Pediatric RESEARCH

POPULATION STUDY ARTICLE

Comorbidities in adolescents with inflammatory bowel disease: findings from a population-based cohort study

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BACKGROUND: Inflammatory bowel diseases are associated with various immune- and non-immune-mediated conditions. We aimed to assess the association of inflammatory bowel diseases with comorbidities at late adolescence.

METHODS: Jewish Israeli adolescents who underwent a general health evaluation prior to enlistment to the Israeli Defense Forces from 2002 to 2016 were included.

RESULTS: Overall, 891 subjects (595 Crohn's disease, 296 ulcerative colitis, median age 17.1 years) and 1,141,841 controls were analyzed. Crohn's disease was associated with arthritis (odds ratio (OR) 4.7, 95% confidence interval (CI) 2.4–9.1), thyroid disease (OR 2.6, 95% CI 1.2–5.5), atopic dermatitis (OR 2, 95% CI 1.1–3.6), autoimmune hepatitis (OR 4.4, 95% CI 2.3–8.6), nephrolithiasis (OR 3.6, 95% CI 1.2–11.4), and pancreatitis (OR 41.8, 95% CI 17.2–101.9). Ulcerative colitis was associated with arthritis (OR 3.6, 95% CI 1.0–9.8), thyroid disease (OR 4.8, 95% CI 1.2–19.4), autoimmune hepatitis (OR 8, 95% CI 4–16.2), and pancreatitis (OR 51, 95% CI 16.1–158.9). Primary sclerosing cholangitis was associated with both diseases. Asthma, celiac, type 1 diabetes, psoriasis, and bone fractures were not more common in both diseases. Male predominance was noted for most associations.

CONCLUSIONS: At adolescence, both Crohn's disease and ulcerative colitis are associated with multiple comorbidities, not limited to autoimmune disorders.

Pediatric Research (2020) 87:1256–1262; https://doi.org/10.1038/s41390-019-0702-3

INTRODUCTION

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are associated with a variety of chronic comorbidities. Its strongest and most studied associations are with other immune-mediated inflammatory diseases, plausibly through shared pathogenic pathways.[1] Immune-mediated diseases that were reported to be more common among patients with IBD include rheumatoid arthritis,[2,3] systemic lupus erythematosus,[2] hypothyroidism,[2] type 1 diabetes,[2] psoriasis,[3] asthma,[3–5] pernicious anemia,[5] and celiac disease.[6] Malabsorption, in addition to prolonged steroid use and inflammation-induced bone loss, also puts patients with IBD at increased risk of osteoporosis[7] and subsequent fractures' risk.

While not as well studied as the described association with other immune-mediated conditions, evidence suggests that IBD is also associated with non-immune-mediated conditions, such as increased risk for nephrolithiasis,[8] venous thromboembolism,[9,10] non-alcoholic fatty liver disease,[11] migraines,[12] and even Parkinson's disease.[13]

The true prevalence of medical conditions associated with IBD is still obscured by limited data, which are mainly derived from relatively small cohorts.[12] Moreover, most studies of comorbidities in IBD examined adult patients, and specific data among children and adolescents with IBD are scarce.[2]

Thus the aim of our study was to investigate the association of IBD diagnosis with various comorbidities in a cross-sectional, population-based study of subjects diagnosed with IBD at late adolescence.

MATERIALS AND METHODS

Study population

Jewish adolescents who were born from 1987 to 1999 underwent a pre-enlistment medical evaluation at median age 17.1 years (interquartile range (IQR) 16.7–17.3 years) from 2004 to 2016. Strictly religious women who were exempt from medical board examination were excluded. For subjects with chronic diseases, enlistment is voluntary, and as such, complete medical history was available only for those who volunteered for military service.

Ascertainment of IBD cases

IBD diagnosis was established and confirmed by a military medical recruitment board. Medical information, including IBD diagnosis, was retrieved from medical history documents provided by the subject's family physician for each individual case (Fig. 1). The diagnosis of IBD also required a confirmation document signed by a gastroenterologist, which included endoscopic, radiologic, histologic, and laboratory results at diagnosis and during follow-up. The minimal requirements for diagnosis included complete ileo-colonoscopy with a histologic report and small bowel imaging study (magnetic resonance enterography, computerized tomographic enterography, or a small bowel follow-through).

