Modifiable lifestyle risk factors for sarcoidosis: a nested case-control study

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Take home message

Smoking is associated with a lower risk of sarcoidosis. Obesity and being physically active separately might increase sarcoidosis risk.

Abstract

We aimed to investigate whether obesity, tobacco use, alcohol consumption, and physical inactivity are associated with sarcoidosis risk.

We conducted a matched case-control study nested within the Northern Sweden Health and Disease Study. Incident sarcoidosis cases (n=165) were identified via medical records and matched to controls (n=660) on sub-cohort, sex, birth, and questionnaire date (1:4). Data on lifestyle factors were obtained through questionnaires, and physical measurements of height, weight and waist were collected prior to sarcoidosis diagnosis. Conditional logistic regression estimated adjusted odds ratios with 95% confidence intervals (aOR; 95%CI).

Compared with never smoking, current smoking was associated with lower sarcoidosis odds (aOR 0.48; 95%CI 0.32–0.71), and former smoking with higher odds (aOR 1.33; 95%CI 0.98–1.81). Snus use was not associated with sarcoidosis. There was an increased odds of sarcoidosis associated with obesity (aOR 1.34 (95%CI 0.94–1.92) but not with overweight (aOR 0.99; 95%CI 0.76–1.30). Compared with those who were physically inactive, those who were active had a 25% higher odds (aOR 1.25; 95%CI 0.91–1.72). No association was found with moderate alcohol consumption (aOR 0.95; 95%CI 0.56–1.62). All results were similar when cases diagnosed within 5 years after exposure assessment were excluded, except the aOR for former smoking decreased to 1.1.

We observed a reduced sarcoidosis risk associated with smoking, which cannot be fully explained by early symptoms of sarcoidosis influencing smoking habits. Results indicate an increased risk associated with obesity, but not overweight, and being physically active.

Introduction

Sarcoidosis is a systemic inflammatory condition characterized by the formation of non-caseating granulomas [1]. The etiology of sarcoidosis is undetermined. However, it has been hypothesized that several modifiable lifestyle factors including obesity and tobacco use play a role in the etiopathogenesis of sarcoidosis through inducing a proinflammatory state [2].

Several recent studies, mostly in women [3], have shown that obesity is associated with a higher sarcoidosis risk, but there is little data on the association between obesity and sarcoidosis in men. Previous studies have measured body mass index (BMI) via self-reported height and weight, and none of them investigated waist circumference. Waist circumference is an indicator of abdominal fat and is more sensitive to the body fat distribution than BMI, which may be a better measurement of adipose tissue [4]. Smoking is also believed to be associated with sarcoidosis, with several studies reporting a protective effect of smoking [5-9] but not all [10, 11]. In contrast, snus, a Swedish smokeless tobacco product that is commonly used in Scandinavia, does not seem to be associated with sarcoidosis risk [5]. All but one of these studies collected smoking status at the time of or after sarcoidosis diagnosis, rendering any inference prone to reverse causation bias (people with sarcoidosis may have stopped smoking and/or reported to be non-smokers). Other modifiable lifestyle factors such as moderate alcohol consumption and physical activity, which have been shown to be anti-inflammatory [12, 13] and decrease the risk of other chronic inflammatory diseases [14, 15], have not yet been investigated in association with sarcoidosis.

We performed a nested case-control study using prospectively collected information from the population-based Northern Sweden Health and Disease Study (NSHDS) cohort. Our aim was

to investigate whether obesity, tobacco use, alcohol consumption, and physical activity are associated with sarcoidosis risk among men and women in Northern Sweden.

Methods

Study population

We used a matched case-control study design with cases and controls selected from the NSHDS cohort, which has been described in detail elsewhere [16]. Briefly, the NSHDS cohort consists of three population-based prospective sub-cohorts: the Västerbotten Intervention Programme (VIP), the Monitoring of Trends and Determinants in Cardiovascular Disease study (MONICA) and the Mammography Screening Project cohort. The present study is based on the VIP and MONICA sub-cohorts. VIP started in 1985, and is still ongoing, where all residents of Västerbotten County are invited to participate by having a general health screening at 10-year intervals at ages 30 (up to 1996), 40, 50, and 60 years [17]. MONICA has performed seven screenings since 1985 in randomly selected individuals aged 25–74 years, living in Västerbotten and Norrbotten Counties [18]. Both cohorts are characterized by a high attendance rate (66% in VIP; 74% between 1986–2009 in MONICA).

At recruitment in both cohorts and during follow-up, subjects were asked to complete a self-administered questionnaire concerning demographics and lifestyle factors. In addition, physical measurements of weight, height and waist circumference were collected.

Identification of cases and controls

Individuals who received their first ever International Classification of Diseases (ICD) code for sarcoidosis (ICD-9 135 or ICD-10 D86) at Umeå University Hospital were identified. Sarcoidosis diagnosis was validated via medical record review, based on the reviewer's

impression using the methods described in Ceder 2021 [19]. In total, 201 incident cases were identified who had participated in NSHDS. Of these, 8 could not be confirmed and were excluded, resulting in a positive predictive value of 0.96. We further excluded 28 cases which were diagnosed before participating in the cohort. After exclusions, we were left with 165 incident cases for analysis. Controls without sarcoidosis were sampled from the NSHDS population and were matched 4:1 to cases on sub-cohort, birthdate (± 6 months), sex and date of questionnaire (±3 months).

Modifiable lifestyle factors

Information on modifiable lifestyle factors was obtained from questionnaires at the time of recruitment in the cohorts (if missing, the follow-up questionnaires were used) prior to sarcoidosis diagnosis.

Body mass index & waist circumference

BMI and waist circumference were used as indicators of obesity (excess body fat). BMI was calculated as weight in kilograms divided by height in meters squared and examined as a continuous and categorical variable (categorized according to World Health Organization (WHO) as underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), and obese (≥30 kg/m^2) [20]). As only two individuals had a BMI<18.5 kg/m^2 (BMI 17.3 and 17.9 kg/m^2), we included those with underweight in the normal weight category. Waist circumference (in cm) was collected in MONICA but not included in VIP until 2004. Waist circumference was considered both as continuous and categorical variable, with categories according to WHO recommendations for men and women separately (men: <94 cm, 94–101.9 cm, ≥102 cm; women: <80 cm, 80–87. 9 cm ≥88 cm) [20].

Smoking & Snus use

Information regarding smoking status (current; former; never), number of cigarettes smoked per day (1–4; 5–14; 15–24; >25), duration of smoking (years), age at smoking cessation (years), snus status (current; former; never), number of snus packets consumed per week (<2; 2–4; 5–6; ≥7), and duration of snus use (years) was obtained from questionnaires. Pack-years, as an indicator of cumulative smoking exposure in former and current smokers, was calculated by multiplying the number of cigarettes smoked/day by the duration of smoking in years, and dividing by 20 (cigarettes/pack) and examined as continuous variable. Age when the participant stopped smoking was used to calculate duration of smoking cessation in years, which was modeled as a continuous variable. Cumulative snus exposure in former and current snus users was calculated in packet-years by multiplying the number of snus packets consumed/day by the duration of snus use in years.

Alcohol consumption

The frequency and average weekly and monthly amount of alcohol intake was used to calculate the average alcohol consumption in drinks per week (1 drink = 500 ml of light beer, 330 ml of strong beer, 100–150 ml of red or white wine, 50–80 ml of fortified wine, e.g. sherry, or 40 ml of spirits, e.g. whisky). According to the National Institute on Alcohol Abuse and Alcoholism classification criteria [21], we classified participants as abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week), and heavy (>14 drinks/week) drinkers. As only two individuals were heavy drinkers (20.5 drinks/week), we merged moderate and heavy drinkers into a single category, herein referred to as moderate drinkers.

Physical activity

Physical activity was measured using the Cambridge Physical Activity Index, which is a validated index based on questions related to physical activity in work and in leisure time [22, 23]. Individuals were categorized into inactive, moderately inactive, moderately active and active.

Other variables

Educational level was classified into ≤9 years, 10–12 years and >12 years. Education was used as a proxy for socioeconomic status which has been found to be associated with sarcoidosis severity [24] and to also be associated with lifestyle-related factors [25-28].

Statistical analysis

Characteristics of sarcoidosis cases and controls were reported as means with standard deviations, as medians with ranges or as proportions. The odds ratios (OR) of sarcoidosis associated with each lifestyle factor were estimated using conditional logistic regression models adjusted for educational level, BMI (continuous), smoking status, snus status, alcohol consumption and physical activity. The model for pack-years of cigarette smoking was not adjusted for smoking status, the model for snus packet-years was not adjusted for snus status, and the model for waist circumference was not adjusted for BMI. The OR was used to estimate the risk ratio. To compare to previous studies, we also estimated the OR associated with ever vs. never smoking. All analyses were stratified by sex.

To minimize selection bias due to missingness, missing values on lifestyle factors and education were 50 times imputed using multiple imputation by chained equations (Supplementary table A1) [29].

In a secondary analysis, we estimated the association between each lifestyle factor with pulmonary sarcoidosis and Löfgren syndrome separately to restrict to more homogenous sarcoidosis phenotypes.

A series of sensitivity analyses were performed to evaluate the consistency of the results. First, cases diagnosed within 2 and 5 years after recruitment in NSDHS were excluded to avoid potential reverse causation. Second, because some variables adjusted for could be mediators rather than confounders since they were retrieved at the same time point as the lifestyle factors, we ran a series of sensitivity analyses removing potential mediators from the model. Third, cigarette smoke and snus use are correlated but have different routes of administration. Thus, to isolate the effect of only cigarette smoke or only snus use, we created the following mutually exclusive exposure categories: (1) former and current smokers who were never snus users (only smoker), (2) former and current snus users who were never-smokers (only snus user), (3) ever-smokers who were also ever snus users (both smoker and snus user), and (4) never-smokers who were also never snus users (never tobacco user). Fourth, we examined the association between time since smoking cessation and sarcoidosis using different definitions and restricting to ever smokers. Lastly, continuous variables were further modeled using restricted cubic splines with 4 knots at fixed and equally spaced percentiles (5%, 35%, 65%, 95%) to evaluate nonlinear effects. To assess how robust our associations are to potential uncontrolled confounding we calculated the E-value [30].

