Incidence and remission rates of self-reported hidradenitis suppurativa - A prospective cohort study conducted in Danish blood donors

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- A prospective cohort study conducted in Danish blood donors.

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This study has been approved by Danish Data Protection Agency, Copenhagen (2012-58-0004, RH-30-0444 / I-suite no.: 00922) and the Committee on Health Research Ethics in the Central Denmark Region (M-20090237).

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Attached: STROBE checklist

Abstract

BACKGROUND: A large discrepancy between physician-diagnosed and self-reported HS exists. Knowledge regarding incidence and remission rates of self-reported HS is missing, but may help bridge the gap in understanding between these two phenotypes.

OBJECTIVES: To determine the incidence and remission rates of self-reported HS, and to what degree these are affected by sex, smoking and BMI.

METHODS: A prospective cohort of 23,930 Danish blood donors. Information on self-reported HS, symptom-localization, sex, age, BMI and smoking status was collected at baseline and study termination. Self-reported HS fulfilled clinical obligatory diagnostic criteria. Cox proportional hazards regression analyses were conducted for both incidence and remission rates providing a hazard ratio (HR) of risk for each variable in the regression.

RESULTS: incidence rate of self-reported HS was 10.8/1,000 person-years (95% CI: 9.9-11.7), decreasing as a function of numbers of areas affected. Female BMI points above 25 (HR=1.11, 95% CI: 1.09–1.13), male BMI points above 25 (HR=1.07, 95% CI: 1.04–1.11) , active smoking (HR=1.72, 95% CI: 1.15–2.57), male sex (HR=0.55, 95% CI: 0.45–0.67) and years of age above 25 (HR=0.97, 95% CI: 0.96–0.97) were all statistically associated with the development of self-reported HS.

Remission rate of self-reported HS was 256.7/1,000 person-years (95% CI: 223.9–292.6), decreasing as a function of numbers of affected areas. Symptoms in ≥3 areas (HR=0.54, 95% CI: 0.34–0.85), active smoking (HR=0.49, 95% CI: 0.32–0.76) and female weight loss (every percentage drop in BMI: HR=1.07, 95%CI: 1.05–1.11) all significantly affected the remission rate.

CONCLUSIONS: Both incidence and remission rates of self-reported HS are high, indicating that many with self-reported HS are unlikely to be diagnosed, as they to a higher degree experience mild transient HS symptoms.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent and painful nodules in inverse regions of the skin. These nodules can evolve into abscesses and/or tunnelswhich may lead to chronic seepage. Ultimately, the inflammatory lesions cause restrictive scars, resulting in physical impairment that can only be surgically corrected [1, 2]. HS is associated with higher rates of depression, suicide, diabetes, myocardial infarction, all-cause mortality and reduced quality of life [3-5].

Despite availability of formalized diagnostic criteria [6], HS is considerably underdiagnosed and diagnostic delay is common/long [7-10]. Self-reported HS prevalence in population studies is 1-2% [11-14], while physician-diagnosed registry data suggest prevalence around 0.1-0.2% [5, 15, 16]. This suggest that self-reported HS is either erroneously overdiagnosed, or that a staggering 90% of those with self-reported HS goes undiagnosed. A recent meta-analysis has estimated the international prevalence of HS to be 0.4% [17], albeit with a large discrepancy from 0.3% to 1.7% based on hospital or community based estimates of HS. While the chance of diagnosis increase with the severity of disease [18], knowledge regarding incidence of undiagnosed cases are still of considerable benefit. Currently, the largest study on HS incidence is a US study on insurance-data from 48 million Americans. It found a standardized HS incidence rate of 11.4/100,000 person-years (95% confidence interval (CI) = 11.1–11.8) [19]. The incidence rate and remission rate of self-reported HS is unknown, but is suspected to be considerable higher.

To help physicians and patients by informing them of symptom development and remission, we decided to estimate the incidence rate of self-reported HS within a population of Danish blood donors, and to calculate the remission rate amongst those with self-reported HS fulfilling the clinical obligatory diagnostic criteria [6]. Furthermore, we investigated which factors (sex, age, BMI, smoking-status, and number of affected anatomical areas) were associated with either development or remission of self-reported HS. Lastly, recognizing that participants with self-reported HS who report lesions in multiple intertriginous areas are likely to better reflect patients with HS treated in the clinic [18], we provide a separate estimate of incidence rate and remission rate for participants based on number of areas affected by self-reported HS.

