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# Lipoprotein (a) and inflammatory bowel disease: a systematic review and meta-analysis

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## Abstract

**Background** Lipid profile alterations have been reported in patients with inflammatory bowel disease (IBD). Our aim was to systematically investigate all relevant evidence on the association between lipoprotein (a) [Lp(a)] and IBD.

**Methods** We searched PubMed and Cochrane Library databases (up to 30 December 2024) for studies with evidence on Lp(a) in patients with IBD. A meta-analysis was performed to evaluate the mean differences (MD) in Lp(a) between patients with Crohn's disease (CD) or ulcerative colitis (UC), and healthy controls (HC).

**Results** The literature search identified 11 studies (2687 participants) investigating the lipid profile of patients with IBD; however, only 6 studies were used for the meta-analysis. Overall, 1978 participants were included in the meta-analysis, of whom 1196 were IBD patients and 782 were HC. The pooled analysis from 4 studies showed that CD patients had significantly higher Lp(a) levels compared to HC (MD 18.36 mg/dL, 95% confidence interval [CI] 14.53-22.20; P<0.001). Similarly, a pooled analysis from 4 studies showed that UC patients had higher Lp(a) levels compared to HC (MD 7.32 mg/dL, 95% CI 2.85-11.79; P=0.001). A pooled analysis of 3 studies revealed a non-significant difference in Lp(a) levels between CD and UC patients. In subgroup analyses based on disease activity, CD patients with active disease exhibited significantly higher Lp(a) levels compared to those with inactive disease. No significant difference was observed in UC patients stratified by disease activity.

**Conclusions** Lp(a) levels are significantly higher in both CD and UC patients compared to HC. Therefore, Lp(a) evaluation is advisable when assessing IBD patients.

**Keywords** Inflammatory bowel disease, Crohn's disease, ulcerative colitis, lipoprotein (a)

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## Introduction

Inflammatory bowel disease (IBD) is a chronic, inflammatory disease primarily affecting the gastrointestinal tract. It encompasses 2 distinct clinical entities: Crohn's disease (CD) and ulcerative colitis (UC). Its precise etiopathogenesis remains unclear, with genetic, environmental and dietary factors driving aberrant immune responses and, ultimately, chronic gastrointestinal inflammation and damage [1,2]. The systemic component of IBD is increasingly recognized [3]; extraintestinal disease mainly involves the musculoskeletal, integumentary, hepatobiliary, ocular and cardiovascular systems, with cardiovascular IBD manifestations including venous and arterial thromboembolic events [4-6].

While aberrations in classic lipid profile parameters fail to fully explain the greater risk of atherosclerotic cardiovascular disease (ASCVD) observed in IBD, emerging evidence suggests that lipoprotein (a) [Lp(a)] may represent a novel link between inflammation and atherosclerosis

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Conflict of Interest: None

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in this population. Lp(a) is a genetically determined low-density lipoprotein cholesterol (LDL)-like lipoprotein, bound to apo(a), that has proinflammatory, pro-atherogenic and prothrombotic properties [7,8]. As such, it is a major determinant of residual cardiovascular risk—that is, elevated Lp(a) levels have been independently associated with an increased risk of cardiovascular events, despite management of classic ASCVD risk factors—and should be measured at least once in a person's lifetime, as per European guidelines [7,9]. Specifically, although a threshold of 50 mg/dL is associated with significant ASCVD risk enhancement, levels >30 mg/dL also confer a modest risk increase, which becomes greater for patients with an already elevated baseline ASCVD risk [10,11].

The role of Lp(a) in IBD remains relatively unexplored; however, isolated reports [12,13] have suggested an association between IBD, Lp(a) and ASCVD. Two recent Mendelian randomization analyses did not identify Lp(a) as a risk factor for IBD onset [14,15]; however, the reverse association—i.e., the effect of IBD on Lp(a)—was not evaluated.

Finally, a recent meta-analysis established that serum lipid levels in IBD patients are lower than those in healthy individuals and are negatively correlated with disease severity [16]. However, no comprehensive analysis has examined the relationship between Lp(a) and IBD. Therefore, we systematically collected and analyzed all relevant evidence in order to address this gap.

## Materials and methods

This systematic review was registered in PROSPERO (ID number: CRD42024620440) and adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (PRISMA Statement, Ottawa, ON, Canada) [17]. The PRISMA checklist is illustrated in Supplementary Table 1. In the present study, the primary outcome was to systematically investigate the association between IBD and Lp(a) levels.