Data management and statistical analyses were performed using SAS software (version 9.4; SAS institute Inc., Cary, NC, USA). The restricted cubic spline analysis was performed in Stata IC (version 16.1)

Results

A total of 165 cases and 660 controls were included in the study. The median age of cases

and controls at the time of entry in NHSDS was 40 (cases range 30–61, controls range 30–60;

Table 1). The median age of the cases at diagnosis was 55 years (range 30–82 years).

Compared with controls, a larger percentage of cases had upper secondary education (44.2%

vs. 38.6%), were overweight (45.5% vs. 40.8%) and obese (14.5% vs. 11.3%), light drinkers

(37.6% vs. 33.5%), and physically active (24.8% vs. 19.7%). A larger percentage of cases

were former (27.3% vs. 24.5%) and never smokers (63.0% vs. 52.9%) compared to controls.

The majority of cases were pulmonary (88%) and 25% had Löfgren syndrome

(Supplementary table B1 for more detailed clinical characteristics).

Table 1. Characteristics of sarcoidosis cases and controls included from Northern Sweden Health and Disease study, 1987–2016.

	Cases (n=165)	Controls (n=660)
Sub-cohort		
VIP	161 (97.6)	644 (97.6)
MONICA	4 (2.4)	16 (2.4)
Age at diagnosis, years	55 (30–82)	
Age at recruitment, years	40 (30–61)	40 (30–60)
Gender		
Female	62 (37.6)	248 (37.6)
Male	103 (62.4)	412 (62.4)
Years of education		
≤9 years	57 (34.6)	219 (33.2)
10–12 years	73 (44.2)	255 (38.6)
>12 years	35 (21.2)	181 (27.4)
Missing	0 (0.0)	5 (0.8)
BMI, kg/m^2	26.2±3.7	25.7±3.9
BMI, kg/m^2, WHO categories		
Normal, <25	66 (40.0)	316 (47.9)
Overweight, 25.0–29.9	75 (45.5)	269 (40.8)
Obesity, ≥30.0	24 (14.5)	75 (11.3)
Waist circumference, cm	94.9±11.1	92.7±11.5
Smoking status		
Current	14 (8.5)	142 (21.5)
Former	45 (27.3)	162 (24.5)

Never	104 (63.0)	349 (52.9)
Missing	2 (1.2)	7 (1.1)
Smoking, pack-years[c]	13.3±10.8	11.8±8.8
Years since smoking cessation[d]	11.4±8.3	13.1±8.3
Snus status		
Current	30 (18.2)	124 (18.8)
Former	20 (12.1)	70 (10.6)
Never	112 (67.9)	442 (67.0)
Missing	3 (1.8)	24 (3.6)
Snus, packet-years[e]	7.9±7.3	7.9±7.1
Alcohol consumption, drinks/week[f]		
Abstainers	21 (12.7)	68 (10.3)
Light drinkers	62 (37.6)	221 (33.5)
Moderate drinkers	9 (5.5)	38 (5.8)
Missing	73 (44.2)	333 (50.5)
Physical activity[g]		
Inactive	24 (14.6)	119 (18.1)
Moderately inactive	49 (29.7)	179 (27.1)
Moderately active	48 (29.1)	204 (30.9)
Active	41 (24.8)	130 (19.7)
Missing	3 (1.8)	28 (4.2)

VIP Västerbotten Intervention Programme; MONICA Monitoring of Trends and Determinants in Cardiovascular Disease study; BMI body mass index, WHO World Health Organization.
[a]among men, N=515; [b]among women, N=310; [c]among current/former smokers, N=363. One pack-year is equivalent to 20 cigarettes per day for 1 year; [d]among former smokers, N=207; [e]among current/former snus users, N=244. One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [f]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [g]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).
Data are presented as median (range), mean±SD or n (%).

Compared with normal weight, obesity was associated with a 34% higher odds of sarcoidosis, although the aOR was not statistically significant (aOR 1.34; 95%CI 0.94–1.92), and there was no association between overweight and sarcoidosis (aOR 0.99; Table 2). A one-centimeter increase in waist circumference was associated with a 2% higher odds of sarcoidosis (aOR 1.02), and the highest waist circumference categories in men and women were associated with a higher odds (aOR 1.24 and 1.42, respectively; Supplementary table B2).

Compared with never smoking, current smoking was associated with a 52% lower odds of sarcoidosis (aOR 0.48; 95%CI 0.32–0.71), and former smoking with a 33% higher odds (aOR 1.33; 95%CI 0.98–1.81). Ever vs. never smoking was associated with a 24% lower odds (aOR 0.76; 95%CI 0.63–0.92). No association was found with snus use (current vs. never snus use: aOR 0.97; 95%CI 0.69–1.34; former vs. never snus use: aOR 1.09; 95%CI 0.75–1.59) or snus packet-years (aOR 0.99; 95%CI 0.95–1.03; Table 2).

No association was found with alcohol consumption (moderate vs. light: aOR 0.95; 95%CI 0.56–1.62; abstainers vs. light: aOR 0.96; 95%CI 0.60–1.52) (Table 2). Those who were physically active had a 25% higher odds (aOR 1.25; 95%CI 0.91–1.72) compared with those who were inactive, but this was not statistically significant.

Table 2. Association between modifiable risk factors and sarcoidosis in a matched case-control study of 165 cases and 660 controls identified from the Northern Sweden Health and Disease study, 1987–2016.

	Total (Cases=165, Controls=660)	
	N cases/controls*	OR [95% CI]†
BMI, kg/m^2	165/660	1.04 [0.99–1.09]
BMI, kg/m^2, WHO categories		
Normal, <25	66/316	ref
Overweight, 25.0–29.9	75/269	0.99 [0.76–1.30]
Obesity, ≥30.0	24/75	1.34 [0.94–1.92]
Waist circumference, cm	165/660	1.02 [1.00–1.05]
Smoking status		
Never	106/352	ref
Current	14/145	0.48 [0.32–0.71]
Former	45/163	1.33 [0.98–1.81]
Smoking, pack-years[a]	165/660	0.98 [0.96–1.01]
Years since smoking cessation[b]	165/660	1.02 [1.00–1.04]
Snus status		
Never	115/460	ref
Current	30/125	0.97 [0.69–1.34]
Former	20/75	1.09 [0.75–1.59]
Snus, packet-years[c]	165/660	0.99 [0.95–1.03]
Alcohol consumption, drinks/week[d]		
Abstainers	28/103	0.96 [0.60–1.52]
Light drinkers	114/458	ref
Moderate drinkers	23/99	0.95 [0.56–1.62]

Physical activity[e]		
Inactive	24/123	ref
Moderately inactive	49/186	1.08 [0.80–1.45]
Moderately active	51/215	0.97 [0.72–1.31]
Active	41/136	1.25 [0.91–1.72]

BMI body mass index; OR odds ratio; CI confidence interval

†Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for waist circumference not adjusted for BMI; Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for years since smoking cessation additionally adjusted for smoking pack-years.

[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snuff daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

*Numbers (n) in cases and controls based on the 50th imputed dataset

The estimates did not change markedly when we stratified by sex and when restricting to cases with pulmonary sarcoidosis or Löfgren syndrome (Supplementary table B2–B3). The results did not change considerably when sarcoidosis cases diagnosed within 2 and 5 years after the inclusion in the study were excluded, except the OR associated with former smoking decreased from 1.3 to 1.1 (Supplementary table B4). Results were also similar when potential mediators were removed from the model (Supplementary table B5). In analyses examining the mutually exclusive exposure categories of tobacco exposure, compared to never tobacco users, only smokers had a 32% decreased sarcoidosis odds (aOR 0.68; 95%CI 0.47–0.98), while only snus users had a 30% increased odds (aOR 1.30 95%CI 0.86–1.98) (Supplementary table B6). There was a 2% increased odds of sarcoidosis for every 1-year increase in years of smoking cessation (aOR 1.02). The results were comparable when using different definitions of time since smoking cessation and restricting to ever smokers (Supplementary table B7). An evaluation using restricted cubic splines did not reveal any statistically significant non-linear effects (supplementary figure C1–C5). The E-value for the association between current smoking and sarcoidosis was 3.59, indicating that unmeasured

confounding would have to be very strong to explain away the effect (Supplementary table B8).

Discussion

In this prospective nested case-control study in Northern Sweden, with information on lifestyle factors obtained prior to sarcoidosis diagnosis, current cigarette smoking was associated with a significantly decreased risk of future sarcoidosis. Results indicated that obesity and being physically active were separately associated with an increased risk of sarcoidosis. No association was found with snus use and alcohol consumption.

Our observation of a reduced sarcoidosis risk with smoking is consistent with previous studies [5-9, 31]. This association could be related to subclinical sarcoidosis causing symptomatic individuals to stop smoking. This is supported by the fact that the association with former smoking decreased when we excluded cases diagnosed within 2 and 5 years after inclusion in the study. However, the results with current smoking were not materially changed and cannot be explained by subclinical sarcoidosis. Furthermore, an elevation in risk with longer time since smoking cessation supports an association between smoking and reduced risk of sarcoidosis.

