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Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Abstract

Objective: To determine whether occupational exposure to silica dust causes an increased risk of developing Crohn's disease and ulcerative colitis.

Design: Case-control study of comorbidity and mortality in people diagnosed with Crohn's disease (K50) and ulcerative colitis (K51) from 2007 through 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Participants: All men and women aged 20-65 years old who were diagnosed with Crohn's disease (K50) and ulcerative colitis (K51) during the years of study were included, resulting 58136 cases and 116272 controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing ulcerative colitis in men and Crohn's disease in women.

Results: The prevalence of ulcerative colitis was significantly higher in the group exposed to silica dust (odds ratio of 1.13) than in controls, particularly in individuals with over 5 years' exposure. When stratified by sex, a significantly increased odds ratio was detected for men. This trend was also consistent with longer exposure times. The prevalence of ulcerative colitis was not increased in exposed women. The prevalence of Crohn's disease was significantly increased among exposed women (odds ratio of 1.29), but not for exposed men.

Conclusions: Silica dust exposure correlates with an increased risk of developing ulcerative colitis in men, and the risk seems to increase with the duration of exposure. Conversely, silica dust exposure correlates positively with the risk of developing Crohn's disease in women, but not in men.

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Strengths and limitations of this study

- This case-control study includes anyone who was diagnosed with Crohn's disease and ulcerative colitis in Sweden in the years 2007-2016, and not just a selection.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area and therefore one could assume the distribution of these confounders among the cases and controls.

Key words: inflammatory bowel disease, silica dust, case control study, Crohn's disease, ulcerative colitis

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Introduction

Silica is a mineral composed of oxygen and silicon that is highly abundant in the Earth's crust and is a component of most types of rocks. Exposure to silica dust is therefore common during, for example, mining operations. Silica's high melting point, hardness, and chemical inertness make it ideal for several industrial applications. During the latter half of the 20th century, extensive efforts were made to reduce the amount of silica dust in Swedish workplaces [1]. Nevertheless, there is still significant occupational silica exposure in Sweden and abroad [2 3].

Exposure to silica dust is known to cause silicosis which is predominantly a pulmonary disease [4]. However, recent studies suggest a correlation between silica and several inflammatory diseases [5 6]. The pathological mechanisms underpinning these relationships are poorly understood [7 8]. No relationship between silicosis and the inflammatory bowel diseases Crohn's disease (CD) or ulcerative colitis (UC) has previously been reported.

The term inflammatory bowel disease (IBD) encompasses many diseases of the gastrointestinal tract. However, in this paper IBD refers only to CD or UC. CD and UC share several pathological features: they are both chronic and have symptoms including diarrhea, hematochezia, abdominal pain, fever, weight loss, and lesion formation. However, the distribution of lesions differs between the two diseases. CD may affect the entire gastrointestinal tract but the distribution of lesions is often discontinuous. Conversely, the UC lesions start in the rectum and are continuous. While these two IBDs share several risk factors, smoking has opposing effects on the risks of their development: it increases the risk of developing CD but reduces that of UC [9 10].

The etiology of IBD has been studied extensively but remains somewhat unclear. There is strong evidence of a familial component to its development [9-12], and a significant effect of environmental factors [12]. This is further supported by the observation that the global prevalence of IBD has risen as increasing numbers of countries outside of Europe and North America have adopted western lifestyles [13].

The identity of the environmental factors that may influence IBD pathogenesis is a subject of ongoing debate [11 14]. The intake of various airborne particles has been posited to contribute to IBD development despite a lack of direct evidence [15 16]. Two early studies suggested silica dust particles may contribute to the etiology of IBD because a fraction of

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the inhaled dust is swallowed with the mucus [17]. One of these studies have reported that silica dust was detected in the intestinal epithelium and distributed systemically after mice were fed a diet enriched with silica dust [18]. The other study showed that injecting silica dust directly into the intestinal lymphatic system of dogs causes the formation of enteric lesions similar to those associated with IBD [19].

IBD has a significant impact on patients' quality of life and an economic impact on society because it increases hospitalization and mortality rates [20]. Furthermore, the prevalence of IBD in Sweden is increasing more rapidly than previously expected [21], making it important to identify agents that cause or exacerbate this disease.

Aim

To determine whether silica dust exposure increases the risk of developing Crohn's disease (CD) or ulcerative colitis (UC).

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Material and Methods

Registers, administrative authorities, and job exposure matrix (JEM)

The Swedish administrative authority known as the National Board of Health and Welfare (NBHW) maintains and validates the "National Non-Primary Outpatient Care Register" (OPR). This register is part of the National Patient Register and has been maintained since 2001. It contains medical data from registered outpatients of Swedish healthcare facilities. The NBHW also maintains the Swedish Cause of Death Register.

Another administrative authority, the Swedish Central Bureau of Statistics (SCB), maintains the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) as well as the National Register of the Total Population (RTB) and the Multi-Generation Register (MGR). LISA holds records going back to 1990 including occupational and domicile information on all individuals resident in Sweden aged 16 years or above, registered as of 31 December in the relevant reference year. The RTB is an extract from the civil register of the Swedish Tax Agency and contains residential data. MGR contains information on individuals' biological relatives.

All data preparation and register matching for this paper was done by the SCB and NBHW with guidance from a statistician working for the Department of Occupational and Environmental Medicine. The processed data were de-identified such that the only personally identifying information remaining in the processed dataset were dates of birth and years of employment. Other information relating to the identities of individuals represented in the data was replaced with a serial number. All statistical analyses were performed using these de-identified data. A job exposure matrix (JEM) was used to estimate rates of occupational exposure to various substances based on individuals' job assignments [22 23].

Study design

Data from the registers were used to conduct a case-control analysis. The cases were selected from the OPR by the NBHW. The inclusion criterion for the cases was a single diagnosis of one of the following conditions (ICD-10-CM codes are given in parentheses): CD (K50) and UC (K51). The study participants were required to be between 20-65 years old at the time of diagnosis and to have been diagnosed between 2005 and 2016.

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Matching controls for the case-control study were randomly selected by the SCB using data from RTB and MGR. The inclusion criteria for the controls included having no previous diagnosis of any condition used to select the positive cases as well as not having sarcoidosis (D86), ankylosing spondylitis (M45), seropositive rheumatoid arthritis (M05), or other rheumatoid arthritis (M06) and not being a first degree relative of the corresponding case. Controls were also required to share the gender, age, and county of residence at the time of diagnosis of the matched case.

Occupational data for all case and control individuals were obtained from LISA. The JEM was then used to determine whether the occupational history of each case and control would have resulted in silica dust exposure.

The cases were selected from the years 2005-2016, with a wash-out period from 2005-2006 in order to include recent diagnoses and avoid including data from follow up medical examinations.

Statistical analysis

The odds of being exposed to silica dust before the time of diagnosis were calculated for cases and controls and expressed as odds ratios (OR). Being exposed to silica dust was defined based on JEM data as being employed in an environment where silica dust was present. A conditional logistic regression was used to find the 95% confidence interval (95% CI) for the OR. The OR was considered to be significantly greater than 1.00 if the lower limit of the 95% CI was above 1.00.

The study population was stratified according to duration of exposure and sex. The stratification for duration of exposure was divided into the following time frames: 1-5 years, 5-10 years and more than 10 years.

Standardized mortality ratios (SMRs) were used to compare UC and CD cases and controls to the general Swedish population. The data were stratified according to gender.

Ethical considerations

The study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2017/252).

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Results

Study population

58 136 cases and 116 272 controls where included in this study. Figure 1 shows a flowchart of the study population. For UC, 19 830 cases were included in this study with a mean age of 42.9 ± 12.9 years at the time of diagnosis. Of these 48.9% were men and 51.13% were women. The mean ages of the men and women were 41.4 ± 13.6 years and 42.0 ± 13.1 years, respectively. 40.0% of the men and 36.3% of the women were 35 years or younger at the time of diagnosis. 39 660 matched controls were randomly selected for these cases.

For CD, 10 261 cases were included with a mean age of 41.1 ± 13.7 at the time of diagnosis. Of these 45.3% were men and 54.7% were women. The mean ages of the men and women were 40.9 ± 13.8 years and 41.3 ± 13.6 years, respectively. 40.9% of the men and 39.7% of the women were 35 years or younger at the time of diagnosis. 20 522 matched controls were randomly selected for these cases.

