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SYSTEMATIC REVIEW

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Sex-related differences in profiles and clinical outcomes of Inflammatory bowel disease: a systematic review and meta-analysis

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Abstract

Background Inflammatory bowel disease (IBD) is a chronic and idiopathic condition that includes both Crohn's disease (CD) and ulcerative colitis (UC). The impact of sex on the disease course and the clinical outcomes not fully understood. Our systematic review and meta-analysis aims to explore the differences in the clinical outcomes in IBD.

Method A systematic review and meta-analysis was done by searching in the PubMed /MEDLINE, Embase, and Scopus databases. We used the Random-Effects model to estimate risk ratios (RR) for binary outcomes and mean difference and hedges' g for continuous outcomes.

Result A total of 44 unique studies were included. Our analysis revealed distinct sex differences in various outcomes of IBD. Anxiety was more prevalent in females (RR: 0.73; 95% CI [0.64, 0.82]) and females in the CD subgroup (RR: 0.76; 95% CI [0.62, 0.93]; $p=0.01$. While depression was diagnosed more frequently in females (RR: 0.80; 95% CI [0.66, 0.97] in the total population of the study, subgroup analysis showed no sex difference. Additionally, quality of life scores were worse in females in the total population (Hedges' g: 0.24; 95% CI [0.05, 0.42]) with no significant difference in subgroup analyses. A significantly higher mortality risk was estimated in males (RR: 1.26; 95% CI [1.07, 1.48]) and in subgroup analysis for males with UC (RR: 1.48; 95% CI [1.19, 1.84]; $p=0.00$) with no significant difference in CD. Regarding disease location, male patients were less likely to present with proctitis (RR: 0.67; 95% CI [0.50, 0.91]) when compared to females. Males had more frequent indications for surgery (RR: 1.10; 95% CI [1.01, 1.20]), however, no significant difference was found in subgroup analyses for CD or UC. Also, males were older at the time of admission (MD: 1.39 years; 95% CI [0.10, 2.68]). No significant sex differences were found in terms of hospitalization rates or disease behavior.

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Conclusion In conclusion, our meta-analysis shows that males face higher risks of early mortality and require more IBD surgeries, whereas females experience greater levels of anxiety and depression. These findings emphasize the need to consider sex disparities in IBD management.

Keywords Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Sex differences, Male, Female

Introduction

Inflammatory bowel disease (IBD) represents a category of conditions causing chronic inflammation of the colon and small intestine. There are two types of IBD which are Crohn's disease (CD) and ulcerative colitis (UC). Overall, IBD carries serious morbidity including requirements for different medical therapies, surgeries and a slight increase in the risk of mortality [1].

Gender preponderance seems to be determined by the specific subtype of the disease. CD has a higher prevalence in females with female-to-male ratios as high as 4:1 [2]. Conversely, there is consistent evidence that males have higher prevalence of UC than females [3]. Nevertheless, gender appears to play a significant role in various aspects of the disease, including IBD onset, progression and phenotype [4, 5]. For example, males are more likely to develop CD earlier in life but seem to present with UC later than females generally do, and have a lower risk of experiencing extraintestinal manifestations of IBD than females [4, 6]. Moreover, hormonal therapies such as oral contraceptives may influence disease progression, although the reasons for this association remain unclear [7].

Given the conflicting evidence on the sex differences in IBD and the potential implications of gender on the evaluation, diagnosis and management of IBD, this systematic review and meta-analysis aim to comprehensively examine and consolidate the existing body of literature on sex-specific differences in clinical outcomes of IBD. By synthesizing data from multiple studies, we aim to provide a quantitative and evidence-based assessment of these disparities across various dimensions of IBD, including: total deaths, surgery for IBD, quality of life, depression, anxiety, hospitalization rate and others.

Methods

Search strategy

In September 2023, PubMed, SCOPUS, and Embase were all searched systematically for observational studies (cohort and cross-sectional studies). We investigated the association between the sex differences and the primary and secondary outcomes of Inflammatory Bowel Disease (IBD). We followed the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) statement and recommended guidelines to guide this research [8]. The search blocks that we used were as follows: ["inflammatory bowel disease" OR "crohn*" OR "ulcerative colitis" OR "indeterminate colitis"] AND ["gender" OR "sex"], with no filters applied. Regarding duplicates, they were removed by Zotero. Moreover, Rayyan was used in the screening stage. More about the screening stage will be discussed in the selection process and eligibility criteria. We registered the protocol of this study in the international prospective register of systematic reviews (PROSPERO), the PROSPERO registration number is CRD42024530875.

Selection process: eligibility criteria

Screening and selections were performed independently in a blinded fashion by two authors, with a third author being introduced later to resolve any conflicts. The screening was conducted using the systematic review screening tool, Rayyan.

The inclusion criteria encompassed the following: observational type of studies (cohort and cross-sectional studies), RCTs and case control (sex related analysis), written in English, with at least 10 human patients (adults only). Moreover, studies compared the differences based on sex or gender and reported either one or all of the following outcomes: Surgery for IBD, total death, anxiety, depression, quality of life, hospitalization rates and medication usage (total biologics, infliximab, adalimumab and steroid) for at least 80% of the study participants.

Concerning the exclusion criteria, they were as follows: non-English studies, systemic reviews, meta-analyses, narrative reviews, case reports/ series, editorials, study protocols, commentaries, letters, abstracts and studies that reported the outcome for only one gender without the other were excluded.

Data extraction

Data extraction was performed independently by all the authors. Data was extracted using Google sheets. Any disagreements that occurred during this process were resolved collaboratively among the authors to ensure high accuracy and maintain consistency.

For categorical data, we extracted the event and total for each group, whereas continuous data was recorded as the mean and standard deviation.

Data was extracted from all selected studies, including authors, publication year, study period, data source, study design, IBD type (CD or UC or others), and number of patients with IBD in gender subgroups. In addition to prioritizing essential demographic characteristics, we included sex, age, age at diagnosis, disease duration, disease behavior (inflammatory, stricturing, penetrating, perianal, and fistula), disease location for CD (Ileal, colonic, Ileocolonic and upper GI), disease location for UC (proctitis, distal colitis, and extensive colitis), disease activity (Remission; mild, moderate and severe), disease symptoms (diarrhea, hematochezia, and abdominal pain), extraintestinal manifestations, family history of IBD, comorbidities (Hypertension or Diabetes mellitus), working, smoking and BMI.

Outcomes were categorized into primary outcomes such as surgery for IBD, total deaths, depression, anxiety, and quality of life.

Secondary outcomes such as hospitalization, steroid use, total biologic use, infliximab use, and adalimumab use.

Study definitions

The study investigated Inflammatory Bowel Disease (IBD) and its outcomes as defined by the American Gastroenterological Association.

The primary endpoints were rigorously defined as follows: surgery for IBD, which referred to any surgery indicated for the resection of an IBD-related diseased part of the intestine (as colectomy, intestinal resection, ileostomy, pouch surgery, etc.), total death related to the IBD which referred to all causes of death (cancer, infection, suicide, any system disease, etc.), depression which was assumed if a patient had a specific score or more in a specific related scale (as HADS-D-D$\geq$11, SDS$\geq$45, PHQ-9$\geq$10), anxiety which was assumed if a patient had a specific score or more in a specific scale (as SAS$\geq$45, GAD-7$\geq$10, HADS-D-A$\geq$11) and quality of life which is defined as mean and standard deviation of various scales (as IBDQ-32 score, SIBDQ score, physical component of SF36, HRLS, WHOQoL).

Secondary endpoint outcomes included hospitalization, steroid use, total biologic use, infliximab use and adalimumab use.

Statistical analysis

In the context of dichotomous data outcomes, the amalgamation of event frequencies and total patient counts in both male and female groups was computed as risk ratios (RR) utilizing the restricted maximum likelihood (REML) model.