It is thought that nicotine, one of the major components of cigarette smoke, has a powerful anti-inflammatory effect, thus lowering sarcoidosis risk. A similar mechanism has been hypothesized for ulcerative colitis [32] − another inflammatory disease in which smoking has also been found to be a protective factor [33]. However, an increased sarcoidosis risk with smoking was reported in studies from the U.S. and Japan [10, 11]. A possible explanation for the discrepancies might be due to different etiopathogeneses responsible for sarcoidosis

development in different populations like in Japan [10]. The study from the U.S. included only ocular sarcoidosis cases while, in our study, the majority of cases were pulmonary, thus, the effect of smoking might be different in certain phenotypes.

Our finding of no association between snus and sarcoidosis risk is in line with a cohort study of construction workers in Sweden [5]. Although snus use leads to similar or higher blood nicotine levels than smoking, it was not associated with sarcoidosis. A cigarette is made up of more than 7000 chemicals, other inhaled chemical component(s) in addition to nicotine might be responsible for the protective effect of cigarette smoke on sarcoidosis.

We found an increased risk of sarcoidosis with obesity (BMI$\geq$30.0 kg/m^2) and abdominal obesity measured using waist circumference. In the Black Women's Health Study and the Nurses' Health Study, a 42% to 74% increased sarcoidosis risk was observed with BMI$\geq$30.0 kg/m2 which is in line with our results [3]. Adipose tissue is a metabolically active endocrine organ that secretes a variety of proinflammatory adipokines that induce a chronic inflammatory state in obese individuals that may play a role in sarcoidosis etiopathogenesis [34].. It is perhaps not obesity itself but all aspects of metabolic syndrome (obesity, diabetes and high blood pressure, which are highly intertwined) that could be important for sarcoidosis risk.

We also observed an elevated sarcoidosis risk associated with being physically active. To our knowledge, this is the first study to investigate the relationship between physical activity and future sarcoidosis. The proinflammatory cytokine milieu with strenuous exercise [35] represents the same cytokine milieu that initiates and progresses the sarcoid granuloma

formation [36] and may play a role in sarcoidosis development. Our findings should be replicated in future studies.

One strength of this study was that sarcoidosis cases were validated via review of medical records, minimizing disease misclassification. We obtained data on multiple modifiable lifestyle factors from the NSHDS cohort, which were prospectively collected prior to sarcoidosis diagnosis, minimizing the possibility of differential exposure misclassification (reverse causation bias). Because the lifestyle factors are highly related to each other, we used mutually adjusted models to isolate the association of each individual factor. Another advantage was that BMI and waist circumference were obtained through physical measurements, minimizing measurement error. We also used multiple imputation by chained equations to minimize selection bias due to missingness [29].

One limitation of this study is that the data available in the NSHDS was mostly on men and women aged 40-60 years. We were unable to assess the risk of sarcoidosis among individuals outside this age range, however, the average age at case diagnosis of 55 is similar to other populations. Moreover, there may be some non-differential misclassification of tobacco use, alcohol consumption and physical activity due to the self-reported nature of these data. In addition, although multiple imputation was performed, some lifestyle factors had a high percentage of missingness. However, to improve the accuracy of imputed values and the efficiency of point estimates, we applied models that used auxiliary variables that were moderately to strongly correlated with the missing lifestyle factors [37]. Another limitation might be unmeasured confounding. However, our E-value sensitivity analysis suggested that a strong unmeasured confounder is needed to explain the observed association with smoking.

It is unclear whether our findings are generalizable to other populations, since the participants in this study were all from Northern Sweden.

In conclusion, the observed lower risk of sarcoidosis associated with smoking may indicate a protective effect or reflect very early symptoms years before sarcoidosis diagnosis that influence smoking habits. Obesity, but not overweight, was associated with an increased risk of sarcoidosis. Results indicate that physically active individuals may have a higher risk of sarcoidosis, which should be replicated in future studies.

Abbreviations

BMI: Body mass index

ICD: International classification of diseases

MONICA: Monitoring of Trends and Determinants in Cardiovascular Disease study

NSHDS: Northern Sweden Health and Disease Study

OR: Odds ratio

VIP: Västerbotten Intervention Programme

WHO: World Health Organization

Author contributions

Marina Dehara: Conceptualization, Methodology, Data Curation, Statistical analysis, Writing—Original Draft, and Writing—review and editing. Michael C. Sachs: Methodology, and Writing—review and editing. Johan Grunewald and Anders Blomberg: Conceptualization, Writing—review and editing. Elizabeth V. Arkema: Conceptualization, Methodology, Funding and Data acquisition, Writing—review and editing, and Supervision.

Declarations

Conflict of interest

All authors declare that they have no conflict of interest to disclose.

Ethics approval

Ethical permission for this study was granted by the regional ethics review board in Umeå

(DNR 2018/336-31).

References

1. Statement on sarcoidosis. Am J Respir Crit Care Med. 1999;160:736–55.
2. Sundkvist A, Myte R, Boden S, *et al.* Targeted plasma proteomics identifies a novel, robust association between cornulin and Swedish moist snuff. Sci Rep. 2018;8(1):2320.
3. Wambui DW, Obi ON, Kearney GD. Association Between Obesity and Sarcoidosis: A Systematic Review and Meta-analysis. American J Intern Med. 2020;8(5):237-45.
4. Snijder MB, van Dam RM, Visser M, *et al.* What aspects of body fat are particularly hazardous and how do we measure them? Int J Epidemiol. 2006;35(1):83-92.
5. Carlens C, Hergens MP, Grunewald J, *et al.* Smoking, use of moist snuff, and risk of chronic inflammatory diseases. Am J Respir Crit Care Med. 2010;181(11):1217-22.
6. Newman LS, Rose CS, Bresnitz EA, *et al.* A case control etiologic study of sarcoidosis: environmental and occupational risk factors. Am J Respir Crit Care Med. 2004;170(12):1324-30.
7. Ungprasert P, Crowson CS, Matteson EL. Smoking, obesity and risk of sarcoidosis: A population-based nested case-control study. Respir Med. 2016;120:87-90.
8. Valeyre D, Soler P, Clerici C, *et al.* Smoking and pulmonary sarcoidosis: effect of cigarette smoking on prevalence, clinical manifestations, alveolitis, and evolution of the disease. Thorax. 1988;43(7):516-24.
9. Le Jeune I, Gribbin J, West J, *et al.* The incidence of cancer in patients with idiopathic pulmonary fibrosis and sarcoidosis in the UK. Respir Med. 2007;101(12):2534-40.
10. Hattori T, Konno S, Shijubo N, *et al.* Increased prevalence of cigarette smoking in Japanese patients with sarcoidosis. Respirology. 2013;18(7):1152-7.
11. Janot AC, Huscher D, Walker M, *et al.* Cigarette smoking and male sex are independent and age concomitant risk factors for the development of ocular sarcoidosis in a New Orleans sarcoidosis population. Sarcoidosis Vasc Diffuse Lung Dis. 2015;32(2):138-43.
12. Pai JK, Hankinson SE, Thadhani R, *et al.* Moderate alcohol consumption and lower levels of inflammatory markers in US men and women. Atherosclerosis. 2006;186(1):113-20.
13. Flynn MG, McFarlin BK, Markofski MM. The Anti-Inflammatory Actions of Exercise Training. Am J Lifestyle Med. 2007;1(3):220-35.
14. Jin Z, Xiang C, Cai Q, *et al.* Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies. Ann Rheum Dis. 2014;73(11):1962-7.
15. Di Giuseppe D, Bottai M, Askling J, *et al.* Physical activity and risk of rheumatoid arthritis in women: a population-based prospective study. Arthritis Res Ther. 2015;17(1):40.
16. Hallmans G, Agren A, Johansson G, *et al.* Cardiovascular disease and diabetes in the Northern Sweden Health and Disease Study Cohort—evaluation of risk factors and their interactions. Scand J Public Health Suppl. 2003;61:18–24.
17. Norberg M, Wall S, Boman K, *et al.* The Vasterbotten Intervention Programme: background, design and implications. Glob Health Action. 2010;3.
18. Benckert M, Lilja M, Soderberg S, *et al.* Improved metabolic health among the obese in six population surveys 1986 to 2009: the Northern Sweden MONICA study. BMC Obes. 2015;2:7.
19. Ceder S, Rossides M, Kullberg S, *et al.* Positive Predictive Value of Sarcoidosis Identified in an Administrative Healthcare Registry: A Validation Study. Epidemiology. 2021;32(3):444-447.
20. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii, 1-253.

21. National Institute on Alcohol Abuse Alcoholism (NIAAA). Drinking levels defined. https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinking. Date last accessed: Feb 14 2022

22. Peters T, Brage S, Westgate K, *et al*. Validity of a short questionnaire to assess physical activity in 10 European countries. Eur J Epidemiol. 2012;27(1):15-25.

23. Wareham NJ, Jakes RW, Rennie KL, *et al*. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr. 2003;6(4):407-13.

24. Rabin DL, Thompson B, Brown KM, *et al*. Sarcoidosis: social predictors of severity at presentation. Eur Respir J. 2004;24(4):601-8.

25. Hiscock R, Bauld L, Amos A, *et al*. Socioeconomic status and smoking: a review. Ann N Y Acad Sci. 2012;1248:107-23.

26. Stalsberg R, Pedersen AV. Are Differences in Physical Activity across Socioeconomic Groups Associated with Choice of Physical Activity Variables to Report? Int J Environ Res Public Health. 2018;15(5).

27. Beard E, Brown J, West R, *et al*. Associations between socio-economic factors and alcohol consumption: A population survey of adults in England. PloS one. 2019;14(2):e0209442.

28. Dinsa GD, Goryakin Y, Fumagalli E, *et al*. Obesity and socioeconomic status in developing countries: a systematic review. Obes Rev. 2012;13(11):1067-79.

