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Original Research

Inflammatory bowel disease and asthma. Results from the RHINE study

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ABSTRACT

Background: Asthma and inflammatory bowel disease (IBD) are common inflammatory diseases. The aim of this study was to investigate the associations of IBD with asthma and respiratory symptoms.
Methods: This study is based on 13,499 participants from seven northern European countries that filled in a postal questionnaire on asthma, respiratory symptoms, IBD including ulcerative colitis and Crohn's disease and various lifestyle variables.
Results: There were 195 participants with IBD. The prevalence of asthma (14.5 vs 8.1%, $p = 0.001$), different respiratory symptoms (range 11.9–36.8% vs range 6.0–18.6%, $p < 0.005$), non-infectious rhinitis (52.1 vs. 41.6%, $p = 0.004$) and chronic rhinosinusitis (11.6 vs 6.0%, $p = 0.001$) were higher in subjects with IBD than in those without IBD. In multivariable regression analysis, the association between IBD and asthma was statistically significant (OR 1.95 (95% CI 1.28–2.96)) after adjusting for confounders such as sex, BMI, smoking history, educational level and physical activity. There was a significant association between asthma and ulcerative colitis (adjusted OR 2.02 (95% CI 1.27–2.19)), and asthma but not Crohn's disease (adjusted OR 1.66 (95% CI 0.69–3.95)). A significant gender interaction was found with a significant association between IBD and asthma in women but not in men ((OR 2.72 (95% CI 1.67–4.46) vs OR 0.87 (95% CI 0.35–2.19), $p = 0.038$).
Conclusions: Patients with IBD, particularly those with ulcerative colitis and female, have a higher prevalence of asthma and respiratory symptoms. Our findings indicate that it is important to consider respiratory symptoms and disorders when examining patients with manifest or suspected IBD.

1. Background

Inflammatory bowel disease (IBD) and asthma are both inflammatory diseases that have become increasingly common in Western countries, and their prevalence is currently growing in developing countries [1,2]. Although the aetiology of both diseases is not fully understood, the conditions share genetic and environmental predisposition. For example, being born and raised on a livestock farm for the first five years was associated with a lower risk of IBD and asthma than city living [3]. Research indicates a cross-talk between the respiratory and gastrointestinal tract, termed the gut-lung axis [4].

IBD consists of a group of chronic conditions, including Crohn's

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disease and ulcerative colitis, characterised by chronic inflammation in the gastrointestinal tract. The inflammation in ulcerative colitis is limited to the colon in a continuous, uninterrupted pattern. In contrast, Crohn's disease can involve any part of the gastrointestinal tract and does so in a discontinuous pattern [5]. Asthma is characterised by chronic inflammation in the respiratory tract and is the most studied extraintestinal comorbidity of IBD [6]. The primary asthma symptoms are shortness of breath, chest tightness, cough and wheezing. Both asthma and IBD account for substantial morbidity and economic burden on patients and health care [7]. Understanding possible links between these two conditions are important to increase knowledge of the underlying aetiology.

Some observational studies reported no association between IBD and asthma [8] or confirmed an association only between asthma and specific types of IBD [9]. Two recent meta-analyses found a link between IBD and asthma [10,11]. However, those reports highlighted the heterogeneity of the included studies. Another knowledge gap in this area is that there are no previous cohort studies on the relationship between respiratory symptoms and IBD. Data on respiratory symptoms in IBD patients are limited to case reports and usually present rare airway entities [12,13]. In addition, few previous studies conducted in the Nordic countries investigated the association between asthma and IBD in adults [9,14].

The aim of the study was to investigate the associations of IBD with asthma and respiratory symptoms in a large population-based study from Northern European cities.

2. Methods

2.1. Study design

This study is cross-sectional and based on a second follow-up of the European Community Respiratory Health Survey (ECRHS), which took place in 1990–1994. ECRHS had a population of 137,619 randomly selected men and women born between 1945 and 1973 from 48 different centres [15,16].

The Respiratory Health in Northern Europe (RHINE) followed participants from seven different centres in Northern Europe: Bergen in Norway, Tartu in Estonia, Uppsala, Umeå and Gothenburg in Sweden, Reykjavik in Iceland and Aarhus in Denmark. This follow-up consisted of 21,659 subjects [17]. A postal questionnaire was sent out to all participants in 1999–2001 (RHINE II), where 16,106 chose to participate. The current study is based on a follow-up questionnaire made in 2010–2012 (RHINE III). A total of 13,499 subjects (62% of those in RHINE I) participated in RHINE III.