For continuous data outcomes, we computed mean differences (MD), Hedges' G and their associated 95% confidence intervals (CI) utilizing the restricted maximum likelihood (REML) model. If the only available data was reported in median, IQR or ranges we employed the method by wan and colleagues [9], to estimate the mean and SD of the outcome of interest. All statistical analyses were performed using Stata MP Version 18 for Windows, developed by StataCorp.

In order to evaluate the presence of statistical heterogeneity among the studies, we applied the chi-square test (Cochran's Q test). Furthermore, we computed the I^2 value, which indicates the proportion of total variation across studies attributable to heterogeneity rather than random variance. Significant heterogeneity among the studies was determined by either a chi-square test result with a p-value less than 0.1 or an I^2 value equal to or exceeding 60%.

To address potential sources of heterogeneity and validate the robustness of our findings, we conducted a sensitivity analysis employing the leave-one-out model for our primary outcomes. This approach involved systematically excluding one study in each iteration to ensure that the overall effect size was not unduly influenced by any single study.

Results

Summary of studies

From the literature search, a total of 1018 studies were identified. After the elimination of duplicates, we screened the titles and abstracts of 570 studies, and only 73 were selected for full-text screening according to our eligibility criteria. The final included studies in this systematic review and meta-analysis were 44: 35 cohorts, eight cross-sectional studies, and one mixed-methods study. The selection process of the study is demonstrated in (Fig. 1). The included studies comprise a total of 15,609 Crohn's disease (46.38% males vs. 53.62% females) and 13,506 ulcerative colitis (54.01% males vs. 46% females) patients. A summary of the characteristics of all the included studies is shown in Table 1.

Demographic characteristics and disease features

The analysis disclosed that compared to females, males had a higher mean age (Mean Difference (MD)=1.39 years; 95% CI [0.10, 2.68]; p=0.04) (Supplementary Fig. 1), higher working rates (RR: 1.12; 95% CI [1.05, 1.20]; p<0.01) (58.8% males vs. 51.2% females) (Supplementary Fig. 2), But there were no significant differences between male and female in mean of disease duration (MD= -0.10; 95% CI [-0.69, 0.48]; p=0.73) (Supplementary Fig. 3) and mean of BMI (MD=0.77; 95% CI [-0.92, 2.46]; p=0.37) (Supplementary Fig. 4).

In terms of disease location in UC, males were less likely to present with procitis with an incidence of 17.15% (RR: 0.67; 95% CI [0.50, 0.91]; p=0.01) (Supplementary Fig. 5) and more likely to present with extensive colitis (RR: 1.15; 95% CI [1.01, 1.31]; p=0.03) (Supplementary Fig. 6). Both genders were similar in the presentation with distal colitis (RR: 1.04; 95% CI [0.89, 1.22]; p=0.61) (Supplementary Fig. 7). Moreover, there were no apparent sex differences in disease location in CD: ileal (RR: 1.05; 95% CI [0.92, 1.18]; p=0.49) (Supplementary Fig. 8), colonic

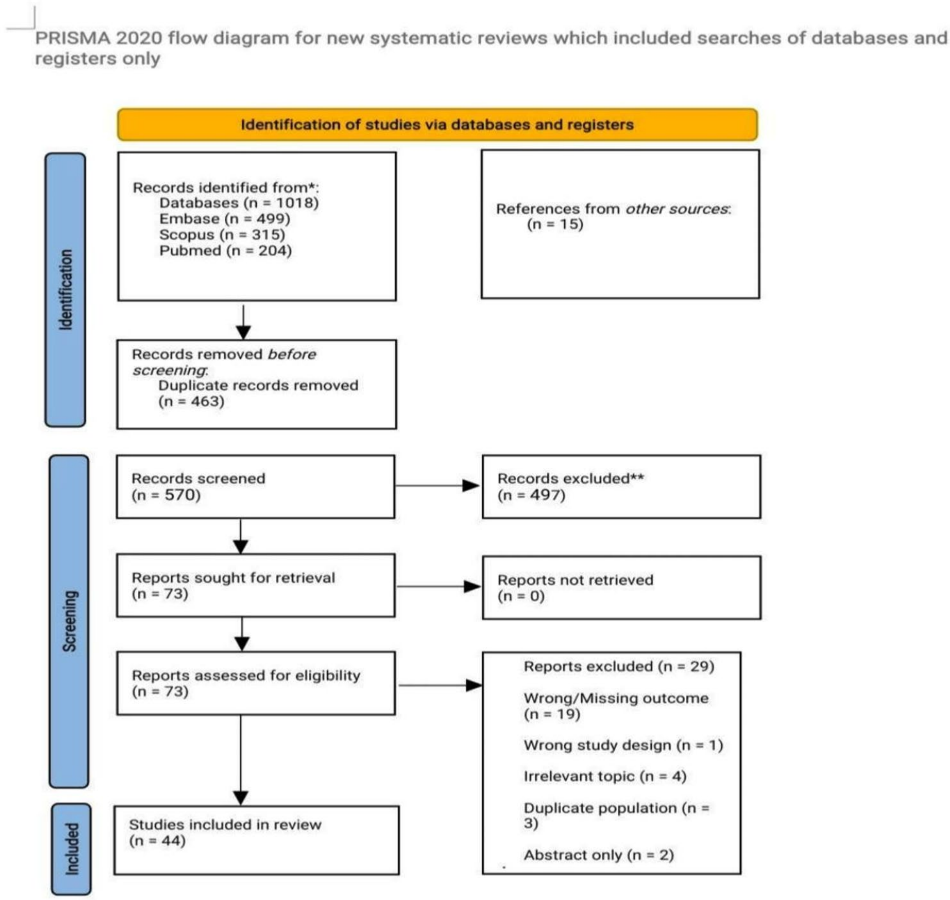

Fig. 1 PRISMA flow chart demonstrates the selection of studies processes

(RR: 0.97; 95% CI [0.88, 1.07]; $p=0.54$) (Supplementary Fig. 9); Ileocolic (RR: 0.96; 95% CI [0.90, 1.03]; $p=0.31$) (Supplementary Fig. 10), upper Gi (RR: 1.19; 95% CI [0.89, 1.59]; $p=0.24$) (Supplementary Fig. 11).

For disease behaviors in CD, the results indicated no significant differences between the two groups in terms of inflammatory (RR: 0.94; 95% CI [0.88, 1.00]; $p=0.06$), stricturing (RR: 0.98; 95% CI [0.87, 1.10]; $p=0.68$), penetrating (RR: 1.10; 95% CI [0.97, 1.24]; $p=0.12$), perianal disease (RR: 1.04; 95% CI [0.92, 1.18]; $p=0.49$), and fistula (RR: 1.05; 95% CI [0.74, 1.49]; $p=0.8$).

Overall, the working rate was significantly higher in males (RR: 1.12; 95% CI [1.05, 1.20]; $p<0.01$). The subgroup analysis showed the same result in CD whereas no differences were observed between the two groups in UC. Regarding disease duration, the results indicated that both genders had similar durations in both CD and UC. Generally, males were found to be older (MD=1.39 years; 95% CI [0.10, 2.68]; $p=0.04$). Similar results were observed for UC patients, but there were no significant differences in mean age between males and females in CD. 'Table 2' shows a detailed summary of the meta-analysis of the baseline demographic characteristics and disease features.

Primary endpoint outcomes

The total deaths related to IBD were significantly higher in male patients (RR: 1.26; 95% CI [1.07, 1.48]; $p=0.01$). Subgroup analysis revealed no significant difference between male and female patients diagnosed with CD, while in patients diagnosed with UC, a significant difference with male predominance was observed (RR: 1.48; 95% CI [1.19, 1.84]; $p=0.00$). Refer to (Supplementary Fig. 12) for the forest plot and subgroup analysis on total deaths related to IBD.