29. Sterne JA, White IR, Carlin JB, *et al*. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

30. Haneuse S, VanderWeele TJ, Arterburn D. Using the E-Value to Assess the Potential Effect of Unmeasured Confounding in Observational Studies. Jama. 2019;321(6):602-3.

31. Gupta D, Singh AD, Agarwal R, *et al*. Is tobacco smoking protective for sarcoidosis? A case-control study from North India. Sarcoidosis Vasc Diffuse Lung Dis. 2010;27(1):19-26.

32. Birrenbach T, Böcker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. Inflamm Bowel Dis. 2004;10(6):848-59.

33. Mahid SS, Minor KS, Soto RE, *et al*. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81(11):1462-71.

34. Cao H. Adipocytokines in obesity and metabolic disease. J Endocrinol. 2014;220(2):T47-59.

35. Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol. 2005;45(10):1563-9.

36. Grunewald J, Grutters JC, Arkema EV, *et al*. Sarcoidosis. Nat Rev Dis Primers. 2019;5(1):45.

37. Hippel Pv, Lynch J. Efficiency Gains from Using Auxiliary Variables in Imputation. 2013.

Supplement

Modifiable lifestyle factors for sarcoidosis: a nested case-control study

Marina Dehara, Michael C Sachs, Johan Grunewald, Anders Blomberg, Elizabeth V Arkema

Contents

APPENDIX A: SUPPLEMENTAL METHODS

Multiple imputation by chained equations

Prior to performing the analyses, we imputed 50 times the missing values on lifestyle factors and education using multiple imputation by chained equations (MICE). Multiple imputation uses a regression-based procedure to generate multiple copies of the data set, each of which contains different estimates of the missing values. For our study, in the MICE process we included 11 main and 4 auxiliary variables (gender, birthyear, questionnaire year, teetotaler) (see Table A1) and we specified 100 iterations to be performed. After creating the complete data sets, we estimated the multiple regression models on each filled-in data set and subsequently used Rubin's (1987) formulas to combine the parameter estimates and standard errors into a single set of results.

Across the 15 variables that we used in the analyses, the missing data proportions ranged between 0.0% and 49.2%. Table A1 gives the missing data percentages for each of the analysis variables.

Table A1. Missing data percentages for each of the analysis variables.	
Analysis variables	Percentage (%)
Gender	0
Birthyear	0
Questionnaire year	0
Education	0.6
Body mass index, kg/m^2	0
Body mass index, kg/m^2, WHO categories	0
Waist circumference, cm	43.8
Smoking status	1.1
Smoking, pack-years	28.1
Years since smoking cessation	2.2
Snus status	3.3
Snus, packet-years	13.7
Teetotaler (binary 0,1)	27.3
Alcohol consumption, drinks/week	49.2
Physical activity	3.8

The below table shows the choices of imputation methods in the SAS MI procedure (PROC MI) according to the type of imputed variable in an arbitrary pattern of missingness which was

Table A2. Choices of imputation methods according to imputed variable type, arbitrary pattern of missingness

Type of imputed variable	Imputation method in PROC MI
Continuous variable	Regression predicted mean matching method (*fcs regpmm*)
Ordinal classification variable	Logistic regression method (cumulative logit model: *fcs logistic)*
Binary classification variable	Discriminant function method (*fcs discrim*)

The process of MICE is divided into four steps (Figure A1):

Step 1: A mean imputation was performed for every missing value in the dataset (filled-in phase), which can be considered as "*place holders*".

Step 2: We started with the variable that had the fewest number of missing values. The "*place holder*" for one variable (e.g. "*Education"*) were set back to missing.

Step 3: The observed values from the variable "*Education*" in Step 2 were regressed on the other variables (e.g. "*Smoking"* and "*Physical activity"*) in the imputation model (e.g. logistic regression). In other words, the variable "*Education*" is the dependent variable and all the other variables (e.g. "*Smoking"* and "*Physical activity"*) are independent variables in the imputation model. The assumptions that we make in these imputation models are the same with the ones that we make when performing linear, logistic, or Poison regression models, outside of the context of imputing missing data.

Step 4: The missing values for "*Education*" were then replaced with predictions (imputations) from the imputation model. When "*Education*" was subsequently used as independent variable in the imputation models for other variables, both the observed and these imputed values were used.

Next fewest missing-values variable was considered. Steps 2–4 were then repeated for each variable that had missing values (e.g. "*Smoking*" and "*Physical activity*"). The cycling through each of the variables comprised one iteration. At the end of one iteration all of the missing values were replaced with predictions from regressions that reflect the associations observed in the data.

Steps 2–4 were repeated for a number of iterations, with the imputations being updated at each iteration. We specified 100 iterations to be performed. At the end of these iterations, the final imputations were retained, resulting in one imputed dataset.
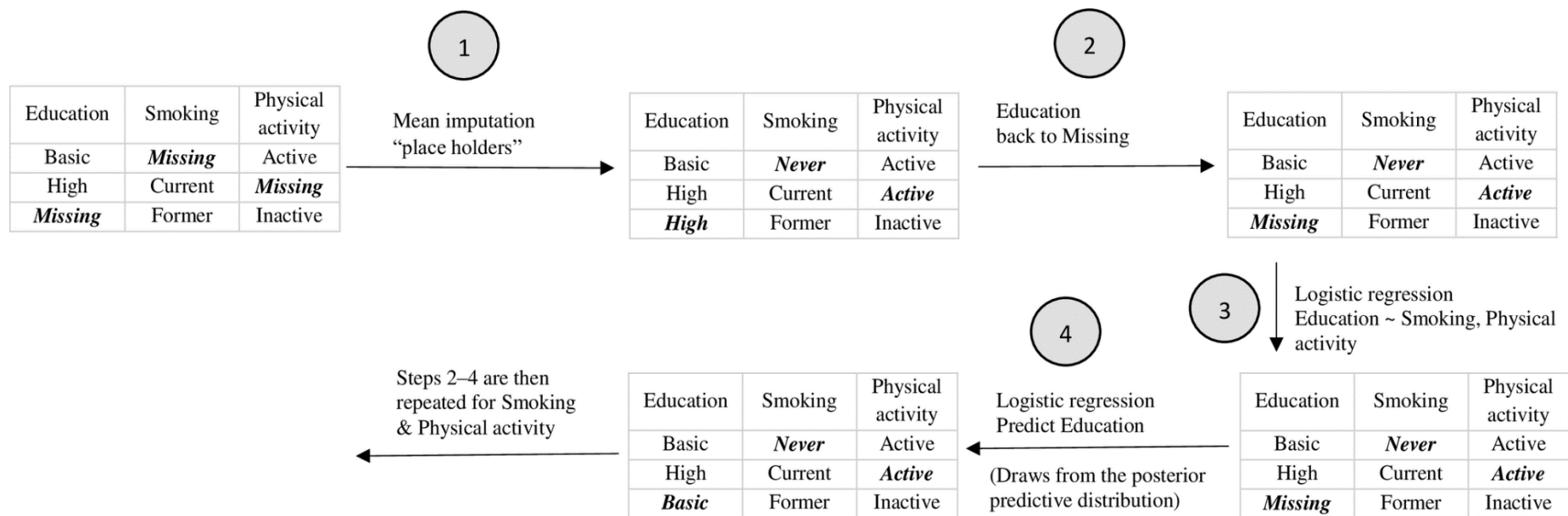
Figure A1. Multiple Imputation by Chained Equations – Single Iteration. Example of the 4 steps of the chained equations process.

APPENDIX B: SUPPLEMENTAL TABLES

Table B1. Clinical characteristics of sarcoidosis patients, Northern Sweden Health and Disease study, 1987–2016 (n=165)

Patient characteristic		N=165
Age at diagnosis, years, mean±SD		55±10
First diagnosis received in respiratory clinic		91%
Symptom onset before first visit		
Days		4%
Months		48%
Years		30%
Missing		18%
Onset type		
Löfgren's syndrome		25%
Non-Löfgren's		13%
Unclear/missing		62%
Disease type		
Pulmonary		88%
Extra-pulmonary		3%
Both pulmonary and extra-pulmonary		8%
Unclear/missing		1%
Clinical symptoms compatible with sarcoidosis		
No		1%
No symptoms		13%
Yes		49%
Unclear/missing		37%
Chest X-ray compatible		
No, not compatible		13%
Not performed initially		21%
Yes, compatible		36%
Unclear/missing		30%
Scadding stage (in those with a compatible chest X-ray)		
	0	9%
	1	19%
	2	9%
	3	8%
	Missing	55%
Other radiographic imaging performed		
CT		75%
CT and MRI		1%
CT and PET-CT		9%
PET-CT		4%
Only chest X-Ray		10%
Missing		1%
Scadding stage (in those with other imaging)		
	0	1%
	1	27%
	2	43%
	3	7%
	Missing	22%
Biopsy performed		78%
Of those with biopsy, % positive		44%
EBUS-TBNA performed		64%
BAL performed		61%
Of those with BAL,		
Lymphocytes >25% of total cell count		46%

CD4/CD8 ratio >3.5	48%
Serum calcium > upper limit of normal	
Yes	4%
No	81%
Not measured/missing	15%
Serum angiotensin converting enzyme > upper limit of normal	
Yes	29%
No	59%
Not measured/missing	12%
Smoking status	
Non-smoker	66%
Ex-smoker	27%
Current smoker	5%
Not mentioned	2%
Spirometry performed at initial diagnosis	89%
Medication at initial diagnosis	22%
Of those with medication, Prednisolone	69%
Follow-up	
Followed for 2 or more years	87%
Followed for less than 2 years	10%
Unclear/not followed	3%
Treating physician's impression	
Definite	79%
Probable but cannot say with 100% certainty	21%
Reviewing physician's impression	
Definite	77%
Probable but cannot say with 100% certainty	23%

BAL bronchoalveolar lavage; EBUS-TBNA endobronchial
ultrasound-guided transbronchial needle aspiration

Table B2. Association between lifestyle factors and sarcoidosis among men and women separately in a matched case-control study, identified from the Northern Sweden Health and Disease study, 1987–2016.

