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Dear Editor,

Superficial fungal infections (SFI) are common diseases affecting the skin, hair, nails, and mucosal membranes. They are often caused by dermatophytes and yeasts, e.g. *Trichophyton, Candida,* and *Malassezia*[1]. Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of the intertriginous areas associated with minor infections[2], peripheral vascular disease, diabetes, and smoking[3], the last three of which are risk factors for the development of SFI[4]. Despite this, and the anatomical overlap between HS and types of SFI e.g. intertriginous candidiasis and tinea cruris, the possibility of an association between HS and SFI has never been investigated.

The aim of this study was, therefore, to investigate if HS and SFI were associated in a cohort of Danish blood donors. We included data on participants in the second iteration of the Danish Blood Donor Study (DBDS2), distributed between May 2015 and June 2017. We defined HS according to a validated questionnaire which have shown high testparameters (sensitivity: 90%, specificity: 97%, PPV 96% and NPV 92%)[5], ensuring that the control group does not contain large group of people with HS symptoms. SFI were defined based on redeemed prescriptions registered in the Danish National Prescription Registry (table legend 1). An additional analysis on vaginitis among females was based on redeemed prescriptions of vaginal miconazole and clotrimazole, types of prescriptions not included in the first analysis. We analysed the number of antifungal prescriptions after study enrolment using the Anderson Gill modified cox regression analysis that allowed for multiple outcome-measures, and adjusted for the effects of age, sex, body mass index (BMI) and current smoking. To account for the possibility of confounding by opportunistic infection after antibiotic treatment, we performed sub-analyses additionally adjusted for antibiotic use <30 days before antifungal prescription. Results are presented as hazard ratios (HR) and 95% confidence intervals (CI).

Amongst the 36,883 included participants, the prevalence of HS was 2.1%, which match those found in other populations when employing a screening questionnaire (table 1). HS was not associated with antifungal prescriptions after study enrolment, HR: 0.87 (CI: 0.73–1.05) (table 1). For female participants, HS was not associated with receiving treatment for vaginitis neither in the standard analysis, HR: 0.86 (CI: 0.35–2.10), nor in the analysis adjusted for antibiotics use, HR: 0.85 (0.31–2.30) (table 1), although females with HS often receive antibiotics, which can increase the risk of *Candida* vaginitis[6].

HS is associated with more frequently self-reported minor infections (common cold and genital herpes)[2], but not with SFI. One explanation for this could be the increased cytokine levels in HS affected skin. Especially IL-17/IL-23 and associated inflammatory cytokine pathways are of importance as these

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cytokines are increased in HS skin[3] and are key players in the antifungal defence[1]. People with HS may therefore be offered some protection against SFI. This is supported by our result, that albeit not statistically significant, showied a lower HR (CI) of 0.87 (0.73-1.05), *P*=0.155) of antifungal prescriptions. However, we did not investigate cytokine levels in the present study, and our results are furthermore limited by the potential use of over-the-counter antifungal agents among the study participants. In addition, HS severity could not be assessed through the screening questionnaire, but intuitively the severity would be lower than what we see in the clinic as severity increase over time[7]. Additionally, active disease that requires treatment would result in temporary deferral from blood donation (four-weeks for antibiotic use), which in turn mean that those with symptoms who do not receive treatment are more likely to be recruited. Lastly while guidelines recommend fungal identification by microscopy, culture and/or polymerase chain reactions prior to initiation of systemic antifungal therapies for fungal infections in skin, nails and hair we cannot be certain that non-dermatologists adhere to this rule.

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HU, CE, KRN, KSB, KB, MTB, TH, HH, and KMD participated in the design of the study, data acquisition, and have critically revised the manuscript. GBJ, DMS and OBP participated in the design of the study, data acquisition and analysis, and have critically revised the manuscript. RKA and PLA participated in the design of the study, performed the data analysis, and wrote the manuscript. All authors have accepted the final version of the manuscript and agree to be accountable for aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The DBDS (M-20090237) and DBDSII (RS-740) are approved by the Scientific Ethical Committees in Central Denmark Region and Region Zealand, respectively, and registered by the Danish Data Protection Agency (2007-58-0015). The study was conducted in accordance with the Helsinki Declaration.