Materials and Methods

Study design and population

In this prospective cohort study, the incidence and remission rates of self-reported HS were determined through a screening-questionnaire [11] constructed to cover all the diagnostic criteria for HS [6] (see below).

Participants were Danish blood donors who participated in the Danish Blood Donor Study (DBDS), previously described in detail elsewhere [7, 20-22], who were screened at two distinct time-point spaced at least six months apart. Briefly, DBDS was initiated in March 2010 as a Danish multicenter, public-health study and biobank (www.dbds.dk). Inclusion is ongoing, currently in its fourth iteration. Participants fill out questionnaires pertaining to several different health-related items, and may be invited to multiple questionnaire iterations if they remain active donors. Since initiation, more than 130,000 blood donors aged 18–70 years have participated, with a participation rate of above 95% [20]. As the objective of this study was to calculate the incidence and remission rates of self-reported HS, only DBDS participants who had filled out both the second and third iteration of the DBDS questionnaire, were eligible for this study.

Questionnaire & HS phenotype

Initial screening took place between June 2015 through May 2018, and the second round of screening from June 2018 through March 2020.

Both times the screening questionnaire consisted of a previously validated HS screening-questionnaire [11] including all the clinical obligatory diagnostic criteria [6]. Screen-positives thus reported: 1) boil formation; 2) in intertriginous skin areas (axillae, groin, genitals, perineal and perianal region, buttocks, infra- and inter-mammary folds); 3) with at least two boils within a 6-month period. Specifically, the questionnaire enquired as to boil formation for each anatomical area described under criteria 2). This information on localization was used to stratify participants with self-reported HS according to number of affected areas (1, 2 or ≥3). The justification for this was, that we wanted to assess the impact of number of affected areas upon the ReR, and that participants with a higher number of affected areas more accurately reflect patients treated for HS in dermatological clinics [18, 23]. Consequently, information on remission rate for this group may be of higher interest to physicians treating patients with HS. The prevalence of the subgroup with self-reported HS from ≥3 areas was 0.3%, a figure that reflects both the cumulative incidence of diagnosed HS patients amongst Danish twins by age 40 years (female: 0.35%, male: 0.13%) [24], and the 0.19% prevalence found in a Danish nation-wide register study on physician diagnosed HS [5]. Ultimately, this indicates that the ≥3 areas subgroup is similar to patients diagnosed with HS by a physician.

At both screening times information on completion date, height, weight and current smoking status were collected. From these, length of follow-up; BMI; change in BMI (percentage change between the two time-points); and cessation or initiation of smoking were calculated. Information on sex and date of birth were available through linkage to the Civil Personal Registry (CPR) at Statistics Denmark, using the unique ten digit CPR number giving to all residents in Denmark at birth or immigration [25]. The CPR number also

allowed for linkage to information from the Danish National Patient Registry (DNPR) which contain information on all diagnoses made at public hospitals from January 1st 1994 until December 31st 2018 [25].

Outcomes and statistical analysis

Incidence rate was calculated as newly developed cases amongst those initially screening HS-negative, divided by their accumulated follow-up time. The same approach was used to calculate remission rates amongst those who initially screened HS-positive. For both groups, a Cox proportional hazards regression analysis was performed to evaluate whether change in self-reported HS-status was associated with sex; age (continuous); BMI (continuous); change in BMI (percentage); current smoking status (yes/no); cessation of smoking; and for remission rate the numbers of affected areas at the initial screening. To adjust for the healthy donor effect [26, 27], both Cox analyses were additionally adjusted for donation frequency (continuous) during the previous five years. The analyses provide a hazard ratio (HR) of risk for each variable in the regression. Relevant interaction terms were included in the Cox proportional hazards regressions if they resulted in a better model, as assessed by the Akaike information criterion (AIC) value.

We used R-3.5.1 for Windows (GNU General Public license) for all statistical analyses. For descriptive statistics [28] means and standard deviations are provided. Differences between groups were calculated with t-tests or Mann–Whitney U-tests, depending on normality. Participants entered into the study the date of initial screening and were censored once they were screened anew. All participants with missing information were included in the descriptive statistics but excluded from further analyses.