Exposure to silica dust, ulcerative colitis and Crohn's disease

Table 1 shows the number of cases and controls for UC and CD along with the OR of exposure and the corresponding 95% CI. For men, regardless of age and duration of occupation, the odds of being exposed to silica dust were 33% (OR = 1.33, 95% CI1.05 – 1.22). The risk of developing UC increases as a function of the duration of occupational exposure across the entire study population as well as in men.

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Table 1. Number of cases and controls for ulcerative colitis and Crohn's disease, with odds ratios for exposure and the corresponding 95% confidence intervals.

	Exposed to quartz during the 5 years before diagnosis in 2007 - 2016							
	Ulcerative colitis				Crohn's disease			
	Cases n[a]	Controls n	OR[b]	95% CI[c]	Cases n	Controls n	OR	95% CI
Total								
Unexposed	18 411	37 116	1		9 672	19 293	1	
Exposed	1 419	2 544	**1.13**	**1.06 - 1.21**	589	1 229	0.95	0.86 - 1.06
Duration of exposure								
0 years	18 411	37 116	1		9 672	19 293	1	
-1 years	318	596	1.08	0.94 - 1.24	122	296	0.82	0.66 - 1.01
1.01 - 5 years	377	717	1.07	0.94 - 1.21	172	363	0.94	0.78 - 1.13
5.01 - 10 years	485	828	**1.19**	**1.06 - 1.33**	199	402	0.99	0.83 - 1.17
More than 10 years	239	403	**1.21**	**1.02 - 1.42**	96	168	1.14	0.89 - 1.48
Men								
Unexposed	8 459	17 172	1		4 095	8 091	1	
Exposed	1 238	2 220	**1.33**	**1.05 - 1.22**	480	1 059	0.89	0.80 - 1.00
Duration of exposure								
0 years	8 459	17 172	1		4 095	8 091	1	
-1 years	261	505	1.04	0.90 - 1.22	90	245	0.72	0.56 – 0.92
1.01 - 5 years	318	613	1.05	0.92 - 1.21	143	301	0.93	0.76 - 1.15
5.01 - 10 years	441	738	**1.21**	**1.08 - 1.37**	164	358	0.90	0.75 - 1.09
More than 10 years	218	364	**1.22**	**1.03 - 1.46**	73	155	1.06	0.81 - 1.39
Women								
Unexposed	9 952	19 944	1		5 577	11 202	1	
Exposed	181	324	1.12	0.93 - 1.34	109	170	**1.29**	**1.01 - 1.65**
Duration of exposure								
0 years	9 952	19 944	1		5 577	11 202	1	
-1 years	57	91	1.25	0.90 - 1.75	32	51	1.25	0.81 - 1.96
1.01 - 5 years	59	104	1.14	0.83 - 1.56	29	62	0.94	0.60 - 1.46
5.01 - 10 years	44	90	0.98	0.68 - 1.41	35	44	**1.62**	**1.03 - 2.54**
More than 10 years	21	39	1.08	0.63 - 1.83	13	13	2.02	0.93 - 4.36

a: number
b: odds ratio
c: confidence interval.

The risk of developing CD was significantly increased among women (OR = 1.29, 95% CI 1.01 – 1.65) and particularly in women exposed to silica for >5-10 years (OR = 1.62, 95% CI 1.03 – 2.54). However, this trend was not observed across the patient population as a whole, or in men.

Mortality rates for ulcerative colitis and Crohn's disease

The SMR for men and women with UC or CD are shown in Table 2. Men diagnosed with either UC or CD exhibit an elevated mortality rate. The mortality rate of UC and CD was increased in both exposed and non-exposed individuals, although there was a higher SMR for those who were identified by the JEM as having been exposed to silica dust (SMR for UC = 1.64, 95% CI 1.16 – 2.24; SMR for CD = 1.88, 95% CI 1.08 – 3.06), but those exposed to silica dust had a higher overall SMR (Table 2). For women, an increased SMR was found for both UC and CD. However, the SMR for women exposed to silica dust could

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not be calculated due to a lack of fatalities in the extracted medical data.

Table 2 Standard mortality rates (SMR) for individuals diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) compared to the Swedish general population.

Sex	UC	Silica exposure	Observed	Expected	SMR	95% CI[a]
Men	Controls	No	299	343.3	0.87	0.78 - 0.98
		Yes	46	43.0	1.07	0.78 - 1.43
	Cases	No	213	**168.4**	**1.26**	**1.10 - 1.45**
		Yes	39	**23.9**	**1.64**	**1.16 - 2.24**
Women	Controls	No	253	245.5	1.03	0.91 - 1.17
		Yes	2	4.5	0.44	0.05 - 1.60
	Cases	No	154	**122.1**	**1.26**	**1.07 - 1.48**
		Yes	0	2.2	-	-

Sex	CD	Silica exposure	Observed	Expected	SMR	95% CI
Men	Controls	No	180	158.6	1.14	0.98-1.31
		Yes	23	19.8	1.16	0.74-1.75
	Cases	No	113	80.1	**1.41**	**1.16-1.70**
		Yes	16	8.5	**1.88**	**1.08-3.06**
Women	Controls	No	136	135.5	1.00	0.84-1.19
		Yes	1	2.4	0.42	0.01-2.31
	Cases	No	134	66.9	**2.00**	**1.68-2.37**
		Yes	0	1.3	-	-

a: confidence interval.

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Discussion and Conclusions

The OR for developing UC was significantly increased among men with an exposure duration of more than 5 years. No significant difference was observed between individuals exposed for >5-10 years and those exposed for over 10 years. This suggests that there is a threshold beyond which further exposure no longer affects the risk of developing UC.

The results obtained indicate that silica dust exposure correlates with an increased risk of developing UC among men. Previous reports suggested that silica exposure among men correlates with an increased incidence of another inflammatory disease; sarcoidosis [6 24]. Both sarcoidosis and UC are less prevalent in smokers [10 25]. It is possible that smoking offers a protective action that interacts with the pathological action of silica dust. The protective effects of smoking are not currently understood but appear to impact men and women differently [26 27].

Helper T cells are thought to play a critical role in the pathology of UC [10] as well as other inflammatory diseases including sarcoidosis, rheumatoid arthritis and systemic lupus erythematosus [28-31]. Silica dust exposure appears to increase the incidence of all these conditions. The immune responses to UC and CD reportedly involve different T cell populations [10 32], which may respond in different ways to silica dust exposure. This may explain the different OR values observed for men and women in this work because there appear to be gender-based differences in immune responses [33-35]. These differences are not well understood but similar effects have been seen for asthma [36 37].

The results from this study show that SMR for UC and CD was increased in both men and women, which is consistent with previous reports [38]. Furthermore, an increased SMR was detected for CD and UC among men exposed to silica dust, possibly due to the potential comorbidities also associated with silica dust exposure.

The large patient population and the validity of the medical data extracted from the registers represent major strengths of this study. The OPR maintains a thorough nationwide database of outpatients, so all individuals resident in Sweden and diagnosed with UC or CD were potentially eligible as cases for this study. Swedish law requires all publicly and privately funded physicians to report data to the OPR; the medical data contained in the OPR has been affirmed by practicing physicians and is therefore

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considered highly valid.

The RTB database from which the controls were selected is also nationwide, making the entire population of Sweden available as potential controls. Consequently, the results presented here are representative of the Swedish population. No medical data originally gathered before 2005 was used in this work. In this study, the time of diagnosis was operationally defined as the first date of entry in the national register from which medical data was extracted for each case. It is possible that some individuals were actually diagnosed prior to the date recorded in the national registry, so we did not consider diagnoses made between 2005 and 2006 to reduce the risk of including previously diagnosed cases. Another limitation of the study was that the individuals excluded from the data set were not further evaluated.

Silica dust exposure was defined on the basis of JEM data as being employed in an environment where silica dust is present. However, the presence of silica dust at a job site does not by itself mean that all employees would have been exposed to the particles, so this definition may have exaggerated the number of exposed individuals. Any such inflation of exposure rates was likely mitigated by the large sample size. However, if the JEM overestimated the detrimental level of silica exposure in the non-exposed cases, the results obtained would be skewed towards a null hypothesis, reducing their significance. It was not feasible to control for certain confounding variables in this study. These variables include smoking habits and socioeconomic factors, both of which correlate with the incidence of IBD [9 10]. However, since the sample was large and the cases and controls were matched, it is reasonable to assume that the incidence of cofounding factors in the two groups is similar. Nevertheless, it is possible that the results presented here do not reflect an intrinsic capability of silica dust to induce inflammation but a masked confounding factor associated with silica dust exposure.

