Hidradenitis suppurativa beyond the skin

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DOI:
10.33612/diss.181193211


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Chapter 2

New insights in hidradenitis suppurativa from a popultion-based Dutch cohort: prevalence, smoking behaviour, socioeconomic status and comorbidities

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Submitted at the BJD

ABSTRACT

Background
Hidradenitis suppurativa (HS) is a chronic, auto-inflammatory skin condition, which is associated with several comorbidities. Previous studies report variable prevalence rates of HS, depending on the methodology, however the exact prevalence remains unknown.

Objectives
To determine the prevalence of HS in a large population-based cohort in the Northern Netherlands, and to compare HS patient characteristics to the general population. Additionally, we aim to identify potential associated comorbidities.

Methods
Data was collected through a cross-sectional survey-based study in the Lifelines Cohort Study, based on the general population located in the Northern Netherlands. A digital questionnaire was developed consisting of validated questions for determining HS.

Results
Among 56.084 respondents, the overall prevalence of HS was 2.1% (95% CI 2.0-2.2). The respondents with HS had a lower socioeconomic status than the controls and were more frequently current smokers. Several new significant associations with HS were revealed, such as fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and migraine. Fibromyalgia and chronic fatigue syndrome remained significantly associated with HS in the multivariate analysis.

Conclusion
Our study showed a higher prevalence of HS (2.1%) in the Northern Netherlands compared to the overall estimated prevalence of 1% and identified several new associated comorbidities. This indicates that HS is subject to underdiagnosis and to an even more extensive comorbidity profile than previously assumed.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic auto-inflammatory skin disease, with debilitating effects on the quality of life of patients.[1] Patients experience stigmatization and feelings of shame.[2] Contributing to the burden of HS, is the average diagnostic delay of seven years, in which the disease can progress.[3] Furthermore, HS is associated with smoking and low socioeconomic status (SES).[4,5] HS has also been associated with several inflammatory comorbidities, such as inflammatory bowel disease and spondyloarthropathies, and metabolic comorbidities like metabolic syndrome and diabetes mellitus, with predominantly a chronic nature.[4–7] Earlier diagnosis of HS and earlier initiation of treatment, including lifestyle interventions, could mitigate the burden for HS patients and may benefit the health care system as well.

The prevalence of HS is thought to be approximately 1% in the general population. However, the prevalence varies widely from 0.02%[1] to 4.10%[2], due to underlying differences in disease susceptibility across the studied populations and differences in applied research methodologies (Figure 1).[8,9] Three methodological approaches have been used to estimate the prevalence of HS, including (I) registry-based studies where information is collected from national registry or insurance databases; (II) hospital-based studies in which HS diagnosis is based on physical examination; and (III) population based survey- or interview-based studies. In registry-based studies, the prevalence estimates are confounded due to channelling bias, selection bias, misdiagnosis, incorrect registry and data management miscoding, and patients who were not covered by insurance. Hospital based studies are often confounded by selection bias, as only patients reaching the doctors at a specific hospital are included. Hence, these approaches are not the most suited for assessing the prevalence of HS in the general population, nor to trace undiagnosed cases. Therefore, we used the unique large population-based cohort Lifelines study to determine the prevalence of HS in the general adult population in the Northern Netherlands. Additionally, we assessed potential factors and comorbidities associated with HS.

METHODS

Design

A nested cross-sectional study within the frame work of the Lifelines Cohort Study was performed.[10] Lifelines is a prospective population-based cohort study examining, in a unique three-generation design, the health and health-related behaviours of 167.729 participants living in the Northern Netherlands. It employs a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioral, physical and psychological factors which contribute to the health and disease of the general population, with a special focus on gene–environmental interaction and multi-morbidity of chronic complex disorders relevant to the healthy ageing. Participants were recruited through their general practitioners, through family members, or by self-registering.

The data collection in Lifelines started in 2006 and was conducted according to the guidelines of the Declaration of Helsinki, and all procedures were approved by the Medical Ethics

Committee of the University Medical Centre Groningen (2007/152).

We performed an add-on study, for which a digital questionnaire was developed, consisting of 23 questions related to HS. This questionnaire was sent to 135.950 adult (≥18 years) Lifelines participants. The add-on study was conducted between February and May 2020.