2.2. Respiratory health

The questionnaires used in all RHINE stages were designed as yes/no questions asking about the presence of respiratory symptoms in the last 12 months. The respiratory symptoms reported were wheezing, nocturnal shortness of breath, nocturnal cough and nocturnal chest tightness. Participants were defined as having asthma if they used medication against asthma or have had an asthma attack in the last 12 months [18]. The questionnaire also included questions about non-infectious rhinitis (nasal symptoms without having a cold in the previous 12 months) [19], allergic rhinitis and chronic rhinosinusitis (CRS) [20]. Participants with asthma were also asked about the age when asthma started.

2.3. Inflammatory bowel disease

The presence of IBD was assessed with the following two questions: "Do you have or have you ever had ulcerative colitis?" and "Do you have or have you ever had Crohn's disease?" [3]. The age when the disease started was also asked for.

2.4. Other risk factors

In addition, RHINE III had questions regarding smoking habits asking if you currently smoke and if you were an ex-smoker. Questions about height and weight were used to calculate body mass index (BMI) in kg/m^2. Physical activity was based on how many times the participants exercised per week on average and then divided into three categories, those who exercise less than one time per week, those who exercise between one and three times per week and those who exercise more than three times per week [21]. The highest level of education achieved was divided into compulsory school, high school, and college/university.

2.5. Statistical analysis

Data were analysed using STATA version 15 (STATA Corp, College Station, Texas, USA). Chi2 test and unpaired *t*-test were used in the bivariable analyses. Logistic regressions were used in multivariable analyses. In these analyses, adjustments were made for age, sex, BMI, smoking history, educational level, exercise and centre. These confounders were chosen based on prior knowledge [21,22]. Interaction analyses were performed regarding the association between IBD and respiratory outcomes regarding gender, age, BMI and smoking history. A p-value <0.05 was regarded as statistically significant.

3. Results

3.1. Characteristics of the study population

In the study population, 195 subjects were in the IBD group (155 with ulcerative colitis and 51 with Crohn's disease, where six reported that they had both conditions), and 11 960 were in the no-IBD group. Subjects with IBD were less often never smokers and more often physically inactive than those without IBD (Table 1). No significant difference in age, sex, educational level or BMI was found between the subjects with or without IBD (Table 1).

When dividing the IBD groups into the two diagnoses, we found a lower mean age in those with Crohn's disease than those without IBD, fewer never-smokers, and more physically inactive subjects in those with ulcerative colitis than in those without IBD (Table 2). Information on the age when the participant's asthma started was available in 692 subjects, of which 21 had IBD. In this group, 16 (76%) reported having asthma before IBD and 5 IBD before asthma. The mean interval between the debut of asthma and IBD was 17 years.

3.2. Respiratory health in subjects with and without IBD

The prevalence of wheeze, wheeze with breathlessness, nocturnal

Table 1
Inflammatory bowel disease (IBD) and patients characteristics. Data are presented as % and mean ± SD where applicable.

	No IBD (n = 11 960)	IBD (n = 195)	p-value
Age	51.6 ± 7.2	52.2 ± 7.0	0.23
Women	53.0	55.9	0.43
BMI	26.0 ± 4.5	25.8 ± 4.4	0.48
Smoke history			<0.01
Never	47.9	33.7	
Ex	34.9	41.6	
Current	17.3	24.7	
Education			0.56
Compulsory school	10.6	11.9	
College	41.5	44.0	
University	47.9	44.0	
Excercise			0.02
<1 week	21.8	30.0	
1–3 week	56.1	52.3	
>3 week	22.1	17.6	

Table 2
Characteristics of patients with no inflammatory bowel disease (IBD) and with IBD divided into ulcerative colitis and Crohn's disease. Data are presented as % and mean ± SD where applicable.

	No IBD (n = 11 960)	Ulcerative colitis (n = 154)	p-value[a]	Crohn's disease (n = 50)	p-value[a]
Age	51.6 ± 7.2	52.4 ± 6.9	0.22	49.2 ± 7.4	0.048
Women	53.0	53.6	0.92	65.8	0.12
BMI	26.0 ± 4.5	25.8 ± 4.1	0.65	24.7 ± 4.8	0.08
Smoke history			0.048		0.050
Never	47.9	36.9		37.8	
Ex	34.9	41.0		29.7	
Current	17.3	22.1		32.4	
Education			0.11		0.81
Compulsory school	10.6	11.3		8.1	
College	41.5	40.3		46.0	
University	47.9	48.4		46.0	
Excercise			0.01		0.46
<1 week	21.8	32.8		29.0	
1–3 week	56.1	50.4		55.3	
>3 week	22.1	16.8		15.8	

[a] Ulcerative colitis or Crohn's disease compared to no IBD.