	Men (Cases=103, Controls=412) OR [95% CI]‡	Women (Cases=62, Controls=248) OR [95% CI]‡
BMI, kg/m^2	1.05 [0.98–1.12]	1.03 [0.96–1.11]
BMI, kg/m^2, WHO categories		
Normal, <25	ref	ref
Overweight, 25.0–29.9	1.00 [0.71–1.40]	0.99 [0.62–1.58]
Obesity, ≥30.0	1.26 [0.78–2.04]	1.43 [0.80–2.55]
Waist circumference, cm	1.03 [1.00–1.05]	1.02 [0.99–1.06]
Waist circumference, cm, categories for men		
<94	ref	
94–101.9	1.08 [0.74–1.58]	
≥102	1.24 [0.83–1.86]	
Waist circumference, cm, categories for women		
<80		ref
80–87. 9		0.93 [0.51–1.70]
≥88		1.42 [0.88–2.28]
Smoking status		
Never	ref	ref
Current	0.51 [0.30–0.86]	0.44 [0.24–0.82]
Former	1.22 [0.82–1.82]	1.53 [0.92–2.54]
Smoking, pack-years[a]	0.98 [0.94–1.02]	0.99 [0.94–1.03]
Years since smoking cessation[b]	1.02 [1.00–1.05]	1.02 [0.99–1.06]
Snus status		
Never	ref	ref
Current	0.90 [0.62–1.30]	1.10 [0.46–2.67]
Former	1.09 [0.72–1.65]	1.19 [0.40–3.53]
Snus, packet-years[c]	0.98 [0.94–1.03]	0.99 [0.83–1.17]
Alcohol consumption, drinks/week[d]		
Abstainers	0.70 [0.36–1.35]	1.46 [0.67–3.18]
Light drinkers	ref	ref
Moderate drinkers	1.16 [0.62–2.18]	0.68 [0.21–2.23]
Physical activity[e]		
Inactive	ref	ref
Moderately inactive	1.03 [0.70–1.52]	1.13 [0.70–1.82]
Moderately active	1.15 [0.79–1.67]	0.76 [0.45–1.28]
Active	1.30 [0.87–1.97]	1.19 [0.69–2.02]

BMI body mass index; OR odds ratio; CI confidence interval
‡Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for waist circumference not adjusted for BMI; Model for years since smoking cessation additionally adjusted for smoking pack-years.
[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

Table B3. Odds ratios (OR) and confidence intervals (CI) of pulmonary sarcoidosis and Löfgren syndrome separately in relation to lifestyle factors in a matched case-control study, identified from the Northern Sweden Health and Disease study, 1987–2016.

	Pulmonary (cases=158, controls=632) OR [95% CI]‡	Löfgren (cases=42, controls=168) OR [95% CI]‡
BMI, kg/m²	1.05 [1.00–1.10]	1.11 [1.01–1.23]
BMI, kg/m², WHO categories		
Normal, <25	ref	ref
Overweight, 25.0–29.9	0.97 [0.74–1.28]	1.07 [0.60–1.90]
Obesity, ≥30.0	1.36 [0.94–1.97]	1.94 [0.89–4.24]
Waist circumference, cm	1.03 [1.01–1.05]	1.06 [1.01–1.10]
Waist circumference, cm, categories for men		
<94	ref	ref
94–101.9	1.12 [0.76–1.67]	1.51 [0.65–3.50]
≥102	1.27 [0.87–1.85]	1.54 [0.63–3.76]
Waist circumference, cm, categories for women		
<80	ref	ref
80–87. 9	0.99 [0.53–1.83]	0.73 [0.15–3.60]
≥88	1.34 [0.82–2.18]	1.34 [0.35–5.08]
Smoking status		
Never	ref	ref
Current	0.46 [0.30–0.69]	0.40 [0.17–0.99]
Former	1.33 [0.97–1.83]	1.84 [0.95–3.58]
Smoking, pack-years[a]	0.98 [0.95–1.01]	1.01 [0.94–1.08]
Years since smoking cessation[b]	1.03 [1.01–1.05]	1.03 [0.98–1.07]
Snus status		
Never	ref	ref
Current	1.03 [0.73–1.46]	0.91 [0.45–1.82]
Former	0.95 [0.63–1.43]	0.90 [0.40–2.01]
Snus, packet-years[c]	0.99 [0.94–1.03]	0.97 [0.90–1.06]
Alcohol consumption, drinks/week[d]		
Abstainers	0.97 [0.59–1.59]	1.22 [0.34–4.42]
Light drinkers	ref	ref
Moderate drinkers	0.92 [0.51–1.66]	0.62 [0.12–3.09]
Physical activity[e]		
Inactive	ref	ref
Moderately inactive	1.13 [0.84–1.53]	1.11 [0.57–2.18]
Moderately active	1.06 [0.79–1.44]	0.92 [0.50–1.71]
Active	1.16 [0.83–1.62]	1.07 [0.57–2.00]

BMI body mass index; OR odds ratio; CI confidence interval

‡Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for waist circumference not adjusted for BMI; Model for years since smoking cessation additionally adjusted for smoking pack-years.

[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

Table B4. Odds ratios (OR) and confidence intervals (CI) of sarcoidosis cases diagnosed more than two and five years after the questionnaire date, separately, in relation to lifestyle factors in a matched case-control study identified from the Northern Sweden Health and Disease study, 1987–2016.

	Cases diagnosed more than 2 years after questionnaire date (cases=148, controls=592)	Cases diagnosed more than 5 years after questionnaire date (cases=135, controls=540)
	OR [95% CI]‡	OR [95% CI]‡
BMI, kg/m²	1.05 [1.00–1.11]	1.05 [0.99–1.11]
BMI, kg/m², WHO categories		
Normal, <25	ref	ref
Overweight, 25.0–29.9	0.99 [0.74–1.31]	0.97 [0.72–1.31]
Obesity, ≥30.0	1.41 [0.96–2.06]	1.43 [0.95–2.15]
Waist circumference, cm	1.02 [1.00–1.05]	1.02 [1.00–1.04]
Waist circumference, cm, categories for men		
<94	ref	ref
94–101.9	1.09 [0.72–1.66]	0.94 [0.59–1.49]
≥102	1.19 [0.80–1.77]	1.28 [0.84–1.96]
Waist circumference, cm, categories for women		
<80	ref	ref
80–87. 9	0.91 [0.48–1.74]	0.92 [0.48–1.78]
≥88	1.34 [0.79–2.28]	1.28 [0.75–2.16]
Smoking status		
Never	ref	ref
Current	0.52 [0.35–0.77]	0.47 [0.30–0.73]
Former	1.17 [0.85–1.63]	1.13 [0.79–1.61]
Smoking, pack-years[a]	0.98 [0.95–1.01]	0.98 [0.95–1.01]
Years since smoking cessation[b]	1.03 [1.01–1.05]	1.04 [1.01–1.06]
Snus status		
Never	ref	ref
Current	0.94 [0.65–1.34]	1.03 [0.70–1.51]
Former	1.13 [0.75–1.71]	1.00 [0.64–1.58]
Snus, packet-years[c]	0.99 [0.95–1.03]	1.00 [0.96–1.05]
Alcohol consumption, drinks/week[d]		
Abstainers	0.85 [0.51–1.43]	0.83 [0.47–1.45]
Light drinkers	ref	ref
Moderate drinkers	1.03 [0.57–1.88]	1.01 [0.50–2.03]
Physical activity[e]		
Inactive	ref	ref
Moderately inactive	1.13 [0.83–1.53]	1.12 [0.81–1.54]
Moderately active	0.99 [0.73–1.36]	1.03 [0.74–1.42]
Active	1.23 [0.87–1.73]	1.18 [0.82–1.70]

BMI body mass index; OR odds ratio; CI confidence interval

‡Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for waist circumference not adjusted for BMI; Model for years since smoking cessation additionally adjusted for smoking pack-years.

[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

Table B5. Odds ratios (OR) and confidence intervals (CI) of sarcoidosis in relation to lifestyle factors in a matched case-control study of 165 cases and 660 controls identified from the Northern Sweden Health and Disease study, 1987–2016. Different models excluding possible mediators one by one (physical activity, alcohol consumption, snus status, smoking status and BMI, respectively) from the analysis.