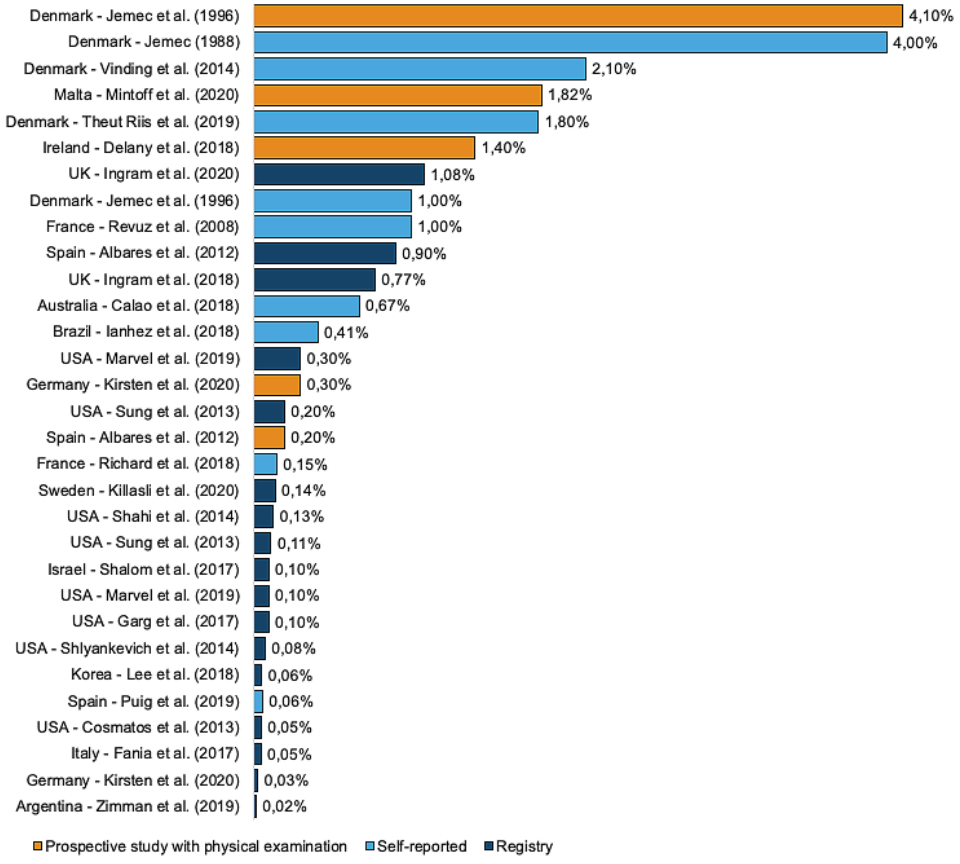

Figure 1. Overview of prevalence rates of hidradenitis suppurativa per country.

Questionnaire

Participants were identified as having HS, so-called 'HS cases', in two ways (Supplement S1). First, if 'yes' was answered to the question "Did you ever (during your life) got the diagnosis hidradenitis suppurativa (HS)?". Second, if 'no' was answered, participants were asked two

validated questions (Esmann *et al.*) for self-diagnosing HS: "Do you have painful, recurring abscesses or boils in your armpits, groin, buttocks, or on other locations, as seen in the images below?" and "Did you have at least 2 outbreaks of abscesses or boils within a period of 6 months?".[11,12] If 'yes' was answered to both questions, the participant was identified as an HS case. Additionally, images showing HS lesions corresponding with the three Hurley stages were shown to the participants, enabling potential patients to perform a self-assessment of the presence and the stage of HS.

All identified HS cases were asked additional questions about the duration of disease, affected areas, history of physician contact, severity, disease course, the physician who diagnosed them, current HS treatment, and HS family history. Furthermore, all participants were asked about HS associated comorbidities including acne vulgaris, polycystic ovary syndrome (PCOS), and psoriasis.

Participant characteristics

From the Lifelines database, several characteristics were extracted from the baseline assessment for the invited population, including sex, age, smoking status and socioeconomic status. For body mass index (BMI) and smoking status data from follow-up assessments were used in the responder-group, since these variables are more likely to change over time. Smoking status was categorized into nonsmoker, current smoker, or ex-smoker.

Socioeconomic status was determined by the Statistics Netherlands (a Dutch governmental institution which gathers statistical information about The Netherlands), based on inhabitants' educational level, income and job prospective.[13] Scores range from approximately -8 to +3, where a lower number represents a lower SES.

Comorbidities were determined by combining the baseline data of Lifelines together with the follow-up data, as the follow-up data provided additional questions asking for the development of diseases between both assessments. For several questions about comorbidities (i.e. migraine, bladder dysfunction, prostate disease, and malignancies), an affirmatory self-reported option was requested from participants, i.e. 'yes'. Participants were considered as not having the indexed disease, when participants did not check the 'yes' answer. Therefore, those five categories of comorbidities lack missing data.

Data analysis

Descriptive statistics

Prevalence of HS was calculated via dividing the number of participants identified with HS by the total number of included participants at risk for HS and 95% CI were determined via binomial exact calculations. Possible bias in the estimation of HS prevalence was examined, as Lifelines included more women than men and HS is a female dominant disease. This could result in an unequal number of respondents among men and woman and therefore we randomly drew 10.000 participants from the total cohort, with an equal proportion of men and women as in HS patients, and recalculated the prevalence of HS using the bootstrap method.

We used group matching to match the identified HS cases set with age matched randomly selected control subjects with a 1 to 5 ratio. Participants' characteristics and comorbidities are presented as number (percentage, %) for categorical variables and as mean ± standard deviation (±SD) or median [interquartile range, IQR] where appropriate for continuous variables. Normality was assessed using the Kolmogorov-Smirnov test. Differences between female and male HS patients were assessed using independent Student T-tests or Mann-Whitney U tests for continuous variables, where appropriate, and Chi-square tests for categorical variables.

Multiple imputations

Multiple imputations were used to impute missing data assuming that missing data was (completely) at random using fully conditionally specified models. The multiple imputations included sex, age and baseline BMI as predictors. Data was imputed m=20 times, so that the pooled results can be considered reliable.

