

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

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## 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.

Analysis variables	Percentage (%)
Gender	0
Birthyear	0
Questionnaire year	0
Education	0.6
Body mass index, kg/m <sup>2</sup>	0
Body mass index, kg/m <sup>2</sup> , 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

<b>Table A2.</b> 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 ( <i>fcs regpmm</i> )
Ordinal classification variable	Logistic regression method (cumulative logit model: <i>fcs logistic</i> )
Binary classification variable	Discriminant function method ( <i>fcs discrim</i> )

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 Poisson 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.

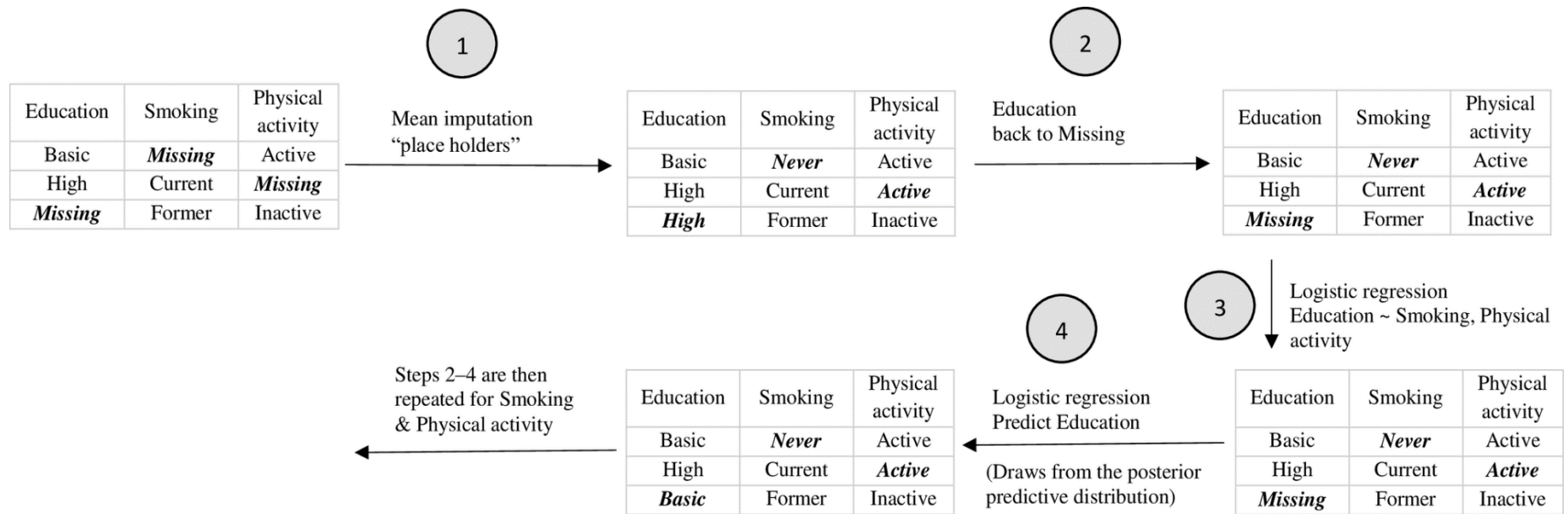


Figure A1. Multiple Imputation by Chained Equations – Single Iteration. Example of the 4 steps of the chained equations process.

## APPENDIX B: SUPPLEMENTAL TABLES

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

<b>Patient characteristic</b>	<b>N=165</b>
<b>Age at diagnosis, years, mean±SD</b>	55±10
<b>First diagnosis received in respiratory clinic</b>	91%
<b>Symptom onset before first visit</b>	
Days	4%
Months	48%
Years	30%
Missing	18%
<b>Onset type</b>	
Löfgren's syndrome	25%
Non-Löfgren's	13%
Unclear/missing	62%
<b>Disease type</b>	
Pulmonary	88%
Extra-pulmonary	3%
Both pulmonary and extra-pulmonary	8%
Unclear/missing	1%
<b>Clinical symptoms compatible with sarcoidosis</b>	
No	1%
No symptoms	13%
Yes	49%
Unclear/missing	37%
<b>Chest X-ray compatible</b>	
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%
<b>Other radiographic imaging performed</b>	
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%
<b>Biopsy performed</b>	78%
Of those with biopsy, % positive	44%
<b>EBUS-TBNA performed</b>	64%
<b>BAL performed</b>	61%

