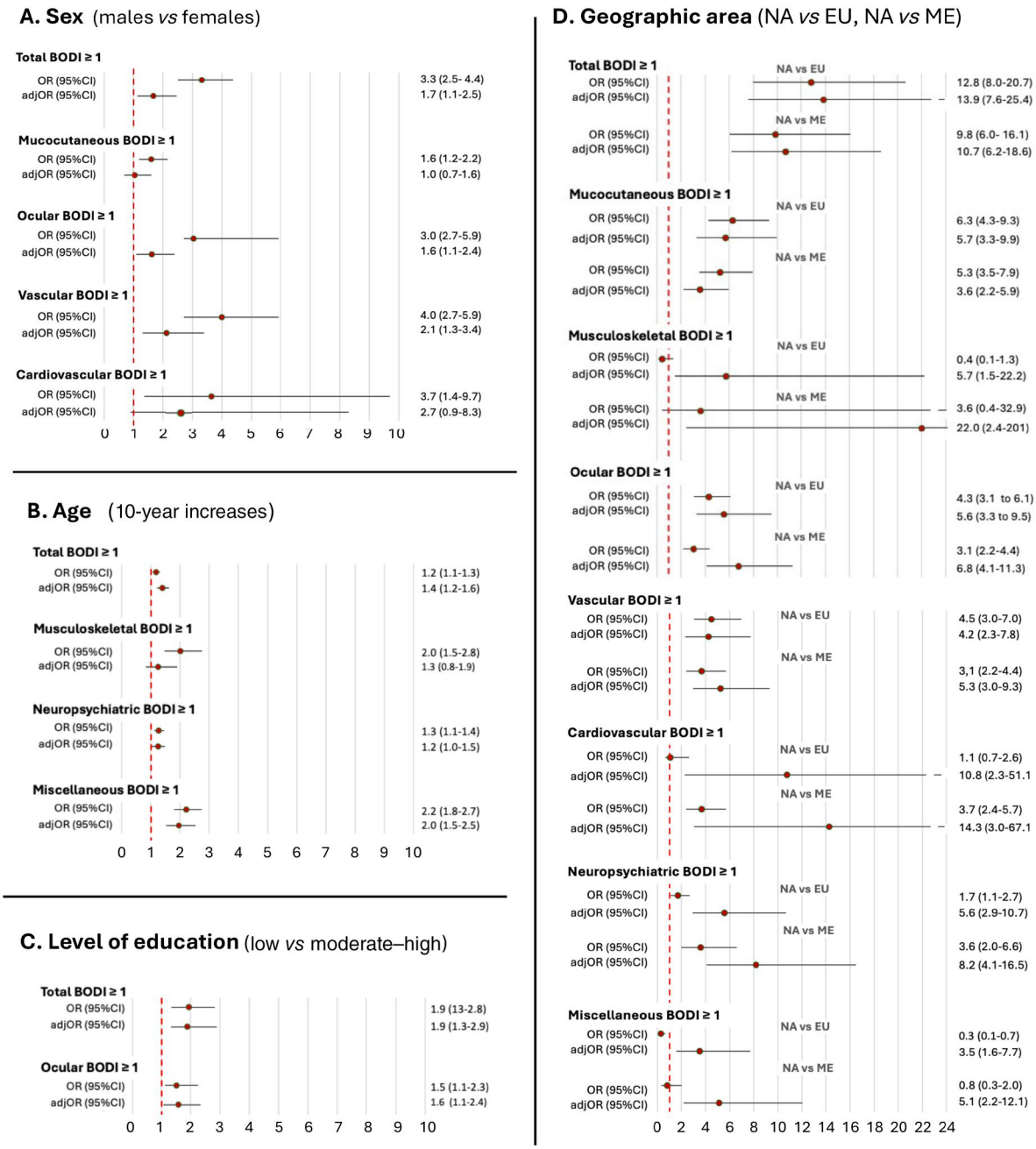

Figure 2. Odds ratios from univariate and multivariate analysis representing the effect of sex, age, education level and geographic area on damage. (**A**) Sex was associated with overall, ocular and vascular damage, as assessed by the BODI, both in univariate and multivariate analysis. (**B**) Age was significantly associated with overall, neuropsychiatric and miscellaneous BODI damage, both in univariate and multivariate analysis. (**C**) Educational level was significantly associated with overall and ocular damage in univariate and multivariate analysis. (**D**) The geographical area of origin was confirmed to affect overall, mucocutaneous, musculoskeletal, ocular, vascular, cardiovascular, neuropsychiatric and miscellaneous damage, with higher damage accrual in North African patients. AdjOR: adjusted odds ratio; BODI: Behçet's syndrome Overall Damage Index; EU: Southern Europe; ME: Middle East; NA: North Africa; OR: odds ratio

regardless of disease duration [22]. Overall, these data highlight the complementary yet distinct nature of disease activity and damage. Specifically, this result may suggest that, although older patients may experience lower levels of disease activity, they are at greater risk of developing damage, which might result directly from the disease itself, its treatment, or other age-related risk factors (e.g. diabetes, osteoporosis and cardiovascular risk factors).