Univariable and multivariable logistic regression analyses

Associations between participant characteristics, potential factors, and comorbidities with HS were assessed using univariable and multivariable logistic regression analyses, with adjusting for age, sex, BMI, smoking status and socioeconomic status. A backward selection procedure was used to identify the most influential factors reaching the best fit model, taking a $p<0.2$ as inclusion and $p>0.05$ as exclusion criteria. The strength of associations was reported as odds ratio with 95% confidence interval (95% CI). For each comparison, the reference category of group was set as the group with the lowest association to HS, i.e. the groups or category with the least prevalence difference between HS cases and control subjects. All statistical tests were two-sided and a p-value ≤0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp., Armonk, NY; USA).

RESULTS

Population

Our questionnaire was sent to 135.197 adult Lifelines participants of whom, 57.779 participants filled out our questionnaire, resulting in a response rate of 42.7%. Of these participants, 1356 respondents did not answer the HS related questions, excluding them from the study. Five cases were familial related, of whom one of the patients were excluded, leaving 56.084 respondents for analysis (Supplement S2).

Comparisons between baseline population characteristics and (non-)responders

Of the total invited population, the majority was female 58.5% with a mean age of 52.8 ± 12.5 years, at the time of sending out the questionnaire (Table 1a). Compared to non-respondents, the respondents were often more female ($p<0.001$), were older ($p<0.001$) and had more frequently a higher socioeconomic status ($p<0.001$) at baseline. The respondents were more

frequent nonsmokers (p<0.001), than the non-respondents.

Prevalence

In total, 448 respondents declared having a diagnosis of HS. The combination of the two other diagnostic questions was positively answered by 708 respondents, identifying a total of 1156 HS prevalent cases out of 56.084 respondents at the baseline, resulting in an overall HS prevalence of 2.1% (95% CI 2.0 to 2.2). When we performed bootstrapping analysis, we observed an overall prevalence of HS of 2.1% (95% CI 1.8 to 2.4), similar to the prevalence obtained from the total cohort.

Of the respondents with HS, 73.5% (n=850) HS cases were female, compared to 60.1% in the control group, resulting in a prevalence of HS of 2.5% (95% CI 2.35 to 2.69) in women. In addition, 26.5% (N=306) of the HS cases were male, resulting in a prevalence of 1.3% (95% CI 1.17 to 1.47) in men, resulting in a female/male ratio of 2.8/1.0.

When calculating with only the HS cases who had a prior medically diagnosed HS at the time of inclusion, the prevalence of HS would be estimated at 0.80% (95% CI 0.73 to 0.88). Of the medically diagnosed HS cases, 330 were female and 118 were male, with an estimated prevalence of 1.0% (95% CI 0.88 to 1.09), and 0.5% (95% CI 0.42 to 0.61), respectively.

Sub analysis in low SES participants

Included Lifelines participants in our add-on study had a higher SES, and thus there is a chance of selection bias, given HS is associated to low SES. Therefore, we reanalyzed the data of 15866 participants with low SES (SES between -6 and -3; as the SES of the total group was ranging from -6 to +3). When calculating with only the low SES participants, we found 374 HS cases, resulting in an estimated HS prevalence of 2.4% (95% CI 2.13 to 2.61).

Comparisons between HS and non-HS participants

In total, 1156 non-familial HS participants aged ≥18 years at baseline were group age-matched randomly to 5000 population-based controls, as described in the method section. Univariate regression analysis showed that female sex was associated with increased risk of HS disease (OR=1.84; 95% CI 1.60 to 2.13). In the HS group, the mean age was 52.1 ± 11.8 years compared to 56.0 ± 12.0 years for the control group. The HS respondents had a significant lower socioeconomic status (-0.65), compared to the control group (-0.55; p<0.001). Furthermore, almost a third of the HS group was a current smoker (31.9%), which was significantly associated with HS (p<0.001), while 51.8% of the control group were nonsmokers (Table 1b).

Characteristics of participants with HS

The overall median age at onset of HS symptoms was 25.0 [17.8 - 40.0] years (Table 2a). The median disease duration was 22.0 [11.0 - 33.0] years for females and 19.0 [8.0 - 34.0] years for males.

Table 1a. Baseline adult population characteristics

	Total n=134.036	**Respondents** n=57.445	**Non-respondents** n=76.591	**P-value***
Sex+				
Female, *n (%)*	78.451 (58.5)	34.661 (60.3)	43.790 (57.2)	
Male, *n (%)*	55.585 (41.5)	22.784 (39.7)	32.801 (42.8)	**<0.001**
Age (years), *mean (SD)*	52.76 (12.52)	55.78 (12.18)	50.50 (12.29)	**<0.001**
Female, *mean (SD)*	52.26 (12.45)	54.78 (12.08)	50.27 (12.37)	**<0.001**
Male, *mean (SD)*	53.47 (12.58)	57.30 (12.17)	50.80 (12.17)	**<0.001**
Socioeconomic status, *mean (SD)*	-0.62 (1.07)	-0.56 (1.06)	-0.66 (1.07)	**<0.001**
Smoking (last month)+				
No, *n (%)*	103.455 (78.9)	47.164 (83.0)	56.291 (75.7)	
Yes, *n (%)*	27.709 (21.1)	9672 (17.0)	18.037 (24.3)	**<0.001**
Missing, *n (%)*	2872	609	2263	

* Associations with responder status

+ First variable was used as reference for analysis

OR: odds ratio; CI: confidence interval; SD: standard deviation

For females, sexual organs were more frequently affected than in males (36.2% versus 10.8%). In contrast, in males the anal region was affected in 31.4%, while in females 22.7% reported involvement. Guided by pictures, 72.0% staged themselves as having mild disease (Hurley I); 22.0% as having Hurley II and 6.0% as having Hurley III. Participants were previously treated by either a general practitioner (70.8%) or a dermatologist (34.3%). When looking at the disease course over time, 40.9% reported a decrease in HS symptoms. In 25.2% of participants a positive family history was reported. Participants with a reported HS diagnosis (448/1156), were diagnosed by a GP in 46.6%, and by a dermatologist in 35.1% of the cases. At the time of filling out the questionnaire, 49 participants (4.2%) were receiving treatment for their HS, of which 30 participants were treated by a dermatologist.

