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Prevalence of metabolic syndrome in inflammatory bowel disease: a systematic review and meta-analysis

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ABSTRACT

Objective: Patients with inflammatory bowel disease (IBD) may experience comorbidities involving metabolic syndrome (MetS). However, the findings remain controversial. Our objective was to estimate the prevalence of MetS in IBD and whether MetS is more strongly associated with ulcerative colitis (UC) or Crohn's disease (CD).

Design: Systematic review and meta-analysis.

Methods: The PRISMA and MOOSE guidelines were followed. Electronic databases were searched for observational studies regarding the prevalence of MetS in IBD cohorts from their inception to July 2022. Pooled prevalence, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects models. The Newcastle-Ottawa Scale and AHRQ checklist were used. Heterogeneity, sensitivity and stratified analyses were performed using R (version 4.2.1).

Results: 11 eligible studies involving 2501 patients were included. Of these studies, four reported MetS prevalence separately by IBD phenotype, and only one contained a non-IBD comparison group. Overall, the methodological quality of the included studies was moderate. The pooled prevalence of MetS in IBD was 19.4% (95% CI 15.1%-23.8%), which was comparable to that in the general population. Stratified analyses demonstrated that the aggregate estimate of comorbid MetS was significantly higher in UC than in CD (38.2% vs 13.6%, χ^2=4.88, P=0.03). We found a positive association between MetS and UC compared to CD (OR=2.11, 95% CI 1.19-3.74, P=0.01). Additionally, four studies identified that age was a risk factor associated with the development of MetS.

Conclusions: MetS is not rare in IBD, especially in UC. MetS is associated with IBD. However, longitudinal studies are needed to further clarify the relationship.

PROSPERO PROTOCOL NUMBER: CRD42022346340.

Key Words: inflammatory bowel disease, metabolic syndrome, ulcerative colitis, crohn's disease, meta-analysis

Strengths and limitations of this study:

Our study is the first comprehensive synthesis of the available evidence on the prevalence and association of comorbid MetS among IBD patients.

MetS is not uncommon in patients with IBD, especially in UC, which provides insights into the potential association between MetS and IBD.

Early detection of MetS can be expected to benefit patients with IBD and contribute to better disease outcomes, in particular the elderly.

Most of the studies included in this study were cross-sectional in design, some potential confounding factors could lead to bias in the association between MetS and IBD.

Abbreviations: IBD, inflammatory bowel disease; MetS, metabolic syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-analysis of Observational Studies in Epidemiology; NOS, Newcastle-Ottawa scale; AHRQ, Agency for Healthcare Research and Quality; CVD, cardiovascular disease; VAT, visceral adipose tissue.

INTRODUCTION

Metabolic syndrome (MetS) is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia.[1] As the lifestyle of modern people changing, lack of exercise, and excessive accumulation of calories is suggested to be the direct causes of this kind of disease.[2] While with deeper cognition about MetS, it is found to be associated with many chronic diseases, like type 2 diabetes, coronary diseases, stroke, and other disabilities. MetS has increased the social burdens with the cost of health care and potential loss of economic.[1,3]

The inflammatory bowel disease (IBD) causes idiopathic chronic inflammation of intestines, the etiology of IBD is unknown, and its incidence is rising worldwide. In the 21st century, the incidence of IBD is more than 0.3% of the total population in western countries like the UK, the USA, Canada, Denmark, Sweden, Germany, and Australia, and also rises in developing countries.[4] Crohn's disease (CD) and ulcerative colitis (UC) are two major phenotypes of IBD. The etiology of IBD (UC or CD) is yet to be elucidated. Currently, IBD is considered to be a multifactorial disease, involving genetic predisposition, environmental factors, and immuno-metabolic disorders.[5,6]

Interestingly, there are many commonalities between IBD and MetS, like dyslipidemia, immune system imbalance, and chronic inflammation state.[3] Many previous studies have shown overlap between IBD and MetS and investigated the prevalence rates. However, the results are diverse.[6-8] Prior studies looking at the relationship between IBD and MetS have been observational studies or from single-

center limited by sample size. The aim of this systematic review and meta-analysis was to determine the overall prevalence of comorbid MetS among IBD patients and to explore the association.

METHODS

This meta-analysis was conducted in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE).[9,10] The protocol was previously registered with PROSPERO (registration number CRD42022346340). No further ethical approval was required since all eligible studies were approved by local institutional review boards and ethical committees.

Search strategy

We initially searched PubMed, Web of Science, EMBASE and MEDLINE from the respective dates of database inception to July 2022 for studies reporting the prevalence of comorbid MetS among IBD patients. A combination of medical subject headings terms and/or free text words was utilized: “metabolic syndrome”, “Inflammatory bowel disease”, “Ulcerative colitis”, “Crohn disease”, “MetS”, “MS”, “IBD”, “UC”, and “CD”. In addition, we also conducted hand-searching of all references of the retrieved studies for further relevant reports. The search was limited to papers published in English. No other restrictions were imposed. The search strategy was undertaken independently by two investigators (YJL and MYZ) who are experienced in the information retrieval. The preliminary search strategy is shown in Table

(Supplementary Table S1), which was adapted according to syntax-related requirements of electronic databases.

Study selection

The inclusion criteria of eligible studies were as follows: (1) patients with confirmed IBD (including UC and CD) and MetS; (2) observational studies (including cross-sectional, case-control and cohort studies) or clinical trials; (3) primary outcome regarding the prevalence of MetS in IBD patients or the association of MetS with IBD; (4) original studies in the English language providing sufficient information to calculate the effect size. All studies were limited to those involving human subjects, animal studies, case reports, review articles, redundant studies or studies that did not report specific outcome were excluded.

Data extraction and risk of bias assessment

Two researchers (YJL and MYZ) independently identified relevant literature by reading the titles, abstracts and full texts of the studies retrieved. The following information was subsequently extracted using a preestablished literature extraction table: author, journal, title, year of publication, contact information, country, study design, study population characteristics (participants, proportion of CD and UC, sample size, diagnosis criteria, general demographic information), clinical characteristics (duration, activity, severity, treatment), outcomes (prevalence, odds ratio, risk ratio, risk factors), conclusion (association of MetS with IBD), etc.

Since all the studies included were observational, the methodological quality was assessed using the Newcastle-Ottawa scale (NOS) and 11-item checklist recommended

by Agency for Healthcare Research and Quality (AHRQ).[11,12] An item was scored '0' if it was answered 'NO' or 'UNCLEAR'; if it was answered 'YES', then the item scored '0'. Study quality was assessed based on the total score. Overall, the results were divided into three levels: low risk of bias, high risk of bias, and unclear risk of bias. Any discrepancies between the two investigators were resolved by consulting a third reviewer (ZFS).

Data synthesis and statistical analysis

Statistical analyses were performed using the packages (i.e., meta and metafor) in R (version 4.2.1, R Foundation for Statistical Computing).[13] The pooled prevalence of MetS among IBD were calculated as an aggregate mean, weighted by the sample size of each included study. Subsequently, we calculated the pooled odds ratio (OR) to compare the comorbid MetS between patients with UC and CD. All the values were estimated with 95% confidence intervals (95% CI). Both the fixed-effect model and random-effects model were applied to estimate the pooled estimates. Given the conservativeness of results, the random-effects model proposed by DerSimonian-Laird (1986) was considered to be the primary method.[14] Subgroup analyses were performed according to IBD phenotypes (UC and CD), and sensitivity analyses were conducted by recalculating the pooled estimates after omitting studies of low quality. Furthermore, we narratively summarized data regarding risk factors for MetS among IBD patients. The statistical heterogeneity was assessed using the inconsistency index (I^2) and Cochrane Q statistic.[15] The results were classified into three levels: low heterogeneity (I^2<25%), moderate heterogeneity (25%< I^2<50%), high heterogeneity (I^2>75%). We

defined significantly heterogeneity if $P < 0.1$ and $I^2>50\%$. The potential publication bias was evaluated by the funnel plot and Egger's test.[16]

RESULTS

Literature search

A total of 3176 relevant records were initially identified. After the preliminary screening, 1499 articles were removed because of duplication. Based on the inspection of titles and abstracts, 85 potential studies were retrieved for further evaluation. After examining the full text, 11 of these publications met the predefined eligibility criteria and were included in our meta-analysis.[6,8,17-25] The PRISMA flow diagram of search strategy and study selection is illustrated in Figure 1.

Study characteristics

We found that all included studies investigated the prevalence of MetS in IBD patients (rather than the prevalence of IBD in MetS patients). All the studies were published after 2010, and 6 (55%) were cross-sectional in design. Three studies were conducted in North America, five in Europe, and three in Asia. In total, 2501 patients with IBD were included in this study, 1678 (67.1%) had a diagnosis of CD and 823 (32.9%) had a diagnosis of UC. In most of the studies, IBD along with UC and CD was defined by international diagnostic criteria (e.g., ECCO), and MetS was identified using the NCEP-ATP-III criteria. Of the 11 included studies, 1 (9.1%) comprised both IBD group and non-IBD comparison group, while 10 (90.9%) included only one disease cohort. Among these studies, 1 (9.1%) was limited to patients with UC, 1 (9.1%) to patients

with CD, and 9 (81.8%) to patients with a mixed sample (i.e., one that contained patients having both UC and CD). Four (44.4%) of the mixed-sample studies reported MetS prevalence separately by different IBD phenotypes (CD and UC). The general characteristics of the studies included were given in Table 1.

Risk of bias of included studies

Given the types of studies included, we used the Newcastle-Ottawa scale and AHRQ checklist to appraise the risk of bias for each study. However, some questions were not applicable. The majority of studies scored well in terms of patient selection and outcome assessment, whereas one study was rated at high risk in that it did not report relevant information. Overall, the risk of bias of the included studies was moderate and acceptable. The results of the assessment were illustrated in Figure 2 and Table 1 (Supplementary Table S2).

Overall prevalence of MetS among patients with IBD

We identified 9 studies that reported available information regarding the prevalence of MetS among patients with IBD. Five of them were limited to analyze the overall prevalence of comorbid MetS in patients with IBD, while the remaining four studies were subsequently pooled into subgroup analyses. A total of 273 MetS cases were detected among 1544 patients with IBD. Overall, the prevalence of comorbid MetS ranged from 10.6% to 32.7%. As a result, the pooled prevalence of MetS in IBD was estimated to be 19.4% (95% CI 15.1% to 23.8%). Since there was substantial statistical heterogeneity across the studies (I^2=81.0%, Cochrane Q statistic=42.2, P<0.001), a random-effect model was used in our study. These unadjusted prevalence estimates and

study heterogeneity were illustrated in the forest plot (Figure 3). There was no evidence of publication bias according to the Egger's test (P= 0.332), and the funnel plot is almost symmetrical (Supplementary Figure S1). It is worth noting that these proportions were determined by type of design, source of subject, quality of study, and method of outcome assessment. Therefore, we conducted further analyses. Sensitivity analyses revealed similar results (pooled estimate 20.7%; 95% CI, 16.6%-24.8%) and Min et al.'s study[21] had the largest influence on the results (Supplementary Figure S2). After excluding two studies with low quality and ambiguous information,[21,23] we found that the overall pooled prevalence was 21.9% (95% CI 18.0% to 25.8%) with moderate heterogeneity (I^2=51.8%, Cochrane Q statistic=12.4, P=0.053).

Overall, only one study[6] reported the prevalence of MetS in non-IBD controls. MetS was more frequent in IBD patients (32.7%) than in non-IBD control group (13.3%), and there was a significant positive association between MetS and CD (P=0.01). To further understand the significance of the prevalence of comorbid MetS in IBD, we compared our result with external data reported by other investigators. It is reported that the prevalence of MetS in the general population ranged from 16.5% to 34.7% [26-33]. The prevalence of the metabolic syndrome from our study appeared to be lower than that in the U.S. adult population.[26,27] while it was comparable to that in the Asia-Pacific regions and the Middle-East countries.[28-33]

Comparisons of comorbid MetS between patients with UC and CD

Taking the subtype of IBD into account, we performed stratified analyses. In total, six included studies provided specific information regarding the prevalence of comorbid

MetS in either UC or CD. All the studies were divided into two groups: 356 patients with UC (n=5 studies) in the UC analyses and 1068 patients with CD (n=5 studies) in the CD analyses. The pooled prevalence of comorbid MetS was 38.2% in UC (95% CI, 20.4%-59.9%), and 13.6% in CD (95% CI, 6.4%-26.7%). Strikingly, the aggregate estimate of MetS was significantly higher in UC than in CD (Cochran-Mantel-Haenszel χ^2= 4.88, P = 0.03). Nevertheless, significant heterogeneity was observed (I^2= 94%, P < 0.01). The detailed information was displayed in Figure 4. Sensitivity analyses by omitting two heterogeneous studies showed that MetS was more frequent in UC than in CD (27.7% vs 20.0%) with decreasing heterogeneity (I^2=40.2%, P = 0.11).[18,19] However, no statistically significant difference (Cochran-Mantel-Haenszel χ^2= 1.64, P = 0.2) was reached (Supplementary Figure S3).