Subgroup analysis based on geographic location demonstrated that males have higher mortality rates in Europe (RR: 1.42; 95% CI [1.22, 1.65]; $p<0.001$). In contrast, no sex differences are found in Asia, Australia and North America. See Fig. 2 for more details.

Regarding surgery related to IBD, male patients showed a greater prevalence (9.17%) compared to female patients (7.94%) (RR: 1.10; 95% CI [1.01, 1.20]; $p=0.03$). However, subgroup analysis didn't report any significant difference

Table 1 Summary of characteristics of all included studies

. No	Study ID	Location	Study center	Study duration (year-year)	Study design	Number of patients		Follow-Up length	
						Male	Female	Male	Female
1	**Hauser 2011** [41]	Croatia	Rijeka Hospital	2007–2009	Cohort Study	62	50	-	-
2	**Sceats 2019** [34]	USA (California)	The Stanford Center for Population Health Sciences Data Core	2007–2015.	Retrospective cohort analysis	18,489	20,362	3.31	**S**3.28
3	**Davoli 1996** [62]	italy	Inflammatory Bowel Disease Clinics in Rome	1970–1989	Retrospective Cohort Study	287	206	Median (range) : 5 (2–19)	Median (range) : 5 (0–20)
4	**Weterman 1990** [63]	Netherlands	Leiden University Hospital	1934–1984	retrospective cohort study	307	351	-	-
5	**Farrokhyar 2001** [64]	England	Multiple Hospitals	1978–1986	prospective cohort study	279	273	-	-
6	**Bel 2015** [65]	Netherlands	Gastroenterology departments of a tertiary referral center (Leiden University Medical Center) and a general hospital (Diaconessenhuis Leiden)	2011–2015	cross-sectional	119	168	-	-
7	**Marı´n 2012** [66]	Spain, Germany	Hospital Universitari Germans Trias i Pujol and Hospital de la Santa Creu i Sant Pau	-	cross-sectional	153	202	Mean + SD = 13.1 ± 8 years, the same for 2 gender	
8	**Manninen 2011** [67]	Finland	Tampere University Hospital	1986–2007	Cohort Study	1009	906	Median (13.5 years)	
9	**Cosnes 1996** [68]	Paris, France	Service d'He´patogastroente´rologie et Nutrition, Ho^pital Rothschild	1995	retrospective cohort study	155	245	-	-
10	**Lin 2019** [69]	Taiwanese nationwide	Taiwan's National Health Insurance. And Health and Welfare Data Science Center, Ministry of Health and Welfare (HWDC, MOHW)	2001–2015	retrospective study	2418	1388	-	-
11	**Laganà 2019** [60]	Italy	4 Rheumatology Units and 3 Gastroenterology Units	-	retrospective study	194	155	-	-
12	**Janke 2005** [70]	Germany	3 tertiary care centers for evaluatn and/or therapy and members of the German's Crohn's Disease/Ulcerative colitis foundation	1997–2001	cross sectional study	214	215	-	-
13	**Liu 2022** [59]	China	Peking Union Medical College Hospital	2000–2020	Retrospective Cohort Study	420	191	-	-
14	**LAW 2014** [58]	China	Tuen Mun Hospital	2000–2012	retrospective cohort study	55	24	median = 5 year (IQR, 6 years)	median = 9 years (IQR 9.75 years)
15	**Lie 2017** [50]	Rotterdam, the Netherlands	Erasmus University Medical Center	2006–2011	Prospective clinical cohort	81	107	up to 2015	
16	**Sarid 2017** [49]	Israel	Out-Patient Gastroenterology Departments of five participating university-affiliated hospitals	2013–2015	Cross- sectional	158	244	-	-
17	**Andreassen 1999** [71]	Denmark	gastrointestinal outpatient clinic of Køge Hospital	-	Case-Control Cross-Sectional Study	45	68	-	-

Table 1 (continued)

. No	Study ID	Location	Study center	Study duration (year-year)	Study design	Number of patients		Follow-Up length	
						Male	Female	Male	Female
18	**García-Alanís 2020** [72]	Mexico	National Institute of Medical Science and Nutrition	-	cross-sectional analytic study	54	50	-	-
19	**Osamura 2017** [73]	Japan	Sakura Medical Center and Toho University	-	retrospectoive analyzed study	165	54	-	-
20	**Wagtmans 2001** [38]	Netherlands	The Leiden University Medical Center	-	Retrospective Cohort Study	266	275	-	-
21	**The Dutch study** [31]	Netherlands	The Parelsnoer Institute	2007–2018	Prospective Cohort Study	773	1,345	-	-
22	**The Coin study** [31]	Netherlands	Multiple hospitals and centers	2010–2018	Prospective Cohort Study	1,069	1,283	3 months	
23	**Zelinkova 2012** [61]	Netherlands	Erasmus MC	-	Cohort Study	386	457	-	-
24	**Goel 2013** [74]	Indian	Christian Medical college	1995–2008	retrospective analysis	129	94	213 patients follow up at least 6 monthes	
25	**Wong 2018** [75]	USA	Stanford University School of Medicine (fromnational administrative claims database)	2007–2015	retrospective cohort study	152,168	179,604	-	-
26	**Heath 2021** [32]	Canada	Western University Personalized Medicine Clinic	2012–2019	retrospective cohort study	456	559	up to 2019	
27	**Matos 2021** [76]	Portugal	Portuguese Association of Inflammatory Bowel Disease (APDI)	2021	Cohort study	20	48	-	-
28	**Pittet 2017** [39]	Switzerland	Swiss IBD Cohort (SIBDC).	-	Mixed-methods study	504	598	-	-
29	**Cioffi 2020** [48]	Italy	Federico II University Hospital,	2016–2018	cross-sectional study	79	56	-	-
30	**Selinger 2013** [77]	Australia	Multiple Hospitals	1977–1992	Cohort Study	384	432	22.7 (median)	22.2 (median)
31	**Karczewski 2015** [78]	Poland	Poznan University of Medical Sciences	-	cohort study	23	32	-	-
32	**Khalili 2020** [79]	Sweden	Swedish Patient Register	2014	cohort study	15,347	14,532	-	
33	**Blumenstein 2010** [57]	Germany	Ten gastroenterological private practices and three hospitals (one university hospital and two municipal hospitals with main focus on IBD) in the Rhein-Main region	2005–2007	Prospective Cohort Study	449	537	-	-
34	**König 2020** [80]	Austria	General Hospital of Vienna	-	prospective, non-interventional trial	52	46	-	-
35	**Liu 2023** [40]	China	42 hospitals	2021–2022	Cross-sectional	1547	931	-	-
36	**Eder 2017** [81]	Poland	gas-troenterology units from both university and non-university hospitals:	2014–2015	prospec-tive, multicenter, observational cohort study	143	113	-	-

Table 1 (continued)

. No	Study ID	Location	Study center	Study duration (year-year)	Study design	Number of patients		Follow-Up length	
						Male	Female	Male	Female
37	**Magro 2018** [30]	Portugal	Portuguese database of inflammatory bowel disease patients.	2015–2016	multicenter cohort study	540	670	median = 12 years, [IQR]: 7–19	
38	**Schulthe-iss 2019** [82]	Netherlands	University Medical Centre Utrech	2011–2017	retrospective study	264	265	minimum follow-up of 12 months	
39	**Aniwan 2018** [83]	Minnesota, USA	Mayo medical center, Olm-sted medical center	1970–2016	retrospective cohort study	479	416	Median follow up for years for CD: 18, for UC: 19	
40	**Lee 2017** [84]	Korea	Asan IBD Center	1989–2013	hospital-based cohort study	3247	1,965	mean follow-up dura-tion was 9 years	
41	**Saha 2015** [85]	USA	Ocean State Crohn's and Colitis Area Registry (OSCCAR)	-	cohort Study	105	169	Minimum 2 years follow up	
42	**Romberg-Camps 2009** [86]	Netherlands	the University Hospital Maastricht and the General District Hospitals of Heerlen and Sittard	1991–2002	cohort Study	580	607	-	-
43	**Prior 1981** [87]	England	University of Birmingham	-	prospective study	243	270	-	-
44	**Jess 2002** [88]	Denmark	Copenhagen County	1962–1997	Cohort Study	157	217	5 years follow up	

between female and male. See (Supplementary Fig. 13) for details.