Comparisons between reported HS diagnosis and self-diagnosed HS

Between the participants with a reported HS diagnoses and self-diagnosed HS no significant difference in age of onset of HS was found (p=0.513) (Table 2b). For disease duration, the group with a reported HS diagnosis had a significant longer disease duration, than the self-diagnosed HS group, 24.0 [13.0 to 35.0] years compared to 20.0 [9.0 to 32.0] years, respectively (p<0.001). For the affected areas no univariable analysis could be performed due to overlap in the answers, but in the respondents-group with reported HS diagnosis, all areas were more

Table 1b. Participants characteristics

				Univariable analysis	
	Total n=6156	**HS** n=1156	**Non-HS** n=5000	**OR (95% CI)**	**P-value***
Sex+					
Female, *n (%)*	3855 (62.6)	850 (73.5)	3005 (60.1)		
Male, *n (%)*	2301 (37.4)	306 (26.5)	1995 (39.9)	0.54 (0.47-0.63)	**<0.001**
Age (years), *mean (SD)*	55.2 (12.1)	52.1 (11.8)	56.0 (12.0)	0.97 (0.97 – 0.98)	**<0.001**
Female, *mean (SD)*	54.1 (12.0)	50.9 (11.4)	55.0 (12.1)	0.97 (0.97 – 0.98)	**<0.001**
Male, *mean (SD)*	57.2 (11.9)	55.5 (12.3)	57.4 (11.9)	0.99 (0.98 -0.99)	**0.011**
Socioeconomic status, *mean (SD)*	-0.57 (1.08)	-0.65 (1.11)	-0.55 (1.07)	0.92 (0.87 – 0.98)	**0.013**
Missing, *n (%)*	783	139	644		
Smoking (last month)+					
Nonsmoker, *n (%)*	2428 (49.0)	319 (36.1)	2109 (51.8)		
Current smoker, *n (%)*	853 (17.2)	282 (31.9)	571 (14.0)	3.27 (2.71 – 3.93)	**<0.001**
Ex-smoker, *n(%)*	1671 (33.7)	282 (32.9)	1389 (34.1)	1.34 (1.13 - 1.60)	**0.001**
Missing, *n (%)*	1204	273	931		

* Associations with responder status

+ First variable was used as reference for analysis

OR: odds ratio; CI: confidence interval; SD: standard deviation

frequently affected than in the self-diagnosed HS group. For the self-reported Hurley stages no significant difference was found between the groups (p=0.282 and p=0.346). Also, no significant difference was found for disease course in case of improvement or deterioration of HS (p=0.222).

Comorbidities

Of the respondents, HS participants were more likely to be obese (BMI ≥30 kg/m²) compared to the control group (OR=2.02; 95% CI 1.70 to 2.40). In the HS group significantly more participants suffered from skin diseases, like acne (OR=3.07; 95% CI 2.53 to 3.73), psoriasis (OR=2.34; 95% CI 1.93 to 2.84) and alopecia areata (OR=2.63; 95% CI 1.15 to 6.03), than in the control group. Further, univariate regression analysis revealed significant associations between HS and diabetes mellitus type II (OR=1.87; 95% CI 1.18 to 3.00), rheumatoid arthritis (OR=1.56; 95% CI 1.06 to 2.29), fibromyalgia (OR=2.26; 95% CI 1.64 to 3.11), bladder dysfunction (for example cystitis) (OR=1.87; 95% CI 1.42 to 2.45), kidney disease (OR=1.70; 95% CI 1.08 to 2.69), and

