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ORIGINAL ARTICLE

The risk for ophthalmological conditions in ulcerative colitis: A population-based case–control study. Is silica dust-exposure associated with inflammatory eye disease?

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Abstract

Purpose: To study the risk for eye diseases in individuals with Ulcerative Colitis (UC), and to assess whether silica dust-exposure could contribute to the development of inflammatory eye diseases.

Methods: A case–control study was conducted using a patient register processed by the National Board of Health and Welfare (NBHW) and *Statistics Sweden*. Cases were diagnosed with UC between 2007 and 2016. Matching was done with two random controls having the same age, sex and county of residence, without a systemic inflammatory disease. Using a job-exposure matrix, cases and controls were assessed for work-related silica dust exposure. The risk for eye disease was estimated by Cox regression analysis with calculation of Hazard Ratio (HR).

Results: A total of 58 989 individuals were included, comprising 19 663 cases and 39 326 controls. The sex distribution was similar. Overall, individuals with UC had an increased risk for eye disease, specified in ICD 10 chapter VII (H00-H59) with HR 1.25 (CI 1.20–1.32). The highest HR on block-level for cases was 1.52 (CI 1.36–1.70), (H15-H22), which includes episcleritis, keratitis and anterior uveitis. The risk for ocular disease was higher in silica dust-exposed than non-exposed with a HR of 1.44 (CI 1.16–1.78) and 1.25 (CI 1.19–1.31), respectively. Among cases, the risk for iridocyclitis (H20) was further elevated by silica dust exposure, with HR of 3.84 (CI 1.64–8.97) in exposed compared to 1.94 (1.57–2.41) in non-exposed.

Conclusion: UC is associated with an increased risk for eye diseases, including inflammatory conditions. Our findings highlight that silica dust-exposure may be of importance in the pathogenesis of uveitis.

KEYWORDS
extraintestinal manifestation, eye disease, inflammatory bowel disease, silica, ulcerative colitis

1 | INTRODUCTION

Ulcerative colitis (UC) is a chronic condition of the colon, part of the disease entity termed inflammatory bowel disease (IBD). It is characterized by an inflammation of the superficial continuous mucosa with ulcerations, which typically engages the rectum and, to a varying degree, spreads proximally to the rest of the colon. Typically, the mucosa and submucosa are affected by inflammation; however, in fulminant colitis deeper parts of the colon can be engaged (Gajendran et al., 2019). UC is classified according to the extent of involvement of the colon and is divided into ulcerative proctitis, left-sided colitis and extensive colitis, signifying an engagement of the entire colon (Dignass et al., 2012).

The annual age-standardized incidence rate of UC in Sweden was 17.9 per 100 000 person years between the years 2002 and 2014 with a lifetime cumulative

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incidence of 1.44% for males and 1.35% for females (Forss et al., 2022). The onset of symptoms usually occurs between the ages of 20 and 30 years, but UC can develop at any age. Previous data from Sweden have shown a slightly higher age at diagnosis for females (Forss et al., 2022). The typical symptoms of UC include loose stools mixed with blood and mucus. The pathogenesis of UC is multifactorial, and risk for development is associated with genetic, psychosocial and environmental factors. Intestinal barrier damage, imbalance of the colonic bacterial flora, upregulation of expression of toll-like receptors (TLR) in dendritic cells and an exaggerated T-cell response are factors that promote inflammation (Ordás et al., 2012).

In UC, there is an increased risk for several ophthalmological diseases or ocular extraintestinal manifestations (EIM), including inflammatory conditions such as episcleritis, scleritis and uveitis, including iritis (Christodoulou et al., 2002; Danese et al., 2005; Lanna et al., 2008; Patil & Cross, 2013; Thomas & Lin, 2016; Troncoso et al., 2017). The specific underlying factors contributing to the development of these are unknown; however, genetic predisposition as well as intestinal microbial factors are considered to be important (Andoh et al., 2011; Cho & Brant, 2011; Das, 1999; Thomas & Lin, 2016; Troncoso et al., 2017; Ungaro et al., 2017).