Subgroup analysis based on geographic location showed that males have higher surgery rates in Asia (RR: 1.30; 95% CI [1.02, 1.66]; $p=0.032$) and North America (RR: 1.43; 95% CI [1.24, 1.64]; $p<0.001$) compared to females but there's no significant difference between males and females in Europe and south America. See Fig. 3.

Analysis of the quality of life indicated a significant difference between groups, with males having a better QoL (Hedges' g: 0.24; 95% CI [0.05, 0.42]; $p=0.01$). Subgroup analysis of CD and UC demonstrated no significant difference. These data are illustrated in (Supplementary Fig. 14).

Subgroup analysis based on geographic location showed that females have a worse quality of life compared to males in North America (hedges' g: 0.37; 95% CI [0.12, 0.61]; $p=0.003$) and South America (hedges' g: 0.37; 95% CI [-0.02, 0.75]; $p=0.061$). However, no sex disparities were found in Asia and Europe. See Fig. 4 for more details.

Depression was reported to be more prevalent in female patients compared to male patients (RR: 0.80; 95% CI [0.66, 0.97]; $p=0.02$). Subgroup analysis indicated no significant difference between female and male groups in both CD and UC subgroups. Refer to (Supplementary Fig. 15) for details.

Subgroup analysis based on geographic location revealed that females exhibit higher levels of depression in Asia (RR: 0.85; 95% CI [0.75, 0.96]; $p=0.010$) and North America (RR: 0.57; 95% CI [0.56, 0.58]; $p<0.001$). While no sex differences were observed in Europe. See Fig. 5.

The analysis of anxiety revealed a significant female predominance (RR: 0.73; 95% CI [0.64, 0.82]; $p=0.00$). Subgroup analysis in CD reported a higher prevalence of anxiety in females (RR: 0.76; 95% CI [0.62, 0.93]; $p=0.01$). However, no significant difference was reported in UC. Please see (Supplementary Fig. 16) for further details. Table 2 demonstrates a summary of the meta-analysis of the primary outcomes.

Figure 6 shows the distribution of countries represented in our study.

Secondary endpoint outcomes

Overall, differences in the use of biologics between the two sexes were marginal. Males were slightly more inclined to use biologics in total (RR: 1.10; 95% CI [1.00, 1.20]; $p=0.04$), with 12.7% for males vs. 11.4% for females) (Supplementary Fig. 17). Conversely, adalimumab prescription was more frequent for female patients (RR: 0.89; 95% CI [0.80, 0.99]; $p=0.03$) (11.7% males vs. 13.2% females) (Supplementary Fig. 18). Analysis showed that there were no significant disparities between the two sex in steroids usage (RR: 1.04; 95% CI [0.97, 1.12]; $p=0.24$) (Supplementary Fig. 19) infliximab usage (RR: 1.06; 95% CI [0.97, 1.17]; $p=0.2$) (Supplementary Fig. 20) or hospitalization rates (RR: 0.97; 95% CI [0.80, 1.19]; $p=0.8$) (Supplementary Fig. 21).

Table 2 Show the results of meta analysis of outcomes and demographic characteristics and disease features

Primary outcomes (Ref. Female)	**Overall**		**CD Subgroup**		**UC subgroup**	
	Effect size [95% CI]	**Sig.**	**Effect size [95% CI]**	**Sig.**	**Effect size [95% CI]**	**Sig.**
Total Death	RR: 1.26 [1.07, 1.48]	*p* = 0.01*	RR: 1.10 [0.88, 1.37]	*p* = 0.40	RR: 1.48 [1.19, 1.84]	p = **0.00***
Indication for Surgery	RR: 1.10 [1.01, 1.20]	*p* = 0.03*	RR: 1.08 [0.98, 1.19]	*p* = 0.13	RR: 1.15 [0.93, 1.43]	*p* = 0.19
Quality of life	H.g: 0.24 [0.05, 0.42]	*p* = 0.01*	H.g. 0.12 [-0.21, 0.44]	*p* = 0.48	H.g. -0.09 [-0.46, 0.28]	*p* = 0.64
Depression	RR: 0.80 [0.66, 0.97]	*p* = 0.02*	RR: 0.90 [0.73, 1.10]	*p* = 0.30	RR: 1.29 [0.42, 3.96]	*p* = 0.65
Anxiety	RR: 0.73 [0.64, 0.82]	*p* < 0.01*	RR: 0.76 [0.62, 0.93]	p = **0.01***	RR: 1.40 [0.35, 5.57]	*p* = 0.64
Secondary outcomes						
Indication for steroids	RR: 1.04 [0.97, 1.12]	*p* = 0.24	RR: 1.01 [0.95, 1.07]	*p* = 0.84	RR: 1.09 [0.95, 1.25]	*p* = 0.19
Indication for biologics	RR: 1.10 [1.00, 1.20]	*p* = 0.04*	RR: 1.01 [0.93, 1.09]	*p* = 0.86	RR: 1.12 [0.91, 1.39]	*p* = 0.29
Indication for Adalimumab	RR: 0.89 [0.80, 0.99]	*p* = 0.03*	RR: 0.96 [0.83, 1.12]	*p* = 0.63	RR: 1.07 [0.66, 1.74]	*p* = 0.78
Indication for Infliximab	RR: 1.06 [0.97, 1.17]	*p* = 0.2	RR: 1.09 [0.95, 1.25]	*p* = 0.22	RR: 0.99 [0.82, 1.21]	*p* = 0.96
Indication for Hospitalization	RR: 0.97 [0.80, 1.19]	*p* = 0.8	RR: 1.04 [0.83, 1.29]	*p* = 0.75	RR: 0.72 [0.58, 0.89]	*p* = 0.00*
demographic characteristics and disease features						
Age	MD: 1.39 [0.10, 2.68]	*p* = 0.04*	MD: 0.02 [-1.94, 1.97]	*p* = 0.99	MD: 3.17 [1.03, 5.30]	*p* = 0.00*
BMI	MD: 0.77 [-0.92, 2.46]	*p* = 0.37	MD: 0.44 [-1.62, 2.50]	*p* = 0.67		
Working	RR: 1.12 [1.05, 1.20]	*p* < 0.01*	RR: 1.17 [1.08, 1.28]	*p* = 0.00*	RR: 1.04 [0.93, 1.15]	*p* = 0.48
Disease duration	MD: -0.10 [-0.69, 0.48]	*p* = 0.73	MD: 0.30 [-0.53, 1.14]	*p* = 0.48	MD: -0.71 [-2.00, 0.58]	*p* = 0.28
Procitis extent (UC)	RR: 0.67 [0.50, 0.91]	*p* = 0.01*				
Distal colitis extent (UC)	RR: 1.04 [0.89, 1.22]	*p* = 0.61				
Extensive colitis extent (UC)	RR: 1.15 [1.01, 1.31]	*p* = 0.03*				
Ileal location (CD)	RR: 1.05 [0.92, 1.18]	*p* = 0.49				
Colonic location (CD)	RR: 0.97 [0.88, 1.07]	*p* = 0.54				
Ileocolic location (CD)	RR: 0.96 [0.90, 1.03]	*p* = 0.31				
Upper Gi location (CD)	RR: 1.19 [0.89, 1.59]	*p* = 0.24				
Inflammatory behavior (CD)	RR: 0.94 [0.88, 1.00]	*p* = 0.06				
Stricturing behavior (CD)	RR: 0.98 [0.87, 1.10]	*p* = 0.68				
Penetrating behavior (CD)	RR: 1.10 [0.97, 1.24]	*p* = 0.12				
Perianal disease (CD)	RR: 1.04 [0.92, 1.18]	*p* = 0.49	RR: 1.10 [1.00, 1.22]	*p* = 0.05		
Fistula	RR: 1.05 [0.74, 1.49]	*p* = 0.80	RR: 1.05 [0.72, 1.51]	*p* = 0.81	RR: 1.12 [0.20, 6.47]	*p* = 0.90