Of those with BAL,	
Lymphocytes >25% of total cell count	46%
CD4/CD8 ratio >3.5	48%
<b>Serum calcium &gt; upper limit of normal</b>	
Yes	4%
No	81%
Not measured/missing	15%
<b>Serum angiotensin converting enzyme &gt; upper limit of normal</b>	
Yes	29%
No	59%
Not measured/missing	12%
<b>Smoking status</b>	
Non-smoker	66%
Ex-smoker	27%
Current smoker	5%
Not mentioned	2%
<b>Spirometry performed at initial diagnosis</b>	89%
<b>Medication at initial diagnosis</b>	22%
Of those with medication, Prednisolone	69%
<b>Follow-up</b>	
<b>Followed for 2 or more years</b>	87%
<b>Followed for less than 2 years</b>	10%
<b>Unclear/not followed</b>	3%
<b>Treating physician's impression</b>	
Definite	79%
Probable but cannot say with 100% certainty	21%
<b>Reviewing physician's impression</b>	
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.

	<b>Men</b> (Cases=103, Controls=412)	<b>Women</b> (Cases=62, Controls=248)
	OR [95% CI]‡	OR [95% CI]‡
BMI, kg/m <sup>2</sup>	1.05 [0.98–1.12]	1.03 [0.96–1.11]
BMI, kg/m <sup>2</sup> , 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 <sup>a</sup>	0.98 [0.94–1.02]	0.99 [0.94–1.03]
Years since smoking cessation <sup>b</sup>	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 <sup>c</sup>	0.98 [0.94–1.03]	0.99 [0.83–1.17]
Alcohol consumption, drinks/week <sup>d</sup>		
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 <sup>e</sup>		
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.

<sup>a</sup>One pack-year is equivalent to 20 cigarettes per day for 1 year; <sup>b</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; <sup>c</sup>One packet-year is the equivalent of consuming one packet of snus daily for 1 year; <sup>d</sup>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; <sup>e</sup>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.

	<b>Pulmonary (cases=158, controls=632)</b>	<b>Löfgren (cases=42, controls=168)</b>
	OR [95% CI]‡	OR [95% CI]‡
BMI, kg/m <sup>2</sup>	1.05 [1.00–1.10]	1.11 [1.01–1.23]
BMI, kg/m <sup>2</sup> , 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 <sup>a</sup>	0.98 [0.95–1.01]	1.01 [0.94–1.08]
Years since smoking cessation <sup>b</sup>	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 <sup>c</sup>	0.99 [0.94–1.03]	0.97 [0.90–1.06]
Alcohol consumption, drinks/week <sup>d</sup>		
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 <sup>e</sup>		
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.

<sup>a</sup>One pack-year is equivalent to 20 cigarettes per day for 1 year; <sup>b</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; <sup>c</sup>One packet-year is the equivalent of consuming one packet of snus daily for 1 year; <sup>d</sup>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; <sup>e</sup>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.

	<b>Cases diagnosed more than 2 years after questionnaire date (cases=148, controls=592)</b>	<b>Cases diagnosed more than 5 years after questionnaire date (cases=135, controls=540)</b>
	OR [95% CI]‡	OR [95% CI]‡
BMI, kg/m <sup>2</sup>	1.05 [1.00–1.11]	1.05 [0.99–1.11]
BMI, kg/m <sup>2</sup> , 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 <sup>a</sup>	0.98 [0.95–1.01]	0.98 [0.95–1.01]
Years since smoking cessation <sup>b</sup>	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 <sup>c</sup>	0.99 [0.95–1.03]	1.00 [0.96–1.05]
Alcohol consumption, drinks/week <sup>d</sup>		
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 <sup>e</sup>		
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.