Exposure to silica dust is known to be of importance in the development of several lung diseases, such as chronic obstructive pulmonary disease (COPD), lung cancer, silicosis and lung infections (Leung et al., 2012). Furthermore, it is of importance in several inflammatory diseases including sarcoidosis, rheumatoid arthritis and IBD (Khuder et al., 2002; Leung et al., 2012; Vihlborg et al., 2017; Wallden et al., 2020). Silicosis is associated with chronic inflammation but there is no established association between silica dust exposure and inflammatory ophthalmological conditions. Although several systemic conditions mentioned are associated with an increased risk for uveitis, to our knowledge, there are no publications describing a direct link between silica dust and uveitis. However, some data have indicated that coal miners, who are exposed to silica dust, may have inflammatory alterations to the retina and choroid that can be visualized using optical coherence tomography (OCT) imaging (Ayar et al., 2017; Yang et al., 2022).

The purpose of this study was, through a case–control approach, to compare the risk for ophthalmic diseases in individuals with and without UC. In addition to this, we intended to investigate if a link between occupational silica dust exposure could be of importance in the development of, in particular, ophthalmological diagnoses associated with inflammation.

2 | METHODS

This was a case–control study, which adhered to the tenets of the Declaration of Helsinki and was approved by the regional ethical board, Uppsala (ref. 217/252). A register was used with data processed by the National Board of Health and Welfare (NBHW) and *Statistics Sweden*. From the NBHW, the Total Population Register and the Multi-Generation Register (MGR) were utilized. Data originating from *Statistics Sweden* were collected from the National Non-Primary Outpatient Care Register and the National Cause of Death Register. Individuals with the International Classification of Diseases, Tenth Revision (ICD-10) diagnosis UC were identified and the time point of diagnosis was determined. The time period between 2005 and 2016 was investigated with a wash-out period of 2 years (between 2005 and 2006) reducing the number of control visits included in the study, to ensure that only newly diagnosed individuals were registered as cases with UC.

Cases included were individuals between the ages of 20 and 65 years who were diagnosed with UC (ICD-10K51) between 1 January 2007 and 31 December 2016. Each case was matched with two randomly selected controls having the same year of birth, sex and county of residence at the time of diagnosis. With the exception of the diagnosis UC, which was one of the defining criteria for case selection, cases as well as controls were selected without any of the following ICD-10 codes: UC (K51), Crohn's disease (K50), Ankylosing spondylitis or Bechterew's disease (M45), Sarcoidosis (D86), Seropositive Rheumatoid Arthritis (M05) and other types of Rheumatoid Arthritis (M06). Using the MGR, the two controls were selected so that they could not be first degree relatives to the corresponding case, defined as sibling, half-sibling, biological parent or biological child. Diagnosis of ophthalmological conditions were defined as any disease categorized in chapter VII (Diseases of the eye and adnexa), ICD-10 (H00-H59). Comparisons between cases and controls were done on a block level according to categories specified in ICD-10. The start of the follow-up time for cases was defined as the year of the UC diagnosis, while the respective follow-up time for the controls was the same year as this diagnosis for the corresponding cases. Given the matching of cases and controls, exclusion of one individual resulted in the automatic loss of two study subjects. As a result, the causes for exclusion between cases and controls could not be separated (Figure 1).

Using data from a previously described job-exposure matrix (JEM) (Graff et al., 2020), cases and controls were individually assessed concerning work-related silica dust exposure. Occupations where a minimum of 5% of the workers were exposed to a yearly mean level of 0.02 mg/m^3 respirable silica dust or more, were considered to be exposed, based on methods used from previous research implementing JEM (Kauppinen et al., 2014). This level of exposure is 80% of the Occupational Exposure Limit (OEL) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) (Hoy et al., 2022). The remaining occupations were defined as non-exposed to respirable silica dust Comparisons were subsequently conducted on ICD diagnosis block-level between exposed and non-exposed individuals. Five specific diagnoses were selected for additional comparisons between cases and controls, based on their inflammatory pathogenesis. These were: (a) h15 = inflammation of the sclera (including episcleritis), (b) h16 = keratitis, (c) h20 = inflammation of iris and the ciliary body, (d) h30 = inflammation