The Bonferroni procedure for multiple testing, with a false discovery rate of 0.05, was applied to the Cox regression analyses.

Sensitivity analysis

Two sensitivity analyses were planned for this study. The first consisted of a Cox proportional hazards regression analysis on remission rate of the subset of participant who initially screened positive for self-reported HS in ≥3 arrears. This was done in order to ascertain if the effect of environmental exposures where the same for this subgroup as for all participants who initially screened positive for HS. The second sensitivity analysis consisted of a Cox proportional hazards regression analysis on remission rate on the subset of initial HS screen-positives who had received a diagnosis of HS at a hospital before the initial screening.

Results

Population characteristics

A total of 23,930 participants completed both screenings, and amongst these 1.8% (430/23,930) had self-reported HS at the initial screening (Table I). A total of 33 participants corresponding to 0.14% had been diagnosed with HS at a hospital before the initial screening. Amongst those with self-reported HS, this number was 12 corresponding to 2.8% (Table I).

HS incidence rate

Of 23,500 participants without self-reported HS, 516 (2.2%) developed self-reported HS during 47,913 person-years of follow-up, equivalent to an incidence rate of 10.8 (95% confidence interval (CI): 9.9–11.7) cases per 1,000 person-years (Table II).

BMI points above 25 for both females (HR = 1.11, 95% CI: 1.09–1.13, $p < 2.0 \times 10^{-16}$), and males (HR = 1.07, 95% CI: 1.04–1.11, $p = 1.1 \times 10^{-5}$) as well as active smoking (HR = 1.72, 95%CI: 1.15–2.57, p = 0.008) were significantly associated with the development of self-reported HS (Table IV and Figure 1). Conversely, both male sex (HR = 0.55, 95% CI: 0.45–0.67, $p = 2.4 \times 10^{-9}$) and every year of age above 25 (HR = 0.97, 95% CI: 0.96–0.97, $p < 2 \times 10^{-16}$) were protective factors against developing self-reported HS.

HS-symptom remission rate

Of 430 participants who had self-reported HS, 215 (50%) experienced remission during 837 person-years of follow-up (Table III). This corresponds to a remission rate of 256.7/1,000 person-years (95% CI: 223.9, 292.6) or 25.7% (95% CI: 22.4–29.3%) annually. Rates of remission were highest for those with fewest affected areas (Table III). Overall, during a median follow-up period of 693 days (interquartile range: 462–955.5) remission, reduction in number of affected areas, unchanged status and increase in number of affected areas were 50.0% (215/430), 11.9% (51/430), 25.8% (111/430) and 12.3% (53/430), respectively.

Self-reported HS in ≥3 areas (HR = 0.54, 95% CI: 0.34–0.85, p = 0.008) and active smoking (HR = 0.49, 95% CI: 0.32–0.76, p = 0.001) were both significantly associated with decreased likelihood of remission (Table IV and Figure 2). Meanwhile, female weight loss as measured in percentage decrease in BMI (HR = 1.07, 95%CI: 1.05–1.11, $p = 6.6 \times 10^{-7}$) was significantly associated with a higher likelihood of remission. Similar findings was not found for males (HR = 1.00, 95%CI: 0.97–1.04, p = 0.86).

Sensitivity analysis

The first sensitivity analysis on the 72 participants with self-reported HS in ≥3 areas is shown in Supplemental Table I. Overall it is in agreement with the results listed in Table IV, indicating that the effect of environmental exposures upon remission rate were similar across the number of areas affected.

The second sensitivity analysis could not be performed as only 12 (2.8%) of the 430 participants who initially had self-reported HS, had previously been diagnosed with HS at a hospital (Table I).