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Received: 18 July 2019 Revised: 25 October 2019 Accepted: 31 October 2019
Published online: 4 December 2019

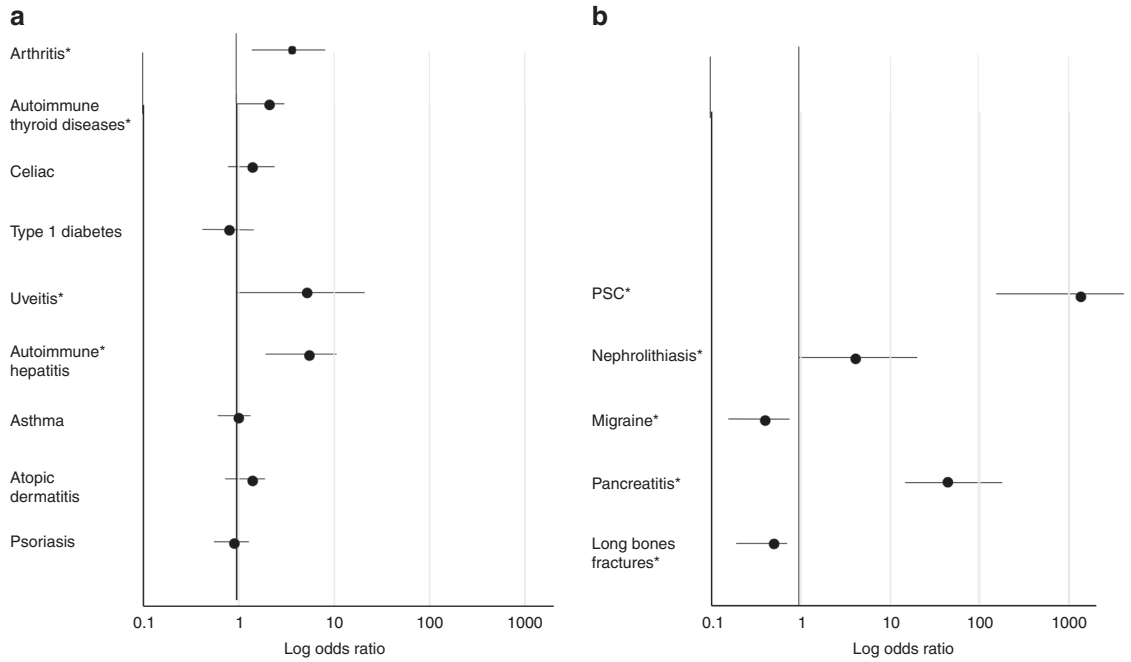

Fig. 1 Comorbidities in pediatric inflammatory bowel diseases. Forest plots depict the prevalence OR and 95% CI for each condition for **a** immune-mediated disorders and **b** non-immune-mediated disorders. *$P < 0.01$ (PSC primary sclerosing cholangitis).

CD and UC are unifacially coded as "IBD" in the Israeli Defense Forces (IDF) computerized database. Consequently, we manually reviewed all medical records in order to retrieve the accurate diagnosis of either CD or UC and also age at the time of diagnosis. IBD unclassified cases (10 cases, 0.004%) were grouped with the UC cases for the statistical analysis.

The control population was defined as all subjects without a diagnosis of IBD.

Covariate data

Covariate baseline adolescent data included year of birth, age at diagnosis, year of data ascertainment, and comorbidities, which were retrieved from a detailed medical history document provided by the subject's family physician as well as from a meticulous medical interview and physical examination performed by a physician at the time of ascertainment. The confirmation of each comorbidity required a confirmatory comprehensive medical document from an expert from the relevant discipline including the results of diagnostic procedures, radiologic assessment, and laboratory findings. Complete detailed medical history, including comorbid conditions, was available for 38% of subjects with the diagnosis of IBD as recruitment is voluntary for these patients, and subsequently, patients who were exempt for duty did not complete the medical documentation process.