Habitual smokers have a reduced risk of developing UC [10]. While this is interesting, it is unlikely that including data on patients who smoke increased the possibility of detecting an increased risk of OR. However, a history of smoking is a known strong risk factor for developing UC, so not controlling for smoking cessation may have introduced a bias towards an alpha error.

In closing, this study suggests a positive correlation between silica dust exposure and the risk of developing UC in men. The risk increases as a function of the duration of exposure

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up to a cumulative exposure of 5 years. Conversely, silica dust exposure in women increases the risk of developing CD but not UC. No comparable findings have been reported previously to the author's knowledge. Both UC and CD also appear to increase mortality, particularly among men exposed to silica dust.

Author statement

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and AW, PV, ILB and PG interpreted the results. AW, LF, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

No additional data are available.

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Figure legend

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

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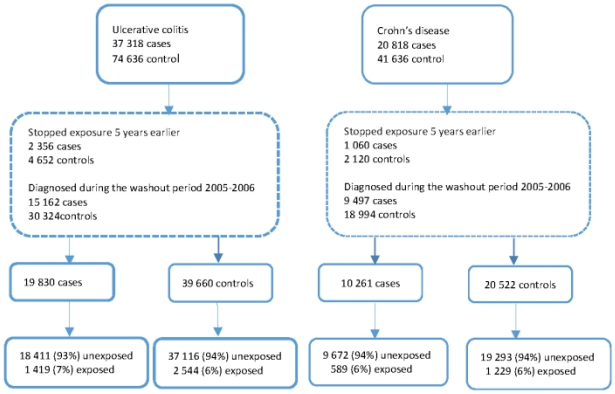

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

210x297mm (200 x 200 DPI)

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Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the STROBE case-controlreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6-7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	6-7

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Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	6-7
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	6-7
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	#13b	Give reasons for non-participation at each stage	figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they	na

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		were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	table 1 and 2
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	table 1 and 2
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12-13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

Notes:

- 16b: table 1 and 2
- 16c: table 1 and 2 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 03. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure in Sweden – a case-control study

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Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure in Sweden – a case-control study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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The study was approved by the Swedish Ethical Review Authority; DNR 2017/252.

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Abstract

Objective: To determine whether occupational exposure to silica dust causes an increased risk of developing Crohn's disease and ulcerative colitis.

Design: Case-control study of Crohn's disease (K50) and ulcerative colitis (K51) from 2007 through 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population.

Participants: All men and women aged 20-65 years old who were diagnosed with Crohn's disease (K50) and ulcerative colitis (K51) during the years of study were included and assigned two controls, resulting 58136 cases and 116272 controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing ulcerative colitis in men and Crohn's disease in women.

Results: The prevalence of ulcerative colitis was significantly higher in the group exposed to silica dust (OR 1.13; 95% CI 1.06-1.21) than in controls, particularly in individuals with over 5 years' exposure. When stratified by sex, a significantly increased odds ratio was detected for men (OR 1.33; 95% CI 1.05-1.22). This trend was also consistent with longer exposure times. The prevalence of ulcerative colitis was not increased in exposed women. The prevalence of Crohn's disease was significantly increased among exposed women (OR 1.29; 95% CI 1.01-1.65), but not for exposed men.

Conclusions: Silica dust exposure correlates with an increased risk of developing ulcerative colitis, especially in men, and the risk seems to increase with the duration and degree of

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exposure. Conversely, silica dust exposure correlates positively with the risk of developing Crohn's disease in women.

Strengths and limitations of this study

- This case-control study includes anyone who was diagnosed with Crohn's disease and ulcerative colitis in Sweden in the years 2007-2016, and not just a selection.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area and therefore one could assume the distribution of these confounders among the cases and controls.

Key words: inflammatory bowel disease, silica dust, case control study, Crohn's disease, ulcerative colitis

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Introduction

Silica is a mineral composed of oxygen and silicon that is highly abundant in the Earth's crust and is a component of most types of rocks. Exposure to silica dust is therefore common during, for example, mining operations. Silica's high melting point, hardness, and chemical inertness make it ideal for several industrial applications. During the latter half of the 20th century, extensive efforts were made to reduce the amount of silica dust in Swedish workplaces [1]. Nevertheless, there is still significant occupational silica exposure in Sweden and abroad [2 3].

Exposure to silica dust is known to cause silicosis which is predominantly a pulmonary disease [4]. However, recent studies suggest a correlation between silica and several inflammatory diseases [5 6]. The pathological mechanisms underpinning these relationships are poorly understood [7 8]. No relationship between silicosis and the inflammatory bowel diseases Crohn's disease (CD) or ulcerative colitis (UC) has previously been reported.

The term inflammatory bowel disease (IBD) encompasses many diseases of the gastrointestinal tract. However, in this paper IBD refers only to CD or UC. CD and UC share several pathological features: they are both chronic and have symptoms including diarrhea, hematochezia, abdominal pain, fever, weight loss, and lesion formation. However, the distribution of lesions differs between the two diseases. CD may affect the entire gastrointestinal tract but the distribution of lesions is often discontinuous. Conversely, the UC lesions start in the rectum and are continuous. While these two IBDs share several risk factors, smoking has opposing effects on the risks of their development: it increases the risk of developing CD but reduces that of UC [9 10].

The etiology of IBD has been studied extensively but remains somewhat unclear. There is strong evidence of a familial component to its development [9-12], and a significant effect of environmental factors [12]. This is further supported by the observation that the global prevalence of IBD has risen as increasing numbers of countries outside of Europe and North America have adopted western lifestyles [13].

The identity of the environmental factors that may influence IBD pathogenesis is a subject of ongoing debate [11 14]. The intake of various airborne particles has been posited to contribute to IBD development despite a lack of direct evidence [15 16]. Two early studies suggested silica dust particles may contribute to the etiology of IBD because a fraction of

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the inhaled dust is swallowed with the mucus [17]. One of these studies have reported that silica dust was detected in the intestinal epithelium and distributed systemically after mice were fed a diet enriched with silica dust [18]. The other study showed that injecting silica dust directly into the intestinal lymphatic system of dogs causes the formation of enteric lesions similar to those associated with IBD [19].

IBD has a significant impact on patients' quality of life and an economic impact on society because it increases hospitalization and mortality rates [20]. Furthermore, the prevalence of IBD in Sweden is increasing more rapidly than previously expected [21], making it important to identify agents that cause or exacerbate this disease.

Aim

To determine whether silica dust exposure increases the risk of developing Crohn's disease (CD) or ulcerative colitis (UC).

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Material and Methods

Registers, administrative authorities, and job exposure matrix (JEM)

The Swedish administrative authority known as the National Board of Health and Welfare (NBHW) maintains and validates the "National Non-Primary Outpatient Care Register" (OPR). This register is part of the National Patient Register and has been maintained since 2001. It contains medical data from registered outpatients of Swedish healthcare facilities. The NBHW also maintains the Swedish Cause of Death Register.

Another administrative authority, the Swedish Central Bureau of Statistics (SCB), maintains the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) as well as the National Register of the Total Population (RTB) and the Multi-Generation Register (MGR). LISA holds records going back to 1990 including occupational and domicile information on all individuals resident in Sweden aged 16 years or above, registered as of 31 December in the relevant reference year. The RTB is an extract from the civil register of the Swedish Tax Agency and contains residential data. MGR contains information on individuals' biological relatives.

All data preparation and register matching for this paper was done by the SCB and NBHW with guidance from a statistician working for the Department of Occupational and Environmental Medicine. The processed data were de-identified such that the only personally identifying information remaining in the processed dataset were dates of birth and years of employment. Other information relating to the identities of individuals represented in the data was replaced with a serial number. All statistical analyses were performed using these de-identified data. A job exposure matrix (JEM) was used to estimate rates of occupational exposure to silica based on individuals' job assignments [22 23].

Study design

Data from the registers were used to conduct a case-control analysis. The cases were selected from the OPR by the NBHW. The inclusion criterion for the cases was a single diagnosis of one of the following conditions (ICD-10-CM codes are given in parentheses): CD (K50) and UC (K51). The study participants were required to be between 20-65 years old at the time of diagnosis and to have been diagnosed between 2005 and 2016.