Discussion

We estimated the incidence rate of self-reported HS to be 10.8/1,000 person-years (95% CI: 9.9–11.7), nearly 100 times higher than the incidence rate for diagnosed HS estimated by Garg et al. [19], who found a US incidence rate of 11.4/100,000 person years (95% CI: 11.1–11.8). As expected, we found a substantially higher incidence rate for self-reported HS than for diagnosed HS. The reason for this difference is likely twofold. Firstly, the US incidence rate originated from health-care records of insured or self-paying patients identified via the International Code of Disease 9 code [19]. This method is affected by underdiagnosis [7, 29], and sampling bias favoring participants with a generally higher socio-economic status (SES) [16]. This constitutes a bias as HS is associated with low SES [30, 31], and consequently HS patients are less likely to have access to affordable healthcare. Conversely, our cases represent self-reported HS identified via a screening questionnaire constructed to match clinical diagnostic criteria [11]. This approach incurs the risk of overestimating the prevalence or incidence rate due to false positives [14, 32]. To account for this we calculated the incidence rate of those with self-reported HS from ≥3 areas specifically due to its higher clinical relevance. In this subgroup the incidence rate was 1.3/1,000 person years (95% CI: 1.0–1.6), only ten times higher than that provided by Garg et al. [19], but more reflective of the number of persons requiring the attention of a dermatologist, and in line with known levels of underdiagnosis [7, 29].

Our analyses indicate that both female and male overweight (each BMI point above 25: HR = 1.11, 95% CI: 1.09–1.13 and HR = 1.07, 95% CI: 1.04–1.11), and active smoking (HR = 1.72, 95% CI: 1.15–2.57) influence the risk of developing self-reported HS. Similar findings were reported by Garg et al. [33], who in a large register-based study found that the odds ratio (OR) for HS was 1.90 (95% CI: 1.84–1.96) for smokers and 1.88 (95% CI: 1.81–1.96) for the obese.

Our results on self-reported HS remission depict the natural progression of HS symptoms over a course of up to 4.4 years (median of 1.90 years), and show an annual remission rate of symptoms of 25.7% (95% CI: 22.4–29.3%), but only 15.6% (10.1–22.6%) for those with self-reported HS from ≥3 areas. Smoking

reduced the likelihood of remission (HR = 0.49, 95% CI: 0.32–0.76) whereas female weight loss increased the likelihood of remission (every percentage drop in BMI: HR = 1.07, 95% CI: 1.05–1.11).

These results are comparable with those of diagnosed HS provided in a retrospective study by Kromann et al. [34] who showed that over a median follow-up period of 22 years 39.4% of 127 patients reported remission, 31.5% improvement, 20.5% unchanged severity and 8.7% worsening of symptoms. Kromann et al. also noted that remission was higher amongst non-smokers (40% vs. 29%) and non-obese patients (45% vs. 23%) [34].

We interpret these findings to suggest that many with self-reported HS will experience a quick and marked improvement, whereas an estimated 1/9 will have more severe and protracted symptoms. This latter group, after experiencing diagnostic delay [9, 10], likely represents the patients encountered in the clinic.

Limitations

One limitation of this study is that the phenotype; self-reported HS likely include a higher level of false positives than those diagnosed by a physician, as participants screening positive for HS in one area, may simply report what could have been bacterial folliculitis. As this condition clears quickly with application of topical or systemic antibiotics it could have affected the high remission rate for self-reported HS in one area. To decrease this limitation, specific analyses for those with self-reported HS in ≥3 anatomical areas were performed as they better reflect the hospital-based HS population [23]. In this regard however, it must be mentioned that the screening-questionnaire is previously validated[11], and that the proportion of the participants with self-reported HS reflects previous estimates identified in other populations (1.19% in UK [12] and 1.08% in Wales [13]), indicating that the screening-questionnaire accurately identify cases of self-reported HS.

Unfortunately, we do not know if participants who underwent remission had received active treatment. However, standard HS treatments with long-term systemic antibiotics [35], only result in temporary deferral from blood donation (until four weeks post-treatment). Additionally, only five DBDS participants who participated in the initial but not the subsequent screening were diagnosed with HS at a hospital during the study period (information from DNPR). Non-participation due to treatment-based deferral from blood donation thus likely present only a small bias.

Lastly, the study by design, suffers from healthy donor bias [26, 27]. While we corrected for donation frequency in our Cox proportional hazards regression analyses, the true incidence rate of self-reported HS in the general population is therefore likely higher, while the remission rate is lower.