Definition of variables

The definitions of various medical conditions were set following a joint decision taken by an expert committee. Definitions were predetermined prior to data extraction and were valid for the entire cohort. The medical information including all diagnoses was retrieved from a detailed medical history documents provided by the subject's family physician. All diagnoses required an expert verification, who provided a detailed medical document.

Arthritis was defined as any chronic joint inflammatory diseases, including juvenile idiopathic arthritis and psoriatic arthritis. Autoimmune thyroid diseases included both Grave's disease and Hashimoto's thyroiditis, whereas type 1 diabetes was defined as diabetes requiring insulin treatment.

Statistical analysis

The characteristics of the participants are presented as arithmetic mean (±SD) or, in the case of characteristics with skewed distributions, as medians and IQRs. Continuous variables were compared using Pearson correlation test and paired *t* test while categorical variables were compared using chi-square test or Fisher exact test. Univariate logistic regression analysis was used to evaluate the association between categorical variables. Multivariable logistic regression was used for analyzing the association between either CD or UC and multiple variables, which were identified in the univariate analysis as associated with IBD with significance of <0.1. The first block in each regression included age at diagnosis and gender. The second block included other comorbidities and medical conditions, which were selected for inclusion in the regression using the forward method. $P < 0.05$ was considered statistically significant. SPSS version 23 was used for all statistical analyses.

Ethical considerations

The Institutional Review Board of the IDF Medical Corps approved the study. Personal identifiers were permanently deleted from the computer file so that all analyses were performed on anonymous records.

RESULTS

Cohort characteristics

Out of 1,142,732 persons being evaluated, 2372 cases of IBD (0.2%; CD, $n = 1612$, 68%; UC, $n = 760$, 32%) were identified. Out of these, 891 cases of IBD (38%) volunteered for medical service and thus had complete and comprehensive medical history. Median age at the time of evaluation was 17.1 years (IQR, 16.7–17.3 years) with 573 males (64%). CD accounted for 67% of the IBD cohort ($n = 595$). Median age of IBD diagnosis for the entire cohort was 15 years (IQR, 12.5–17 years).

Association of IBD with other comorbidities

Fig. 1 depicts the associations of the entire IBD cohort with immune- and non-immune-mediated conditions. The diagnosis of

Table 1. Immune-mediated comorbidities of Jewish adolescents with and without CD.

		Controls (1,141,841, 99.95%)	CD (595, 0.05%)	Univariate analysis (*P* value)	Multivariate analysis (OR)	95% CI	*P* value
Arthritis (No., %)	All	3709 (0.30%)	9 (1.5%)	<0.001	4.7	2.4–9.1	<0.001
	Males	1960 (0.28%)	7 (1.7%)	<0.001	3.7	2.1–6.6	<0.001
	Females	1749 (0.38%)	2 (1.0%)	0.13			
Autoimmune thyroid diseases (No., %)	All	5142 (0.45%)	7 (1.2%)	<0.001	2.6	1.2–5.5	0.008
	Males	1766 (0.25%)	4 (1.0%)	<0.001	3.8	1.4–10.2	0.004
	Females	3376 (0.73%)	3 (1.6%)	0.17			
Celiac disease (No., %)	All	1514 (0.13%)	2 (0.33%)	0.17			
	Males	645 (0.09%)	1 (0.25%)	0.32			
	Females	869 (0.19%)	1 (0.5%)	0.28			
Type 1 diabetes (No., %)	All	1900 (0.16%)	0 (0.0%)	0.32			
	Males	1169 (0.17%)	0 (0.0%)	0.40			
	Females	731 (0.16%)	0 (0.0%)	0.58			
Uveitis (No., %)	All	299 (0.02%)	2 (0.3%)	<0.001	12.8	3.2–52	<0.001
	Males	168 (0.02%)	2 (0.5%)	<0.001	20	5.0–81	<0.001
	Females	131 (0.03%)	0 (0.0%)	0.51			
Autoimmune hepatitis (No., %)	All	3928 (0.3%)	9 (1.5%)	<0.001	4.4	2.3–8.6	<0.001
	Males	3115 (0.45%)	8 (2.0%)	<0.001	4.4	2.2–8.8	<0.001
	Females	813 (0.18%)	1 (0.52%)	0.25			
Asthma (No., %)	All	56,861 (5.0%)	37 (6.2%)	0.16			
	Males	37,750 (5.5%)	25 (6.1%)	0.58			
	Females	19,111 (4.1%)	12 (6.3%)	0.13			
Atopic dermatitis (No., %)	All	10,524 (0.9%)	11 (1.8%)	0.01	2.0	1.1–3.6	0.018
	Males	5520 (0.81%)	6 (1.5%)	0.13			
	Females	5004 (1.1%)	5 (2.6%)	0.026	2.5	1.0–6.0	0.039
Psoriatic skin disorders (No., %)	All	3654 (0.32%)	28 (0.47%)	0.51			
	Males	2095 (0.31%)	21 (0.51%)	0.46			
	Females	1538 (0.33%)	7 (0.38%)	0.90			