When we only included mixed-sample studies that reported comorbidity of MetS separately by different IBD phenotypes (n = 4 studies), the meta-analysis demonstrated a negative association between MetS and UC compared to CD controls (pooled OR = 1.52, 95% CI 0.96-2.41, P = 0.073). Except for the study by Sanja et al. (OR = 0.748), [6] the remaining 3 studies reported an OR above 1.00. As shown in Figure 5, a low to moderate heterogeneity was detected (I^2=35.9%, Cochrane Q statistic = 4.68, P = 0.197). Similarly, sensitivity analyses were conducted to investigate the stability of the results. We found that Sanja et al.'s study had a significant impact on the results. After omitting Sanja et al.'s study, the pooled estimate appreciably changed to be 2.11 (95% CI 1.19-3.74, P = 0.01), which implies a risk approximately twice higher in UC than in CD (Supplementary Figure S4). Although there was no evidence of statistical heterogeneity

(I^2 = 0%, Cochrane Q statistic = 4.68, P = 0.197), the number of studies that separately reported the outcome was small.

Risk factors for MetS among IBD patients

There were four studies that specifically investigated relevant risk factors associated with MetS among IBD patients. One of these by Masakazu et al. found no statistical difference on gender, IBD phenotype, treatment, social history, or health-related lifestyle between IBD patients with and without MetS.[8] However, IBD patients with MetS were older than those without, indicating that age was the independent risks factors for MetS (OR=1.064, 95%CI 1.017 to 1.114). The retrospective cohort study based on electronic healthcare record demonstrated that IBD patients with concomitant MetS were statistically significantly older at the time of IBD diagnosis (P = 0.005). In addition, IBD patients with MetS had overall higher values of ALT and AST than non-MetS IBD patients. Similarly, Paul et al. from the USA reported that CD Patients with MetS were older as compared with those without MetS (P<0.001), and there was no statistically significant difference in gender, race, or duration of disease between those two groups (P >0.05).[18] Remarkably, after multivariate adjustment (e.g., age, sex, race), MetS was significantly associated with increased risk of CD-related hospitalization among CD patients (OR=1.91, 95%CI 1.12 to 3.00). Interestingly, the study by Marina et al. revealed similar results that patients with UC and MetS were significantly older compared to UC patients without MetS (P=0.001).[19] Furthermore, UC patients with MetS reported higher values in cholesterol, triglycerides, low-density lipoprotein, interleukin-10, and Galectin-3, compared to patients suffering from UC only. As a

result, UC patients with MetS had lower Mayo endoscopic subscore (P=0.038) and Mayo clinical score (P=0.005) milder form of UC, indicating that patients with UC and MetS were milder. Overall, four studies identified that age was a statistically significant risk factor associated with the development of MetS. However, only one study further performed a multivariate analysis, and only two satisfied the criteria. Given the limited number of studies, we failed to conduct a meta-analysis to elucidate the association between age and the incidence of MetS. Other variables (e.g., Obesity, Diabetes) were also potential risk factors for the development of MetS among patients with IBD. Unfortunately, most of the included studies did not provide valuable data.

DISCUSSION

Our study demonstrates the pooled prevalence of MetS in the IBD population from 11 studies, having a combined total of 2501 subjects. The present data reveal that the prevalence of MetS in IBD was comparable to that of the general population, suggesting that MetS is not a rare complication among IBD patients. However, the prevalence of MetS in the general population varies by regions. MetS tends to be more frequent in Western countries.[34] A cross-sectional study from the USA evaluated the MetS prevalence among 17048 adult participants, from 2011 to 2016, and the result was 34.7% (95% CI, 33.1%-36.3%).[26] Overall, MetS affects 16.5%-34.7% of the general population globally. Given the fact that the studies included in this Meta-analysis were mainly from Europe, America, and Asia, we suspect the prevalence of MetS in IBD was determined by region, age and method of outcome assessment. Therefore, the

calculated comorbidity rate of MetS and IBD may not fully reflect its actual global prevalent status.

MetS develops as a result of progressive weight gain, fat mass accumulation and insulin resistance. MetS is a complex pathophysiologic state that originates primarily from an imbalance of calorie intake and energy expenditure, genetic/epigenetic make up of individual, predominance of sedentary, and other factors like quality and composition of food and composition of gut microbes. MetS is associated with a marked increase in risk of cardiovascular disease and type 2 diabetes, possibly due to abdominal obesity, hyperglycemia, dyslipidemia, and hypertension.[34,35] A clear increase in the prevalence of MetS with aging has been largely recognized, there are many commonalities in biochemical changes of aging process and metabolic syndrome. According to our analysis, that age might be a statistically significant risks factor involved in the association between MetS and IBD, so evaluation for MetS is needed for elderly IBD patients.

Attention on comorbidity is crucial when managing patients with IBD because they can alter disease activity and extraintestinal manifestations, influence disease prognosis, and influence pharmacological therapeutic effects. Both of MetS and IBD are increasingly globally prevalent diseases. The pathogenesis and characteristics of disease course of MetS in the IBD population are not entirely clear, and the pathogenesis of MetS in the IBD population may be more complex. Researchers have reported MetS and IBD share common pathophysiological features such as immune imbalance, chronic inflammation, disturbed secretion of adipokines, and increased risk

of cardiovascular disease (CVD).[3,36] Although our data did not show a close association of CVD risk in IBD with MetS, given the fact that MetS accelerates atherogenesis and eventually resulting CVD, and systemic inflammation can contribute to atherogenesis, an increased risk of CVD in patients with IBD and MetS is just can not be ignored.

The adipose tissue (AT), and particularly the visceral adipose tissue (VAT) plays an important part in the pathophysiology of MetS. It is suggested that VAT may participate in chronic systemic inflammation of both MetS and IBD.[3,37] The VAT composed of hypertrophic adipocytes that secrete abnormal levels of adipokines, for example, it may downregulate synthesis of leptin, adiponectin, and adipocytokines responsible for pro- and anti-inflammatory effects.[38] A lower level of serum and mesenteric adiponectin was observed in active CD, indicating adiponectin is associated with a defective regulation of anti-inflammatory pathways in CD pathogenesis.[39] The VAT also produces proinflammatory cytokines like interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein 1 (MCP-1), leading to infiltration of M1 macrophages and causing low-grade chronic inflammation. M1 macrophages can also promote hepatic steatosis and adipogenesis.[3,37] Reversely, the inflammation may also affect adipose tissue and disturb the adipokine secretion In MetS and IBD. It is reported that inflammation may induce dyslipidemia through downregulation of lipoprotein lipase enzyme affected by the action of proinflammatory cytokines TNF-α, IL-6, and interferon (IFN)-γ.[40] In the included studies, some of them showed that IBD lipid profile was characterized by decreased total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol. HDL performs many anti-inflammatory

activities, indicates that decrease in its level could not only be the effect but also the cause of intestinal chronic inflammation.[41]

As reported, gut dysbiosis is probably an additional factor that could alter immune-metabolic state in IBD and MetS.[34] Inflammation and the gut microbiome can trigger intestinal barrier dysfunction, while in IBD, disruption of the gut barrier allows microbe infiltration into the submucosae, which enhances the probability that gut-derived metabolites translate from the gut to the liver and pancreas. So gut microbial dysbiosis may be one of the potential mechanisms contributing to comorbidity of MetS and IBD via increased intestinal permeability.[2] Refer to a recent study that reported gut virome changes have association with MetS and exhibit decreased richness and diversity, provided a starting point to studies of phage effects on gut bacteria and the role that this plays in MetS.[42] Akkermansia muciniphila is a gram-negative and mucin-degrading bacterium, which is highly abundant in the gut microbiota. Reduced levels of A. muciniphila have been observed in patients with inflammatory bowel diseases (mainly ulcerative colitis) and metabolic disorders, which suggests it may have potential anti-inflammatory properties linked to impaired gut-barrier integrity.[43] A recent study shows that pasteurization of Akkermansia muciniphila enhances the bacterium's ability to reduce fat mass and metabolic syndrome in mice with diet-induced obesity, which may be a strategy to fight against obesity and IBD.[44] It is reported that intestinal microbiota protects against development of metabolic syndrome by inducing Th17 cells and regulating lipid absorption across intestinal epithelium. However, high-fat, high-sugar diet will promote metabolic disease by depleting Th17-inducing

microbes. The findings highlight an interaction between diet, microbiota, and intestinal immunity in metabolic disorders.[45]

In our current meta-analysis, MetS prevalence is found to be significantly lower in CD than in UC (OR=2.11, 95% CI 1.19-3.74, P=0.01), which should be noticed that the average age of patients with UC is older in these studies. A study reported a prevalence of MetS reached to 81% in UC, and the average age of the patients is 50 (21-80). The study also indicated that patients with MetS have milder form of UC, with higher serum level of immunosuppressive cytokine interleukin-10 (IL-10) and fecal content of Galectin3 (Gal-3), they supposed the presence of MetS may limit the inflammatory process and subsequent tissue damage in UC possibly by deviating local inflammatory response toward enhanced participation of immunosuppressive cells and molecules.[19] CD and UC have been postulated to involve different immunological backgrounds. The inflammation of UC primarily involves the colonic mucosa. Differently, features of Crohn's disease are transmural inflammation affecting all layers of the intestinal wall and mesenteric lymph nodes and chronic noncaseating granulomatous inflammation.[46] Underweight is more frequently observed in patients with CD, as lack of proper gut function reduces nutrient absorption. CD often accompanies with malnutrition and, thus, might not present classic symptoms of MetS.[47] The presence of MetS has been shown to increase the rate of hospitalizations in patients with CD.[36,37] A study focused on CD patients showed a 4.3% commobidity rate of MetS, and it presented the CD-related hospitalization rate twice that of those who did not have MetS. MetS is supposed to exacerbate mesenteric inflammation and

may trigger symptomatic CD, which may be associated with risk factors including high triglycerides (TG), low HDL cholesterol and diabetes mellitus (DM).[18] What makes sense is that a healthy lifestyle should always be advised and promoted in IBD care to prevent metabolic disorders. In terms of diet, nutritional and metabolic interventions to avoid the development of metabolic complications associated with an unbalanced diet is necessary. Consumption of a Western dietary pattern, meat, and fried foods promotes the incidence of MetS.[48] PREDIMED and other studies had evidenced a beneficial role of traditional Mediterranean diet (higher in monounsaturated fatty acids) in preventing both MetS and IBD.[49] Secondly, it is suggested that patients with IBD who smoke quit to prevent the risks of long-term extra-digestive effects. Especially in Crohn's disease, smoking is reported to increase the risk of hospitalization.[36] In addition, physical activity is encouraged, as exercise are key components of energy expenditure and energy balance.

To the best of our knowledge, no epidemiological meta-analysis has yet systematically investigated the association between MetS and IBD. Our study presents the most comprehensive meta-analysis of the prevalence of MetS in patients with IBD. However, this review has several limitations. Above all, given the fact that most of the studies included in our study were cross-sectional in design, some potential confounding factors could lead to bias in the association between MetS and IBD. Additionally, most studies did not establish a control group of patients without IBD, a weakness of this meta-analysis is the lack of a calculation of odds ratio of MetS compared with IBD. Therefore, we can't confirm whether MetS is more common in

IBD than in the general population or not. Besides, as the number of studies included is little, the MetS prevalence estimates may be unstable due to the small sample sizes of some studies. Meanwhile, region, ethnicity, age, and different diagnostic criteria for MetS may also be the sources of heterogeneity, and publication bias may limit the generalizability of the results.

The principal conclusion of this meta-analysis is that MetS is not uncommon in patients with IBD, especially in UC and the elderly. Additional studies would be required to determine more precisely the prevalence of metabolic syndrome in the general population of individuals with inflammatory bowel disease. These studies should report and do further analysis of potential risk factors so that both adjusted and unadjusted prevalence of IBD with MetS can be calculated. Collectively, early detection of MetS can be expected to benefit patients with IBD and lead to better disease outcomes. Application of prevention measures for diabetes and CVD in patients with MetS and IBD may be required to improve their long-term prognosis, in particular the elderly. Future mechanistic studies are necessary to identify the potential relationships between MetS and IBD.

Author contribution: ZFS, MYZ and YJL contributed equally. Concept and design: LZ, HS and ZFS; Literature retrieval, study selection: YJL and MYZ; Data extraction and collection: YJL and ZFS; Analysis and interpretation of data: ZFS and LZ; Supervision and validation: HS and LZ; Drafting of the original manuscript: MYZ and ZFS. All authors have approved the final draft of the manuscript.

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FIGURE LEGENDS

Figure 1. Flowchart of the Meta-analysis. This flow chart is based on PRISMA framework, which shows the whole process of literature retrieving, screening, inclusion and exclusion.