Conclusion

Our study suggests a high incidence rate of self-reported HS (10.8/1,000 person years, 95% CI: 9.9–11.7), while the remission rate is also high (256.7/1,000 person-years, 95% CI: 223.9–292.6). The incidence rate and remission rate of those participants most likely to reflect patients seen at a dermatological clinic, were 1.3 (95% CI: 1.0–1.6) and 155.6 (95% CI: 101.4–226.4) per 1,000 person years, respectively.

Active smoking and each BMI point above 25 was significantly associated with development of self-reported HS for both men and women, whereas male sex and each year of age above 25 decreased the risk of developing self-reported HS. Remission was negatively associated with ≥3 affected areas and active smoking, whereas female weight loss was found to increase the chance of remission.

The combined high incidence and remission rates of self-reported HS, indicate that many of those with self-reported HS are unlikely to be diagnosed, as they to a higher degree experience mild transient HS symptoms.

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DATA ACCESS, RESPONSIBILITY AND ANALYSIS: Authors RK Andersen and IC Loft had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA SHARING STATEMENT: Data from Danish registries are protected by the Danish Act on Processing of Personal Data and can only be accessed following application. Therefore, data sharing for this study is not possible.

ADDITIONAL INFORMATION: The Department of Dermatology, Zealand University Hospital, Roskilde, Denmark, is a part of the European Reference Network for rare, complex, and undiagnosed skin diseases.

Figure legends:

Figure 1: Hazard ratio for developing self-reported HS

Legend: Forest plot showing the hazard ratio of developing self-reported HS, in regards to the effect of each of the following variables: Sex, smoking status, smoking cessation, BMI points above 25 for females, BMI points above 25 for males, percentage drop in BMI, every year of age above 25, every year of above 25 for smokers and donation frequency.

Figure 2: Hazard ratio for remission of self-reported HS

Legend: Forest plot showing the hazard ratio of self-reported HS remission, in regards to the effect of each of the following variables: Number of affected areas, sex, smoking status, BMI points above 25, percentage drop in BMI for females, percentage drop in BMI for males, every year of age above 25 and donation frequency.

Table I: Self-reported HS status in the initial screening

Self-reported HS at the initial screening					
	Self-reported in 1 area	Self-reported in 2 areas	Self-reported in ≥3 areas	All cases	All participants
N, (% of all cases)	191 (44.4)	167 (38.8)	72 (16.7)	430	23,930
% of participants	0.80	0.70	0.30	1.80	
Diagnosed with HS in the DNPR N, (%) (for use in sensitivity analysis)	5 (2.6)	4 (2.4)	3 (4.2)	12 (2.79)	33 (0.14)

Number and percentile distribution of self-reported HS amongst participants at the initial screening.

DNPR = Danish National patient registry, N = number.

Table II: Descriptive statistics and incidence rates of initial screen-negatives

Participants without self-reported HS during the initial screening						
Self-reported HS during the second screening		HS-negative	Self-reported HS in 1 area	Self-reported HS in 2 areas	Self-reported HS in ≥3 areas	p-value
Number (%)		22,984 (97.8)	304 (1.3)	151 (0.6)	61 (0.3)	
Sex, male/female N (male %/female %)		12,753/10,231 (55.5/44.5) [a, b, c]	121/183 (39.8/60.2) [a, e]	66/85 (43.7/56.3) [b, f]	14/47 (23.0/77.0) [c, e, f]	1.0×10^{-13} ***
Age at enrolment, median years (IQR)		42.1 (30.0; 51.7) [a, b, c]	38.1 (27.4; 48.0) [a, e]	34.0 (25.3; 43.9) [b]	28.9 (23.8; 39.4) [c, e]	$<2 \times 10^{-16}$ ***
BMI	BMI, points	25.3 (23.1; 28.0) [a, b, c]	26.6 (24.1; 29.9) [a]	26.9 (23.5; 30.3) [b]	27.1 (24.5; 31.5) [c]	$<2 \times 10^{-16}$ ***
	ΔBMI, %	-1.1 (-3.7; 1.3)	-1.3 (-4.5; 1.3)	-1.6 (-5.3; 1.2)	-2.1 (-5.4; 1.8)	0.13
	NA	245 (1.1)	3 (1.0)	0 (0)	1 (1.6)	
Smoking status, N (%)	Smoker at enrolment	1,537 (6.7) [a, b, c]	37 (12.2) [a, e]	17 (11.3) [b, f]	11 (18.0) [c, e, f]	8.6×10^{-7} ***
	Stopped afterwards	531 (34.5)	10 (27.0)	5 (29.4)	3 (27.3)	0.30
	Initiated afterward	197 (0.6) [a, b, c]	1 (0.4) [a, d, e]	4 (3.0) [b, d, f]	3 (6.0) [c, e, f]	9×10^{-6} ***
	NA, %	21 (0.1)	0 (0)	0 (0)	0 (0)	
Follow-up time, median days (IQR)		720 (508; 982)	711.5 (486.5; 985.2)	757 (509; 1005.5)	686 (473; 922)	0.69
Donations from Apr. 2014 to Mar. 2019, N (IQR)		11 (8; 15)	11 (7; 16)	11 (10; 14.5)	10 (7; 15)	0.40
HS Incidence rates, per 1,000 person years			6.3 (5.7; 7.1)	3.2 (2.7; 3.7)	1.3 (1.0; 1.6)	