<sup>a</sup>One pack-year is equivalent to 20 cigarettes per day for 1 year; <sup>b</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; <sup>c</sup>One packet-year is the equivalent of consuming one packet of snus daily for 1 year; <sup>d</sup>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; <sup>e</sup>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/m <sup>2</sup>	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/m <sup>2</sup> , 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 <sup>a</sup>	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 <sup>b</sup>	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 <sup>c</sup>	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 <sup>d</sup>					
Abstainers	0.96 [0.60–1.52]	0.94 [0.60–1.49]		0.95 [0.60–1.51]	0.95 [0.60–1.49]
Light drinkers	ref	ref		ref	ref
Moderate drinkers	0.95 [0.56–1.62]	0.97 [0.57–1.65]		0.96 [0.57–1.63]	0.99 [0.59–1.67]
Physical activity <sup>e</sup>					
Inactive	ref		ref	ref	ref
Moderately inactive	1.08 [0.80–1.45]		1.09 [0.81–1.46]	1.08 [0.81–1.45]	1.09 [0.81–1.46]
Moderately active	0.97 [0.72–1.31]		0.97 [0.72–1.31]	0.97 [0.72–1.31]	0.96 [0.72–1.29]
Active	1.25 [0.91–1.72]		1.24 [0.90–1.70]	1.25 [0.91–1.71]	1.21 [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.

<sup>a</sup>One pack-year is equivalent to 20 cigarettes per day for 1 year; <sup>b</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; <sup>c</sup>One packet-year is the equivalent of consuming one packet of snus daily for 1 year; <sup>d</sup>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; <sup>e</sup>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.

			Total		Men	Women
	Cases (n=165) N (%)	Controls (n=660) N (%)	Model 1	Model 2	(cases=103, controls=412)	(cases=62, controls=248)
			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	Total (Cases=165, Controls=660)		
		1-year increments OR [95% CI]	5-year increments OR [95% CI]	10-year increments OR [95% CI]
Years since smoking cessation <sup>a, ±</sup>	165/660	1.02 [1.00–1.04] <sup>†</sup>	1.12 [1.02–1.23] <sup>†</sup>	1.25 [1.04–1.51] <sup>†</sup>
Years since smoking cessation among current and former smokers	59/304	1.04 [0.98–1.10] <sup>‡</sup>	1.20 [0.90–1.60] <sup>‡</sup>	1.44 [0.81–2.56] <sup>‡</sup>
Years free from smoking <sup>a, ¥</sup>	165/660	1.03 [1.01–1.05] <sup>†</sup>	1.15 [1.06–1.26] <sup>†</sup>	1.33 [1.12–1.59] <sup>†</sup>
Years free from smoking among current and former smokers	59/304	1.08 [1.02–1.13] <sup>‡</sup>	1.44 [1.12–1.86] <sup>‡</sup>	2.08 [1.24–3.48] <sup>‡</sup>

OR odds ratio; CI confidence interval

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

<sup>‡</sup> 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.

<sup>a</sup>among current, former and never smokers;

<sup>±</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study.

<sup>¥</sup>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/m <sup>2</sup>	1.04 [0.99–1.09]	1.24	1
BMI, kg/m <sup>2</sup> , 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 <sup>a</sup>	0.98 [0.96–1.01]	1.16	1
Years since smoking cessation <sup>b</sup>	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 <sup>c</sup>	0.99 [0.95–1.03]	1.11	1
Alcohol consumption, drinks/week <sup>d</sup>			
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 <sup>e</sup>			
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.

<sup>a</sup>One pack-year is equivalent to 20 cigarettes per day for 1 year; <sup>b</sup>current=0, former=age at recruitment in the study minus age at smoking cessation, never=age at recruitment in the study; <sup>c</sup>One packet-year is the equivalent of consuming one packet of snus daily for 1 year; <sup>d</sup>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; <sup>e</sup>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	$E\text{-Value} = OR + \sqrt{OR \times (OR - 1)}$
	Confidence interval	If $LB \leq 1$ then $E\text{-Value} = 1$ If $LB > 1$ then $E\text{-Value} = LB + \sqrt{LB \times (LB - 1)}$
OR<1	Estimate	Let $OR^* = 1/OR$ $E\text{-Value} = OR^* + \sqrt{OR^* \times (OR^* - 1)}$
	Confidence interval	If $UB \geq 1$ then $E\text{-Value} = 1$ If $UB < 1$ then let $UB^* = 1/UB$ and $E\text{-Value} = UB^* + \sqrt{UB^* \times (UB^* - 1)}$

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.