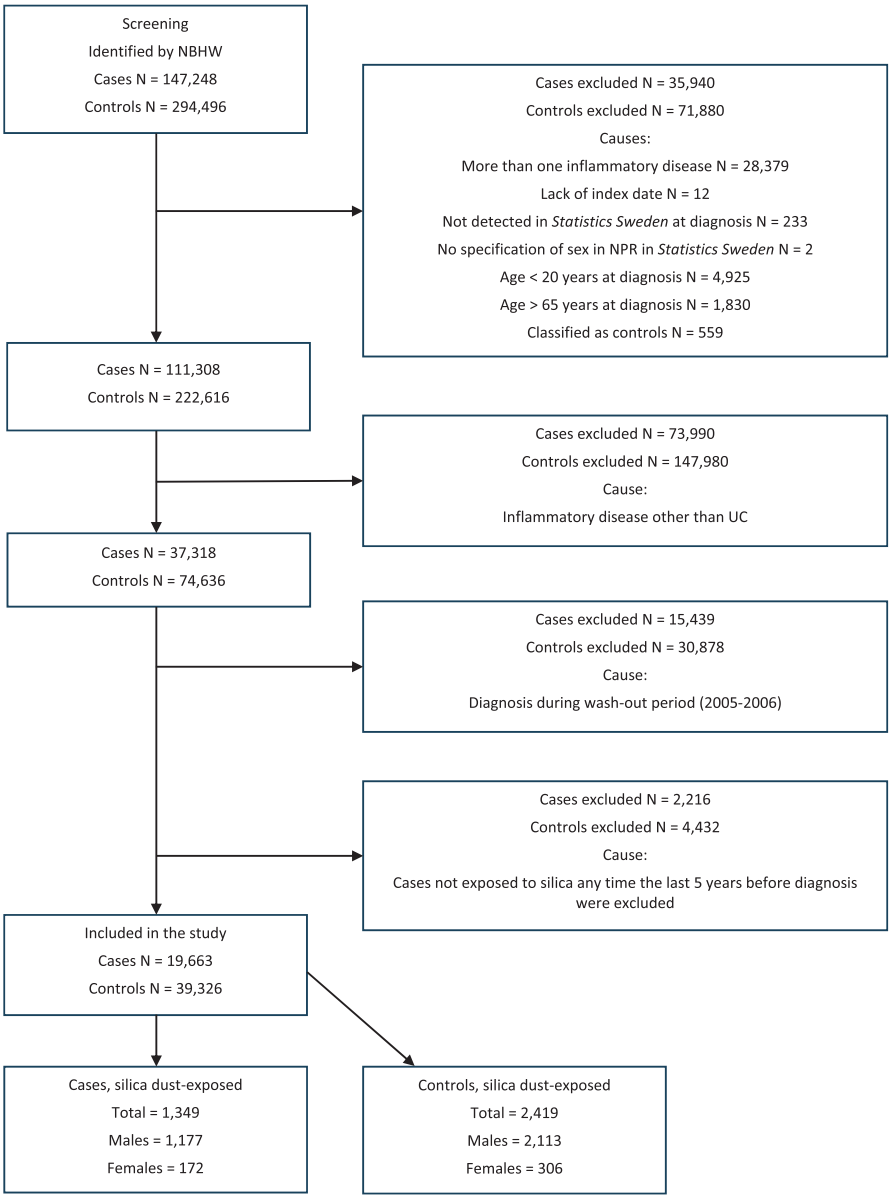

FIGURE 1 Study flow chart depicting inclusion and exclusion of cases and controls, including silica dust-exposure. Inflammatory disease defined according to study inclusion criteria: Ulcerous Colitis (UC) (K51), Crohn's disease (K50), Ankylosing spondylitis or Bechterew's disease (M45), Sarcoidosis (D86), Seropositive Rheumatoid Arthritis (M05) and other types of Rheumatoid Arthritis (M06).

of the choroid and retina, and (e) h35 = other diseases of the retina (including age-related macular degeneration).