IBD: Inflammatory bowel disease; CD: Crohn's disease; UC: Ulcerative colitis; RR: Relative Risk; CI: Confidence Interval; H.g: Hedges's g; MD: Mean Difference; p: p-value (significance level)

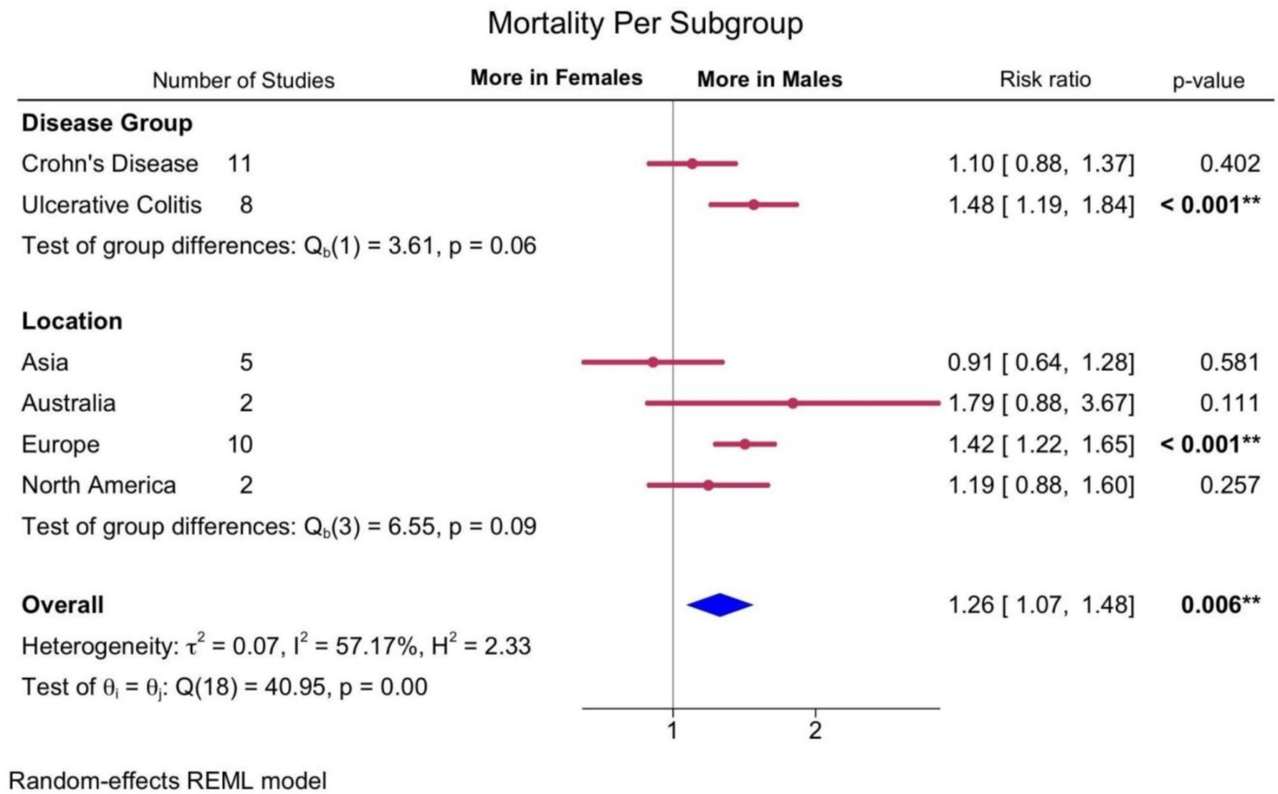

Fig. 2 Forest plot of random effect model meta-analysis of risk ratio for total death between males and females according to disease group and continent

Overall, males were more likely to use biologics (RR: 1.10; 95% CI [1.00, 1.20]; $p=0.04$) and less likely to use adalimumab (RR: 0.89; 95% CI [0.80, 0.99]; $p=0.03$). for both drugs, no significant disparities between sexes were found in CD and UC, Other drugs (steroids and infliximab) had the same indication rates for males and females in UC and CD. In terms of hospitalization rates, both genders showed similar overall rates (RR: 0.97; 95% CI [0.80, 1.19]; $p=0.8$), but males had lower rates compared to females in UC, with no significant differences in CD. All results are demonstrated in Table 2.

Publication bias for studies assessing primary outcomes

For studies focusing on indication for surgery, a minor asymmetry was observed in the funnel plot, but the Egger's regression test didn't provide significant evidence of publication bias (Z=0.20; $p=0.83$) (Supplementary Fig. 22).

Similarly, when evaluating studies focusing on quality of life, the funnel plot revealed a slight asymmetry. However, the Egger's regression test found no significant evidence of asymmetry, with a p-value of 0.91 (Supplementary Fig. 23).

A slight asymmetry was observed in the funnel plot of the studies focusing on total deaths, but the Egger's regression test showed no significant evidence of asymmetry, with a p-value of 0.28 (Supplementary Fig. 24).

In contrast, the funnel plot for studies on depression exhibited subjective asymmetry. Nevertheless, the Egger's regression test didn't support the observed asymmetry, showing a non-significant p-value of 0.47 (Supplementary Fig. 25).

Discussion

In our study, we aimed to highlight the primary outcomes that differ between male and female groups, such as total death rates, surgery rates, quality of life, depression, and anxiety. Secondary outcomes included hospitalization rates, biologic medication usage, adalimumab and infliximab use, and steroid use. The analysis revealed that males exhibited significantly higher rates of death and surgery related to IBD, as well as a better quality of life. On the other hand, females were more likely to experience anxiety and depression. Analysis of quality of life also showed significant differences, with males reporting better outcomes. Overall, males were more likely to use biologics, while adalimumab usage was more common among females. Hospitalization rates were similar between the two groups, but females in the UC subgroup had higher rates of hospitalization. Significant demographic differences were apparent in this study, with