(95% CI)					

Participants without self-reported HS at the initial screening subdivided based on number of affected areas at the second screening. Note that "smoker at enrolment" refers to all who were active smokers at the initial screening, and "Stopped afterwards" refers to those who had subsequently quit smoking by the second screening. Contrary to this "Started afterwards" refers to initial non-smokers who had started smoking by the second screening.

IQR = inter quartile range, BMI = body mass index, ΔBMI = percentage change in BMI between the initial and secondary screening, NA = not available. * indicate significance after Bonferroni correction for multiple testing.

[a]: indicates a statistically significant difference between HS screen-negatives and those with self-reported HS in 1 area in a post hoc analysis.

[b]: indicates a statistically significant difference between HS screen-negatives and those with self-reported HS in 2 areas in a post hoc analysis.

[c]: indicates a statistically significant difference between HS screen-negatives and those with self-reported HS in 3 areas in a post hoc analysis.

[d]**:** indicates a statistically significant difference between those with self-reported HS in 1 area and those with self-reported HS in 2 areas in a post hoc analysis.

[e]: indicates a statistically significant difference between those with self-reported HS in 1 area and those with self-reported HS in 3 areas in a post hoc analysis.

[f]: indicates a statistically significant difference between those with self-reported HS in 2 areas and those with self-reported HS in 3 areas in a post hoc analysis.

Table III: Descriptive statistics and remission rates of initial screen-positives

Descriptive statistics at the initial screening					
Initial screening status		Self-reported HS in 1 area	Self-reported HS in 2 areas	Self-reported HS in ≥3 areas	p-value
Number (%)		191 (44.4)	167 (38.8)	72 (16.7)	
Sex, male/female N (male %/female %)		71/120 (37.2/62.8)	75/92 (44.9/55.1)	28/44 (38.9/61.1)	0.32
Age at enrolment, median years (IQR)		39.3 (27.0; 48.3)	36.5 (27.7; 47.4)	33.5 (25.8; 44.2)	0.11
BMI	BMI, points	26.6 (23.4; 30.4) [a]	26.3 (24.5; 31.2)	28.4 (25.1; 32.9) [a]	0.05 *
	ΔBMI, %	-1.2 (-4.3; 2.0)	-1.0 (-4.1; 1.3)	-2.3 (-5.6; 0.2)	0.53
	NA, %	0 (0)	2 (1.2)	0 (0)	
Smoking status, N (%)	Smoker at enrolment	29 (15.2)	31 (18.6)	14 (19.4)	0.60
	Stopped afterwards	10 (34.5)	10 (32.3)	5 (35.7)	0.97
	Initiated afterward	2 (1.2)	6 (4.4)	0 (0)	0.09
Donations from Apr. 2014 to Mar. 2019, N (IQR)		10 (7.5; 15)	10 (7; 14)	10 (7.75; 13.5)	0.98
Changes in Self-reported HS status including full remission					
Follow-up time, median days (IQR)		700 (469; 961)	644 (388; 936)	795 (570; 980)	0.05
Self-reported HS during the second screening	Negative	109 (57.1)	82 (49.1)	24 (33.3)	1.6×10^{-11} ***
	HS in 1 area	51 (26.7)	31 (18.6)	11 (15.3)	
	HS in 2 areas	24 (12.6)	32 (19.2)	9 (12.5)	

