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

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Smoking is associated with a lower risk of sarcoidosis. Obesity and being physically active separately might increase sarcoidosis risk. https://bit.ly/3IHMvlA

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Abstract

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

Methods 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).

Results 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 of sarcoidosis (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.

Conclusion 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 characterised by the formation of non-caseating granulomas [1]. The aetiology of sarcoidosis is undetermined. However, it has been hypothesised that several modifiable lifestyle factors including obesity and tobacco use play a role in the aetiopathogenesis 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, but none of them have 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 nonsmokers). 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 characterised by a high attendance rate (66% in VIP; 74% between 1986 and 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 *et al.* [19]. In total, 201 incident cases were identified who had participated in NSHDS. Of these, eight 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.

BMI and 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 metres squared and examined as a continuous and categorical variable (categorised according to World Health Organization (WHO) as underweight (<18.5 $kg \cdot m^{-2}$), normal (18.5–24.9 $kg \cdot m^{-2}$), overweight (25.0–29.9 $kg \cdot m^{-2}$) and obese (⩾30 $kg \cdot m^{-2}$) [20]). As only two individuals had a BMI <18.5 $kg \cdot m^{-2}$ (BMI 17.3 and 17.9 $kg \cdot m^{-2}$), we included those with underweight in the normal weight category. Waist circumference (in centimetres) was collected in MONICA but not included in VIP until 2004. Waist circumference was considered as both a 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 and 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 a continuous variable. Age when the participant stopped smoking was used to calculate duration of smoking cessation in years, which was modelled 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 mean weekly and monthly amount of alcohol intake was used to calculate the mean 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), and 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 categorised 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 *versus* never smoking. All analyses were stratified by sex.

To minimise 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 homogeneous 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 NSHDS 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 modelled using restricted cubic splines with four 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 NSHDS 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% *versus* 38.6%), were overweight (45.5% *versus* 40.8%) and obese (14.5% *versus* 11.3%), light drinkers (37.6% *versus* 33.5%) and physically active (24.8% *versus* 19.7%). A larger percentage of cases were former (27.3% *versus* 24.5%) and never-smokers (63.0% *versus* 52.9%) compared to controls. The majority of cases were pulmonary (88%) and 25% had Löfgren syndrome (see supplementary table B1 for more detailed clinical characteristics).

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 1-cm 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 *versus* 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 *versus* never snus use: aOR 0.97, 95% CI 0.69–1.34; former *versus* 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 *versus* light: aOR 0.95, 95% CI 0.56–1.62; abstainers *versus* 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.

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 nonlinear effects (supplementary figures 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 hypothesised for ulcerative colitis [32] – another inflammatory disease in which smoking has also been found to be a

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

	Cases	Controls
Subjects n	165	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)
Sex		
Female	62 (37.6)	248 (37.6)
Male	103 (62.4)	412 (62.4)
Years of education		
⩽9	57 (34.6)	219 (33.2)
10–12	73 (44.2)	255 (38.6)
>12	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
WHO categories of BMI kg·m^{-2}		
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[#]	13.3±10.8	11.8±8.8
Years since smoking cessation[¶]	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[+]	7.9±7.3	7.9±7.1
Alcohol consumption drinks/week[§]		
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[f]		
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)

Data are presented as median (range), mean±SD or n (%) unless otherwise stated. VIP: Västerbotten Intervention Programme; MONICA: Monitoring of Trends and Determinants in Cardiovascular Disease study; BMI: body mass index; WHO: World Health Organization. [#]: among current/former smokers, n=363. One pack-year is equivalent to 20 cigarettes per day for 1 year. [¶]: among former smokers, n=207. [+]: among current/former snus users, n=244. One packet-year is the equivalent of consuming one packet of snus daily for 1 year. [§]: 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. [f]: inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ⩽3.5 h leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ⩽7.0 h leisure-time activity per week or standing work with ⩽3.5 h leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0 h leisure-time activity per week or standing work with >3.5 h leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

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

	Cases/controls n[#]	OR (95% CI)[¶]
Subjects n	165	660
BMI kg·m^{-2}	165/660	1.04 (0.99–1.09)
WHO categories of BMI kg·m^{-2}		
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[+]	165/660	0.98 (0.96–1.01)
Years since smoking cessation[§]	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[f]	165/660	0.99 (0.95–1.03)
Alcohol consumption, drinks/week[##]		
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[¶¶]		
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; WHO: World Health Organization. [#]: numbers (n) in cases and controls based on the 50th imputed dataset. [¶]: 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. [+]: one pack-year is equivalent to 20 cigarettes per day for 1 year. [§]: current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study. [f]: one packet-year is the equivalent of consuming one packet of snus daily for 1 year. [##]: 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. [¶¶]: inactive (sedentary work and no leisure-time activity), moderately inactive (sedentary work with ⩽3.5 h leisure-time activity per week or standing work with no leisure-time activity), moderately active (sedentary work with >3.5 to ⩽7.0 h leisure-time activity per week or standing work with ⩽3.5 h leisure-time activity per week or manual work with no leisure-time activity), active (sedentary work with >7.0 h leisure-time activity per week or standing work with >3.5 h leisure-time activity per week or manual work with at least some leisure-time activity or heavy manual work).

protective factor [33]. However, an increased sarcoidosis risk with smoking was reported in studies from the USA and Japan [10, 11]. A possible explanation for the discrepancies might be due to different aetiopathogeneses responsible for sarcoidosis development in different populations like in Japan [10]. The study from the USA 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 >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 ⩾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 ⩾30.0 kg m^{-2}, 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, which may play a role in sarcoidosis aetiopathogenesis [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, minimising disease misclassification. We obtained data on multiple modifiable lifestyle factors from the NSHDS cohort, which were prospectively collected prior to sarcoidosis diagnosis, minimising 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, minimising measurement error. We also used multiple imputation by chained equations to minimise selection bias due to missingness [29].

One limitation of this study is that the data available in the NSHDS were 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 median 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 generalisable 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.

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