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Matching controls for the case-control study were randomly selected by the SCB using data from RTB and MGR. The inclusion criteria for the controls included having no previous diagnosis of any condition used to select the positive cases as well as not having sarcoidosis (D86), ankylosing spondylitis (M45), seropositive rheumatoid arthritis (M05), or other rheumatoid arthritis (M06) and not being a first degree relative of the corresponding case. Controls were also required to share the gender, age, and county of residence at the time of diagnosis of the matched case (Figure 1).

Occupational data for all case and control individuals were obtained from LISA. The JEM was then used to determine whether the occupational history of each case and control would have resulted in silica dust exposure as well as to assess the cumulative exposure. Cases not exposed to silica any time the last 5 years before diagnosis were excluded (Figure 1). Jobs among the cases and controls that according to the JEM were classified as containing exposure to silica included concrete workers, casters, masons, ceramic and glass manufacturers, miners etc.

The cases were selected from the years 2005-2016, with a wash-out period from 2005-2006 in order to include recent diagnoses and avoid including data from follow up medical examinations.

Statistical analysis

The odds of being exposed to silica dust before the time of diagnosis were calculated for cases and controls and expressed as odds ratios (OR). Being exposed to silica dust was defined based on JEM data as being employed in an environment where silica dust was present. A conditional logistic regression was used to find the 95% confidence interval (95% CI) for the OR. The OR was considered to be significantly greater than 1.00 if the lower limit of the 95% CI was above 1.00.

The study population was stratified according to duration of exposure and sex. The stratification for duration of exposure was divided into the following time frames: 1-5 years, 5-10 years and more than 10 years. Based on the JEM a cumulative exposure to silica was also calculated with regards to both prevalence and level of exposure for the different jobs. The cumulative exposure was stratified into 0.01-0.99 mg/m^3 and more than 1 mg/m^3.

Standardized mortality ratios (SMRs) were used to compare UC and CD cases and controls to the general Swedish population. The data were stratified according to gender.

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Ethical considerations

The study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2017/252).

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Results

Study population

58 136 cases and 116 272 controls where included in this study. Figure 1 shows a flowchart of the study population. For UC, 19 830 cases were included in this study with a mean age of 42.9 ± 12.9 years at the time of diagnosis. Of these 48.9% were men and 51.13% were women. The mean ages of the men and women were 41.4 ± 13.6 years and 42.0 ± 13.1 years, respectively. 40.0% of the men and 36.3% of the women were 35 years or younger at the time of diagnosis. 39 660 matched controls were randomly selected for these cases.

For CD, 10 261 cases were included with a mean age of 41.1 ± 13.7 at the time of diagnosis. Of these 45.3% were men and 54.7% were women. The mean ages of the men and women were 40.9 ± 13.8 years and 41.3 ± 13.6 years, respectively. 40.9% of the men and 39.7% of the women were 35 years or younger at the time of diagnosis. 20 522 matched controls were randomly selected for these cases.

Exposure to silica dust, ulcerative colitis and Crohn's disease

Table 1 shows the number of cases and controls for UC and CD along with the OR of exposure and the corresponding 95% CI. For men, regardless of age and duration of occupation, the odds of developing UC while exposed to silica dust were 33% (OR = 1.33, 95% CI 1.05 – 1.22). The risk of developing UC increases as a function of the duration of occupational exposure across the entire study population as well as in men (Table 1).

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Table 1. Number of cases and controls for ulcerative colitis and Crohn's disease, with odds ratios for exposure and the corresponding 95% confidence intervals. Data for the total study population are presented as well as data stratified into men and women. Both duration of exposure in years and the cumulative exposure were calculated using the job exposure matrix.

	Exposed to quartz during the 5 years before diagnosis in 2007 - 2016							
	Ulcerative colitis				Crohn's disease			
	Cases n[a]	Controls n	OR[b]	95% CI[c]	Cases n	Controls n	OR	95% CI
Total								
Unexposed	18 411	37 116	1		9 672	19 293	1	
Exposed	1 419	2 544	**1.13**	**1.06 - 1.21**	589	1 229	0.95	0.86 - 1.06
Duration of exposure								
0 years	18 411	37 116	1		9 672	19 293	1	
-1 years	318	596	1.08	0.94 - 1.24	122	296	0.82	0.66 - 1.01
1.01 - 5 years	377	717	1.07	0.94 - 1.21	172	363	0.94	0.78 - 1.13
5.01 - 10 years	485	828	**1.19**	**1.06 - 1.33**	199	402	0.99	0.83 - 1.17
More than 10 years	239	403	**1.21**	**1.02 - 1.42**	96	168	1.14	0.89 - 1.48
Cumulative exposure mg/m^3								
0	18 411	37 116	1		9 672	19 293	1	
0.01-0.99	1 283	2 347	**1.11**	**1.03-1.19**	525	1 120	0.93	0.84 - 1.04
Equal to, or more than 1.0	136	197	**1.40**	**1.12-1.74**	64	109	1.17	0.86 - 1.60
Men								
Unexposed	8 459	17 172	1		4 095	8 091	1	
Exposed	1 238	2 220	**1.33**	**1.05 - 1.22**	480	1 059	0.89	0.80 - 1.00
Duration of exposure								
0 years	8 459	17 172	1		4 095	8 091	1	
-1 years	261	505	1.04	0.90 - 1.22	90	245	0.72	0.56 - 0.92
1.01 - 5 years	318	613	1.05	0.92 - 1.21	143	301	0.93	0.76 - 1.15
5.01 - 10 years	441	738	**1.21**	**1.08 - 1.37**	164	358	0.90	0.75 - 1.09
More than 10 years	218	364	**1.22**	**1.03 - 1.46**	73	155	1.06	0.81 - 1.39
Cumulative exposure mg/m^3								
0	8 459	17 172	1		4 095	8 091	1	
0.01-0.99	1 131	2 057	**1.12**	**1.03-1.21**	434	978	0.87	0.78 - 0.99
Equal to, or more than 1.0	107	163	**1.34**	**1.05-1.71**	46	81	1.12	0.78 - 1.62
Women								
Unexposed	9 952	19 944	1		5 577	11 202	1	
Exposed	181	324	1.12	0.93 - 1.34	109	170	**1.29**	**1.01 - 1.65**
Duration of exposure								
0 years	9 952	19 944	1		5 577	11 202	1	
-1 years	57	91	1.25	0.90 - 1.75	32	51	1.25	0.81 - 1.96
1.01 - 5 years	59	104	1.14	0.83 - 1.56	29	62	0.94	0.60 - 1.46
5.01 - 10 years	44	90	0.98	0.68 - 1.41	35	44	**1.62**	**1.03 - 2.54**
More than 10 years	21	39	1.08	0.63 - 1.83	13	13	2.02	0.93 - 4.36
Cumulative exposure mg/m^3								
0	9 952	19 944	1		5 577	11 202	1	
0.01-0.99	152	290	1.05	0.86-1.29	91	142	1.29	0.99 - 1.68
Equal to, or more than 1.0	29	34	**1.71**	**1.04-2.80**	18	28	1.29	0.72 - 2.34

a: number
b: odds ratio
c: confidence interval.

When data on exposure levels from the JEM was added, a cumulative exposure level could be calculated. The cumulative exposure showed a dose-dependent increase in risk for developing UC for both the total study population (among the highest exposed OR was 1.4, 95% CI 1.12 – 1.74), as well as for both men and women (OR of respectively 1.34, 95% CI

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1.05 – 1.71 and 1.71, 95% CI 1.04 – 2.08 among the highest exposed men and women) (Table 1)

The risk of developing CD was significantly increased among women (OR = 1.29, 95% CI 1.01 – 1.65) and particularly in women exposed to silica for >5-10 years (OR = 1.62, 95% CI 1.03 – 2.54). However, this trend was not observed across the patient population as a whole, or in men.

Mortality rates for ulcerative colitis and Crohn's disease

The SMR for men and women with UC or CD are shown in Table 2. Men diagnosed with either UC or CD exhibit an elevated mortality rate. The mortality rate of UC and CD was increased in both exposed and non-exposed individuals, although there was a higher SMR for those who were identified by the JEM as having been exposed to silica dust (SMR for UC = 1.64, 95% CI 1.16 – 2.24; SMR for CD = 1.88, 95% CI 1.08 – 3.06), but those exposed to silica dust had a higher overall SMR (Table 2). For women, an increased SMR was found for both UC and CD. However, the SMR for women exposed to silica dust could not be calculated due to a lack of fatalities in the extracted medical data. For both UC and CD neoplasms (ICD 10 C00 - D48) was the main cause of death, with the highest SMR for cases exposed to silica (SMR for UC = 2.21, 95% CI 1.35 – 3.41; SMR for CD = 2.95, 95% CI 1.41 – 5.42). For cases not exposed to silica the SMR was lower, but still statistically significant (SMR for UC = 1.41, 95% CI 1.20 – 1.63; SMR for CD = 1.45, 95% CI 1.17 – 1.79).