Table 3
The percent (%) of patients with ulcerative colitis or Crohn's disease and different respiratory symptoms and disease.

	Ulcerative colitis			Crohn's disease		
	No (n = 11 894)	Yes (n = 154)	p-value[a]	No (n = 11 927)	Yes (n = 50)	p-value[a]
Wheeze	18.7	26.5	0.01	18.7	22.0	0.54
Wheeze with breathlessness	10.1	18.3	0.001	10.1	10.2	0.98
Wheeze without having a cold	11.9	16.3	0.09	11.9	8.2	0.42
Nocturnal chest tightness	10.4	17.5	0.004	10.4	14.0	0.40
Nocturnal breathlessness	5.2	13.0	<0.001	5.2	10.0	0.13
Nocturnal cough	27.0	39.9	<0.001	27.0	24.0	0.63
Asthma	8.1	14.9	0.002	8.1	14.3	0.12
Non-infectious rhinitis	41.6	53.7	0.003	41.6	40.8	0.91
Allergic rhinitis	24.4	28.3	0.27	24.4	26.5	0.73
Chronic rhinosinusitis	6.0	11.9	0.002	6.0	8.3	0.49

[a] A difference between those with and without ulcerative colitis or Crohn's disease.

symptoms of chest tightness, nocturnal breathlessness, nocturnal cough, asthma, non-infectious rhinitis and CRS was higher in subjects with IBD than in those without IBD (Fig. 1).

There was a significantly higher prevalence of most respiratory symptoms, asthma and CRS in those with ulcerative colitis than in subjects without ulcerative colitis. No significant difference was found in those with and without Crohn's disease in relation to respiratory symptoms and respiratory disorders (Table 3).

The association between IBD and several respiratory symptoms, asthma, non-infectious rhinitis, and CRS remained significant after adjusting for age, sex, BMI, smoking history, educational level, exercise, and centre. The same was true for the association between ulcerative colitis and respiratory symptom, asthma and CRS. No significant associations were found between Crohn's disease and respiratory symptoms and disorders (Table 4).

A significant gender interaction was found with a significant association between IBD and asthma in women but not in men (OR 2.72 (95% CI 1.67–4.46) vs OR 0.87 (95% CI 0.35–2.19), p = 0.038. No significant gender interaction was found regarding any of the other respiratory outcomes, and no significant interaction was found in relation to age, BMI or smoking history.

4. Discussion

The main finding in our cross-sectional study was that participants with IBD reported a significantly higher prevalence of respiratory symptoms, asthma and CRS than those without IBD and that associations of ulcerative colitis with respiratory outcomes drove this. In contrast, associations with Crohn's disease were inconsistent and not significant.

This study showed an association between several respiratory symptoms and ulcerative colitis but not Crohn's disease. We also found an almost twofold increased asthma risk in IBD patients, which is in line with a previous meta-analysis [11]. Then, we showed the association between asthma and ulcerative colitis but not Crohn's disease, which was in accordance with an earlier British study [21]. On the other hand, a meta-analysis showed that ulcerative colitis and Crohn's disease

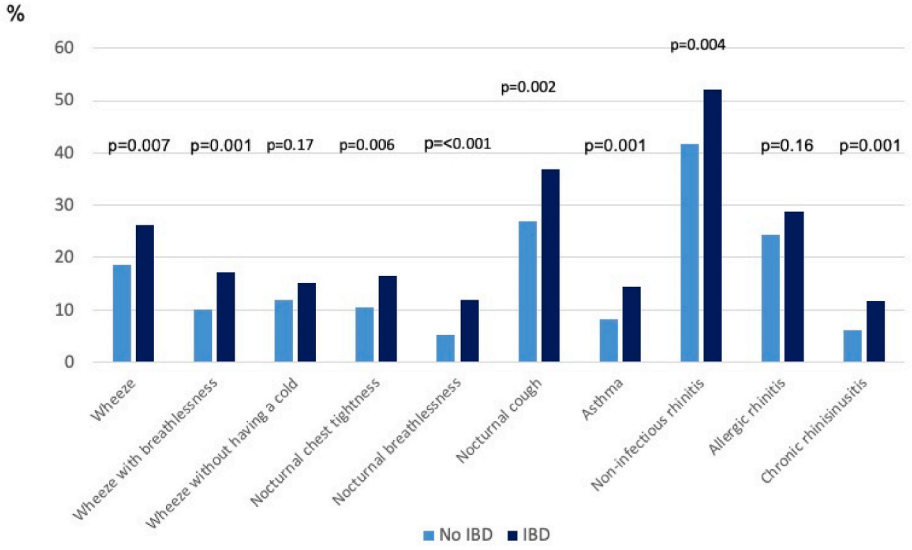

Fig. 1. The prevalence (%) of patients with different respiratory symptoms and disease and with or without inflammatory bowel disease (IBD/No IBD). P-value (over bars) shows the difference between no IBD and IBD patients.