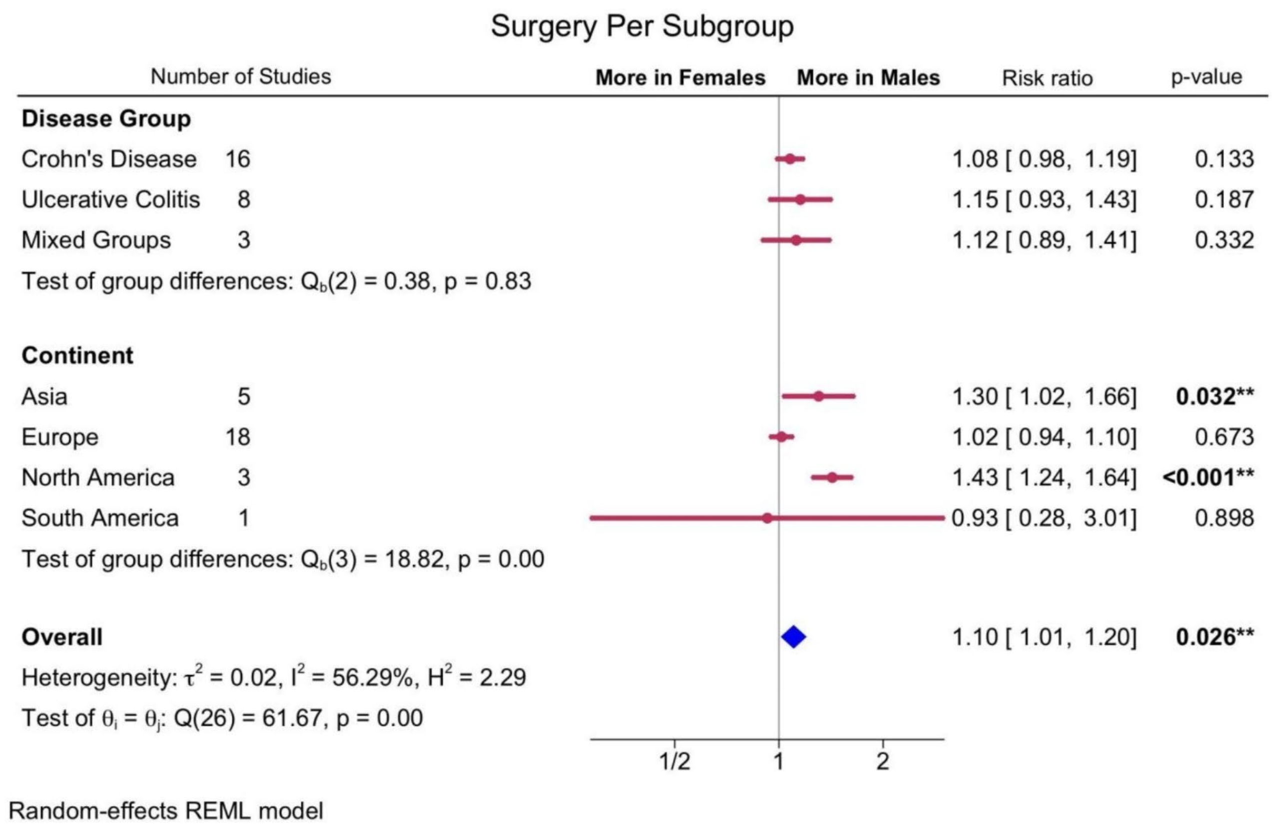

Fig. 3 Forest plot of random effect model meta-analysis of risk ratio for surgery rates between males and females according to disease group and continent

males having higher employment rates and a higher mean age. In terms of disease location, male patients were less likely to present with proctitis but had a greater incidence of extensive colitis. Additionally, the study found that males in the CD subgroup had significantly higher employment rates and that the UC subgroup of males had a higher mean age.

Sex difference in the pathogenesis of IBD

While the pathogenesis of IBD is nuanced and involves several factors, sex influences the clinical profile and outcomes of IBD through environmental factors, hormones and genetics. The X chromosome is known to have multiple susceptibility loci for IBD [10–12]. As with some other autoimmune diseases, haplotypes of toll-like receptor 8 were found on X chromosome [10, 11]. The likelihood of having CD was found to be lower in females -but not males- who have the R30Q DLG5 variant [13–15]. On the other hand, a variant of interleukin-23 (IL-23) was linked to a lower risk of UC in females and a variant of interleukin-10 (IL-10) was associated with a higher risk of UC in females not in males [16, 17]. Estrogen is involved in the pathophysiology of many autoimmune conditions [18]. In vitrio, active inflammation in colonic mucosa of rats as a result of reduced epithelial permeability is appreciated with decreased signalling of estrogen receptor beta (ERbeta) [19–23]. In human studies, emerging evidence shows lower ERbeta expression in healthy individuals and in IBD patients who are in remission compared with patients with active IBD [24]. Furthermore, ERbeta has been investigated as an influencing factor involved in the response to biologic agents in IBD [24] and hence, sex should be expected to affect how IBD patients respond to medications. In males, lower levels of testosterone before diagnosis was linked to a high risk of CD but not UC [25]. Whereas in females, oral contraceptive (OCP) use and hormone replacement therapy are associated with increased risks of IBD [26–29]. In a meta-analysis by Cornish et al. [7], OCP use was associated with increased risks of CD (odds ratio 1.51, 95% CI [1.17–1.96]) and UC (odds ratio 1.53, 95% CI [1.21–1.94]).

Impact of sex on working rates

It's not surprising that males have higher employment rates compared to females. This disparity may be attributed to the fact that females experience higher levels of depression and anxiety than males, which can impede

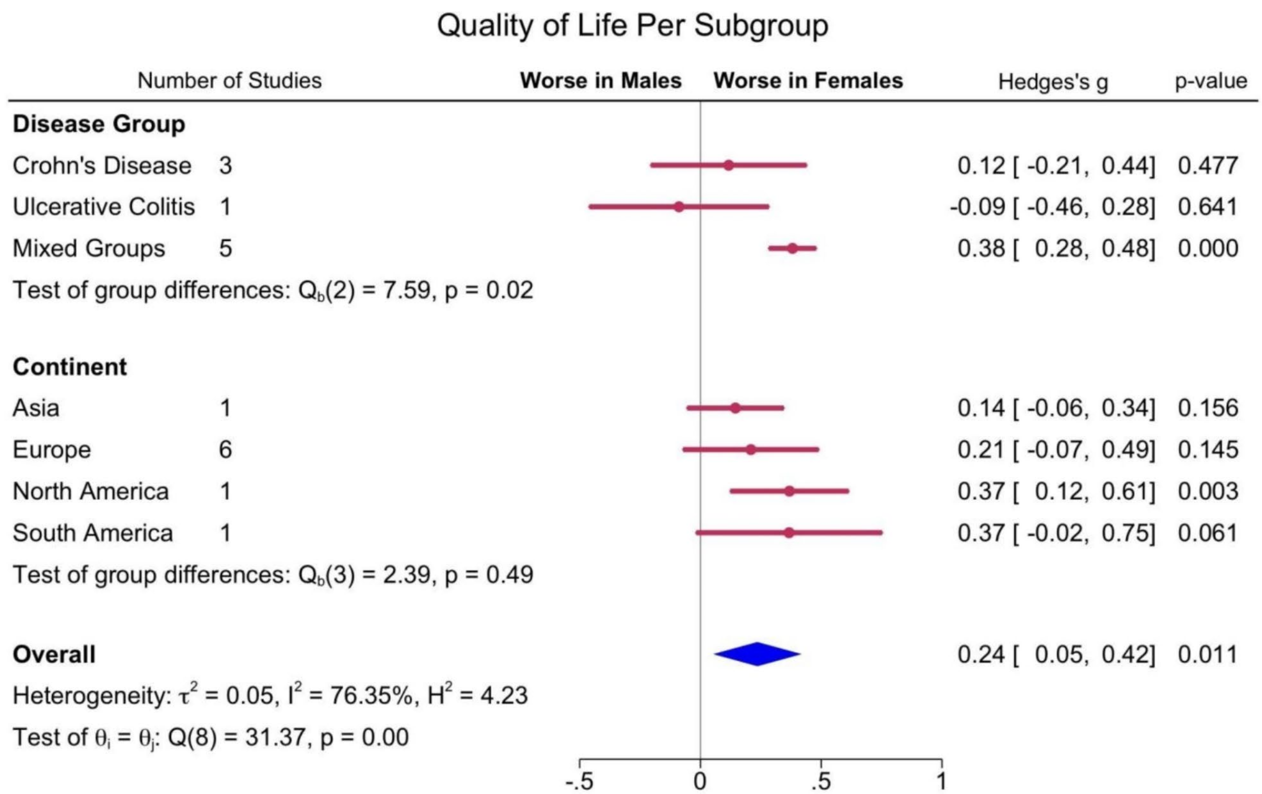

Fig. 4 Forest plot of random effect model meta-analysis of hedges' g for quality of life between males and females according to disease group and continent

their ability to work, ultimately affecting their quality of life.