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Table 2 Standard mortality rates (SMR) for individuals diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) compared to the Swedish general population.

Sex	UC	Silica exposure	Observed	Expected	SMR	95% CI[a]
Men	Controls	No	299	343.3	0.87	0.78 - 0.98
		Yes	46	43.0	1.07	0.78 - 1.43
	Cases	No	213	**168.4**	**1.26**	**1.10 - 1.45**
		Yes	39	**23.9**	**1.64**	**1.16 - 2.24**
Women	Controls	No	253	245.5	1.03	0.91 - 1.17
		Yes	2	4.5	0.44	0.05 - 1.60
	Cases	No	154	**122.1**	**1.26**	**1.07 - 1.48**
		Yes	0	2.2	-	-

Sex	CD	Silica exposure	Observed	Expected	SMR	95% CI
Men	Controls	No	180	158.6	1.14	0.98 - 1.31
		Yes	23	19.8	1.16	0.74 - 1.75
	Cases	No	113	80.1	**1.41**	**1.16 - 1.70**
		Yes	16	8.5	**1.88**	**1.08 - 3.06**
Women	Controls	No	136	135.5	1.00	0.84 - 1.19
		Yes	1	2.4	0.42	0.01 - 2.31
	Cases	No	134	66.9	**2.00**	**1.68 - 2.37**
		Yes	0	1.3	-	-

a: confidence interval.

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Discussion and Conclusions

The OR for developing UC was significantly increased among men with an exposure duration of more than 5 years. No significant difference was observed between individuals exposed for >5-10 years and those exposed for over 10 years. The OR also increased with and increased cumulative exposure (Table 1). This suggests that there is a threshold beyond which further exposure no longer affects the risk of developing UC.

The results obtained indicate that silica dust exposure correlates with an increased risk of developing UC among men. Previous reports suggested that silica exposure among men correlates with an increased incidence of another inflammatory disease; sarcoidosis [6 24]. Among women and increased risk for developing UC was seen when data was analyzed according to cumulative exposure.

Both sarcoidosis and UC are less prevalent in smokers [10 25]. It is possible that smoking offers a protective action that interacts with the pathological action of silica dust. The protective effects of smoking are not currently understood but appear to impact men and women differently [26 27]. Helper T cells are thought to play a critical role in the pathology of UC [10] as well as other inflammatory diseases including sarcoidosis, rheumatoid arthritis and systemic lupus erythematosus [28-31]. Silica dust exposure appears to increase the incidence of all these conditions. The immune responses to UC and CD reportedly involve different T cell populations [10 32], which may respond in different ways to silica dust exposure. This may explain the different OR values observed for men and women in this work because there appear to be gender-based differences in immune responses [33-35]. These differences are not well understood but similar effects have been seen for asthma [36 37].

The results from this study show that SMR for UC and CD was increased in both men and women, which is consistent with previous reports [38]. Furthermore, an increased SMR was detected for CD and UC among men exposed to silica dust, possibly due to the potential comorbidities also associated with silica dust exposure.

The large patient population and the validity of the medical data extracted from the registers represent major strengths of this study. The OPR maintains a thorough nationwide database of outpatients, so all individuals resident in Sweden and diagnosed with UC or CD were potentially eligible as cases for this study. Swedish law requires all

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publicly and privately funded physicians to report data to the OPR; the medical data contained in the OPR has been affirmed by practicing physicians and is therefore considered highly valid.

The RTB database from which the controls were selected is also nationwide, making the entire population of Sweden available as potential controls. Consequently, the results presented here are representative of the Swedish population. No medical data originally gathered before 2005 was used in this work. In this study, the time of diagnosis was operationally defined as the first date of entry in the national register from which medical data was extracted for each case. It is possible that some individuals were actually diagnosed prior to the date recorded in the national registry, so we did not consider diagnoses made between 2005 and 2006 to reduce the risk of including previously diagnosed cases. Another limitation of the study was that the individuals excluded from the data set were not further evaluated.

A limitation of this study is that silica dust exposure was defined on the basis of JEM data as being employed in an environment where silica dust is present when duration of exposure was calculated. However, the presence of silica dust at a job site does not by itself mean that all employees would have been exposed to the particles, so this definition may have exaggerated the number of exposed individuals. Any such inflation of exposure rates was likely mitigated by the large sample size. However, if the JEM overestimated the detrimental level of silica exposure in the non-exposed cases, the results obtained would be skewed towards a null hypothesis, reducing their significance. Another limitation of this study is that as this is a register study there are a lack in information on potential confounders. Among these possible confounders are smoking habits and socioeconomic factors, both of which correlate with the incidence of IBD [9 10]. However, since the sample was large and the cases and controls were matched, it is reasonable to assume that the incidence of cofounding factors in the two groups is similar. Nevertheless, it is possible that the results presented here do not reflect an intrinsic capability of silica dust to induce inflammation but a masked confounding factor associated with silica dust exposure.

Habitual smokers have a reduced risk of developing UC [10]. While this is interesting, it is unlikely that including data on patients who smoke increased the possibility of detecting an increased risk of OR. However, a history of smoking is a known strong risk factor for developing UC, so not controlling for smoking cessation may have introduced a bias towards an alpha error.

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In closing, this study suggests a positive correlation between silica dust exposure and the risk of developing UC. The risk increases as a function of the duration of exposure up to a as well with increased cumulative exposure, especially for men. Conversely, silica dust exposure in women increases the risk of developing CD. No comparable findings have been reported previously to the author's knowledge. Both UC and CD also appear to increase mortality, particularly among individuals exposed to silica dust.

Author statement

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and AW, PV, ILB and PG interpreted the results. AW, LF, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

The data used in this study was derived from The Swedish National Patient Register, which is collected, maintained and owned by the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se). Access to data on the incidence of cardiovascular diseases in our cohort was granted based on the ethical committee's approval of undertaking this study. Any researcher, granted that they have an ethical approval from a regional ethical board, can use the data in the Swedish National Patient Register. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information. Data access requests can be directed to the Regional Ethical Board in Uppsala: https://www.epn.se/start/

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Figure legend

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

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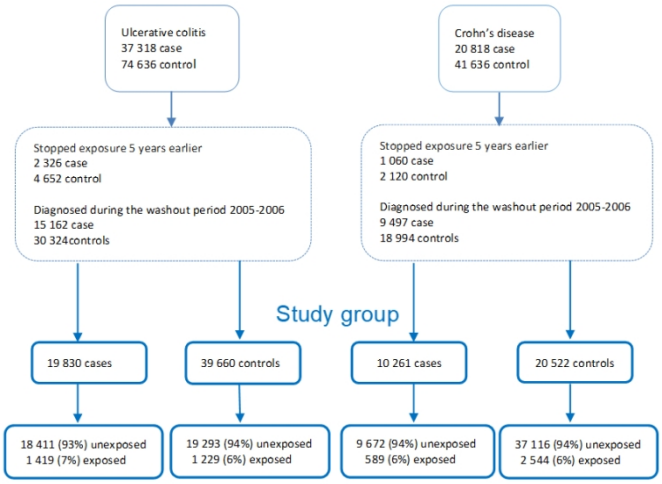

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

338x190mm (96 x 96 DPI)

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6-7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	6-7

Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	6-7
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	6-7
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	#13b	Give reasons for non-participation at each stage	figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they	na

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		were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	table 1 and 2
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	table 1 and 2
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12-13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

Notes:

- 16b: table 1 and 2
- 16c: table 1 and 2 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 03. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure in Sweden – a case-control study

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Risks of developing ulcerative colitis and Crohn's disease in relation to silica dust exposure in Sweden – a case-control study

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Pål Graff (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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The study was approved by the Swedish Ethical Review Authority; DNR 2017/252.

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Abstract

Objective: To determine whether occupational exposure to silica dust causes an increased risk of developing Crohn's disease and ulcerative colitis.

Design: Case-control study of Crohn's disease (K50) and ulcerative colitis (K51) from 2007 through 2016. Controls were matched to cases (2:1) based on age, sex and county at the time of diagnosis. A Job Exposure Matrix was used to estimate the occupational silica exposure of all cases and controls.