Table 4
The association between inflammatory bowel disease (IBD) or ulcerative colitis or Crohn's disease, and different respiratory symptoms/disorders. The results are presented as Odds ratios (OR) with 95% confidence intervals (95% CI) and adjusted for age, sex, BMI, smoking history, educational level, exercise and centre.

	IBD	Ulcerative colitis	Crohn's disease
Wheeze	1.37 (0.96–1.95)	1.39 (0.94–2.05)	1.05 (0.50–2.18)
Wheeze with breathlessness	1.64 (1.09–2.46)	1.82 (1.17–2.82)	0.75 (0.26–2.14)
Wheeze without having a cold	1.11 (0.72–1.72)	1.26 (0.79–2.00)	0.43 (0.13–1.43)
Nocturnal chest tightness	1.59 (1.06–2.38)	1.62 (1.03–2.53)	1.34 (0.56–3.20)
Nocturnal breathlessness	2.20 (1.36–3.56)	2.27 (1.34–3.83)	1.86 (0.66–5.26)
Nocturnal cough	1.57 (1.15–2.14)	1.82 (1.29–2.58)	0.79 (0.40–1.58)
Asthma	1.95 (1.28–2.96)	2.02 (1.27–3.21)	1.66 (0.69–3.95)
Non-infectious rhinitis	1.52 (1.13–2.05)	1.57 (1.12–2.19)	1,13 (0.58–2.20)
Allergic rhinitis	1.33 (0.96–1.84)	1.29 (0.89–1.86)	1.05 (0.58–1.88)
Chronic rhinisinusitis	2.00 (1.25–3.20)	1.99 (1.19–3.53)	1.51 (0.53–4.27)

increase the risk of asthma [10].

In addition, we showed that in most IBD patients, asthma was diagnosed before IBD. It is in line with a previous population-based cohort study from Canada [7]. Other studies observed that the association between IBD and asthma depended on the age of the respiratory or gastrointestinal condition diagnosis. However, whether one disease predisposes to the other or co-occurs due to shared risk factors is not understood [9,10,22]. One previous study found a positive correlation between pediatric asthma and the subsequent development of another autoimmune disorder, type 1 diabetes, and reduced risk of asthma if type 1 diabetes appeared first [23].

Our study demonstrated that the association between asthma and IBD was significantly stronger in women than men. It is in accordance with a previous study that immune-mediated diseases such as IBD and asthma predominantly occur in females [24]. Previous studies have reported a stronger association between asthma and Crohn's disease in women than men, whereas conflicting findings were found for ulcerative colitis [22,25,26].

A correlation between chronic lung diseases, such as asthma and COPD and low microbial diversity in the gut has been reported [27]. The mechanism between this so-called gut-lung axis [4,28] may be related to several mechanisms, such as respiratory inflammation leading to systemic inflammation that causes damage in the gut but also the opposite that gut microbiota dysbiosis has a negative effect on the immune system, which leads to lung damage. Cesarean-section birth, formula feeding in infancy and use of antibiotics in childhood may be related to microbiota dysbiosis and increase the risk of development of asthma later in life [29,30]. On the other hand, a high intake of dietary fibres, particularly their fermentation products: short-chain fatty acids, may protect against allergic airway inflammation by modulating immune function [31]. Regarding COPD, smoking which is the main cause of this respiratory disease, causes changes in the gut microbiota [32].

One hypothesis of the relationship between IBD and respiratory disease is that the pulmonary and intestinal systems share embryological origins [33]. According to another theory based on mice model, the gut microbiota and its metabolites through the blood and lymphatic system regulate the immune- and inflammatory response in the lung [28,31]. Crohn's disease is generally considered to be mediated by a Th-1 response and ulcerative colitis by a Th-2 response, while allergic asthma is also mediated by a Th-2 response [34]. The exact pathophysiological mechanism of interplay between gut microbiota and airways is still not known [28]. Therefore, more studies on the bacterial composition and metabolites in patients with respiratory disease are needed.