Figure 2. Risk of bias of included studies using 11-item checklist recommended by Agency for Healthcare Research and Quality (AHRQ). A navy blue dot denotes low risk of bias, orange for unclear risk of bias, and light green for high risk of bias.

Figure 3. Forest plots for the overall pooled prevalence of comorbid MetS among patients with IBD.

Figure 4. Stratified analyses by type of IBD. The summary estimates were obtained using a random-effects model. The diamond data markers indicate the pooled proportion. CI indicates confidence interval.

Figure 5. Forest plots for the association of MetS with CD and UC. The size of the data markers indicates the weight of the study.

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Search strategy used in MEDLINE database. This search strategy will be modified as required for other electronic databases.

Supplementary Table S2. Quality assessment for studies using the Newcastle-Ottawa Scale.

Supplementary Table S3. Reporting checklist for a systematic review with meta-analysis.

Supplementary Figure S1. Funnel plot showing the overall prevalence of MetS in patients with IBD.

Supplementary Figure S2. Forest plot of sensitivity analyses by recalculating the pooled estimates of MetS in patients with IBD.

Supplementary Figure S3. Forest plots of stratified analyses by IBD subtype after omitting two heterogeneous studies. The pooled prevalence with 95% confidence intervals were calculated using the random effects model.

Supplementary Figure S4. Forest plot of sensitivity analyses showing the association between MetS and IBD. The pooled odds ratios with 95% confidence intervals were calculated using the fixed-effect model.

Table 1. Main characteristics of studies included in the meta-analysis.

Source	Region	Study design	No. of participants			Age (years)	MetS measures	Prevalence of MetS				NOS
			IBD	UC	CD			IBD	UC	CD	non-IBD	
Masakazu et al,[8] 2010	Japan	Prospective cross-sectional cohort	102	74	28	UC:43.6±13.5 CD:31.5±8.1	the modified National Cholesterol Education Program ATP-III	(17/102) 16.6%	(17/74) 23.0%	(2/28) 7.1%	NA	8
Sanja et al,[6] 2019	Serbia	Prospective cross-sectional cohort	104	54	50	UC:43.5(20–78) CD:35(19–72)	the International Diabetes Federation and ATP-III	(31/104) 29.7%	(16/54) 29.6%	(18/50) 36.0%	(6/45) 13.3%	7
Rotonya et al,[17] 2017	USA	Retrospective cohort	84	24	60	52.4±14.5	ATP-III	(19/84) 23%	(7/24) 29%	(12/60) 20%	NA	6
Paul et al, [18] 2015	USA	Retrospective cohort	—	—	868	40.4	the International Diabetes Federation definition	—	—	(37/868) 4.3%	NA	7
Marina et al, [19] 2019	Serbia	Prospective cross-sectional cohort	—	89	—	50(21-80)	ATP-III	—	(72/89) 81%	—	NA	3
Elif et al,[20] 2015	Turkish	Prospective cross-sectional cohort	177	115	62	UC:43.9±13.6 CD:36.7±13.9	the International Diabetes Federation	(47/177) 26.4%	(34/115) 29.5%	(11/62) 17.7%	NA	4
Min et al,[21] 2020	Korea	Retrospective cohort	443	169	274	35(26.0-49.5)	ATP-III	(47/443) 10.6%			NA	7
Catia et al, [23] 2019	Portugal	Prospective cross-sectional cohort	161	60	101	40.6±12.8	the American Heart Association	(21/161) 13.0%			NA	5
Salvatore et al, [22] 2019	Italy	Prospective cohort	178	95	83	49.7	ATP-III	(34/178) 19.1%			NA	8
Alessandro et al,[24] 2018	Italy	Retrospective cohort	78	36	42	51.2±11.8	ATP-III	(18/78) 23.1%			NA	7
Achuthan et al, [25] 2013	USA	Retrospective cohort	217	107	110	42±14.1	ATP-III	(36/217) 16.6%			NA	7

NA, not available; ATP-III, Adult Treatment Panel III; IBD, inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; MetS, metabolic syndrome; NOS, Newcastle-Ottawa scale.

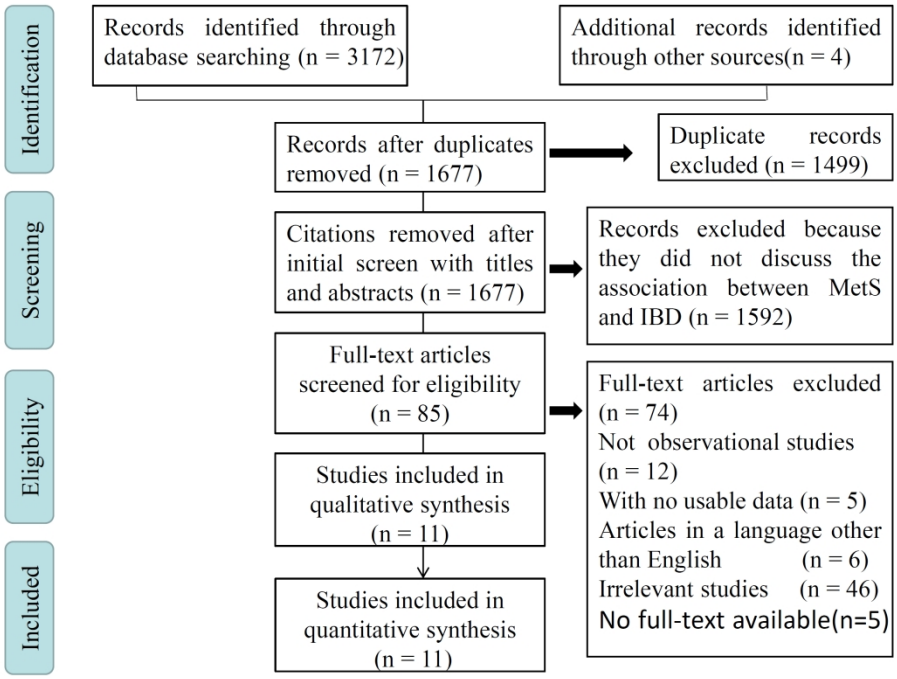

Figure 1. Flowchart of the Meta-analysis. This flow chart is based on PRISMA framework, which shows the whole process of literature retrieving, screening, inclusion and exclusion.

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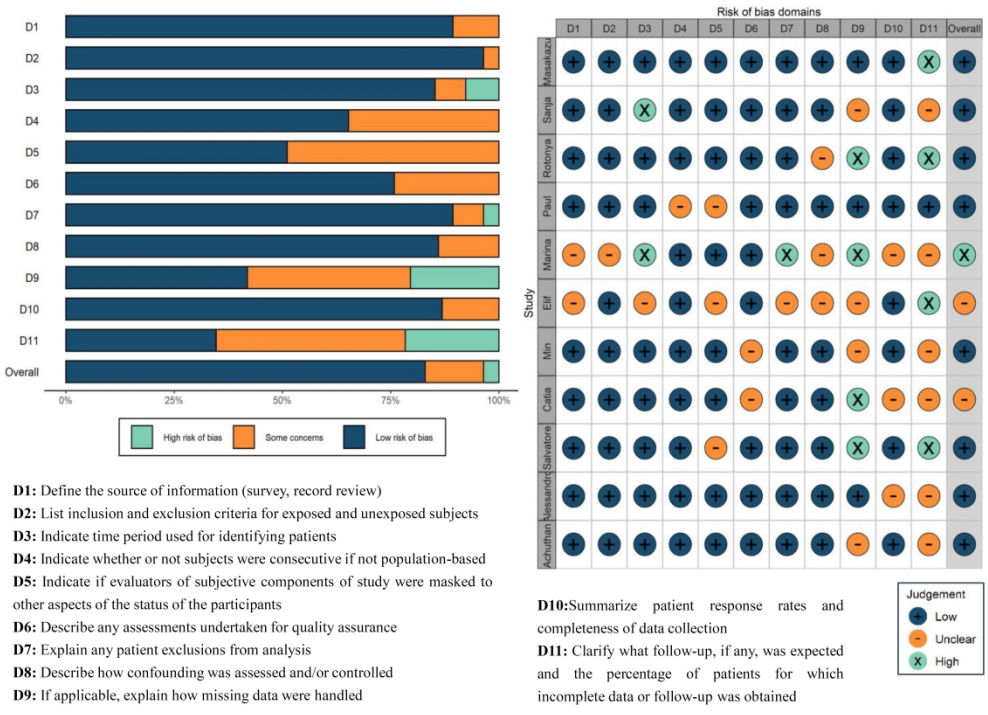

Figure 2. Risk of bias of included studies using 11-item checklist recommended by Agency for Healthcare Research and Quality (AHRQ). A navy blue dot denotes low risk of bias, orange for unclear risk of bias, and light green for high risk of bias.

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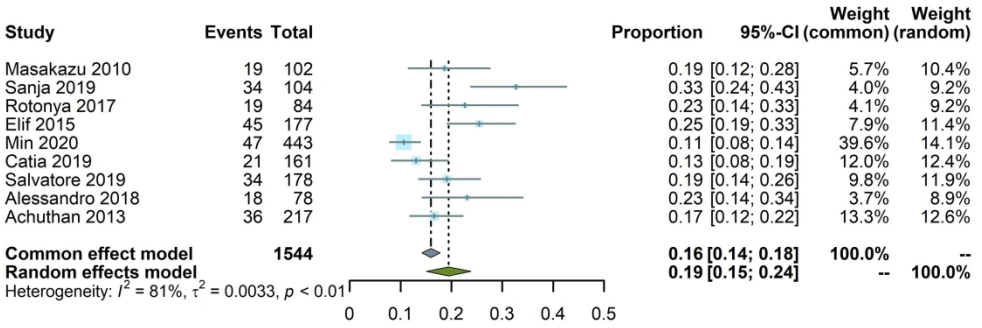

Figure 3. Forest plots for the overall pooled prevalence of comorbid MetS among patients with IBD.

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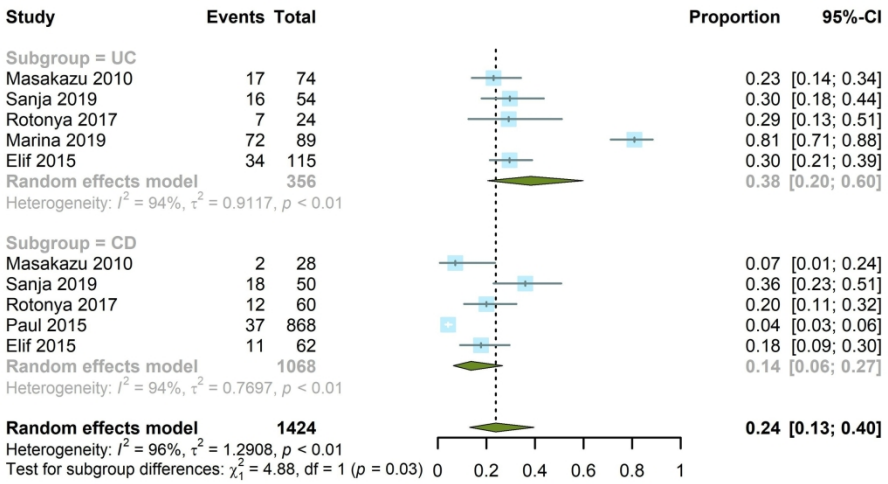

Figure 4. Stratified analyses by type of IBD. The summary estimates were obtained using a random-effects model. The diamond data markers indicate the pooled proportion. CI indicates confidence interval.

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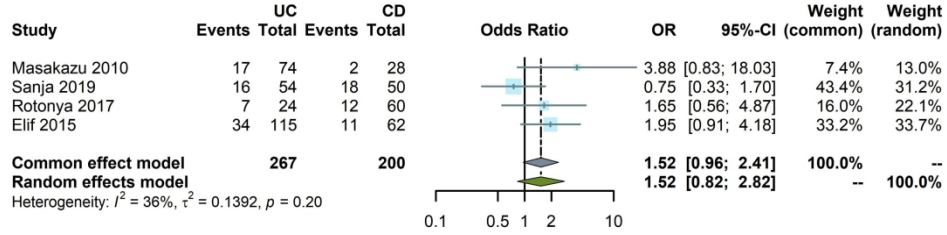

Figure 5. Forest plots for the association of MetS with CD and UC. The size of the data markers indicates the weight of the study.

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1	exp Inflammatory Bowel Diseases/
2	inflammatory bowel disease. mp.
3	IBD.mp
4	(ulcerative colitis or uc).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5	(crohn* or crohn* disease).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
6	1 or 2 or 3 or 4 or 5
7	Metabolic syndrome.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
8	MS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9	Mets.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10	7 or 8 or 9
11	6 and 10

Supplementary table S1: Search strategy used in MEDLINE database.

Supplementary table S2: Quality assessment for studies using the Newcastle-Ottawa Scale.