	Primary Analysis (Model 2)	Primary analysis, Excluding physical activity	Primary analysis, Excluding alcohol consumption	Primary analysis Excluding snus	Primary analysis Excluding smoking	Primary analysis Excluding BMI
	OR [95% CI]†	OR [95% CI]†	OR [95% CI]†	OR [95% CI]†	OR [95% CI]†	OR [95% CI]†
BMI, kg/m²	1.04 [0.99–1.09]	1.04 [0.99–1.09]	1.04 [0.99–1.09]	1.04 [0.99–1.09]	1.04 [0.99–1.09]	
BMI, kg/m², WHO categories						
Normal, <25	ref	ref	ref	ref	ref	
Overweight, 25.0–29.9	0.99 [0.76–1.30]	1.02 [0.78–1.32]	1.01 [0.77–1.31]	1.00 [0.77–1.30]	1.03 [0.79–1.33]	
Obesity, ≥30.0	1.34 [0.94–1.92]	1.27 [0.89–1.81]	1.32 [0.93–1.89]	1.34 [0.94–1.92]	1.27 [0.89–1.80]	
Waist circumference, cm	1.02 [1.00–1.05]	1.02 [1.00–1.04]	1.02 [1.00–1.04]	1.02 [1.00–1.04]	1.02 [1.00–1.04]	
Waist circumference, cm, categories for men						
<94	ref	ref	ref	ref	ref	
94–101.9	1.08 [0.74–1.58]	1.09 [0.75–1.58]	1.10 [0.76–1.59]	1.09 [0.75–1.58]	1.09 [0.75–1.57]	
≥102	1.24 [0.83–1.86]	1.19 [0.80–1.76]	1.24 [0.83–1.85]	1.24 [0.83–1.85]	1.26 [0.85–1.87]	
Waist circumference, cm, categories for women						
<80	ref	ref	ref	ref	ref	
80–87. 9	0.93 [0.51–1.70]	0.92 [0.51–1.66]	0.91 [0.51–1.63]	0.93 [0.52–1.68]	0.93 [0.52–1.65]	
≥88	1.42 [0.88–2.28]	1.40 [0.87–2.25]	1.41 [0.88–2.27]	1.44 [0.90–2.30]	1.40 [0.87–2.25]	
Smoking status						
Never	ref	ref	ref	ref		ref
Current	0.48 [0.32–0.71]	0.48 [0.32–0.70]	0.48 [0.32–0.71]	0.48 [0.32–0.71]		0.47 [0.32–0.70]
Former	1.33 [0.98–1.81]	1.33 [0.98–1.81]	1.32 [0.98–1.80]	1.34 [0.99–1.81]		1.34 [0.99–1.83]
Smoking, pack-years[a]	0.98 [0.96–1.01]	0.98 [0.96–1.01]	0.98 [0.96–1.01]	0.98 [0.96–1.01]		0.98 [0.96–1.01]
Years since smoking cessation[b]	1.02 [1.00–1.05]	1.02 [1.00–1.05]	1.02 [1.00–1.04]	1.02 [1.00–1.04]		1.02 [1.00–1.05]
Snus status						
Never	ref	ref	ref		ref	ref
Current	0.97 [0.69–1.34]	0.98 [0.71–1.36]	0.97 [0.70–1.35]		0.92 [0.67–1.28]	0.98 [0.70–1.36]

Former	1.09 [0.75–1.59]	1.08 [0.74–1.58]	1.08 [0.74–1.58]		1.08 [0.74–1.56]	1.09 [0.75–1.59]
Snus, packet-years[c]	0.99 [0.95–1.03]	0.99 [0.95–1.03]	0.99 [0.95–1.03]		0.99 [0.95–1.03]	0.99 [0.95–1.03]
Alcohol consumption, drinks/week[d]						
Abstainers	0.96 [0.60–1.52]	0.94 [0.60–1.49]		0.95 [0.60–1.51]	1.06 [0.68–1.64]	0.95 [0.60–1.49]
Light drinkers	ref	ref		ref	ref	ref
Moderate drinkers	0.95 [0.56–1.62]	0.97 [0.57–1.65]		0.96 [0.57–1.63]	0.90 [0.54–1.50]	0.99 [0.59–1.67]
Physical activity[e]						
Inactive	ref		ref	ref	ref	ref
Moderately inactive	1.08 [0.80–1.45]		1.09 [0.81–1.46]	1.08 [0.81–1.45]	1.06 [0.79–1.42]	1.09 [0.81–1.46]
Moderately active	0.97 [0.72–1.31]		0.97 [0.72–1.31]	0.97 [0.72–1.31]	0.95 [0.71–1.26]	0.96 [0.72–1.29]
Active	1.25 [0.91–1.72]		1.24 [0.90–1.70]	1.25 [0.91–1.71]	1.28 [0.93–1.75]	1.21 [0.88–1.65]

BMI body mass index; OR odds ratio; CI confidence interval

†Model 2: Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for waist circumference not adjusted for BMI; Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for years since smoking cessation additionally adjusted for smoking pack-years.

[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

Table B6. Odds ratios (OR) and confidence intervals (CI) of sarcoidosis in relation to tobacco status in a matched case-control study of 165 cases and 660 controls identified from the Northern Sweden Health and Disease study, 1987–2016.

| | Cases (n=165) N (%) | Controls (n=660) N (%) | Total | | Men (cases=103, controls=412) | Women (cases=62, controls=248) |
| | | | Model 1 | Model 2 | | |
			OR [95% CI]‡	OR [95% CI]†	OR [95% CI]†	OR [95% CI]†
Tobacco status						
Never tobacco user	80 (48.5)	263 (39.9)	ref	ref	ref	ref
Only smoker	31 (18.8)	177 (26.8)	0.68 [0.48–0.98]	0.68 [0.47–0.98]	0.68 [0.40–1.16]	0.59 [0.30–1.15]
Only snus user	22 (13.3)	73 (11.0)	1.28 [0.85–1.93]	1.30 [0.86–1.98]	1.25 [0.79–1.99]	1.95 [0.58–6.52]
Both smoker and snus user	27 (16.4)	117 (17.7)	0.94 [0.66–1.34]	0.88 [0.61–1.27]	0.82 [0.54–1.25]	0.95 [0.37–2.41]

OR odds ratio; CI confidence interval

‡Model 1: Odds ratios from conditional logistic regression (which accounts for the matching variables - sub-cohort, birthdate, sex and date of questionnaire).

†Model 2: Odds ratios from conditional logistic regression adjusted for education, body mass index, alcohol consumption and physical activity.

Table B7. Association between years since smoking cessation and years of smoke-free with sarcoidosis in a matched case-control study of 165 cases and 660 controls identified from the Northern Sweden Health and Disease study, 1987–2016.

	N cases/controls	1-year increments OR [95% CI]	5-year increments OR [95% CI]	10-year increments OR [95% CI]
		Total (Cases=165, Controls=660)		
Years since smoking cessation[a, ±]	165/660	1.02 [1.00–1.04]†	1.12 [1.02–1.23]†	1.25 [1.04–1.51]†
Years since smoking cessation among current and former smokers	59/304	1.04 [0.98–1.10]‡	1.20 [0.90–1.60]‡	1.44 [0.81–2.56]‡
Years free from smoking[a, ¥]	165/660	1.03 [1.01–1.05]†	1.15 [1.06–1.26]†	1.33 [1.12–1.59]†
Years free from smoking among current and former smokers	59/304	1.08 [1.02–1.13]‡	1.44 [1.12–1.86]‡	2.08 [1.24–3.48]‡

OR odds ratio; CI confidence interval
†Odds ratios from conditional logistic regression adjusted for education, body mass index, snus status, alcohol consumption, physical activity and smoking pack-years.
‡ Odds ratios from unconditional logistic regression adjusted for sex, birthyear, questionnaire year, education, body mass index, snus status, alcohol consumption, physical activity and smoking pack-years.
[a]among current, former and never smokers;
±current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study.
¥current=0, former=age of smoking initiation, never=age at recruitment in the study.
1, 5 or 10-year increments can be interpreted as for every 1-, 5-, 10-year increase (separately) in years since smoking cessation/years free from smoking the odds of sarcoidosis increase by x%.

Table B8. Association between lifestyle factors and sarcoidosis in a matched case-control study of 165 cases and 660 controls in the Northern Sweden Health and Disease study together with the E-Values, 1987–2016.

	OR [95% CI]‡	E-Value for OR	E-Value for CI
BMI, kg/m²	1.04 [0.99–1.09]	1.24	1
BMI, kg/m², WHO categories			
Normal, <25	ref		
Overweight, 25.0–29.9	0.99 [0.76–1.30]	1.11	1
Obesity, ≥30.0	1.34 [0.94–1.92]	2.01	1
Waist circumference, cm	1.02 [1.00–1.05]	1.16	1
Waist circumference, cm, categories for men			
<94	ref		
94–101.9	1.08 [0.74–1.58]	1.37	1
≥102	1.24 [0.83–1.86]	1.79	1
Waist circumference, cm, categories for women			
<80	ref		
80–87. 9	0.93 [0.51–1.70]	1.36	1
≥88	1.42 [0.88–2.28]	2.19	1
Smoking status			
Never	ref		
Current	0.48 [0.32–0.71]	3.59	2.17
Former	1.33 [0.98–1.81]	1.99	1
Smoking, pack-years[a]	0.98 [0.96–1.01]	1.16	1
Years since smoking cessation[b]	1.02 [1.00–1.04]	1.16	1
Snus status			
Never	ref		
Current	0.97 [0.69–1.34]	1.21	1
Former	1.09 [0.75–1.59]	1.40	1
Snus, packet-years[c]	0.99 [0.95–1.03]	1.11	1
Alcohol consumption, drinks/week[d]			
Abstainers	0.96 [0.60–1.52]	1.25	1
Light drinkers	ref		
Moderate drinkers	0.95 [0.56–1.62]	1.29	1
Physical activity[e]			
Inactive	ref		
Moderately inactive	1.08 [0.80–1.45]	1.37	1
Moderately active	0.97 [0.72–1.31]	1.21	1
Active	1.25 [0.91–1.72]	1.81	1

OR Odds ratios; CI confidence interval; BMI body mass index.

‡Odds ratios from conditional logistic regression adjusted for education, BMI, smoking status, snus status, alcohol consumption and physical activity. Model for smoking pack-years not adjusted for smoking status; Model for snus packet-years not adjusted for snus status; Model for waist circumference not adjusted for BMI; Model for years since smoking cessation additionally adjusted for smoking pack-years.