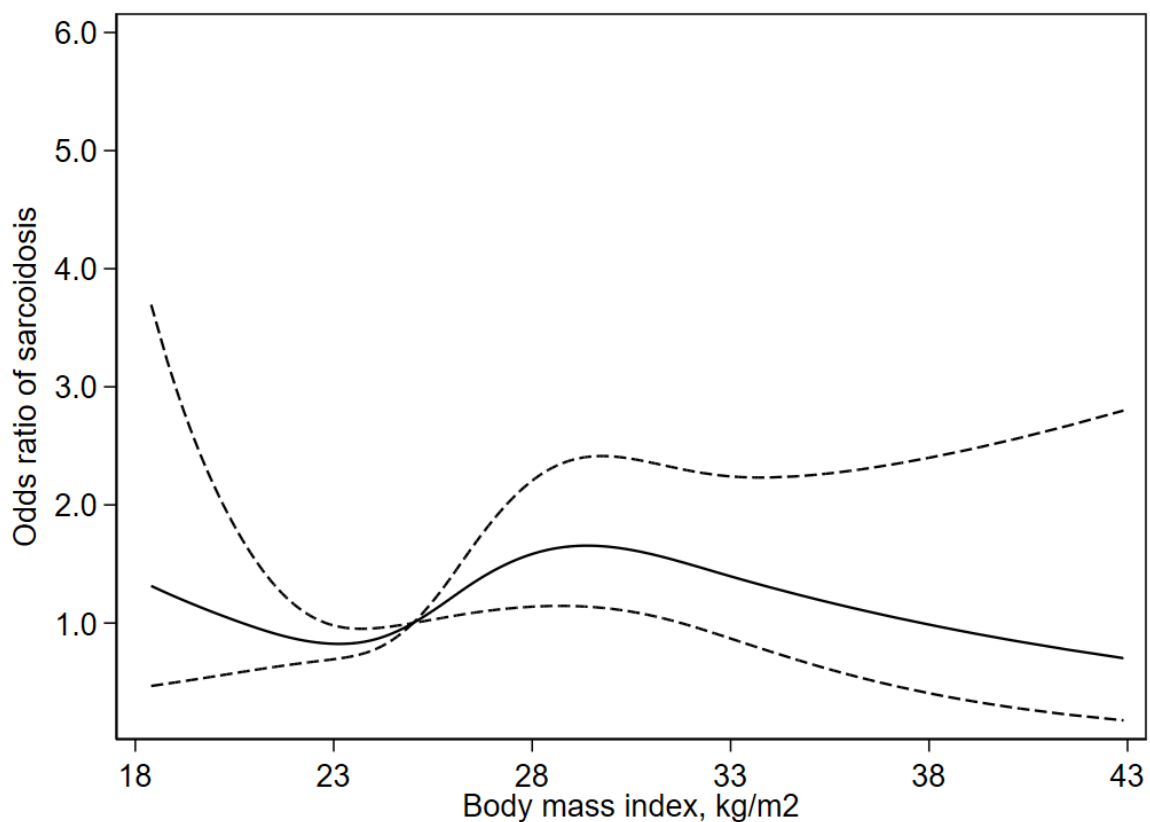
An example of interpretation of E-value for smoking is presented below:

	OR [95% CI]‡	E-Value for OR	E-Value for CI
<b>Smoking status</b>			
<b>Never</b>	ref		
<b>Current</b>	0.48 [0.32–0.71]	3.59	2.17
<b>Former</b>	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.