Study, year	Selection				Comparability	Outcome			Total score	Quality of evidence
	Representatives of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration outcome not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow up of cohorts		
	Representativeness of the sample	Sample size	Ascertainment of exposure	Non-respondents	based on the study design or analysis	Assessment of outcome	Statistical Test			
Masakazu et al, 2010[8]	1	1	1	1	2	1	NA		8	high
Sanja et al, 2019[6]	1	1	1	1	1	1	NA		7	high
Rotonya et al, 2017[17]	1	1	1	1	0	1	NA		6	high
Paul et al, 2015[18]	1	1	0	1	2	1	NA		7	high
Marina et al, 2019[19]	0	1	1	0	0	1	NA		3	low
Elif et al, 2015[20]	0	1	0	1	0	1	NA		4	medium
Min et al, 2020[21]	1	1	1	1	1	1	NA		7	high
Catia et al, 2019[23]	1	1	0	0	1	1	NA		5	medium
Salvatore et al, 2019[22]	1	1	1	1	1	1	1		8	high
Alessandro et al, 2018[24]	1	1	1	1	1	1	NA		7	high
Achuthan et al, 2013[25]	1	1	1	1	1	1	NA		7	high

[a] Quality assessment of the included studies was assessed using the modified Newcastle-Ottawa scale (rated on a 0-6 scale for studies without a comparator group and 0-9 for studies with a comparator group), studies with scores 5 or 6 (out of 6, for point prevalence studies) and 8 or 9 (out of 9, for comparative studies on risk in exposed vs. non-exposed cohorts) were considered high quality, studies with scores 4/6 or 6 or 7 out of 9, were considered medium quality, and all other studies were considered low quality.

Abbreviations: NA, Not Available; IBD, Inflammatory bowel disease.

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1,4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1,2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1,2,3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1,4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	1,4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5,6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5,6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6
Reporting bias	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
assessment			
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	6,7, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7, Figure 2, Table 1, supplementary Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3, Figure 4, Figure 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7-11, Figure 3, Figure 4, Figure 5,
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-11, Figure 3, Figure 4, Figure 5,
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9,10, Figure 3, Figure 4, Figure 5,
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9,10, supplementary Figure S2, Figure S3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9,10, Figure 2, Table S2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9,10, Figure S2, Figure S4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-15
	23b	Discuss any limitations of the evidence included in the review.	15,16
	23c	Discuss any limitations of the review processes used.	11,15,16
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4

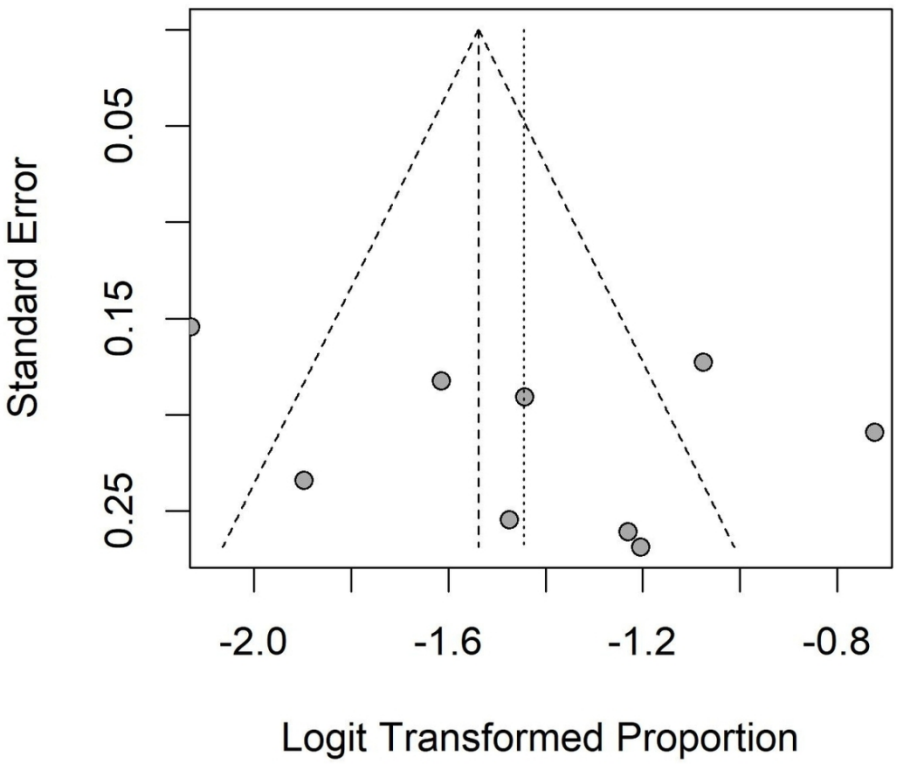
PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	17, Table 1, supplementary Table S1, Table S2, Table S3,

Supplementary Table S3. Reporting Checklist for a systematic review with meta-analysis.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/



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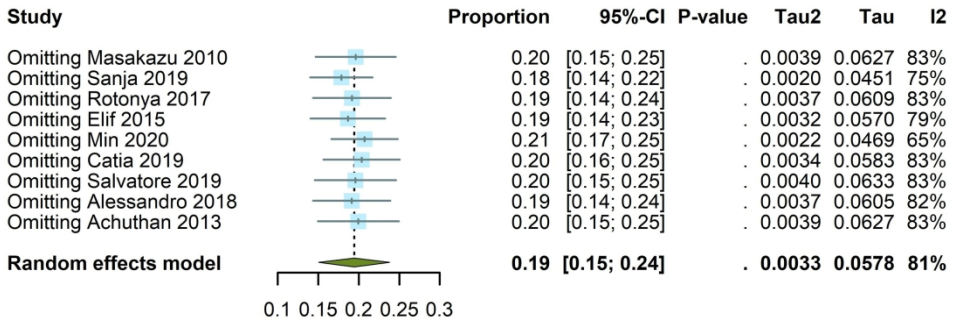

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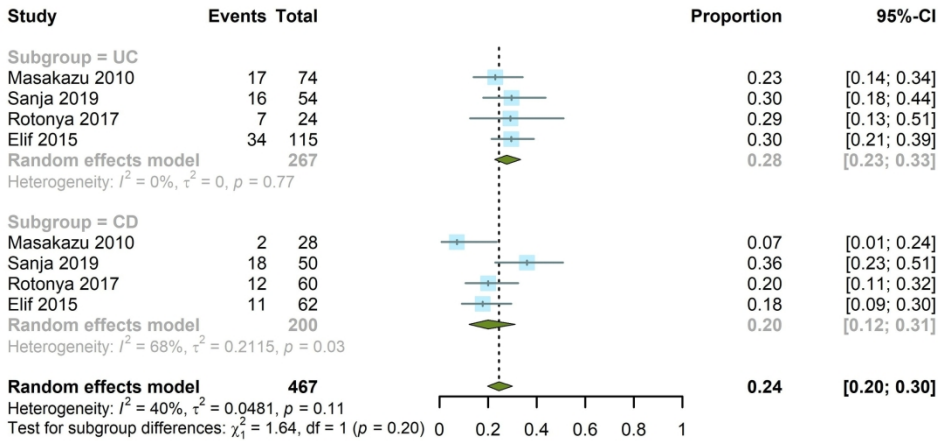

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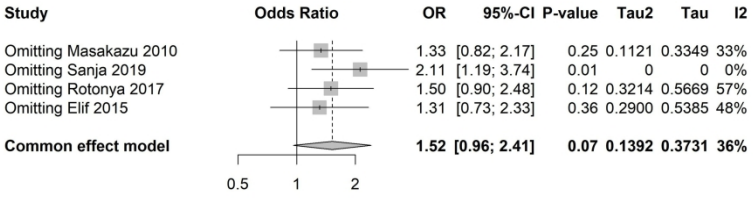

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BMJ Open

Prevalence of metabolic syndrome in patients with inflammatory bowel disease: a systematic review and meta-analysis

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Complete List of Authors:	Shen, Zhaofeng; Affiliated Hospital of Nanjing University of Chinese Medicine, Department of Science and Technology; School of Public Health Zhang, Mengyuan; Nanjing University of Chinese Medicine, Department of Gastroenterology Liu, Yijing; Nanjing University of Chinese Medicine, Department of Gastroenterology Ge, Changchang; Nanjing University of Chinese Medicine, Department of Gastroenterology Lu, Yi; Nanjing University of Chinese Medicine, Department of Gastroenterology Shen, Hong; Affiliated Hospital of Nanjing University of Chinese Medicine, Department of Gastroenterology Zhu, Lei; Affiliated Hospital of Nanjing University of Chinese Medicine, Department of Gastroenterology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Epidemiology, Qualitative research
Keywords:	Inflammatory bowel disease < GASTROENTEROLOGY, QUALITATIVE RESEARCH, Systematic Review

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Prevalence of metabolic syndrome in patients with inflammatory bowel disease: a systematic review and meta-analysis

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ABSTRACT

Objectives: Patients with inflammatory bowel disease (IBD) may experience comorbidities involving metabolic syndrome (MetS). However, this association remains controversial. Our objective was to estimate the prevalence of MetS in patients with IBD and assess whether MetS is more strongly associated with ulcerative colitis (UC) or Crohn's disease (CD).

Design: Systematic review and meta-analysis.

Data sources: PubMed, Cochrane Library, Web of Science, EMBASE and MEDLINE were searched from their inception to July 2022.

Eligibility criteria: Observational studies reporting data regarding the rate of comorbid MetS among patients with IBD and published in English.

Data extraction and synthesis: The PRISMA and MOOSE reporting guidelines were followed. Pooled prevalence, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using random-effects models. The Newcastle-Ottawa Scale and AHRQ checklist were used. Heterogeneity, sensitivity and stratified analyses were performed using R (version 4.2.1).

Results: 11 eligible studies involving 2501 patients were included. Of these studies, four reported MetS prevalence separately by IBD phenotype, and only one contained a non-IBD comparison group. Overall, the methodological quality of the included studies was moderate. The pooled prevalence of MetS in IBD was 19.4% (95% CI 15.1%-23.8%), with a moderate heterogeneity (I^2=51.8%, Cochrane Q statistic=12.4, P=0.053). Stratified analyses demonstrated that the aggregate estimate of comorbid MetS was significantly higher in UC than in CD (38.2% vs 13.6%, χ^2=4.88, P=0.03). We found a positive association between MetS and UC compared with CD (OR=2.11, 95% CI 1.19-3.74, P=0.01). Additionally, four studies identified that higher age was a risk factor associated with the development of MetS.

Conclusions: MetS is not rare in IBD, especially in UC. However, longitudinal studies are needed to further clarify the relationship between IBD and MetS.

Study registration: PROSPERO, CRD42022346340.

Keywords: inflammatory bowel disease, metabolic syndrome, ulcerative colitis, Crohn's disease, meta-analysis

Strengths and limitations of this study

- Our study was registered on PROSPERO and represents a comprehensive synthesis of the available evidence on the prevalence and association of comorbid metabolic syndrome (MetS) among patients with inflammatory bowel disease (IBD).
- NOS and AHRQ were used to assess the quality of individual studies and the PRISMA and MOOSE guidelines were followed in reporting the results.
- Heterogeneity, sensitivity and stratified analyses were performed.
- Most of the studies included in this meta-analysis were cross-sectional in design, and some potential confounding factors could lead to bias in the association between MetS and IBD.
- The number of studies included in the subgroup analyses was limited.

Abbreviations: IBD, inflammatory bowel disease; MetS, metabolic syndrome; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; MOOSE, Meta-analysis of Observational Studies in Epidemiology; NOS, Newcastle-Ottawa scale; AHRQ, Agency for Healthcare Research and Quality; CVD,

cardiovascular disease; VAT, visceral adipose tissue.

INTRODUCTION

Metabolic syndrome (MetS) is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia.[1] As the lifestyle of modern people changing, lack of exercise, and excessive accumulation of calories is suggested to be the direct causes of this kind of disease.[2] While with deeper cognition about MetS, it is found to be associated with many chronic diseases, like type 2 diabetes, coronary diseases, stroke, and other disabilities. MetS has increased the social burdens with the cost of health care and potential loss of economic.[1,3]

The inflammatory bowel disease (IBD) causes idiopathic chronic inflammation of intestines, the etiology of IBD is unknown, and its incidence is rising worldwide. In the 21st century, the incidence of IBD is more than 0.3% of the total population in western countries like the UK, the USA, Canada, Denmark, Sweden, Germany, and Australia, and also rises in developing countries.[4] Crohn's disease (CD) and ulcerative colitis (UC) are two major phenotypes of IBD. The etiology of IBD (UC or CD) is yet to be elucidated. Currently, IBD is considered to be a multifactorial disease, involving genetic predisposition, environmental factors, and immuno-metabolic disorders.[5,6]

Interestingly, there are many commonalities between IBD and MetS, like dyslipidemia, immune system imbalance, and chronic inflammation state.[3] Many previous studies have shown overlap between IBD and MetS and investigated the

prevalence rates. However, the results are diverse.[6-8] Prior studies looking at the relationship between IBD and MetS have been observational studies or from single-center limited by sample size. The aim of this systematic review and meta-analysis was to determine the overall prevalence of comorbid MetS among IBD patients and to explore the association.