CD Crohn's disease, *CI* confidence interval, *OR* odds ratio

IBD was associated with increased risk for arthritis, autoimmune thyroid diseases, uveitis, and autoimmune hepatitis but not for celiac disease, type 1 diabetes, asthma, atopic dermatitis, and psoriasis. It was also associated with increased risk for primary sclerosing cholangitis (PSC), nephrolithiasis and pancreatitis and with decreased risk for migraines and long-bone fractures.

Association of CD with other comorbidities

Tables 1 and 2 present the univariate and multivariate analysis for the associations of immune- and non-immune-mediated comorbidities (respectively) with CD. Multivariate analysis showed that arthritis, thyroid diseases, autoimmune hepatitis, uveitis, and atopic dermatitis were significantly associated with CD. Asthma, type 1 diabetes, celiac disease, and psoriatic skin disorders were not associated with the diagnosis of CD. Positive correlation in multivariate analysis was observed in subjects with CD for urolithiasis, pancreatitis, and PSC.

Negative correlations in the multivariate analysis were observed for long-bone fractures and migraine. The prevalence of cholelithiasis, thromboembolism, and axial fractures did not differ between groups (data not shown).

Association of UC with other comorbidities

Tables 3 and 4 present the univariate and multivariate analysis for the associations of immune- and non-immune-mediated comorbidities (respectively) with UC. Positive correlations in the multivariate analysis were observed for arthritis, autoimmune thyroid disease, and autoimmune hepatitis. Celiac, type 1 diabetes, uveitis, atopic dermatitis, and psoriatic skin disorders were not associated with the diagnosis of UC. A marginal negative correlation was observed for asthma.

Positive correlations in the multivariate analysis were also observed for PSC, pancreatitis, and nephrolithiasis. Long-bone fractures and migraine were not more common in UC compared with controls. In UC as well, the prevalence of biliary stones, thromboembolism, and axial fractures did not differ between groups (data not shown).

Associations based on gender

After performing a sub-analysis based on gender, we noted that some of the significant associations described above remained statistically significant only among male patients (Tables 1–4).

This was valid for the positive associations with arthritis, thyroid diseases, autoimmune hepatitis, uveitis, urolithiasis, and PSC and also for the negative association with long-bone fractures. These associations were not significant for female patients with CD in the gender subgroup analysis.

The same applied for male patients with UC with autoimmune thyroid disease, PSC, and nephrolithiasis. These associations were not significant for female patients with UC in the gender subgroup analysis.

It is worth noting that there were no cases of PSC among female patients with IBD in our cohort.

We also analyzed the entire IBD cohort (CD and UC compiled together) against the control group to increase sample size and to re-assess whether the gender effect still exists. For all

Table 2. Non-immune-mediated medical conditions in Jewish adolescents with and without CD.