Table 2a. Additional HS patient characteristics female versus male

	Total n=1156	**Female** n=850	**Male** n=306
Age at onset of HS, *median [IQR]*	25.0 [17.8 - 40.0]	24.0 [16.0-38.0]	30.0 [18.25 - 45.0]
Missing, *n*	41	21	20
Disease duration (years), *median [IQR]*	21.0 [10.8-33.0]	22.0 [11.0-33.0]	19.0 [8.0-34.0]
Missing, *n*	41	21	20
Affected areas			
Armpit(s), *n (%)*	348 (30.1)	272 (32.0)	76 (24.8)
Under the breasts, *n (%)*	71 (6.1)	70 (8.2)	1 (0.3)
Groin, *n (%)*	599 (51.8)	509 (59.9)	90 (29.4)
Sexual organs, *n (%)*	341 (29.5)	308 (36.2)	33 (10.8)
Anal region, *n (%)*	289 (25.0)	193 (22.7)	96 (31.4)
Other, *n (%)*	266 (23.0)	128 (15.1)	138 (45.1)
Self-reported Hurley stage			
Hurley I, *n (%)*	817 (72.0)	602 (71.7)	215 (73.1)
Hurley II, *n (%)*	249 (22.0)	191 (22.7)	58 (19.7)
Hurley III, *n (%)*	68 (6.0)	47 (5.6)	21 (7.1)
Missing, *n*	22	10	12
Disease course			
Improvement, *n (%)*	468 (40.9)	357 (42.3)	111 (37.0)
Deterioration, *n (%)*	145 (12.7)	104 (12.3)	41 (13.7)
Not better or worse, *n (%)*	452 (39.5)	329 (39.0)	123 (41.0)
Remission, *n (%)*	38 (3.3)	26 (3.1)	12 (4.0)
Other, *n (%)*	41 (3.6)	28 (3.3)	13 (4.3)
Missing, *n*	12	6	6
Family members with HS			
Yes, *n (%)*	110 (25.2)	87 (26.9)	23 (20.5)
No, *n (%)*	154 (35.3)	116 (35.8)	38 (33.9)
Don't know, *n (%)*	172 (39.4)	121 (37.3)	51 (45.5)
Missing, *n*	720	526	194

Table 2a continued

	Total n=1156	**Female** n=850	**Male** n=306
Diagnosed by			
GP, *n (%)*	204 (46.6)	151 (46.5)	53 (46.9)
Dermatologist, *n (%)*	154 (35.1)	110 (33.8)	44 (38.9)
Surgeon, *n (%)*	27 (6.2)	20 (6.2)	7 (6.2)
Plastic surgeon, *n (%)*	4 (0.9)	3 (0.9)	1 (0.9)
Gynecologist, *n (%)*	3 (0.7)	3 (0.9)	0
Emergency room doctor, *n (%)*	5 (1.1)	5 (1.5)	0
Myself, *n (%)*	32 (7.3)	25 (7.7)	7 (6.2)
Other, *n (%)*	9 (2.1)	8 (2.5)	1 (0.9)
Missing, *n*	718	525	193
Current treatment			
Yes, by, *n (%)*	49 (11.3)	36 (11.2)	13 (11.6)
GP, *n (%)*	18 (36.7)	14 (38.9)	4 (30.8)
Dermatologist, *n (%)*	30 (61.2)	21 (58.3)	9 (69.2)
Other specialists *n (%)*	1 (2.0)	1 (2.8)	0
No, reason, *n (%)*	384 (88.7)	285 (88.8)	99 (88.4)
HS in remission, *n (%)*	131 (34.1)	90 (31.6)	41 (41.4)
Currently no boils, *n (%)*	193 (50.3)	153 (53.7)	40 (40.4)
Medication has no effect, *n (%)*	32 (8.3)	23 (8.1)	9 (9.1)
Other, *n (%)*	28 (7.3)	20 (7.0)	8 (8.1)
Missing, *n*	723	529	194
Treated in the past by			
GP, *n (%)*	819 (70.8)	598 (70.4)	221 (72.2)
Dermatologist, *n (%)*	397 (34.4)	291 (34.2)	106 (34.6)
Other specialists, *n (%)*	408 (35.3)	328 (38.6)	80 (26.1)
None, *n (%)*	206 (17.8)	157 (18.5)	49 (16.0)
Other, *n (%)*	15 (1.3)	10 (1.2)	5 (1.6)

Table 2b. Additional HS patient characteristics: reported diagnosis versus self-diagnosed HS

				Univariable analysis	
	Total HS n=1156	**Reported HS diagnosis** n=448	**Self-diagnosed HS** n=708	**OR (95% CI)**	**P-value***
Age at onset of HS, *median [IQR]*	25.0 [17.8 - 40.0]	25.0 [16.0-40.0]	25.0 [18.0-40.0]	0.99 (0.99 to 1.01)	0.513
Missing, *n*	41	28	13		
Disease duration (years), *median [IQR]*	21.0 [10.8-33.0]	24.0 [13.0- 35.0]	20.0 [9.0-32.0]	1.02 (1.01 to 1.03)	**<0.001**
Missing, *n*	41	28	13		
Affected areas					
Armpit(s), *n (%)*	348 (30.1)	153 (34.1)	195 (27.5)		
Under the breasts, *n (%)*	71 (6.1)	39 (8.7)	32 (4.5)		
Groin, *n (%)*	599 (51.8)	233 (52.0)	366 (51.7)		
Sexual organs, *n (%)*	341 (29.5)	140 (31.3)	201 (28.4)		
Anal region, *n (%)*	289 (25.0)	102 (22.8)	187 (26.4)		
Other, *n (%)*	266 (23.0)	120 (26.8)	146 (20.4)		
Self-reported Hurley stage					
Hurley I, *n (%)*	817 (72.0)	313 (73.0)	504 (71.5)		
Hurley II, *n (%)*	249 (22.0)	86 (20.0)	163 (23.1)	0.85 (0.63 to 1.14)	0.282
Hurley III, *n (%)*	68 (6.0)	30 (7.0)	38 (5.4)	1.27 (0.77 to 2.09)	0.346
Missing, *n*	22	19	3		