Educational level is one of the least-explored variables in the existing literature. The few studies addressing this topic have reported an association between low educational attainment and poorer quality of life [6]. Furthermore, low socioeconomic status, of which education is a component, has been linked to more severe manifestations such as uveitis and neuro-Behçet's [11]. Our study demonstrated that low education is associated with a higher prevalence of overall damage and ocular damage. This was confirmed after adjusting the analysis for other factors that could potentially affect the socio-cultural level, such as geographic area. The mechanisms underlying such an association are challenging to understand

Table 2. Prevalence and head-to-head comparison of damage in different geographic areas

	NA ($n = 289$)	ME ($n = 261$)	EU ($n = 344$)	*P*-value		
				NA *vs* ME	NA *vs* EU	ME *vs* EU
Total BODI, median (IQR)	3 (2–5)	1 (0–2)	0 (0–2)	<0.001	<0.001	0.159
Total BODI ≥ 1, *n* (%)	266 (92.0)	141 (54.0)	163 (47.4)	<0.001	<0.001	0.106
Mucocutaneous BODI ≥ 1, *n* (%)	141 (48.8)	40 (15.3)	45 (13.1)	<0.001	<0.001	0.431
Musculoskeletal BODI ≥ 1, *n* (%)	4 (1.4)	1 (0.4)	11 (3.2)	0.217	0.135	0.014
Ocular BODI ≥ 1, *n* (%)	160 (55.4)	75 (28.7)	77 (22.4)	<0.001	<0.001	0.074
Vascular BODI ≥ 1, *n* (%)	103 (35.6)	34 (13.0)	37 (10.8)	<0.001	<0.001	0.390
Cardiovascular BODI ≥ 1, *n* (%)	15 (5.2)	3 (1.1)	7 (2.0)	0.008	0.031	0.398
Neuropsychiatric BODI ≥ 1, *n* (%)	52 (18.0)	15 (5.7)	39 (11.3)	<0.001	0.018	0.017
Gastrointestinal BODI ≥ 1, *n* (%)	4 (1.4)	3 (1.1)	2 (0.6)	1.00	0.299	0.657
Reproductive BODI ≥ 1, *n* (%)	0	0	3 (0.9)	1.00	0.254	0.263
Miscellaneous BODI ≥ 1, *n* (%)	9 (3.1)	10 (3.8)	32 (9.3)	0.646	0.002	0.009

BODI: Behçet's syndrome Overall Index; IQR: interquartile range; ME: Middle East; NA: North Africa.