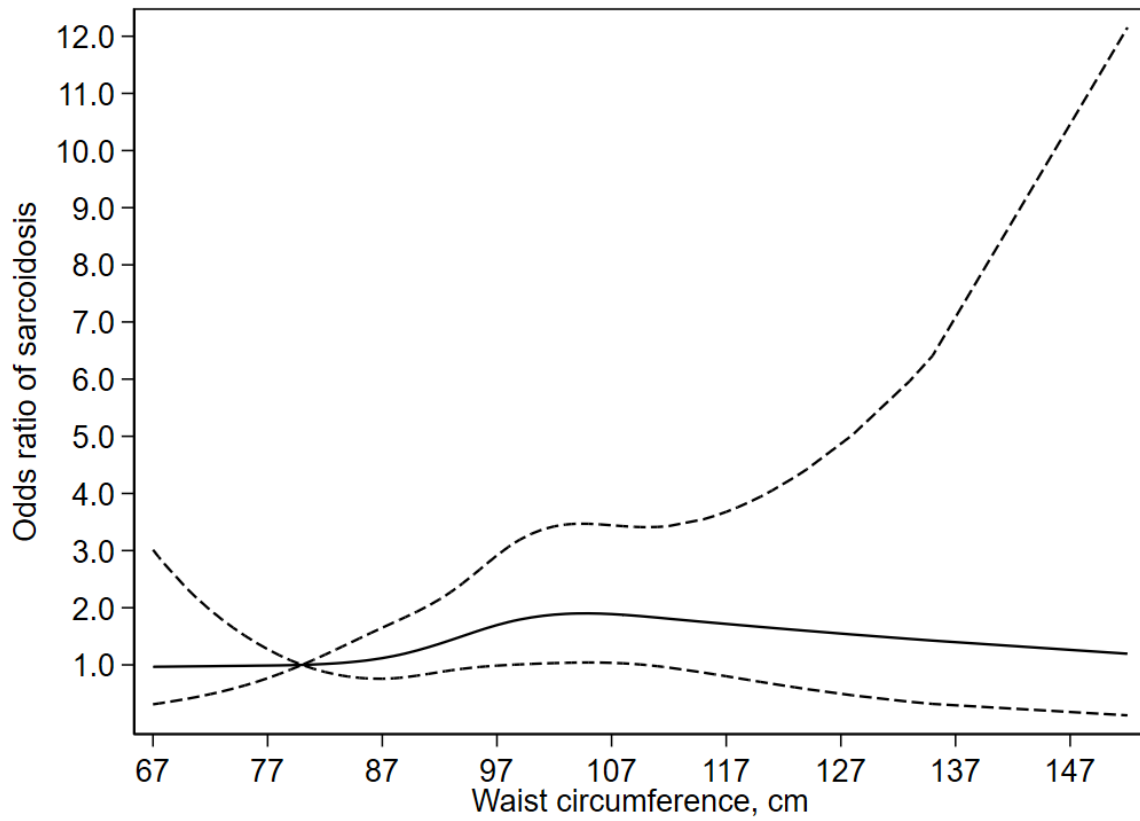
APPENDIX C: SUPPLEMENTAL FIGURES



**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.

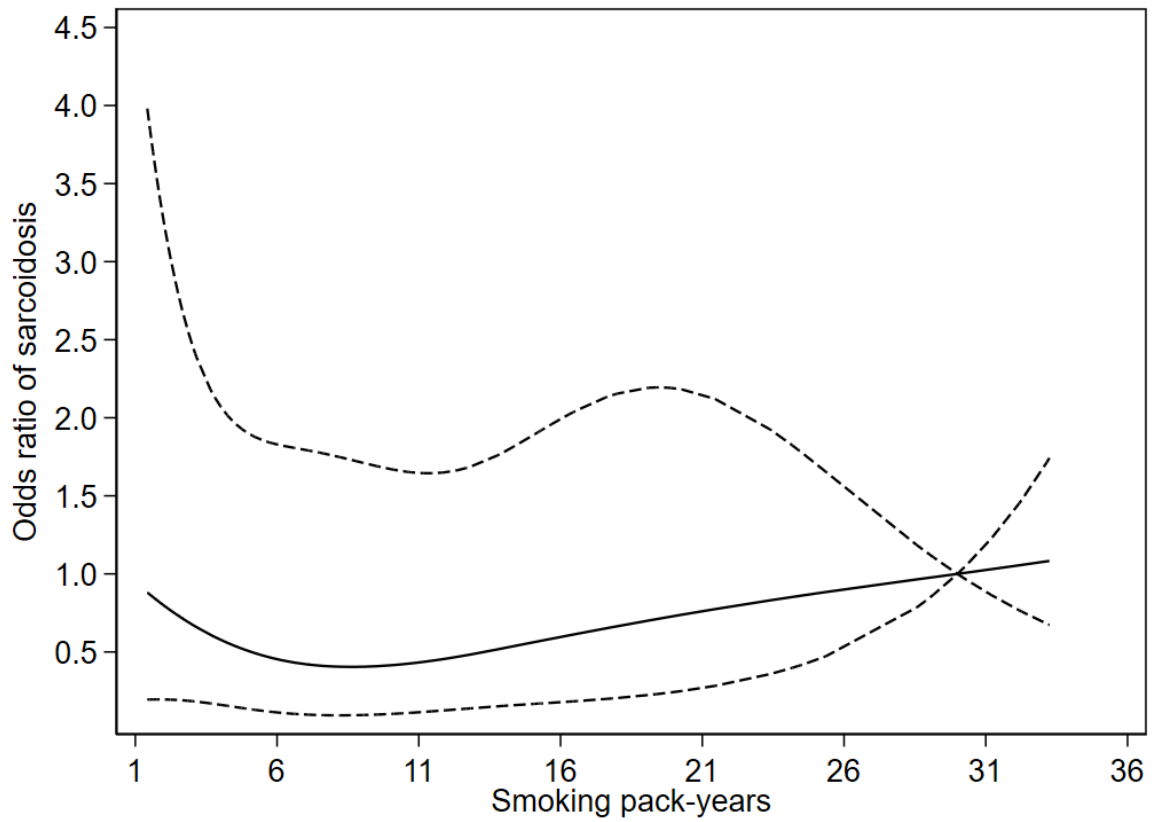