	HS in ≥3 areas	7 (3.7)	22 (13.2)	28 (38.9)	
HS severity specific remission rate, per 1,000 person years (95% CI)		287.3 (236.7; 344.7)	269.8 (215.6; 332.5)	155.6 (101.4; 226.4)	

Participants with self-reported HS at the initial screening subdivided based on number of affected areas. Note that "smoker at enrolment" refers to all who were active smokers at the initial screening, and "Stopped afterwards" refers to those who had subsequently quit smoking by the second screening. Contrary to this "Started afterwards" refers to initial non-smokers who had started smoking by the second screening.

IQR = inter quartile range, BMI = body mass index, ΔBMI = percentage change in BMI between the initial and secondary screening, NA = not available. * indicate significance after Bonferroni correction for multiple testing.

[a]: indicates a statistically significant difference between those with self-reported HS in 1 area and those with self-reported HS in 3 areas in a post hoc analysis.

Table IV: Cox proportional hazards regression analysis

Association with developing self-reported HS				
Variable		Coefficient	HR (95% CI)	p-value
BMI	BMI, points above 25 (females)	0.102	1.11 (1.09; 1.13)	$< 2 \times 10^{-16}$ ***
	BMI, points above 25 (males)	0.070	1.07 (1.04; 1.11)	1.1×10^{-5} ***
	%Δ in BMI	0.004	1.00 (0.99; 1.02)	0.59
Age at enrolment	years above 25	-0.035	0.97 (0.96; 0.97)	$< 2 \times 10^{-16}$ ***
	years above 25 (for smokers)	0.018	1.02 (1.00; 1.04)	0.08
Smoking-status	Smoker at enrolment	0.543	1.72 (1.15; 2.57)	0.008 **
	Stopped afterwards	-0.379	0.68 (0.40; 1.17)	0.16
Male sex		-0.605	0.55 (0.45; 0.67)	2.4×10^{-9} ***
Donations, N		0.010	1.01 (1.00; 1.02)	0.06
Observations deleted due to missing data: 298 (1.3%)				
Association with remission of self-reported HS				
Variable		Coefficient	HR (95% CI)	p-value
Distribution of self-reported HS	2 areas	0.079	1.08 (0.81; 1.45)	0.60
	≥3 areas	-0.617	0.54 (0.34; 0.85)	0.008 **
BMI	BMI, points above 25	-0.024	0.98 (0.95; 1.01)	0.11
	%Δ in BMI (female)	0.075	1.07 (1.05; 1.11)	6.6×10^{-7} ***
	%Δ in BMI (male)	0.003	1.00 (0.97; 1.04)	0.86
Age at enrolment, years above 25		0.010	1.01 (1.00; 1.02)	0.10
Smoking-status	Smoker at enrolment	-0.705	0.49 (0.32; 0.76)	0.0014 **
Male sex		-0.086	0.92 (0.69; 1.22)	0.55
Donations, N		-0.014	0.99 (0.97; 1.01)	0.18
Observations deleted due to missing data: 3 (0.7%)				

Cox proportional hazards regression analyses of different factors association with development and remission of self-reported HS. Association with development was conducted for the 23,202 initially screen-negatives, and the association with remission was conducted amongst the 427 initially screen positives without missing information. Note that "smoker at enrolment" refers to all who were active smokers at the initial screening, and "Stopped afterwards" refers to those who had subsequently quit smoking by the second screening.

CI = confidence interval, BMI = body mass index, ΔBMI = percentage change in BMI between the initial and secondary screening. * signifies order of significance after Bonferroni correction for multiple testing.