Setting: Medical and occupational data from the National Outpatient Register were used to implement a case-control analysis, while the two controls used for each case were selected from the National Register of the Total Population.

Participants: All men and women aged 20-65 years old who were diagnosed with Crohn's disease (K50) and ulcerative colitis (K51) during the years of study were included and assigned two controls, resulting 58136 cases and 116272 controls.

Main Outcomes: Silica dust exposure correlates with an increased risk of developing ulcerative colitis in men and Crohn's disease in women.

Results: The prevalence of ulcerative colitis was significantly higher in the group exposed to silica dust (OR 1.13; 95% CI 1.06-1.21) than in controls, particularly in individuals with over 5 years' exposure. When stratified by sex, a significantly increased odds ratio was detected for men (OR 1.33; 95% CI 1.05-1.22). This trend was also consistent with longer exposure times. The prevalence of ulcerative colitis was not increased in exposed women. The prevalence of Crohn's disease was significantly increased among exposed women (OR 1.29; 95% CI 1.01-1.65), but not for exposed men.

Conclusions: Silica dust exposure correlates with an increased risk of developing ulcerative colitis, especially in men, and the risk seems to increase with the duration and degree of

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exposure. Conversely, silica dust exposure correlates positively with the risk of developing Crohn's disease in women.

Strengths and limitations of this study

- This case-control study includes anyone who was diagnosed with Crohn's disease and ulcerative colitis in Sweden in the years 2007-2016, and not just a selection.
- Sweden maintains high-quality registers that cover the entire population, together with unique personal identification numbers that can link patient data across different nationwide registers.
- The diagnoses were based on data recorded in the national non-primary outpatient visits register, which is significantly more accurate than diagnoses based on questionnaires.
- This study lack information on potential confounders such as smoking habits, however cases and controls are matched based on age, sex and geographical area and therefore one could assume the distribution of these confounders among the cases and controls.

Key words: inflammatory bowel disease, silica dust, case control study, Crohn's disease, ulcerative colitis

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Introduction

Silica is a mineral composed of oxygen and silicon that is highly abundant in the Earth's crust and is a component of most types of rocks. Exposure to silica dust is therefore common during, for example, mining operations. Silica's high melting point, hardness, and chemical inertness make it ideal for several industrial applications. During the latter half of the 20th century, extensive efforts were made to reduce the amount of silica dust in Swedish workplaces [1]. Nevertheless, there is still significant occupational silica exposure in Sweden and abroad [2 3].

Exposure to silica dust is known to cause silicosis which is predominantly a pulmonary disease [4]. However, recent studies suggest a correlation between silica and several inflammatory diseases [5 6]. The pathological mechanisms underpinning these relationships are poorly understood [7 8]. No relationship between silicosis and the inflammatory bowel diseases Crohn's disease (CD) or ulcerative colitis (UC) has previously been reported.

The term inflammatory bowel disease (IBD) encompasses many diseases of the gastrointestinal tract. However, in this paper IBD refers only to CD or UC. CD and UC share several pathological features: they are both chronic and have symptoms including diarrhea, hematochezia, abdominal pain, fever, weight loss, and lesion formation. However, the distribution of lesions differs between the two diseases. CD may affect the entire gastrointestinal tract but the distribution of lesions is often discontinuous. Conversely, the UC lesions start in the rectum and are continuous. While these two IBDs share several risk factors, smoking has opposing effects on the risks of their development: it increases the risk of developing CD but reduces that of UC [9 10].

The etiology of IBD has been studied extensively but remains somewhat unclear. There is strong evidence of a familial component to its development [9-12], and a significant effect of environmental factors [12]. This is further supported by the observation that the global prevalence of IBD has risen as increasing numbers of countries outside of Europe and North America have adopted western lifestyles [13].

The identity of the environmental factors that may influence IBD pathogenesis is a subject of ongoing debate [11 14]. The intake of various airborne particles has been posited to contribute to IBD development despite a lack of direct evidence [15 16]. Two early studies suggested silica dust particles may contribute to the etiology of IBD because a fraction of

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the inhaled dust is swallowed with the mucus [17]. One of these studies have reported that silica dust was detected in the intestinal epithelium and distributed systemically after mice were fed a diet enriched with silica dust [18]. The other study showed that injecting silica dust directly into the intestinal lymphatic system of dogs causes the formation of enteric lesions similar to those associated with IBD [19].

IBD has a significant impact on patients' quality of life and an economic impact on society because it increases hospitalization and mortality rates [20]. Furthermore, the prevalence of IBD in Sweden is increasing more rapidly than previously expected [21], making it important to identify agents that cause or exacerbate this disease.

Aim

To determine whether silica dust exposure increases the risk of developing Crohn's disease (CD) or ulcerative colitis (UC).

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Material and Methods

Registers, administrative authorities, and job exposure matrix (JEM)

The Swedish administrative authority known as the National Board of Health and Welfare (NBHW) maintains and validates the "National Non-Primary Outpatient Care Register" (OPR). This register is part of the National Patient Register and has been maintained since 2001. It contains medical data from registered outpatients of Swedish healthcare facilities. The NBHW also maintains the Swedish Cause of Death Register.

Another administrative authority, the Swedish Central Bureau of Statistics (SCB), maintains the Longitudinal Integration Database for Health Insurance and Labor Market Studies (LISA) as well as the National Register of the Total Population (RTB) and the Multi-Generation Register (MGR). LISA holds records going back to 1990 including occupational and domicile information on all individuals resident in Sweden aged 16 years or above, registered as of 31 December in the relevant reference year. The RTB is an extract from the civil register of the Swedish Tax Agency and contains residential data. MGR contains information on individuals' biological relatives.

All data preparation and register matching for this paper was done by the SCB and NBHW with guidance from a statistician working for the Department of Occupational and Environmental Medicine. The processed data were de-identified such that the only personally identifying information remaining in the processed dataset were dates of birth and years of employment. Other information relating to the identities of individuals represented in the data was replaced with a serial number. All statistical analyses were performed using these de-identified data. A job exposure matrix (JEM) was used to estimate rates of occupational exposure to silica based on individuals' job assignments [22 23].

Study design

Data from the registers were used to conduct a case-control analysis. The cases were selected from the OPR by the NBHW. The inclusion criterion for the cases was a single diagnosis of one of the following conditions (ICD-10-CM codes are given in parentheses): CD (K50) and UC (K51). The study participants were required to be between 20-65 years old at the time of diagnosis and to have been diagnosed between 2005 and 2016.

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Matching controls for the case-control study were randomly selected by the SCB using data from RTB and MGR. The inclusion criteria for the controls included having no previous diagnosis of any condition used to select the positive cases as well as not having sarcoidosis (D86), ankylosing spondylitis (M45), seropositive rheumatoid arthritis (M05), or other rheumatoid arthritis (M06) and not being a first degree relative of the corresponding case. Controls were also required to share the gender, age, and county of residence at the time of diagnosis of the matched case (Figure 1).

Occupational data for all case and control individuals were obtained from LISA. The JEM was then used to determine whether the occupational history of each case and control would have resulted in silica dust exposure as well as to assess the cumulative exposure. Cases not exposed to silica any time the last 5 years before diagnosis were excluded (Figure 1). Jobs among the cases and controls that according to the JEM were classified as containing exposure to silica included concrete workers, casters, masons, ceramic and glass manufacturers, miners etc.

The cases were selected from the years 2005-2016, with a wash-out period from 2005-2006 in order to include recent diagnoses and avoid including data from follow up medical examinations.

Statistical analysis

The odds of being exposed to silica dust before the time of diagnosis were calculated for cases and controls and expressed as odds ratios (OR). Being exposed to silica dust was defined based on JEM data as being employed in an environment where silica dust was present. A conditional logistic regression was used to find the 95% confidence interval (95% CI) for the OR. The OR was considered to be significantly greater than 1.00 if the lower limit of the 95% CI was above 1.00.

The study population was stratified according to duration of exposure and sex. The stratification for duration of exposure was divided into the following time frames: 1-5 years, 5-10 years and more than 10 years. Based on the JEM a cumulative exposure to silica was also calculated with regards to both prevalence and level of exposure for the different jobs. The cumulative exposure was stratified into 0.01-0.99 mg/m^3 and more than 1 mg/m^3.

Standardized mortality ratios (SMRs) were used to compare UC and CD cases and controls to the general Swedish population. The data were stratified according to gender.

