healthcare (UK and Denmark), using harmonized methodology. Previous studies have been limited by small sample size, difficulty in measuring stress, and potential misclassification of adverse life events due to recall bias. We undertook our study in two similar cohorts to enable replication, and used partner bereavement as a proxy for acute severe stress, with specific onset date. Limitations include a lack of information on the level and duration of stress arising from bereavement, individual responses to bereavement, social support, potential misclassification of partnership status, possible delay between disease onset and diagnosis, overrepresentation of severe cases in the Danish hospital setting, and absence (Denmark) and missingness (UK) of body mass index and lifestyle covariates. People with mild skin conditions may be less likely to seek medical advice immediately after bereavement, which may have led to underestimation during short-term follow-up, and an overrepresentation of the most severe skin diseases.

In conclusion, this large study showed no evidence of associations between partner bereavement and chronic urticaria, alopecia areata or vitiligo. Despite a large study population, precision was limited by low event rates for alopecia areata and vitiligo, especially in early time periods. Details of the methods, additional and sensitivity analyses, and discussion of results, can be found via https://doi.org/10.17037/pubs.04656104.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Appendix S1 Funding sources and conflicts of interest statements.

Funding sources and conflicts of interest can be found in Appendix S1 (see Supporting Information).

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High and discordant prevalences of clinical and sonographic enthesitis in patients with hidradenitis suppurativa

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Dear Editor, The prevalence of spondyloarthritis (SpA) reported among patients with hidradenitis suppurativa (HS) ranges from 2.3% to 28.2%, depending on the diagnostic method used.1 A key feature of SpA and one of the European Spondyloarthropathy Study Group diagnostic criteria for this group of diseases is enthesitis: inflammation at the insertion of tendons, ligaments and capsules. However, pain at an enthesal site is nonspecific and does not always indicate inflammation. Objective assessment of the presence of enthesitis can be done using ultrasound.2 Therefore, the aim of this cross-sectional study was to investigate the prevalence of clinical enthesitis among patients with HS and to correlate it with sonographic enthesitis.

Patients were selected randomly prior to their routine visit at the specialized HS outpatient clinic of a tertiary centre in the Netherlands between October 2018 and February 2019. The study was approved by the medical ethical committee of the Erasmus University Medical Center (MEC-2018-158). Patient characteristics were collected through the HiScreen Registry (MEC-2016-426) and patient charts.

Clinical enthesitis, defined as pain elicited by local pressure at the enthesis, was assessed bilaterally at eight enthesal points (total 16 sites) according to the Spondyloarthritis Research Consortium of Canada (SPARCC) criteria.3 Ultrasound examination was performed according to the Madrid Sonographic Enthesitis Index at six bilateral entheses and...
In summary, this is the first cross-sectional study in patients with HS in which clinical assessment of enthesitis was objectified by ultrasound. The 25% prevalence of sonographic enthesitis in our study is slightly higher than the 20% prevalence found in patients with psoriasis.⁵

The prevalence of clinical enthesitis (53%) was over twice that of sonographic enthesitis in our HS population, and many painful entheses could not be explained by underlying sonographic abnormalities. This high rate could be a consequence of the unspecific nature of enthesal tenderness, which is further supported by the high percentage of patients that had over four affected entheses.

A study on patients with psoriasis, psoriatic arthritis and fibromyalgia showed that the frequency of enthesal tenderness was higher in patients with fibromyalgia than in patients with psoriatic arthritis or psoriasis: respectively, 92% vs. 66% and 59%.⁶ Moreover, the number of affected entheses was higher in the fibromyalgia group (46%) than in the psoriatic arthritis (23%) or psoriasis (18%) groups.⁶ This raises the question of whether the chronic, widespread musculoskeletal pain associated with HS could in part be due to other causes. Tenderness at enthesal sites has an overlap with the tender point points originally used for the diagnosis of fibromyalgia according to the American College of Rheumatology (ACR)-1990 criteria (changed to pain points in the ACR-2010/2011 and ACR-2016 criteria). The underlying rationale is similar and studies have shown that clinical differentiation between fibromyalgia and enthesitis can be extremely challenging.⁷