Disease course					
Improvement, *n (%)*	468 (40.9)	224 (51.3)	244 (34.5)		
Deterioration, *n (%)*	145 (12.7)	61 (14.0)	84 (11.9)	1.27 (0.87 to 1.84)	0.222
Not better or worse, *n (%)*	452 (39.5)	109 (24.9)	343 (48.4)	0.44 (0.30 to 0.65)	**<0.001**
Remission, *n (%)*	38 (3.3)	28 (6.4)	10 (1.4)	0.79 (0.39 to 1.63)	0.529
Other, *n (%)*	41 (3.6)	15 (3.4)	26 (3.7)	3.86 (1.74 to 8.53)	**0.001**
Missing, *n*	12	11	1		

* Associations with responder status

+ First variable was used as reference for analysis

OR: odds ratio; CI: confidence interval; SD: standard deviation

Table 3. Comorbidities

				Univariable analysis		*Multivariable analysis*⁺	
	Total	**HS**	**Non-HS**				
	n=6156	n=1156	n=5000	**OR (95% CI)**	**P-value***	**OR (95% CI)**	**P-value***
BMI[a]							
BMI ≤ 25 kg/m², *n (%)*	2632 (42.8)	422 (36.5)	2210 (44.2)				
BMI 25-30 kg/m², *n (%)*	2476 (40.2)	443 (38.3)	2033 (40.7)	1.14 (0.99 to 1.32)	0.079		
BMI ≥30 kg/m², *n (%)*	1048 (17.0)	291 (25.2)	757 (15.1)	2.02 (1.70 to 2.40)	**<0.001**		
Skin disorders							
Acne, *n (%)*	491 (8.0)	189 (16.3)	302 (6.0)	3.07 (2.53 to 3.73)	**<0.001**	3.13 (2.71 to 3.62)	**<0.001**
Psoriasis, *n (%)*	532 (8.6)	175 (15.1)	357 (7.1)	2.34 (1.93 to 2.84)	**<0.001**	2.37 (2.10 to 2.69)	**<0.001**
Eczema, *n (%)*	655 (10.6)	207 (17.9)	448 (9.0)	0.79 (0.65 to 0.97)	**0.023**		
Alopecia areata, *n (%)*	24 (0.4)	9 (0.8)	15 (0.3)	2.63 (1.15 to 6.03)	**0.022**		
Metabolic diseases							
Diabetes type II, *n (%)*	161 (2.6)	44 (3.8)	117 (2.3)	1.87 (1.18 to 3.00)	**0.007**	2.66 (1.88 to 3.75)	**0.005**
Hypertension, *n (%)*	1359 (22.1)	280 (24.2)	1079 (21.6)	1.17 (1.00 to 1.36)	**0.045**		
Hypercholesterolemia, *n (%)*	830 (13.5)	139 (12.0)	691 (13.8)	1.15 (0.94 to 1.40)	0.173		
Heart diseases							
Heart failure, *n (%)*	61 (1.0)	13 (1.1)	48 (1.0)	1.42 (0.79 to 2.55)	0.241		
Heart attack, *n (%)*	56 (0.9)	8 (0.7)	48 (1.0)	0.72 (0.34 to 1.53)	0.393		
Lung diseases							
COPD, *n (%)*	331 (5.4)	92 (8.0)	239 (4.8)	1.74 (1.35 to 2.23)	**<0.001**	1.63 (1.38 to 1.92)	**0.003**
Asthma, *n (%)*	561 (9.1)	136 (11.6)	425 (8.5)	1.44 (1.17 to 1.77)	**<0.001**		
Gastrointestinal disorders							
Crohn's disease, *n (%)*	30 (0.5)	12 (1.0)	18 (0.4)	2.69 (1.25 to 5.79)	**0.011**		
Ulcerative colitis, *n (%)*	47 (0.8)	8 (0.7)	39 (0.8)	0.80 (0.36 to 1.78)	0.588		
Irritable bowel syndrome, *n (%)*	647 (10.5)	176 (15.2)	471 (9.4)	1.63 (1.18 to 2.26)	**0.003**		

Musculoskeletal disorders							
Rheumatoid arthritis, *n (%)*	168 (2.7)	44 (3.8)	124 (2.5)	1.56 (1.06 to 2.29)	**0.026**		
Fibromyalgia, *n (%)*	261 (4.2)	86 (7.4)	175 (3.5)	2.26 (1.64 to 3.11)	**<0.001**	1.51 (1.23 to 1.86)	**0.044**
Neurological disorders							
Migraine, *n (%)*	1286 (20.9)	296 (25.6)	990 (19.8)	1.48 (1.11 to 1.96)	**0.007**		
Chronic fatigue syndrome, *n (%)*	99 (1.6)	30 (2.6)	69 (1.4)	1.72 (1.06 to 2.78)	**0.028**	2.16 (1.19 to 3.90)	**0.010**
Urological disorders							
Kidney disease, *n (%)*	93 (1.5)	26 (2.2)	67 (1.3)	1.70 (1.08 to 2.69)	**0.023**	2.36 (1.69 to 3.30)	**<0.001**
Bladder dysfunction, *n (%)*	268 (4.4)	79 (6.8)	189 (3.8)	1.87 (1.42 to 2.45)	**<0.001**	1.83 (1.54 to 2.17)	**0.001**
Gynecological disorders							
PCOS, *n (%)*	91 (1.5)	31 (2.7)	60 (1.2)	2.29 (1.48 to 3.55)	**<0.001**		
Mental disorders							
Depression, *n (%)*	754 (12.2)	228 (19.7)	526 (10.5)	2.03 (1.43 to 2.79)	**<0.001**		
Anxiety, *n (%)*	386 (6.3)	106 (9.2)	280 (5.6)	1.60 (1.15 to 2.22)	**0.005**		
Malignancies of any kind, *n (%)*	390 (6.3)	76 (6.6)	314 (6.3)	1.05 (0.81 to 1.36)	0.711		

[+]Corrected for sex, age, BMI, smoking status and socioeconomic status

*Associations with HS status

[a]BMI ≤ 25 kg/m², was used as reference for univariable and multivariable analysis. For the multivariable analysis only the significant results are showed.