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Ethical considerations

The study protocol was approved by the Regional Ethical Review Board in Uppsala, Sweden (Dnr 2017/252).

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Results

Study population

58 136 cases and 116 272 controls where included in this study. Figure 1 shows a flowchart of the study population. For UC, 19 830 cases were included in this study with a mean age of 42.9 ± 12.9 years at the time of diagnosis. Of these 48.9% were men and 51.13% were women. The mean ages of the men and women were 41.4 ± 13.6 years and 42.0 ± 13.1 years, respectively. 40.0% of the men and 36.3% of the women were 35 years or younger at the time of diagnosis. 39 660 matched controls were randomly selected for these cases.

For CD, 10 261 cases were included with a mean age of 41.1 ± 13.7 at the time of diagnosis. Of these 45.3% were men and 54.7% were women. The mean ages of the men and women were 40.9 ± 13.8 years and 41.3 ± 13.6 years, respectively. 40.9% of the men and 39.7% of the women were 35 years or younger at the time of diagnosis. 20 522 matched controls were randomly selected for these cases.

Exposure to silica dust, ulcerative colitis and Crohn's disease

Table 1 shows the number of cases and controls for UC and CD along with the OR of exposure and the corresponding 95% CI. For men, regardless of age and duration of occupation, the odds of developing UC while exposed to silica dust were 33% (OR = 1.33, 95% CI 1.05 – 1.22). The risk of developing UC increases as a function of the duration of occupational exposure across the entire study population as well as in men (Table 1).

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Table 1. Number of cases and controls for ulcerative colitis and Crohn's disease, with odds ratios for exposure and the corresponding 95% confidence intervals. Data for the total study population are presented as well as data stratified into men and women. Both duration of exposure in years and the cumulative exposure were calculated using the job exposure matrix.

	Exposed to quartz during the 5 years before diagnosis in 2007 - 2016							
	Ulcerative colitis				Crohn's disease			
	Cases n[a]	Controls n	OR[b]	95% CI[c]	Cases n	Controls n	OR	95% CI
Total								
Unexposed	18 411	37 116	1		9 672	19 293	1	
Exposed	1 419	2 544	**1.13**	**1.06 - 1.21**	589	1 229	0.95	0.86 - 1.06
Duration of exposure								
0 years	18 411	37 116	1		9 672	19 293	1	
-1 years	318	596	1.08	0.94 - 1.24	122	296	0.82	0.66 - 1.01
1.01 - 5 years	377	717	1.07	0.94 - 1.21	172	363	0.94	0.78 - 1.13
5.01 - 10 years	485	828	**1.19**	**1.06 - 1.33**	199	402	0.99	0.83 - 1.17
More than 10 years	239	403	**1.21**	**1.02 - 1.42**	96	168	1.14	0.89 - 1.48
Cumulative exposure mg/m^3								
0	18 411	37 116	1		9 672	19 293	1	
0.01-0.99	1 283	2 347	**1.11**	**1.03-1.19**	525	1 120	0.93	0.84 - 1.04
Equal to, or more than 1.0	136	197	**1.40**	**1.12-1.74**	64	109	1.17	0.86 - 1.60
Men								
Unexposed	8 459	17 172	1		4 095	8 091	1	
Exposed	1 238	2 220	**1.33**	**1.05 - 1.22**	480	1 059	0.89	0.80 - 1.00
Duration of exposure								
0 years	8 459	17 172	1		4 095	8 091	1	
-1 years	261	505	1.04	0.90 - 1.22	90	245	0.72	0.56 - 0.92
1.01 - 5 years	318	613	1.05	0.92 - 1.21	143	301	0.93	0.76 - 1.15
5.01 - 10 years	441	738	**1.21**	**1.08 - 1.37**	164	358	0.90	0.75 - 1.09
More than 10 years	218	364	**1.22**	**1.03 - 1.46**	73	155	1.06	0.81 - 1.39
Cumulative exposure mg/m^3								
0	8 459	17 172	1		4 095	8 091	1	
0.01-0.99	1 131	2 057	**1.12**	**1.03-1.21**	434	978	0.87	0.78 - 0.99
Equal to, or more than 1.0	107	163	**1.34**	**1.05-1.71**	46	81	1.12	0.78 - 1.62
Women								
Unexposed	9 952	19 944	1		5 577	11 202	1	
Exposed	181	324	1.12	0.93 - 1.34	109	170	**1.29**	**1.01 - 1.65**
Duration of exposure								
0 years	9 952	19 944	1		5 577	11 202	1	
-1 years	57	91	1.25	0.90 - 1.75	32	51	1.25	0.81 - 1.96
1.01 - 5 years	59	104	1.14	0.83 - 1.56	29	62	0.94	0.60 - 1.46
5.01 - 10 years	44	90	0.98	0.68 - 1.41	35	44	**1.62**	**1.03 - 2.54**
More than 10 years	21	39	1.08	0.63 - 1.83	13	13	2.02	0.93 - 4.36
Cumulative exposure mg/m^3								
0	9 952	19 944	1		5 577	11 202	1	
0.01-0.99	152	290	1.05	0.86-1.29	91	142	1.29	0.99 - 1.68
Equal to, or more than 1.0	29	34	**1.71**	**1.04-2.80**	18	28	1.29	0.72 - 2.34

a: number
b: odds ratio
c: confidence interval.

When data on exposure levels from the JEM was added, a cumulative exposure level could be calculated. The cumulative exposure showed a dose-dependent increase in risk for developing UC for both the total study population (among the highest exposed OR was 1.4, 95% CI 1.12 – 1.74), as well as for both men and women (OR of respectively 1.34, 95% CI

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1.05 – 1.71 and 1.71, 95% CI 1.04 – 2.08 among the highest exposed men and women) (Table 1)

The risk of developing CD was significantly increased among women (OR = 1.29, 95% CI 1.01 – 1.65) and particularly in women exposed to silica for >5-10 years (OR = 1.62, 95% CI 1.03 – 2.54). However, this trend was not observed across the patient population as a whole, or in men.

Mortality rates for ulcerative colitis and Crohn's disease

The SMR for men and women with UC or CD are shown in Table 2. Men diagnosed with either UC or CD exhibit an elevated mortality rate. The mortality rate of UC and CD was increased in both exposed and non-exposed individuals, although there seems to be a higher SMR for those who were identified by the JEM as having been exposed to silica dust (SMR for UC = 1.64, 95% CI 1.16 – 2.24; SMR for CD = 1.88, 95% CI 1.08 – 3.06) (Table 2). For women, an increased SMR was found for both UC and CD. However, the SMR for women exposed to silica dust could not be calculated due to a lack of fatalities in the extracted medical data. For both UC and CD neoplasms (ICD 10 C00 - D48) was the main cause of death, with the highest SMR for cases exposed to silica (SMR for UC = 2.21, 95% CI 1.35 – 3.41; SMR for CD = 2.95, 95% CI 1.41 – 5.42). For cases not exposed to silica the SMR was lower, but still statistically significant (SMR for UC = 1.41, 95% CI 1.20 – 1.63; SMR for CD = 1.45, 95% CI 1.17 – 1.79).

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Table 2 Standard mortality rates (SMR) for individuals diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) compared to the Swedish general population.

Sex	UC	Silica exposure	Observed	Expected	SMR	95% CI[a]
Men	Controls	No	299	343.3	0.87	0.78 - 0.98
		Yes	46	43.0	1.07	0.78 - 1.43
	Cases	No	213	**168.4**	**1.26**	**1.10 - 1.45**
		Yes	39	**23.9**	**1.64**	**1.16 - 2.24**
Women	Controls	No	253	245.5	1.03	0.91 - 1.17
		Yes	2	4.5	0.44	0.05 - 1.60
	Cases	No	154	**122.1**	**1.26**	**1.07 - 1.48**
		Yes	0	2.2	-	-

Sex	CD	Silica exposure	Observed	Expected	SMR	95% CI
Men	Controls	No	180	158.6	1.14	0.98 - 1.31
		Yes	23	19.8	1.16	0.74 - 1.75
	Cases	No	113	80.1	**1.41**	**1.16 - 1.70**
		Yes	16	8.5	**1.88**	**1.08 - 3.06**
Women	Controls	No	136	135.5	1.00	0.84 - 1.19
		Yes	1	2.4	0.42	0.01 - 2.31
	Cases	No	134	66.9	**2.00**	**1.68 - 2.37**
		Yes	0	1.3	-	-

a: confidence interval.