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Table 1

	All participants in DBDS2, n=53,175				Participants with redeemed prescriptions after enrolment in DBDS2, n=36,883			
	HS		Controls		HS		Controls	
	Males (n=394)	Females (n=618)	Males (n=26,923)	Females (n=25,240)	Males (n=249)	Females (n=513)	Males (n=16,075)	Females (n=20,046)
Median age, years (IQR)	33.9 (27.4-45.6)	36.1 (26.1-46.0)	41.3 (29.9-51.6)	39.3 (26.7-50.7)	36.5 (28.9-48.2)	35.9 (25.7-45.7)	42.7 (31.3-52.6)	37.4 (25.8-49.9)
Median BMI (n=53,019 / n=36,783)	26.5 (24.3-30.0)	26.5 (23.4-31.2)	25.5 (23.6-27.8)	24.4 (22.1-27.5)	26.9 (24.4-30.4)	26.6 (23.5-31.2)	25.7 (23.7-28.1)	24.3 (22.1-27.5)
Current smokers, n (%) (n=53,041 / n=36,802)	83 (21.1)	184 (29.8)	3,448 (12.8)	3,320 (13.2)	62 (24.9)	155 (30.2)	2,049 (12.7)	2,713 (16.8)
Participants with SFI, n (%)	201 (51.0)	456 (73.8)	13,775 (51.2)	16,540 (65.5)	38 (15.3)	73 (14.2)	2,271 (14.1)	2,600 (16.2)
Median antifungal prescriptions (IQR)	2 (1-4)	3 (1-5)	2 (1-4)	2 (1-5)	3 (2-6)	5 (2-7)	3 (2-7)	4 (2-9)
Cox regressions, Andersson Gill variant								
Superficial fungal infections *not* adjusted for antibiotics use <30 days prior to antifungal prescription. Number of events = 6,854		Superficial fungal infections adjusted for antibiotics use <30 days prior to antifungal prescription. Number of			Vaginitis (among females) *not* adjusted for antibiotics use <30 days prior to antifungal prescription. Number of		Vaginitis (among females) adjusted for antibiotics use <30 days prior to antifungal prescription. Number of	

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			events = 6,412		events = 205		events = 170	
	Hazard ratio (95-CI)	P-value	Hazard ratio (95-CI)	P-value	Hazard ratio (95-CI)	P-value	Hazard ratio (95-CI)	P-value
HS	0.97 (0.76-1.08)	0.269	0.87 (0.73-1.05)	0.155	0.86 (0.35-2.10)	0.740	0.85 (0.31-2.30)	0.750
Female sex	0.85 (0.81-0.90)	<0.001*	0.81 (0.77-0.85)	<0.001*	N/A		N/A	
Age, year	0.78 (0.76-0.81)	<0.001*	0.78 (0.76-0.81)	<0.001*	0.70 (0.57-0.86)	<0.001*	0.69 (0.55-0.87)	0.001*
BMI >30	0.89 (0.82-0.95)	<0.001*	0.86 (0.79-0.92)	<0.001*	1.35 (0.94-1.96)	0.106	1.32 (0.88-1.99)	0.181
Current smoking	0.89 (0.83-0.96)	0.002*	0.86 (0.80-0.93)	<0.001*	1.16 (0.81-1.68)	0.413	0.97 (0.64-1.49)	0.898

Table legend 1. HS: Hidradenitis suppurativa. DBDS2: The second iteration of the Danish Blood Donor Study. IQR: Interquartile range. BMI: Body mass index. SFI: Superficial fungal infections. N/A: Not applicable as only females were included in the analysis. Redeemed prescription as registered in the Danish National Prescription Registry are described in parenthesis below using the Anatomical Therapeutic Chemical Classification system (ATC codes). *Significant after Holm-Bonferroni correct.

Superficial fungal infections were defined as redeemed prescription(s) on antifungal agents, and included the topical therapies: clotrimazole (D01AC01), miconazole (D01AC02), ketoconazole (D01AC08), imidazoles/triazoles in combination with corticosteroids (D01AC20), ciclopirox (D01AE14), terbinafine (D01AE15), and amorolfine (D01AE16), and the systemic therapies: terbinafine (D01BA02), fluconazole (J02AC01) and itraconazole (J02AC02).

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