[a]One pack-year is equivalent to 20 cigarettes per day for 1 year; [b]current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; [c]One packet-year is the equivalent of consuming one packet of snus daily for 1 year; [d]abstainers (0 drinks/week), light (>0 to ≤3 drinks/week), moderate (>3 to ≤14 drinks/week) drinkers. One drink is equivalent to 500 ml of light beer, 330 ml of strong beer, 100–150 ml of wine, 50–80 ml of fortified wine, or 40 ml of spirits; [e]Inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ≤3.5-hour leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ≤7.0-hour leisure-time activity per week or standing work with ≤3.5-hour leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0-hour leisure-time activity per week or standing work with >3.5-hour leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

Table B9. Calculation of E-values for the odd ratios		
Direction of OR	**Estimate or CI**	**Computation of E-value for the OR and CI**
OR>1	Estimate	E-Value= OR + sqrt{ORx(OR-1)}
	Confidence interval	If LB≤1 then E-Value=1 If LB>1 then E-Value=LB + sqrt{LBx(LB-1)}
OR<1	Estimate	Let OR*=1/OR E-Value=OR* + sqrt{OR*x(OR*-1)}
	Confidence interval	If UB≥1 then E-Value=1 If UB<1 then let UB*=1/UB and E-Value= UB* + sqrt{UB*x(UB*-1)}

OR Odds ratios; CI confidence interval; LB lower bound of the confidence interval; UB upper bound of the confidence interval

Interpretation of E-Value:

The E-value is a continuous measure of how robust the association is to potential uncontrolled confounders. The lowest possible E-value is 1 which means that no unmeasured confounding is needed to explain away the observed association. The higher the E-value the stronger the confounder associations would have to be to explain away the effect.

An example of interpretation of E-value for smoking in presented below:

	OR [95% CI]‡	E-Value for OR	E-Value for CI
Smoking status			
Never	ref		
Current	0.48 [0.32–0.71]	3.59	2.17
Former	1.33 [0.98–1.81]	1.99	1

After adjustment for measured confounding, current smoking was associated with a 52% lower risk of sarcoidosis (adjusted odds ratio 0.48: 95% confidence interval 0.32–0.71). The corresponding E-value for this odds ratio was 3.59, meaning that an unmeasured confounder would need to be associated with both current smoking and sarcoidosis with an odds ratio of 3.59 to increase the point estimate from 0.48 to 1.00.
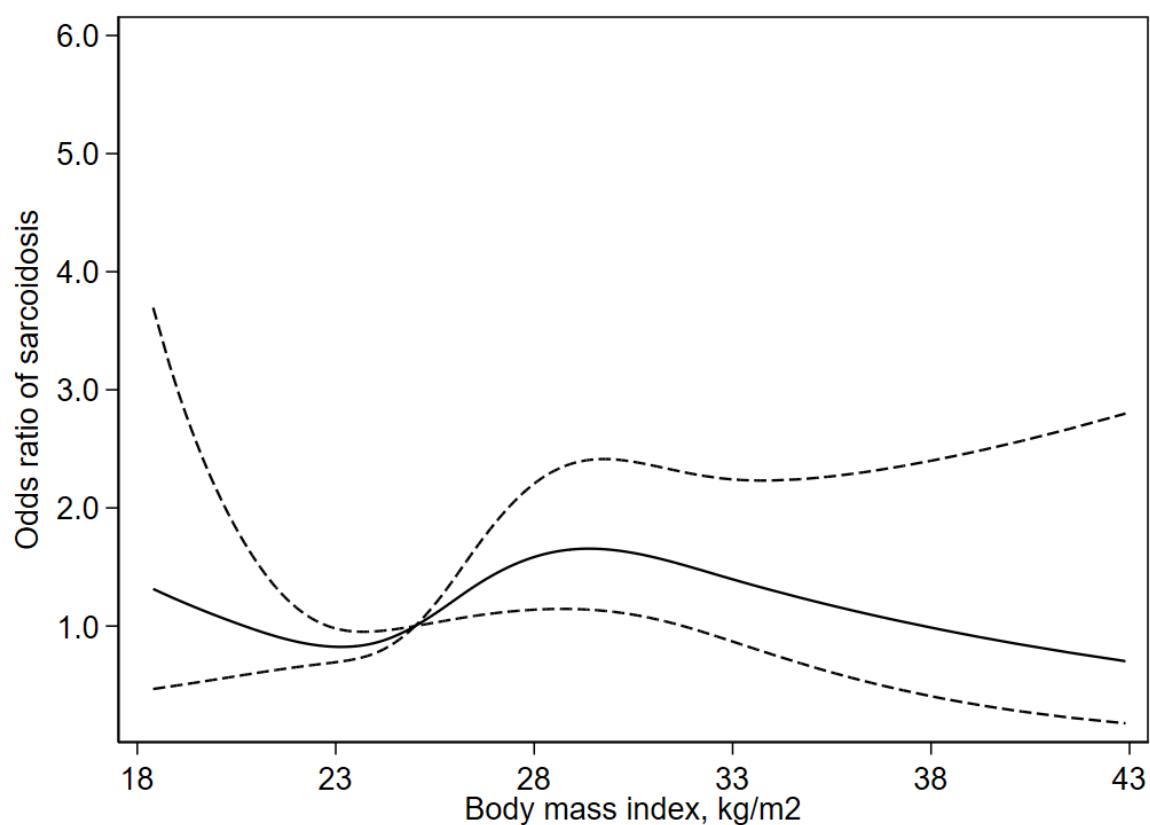
Figure C1. Odds ratio estimation with 95% confidence interval for the association between body mass index and sarcoidosis, allowing for nonlinear effects.

Odds ratios from conditional logistic regression adjusted for education, smoking status, snus status, alcohol consumption and physical activity.

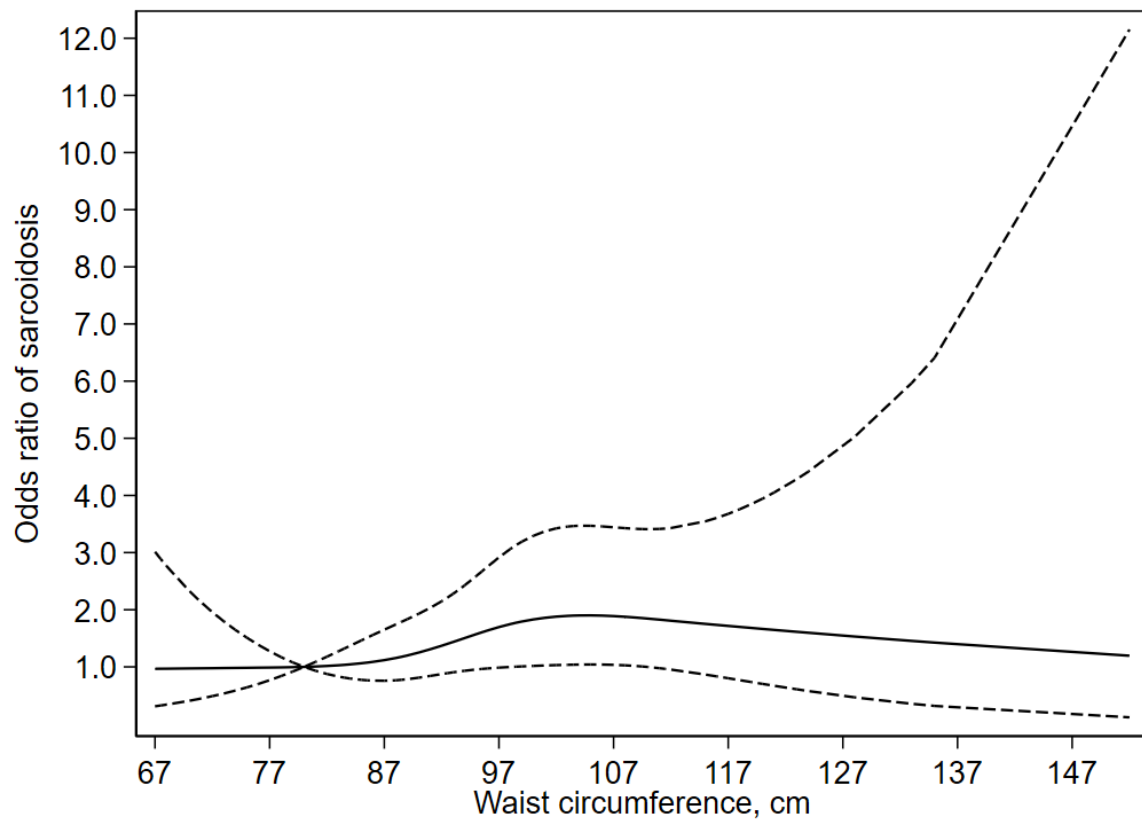Splines have 4 knots at 20.7, 24, 26.4 and 32.8 body mass index.

Figure C2. Odds ratio estimation with 95% confidence interval for the association between waist circumference and sarcoidosis, allowing for nonlinear effects.

Odds ratios from conditional logistic regression adjusted for education, smoking status, snus status, alcohol consumption and physical activity.