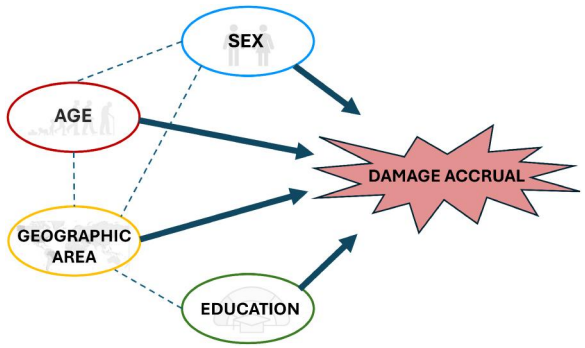

Figure 3. Relationships of different demographic variables with damage. Sex, age, educational level and geographic area are mutually interrelated, yet each appears to play an independent role in increasing the risk of damage. The dashed lines indicate the relationships among the different demographic variables, while the arrows show the impact of each variable on the risk of damage accumulation

fully and are likely multifactorial, possibly linked to lower health literacy, a limited understanding of medical care, and socioeconomic vulnerability. These findings highlight the importance of providing tailored communication and support to patients with lower educational levels, with the goal of improving disease management and outcomes.

The geographic area emerged as the variable most strongly associated with the extent, prevalence and characteristics of damage. Interestingly, geographic area also showed the greatest variability associated with other demographic and clinical characteristics. For instance, patients from North Africa had a significantly higher prevalence of males, major organ involvement, smoking history and glucocorticoid use, while reporting the lowest use of biologic therapies. Although these factors may undoubtedly contribute to the higher frequency of organ damage, multivariate analysis confirmed that geographic area retains an independent effect on damage risk, beyond other associated variables. This could be related to underlying differences in the ethnic composition of the various geographic regions, considering ethnicity as a complex construct that includes genetic, cultural, linguistic and historical elements. Another potentially relevant, though unexplored, factor is socioeconomic status and access to healthcare, whether through private, universal or hybrid systems, which may further impact disease outcomes.

This study has notable strengths, as well as some limitations. The main strengths include the large sample size, placing it among the largest cohorts reported in the literature, the diverse geographic backgrounds, and the comprehensive methodological approach. Indeed, this approach assessed the individual impact of each variable on damage and examined its mutual interactions. Regarding limitations, the study did not permit the analysis of certain additional demographic elements that may influence the expression of BS and damage accumulation. In particular, we were unable to include other dimensions of individual or regional socioeconomic status. Due to its complexity in definition and measurement, socioeconomic status is often neglected in most studies. In our analysis, we used educational level as a proxy for sociocultural status, while acknowledging it as an approximation. Regarding geographic representation, although this cohort includes a relatively broad range of regions, the Americas and Central Asia were underrepresented, and East Asia was entirely absent. Finally, since all participants were enrolled in tertiary referral centres, this may have resulted in the inclusion of more severe cases. However, given that BS is a complex disease, most patients are typically managed in specialized centres.

In conclusion, this study provides robust evidence that the prevalence and type of organ damage vary according to sex, age, educational level and geographic area of residence in patients with BS. The comprehensive analysis of their interactions highlights the complex interplay between biological and socio-demographic factors. These findings underscore the need for developing effective damage-preventing strategies, individualized patient care and stratified approaches in clinical trials.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The study dataset is not publicly available, but it is available from the corresponding author on reasonable request.

Contribution statement

Conceptualization: A.F., A.C., G.H., M.P. Data curation: A. F., R.L., P.C., M.P. Methodology: A.F., M.P., L.A.

Investigation: R.L., S.C., A.L., M.T.H., Y.Y.O., Y.O., L.S.P., M.A., N.L.O., J.S., G.L., P.C., D.P., N.K., A.K., A.W.S.S., A. L., G.E., R.B., M.G., B.I., F.I., C.M.F., L.C., F.S., J.C., Z.T. M., G.R., A.C., G.H. Writing—original draft: A.F., R.L., M. P. Writing—review & editing: S.C., A.L., M.T.H., Y.Y.O., Y. O., L.S.P., M.A., N.L.O., J.S., G.L., P.C., D.P., N.K., A.K., A.W.S.S., A.L., G.E., R.B., M.G., B.I., F.I., C.M.F., L.C., F. S., J.C., Z.T.M., G.R., L.A., A.C., G.H. All authors read and approved the final manuscript.

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