Splines have 4 knots at 20.7, 24, 26.4 and 32.8 body mass index.



**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.

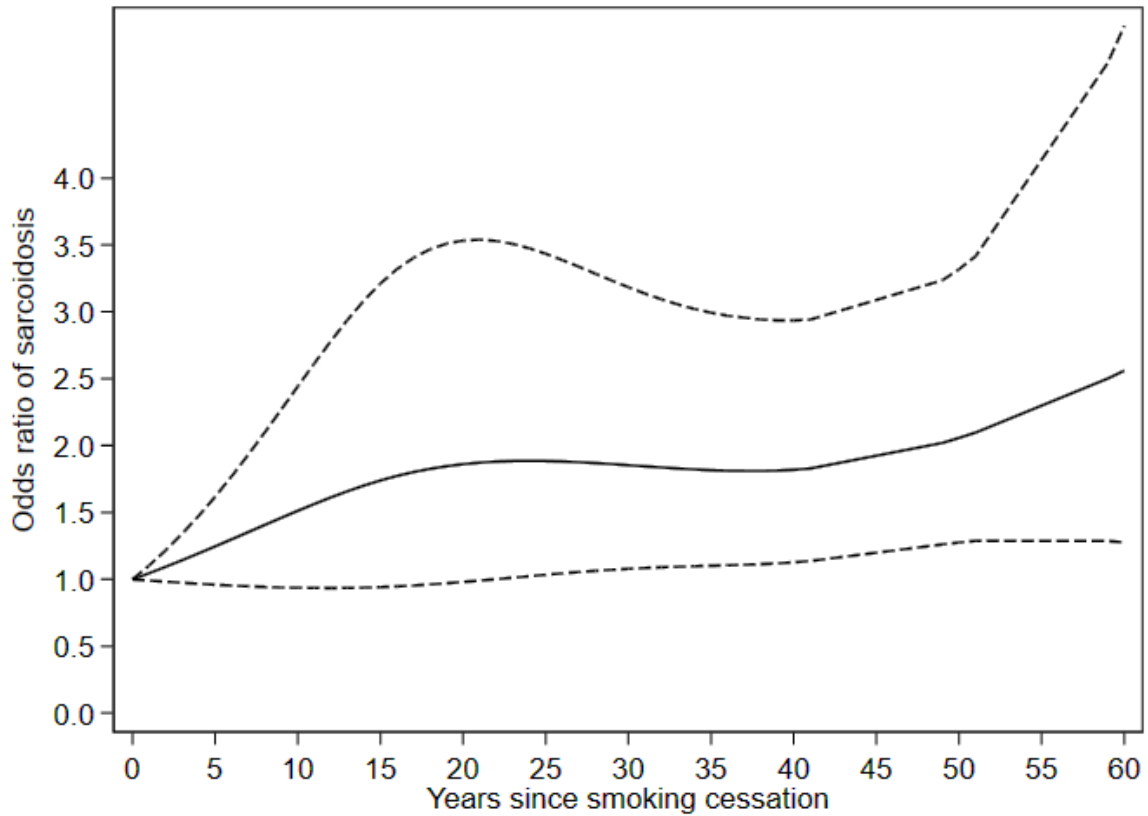
Splines have 4 knots at 76, 88, 97 and 112 waist circumference.