Impact of sex on risk of surgery

The higher surgery rates among males may be attributed to several factors. Firstly, males exhibited a more progressive disease extent, such as extensive colitis, necessitating surgical treatments like colectomy. Additionally, factors such as prior hospitalization, utilization of immunomodulatory drugs, and corticosteroid refractoriness could influence the risk of colectomy [30]. Secondly, males tend to develop a more complicated disease, leading to an increased risk of surgery [31, 32]. Additionally, males are generally predisposed to a more severe disease course due to the influence of sex hormones on intestinal physiology and immune system activation. Disparities in environmental factors, such as smoking and diet, may also contribute to these differences [33]. Thirdly, health-seeking behavior plays a crucial role in determining the treatment approach. Males often resort to surgery due to delayed access to medical care, exacerbating disease progression and leaving surgery as the only viable option. Conversely, females are less inclined to undergo surgery due to concerns about the associated risks, impacts on fertility, and post-surgery body image [34, 35]. Finally, colorectal cancer is more likely to occur in males than females, which may contribute to the disparities between the two sexs in the risk of surgery [36].

According to Rabinowitz (2021), sex hormones may influence the development of Crohn's disease (CD). Estrogen, for instance, could inhibit the activity of FXR (farnesoid X receptor), making females with the FXR-1G > T genotype more susceptible to early surgery [37].

Although our results showed no significant differences regarding ileal involvement, one study in this review suggested that males with IBD experience more frequent ileal involvement, leading to a higher rate of bowel resections compared to females [31]. Other study said that females are more likely to undergo ileocecal resection compared to males [38].

Impact of sex on risk of depression and anxiety

Possible explanations for the higher levels of anxiety in females include: first, females tend to experience higher levels of anxiety due to concerns about symptoms such as fatigue, pain, and the impact of stress on disease activity and energy levels. Additionally, they may be burdened by the frequency of medical consultations and exams, as well as the social implications of living with the disease [39].

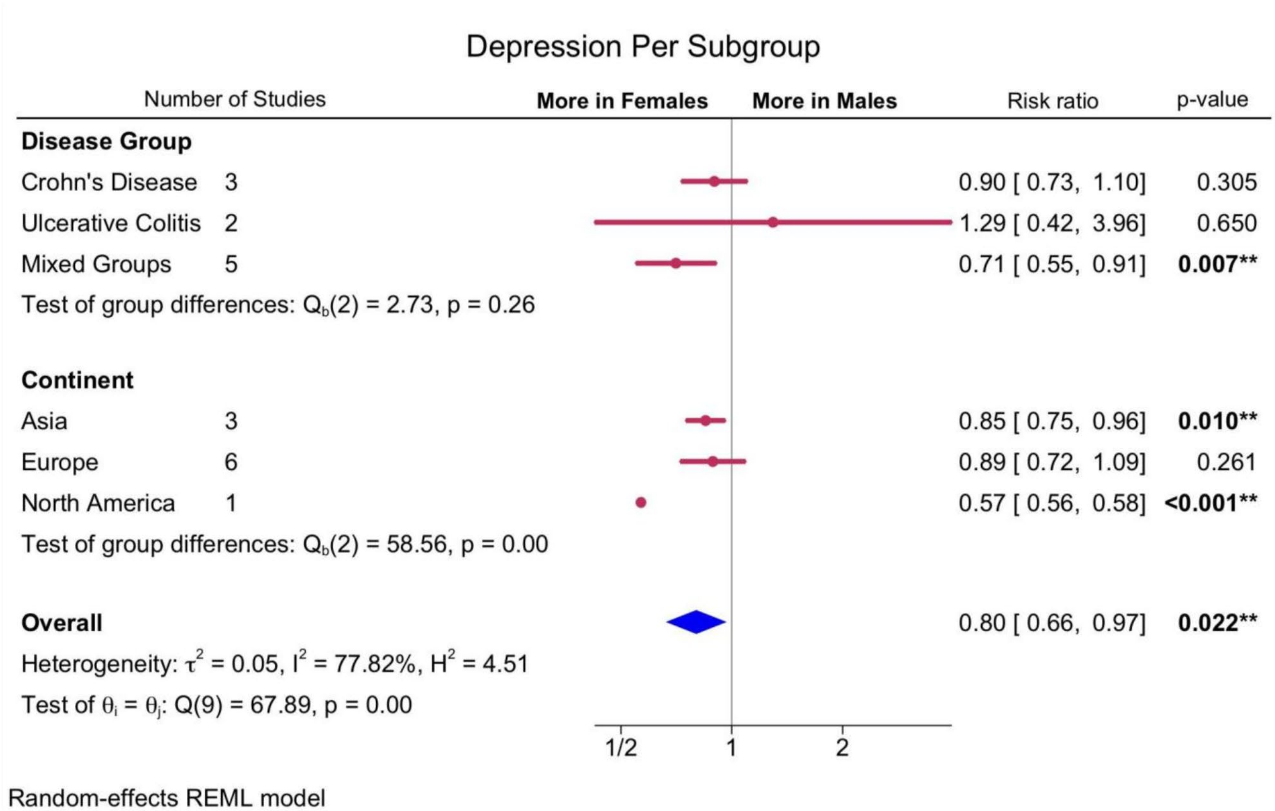

Fig. 5 Forest plot of random effect model meta-analysis of risk ratio for depression between males and females according to disease group and continent

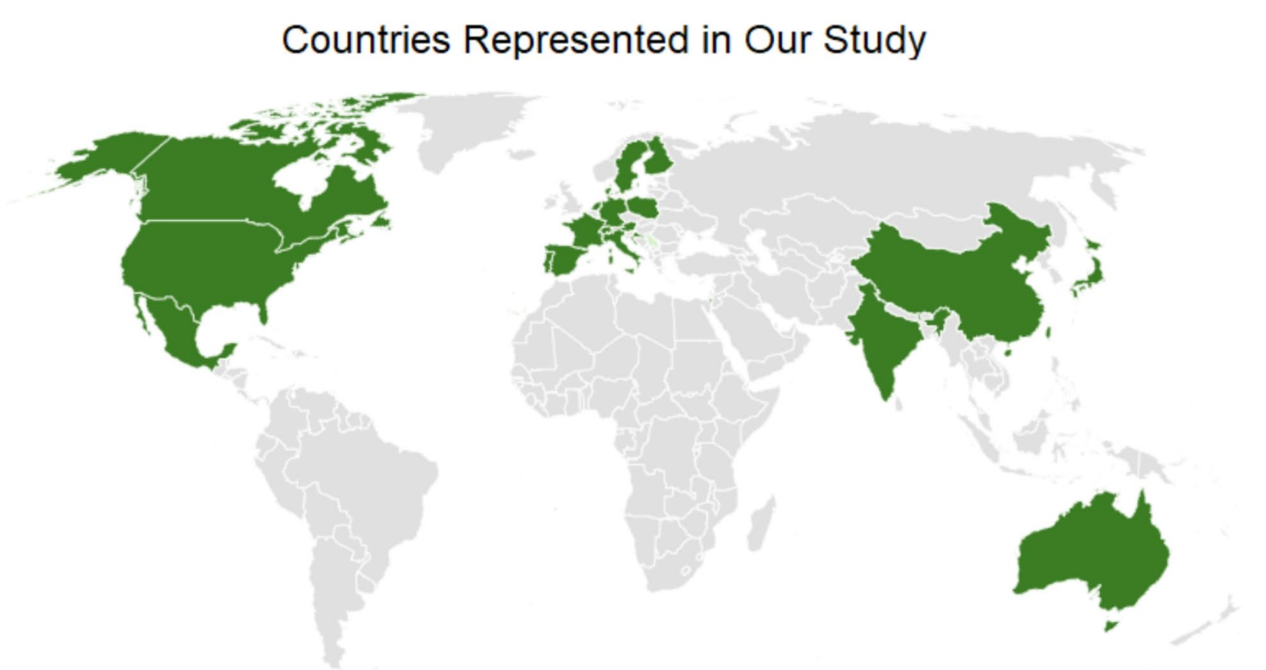

Fig. 6 Geographic locations of our study

Second, Females tend to experience more gastrointestinal symptoms than males, which increases the risk of anxiety and depression among them. Disease activity was observed to be higher in females, and factors such as physical and psychological tolerance may also contribute to these differences [40].