		Controls (1,141,841, 99.95%)	CD (595, 0.05%)	Univariate analysis (*P* value)	Multivariate analysis (OR)	95% CI	*P* value
Primary sclerosing cholangitis (No., %)	All	4 (0.0%)	2 (0.3%)	<0.001	963	176–5266	<0.001
	Males	1 (0.0%)	2 (0.5%)	<0.001	1214	110–13,402	<0.001
	Females	3 (0.0%)	0 (0.05%)	0.97			
Nephrolithiasis (No., %)	All	1572 (0.13%)	3 (0.5%)	0.027	3.6	1.2–11.4	0.016
	Males	1023 (0.15%)	3 (0.73%)	<0.001	4.9	1.6–15.4	0.002
	Females	549 (0.12%)	0 (0.0%)	0.63			
Migraine (No., %)	All	37,576 (3.3%)	8 (1.3%)	<0.001	0.4	0.2–0.8	0.008
	Males	20,946 (3.1%)	3 (0.73%)	<0.001	0.23	0.07–0.73	0.006
	Females	16,630 (3.6%)	5 (2.6%)	0.47			
Pancreatitis (No., %)	All	231 (0.02%)	5 (0.84%)	<0.001	42.0	17–101	<0.001
	Males	146 (0.02%)	3 (0.73%)	<0.001	35.0	11–109	<0.001
	Females	85 (0.02%)	2 (1.0%)	<0.001	58.0	14–237	<0.001
Long-bone fractures (No., %)	All	110,734 (9.7%)	31 (5.2%)	<0.001	0.51	0.35–0.73	<0.001
	Males	81,380 (11.9%)	24 (5.9%)	<0.001	0.46	0.3–0.7	<0.001
	Females	29,354 (6.4%)	7 (3.7%)	0.13			

CD Crohn's disease, *CI* confidence interval, *OR* odds ratio

disease-specific associations, there was no significant change in the gender effect except for a new positive association for arthritis in females (0.38% in controls vs 1.2% in IBD: OR 2.9, 95% CI 1.2–5.2, $P = 0.04$) and a new negative association for long-bone fractures (6.4% in controls vs. 3.1% in IBD: OR 0.65, 95% CI 0.4–0.9. $P = 0.03$).

DISCUSSION

Here, in this cross-sectional population-based study of a large cohort, looking at the prevalence of various medical conditions in adolescents diagnosed with IBD, we had the opportunity to assess the rate of immune-mediated conditions as well as other medical conditions from the analysis of the data collected from a large cohort of Israeli Jewish adolescents at a median age of 17.1 years. The magnitude of our cohort enabled us to explore differences in prevalence of both common and rare conditions even when only small number of patients are co-diagnosed.

Most large population-based studies of comorbidities in patients with IBD were performed in adult patients[12,14–16] with only limited evidence in children and adolescents,[2] which described associations of IBD with immune-mediated conditions only.

While it is generally agreed upon that IBD is associated with increased risk of immune-mediated disorders,[12,14–16] there is conflicting data on the association between IBD and specific autoimmune disorders. A recent Israeli study of immune-mediated disorders among adult patients with IBD[14] found increased prevalence of type 1 diabetes, psoriasis, Sjögren syndrome, celiac disease, systemic lupus erythematosus, and PSC compared with controls. Interestingly, the prevalence of autoimmune thyroiditis, which was significantly higher among patients with CD in our study, was not increased in this cohort.

The association between IBD and thyroid disorders was discussed in a recent review.[17] This review concluded that there are no obvious differences in the prevalence of thyroid dysfunction, Graves' disease, and thyroid cancer between patients with IBD and the general population. It did suggest that concomitant UC and autoimmune thyroiditis might be relatively common in particular patients with multiple immune-mediated disorders. Our findings (which are confined to adolescents with CD) are in agreement with the previous population-based North-American study,[2] which demonstrated similar OR in adolescents with IBD (OR 2.9).

The increased prevalence of arthritis among both patients with CD and UC in our study was expected, as joint manifestations are considered as the most common extra-intestinal manifestations in IBD.[18,19] Recent studies with similar findings further supported this notion.[12,20]

Surprisingly, celiac disease was not more common among our cohort of patients with IBD when compared with the control group. This contradicts other recent large population-based studies of patients with IBD, which found a rather strong association between celiac disease and IBD.[14,15] Recently, Shah et al.[21] showed that celiac disease is a risk factor for IBD but that adult patients with IBD have only modest increased risk of celiac disease. The notion, strengthened by our results, that the risk for IBD in children with celiac outweighs the opposite risk for celiac in patients with IBD is also supported by other recent studies.[6,22]

There is conflicting evidence regarding the association of IBD and type 1 diabetes. We were unable to find a significant association between the two conditions. A recent large Swiss study also failed to demonstrate such association.[12] However, other studies did find an increased prevalence of type 1 diabetes among adult patients with IBD,[14,15] including a positive association for adolescents with UC.[2] Further research is needed in order to clarify this matter.