OR: odds ratio; CI: confidence interval; SD: standard deviation; BMI: body mass index; PCOS: polycystic ovary syndrome; COPD: chronic obstructive pulmonary disease

polycystic ovary syndrome (PCOS) (OR=2.29; 95% CI 1.48 to 3.55). As for lung diseases, both COPD and asthma, were significant associated with HS, with ORs of 1.74, 95% CI 1.35 to 2.23, and 1.44, 95% CI 1.17 to 1.77. Crohn's disease (OR=2.69; 95% CI 1.25 to 5.79) and irritable bowel syndrome (OR 1.63; 95% CI 1.18 to 2.26), were significantly more common in the HS participants, while ulcerative colitis was negatively associated with HS disease (OR=0.80; 95% CI 0.36 to 1.78), however not significant. For neurological disorders, like migraine (OR=1.48; 95% CI 1.11 to 1.96) and chronic fatigue syndrome (OR=1.72; 95% CI 1.06 to 2.78), as well as mental disorders, like depression (OR=2.03; 95% CI 1.43 to 2.79) and anxiety (OR=1.60; 95% CI 1.15 to 2.22), significant more patients in the HS group were affected compared to the controls. Malignancies, and the different subtypes of cancer, were not significantly associated with HS (p=0.711). Several comorbidities remained significantly associated with HS in the multivariate model, such as acne (OR=3.13; 95% CI 2.71 to 3.62) chronic fatigue syndrome (OR=2.16; CI 95% 1.19 to 3.90) and fibromyalgia (OR=1.51; CI 95% 1.23 to 1.86) (Table 3).

Comorbidities compared between male and female HS cases

For female HS patients, hypertension (OR=1.48; 95% CI 1.07 to 2.05), irritable bowel syndrome (OR=2.67; 95% CI 1.23 to 5.81), fibromyalgia (OR=6.43; 95% CI 2.19 to 18.93) and bladder dysfunction (OR=2.30; 95% CI 2.30 to 14.34) were significantly associated with HS, when compared to male HS patients. In contrast, psoriasis (OR=0.58; 95% CI 0.41 to 0.81) and heart attack (OR=0.21; 95% CI 10.50 to 0.89) were negatively associated with HS in female patients, compared to males with HS (Supplement Table S3).

DISCUSSION

In our study, we aimed to determine the prevalence of HS in the general adult population in the Northern Netherlands and to assess the potential factors and comorbidities associated with HS. We determined an overall prevalence of 2.1% of HS in the general population of the Northern Netherlands. Additionally, we newly identified fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and migraine to be associated with HS.

Since our results demonstrated an overall prevalence of 2.1% of HS in our cohort, we argue that the previously estimated prevalence of 1% is an underestimation of the actual prevalence, especially in Northern European countries, like the Netherlands.[9,14,15] Taking into account that our study investigated solely adult participants, the actual prevalence might be even higher, considering HS generally appears around late puberty or early adulthood.[16] When comparing respondents to the non-respondents, respondents were more likely to have higher socioeconomic status and be non-smokers. Again, this suggests that the overall prevalence of 2.1% is likely an underestimation of the real HS prevalence, since HS is associated with low SES and smoking, and therefore our respondent group had a lower risk of developing HS.[16,17] For that reason, we reanalyzed our data with participants with only low SES, resulting in an higher estimated HS prevalence of 2.4%. We confirmed in our cohort the associations between HS and low SES, and HS and smoking. The female/male ratio of 2.8 to 1 found in our cohort is in concordance with previous reports of HS affecting females three times more often than men.[17] Both suggesting that our cohort is a representative HS population.

Prior studies exploring the prevalence of HS based their study population on selective groups.[18–20] Other studies used insurance or healthcare data in which cases can be missed due to miscoding, uninsured patients, and underdiagnosis.[8,15,21–30] Moreover, the prevalence of HS in the current study would be 0.80%, using only previously diagnosed HS cases. This indicates, that HS is still subject to under-diagnosis in The Netherlands. This could be due to feelings of shame consequently preventing patients from seeing a doctor (patient delay), or due not recognizing HS by the treating physician (doctors delay). Nevertheless, in 2015 Blok *et al.* showed that only 19% of HS patients were diagnosed by a general practitioner (GP), while our current study demonstrates that 46.6% of the HS participants were diagnosed by a GP.[31] This suggests an increased awareness for HS among general practitioners, possibly due to improved knowledge of the disease as a result of education and a prominent patient association.