2.1 | Statistics

Statistical analysis was done using STATA version 14.1 software (StataCorp, Texas, USA) and IBM SPSS® (IBM SPSS Statistics for Windows, Version 29.0, Armonk, NY, IBM Corp, 2022). Comparisons between cases and control were conducted using Cox regression analysis, with presentation of results as Hazard Ratio (HR) and 95% confidence intervals (CI). For differences in the age of death, independent samples *t*-test were used. A statistically significant difference was defined as a HR value with the lower level of CI above 1. Each individual in the study population contributed with person-years, counted from the diagnosis of UC until the development of an ophthalmological disease, emigration, death or end of study period. The Total Population Register and the National Cause of Death Register were used to calculate person-years in the study.

3 | RESULTS

A total of 58 989 individuals were included, comprising 19 663 cases and 39 326 controls. Figure 1 is a flowchart describing the inclusion of study subjects. The sex distribution was relatively equal with 48.6% males and 51.4% females. The mean age at diagnosis for the total population was 42 years (SD 13.32) and similar for both sexes, being slightly lower for males at 41 years (SD 13.58) than females at 42 years (SD 13.06). Information on the study population can be found in Table 1.

Patients with UC had a higher incidence of diseases in the eye and adnexa compared to controls, specified in ICD-10 chapter VII (H00-H59) (Table 2), with a significant difference in 9 out of 11 blocks of diagnoses.

TABLE 1 Characteristics of study population regarding sex distribution, silica dust exposure, age at inclusion (diagnosis of UC), number of deceased individuals and age of death.

	Cases	Controls
Total	19 663	39 326
Men (*n*) [%]	9557 [48.6]	19 112 [48.6]
Women (*n*) [%]	10 106 [51.4]	20 214 [51.4]
Silica dust-exposed, total (*n*) [%]	1349 [6.9]	2419[6.2]
Silica dust-exposed, males (*n*) [%]	1177 [12.3]	2113 [11.1]
Silica dust-exposed, females (*n*) [%]	172 [1.7]	306 [1.5]
Age, inclusion, total (mean ± SD)	42 ± 13.32	42 ± 13.32
Age, men (mean ± SD)	41 ± 13.58	41 ± 13.58
Age, women (mean ± SD)	42 ± 13.06	42 ± 13.06
Deceased, total (*n*) [%]	402 [2.0]	593 [1.5]
Deceased, men (*n*) [%]	248 [2.6]	338 [1.8]
Deceased, women (*n*) [%]	154 [1.5]	255 [1.3]
Age of death, total (mean ± SD)	57 ± 11.33	58 ± 10.88
Age of death, men (mean ± SD)	56 ± 12.22	58 ± 11.64
Age of death, women (mean ± SD)	59 ± 9.60	58 ± 9.80

Note: Units are specified within brackets.
Abbreviation: SD, standard deviation.

In total, 2525 cases (12.8%) had at least one diagnosis during the study period compared to 3979 (10.1%) among controls, which constituted a statistically significant difference with HR 1.25 (CI 1.20–1.32). The mean time, from diagnosis of UC for cases and inclusion for controls, to a diagnosis in the eye and adnexa was for cases 2.8 years and for controls 2.9 years.

The highest HR of 1.52 for cases with UC (CI 1.36–1.70) (Table 2) was found in block 3 (H15-H22), including diagnoses with disorders of sclera cornea, iris and ciliary body, which comprises inflammation of the anterior segment, such as episcleritis and anterior uveitis. In this block, the diagnoses most frequently found were iritis, keratitis and corneal ulcers, and episcleritis. Statistically significantly differences between the cases and controls were also detected in block 2, disorders of conjunctiva (HR 1.47, CI 1.28–1.70), block 1, eyelid, lacrimal system and orbit (HR 1.37 CI 1.22–1.52), block 10, visual disturbances and blindness (HR1.32 CI 1.11–1.57), and block 9, comprising diagnoses of ocular muscles, binocular movement, accommodation and refraction (HR 1.30 CI 1.13–1.51). Within block 1 (disorders of lacrimal system), dry eye syndrome was the most common diagnosis followed by conjunctivitis, and blepharitis. The most frequently diagnosed conditions in block 10 were unspecified visual disturbances and visual field defects, whereas in block 9 unspecified disorders of refraction and myopia were most common.