METHODS

This meta-analysis is reported in accordance with the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE).[9,10] The protocol was registered with PROSPERO (CRD42022346340). No ethical approval was required.

Search strategy

We searched PubMed, Cochrane Library, Web of Science, EMBASE and MEDLINE from the respective dates of database inception to July 2022 for studies reporting the prevalence of comorbid MetS among IBD patients. A combination of medical subject headings terms and/or free text words was utilized: “metabolic syndrome”, “Inflammatory bowel disease”, “Ulcerative colitis”, “Crohn disease”, “MetS”, “MS”, “IBD”, “UC”, and “CD”. In addition, we also conducted hand-searching of all references of the retrieved studies for further relevant reports. The search was limited to papers published in English. No other restrictions were imposed. The search strategy was undertaken independently by two investigators (YJL and MYZ) who are experienced in the information retrieval. The preliminary search strategy is shown in

Table (Supplementary Table S1), which was adapted according to syntax-related requirements of electronic databases.

Study selection

The inclusion criteria of eligible studies were as follows: (1) patients with confirmed IBD (including UC and CD) and MetS; (2) observational studies (including cross-sectional, case-control and cohort studies) ; (3) primary outcome regarding the prevalence of MetS in IBD patients or the association of MetS with IBD; (4) original studies in the English language providing sufficient information to calculate the effect size. All studies were limited to those involving human subjects, animal studies, case reports, review articles, redundant studies or studies that did not report specific outcome were excluded.

Data extraction and risk of bias assessment

Two researchers (YJL and MYZ) independently identified relevant literature by reading the titles, abstracts and full texts of the studies retrieved. The following information was subsequently extracted using a preestablished literature extraction table: author, journal, title, year of publication, contact information, country, study design, study population characteristics (participants, proportion of CD and UC, sample size, diagnosis criteria, general demographic information), clinical characteristics (duration, activity, severity, treatment), outcomes (prevalence, odds ratio, risk ratio, risk factors), conclusion (association of MetS with IBD), etc.

Since all the eligible studies were observational, the methodological quality was assessed using the Newcastle-Ottawa scale (NOS) and 11-item checklist recommended

by Agency for Healthcare Research and Quality (AHRQ).[11,12] The NOS was used to evaluate the quality of cross-sectional or cohort studies, including three categories: selection (four items, one star for each item), comparability (one item, up to two stars) and outcome (three items, one star for each item). Thus, a study can be awarded up to a maximum of nine points. The quality of the study was classified as low (0-4 points), moderate (4–6 points) and high (7-9 points). The AHRQ was employed to assess the risk of bias in cross-sectional studies based on 11-item questions. An item was scored '0' if it was answered 'NO' or 'UNCLEAR'; if it was answered 'YES', then the item scored '1'. The quality of the study was assessed based on the total score. Overall, the results were divided into three levels: high quality (8–11 points) , moderate quality (4–7 points) and low quality (0–3 points). Any discrepancies between the two investigators were resolved by consulting a third reviewer (ZFS).

Data synthesis and statistical analysis

Statistical analyses were performed using the packages (i.e., meta and metafor) in R (version 4.2.1, R Foundation for Statistical Computing).[13] The pooled prevalence of MetS among IBD were calculated as an aggregate mean, weighted by the sample size of each included study. The Log transformed proportions (PLN), Logit transformed proportions (PLOGIT), Arcsine transformed proportions (PAS) and Freeman-Tukey Double arcsine transformed proportions (PFT) were used to stabilize the variance of individual studies. If the results were inconsistent, the Freeman-Tukey Double arcsine transformation was preferred over other methods. Subsequently, the unadjusted odds ratios (OR) were pooled from studies that had included a comparison group to give

overall estimates of the association between MetS and IBD (UC or CD). All the values were estimated with 95% confidence intervals (95% CI). Both the fixed-effect model and random-effects model were applied to estimate the pooled estimates. Given the conservativeness of results, the random-effects model proposed by DerSimonian-Laird (1986) was considered to be the primary method.[14] Subgroup (stratified) analyses were performed according to IBD phenotypes (UC and CD), and sensitivity analyses were conducted by recalculating the pooled estimates after omitting studies of low quality. Furthermore, we narratively summarized data regarding risk factors for MetS among IBD patients. The statistical heterogeneity was assessed using the inconsistency index (I^2) and Cochrane Q statistic.[15] The results were classified into three levels: low heterogeneity (I^2<25%), moderate heterogeneity (25%< I^2<50%), high heterogeneity (I^2>75%). We defined significantly heterogeneity if $P < 0.1$ and I^2>50%. The potential publication bias was evaluated by the funnel plot and Egger's test.[16]

Patient and public involvement

None.

RESULTS

Literature search

A total of 3176 relevant records were initially identified. After the preliminary screening, 1499 articles were removed because of duplication. Based on the inspection of titles and abstracts, 85 potential studies were retrieved for further evaluation. After examining the full text, 11 of these publications met the predefined eligibility criteria

and were included in our meta-analysis.[6,8,17-25] The PRISMA flow diagram of search strategy and study selection is illustrated in Figure 1.

Study characteristics

We found that all included studies investigated the prevalence of MetS in IBD patients (rather than the prevalence of IBD in MetS patients). All the studies were published after 2010, and 6 (55%) were cross-sectional in design. Three studies were conducted in North America, five in Europe, and three in Asia. In total, 2501 patients with IBD were included in this study, 1678 (67.1%) had a diagnosis of CD and 823 (32.9%) had a diagnosis of UC. In most of the studies, IBD along with UC and CD was defined by international diagnostic criteria (e.g., ECCO), and MetS was identified using the NCEP-ATP-III criteria. Of the 11 included studies, 1 (9.1%) comprised both IBD group and non-IBD comparison group, while 10 (90.9%) included only one disease cohort. Among these studies, 1 (9.1%) was limited to patients with UC, 1 (9.1%) to patients with CD, and 9 (81.8%) to patients with a mixed sample (i.e., one that contained patients having both UC and CD). Four (44.4%) of the mixed-sample studies reported MetS prevalence separately by different IBD phenotypes (CD and UC). The general characteristics of the studies included were given in Table 1.

Risk of bias of included studies

Given the types of studies included, we used the Newcastle-Ottawa scale and AHRQ checklist to appraise the risk of bias for each study. However, some questions were not applicable. The majority of studies scored well in terms of patient selection and outcome assessment, whereas one study was rated at high risk in that it did not report

relevant information. Overall, the risk of bias of the included studies was moderate and acceptable. The results of the assessment were illustrated in Figure 2 and Table 1 (Supplementary Table S2).

Overall prevalence of MetS among patients with IBD

We identified 9 studies that reported available information regarding the prevalence of MetS among patients with IBD. Five of them were limited to analyze the overall prevalence of comorbid MetS in patients with IBD, while the remaining four studies were subsequently pooled into subgroup analyses. A total of 273 MetS cases were detected among 1544 patients with IBD. Overall, the prevalence of comorbid MetS ranged from 10.6% to 32.7%. As a result, the pooled prevalence of MetS in IBD was estimated to be 19.4% (95% CI 15.1% to 23.8%). Since there was substantial statistical heterogeneity across the studies (I^2=81.0%, Cochrane Q statistic=42.2, P<0.001), a random-effect model was used in our study. These unadjusted prevalence estimates and study heterogeneity were illustrated in the forest plot (Figure 3). There was no evidence of publication bias according to the Egger's test (P= 0.332), and the funnel plot is almost symmetrical (Supplementary Figure S1). It is worth noting that these proportions were determined by type of design, source of subject, quality of study, and method of outcome assessment. Therefore, we conducted further analyses. Sensitivity analyses revealed similar results (pooled estimate 20.7%; 95% CI, 16.6%-24.8%) and Min et al.' s study[21] had the largest influence on the results (Supplementary Figure S2). After excluding two studies with low quality and ambiguous information,[21,23] we found that the overall pooled prevalence was 21.9% (95% CI 18.0% to 25.8%) with moderate

heterogeneity (I^2=51.8%, Cochrane Q statistic=12.4, P=0.053). Overall, only one study reported the prevalence of MetS in non-IBD controls.[6] MetS was more frequent in IBD patients (32.7%) than in non-IBD control group (13.3%), and there was a significant positive association between MetS and CD (P=0.01).

Stratified analyses of comorbid MetS between patients with UC and CD

Taking the subtype of IBD into account, we performed stratified analyses. In total, six included studies provided specific information regarding the prevalence of comorbid MetS in either UC or CD.[6,8,17-20] All the studies were divided into two groups: 356 patients with UC (n=5 studies) in the UC analyses and 1068 patients with CD (n=5 studies) in the CD analyses. The pooled prevalence of comorbid MetS was 38.2% in UC (95% CI, 20.4%-59.9%), and 13.6% in CD (95% CI, 6.4%-26.7%). Strikingly, the aggregate estimate of MetS was significantly higher in UC than in CD (Cochran-Mantel-Haenszel χ^2= 4.88, P = 0.03). Nevertheless, significant heterogeneity was observed (I^2= 94%, P < 0.01). Detailed information is shown in Figure 4. Sensitivity analyses by omitting two heterogeneous studies showed that MetS was more frequent in UC than in CD (27.7% vs 20.0%) with decreasing heterogeneity (I^2=40.2%, P = 0.11).[18,19] However, no statistically significant difference (Cochran-Mantel-Haenszel χ^2= 1.64, P = 0.2) was reached (Supplementary Figure S3).

When we only included mixed-sample studies that reported comorbidity of MetS separately by different IBD phenotypes (n = 4 studies), the meta-analysis demonstrated a negative association between MetS and UC compared to CD controls (pooled OR = 1.52, 95% CI 0.96-2.41, P = 0.073).[6,8,17,20] Except for the study by Sanja et al. (OR

= 0.748),[6] the remaining 3 studies reported an OR above 1.00. As shown in the forest plot (Supplementary Figure S4), a low to moderate heterogeneity was detected (I^2=35.9%, Cochrane Q statistic = 4.68, P = 0.197). Similarly, sensitivity analyses were conducted to investigate the stability of the results. We found that Sanja et al.'s study had a significant impact on the results. After omitting Sanja et al.'s study, the pooled estimate appreciably changed to be 2.11 (95% CI 1.19-3.74, P = 0.01), which implies a risk approximately twice higher in UC than in CD (Supplementary Figure S5). Although there was no evidence of statistical heterogeneity (I^2 = 0%, Cochrane Q statistic = 4.68, P = 0.197), the number of studies that separately reported the outcome was small.

Risk factors for MetS among IBD patients

There were four studies that specifically investigated relevant risk factors associated with MetS among IBD patients.[8,17-19] One of these by Masakazu et al. found no statistical difference on gender, IBD phenotype, treatment, social history, or health-related lifestyle between IBD patients with and without MetS.[8] However, IBD patients with MetS were older than those without (50.2 ± 15.0 vs. 38.0 ± 11.9, P = 0.013). Moreover, age was the independent risks factors for MetS among IBD patients in a multivariate logistic regression analysis (OR=1.064, 95%CI 1.017 to 1.114). The retrospective cohort study based on electronic healthcare record demonstrated that IBD patients with concomitant MetS were statistically significantly older at the time of IBD diagnosis (P = 0.005).[17] In addition, IBD patients with MetS had overall higher prevalence of obesity, hypertension and diabetes or insulin resistance than non-MetS

IBD patients (P < 0.001). Similarly, Paul et al. from the USA reported that CD Patients with MetS were older as compared with those without MetS (P<0.001). However, there was no statistically significant difference in gender, race, or duration of disease between those two groups (P > 0.05).[18] Remarkably, after multivariate adjustment (e.g., age, sex, race, duration of CD), patients with MetS had a CD-related hospitalization rate twice that of those without MetS (OR=1.91, 95%CI 1.12 to 3.26). Interestingly, the study by Marina et al. revealed similar results that patients with UC and MetS were significantly older compared to UC patients without MetS (P=0.001).[19] Furthermore, UC patients with MetS reported higher values in cholesterol, triglycerides, low-density lipoprotein, interleukin-10, and Galectin-3, compared to patients suffering from UC only. As a result, UC patients with MetS had lower Mayo endoscopic subscore (P=0.038) and Mayo clinical score (P=0.005), indicating that patients with UC and MetS were milder. Overall, four studies identified that age was a statistically significant risk factor associated with the development of MetS. However, only one study further performed a multivariate analysis, and only two satisfied the criteria. Given the limited number of studies, we failed to conduct a meta-analysis to elucidate the association between age and the incidence of MetS. Other variables (e.g., Obesity, Diabetes) were also potential risk factors for the development of MetS among patients with IBD. Unfortunately, most of the included studies did not provide valuable data.