**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.

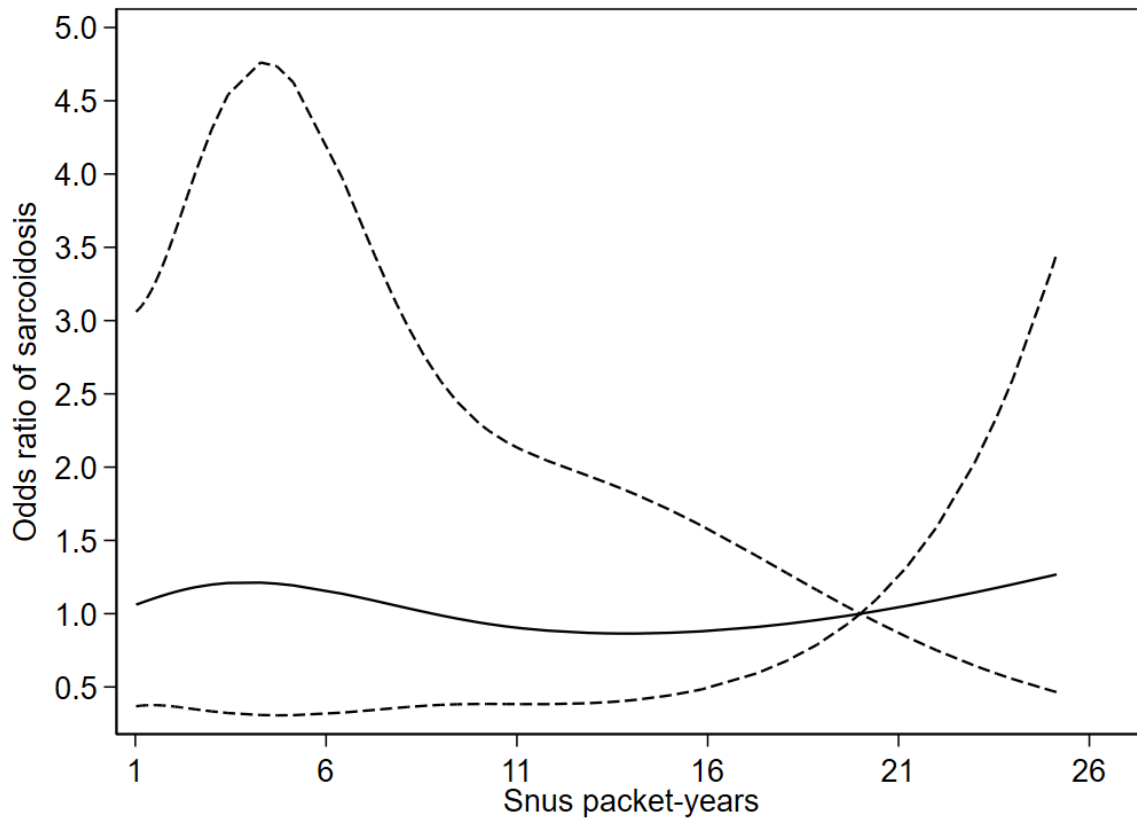
Splines have 4 knots at 1.5, 6.6, 14.3 and 31.2 smoking pack-years.



**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.