Impact of sex on quality of life

Possible explanations for the poorer quality of life in females may include higher rates of depression and anxiety among females, as well as increased concerns about body image, attractiveness, and the prospect of having children. Additionally, disease can alter social functioning, which may be perceived differently by males and females [41]. According to Moradkhani et al. (2013), females are more prone to expressing concerns about feeling burdensome or being treated differently due to their illness and report worries regarding attractiveness and body image, along with rating their symptoms as more severe resulting in a poor QoL in females [42]. Moreover, females are less likely to use biologics, which have the potential to enhance their quality of life (QoL) [43]. Females often exhibit a greater inclination than males to seek medical advice for their symptoms and to consider disease-related factors when evaluating their health-related quality of life. Consequently, despite potentially being in good health, females tend to report lower health-related quality of life scores compared to males [44, 45]. Additionally, patients who visit the doctor for the first time may enter a state of denial, impacting their QoL [40]. Furthermore, females experience more gastrointestinal symptoms which reduce their quality of life [40, 46]. Moreover, higher disease activity may contribute to a decline in QoL [40, 47]. Finally, female UC patients have higher hospitalization rates, which may adversely affect their QoL [40, 47].

Other studies have found that females tend to have a lower QoL than males when their disease is inactive, but this sex difference diminishes during a flare-up, with both sexes experiencing similarly low levels of QoL [48, 49].

Impact of sex on risk of total deaths

The higher mortality rates among males could be attributed to several factors: males tend to have a more aggressive disease course, higher rates of surgeries, increased smoking rates, and more complications, all of which contribute to a higher risk of mortality among males. Additionally, the older age of males compared to females may also be associated with higher mortality rates.

Impact of sex on the usage of biologics.

The lower usage of biologics among females, despite their non-teratogenic nature during pregnancy or breastfeeding [34], may be explained by the higher incidence of side effects in females, resulting in lower adherence to treatment [50]. Additionally, factors such as care-seeking behaviors, physician bias related to sex, and patient choice may also contribute to this outcome [32].

Impact of sex on risk of hospitalization

While our results indicate no significant differences between males and females in hospitalization rates for inflammatory bowel disease (IBD) overall, we did find that females are hospitalized more frequently than males in cases of ulcerative colitis (UC), although there is no difference between males and females in UC related surgeries rates. This disparity may be attributed to care-seeking behaviors that could lead to hospitalization, or it could be linked to the more frequently reported psychosocial impacts of disease flares in females [32].

Additionally, hormones play an important role in the sex differences in IBD. For example, estrogen has anti-inflammatory effects which may influence disease course in females compared to males. progesterone exhibits immunosuppressive actions. However, it’s effects on IBD still controversial [51].

Recent reviews support our findings, indicating that males exhibit higher surgery rates [52–55] and greater usage of biologics compared to females [52–54]. Additionally, these reviews highlight that females generally report a lower quality of life than males [53, 54] and are more prone to developing anxiety and depression [56].

In our systematic review, four studies indicated that females exhibit higher disease activity compared to males [31, 40, 49, 57]. Liu (2023) specifically noted that females experienced gastrointestinal symptoms more frequently than males [40]. Additionally, several studies within our cohort revealed that females are more likely to manifest extraintestinal symptoms compared to males [31, 32, 38, 39, 57, 58].

Two studies from our systematic review reported that IBD complications, such as bowel obstruction and perforation, are more common in males than females [58, 59]. Concerning adverse events related to Anti-TNF therapy, Lagana (2019) found no significant differences between males and females [60]. However, Zelinkova (2012) discovered that adverse events associated with Anti-TNF drugs, including infliximab and adalimumab, tend to occur more frequently in females [61] and Lie 2017 also found that adalimumab adverse effects tend to occur in females [50]. Moreover, Heath (2012) reported that female CD patients are more prone to experience adverse events from infliximab compared to males [32].

The strengths of our systematic review include a large sample size (n > 29,116) and the inclusion of over 44 studies. Additionally, our study encompasses various study designs, including cross-sectional, cohort, prospective, and retrospective analyses. However, our study has limitations. Firstly, we only included studies conducted in the

English language, potentially excluding relevant research in other languages. Secondly, there is heterogeneity in certain disease characteristics and outcomes, such as disease duration, proctitis extent, fistula presence, BMI, age, steroid use, hospitalization rates, biologics utilization, depression, and quality of life. Inconsistency in the overall results can be due to the differences between hospital protocols across the studies or influence of large studies.

Our study reinforces previous findings regarding the impacts of sex differences on anxiety, depression, QoL, surgery and others but it's the first systematic review that highlight the influence of sex difference on total deaths in IBD patients. IBD physicians should pay attention to these sex disparities and their potential implications for diagnosis and treatment, aiming to develop tailored treatment approaches for each demographic group. Based on our findings, we suggest prioritizing supportive psychological therapy for females, with psychiatrists and psychologists playing integral roles in IBD treatment. To decrease mortality rates, male patients may require intensified follow-up. Furthermore, education programs, particularly targeting males, could promote earlier symptom recognition and medical consultation, thereby reducing complications and the need for surgeries, ultimately lowering mortality rates. Physicians should actively engage patients in the decision-making process to achieve satisfactory clinical outcomes. Additionally, impact of patient preferences and differences in care-seeking behavior should be considered. Further laboratory tests are needed to understand the influence of sex hormones on sex differences in IBD. For future research, well-conducted observational studies are necessary to deepen our understanding of sex disparities in the clinical outcomes of IBD.

Conclusion

In conclusion, our systematic review has highlighted the sex disparities in IBD patients in several outcomes such as depression, anxiety, quality of life, total deaths and others which must be considerable in daily care for IBD patients. Our findings have revealed that women have higher rates of anxiety and depression than males. Also, their quality of life is worse than males. Therefore, it is recommended that women with IBD should be followed up with a psychologist and should have the required support. In addition, males need better education about the disease symptoms and progression as well as intensified follow-up. Further well-conducted observational studies are needed to fully understood the sex impact on clinical outcomes of IBD.

Abbreviations

IBD	Inflammatory Bowel Disease
CD	Crohn's Disease
UC	Ulcerative Colitis
RR	Risk Ratio
CI	Confidence Interval
MD	Mean Difference
RCTs	Randomized Controlled Trials
GI	Gastroenterology
BMI	Body Mass Index
SDS	Self-Rating Depression Scale
PHQ-9	Patient Health Questionnaire-9
SAS	Self-Rating Anxiety Scale
GAD-7	Generalized Anxiety Disorder 7-item
HADS-D-A	Hospital Anxiety And Depression Scale
IBDQ	Inflammatory Bowel Disease Questionnaire
SIBDQ	Short Inflammatory Bowel Disease Questionnaire
SF36	Short Form 36 Health Survey Questionnaire
HRLS	Health-Related Life Satisfaction
WHOQoL	World Health Organization Quality of Life
REML	Restricted Maximum likelihood
IQR	Inter Quartile Range
SD	Standard Deviation
QoL	Quality of Life
Anti- TNF	Anti-Tumor Necrotizing Factor

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
DAS: screening+ data extration+ writing manuscript (original draft) + meta analysisRE: screening+ data extraction+ writing manuscript (original draft) + meta analysisRRA: screening+ data extraction+ writing manuscript (original draft) + meta analysisKAZ: screening+ data extraction+ writing manuscript (original draft)AYA: screening+ data extraction+ writing manuscript (original draft)MTA: screening+ data extraction+ writing manuscript (original draft) YMB: screening+ data extraction+ writing manuscript (original draft)BFA: writing manuscript (review and edit)MA: writing manuscript (review and edit) + supervision KM: supervision All authors read and approved the final manuscript.

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Data availability
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Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare no competing interests.

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