Despite the above, as more than half of the identified HS cases were self-reported, we still do not reach the majority of the HS patients in the Northern Netherlands. Our results showed, that participants who self-diagnosed their HS had comparable ages at onset of disease and no difference in self-reported severity of HS, compared to the HS diagnosed participants. As the main characteristics of participants with self-reported HS versus diagnosed HS were similar, this indirectly validated once more the diagnostic questions for HS by Esmann *et al.*[13] However, there were still some slight noteworthy differences between the two groups. The self-diagnosed HS respondents reported more frequently a stable HS course and had a significant shorter disease duration, than the group with reported HS diagnosis, 20.0 years versus 24.0 years ($p<0.001$), respectively. Both stable HS disease and shorter disease duration could be an explanation, that no physician was consulted yet nor a diagnosis was made. However, a median disease duration of 20.0 years is still a long time for not seeking medical care. Since an earlier diagnosis could prevent progression of disease and could contribute to a lower burden of disease, even more awareness is needed for identifying the undiagnosed HS patients.

We could also confirmed previously reported associated comorbidities, such as rheumatoid arthritis, depression and anxiety.[32,33] Our findings are consistent with those of previous studies on the association between HS and Crohn's disease (ORs 2.69 versus 2.21), diabetes mellitus type II (ORs 1.87 versus 2.17) and PCOS (ORs 2.29 versus 2.64).[34–36] In addition, both COPD and asthma were also associated with HS.[37] For urological disorders, kidney disease and bladder dysfunction (of any kind), were associated with HS as well. While occurrence of fistulas to the urinary tracts and bladder are mentioned in literature, this is unlikely the cause of any bladder dysfunction in our cohort, as the majority classified themselves as having mild disease (stage I). In stage I sinus tracts are per definition absent. Interestingly, we identified new associations between HS and other diseases, such as fibromyalgia (OR 2.26), chronic fatigue syndrome (OR 2.72) and migraine (OR 1.48). Irritable bowel syndrome was also significantly more common in the HS group (OR 1.63), which is a compelling finding, since both irritable bowel syndrome and HS are associated with metabolic disease.[38] In addition, sub analysis stratifying the HS cohort based on sex, showed new significant associations as more women with HS were suffering from irritable bowel syndrome (2.67) and fibromyalgia (OR 6.43) than men.

Contrastingly to previous findings, our results from the total cohort showed that heart diseases

and malignancies were not significantly associated with HS.[39,40] A possible explanation for this discrepancy could be, that Egeberg *et al.* studied patients and controls in a hospital setting.[39] Moreover, Tannebaum *et al.* did not assess severity of HS in their study population.[40] In consideration of the predominant mild reported HS disease of our population, this could be the cause of not finding an association of heart disease and malignancies among HS participants.

Our study was limited by the self-reported HS diagnosis. However, validated questions and images of HS were used to minimize the chance of false positive cases. Since no significant difference between the reported HS diagnosed and self-diagnosed HS groups was found for most disease characteristics, it is convincing that the self-diagnosed HS group could be considered representative for our investigated HS cohort. For this study, data from the Lifelines baseline assessment was partially used, which was collected up to 10 years before our questionnaire was filled out. Respondent characteristics, might have changed overtime, which could have influenced our results. However, when possible, we used the most recent data available. Also, non-response was high for several different questions, which could interfere the outcomes, as well as the lack of possibility of answering 'no' if a certain comorbidity was not present. Strengths of our study are the substantial sample size, population-based setting and generalizable results to Northern European countries.[41]

CONCLUSION

In conclusion, our study demonstrates an overall prevalence of 2.1% of HS in the general population of the Northern Netherlands. The majority of HS cases in this cohort did not have a diagnosis of HS, indicating that underdiagnosis is still an issue in the Netherlands. Furthermore, we newly identified fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome and migraine to be associated with HS in this cohort. HS is associated with even more comorbidities, stressing the need for early diagnosis and initiation of treatment.

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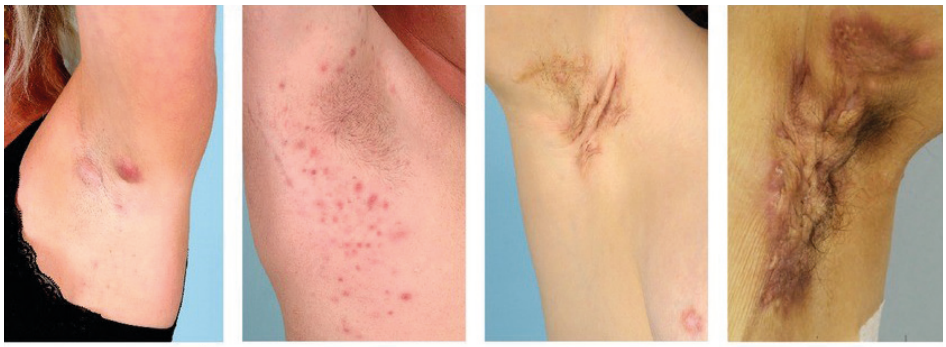
Supplement S1. Overview of questions used for identifying HS status

1. **Did you ever (during your life) got the diagnosis hidradenitis suppurativa (HS)?**

   Yes
   No - *Go to question 2 and 3*

2. **Do you have painful, recurring abscesses or boils in your armpits, groin, buttocks or on other locations, as seen in the images below?**

   Yes - *Go to next question*
   No



3. **Did you have at least 2 outbreaks of abscesses or boils within a period of 6 months?**

   Yes
   No

Supplement S2. Flowchart demonstrating which participants were eligible for analysis