There were minor differences between the sexes. The increased HR in patients with UC regarding blocks 6 (glaucoma) and 10 (visual disturbances and blindness) showed statistically significant differences between cases and controls for the total population but these differences could only be confirmed in males and not females. Conversely, the differences observed in the total population regarding block 4 (lens, including cataract) and block 7 (vitreous body and the globe) were only

TABLE 2 Number of cases and corresponding controls with an ICD-10 diagnosis in chapter VII (H00-H59, Diseases of the eye and adnexa) after the diagnosis of UC, subdivided into the diagnosis blocks.

ICD-10 diagnosis, chapter VII (H00-H59), between years 2007 and 2016				
Diagnosis block	**Cases (*n*)**	**Controls (*n*)**	**HR**	**95% CI**
H00-H59	2525	3979	**1.25**	**1.20–1.32**
Males	1116	1732	**1.27**	**1.18–1.37**
Females	1409	2247	**1.25**	**1.17–1.33**
1. H00-H06	556	805	**1.37**	**1.22–1.52**
Males	207	284	**1.44**	**1.20–1.72**
Females	349	521	**1.33**	**1.16–1.53**
2. H10-H13	328	441	**1.47**	**1.28–1.70**
Males	159	176	**1.78**	**1.44–2.21**
Females	169	265	**1.27**	**1.05–1.54**
3. H15-H22	545	710	**1.52**	**1.36–1.70**
Males	265	345	**1.51**	**1.29–1.78**
Females	280	365	**1.53**	**1.31–1.78**
4. H25-H28	535	896	**1.18**	**1.06–1.32**
Males	233	405	**1.13**	**0.96–1.33**
Females	302	491	**1.22**	**1.06–1.41**
5. H30-H36	316	504	**1.24**	**1.08–1.43**
Males	159	255	**1.23**	**1.02–1.50**
Females	157	249	**1.25**	**1.03–1.53**
6. H40-H42	281	445	**1.25**	**1.08–1.45**
Males	139	205	**1.34**	**1.08–1.66**
Females	142	240	1.18	0.96–1.45
7. H43-H45	425	697	**1.21**	**1.07–1.36**
Males	147	247	1.17	0.96–1.44
Females	278	450	**1.23**	**1.06–1.43**
8. H46-H48	25	53	0.94	0.58–1.50
Males	10	24	0.82	0.39–1.72
Females	15	29	1.03	0.55–1.92
9. H49-H52	301	457	**1.30**	**1.13–1.51**
Males	137	196	**1.38**	**1.11–1.71**
Females	164	261	**1.25**	**1.03–1.52**
10. H53-H54	211	317	**1.32**	**1.11–1.57**
Males	101	139	**1.44**	**1.11–1.85**
Females	110	178	1.23	0.97–1.56
11. H55-H59	38	69	1.09	0.74–1.62
Males	13	30	0.86	0.45–1.64
Females	25	39	1.28	0.77–2.11

Note: Bold numbers represent statistical significance, specified as $p<0.05$.
Blocks of ICD-10 diagnoses with numbered disorders of: 1. Eyelid, lacrimal system and orbit; 2. Conjunctiva; 3. sclera, cornea, iris and ciliary body; 4. Lens; 5. Choroid and retina; 6. Glaucoma; 7. Vitreous body and globe; 8. Optic nerve and visual pathways; 9. Ocular muscles, binocular movement, accommodation and refraction; 10. Visual disturbances and blindness; 11. Other disorders of eye and adnexa.
Abbreviations: CI, confidence interval; HR, hazard ratio.

TABLE 3 Number of cases and corresponding controls, exposed and non-exposed to silica dust after the diagnosis of UC, with a diagnosis in ICD-10 chapter VII (H00-H59, Diseases of the eye and adnexa) and diagnoses specified with focus on inflammatory eye diseases.