Our study could have been influenced by inclusion bias as patients who experience joint complaints could be more inclined to participate. Moreover, observer expectancy bias could have influenced our results as both clinical and ultrasound examination were performed by the same investigator. In addition, it is known that age and body mass index (BMI) are positively correlated with the presence of enthesitis in the lower limbs.⁸ Therefore, the high BMI and age in our population could have influenced the prevalence of enthesitis. Yet this does not explain the discrepancy between clinical and sonographic enthesitis.

In conclusion, the high number of clinically painful entheses could be explained only in part by underlying sonographic enthesitis. This finding, in combination with the high proportion of patients with more than four clinical enthesitis sites, suggests that different pathologies might explain the widespread (enthesal) pain among patients with HS and requires further investigation as treatment differs for the different causes. Therefore, we urge dermatologists to refer patients with HS with musculoskeletal complaints to a rheumatologist to identify the underlying cause.

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**Table 1 Patient characteristics**

|                      | N = 100 |
|----------------------|---------|
| Sex                  |         |
| Female, n (%)        | 80 (80) |
| Age, mean (SD)       | 39.0 (11.0) |
| Age of onset, median (IQR) | 18.0 (14.0–29.0) |
| Missing, n           | 3       |
| Body mass index, mean (SD) | 29.8 (6.0) |
| Missing, n           | 14      |
| Smoking status       |         |
| Current or former smoker, n (%) | 70 (75.3) |
| Never smoked, n (%)  | 23 (24.7) |
| Missing, n           | 7       |
| Family history of HS |         |
| Positive in 1st of 2nd degree, n (%) | 32 (33.3) |
| Negative, n (%)      | 55 (57.3) |
| Unknown, n (%)       | 9 (9.4)  |
| Missing, n           | 4       |
| Comorbidities        |         |
| Rheumatological comorbidities, n (%) | 8 (8.1) |
| Missing, n           | 1       |
| Inflammatory bowel disease, n (%) | 5 (5.1) |
| Missing, n           | 2       |
| Family history of SpA, n (%) | 12 (12.0) |
| Missing, n           | 0       |
| Hurley stage         |         |
| I, n (%)             | 47 (47.5) |
| II, n (%)            | 44 (44.4) |
| III, n (%)           | 8 (8.1)  |
| Missing, n           | 1       |
| IHS4, mean (SD)      | 4.3 (0.7) |
| Current use of anti-TNF-α biologics, n (%) | 6 (6.1) |
| Missing, n           | 1       |
| Use of pain medication, n (%) | 36 (36) |
| Use of opioids, n (%) | 6 (6)   |

HS, hidradenitis suppurativa; IHS4, International Hidradenitis Suppurativa Severity Score System; IQR, interquartile range; SpA, spondyloarthritis; TNF, tumour necrosis factor

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sonographic enthesitis was defined according to the Outcome Measures in Rheumatology criteria.⁴

In total, 100 patients were included; see Table 1 for patient characteristics. Eighteen patients had visited a rheumatologist previously, five of whom were diagnosed with SpA, one with rheumatoid arthritis and one with sarcoidosis. Eleven patients were seen for nonrheumatic pain complaints, three of whom were diagnosed with fibromyalgia. On clinical examination, 53% of patients could be diagnosed with clinical signs of enthesitis in at least one enthesis. The number of painful entheses in these patients ranged from one to 14 per individual; 58.5% had four or more affected entheses, and seven patients had an enthesitis count of over 10. Sonographic enthesitis was seen in 25% of patients. Assessing the entheses that were evaluated both clinically and sonographically showed that 13.2% of clinically painful entheses had an underlying sonographic enthesitis. Neither clinical nor sonographic enthesitis was associated with Hurley stage or the International Hidradenitis Suppurativa Severity Score System (IHS4) score.
Disease characteristics in female and male patients with hidradenitis suppurativa