Our results also support the findings reported by Kappelman et al.[2] that patients with IBD are not at increased risk for bronchial asthma or psoriasis. A recent meta-analysis demonstrated an association between asthma and both CD and UC (pooled relative risk of 1.3 for both); however, following age stratification, there was no association between asthma and either pediatric-onset CD or UC.[23]

In addition to immune-mediated disorders, we found that adolescent patients with IBD are more likely to suffer from a variety of non-immune-mediated disorders. The association of IBD with conditions such as urolithiasis[24–26] and pancreatitis[27,28] has been well documented and was an expected finding in this study.

Decreased bone density is another frequently associated comorbidity in patients with IBD.[29–31] Thus those patients, and especially those with CD, are thought to be at increased risk for fractures.[32,33] Intriguingly, adolescents with IBD in our cohort had lower risk of long-bone fractures. This surprising finding could be

Table 3. Immune-mediated comorbidities of Jewish adolescents with and without UC.

		Controls (1,141,841, 99.97%)	UC (296, 0.03%)	Univariate analysis (*P* value)	Multivariate analysis (OR)	95% CI	*P* value
Arthritis (No., %)	All	3709 (0.32%)	3 (1.0%)	0.015	3.1	1.0–9.8	0.037
	Males	1960 (0.29%)	1 (0.62%)	0.43			
	Females	1749 (0.38%)	2 (1.5%)	0.036	4.0	1.0–16	0.06
Autoimmune thyroid diseases (No., %)	All	5142 (0.45%)	3 (1.0%)	0.14			
	Males	1766 (0.26%)	2 (1.2%)	<0.0001	4.8	1.2–19.4	0.015
	Females	3376 (0.73%)	1 (0.76%)	0.98			
Celiac disease (No., %)	All	1514 (0.13%)	1 (0.33%)	0.33			
	Males	645 (0.09%)	1 (0.62%)	0.031	6.5	0.9–47	0.14
	Females	869 (0.19%)	0 (0.0%)	0.61			
Type 1 diabetes (No., %)	All	1900 (0.17%)	0 (0.0%)	0.48			
	Males	1169 (0.17%)	0 (0.0%)	0.60			
	Females	731 (0.16%)	0 (0.0%)	0.64			
Uveitis (No., %)	All	299 (0.03%)	0 (0.0%)	0.78			
	Males	168 (0.02%)	0 (0.0%)	0.84			
	Females	131 (0.03%)	0 (0.0%)	0.84			
Autoimmune hepatitis (No., %)	All	3928 (0.34%)	8 (2.7%)	<0.001	8.0	4.0–16.2	<0.001
	Males	3115 (0.45%)	6 (3.7%)	<0.001	8.4	3.7–18.9	<0.001
	Females	813 (0.18%)	2 (1.5%)	<0.001	8.6	2.1–34.7	<0.001
Asthma (No., %)	All	56,861 (5%)	7 (2.4%)	0.02	0.46	0.21–0.97	0.039
	Males	37,750 (5.5%)	4 (2.5%)	0.09			
	Females	19,111 (4.1%)	3 (2.3%)	0.27			
Atopic dermatitis (No., %)	All	10,524 (0.92%)	2 (0.67%)	0.66			
	Males	5520 (0.81%)	0 (0.0%)	0.25			
	Females	5004 (1.1%)	2 (1.3%)	0.65			
Psoriatic skin disorders (No., %)	All	3654 (0.32%)	8 (0.27%)	0.87			
	Males	2095 (0.31%)	5 (0.31%)	1.00			
	Females	1538 (0.33%)	3 (0.22%)	0.82			

CI confidence interval, *OR* odds ratio, *UC* ulcerative colitis

Table 4. Non-immune-mediated medical conditions in Jewish adolescents with and without UC.