Silica dust-exposed and ophthalmological diagnoses during study period				
Diagnosis	**Cases (*n*)**	**Controls (*n*)**	**HR**	**95% CI**
H00-H59	2525	3979	**1.25**	**1.20–1.32**
Exposed	146	193	**1.44**	**1.16–1.78**
Non-exposed	2379	3786	**1.25**	**1.19–1.31**
Males	1116	1732	**1.27**	**1.18–1.37**
Exposed	119	162	**1.41**	**1.11–1.78**
Non-exposed	997	1570	**1.26**	**1.16–1.36**
Females	1409	2247	**1.25**	**1.17–1.33**
Exposed	27	31	1.54	0.91–2.61
Non-exposed	1382	2216	**1.24**	**1.16–1.33**
1. H15	83	72	**2.28**	**1.67–3.13**
Exposed	3	4	1.43	0.32–6.37
Non-exposed	80	68	**2.33**	**1.69–3.23**
Males	30	24	**2.47**	**1.44–4.22**
Exposed	1	2	0.97	0.09–10.71
Non-exposed	29	22	**2.61**	**1.50–4.55**
Females	53	48	**2.20**	**1.49–3.25**
Exposed	2	2	1.79	0.25–12.72
Non-exposed	51	46	**2.22**	**1.49–3.30**
2. H16	247	354	**1.38**	**1.17–1.63**
Exposed	13	31	0.79	0.41–1.51
Non-exposed	234	323	**1.44**	**1.22–1.70**
Males	119	170	**1.38**	**1.09–1.74**
Exposed	10	24	1.99	0.38–1.67
Non-exposed	109	146	**1.61**	**1.15–1.90**
Females	128	184	**1.38**	**1.11–1.74**
Exposed	3	7	0.77	0.20–2.97
Non-exposed	125	177	**1.41**	**1.12–1.77**
3. H20	180	176	**2.03**	**1.65–2.49**
Exposed	16	8	**3.84**	**1.64–8.97**
Non-exposed	164	168	**1.94**	**1.57–2.41**
Males	91	88	**2.04**	**1.52–2.74**
Exposed	14	7	**3.87**	**1.56–9.60**
Non-exposed	77	81	**1.88**	**1.38–2.57**
Females	89	88	**2.01**	**1.50–2.70**
Exposed	2	1	3.57	0.32–39.35
Non-exposed	87	87	**1.99**	**1.48–2.68**
4. H30	10	7	**2.83**	**1.08–7.43**
Exposed	1	0	–	–
Non-exposed	9	7	2.56	0.95–6.87
Males	6	2	**5.93**	**1.20–29.37**
Exposed	1	0	–	–
Non-exposed	5	2	5.00	0.97–25.79
Females	4	5	1.59	0.43–5.92
Exposed	0	0	–	–
Non-exposed	4	5	1.59	0.43–5.92
5. H35	204	310	**1.30**	**1.09–1.55**
Exposed	12	17	1.36	0.65–2.85
Non-exposed	192	293	**1.30**	**1.08–1.56**
Males	93	152	1.20	0.93–1.56
Exposed	9	15	1.17	0.51–2.68
Non-exposed	84	137	1.21	0.92–1.59
Females	111	158	**1.40**	**1.10–1.78**
Exposed	3	2	2.66	0.44–15.96
Non-exposed	108	156	**1.38**	**1.08–1.76**

Note: Bold numbers represent statistical significance, specified as $p<0.05$.
ICD-10 diagnoses with numbered disorders: 1. Sclera; 2. Keratitis; 3. Iridocyclitis; 4. Chorioretinal inflammation; 5. Other retinal disorders.
Abbreviations: CI, confidence interval; HR, hazard ratio.

statistically significant in females and not males. Data on HR including 95% CI as well as incidence rate for each block in the total population and in males and females, for cases and controls, are presented in Table 2.

The diagnoses evaluated (Table 3) were all more common in the cases with UC than in controls. These differences were all statistically significant for the groups as a whole. Disorders of the sclera (H15), which contains both episcleritis and scleritis, had a HR of 2.28 (CI 1.67–3.13). Keratitis (H16), comprising microbial and inflammatory keratitis, corneal ulceration and keratoconjunctivitis, had a HR of 1.38 (CI 1.17–1.63). Iridocyclitis (H20), which includes both acute and chronic anterior uveitis as well as other types of iridocyclitis, was associated with a HR of 2.03 (CI 1.65–2.49). Chorioretinal inflammation (H30), which comprises different types of chorioretinal inflammation and posterior uveitis, was linked to a HR of 2.83 (CI 1.08–7.43). However, a statistical significance was only present in males and not females. Other retinal disorders (H35), which involve dry and exudative macular degeneration and other retinopathies, had a HR of 1.30 (CI 1.09–1.55), with a statistical significance only in females and not in males.