DISCUSSION

Our study demonstrates the pooled prevalence of MetS in the IBD population from 11

studies, having a combined total of 2501 subjects. The present data reveal that MetS is not a rare complication among IBD patients, as the pooled prevalence of MetS in IBD was 19.4% (95% CI 15.1%-23.8%). To further understand the significance of the prevalence of comorbid MetS in IBD, we compared our result with external data reported by other investigators. It is reported that the prevalence of MetS in the general population ranged from 16.5% to 34.7% [26-33], and it tends to be more frequent in Western countries.[34] A cross-sectional study from the USA evaluated the MetS prevalence among 17048 adult participants, from 2011 to 2016, and the result was 34.7% (95% CI, 33.1%-36.3%).[26] The prevalence of the metabolic syndrome from our study appeared to be lower than that in the U.S. adult population.[26,27] While it was comparable to that in the Asia-Pacific regions and the Middle-East countries.[28-33] Given the fact that the studies included in this Meta-analysis were mainly from Europe, America, and Asia, we suspect the prevalence of MetS in IBD was determined by region, age and method of outcome assessment. Therefore, the calculated comorbidity rate of MetS and IBD may not fully reflect its actual global prevalent status.

MetS develops as a result of progressive weight gain, fat mass accumulation and insulin resistance. MetS is a complex pathophysiologic state that originates primarily from an imbalance of calorie intake and energy expenditure, genetic/epigenetic make up of individual, predominance of sedentary, and other factors like quality and composition of food and composition of gut microbes. MetS is associated with a marked increase in risk of cardiovascular disease and type 2 diabetes, possibly due to abdominal obesity, hyperglycemia, dyslipidemia, and hypertension.[34,35] A clear

increase in the prevalence of MetS with aging has been largely recognized, there are many commonalities in biochemical changes of aging process and metabolic syndrome. According to our analysis, that age might be a statistically significant risks factor involved in the association between MetS and IBD, so evaluation for MetS is needed for elderly IBD patients.

Attention on comorbidity is crucial when managing patients with IBD because they can alter disease activity and extraintestinal manifestations, influence disease prognosis, and influence pharmacological therapeutic effects. Both of MetS and IBD are increasingly globally prevalent diseases. The pathogenesis and characteristics of disease course of MetS in the IBD population are not entirely clear, and the pathogenesis of MetS in the IBD population may be more complex. Researchers have reported MetS and IBD share common pathophysiological features such as immune imbalance, chronic inflammation, disturbed secretion of adipokines, and increased risk of cardiovascular disease (CVD).[3,36] Although our data did not show a close association of CVD risk in IBD with MetS, given the fact that MetS accelerates atherogenesis and eventually resulting CVD, and systemic inflammation can contribute to atherogenesis, an increased risk of CVD in patients with IBD and MetS is just can not be ignored.

The adipose tissue (AT), and particularly the visceral adipose tissue (VAT) plays an important part in the pathophysiology of MetS. It is suggested that VAT may participate in chronic systemic inflammation of both MetS and IBD.[3,37] The VAT composed of hypertrophic adipocytes that secrete abnormal levels of adipokines, for

example, it may downregulate synthesis of leptin, adiponectin, and adipocytokines responsible for pro- and anti-inflammatory effects.[38] A lower level of serum and mesenteric adiponectin was observed in active CD, indicating adiponectin is associated with a defective regulation of anti-inflammatory pathways in CD pathogenesis.[39] The VAT also produces proinflammatory cytokines like interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein 1 (MCP-1), leading to infiltration of M1 macrophages and causing low-grade chronic inflammation. M1 macrophages can also promote hepatic steatosis and adipogenesis.[3,37] Reversely, the inflammation may also affect adipose tissue and disturb the adipokine secretion In MetS and IBD. It is reported that inflammation may induce dyslipidemia through downregulation of lipoprotein lipase enzyme affected by the action of proinflammatory cytokines TNF-α, IL-6, and interferon (IFN)-γ.[40] In the included studies, some of them showed that IBD lipid profile was characterized by decreased total cholesterol (TC) and high-density lipoprotein (HDL) cholesterol. HDL performs many anti-inflammatory activities, indicates that decrease in its level could not only be the effect but also the cause of intestinal chronic inflammation.[41]

As reported, gut dysbiosis is probably an additional factor that could alter immune-metabolic state in IBD and MetS.[34] Inflammation and the gut microbiome can trigger intestinal barrier dysfunction, while in IBD, disruption of the gut barrier allows microbe infiltration into the submucosae, which enhances the probability that gut-derived metabolites translate from the gut to the liver and pancreas. So gut microbial dysbiosis may be one of the potential mechanisms contributing to comorbidity of MetS and IBD

via increased intestinal permeability.[2] Refer to a recent study that reported gut virome changes have association with MetS and exhibit decreased richness and diversity, provided a starting point to studies of phage effects on gut bacteria and the role that this plays in MetS.[42] Akkermansia muciniphila is a gram-negative and mucin-degrading bacterium, which is highly abundant in the gut microbiota. Reduced levels of A. muciniphila have been observed in patients with inflammatory bowel diseases (mainly ulcerative colitis) and metabolic disorders, which suggests it may have potential anti-inflammatory properties linked to impaired gut-barrier integrity.[43] A recent study shows that pasteurization of Akkermansia muciniphila enhances the bacterium's ability to reduce fat mass and metabolic syndrome in mice with diet-induced obesity, which may be a strategy to fight against obesity and IBD.[44] It is reported that intestinal microbiota protects against development of metabolic syndrome by inducing Th17 cells and regulating lipid absorption across intestinal epithelium. However, high-fat, high-sugar diet will promote metabolic disease by depleting Th17-inducing microbes. The findings highlight an interaction between diet, microbiota, and intestinal immunity in metabolic disorders.[45]

In our current meta-analysis, MetS prevalence is found to be significantly lower in CD than in UC (OR=2.11, 95% CI 1.19-3.74, P=0.01), which should be noticed that the average age of patients with UC is older in these studies. A study reported a prevalence of MetS reached to 81% in UC, and the average age of the patients is 50 (21-80). The study also indicated that patients with MetS have milder form of UC, with higher serum level of immunosuppressive cytokine interleukin-10 (IL-10) and fecal

content of Galectin3 (Gal-3), they supposed the presence of MetS may limit the inflammatory process and subsequent tissue damage in UC possibly by deviating local inflammatory response toward enhanced participation of immunosuppressive cells and molecules.[19] CD and UC have been postulated to involve different immunological backgrounds. The inflammation of UC primarily involves the colonic mucosa. Differently, features of Crohn's disease are transmural inflammation affecting all layers of the intestinal wall and mesenteric lymph nodes and chronic noncaseating granulomatous inflammation.[46] Underweight is more frequently observed in patients with CD, as lack of proper gut function reduces nutrient absorption. CD often accompanies with malnutrition and, thus, might not present classic symptoms of MetS.[47] The presence of MetS has been shown to increase the rate of hospitalizations in patients with CD.[36,37] A study focused on CD patients showed a 4.3% comorbidity rate of MetS, and it presented the CD-related hospitalization rate twice that of those who did not have MetS. MetS is supposed to exacerbate mesenteric inflammation and may trigger symptomatic CD, which may be associated with risk factors including high triglycerides (TG), low HDL cholesterol and diabetes mellitus (DM).[18] What makes sense is that a healthy lifestyle should always be advised and promoted in IBD care to prevent metabolic disorders. In terms of diet, nutritional and metabolic interventions to avoid the development of metabolic complications associated with an unbalanced diet is necessary. Consumption of a Western dietary pattern, meat, and fried foods promotes the incidence of MetS.[48] PREDIMED and other studies had evidenced a beneficial role of traditional Mediterranean diet (higher

in monounsaturated fatty acids) in preventing both MetS and IBD.[49] Secondly, it is suggested that patients with IBD who smoke quit to prevent the risks of long-term extra-digestive effects. Especially in Crohn's disease, smoking is reported to increase the risk of hospitalization.[36] In addition, physical activity is encouraged, as exercise are key components of energy expenditure and energy balance.

To the best of our knowledge, no epidemiological meta-analysis has yet systematically investigated the association between MetS and IBD. Our study presents the most comprehensive meta-analysis of the prevalence of MetS in patients with IBD. However, this review has several limitations. Above all, given the fact that most of the studies included in our study were cross-sectional in design, some potential confounding factors could lead to bias in the association between MetS and IBD. Additionally, most studies did not establish a control group of patients without IBD, a weakness of this meta-analysis is the lack of a calculation of odds ratio of MetS compared with IBD. Therefore, we can't confirm whether MetS is more common in IBD than in the general population or not. Besides, as the number of studies included is little, the MetS prevalence estimates may be unstable due to the small sample sizes of some studies. Meanwhile, region, ethnicity, age, and different diagnostic criteria for MetS may also be the sources of heterogeneity, and publication bias may limit the generalizability of the results.

The principal conclusion of this meta-analysis is that MetS is not uncommon in patients with IBD, especially in UC and in older patients. Additional studies would be required to determine more precisely the prevalence of metabolic syndrome in the

general population of individuals with inflammatory bowel disease. Such studies could also further investigate potential risk factors so that both adjusted and unadjusted prevalence of IBD with MetS can be calculated. Collectively, early detection of MetS can be expected to benefit patients with IBD and lead to better disease outcomes. Application of prevention measures for diabetes and CVD in patients with MetS and IBD may be required to improve their long-term prognosis, particularly in older patients. Mechanistic studies are also needed to further explore the potential relationships between MetS and IBD.

Contributors: ZFS, MYZ and YJL contributed equally. Concept and design: LZ, HS and ZFS; Literature retrieval, study selection: YJL and MYZ; Data extraction and collection: YJL, CCG and ZFS; Analysis and interpretation of data: ZFS, YL and LZ; Supervision and validation: LZ, CCG, HS and LZ; Drafting of the original manuscript: MYZ and ZFS. All authors have approved the final draft of the manuscript.

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FIGURE LEGENDS

Figure 1. Flowchart of the meta-analysis. This flowchart is based on PRISMA framework, which shows the whole process of literature retrieving, screening, inclusion and exclusion.

Figure 2. Risk of bias of included studies using 11-item checklist recommended by Agency for Healthcare Research and Quality (AHRQ). A navy blue dot denotes low risk of bias, orange for unclear risk of bias, and light green for high risk of bias.

Figure 3. Forest plots for the overall pooled prevalence of comorbid MetS among patients with IBD.

Figure 4. Stratified analyses by type of IBD. The summary estimates were obtained using a random-effects model. The diamond data markers indicate the pooled proportion. CI indicates confidence interval.

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Search strategy used in PubMed, Cochrane Library, Web of Science, EMBASE and MEDLINE database.

Supplementary Table S2. Quality assessment for studies using the Newcastle-Ottawa Scale.

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Supplementary Figure S3. Forest plots of stratified analyses by IBD subtype after omitting two heterogeneous studies. The pooled prevalence with 95% confidence intervals were calculated using the random effects model.

Supplementary Figure S4. Forest plots for the association of MetS with CD and UC. The size of the data markers indicates the weight of the study.

Supplementary Figure S5. Forest plot of sensitivity analyses showing the association between MetS and IBD. The pooled odds ratios with 95% confidence intervals were calculated using the fixed-effect model.

Table 1. Main characteristics of studies included in the meta-analysis

Source	Region	Study design	No. of participants			Age (years)	MetS measures	Prevalence of MetS				NOS
			IBD	UC	CD			IBD	UC	CD	non-IBD	
Masakazu et al,[8] 2010	Japan	Prospective cross-sectional cohort	102	74	28	UC:43.6±13.5 CD:31.5±8.1	the modified National Cholesterol Education Program ATP-III	(23/102) 22.6%	(17/74) 23.0%	(2/28) 7.1%	NA	8
Sanja et al,[6] 2019	Serbia	Prospective cross-sectional cohort	104	54	50	UC:43.5(20–78) CD:35(19–72)	the International Diabetes Federation and ATP-III	(32/104) 30.7%	(16/54) 29.6%	(18/50) 36.0%	(6/45) 13.3%	7
Rotonya et al,[17] 2017	USA	Retrospective cohort	84	24	60	52.4±14.5	ATP-III	(19/84) 23%	(7/24) 29%	(12/60) 20%	NA	6
Paul et al, [18] 2015	USA	Retrospective cohort	—	—	868	40.4	the International Diabetes Federation definition	—	—	(37/868) 4.3%	NA	7
Marina et al, [19] 2019	Serbia	Prospective cross-sectional cohort	—	89	—	50(21-80)	ATP-III	—	(72/89) 81%	—	NA	3
Elif et al,[20] 2015	Turkish	Prospective cross-sectional cohort	177	115	62	UC:43.9±13.6 CD:36.7±13.9	the International Diabetes Federation	(47/177) 26.4%	(34/115) 29.5%	(11/62) 17.7%	NA	4
Min et al,[21] 2020	Korea	Retrospective cohort	443	169	274	35(26.0-49.5)	ATP-III	(47/443) 10.6%			NA	7
Catia et al, [23] 2019	Portugal	Prospective cross-sectional cohort	161	60	101	40.6±12.8	the American Heart Association	(21/161) 13.0%			NA	5
Salvatore et al, [22] 2019	Italy	Prospective cohort	178	95	83	49.7	ATP-III	(31/178) 17.1%			NA	8
Alessandro et al,[24] 2018	Italy	Retrospective cohort	78	36	42	51.2±11.8	ATP-III	(18/78) 23.1%			NA	7
Achuthan et al, [25] 2013	USA	Retrospective cohort	217	107	110	42±14.1	ATP-III	(36/217) 16.6%			NA	7

NA, not available; ATP-III, Adult Treatment Panel III; IBD, inflammatory bowel disease; UC, Ulcerative colitis; CD, Crohn's disease; MetS, metabolic syndrome; NOS, Newcastle-Ottawa scale.