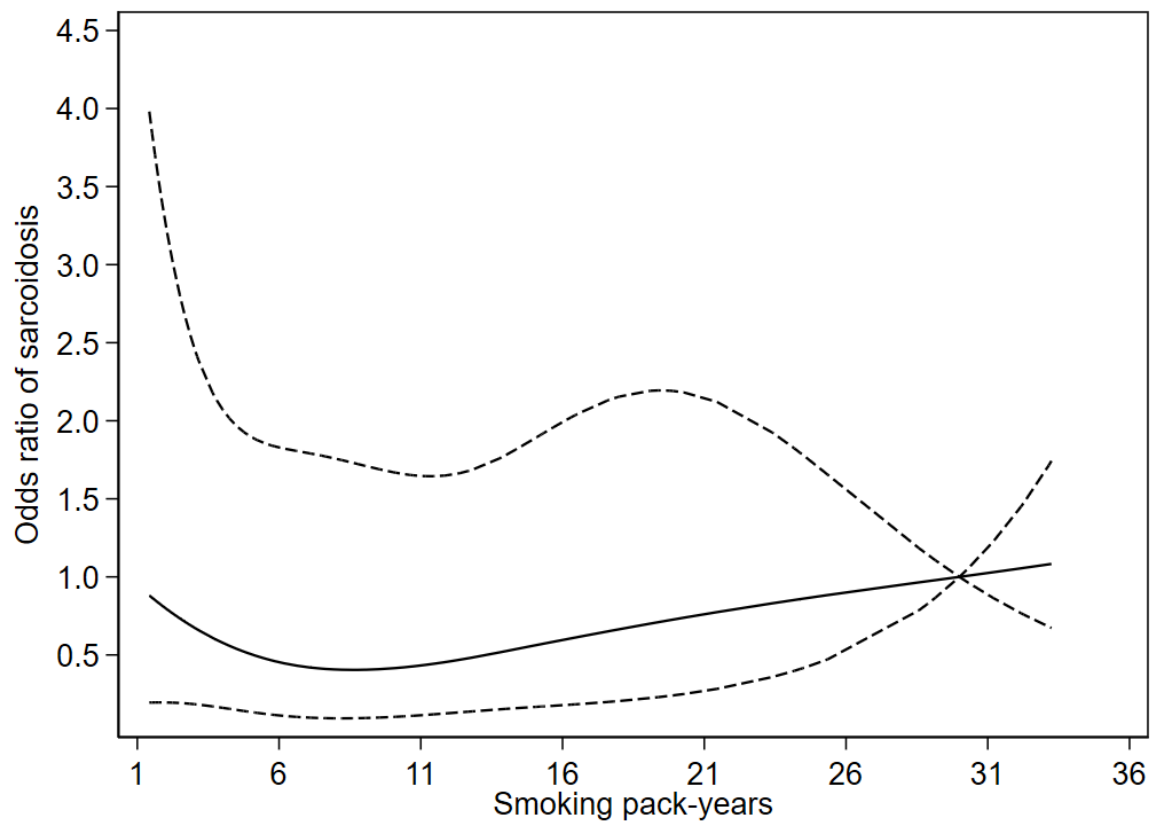Splines have 4 knots at 76, 88, 97 and 112 waist circumference.

Figure C3. Odds ratio estimation with 95% confidence interval for the association between smoking pack-years and sarcoidosis among current and former smokers, allowing for nonlinear effects.

Odds ratios from conditional logistic regression adjusted for education, body mass index, snus status, alcohol consumption and physical activity.

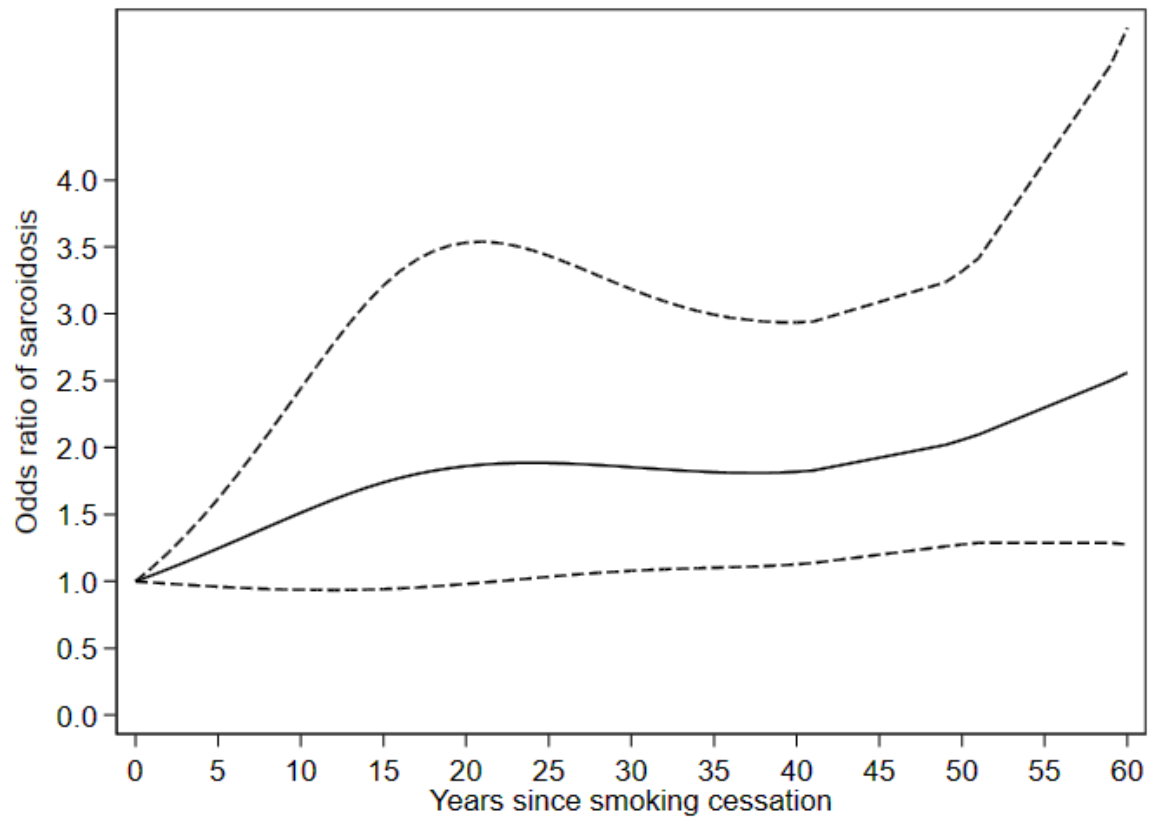Splines have 4 knots at 1.5, 6.6, 14.3 and 31.2 smoking pack-years.

Figure C4. Odds ratio estimation with 95% confidence interval for the association between years since smoking cessation and sarcoidosis among current, former and never smokers, allowing for nonlinear effects.

Odds ratios from conditional logistic regression adjusted for education, body mass index, snus status, alcohol consumption, physical activity and smoking pack-years.

current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study. Splines have 4 knots at 0, 15, 40 and 60 years since smoking cessation.
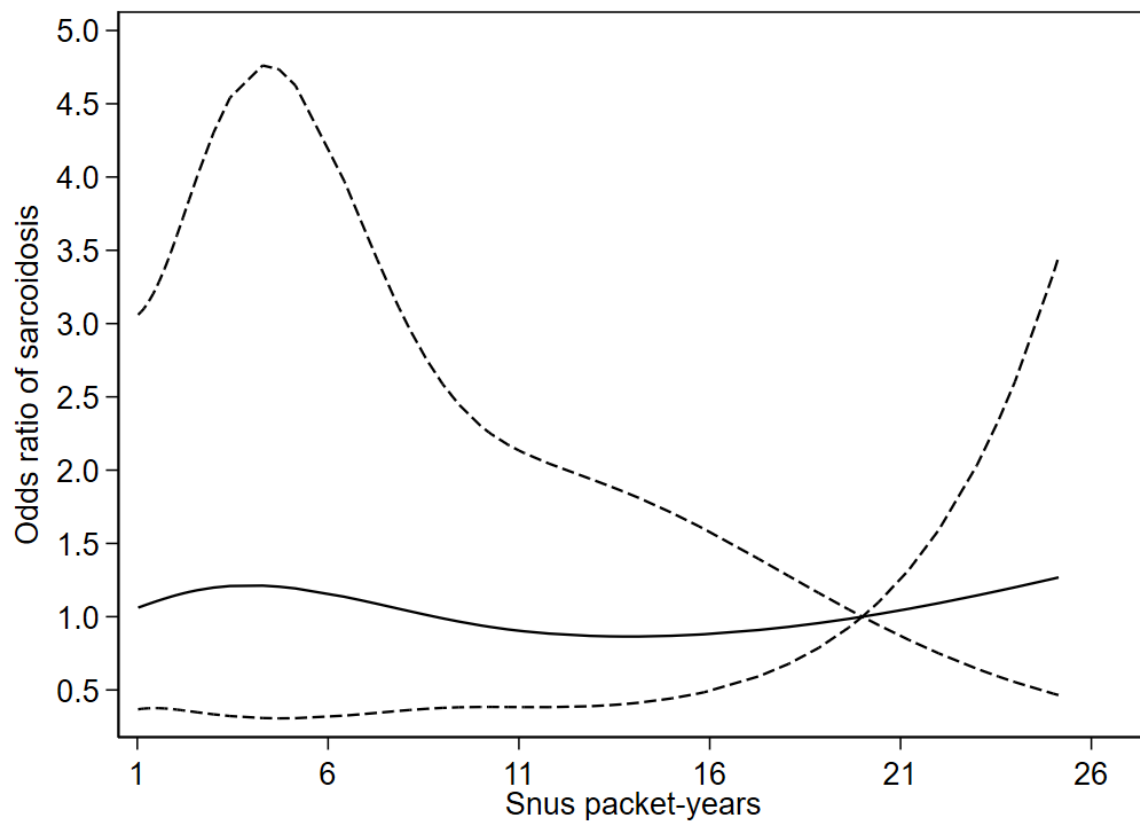
Figure C5. Odds ratio estimation with 95% confidence interval for the association between snus packet-years and sarcoidosis among current and former snus users, allowing for nonlinear effects.

Odds ratios from conditional logistic regression adjusted for education, body mass index, smoking status, alcohol consumption and physical activity.

Splines have 4 knots at 0.2, 2.2, 10.3 and 23.6 snus packet-years.