Environmental, microbial and genetic factors may also be involved in asthma and IBD co-occurrence [10,11]. Growing up in an urbanised environment, frequent exposure to antibiotics and not being breastfed early in life are factors linked to an increased risk of IBD and asthma [35]. Thus, reduced diversity or other types of disruption of the microbiome have been suggested to impact the development of both asthma and IBD [36]. In addition, gene polymorphism in the form of single nucleotide polymorphism in a protein called gasdermin-B increases the risk of developing both IBD and asthma [37]. This suggests that a genetic component is a possible explanation for why the correlation between the two diseases may vary by geographical region [10].

We found no association between IBD and allergic rhinitis. In our study, CRS was significantly associated with ulcerative colitis but not Crohn's disease. Previous studies showed discrepancies in the co-occurrence of CRS and IBD. Some reports indicated an association, whereas others did not [34]. This is partially in line with earlier epidemiological research that shows that atopic sensitisation is more common in those with ulcerative colitis, whereas this is not found in those with Crohn's disease [33].

In the present study, we found that subjects with IBD were more likely to be current or ex-smokers than those without IBD. This founding was in accordance with the previous research on individuals between 40 and 60 years old, where the risk of developing IBD was higher in current smokers [38]. We also demonstrated that being physically inactive was more common among subjects with IBD than those without IBD. Similar results were reported in the review, where 12/16 studies reported lower levels of habitual exercise in those with IBD compared to controls [39]. Some studies found an association between IBD and sedentary work. However, it was unclear if sedentary work was the cause of IBD or if the disease led to seeking a less physically demanding job [40].

The strengths of our study were the large number of participants from different Nordic countries. This dataset has been used in multiple published studies and was proven reliable on the risk association of several conditions [16,17]. The results remained significant after adjusting for centre, even though the prevalence of IBD can vary in various geographical regions [10]. Another strength was that we considered several respiratory symptoms and disorders that may co-occur with IBD.

Our study also had limitations. All data were self-reported, which makes it susceptible to bias. Asthma is, in many cases, a clinical diagnosis where the adherence to strict diagnostic procedures is varying, and there might be a risk of overdiagnosis of asthma in those with more regular healthcare contacts because of IBD [41]. However, the fact that there also was an association between asthma-related symptoms and IBD reduced the risk of this kind of bias. Another limitation is that we did not have information on the severity and specific disease characteristics of IBD and could not investigate whether the duration and the severity of the condition were related to the concurrence of asthma or asthma-related symptoms.

In addition, our study's incidence of Crohn's disease was three times lower than ulcerative colitis, which may limit statistical power to detect the reported effect size. Also, due to the small sample size, we did not study whether specific age groups were more prone to have an association between IBD and asthma, which was suggested by other studies [10,11]. Furthermore, we had no information on the medication and systemic use of corticosteroids that may mitigate or slow asthma progress [8].

5. Conclusions

We found respiratory symptoms, asthma, non-infectious rhinitis, and

CRS to be significantly associated with IBD. The association between asthma and IBD was stronger in women than in men. The clinical implications of the present study results include making it standard practice to ask patients with IBD about respiratory symptoms and disorders and recommend examination to ensure early detection.

Ethical approval

The study was approved by The Regional Committees for Medical and Health Research Ethics West in Norway, the National Bioethics Committee in Iceland, the Research Ethics Committee of the University of Tartu in Estonia, The Regional Ethical Review Board in Uppsala, Sweden and the Scientific Committee for Central Denmark. All the participants gave written informal consent. All methods were carried out in accordance with relevant guidelines and regulations.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Consent for publication

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Authors contribution

MAK - study design and analysis, interpretation, preliminary and final manuscript writing, MS - study analysis, interpretation, discussion, read and approved the final manuscript., AM - interpretation, discussion, read and approved the final manuscript, KAF - interpretation, discussion, read and approved the final manuscript, TG - interpretation, discussion, read and approved the final manuscript, VS - interpretation, discussion, read and approved the final manuscript, AJ - interpretation, discussion, read and approved the final manuscript, LM - interpretation, discussion, read and approved the final manuscript, RJ - interpretation, discussion, read and approved the final manuscript, MH - interpretation, discussion, read and approved the final manuscript, CS - interpretation, discussion, read and approved the final manuscript, LL - interpretation, discussion, read and approved the final manuscript, MC - interpretation, discussion, read and approved the final manuscript, CJ – study design, analysis and interpretation, discussion, read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2023.107307.

List of abbreviations

IBD inflammatory bowel disease

CRS chronic rhinosinusitis

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