		Controls (No, %)	UC (No, %)	Univariate analysis (*P* value)	Multivariate analysis (OR)	95% CI	*P* value
Primary sclerosing cholangitis (No., %)	All	4 (0.0%)	3 (1.0%)	<0.001	2923	651–13,116	<0.001
	Males	1 (0.0%)	3 (1.8%)	<0.001	4731	491–45,574	<0.001
	Females	3 (0.0%)	0 (0.0%)	0.97			
Nephrolithiasis (No., %)	All	1572 (0.14%)	2 (0.67%)	0.002	4.9	1.2–19.8	0.013
	Males	1023 (0.15%)	2 (1.2%)	<0.001	8.3	2.1–33.6	<0.001
	Females	549 (0.12%)	0 (0.0%)	0.69			
Migraine (No., %)	All	37,576 (3.3%)	0 (0.0%)	0.002	N/A		
	Males	20,946 (3.1%)	0 (0.0%)	0.02	N/A		
	Females	16,630 (3.6%)	0 (0.0%)	0.02	N/A		
Pancreatitis (No., %)	All	231 (0.02%)	3 (1.0%)	<0.001	50.6	16–159	<0.001
	Males	146 (0.02%)	2 (1.2%)	<0.001	58.3	14–237	<0.001
	Females	85 (0.02%)	1 (0.8%)	<0.001	40.7	5.6–295	<0.001
Long-bone fractures (No., %)	All	110,734 (9.7%)	21 (7.1%)	0.13			
	Males	81,380 (11.9%)	18 (11.1%)	0.74			
	Females	29,354 (6.4%)	3 (2.3%)	0.05	0.3	0.1–1.1	0.06

CI confidence interval, *N/A* not available (0 patients prevent OR analysis), *OR* odds ratio, *UC* ulcerative colitis

attributed to decreased levels of physical activity among patients with IBD compared to healthy adolescents as was recently reported by Greenley et al.[34]

We could not confirm an association between migraines and IBD, which was described previously for adults with IBD.[35,36]

Interestingly, male patients with IBD in our cohort were more likely to be at risk for certain comorbidities than female patients. This applies for arthritis, autoimmune thyroid disease, nephrolithiasis, and PSC for both patients with UC and CD. These findings could be partially attributed to the smaller sample size of females in our cohort. Remarkably, no cases of PSC were noted among female patients in our cohort. These findings are in line with recent Swiss study which reported that PSC was significantly more common in adult males with IBD.[37]

The increased prevalence of comorbid conditions among adolescents with IBD has important implications. The presence of comorbidities among patients with IBD was shown to be associated with an increased risk of postoperative mortality and an increased length of hospital stay.[38] They are also associated with higher healthcare costs, especially in the outpatient settings.[12] In addition, comorbid conditions have a negative impact on health-related quality of life of patients with IBD.[5]

Our study has several limitations. First, it does not represent the entire Israeli population, as only Jewish adolescents are obliged by law to attend army recruitment centers. Thus we were unable to describe IBD-related comorbidities among non-Jewish (mainly Arab) adolescents, which account for about 20% of the Israeli population. Second, some of the described associations are confounded by small number of subjects diagnosed with specific medical conditions (type 2 error). Third, our results might be limited by selection bias as not all subjects with IBD are recruited, thus only those who volunteered for duty had complete medical documentation. Another selection bias may derive from the fact that patients with IBD are more tightly monitored, thus other medical conditions are more likely to be found. Moreover, medical history provided by the subject's physicians does not guarantee standardized diagnoses for the entire cohort and this could represent a detection bias. Nevertheless, this study enabled us to capture one of the largest cohorts of adolescents with IBD, with the virtue of a cross-sectional analysis of various comorbidities (not restricted to immune-mediated ones) at the age of 17 years.

In conclusion, we found that, already at adolescence, IBD is associated with both immune- and non-immune-mediated comorbidities. Contrary to previous studies, male patients in our study were more likely to have comorbid medical conditions than female patients, a finding which requires further investigation.

ACKNOWLEDGEMENTS

Statistical analysis was performed by Dr. Ron Kedem (PhD), Statistician, Medical Corps, Israel Defense Force, Israel.

AUTHOR CONTRIBUTIONS

I.G. acquired and analyzed the data and drafted the manuscript. L.H.K., S.D., and R.S. have participated in study design and critically reviewed the manuscript. A.A. was responsible for study conceptualization and design, participated in data analysis, and critically reviewed the manuscript. All authors approve the final version of the manuscript.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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