Regarding silica dust exposure analysis, 1349 (6.9%) of the cases and 2419 (6.2%) of controls were exposed, of which the majority in both groups were male (Table 1). The risk for ocular disease, defined as an ICD10 diagnosis in chapter VII, in the total group was higher in exposed (5.8%) than non-exposed (4.9%) (HR 1.44 and 1.25, respectively). Among cases, 146 individuals (119 males and 27 females) were exposed compared to 193 in controls (162 males and 31 females). On diagnosis block level, no significant differences were observed between cases and controls. However, the analysis for the selected conditions specified above showed that the risk for iridocyclitis (H20) was increased for cases in both exposed and non-exposed groups but with a HR of 3.84 (CI 1.64–8.97) in exposed individuals compared to 1.94 (CI 1.57–2.41) in non-exposed individuals. The specific values for the total group on diagnosis-level, with and without silica dust exposure, as well as separated based on sex are found in Table 3.

4 | DISCUSSION

In this work, we studied the incidence of eye diseases, with diagnoses in chapter VII, ICD-10, in patients diagnosed with UC. The majority of ocular extraintestinal manifestations were overrepresented among cases compared to controls with a statistical significance in all but two blocks of eye diseases. Hence, our general interpretation is that individuals with UC are at an increased risk of developing ophthalmological disease, including ocular EIMs. The most frequently reported diagnoses were within the anterior segment classified in block 3, which includes inflammatory diseases such as anterior uveitis, keratitis and episcleritis. Our study is consistent with previous publications regarding the increased risk for inflammatory keratitis and iritis in individuals with IBD (Cuny et al., 2022; Felekis et al., 2009; Karmiris et al., 2016; Lee et al., 2017; Manser et al., 2016; Vavricka et al., 2011). We detected a statistically significantly increased risk for anterior uveitis (20), with similar risk in both males and females, although previous research has reported conflicting results regarding the association between UC and this inflammatory condition (Christodoulou et al., 2002; Cuny et al., 2022; Manser et al., 2016; Troncoso et al., 2017; Vavricka et al., 2011). Similarly, we found an elevated HR regarding disorders of the sclera (H15), encompassing episcleritis and scleritis, which also has not been consistently reported in UC (Bandyopadhyay et al., 2015; Cuny et al., 2022; Karmiris et al., 2016; Troncoso et al., 2017). In this study, there was also a significant difference between cases and controls with regards to chorioretinal inflammation (H30), which comprises diagnoses such as posterior uveitis and pars planitis.

Previous publications have highlighted that patients with CD are at higher risk of developing ocular EIMs than patients with UC (Karmiris et al., 2016; Lin et al., 2023; Manser et al., 2016; Vavricka et al., 2011). Although we did not investigate CD, the results presented in this article indicate that individuals with UC are at an increased risk for ophthalmological diseases than individuals without the condition. It is a possibility that a chronic condition like UC, with irregular relapses of inflammation may not be detected in smaller, prospective studies. The pathophysiology for uveitis in UC is linked to the underlying inflammatory bowel disease and genetic predisposition with HLA polymorphism, which may be associated with or influence the development of ocular inflammation (Greuter & Vavricka, 2019; Orchard et al., 2002).

Larger population-based studies of patients with IBD have reported an increased incidence of ophthalmological diseases compared to the general population (Isene et al., 2015; Karmiris et al., 2016; Vavricka et al., 2011; Zippi et al., 2014). In addition to anterior segment inflammation, several studies have demonstrated an overrepresentation of symptoms related to dry eyes and eyelid problems (Cuny et al., 2022; Felekis et al., 2009; Lee et al., 2017; Yilmaz et al., 2007), which often can be diagnosed within block 1 as well as block 3. However, symptoms from dry eyes may sometimes fall within conjunctival diseases (block 2). All these findings were consistent with the findings in our study, with statistically significant differences compared to controls irrespective of sex. Overall, our results on block-level diagnoses support that individuals with ulcerative colitis more often suffer from anterior segment symptoms compared to controls. Unspecific symptoms from the conjunctiva and eyelids have been reported previously. A link between dry eyes and treatment with 5-aminosalicylic acid (5-ASA) has been published (Czompa et al., 2019); however, it is not clear whether this therapy is associated with the development of symptoms from dry eyes in IBD.