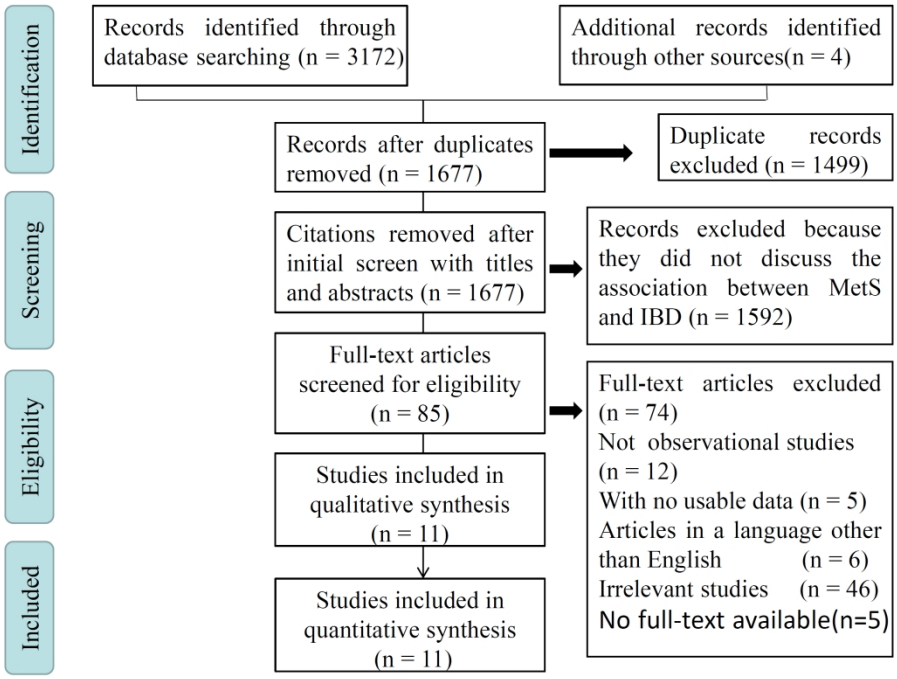

Figure 1. Flowchart of the Meta-analysis. This flow chart is based on PRISMA framework, which shows the whole process of literature retrieving, screening, inclusion and exclusion.

1998x1554mm (38 x 38 DPI)

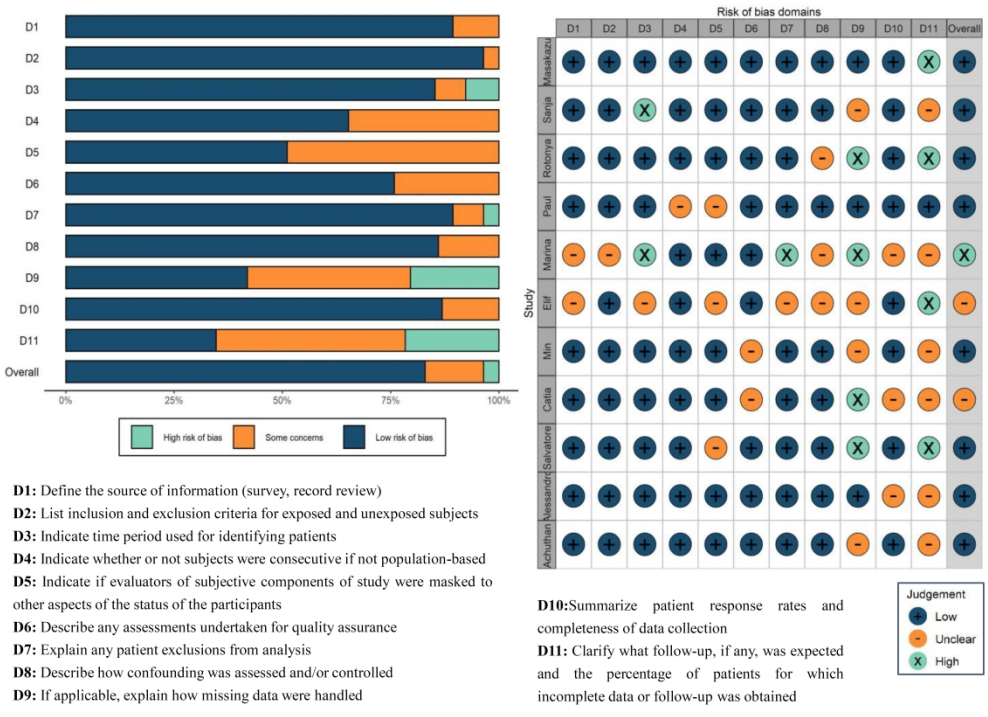

Figure 2. Risk of bias of included studies using 11-item checklist recommended by Agency for Healthcare Research and Quality (AHRQ). A navy blue dot denotes low risk of bias, orange for unclear risk of bias, and light green for high risk of bias.

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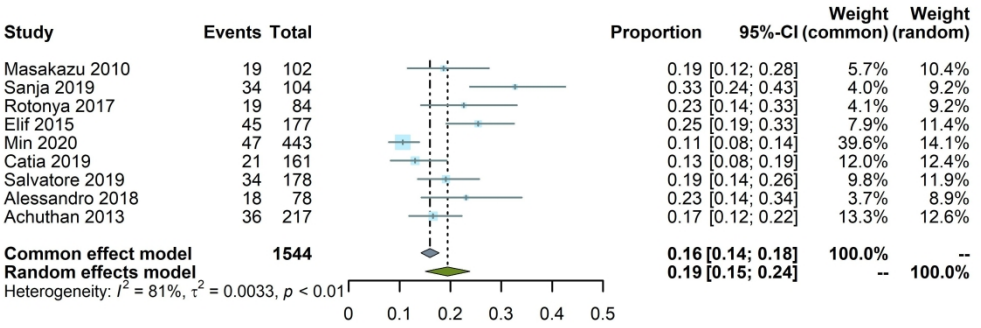


Figure 3. Forest plots for the overall pooled prevalence of comorbid MetS among patients with IBD.

275x98mm (360 x 360 DPI)

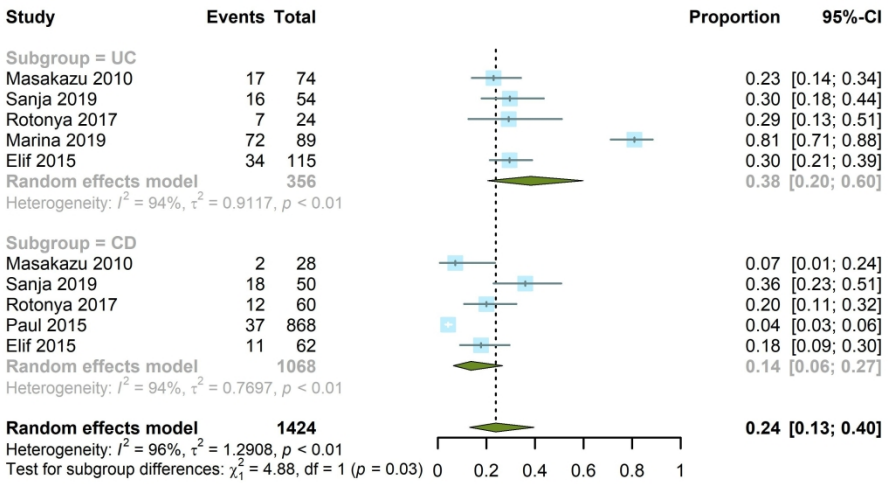


Figure 4. Stratified analyses by type of IBD. The summary estimates were obtained using a random-effects model. The diamond data markers indicate the pooled proportion. CI indicates confidence interval.

246x141mm (360 x 360 DPI)

SUPPLEMENTARY MATERIALS

Supplementary Table S1. Search strategy used in PubMed, Cochrane Library, Web of Science, EMBASE and MEDLINE database.

1	exp Inflammatory Bowel Diseases/
2	inflammatory bowel disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3	inflammatory bowel disease*.mp.
4	exp Crohn Disease/
5	(crohn* or crohn* disease or cd).mp.
6	exp Colitis, Ulcerative/
7	(ulcerative colitis or uc).mp.
8	1 or 2 or 3 or 4 or 5 or 6 or 7
9	metabolic syndrome.mp.
10	MS.mp.
11	Mets.mp.
12	9 or 10 or 11
13	8 and 12

Search strategy used in MEDLINE & Cochrane Library database.

1	TS=(inflammatory bowel disease OR IBD OR ulcerative colitis OR uc OR crohn* OR crohn* disease) AND TS=(metabolic syndrome OR MS OR Mets)

Search strategy used in Web of Science database.

1	metabolic syndrome.mp.
2	MS.mp.
3	Mets.mp.
4	#1 or #2 or #3
5	'inflammatory bowel disease'/exp
6	'inflammatory bowel disease'
7	'crohn disease'/exp
8	'crohn$ disease' or 'crohn$ colitis'
9	'ulcerative colitis'/exp
10	'ulcerative colitis' or uc
11	or/5-10
12	#4 and #11

Search strategy used in EMBASE CLASSIC+EMBASE database.

1	“metabolic syndrome” [MeSH Terms] OR “metabolic syndrome” [Title/Abstract] OR MS [Title/Abstract] OR Mets [Title/Abstract]
2	“inflammatory bowel diseases” [MeSH Terms] OR “Crohn Disease”[MeSH Terms] OR “Colitis, Ulcerative”[MeSH Terms] OR “inflammatory bowel disease*”[Title/Abstract] OR IBD [Title/Abstract] OR “ulcerative colitis” [Title/Abstract] OR UC [Title/Abstract] OR “Colitis Gravis” [Title/Abstract] OR “Colitis ulcerosa” [Title/Abstract] OR “crohn disease”[Title/Abstract] OR CD[Title/Abstract] OR Crohn*[Title/Abstract] OR “Granulomatous Enteritis” [Title/Abstract] OR “Granulomatous Colitis”[Title/Abstract] OR “Terminal Ileitis” [Title/Abstract]
3	#1 AND #2

Search strategy used in Pubmed database.

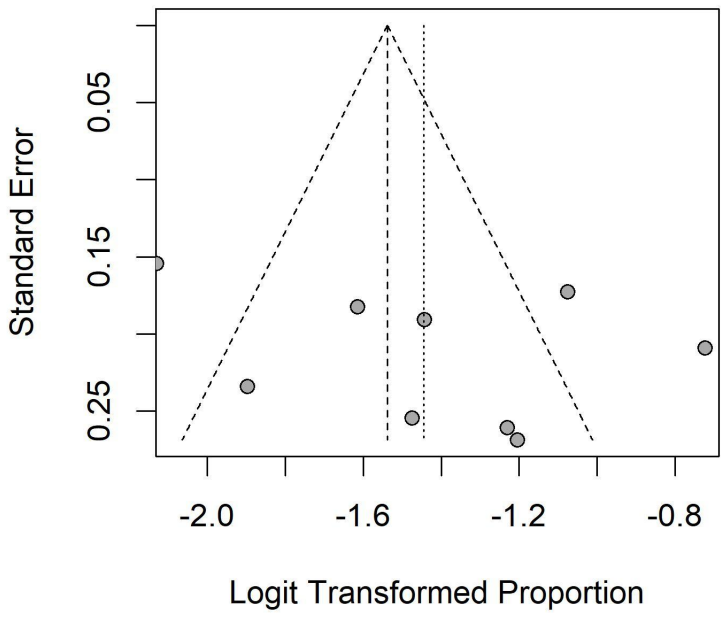
Supplementary Table S2. Quality assessment for studies using the Newcastle-Ottawa Scale.