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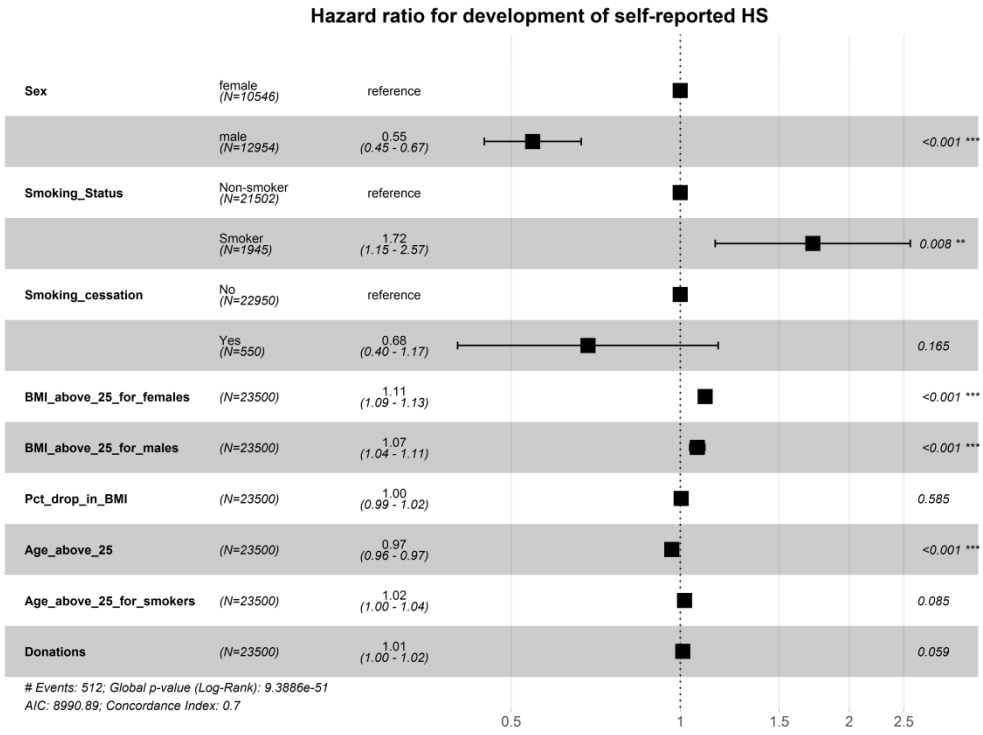

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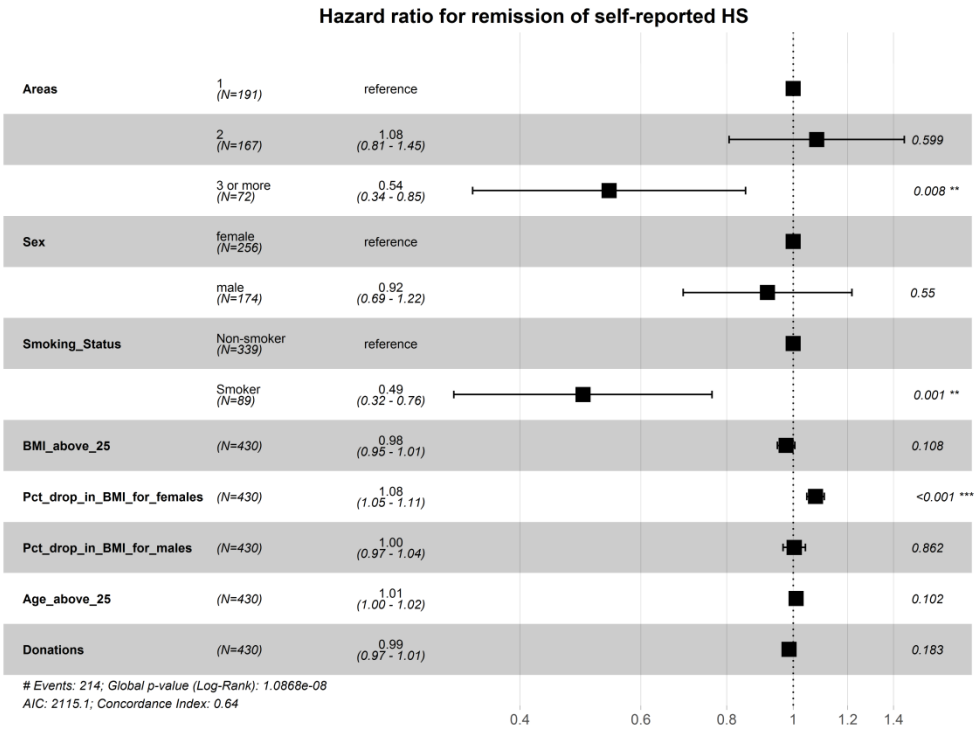

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