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Dear Editor, The continuously growing interest in the study of ‘gender medicine’ in recent years has led to increased awareness of the differences between males and females in the clinical presentation, pathophysiology, management and prognosis of a wide variety of diseases, including skin diseases.1 Sex differences in disease characteristics can be influenced by numerous factors, e.g. the effect of sex hormones, anatomy, physiology and genetics. Viances in skin structure and physiology between the sexes can also contribute to different expressions of certain skin disorders.1,2

Hidradenitis suppurativa (HS) affects women more frequently than men3 and there is an emerging awareness of a phenotypical heterogeneity within the HS disease spectrum.4 The effects of sex on HS is not well established and published data on this specific subject are sparse and inconclusive.

The objective of this study was to investigate the sex-specific disease characteristics of HS, including demographics, risk factors and disease severity, as well as anatomical localization of HS lesions, serum lipid levels and blood glucose. We explored the potential differences between female and male patients with HS in a prospective cohort of 447 consecutive newly referred patients with HS attending a tertiary dermatological university centre (Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark).3

In total, 284 (63.5%) female and 163 (36.5%) male patients with HS were included (Table 1). We found significant differences between the sexes with female patients having a lower age of onset of HS compared with male patients [mean ± SD: 23.1 ± 10.3 vs. 29.3 ±13.6 years, respectively, P < 0.001]. Also, female patients were more often obese compared with male patients with HS (40.1% vs. 30.7%, P = 0.040); less likely to smoke (52.1% vs. 63.8%, P = 0.02); more often had a first-degree relative with HS (39.8% vs. 28.2%, P = 0.014); had lower disease severity measured by Hurley stage with more females represented in Hurley stage I (39.4% vs. 24.5%) and more males in Hurley stage III (27.0% vs. 7.0%, P < 0.001).

Furthermore, anatomical localization of HS lesions varied significantly between the sexes. Female patients with HS were more likely to have involvement of the groin (81.3% vs. 59.5%, P < 0.001), whereas a higher proportion of the male patients had involvement of the gluteal region (49.7% vs. 31.7%, P < 0.001).

Additionally, there were significant differences in inflammatory markers in the blood. Male patients with HS had a higher inflammatory load compared with female patients with HS: C-reactive protein [9.1 ± 16.3 vs. 6.1 ± 9.1, P = 0.013]; neutrophils [5.9 ± 2.7 vs. 5.2 ± 2.1, P = 0.007] and neutrophil/lymphocyte ratio (NLR) [2.7 ± 1.5 vs. 2.3 ± 0.9, P = 0.002]. No statistically significant differences between the sexes were observed for ethnicity, Dermatology Life Quality Index, number of boils in the past month, and blood cholesterol.

After multivariate adjustment, we found statistically significant differences between female and male patients for age (P < 0.001), age of onset of HS (P < 0.001), obesity (P = 0.025), smoking (P = 0.008), first-degree relative with HS (P = 0.001), disease severity (Hurley stage) (P < 0.001), involvement of the groin (P < 0.001), involvement of the gluteal region (P < 0.001), higher inflammatory markers in blood: neutrophils (P = 0.014), NLR (P = 0.002), and cholesterol (P = 0.014). However, some of these associations should be interpreted with caution due to the multiple comparisons; after Bonferroni correction, we recognize that a significance level below 0.003 (P = 0.05 for 17 independent tests) rather than 0.05 is more appropriate (Table 1).

In contrast to our findings, a retrospective study of 214 patients from a HS clinic found no differences between female and male patients for age of onset, body mass index, smoking status and disease severity.6 However, the study was limited by recall bias, small sample size and a lower fraction of male patients (20%), which could have led to chance findings.

Several clinical observations suggest that sex hormones may play a role in the pathogenesis of HS. It is well recognized

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