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Discussion and Conclusions

The OR for developing UC was significantly increased among men with an exposure duration of more than 5 years. No significant difference was observed between individuals exposed for >5-10 years and those exposed for over 10 years. The OR also increased with and increased cumulative exposure (Table 1). This suggests that there is a threshold beyond which further exposure no longer affects the risk of developing UC.

The results obtained indicate that silica dust exposure correlates with an increased risk of developing UC among men. Previous reports suggested that silica exposure among men correlates with an increased incidence of another inflammatory disease; sarcoidosis [6 24]. Among women and increased risk for developing UC was seen when data was analyzed according to cumulative exposure.

Both sarcoidosis and UC are less prevalent in smokers [10 25]. It is possible that smoking offers a protective action that interacts with the pathological action of silica dust. The protective effects of smoking are not currently understood but appear to impact men and women differently [26 27]. Helper T cells are thought to play a critical role in the pathology of UC [10] as well as other inflammatory diseases including sarcoidosis, rheumatoid arthritis and systemic lupus erythematosus [28-31]. Silica dust exposure appears to increase the incidence of all these conditions. The immune responses to UC and CD reportedly involve different T cell populations [10 32], which may respond in different ways to silica dust exposure. This may explain the different OR values observed for men and women in this work because there appear to be gender-based differences in immune responses [33-35]. These differences are not well understood but similar effects have been seen for asthma [36 37].

The results from this study show that SMR for UC and CD was increased in both men and women, which is consistent with previous reports [38]. Furthermore, for men exposure to silica dust seems to increase the SMR for CD and UC compared to unexposed, however not statistically significant.

The large patient population and the validity of the medical data extracted from the registers represent major strengths of this study. The OPR maintains a thorough nationwide database of outpatients, so all individuals resident in Sweden and diagnosed with UC or CD were potentially eligible as cases for this study. Swedish law requires all

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publicly and privately funded physicians to report data to the OPR; the medical data contained in the OPR has been affirmed by practicing physicians and is therefore considered highly valid.

The RTB database from which the controls were selected is also nationwide, making the entire population of Sweden available as potential controls. Consequently, the results presented here are representative of the Swedish population. No medical data originally gathered before 2005 was used in this work. In this study, the time of diagnosis was operationally defined as the first date of entry in the national register from which medical data was extracted for each case. It is possible that some individuals were actually diagnosed prior to the date recorded in the national registry, so we did not consider diagnoses made between 2005 and 2006 to reduce the risk of including previously diagnosed cases. Another limitation of the study was that the individuals excluded from the data set were not further evaluated.

A limitation of this study is that silica dust exposure was defined on the basis of JEM data as being employed in an environment where silica dust is present when duration of exposure was calculated. However, the presence of silica dust at a job site does not by itself mean that all employees would have been exposed to the particles, so this definition may have exaggerated the number of exposed individuals. Any such inflation of exposure rates was likely mitigated by the large sample size. However, if the JEM overestimated the detrimental level of silica exposure in the non-exposed cases, the results obtained would be skewed towards a null hypothesis, reducing their significance. Another limitation of this study is that as this is a register study there are a lack in information on potential confounders. Among these possible confounders are smoking habits and socioeconomic factors, both of which correlate with the incidence of IBD [9 10]. However, since the sample was large and the cases and controls were matched, it is reasonable to assume that the incidence of cofounding factors in the two groups is similar. Nevertheless, it is possible that the results presented here do not reflect an intrinsic capability of silica dust to induce inflammation but a masked confounding factor associated with silica dust exposure.

Habitual smokers have a reduced risk of developing UC [10]. While this is interesting, it is unlikely that including data on patients who smoke increased the possibility of detecting an increased risk of OR. However, a history of smoking is a known strong risk factor for developing CD, so not controlling for smoking cessation may have introduced a bias towards an alpha error.

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In closing, this study suggests a positive correlation between silica dust exposure and the risk of developing UC. The risk increases as a function of the duration of exposure up to a as well with increased cumulative exposure, especially for men. Conversely, silica dust exposure in women increases the risk of developing CD. No comparable findings have been reported previously to the author's knowledge. Both UC and CD also appear to increase mortality, and exposure to silica dust seems to be an aggravating factor.

Author statement

PV, ILB and PG conceived and designed the study. PW constructed the adopted JEM. ILB did the main data analysis and AW, PV, ILB and PG interpreted the results. AW, LF, PV, ILB and PG participated in the writing of the manuscript. All authors approved the final version.

Competing interests

The authors have no competing interests in connection with this paper

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Patient and Public Involvement

This research was done without patient involvement.

Data sharing statement

The data used in this study was derived from The Swedish National Patient Register, which is collected, maintained and owned by the Swedish National Board of Health and Welfare (http://www.socialstyrelsen.se). Access to data on the incidence of cardiovascular diseases in our cohort was granted based on the ethical committee's approval of undertaking this study. Any researcher, granted that they have an ethical approval from a regional ethical board, can use the data in the Swedish National Patient Register. However, the Swedish National Board of Health and Welfare will also put restrictions on sharing sensitive information. Data access requests can be directed to the Regional Ethical Board in Uppsala: https://www.epn.se/start/

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Figure legend

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

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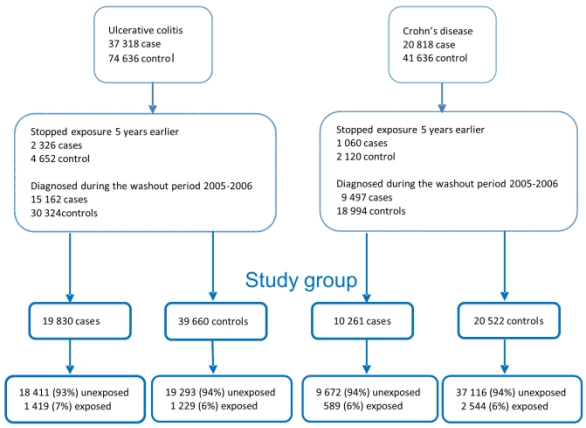

Figure 1: Flowchart showing the total number of individuals with ulcerative colitis and Crohn's disease, along with the numbers of individuals exposed to silica dust as well as unexposed.

254x190mm (300 x 300 DPI)

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Reporting checklist for case-control study.

Based on the STROBE case-control guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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In your methods section, say that you used the STROBE case-controlreporting guidelines, and cite them as:

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		Reporting Item	Page Number
Title and abstract			
Title	#1a	Indicate the study's design with a commonly used term in the title or the abstract	2
Abstract	#1b	Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background / rationale	#2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	#3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	#4	Present key elements of study design early in the paper	6-7
Setting	#5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Eligibility criteria	#6a	Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. For matched studies, give matching criteria and the number of controls per case	6-7

Eligibility criteria	#6b	For matched studies, give matching criteria and the number of controls per case	6-7
	#7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources / measurement	#8	For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for cases and controls.	6-7
Bias	#9	Describe any efforts to address potential sources of bias	6-7
Study size	#10	Explain how the study size was arrived at	6-7
Quantitative variables	#11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	7
Statistical methods	#12a	Describe all statistical methods, including those used to control for confounding	7
Statistical methods	#12b	Describe any methods used to examine subgroups and interactions	7
Statistical methods	#12c	Explain how missing data were addressed	6-7
Statistical methods	#12d	If applicable, explain how matching of cases and controls was addressed	6-7
Statistical methods	#12e	Describe any sensitivity analyses	na
Results			
Participants	#13a	Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for cases and controls.	8
Participants	#13b	Give reasons for non-participation at each stage	figure 1
Participants	#13c	Consider use of a flow diagram	figure 1
Descriptive data	#14a	Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. Give information separately for cases and controls	8
Descriptive data	#14b	Indicate number of participants with missing data for each variable of interest	8
Outcome data	#15	Report numbers in each exposure category, or summary measures of exposure. Give information separately for cases and controls	8
Main results	#16a	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they	na

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		were included	
Main results	#16b	Report category boundaries when continuous variables were categorized	table 1 and 2
Main results	#16c	If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	table 1 and 2
Other analyses	#17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	#18	Summarise key results with reference to study objectives	11
Limitations	#19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias.	12-13
Interpretation	#20	Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	12-13
Generalisability	#21	Discuss the generalisability (external validity) of the study results	13
Other Information			
Funding	#22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

Notes:

- 16b: table 1 and 2
- 16c: table 1 and 2 The STROBE checklist is distributed under the terms of the Creative Commons Attribution License CC-BY. This checklist was completed on 03. October 2019 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

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