Other studies have reported a higher degree of EIMs in women with IBD compared to men (Algaba et al., 2021; Bernstein et al., 2001; Orchard et al., 2002) but in the current study, we found similar patterns regarding most blocks of diagnoses comprising ocular EIMs. Some exceptions were an increased risk in males but not in females for glaucoma, and an increased risk in females but not in males for disorders of the lens, which includes different types of cataract.

This study also analysed the importance of silica dust exposure in the potential pathogenesis of eye diseases in UC, which was overall more common in exposed individuals than in non-exposed individuals, with HRs of 1.44 and 1.25 respectively. Notably, with regards to anterior uveitis the risk was considerably higher among exposed individuals with a HR of 3.84 (CI 1.64–8.97) compared to a HR of 1.94 (CI 1.57–2.41) in non-exposed. Among these individuals, 14 of 16 were male. The number of individuals in this subcategory was small but it seems relevant to investigate this aspect in future research since silica particles can cause several inflammatory diseases with an established risk for the development of eye diseases, such as rheumatoid arthritis, IBD, sarcoidosis and tuberculosis (Khuder et al., 2002; Leung et al., 2012; Wallden et al., 2020). Furthermore, ocular changes on optical coherence tomography (OCT) imaging have been demonstrated in coal mine workers, which may be associated with silica dust exposure (Ayar et al., 2017; Yang et al., 2022). Differences described compared to non-exposed individuals included retinal blood vessel diameters, retinal nerve fibre layer thickness and choroidal thickness. These were consistent with findings secondary to inflammatory conditions (Kriegel et al., 2019; Petzold et al., 2017). To our knowledge, no previous research has investigated the association between silica dust exposure and inflammation in the eye. If such a link is established, investigation of silica dust exposure may be relevant in recalcitrant cases of ocular inflammation.

In this study, we followed a large number of individuals with matched controls over time. It was possible to demonstrate a significantly increased risk for anterior uveitis as well as data corresponding to dry eyes and anterior segment disease, including corneal ulcers. Since the study was conducted using ICD coding, it was not possible to access data regarding specific information such as disease activity, previous surgery, smoking, lifestyle factors, medication and exact ophthalmological findings, which is unarguably a weakness of the current study.

It would undoubtedly have strengthened the study if we could have analysed the importance of different

pharmacological and surgical therapies, as well as had access to other lifestyle-variables and possible confounders. Regarding ocular conditions resulting from medication, we consider it plausible that some, particularly cataracts and glaucoma, could be secondary to corticosteroid treatment (Carnahan & Goldstein, 2000). However, it is unlikely that the main findings would result from pharmacological side-effects. It is even less probable that inflammatory eye diseases would be complications to anti-inflammatory therapies. Instead, we consider it more likely that these therapies would underestimate the risk for inflammatory eye conditions.

Access to such confounders could alter the interpretation of the results and would, hence, further increase the understanding of underlying pathophysiology. Nevertheless, we consider the data sufficiently accurate to conclude that individuals with UC are at an increased risk of developing eye diseases compared to the general population. In particular conditions associated with inflammation were more common in cases than controls, as there was a significantly increased risk of disorders of the sclera (episcleritis and scleritis), corneal ulcers and uveitis (anterior and chorioretinal inflammation). Our findings suggest that exposure to silica dust may be a risk factor for ocular EIMs, such as anterior uveitis, in individuals with UC. We consider it relevant to further study whether silica dust exposure potentially could induce intraocular inflammation.

5 | CONCLUSION

Ulcerative colitis increases the risk for the development of several eye diseases. These data support that inflammatory ocular extraintestinal manifestations, such as anterior and posterior uveitis, episcleritis and corneal ulceration are more common in ulcerative colitis. Exposure to respirable silica dust may further augment the risk for uveitis.

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