Study, year	Selection				Comparability	Outcome			Total score	Quality of evidence
	Representatives of the exposed cohort Representativeness of the sample	Selection of the non-exposed cohort Sample size	Ascertainment of exposure Ascertainment of exposure	Demonstration outcome not present at start of study Non-respondents	Comparability of cohorts on the basis of the design or analysis based on the study design or analysis	Assessment of outcome Assessment of outcome	Follow up long enough for outcomes to occur Statistical test	Adequacy of follow up of cohorts		
Masakazu et al, 2010[8]	1	1	1	1	2	1	NA		8	high
Sanja et al, 2019[6]	1	1	1	1	1	1	NA		7	high
Rotonya et al, 2017[17]	1	1	1	1	0	1	NA		6	high
Paul et al, 2015[18]	1	1	0	1	2	1	NA		7	high
Marina et al, 2019[19]	0	1	1	0	0	1	NA		3	low
Elif et al, 2015[20]	0	1	0	1	0	1	NA		4	medium
Min et al, 2020[21]	1	1	1	1	1	1	NA		7	high
Catia et al, 2019[23]	1	1	0	0	1	1	NA		5	medium
Salvatore et al, 2019[22]	1	1	1	1	1	1	1		8	high
Alessandro et al, 2018[24]	1	1	1	1	1	1	NA		7	high
Achuthan et al, 2013[25]	1	1	1	1	1	1	NA		7	high

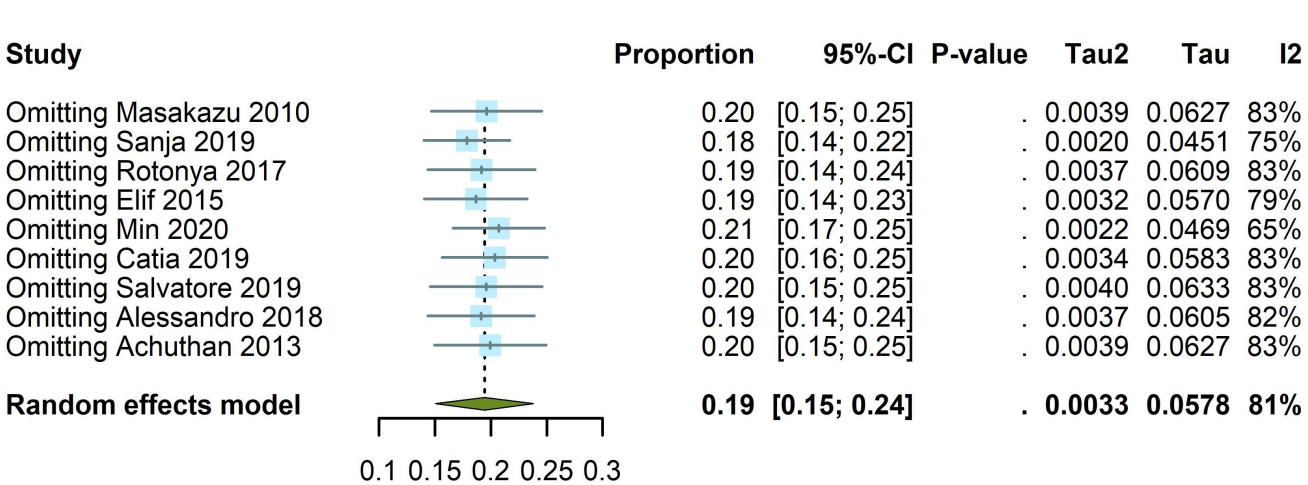
[a] Quality assessment of the included studies was assessed using the modified Newcastle-Ottawa scale (rated on a 0-6 scale for studies without a comparator group and 0-9 for studies with a comparator group), studies with scores 5 or 6 (out of 6, for point prevalence studies) and 8 or 9 (out of 9, for comparative studies on risk in exposed vs. non-exposed cohorts) were considered high quality, studies with scores 4/6 or 6 or 7 out of 9, were considered medium quality, and all other studies were considered low quality.

Abbreviations: NA, Not Available; IBD, Inflammatory bowel disease.

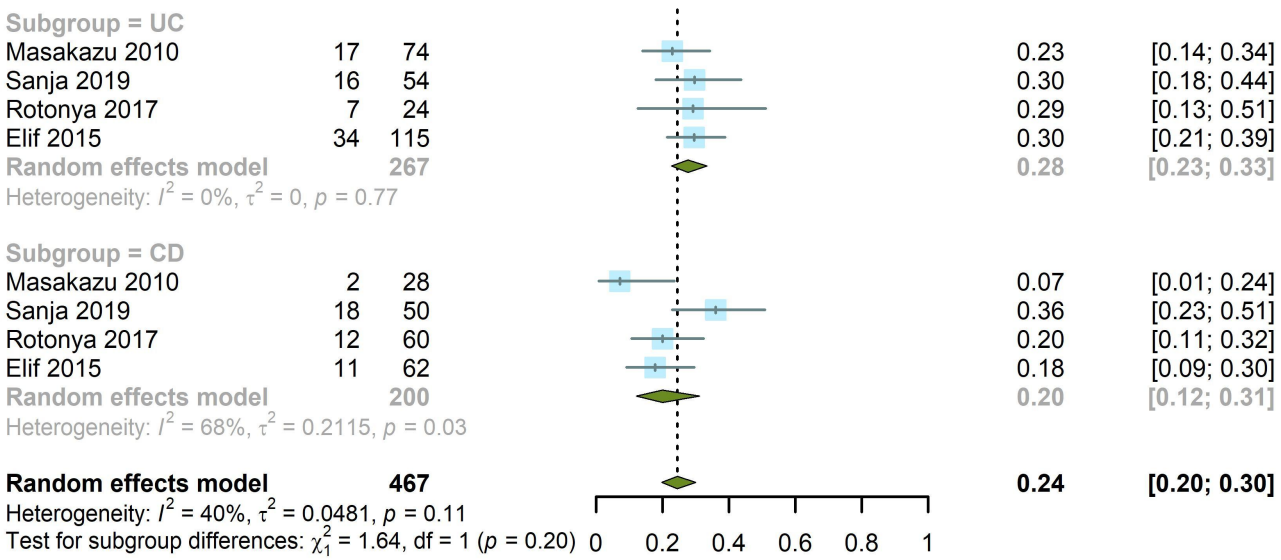
Supplementary Figure S1. Funnel plot showing the overall prevalence of MetS in patients with IBD.



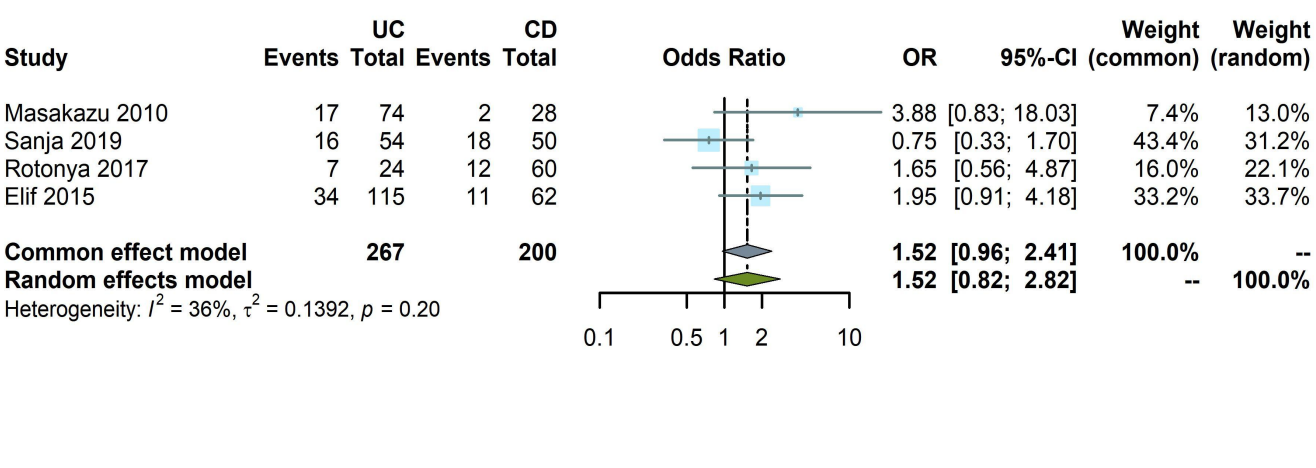
Supplementary Figure S2. Forest plot of sensitivity analyses by recalculating the pooled estimates of MetS in patients with IBD.



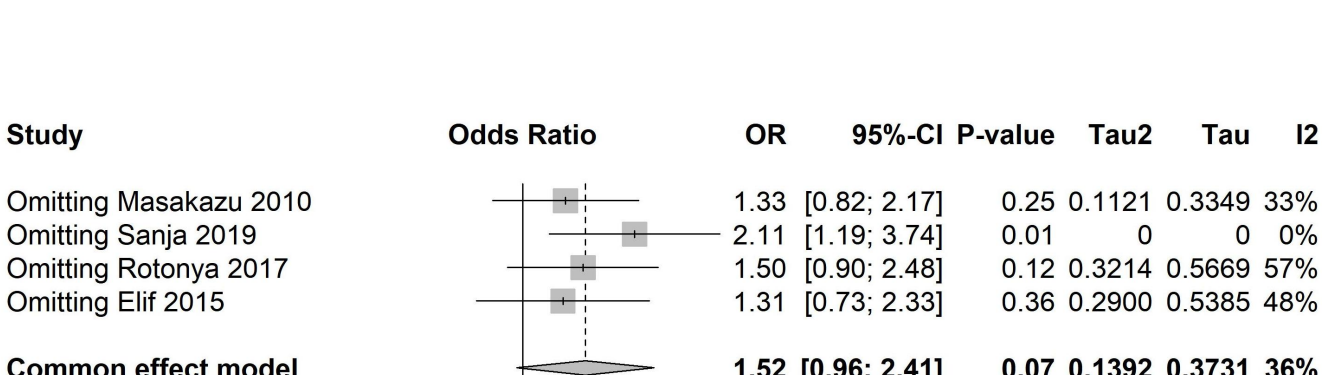
Supplementary Figure S3. Forest plots of stratified analyses by IBD subtype after omitting two heterogeneous studies. The pooled prevalence with 95% confidence intervals were calculated using the random effects model.



Supplementary Figure S4. Forest plots for the association of MetS with CD and UC. The size of the data markers indicates the weight of the study.



Supplementary Figure S5. Forest plot of sensitivity analyses showing the association between MetS and IBD. The pooled odds ratios with 95% confidence intervals were calculated using the fixed-effect model.



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1,4
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	1,2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	1,2,3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	1,4
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	5
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	1,4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	4
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	5
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	5,6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	5,6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	6
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	5,6
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	6
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	6
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	6
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	6
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	6
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	6

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	6
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	6, Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	6, Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	6,7, Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	7, Figure 2, Table 1, supplementary Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 3, Figure 4, Figure 5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	7-11, Figure 3, Figure 4, Figure 5,
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	7-11, Figure 3, Figure 4, Figure 5,
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	9,10, Figure 3, Figure 4, Figure 5,
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	9,10, supplementary Figure S2, Figure S3
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	9,10, Figure 2, Table S2
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	9,10, Figure S2, Figure S4
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	11-15
	23b	Discuss any limitations of the evidence included in the review.	15,16
	23c	Discuss any limitations of the review processes used.	11,15,16
	23d	Discuss implications of the results for practice, policy, and future research.	
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	4
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	4

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	4
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	16
Competing interests	26	Declare any competing interests of review authors.	16
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	17, Table 1, supplementary Table S1, Table S2

Reporting Checklist for a systematic review with meta-analysis: PRISMA Checklist

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

MOOSE (Meta-analyses Of Observational Studies in Epidemiology) Checklist

A reporting checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Reporting of Background		
Problem definition		
Hypothesis statement		
Description of Study Outcome(s)		
Type of exposure or intervention used		
Type of study design used		
Study population		
Reporting of Search Strategy		
Qualifications of searchers (eg, librarians and investigators)		
Search strategy, including time period included in the synthesis and keywords		
Effort to include all available studies, including contact with authors		
Databases and registries searched		
Search software used, name and version, including special features used (eg, explosion)		
Use of hand searching (eg, reference lists of obtained articles)		
List of citations located and those excluded, including justification		
Method for addressing articles published in languages other than English		
Method of handling abstracts and unpublished studies	No	NA
Description of any contact with authors	No	NA
Reporting of Methods		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes	7-8
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes	8-10
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes	8
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate	Yes	8, Table S2

Reporting Criteria	Reported (Yes/No)	Reported on Page No.
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	Yes	10-11, Table
Assessment of heterogeneity	Yes	, Table S2 &
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes	12-13, Table
Provision of appropriate tables and graphics	Yes	Table S2
Reporting of Results		
Table giving descriptive information for each study included	Yes	Table 1
Results of sensitivity testing (eg, subgroup analysis)	Yes	, Figure 4 &
Indication of statistical uncertainty of findings	Yes	12 & 15
Reporting of Discussion		
Quantitative assessment of bias (eg, publication bias)	Yes	10-11, Fugre
Justification for exclusion (eg, exclusion of non–English-language citations)	Yes	Figure 1
Assessment of quality of included studies	Yes	10, Table S2
Reporting of Conclusions		
Consideration of alternative explanations for observed results	Yes	16
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes	15
Guidelines for future research	Yes	21
Disclosure of funding source	Yes	1

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