### Search strategy

We searched PubMed and Cochrane Library databases up to December 30, 2024, using the following keywords: [(Inflammatory bowel disease) OR (Crohn's disease) OR (ulcerative colitis)] AND [(Lipoprotein a) OR (Lp a)].

### Study design

We performed qualitative and quantitative syntheses of both prospective and retrospective studies to evaluate the role of Lp(a) levels in IBD.

### Screening and eligibility

Deduplication of records was carried out using Zotero reference management software. The screening process was conducted in 2 stages. Initially, 1 author (CMK) screened titles and abstracts to exclude studies that did not meet the inclusion criteria, then performed a full-text assessment of the remaining articles. A second author (AA) independently reviewed and verified the inclusion decisions. Any discrepancies between reviewers were resolved through consensus. Eligibility criteria followed the PICOS (population, intervention, comparators/controls, outcomes, and study design) study question format, as follows:

- Population: Patients with IBD.
- Intervention: Measurement of Lp(a).
- Comparator/controls: Healthy controls (HC) (where applicable).
- Outcomes: Mean differences in Lp(a) levels between CD patients and HC, UC patients and HC, CD and UC patients, active CD and inactive CD, active UC and inactive UC.
- Study design: Observational studies (prospective or retrospective) were included.

The exclusion criteria included studies without IBD (CD or UC) patients, without Lp(a) measurements, non-original publications (e.g., reviews, editorials, letters without primary data), conference abstracts, case reports, case series, animal studies and *in vitro* studies, as well as non-English language studies. Instead, studies on pediatric patients were not excluded, given the genetically determined nature of Lp(a) levels.

### Data extraction

Two authors (CMK and AA) independently assessed the included studies and extracted relevant study characteristics, as summarized in Table 1. Any discrepancies between the reviewers were resolved through consensus. Data extraction followed the PRISMA guidelines to ensure methodological rigor. In addition, reference lists of eligible studies and the related literature were thoroughly screened to identify any potentially missed studies.

### Methodological assessment of included studies

The quality of the included studies was independently evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist, which assesses methodological rigor across key domains such as study design, participant selection, data collection and analysis. Each checklist comprises a series of specific questions tailored to the study type (e.g., cross-sectional, cohort, case-control), allowing for a detailed assessment of potential biases and methodological limitations. Studies were scored based on the number of criteria met, with higher scores indicating greater methodological quality and

**Table 1** Characteristics of eligible studies

| First author [ref.] | Year | Country | Study Design | IBD Patients (n) | | Controls | IBD Lp (a) (mg/dL) | |
|---|---|---|---|---|---|---|---|---|
| | | | | CD (n) | UC (n) | (n) | CD | UC |
| Hudson [18] | 1996 | UK | CC | 75 | 35 | 85 | | |
| | | | | Males n=26 | Males n=22 | Males n=38 | 31.4±32.5 | 30.4±41 |
| | | | | Females n=49 | Females n=13 | Females n=47 | 38.3±32.4 | 34±108.8 |
| Levy [19] | 1999 | Canada | CC | 22 (pediatric) | NR | 10 | | NR |
| | | | | Active disease n=13 | NR | NR | 97±22 | NR |
| | | | | Inactive disease n=8 | NR | NR | 63±19 | NR |
| Sood [20] | 2000 | India | CC | NR | 44 | 35 | NR | 24.3±21.1 |
| | | | | | Active disease n=28 | NR | NR | 25.3±21.5 |
| | | | | | Proctosigmoiditis | | | 17.4±9.8 |
| | | | | | Left-sided disease | | | 30.8±28 |
| | | | | | Pancolitis | | | 26.4±20.9 |
| | | | | | Inactive disease n=26 | NR | NR | 23.4±19.8 |
| Koutroubakis [21] | 2001 | Greece | CC | 63 | 66 | 66 | 41.2±37 | 30.1±28.4 |
| Eren [22] | 2006 | Turkey | PC | 14 | 14 | NR | 16.1±11.7 | |
| Koutroubakis [23] | 2009 | Greece | PC | 19 | 3 | NR | 6.3±4.3 before Infliximab<br>6.4±4.5 after Infliximab | |
| Pac-Kożuchowska [24] | 2016 | Poland | CC | 14 (pediatric) | 16 | 20 | 20.1±19.5 | 18.8±20.1 |
| Üstün [25] | 2016 | Turkey | CC | 38 | 58 | 65 | NR | NR |
| Lu [26] | 2022 | China | CS | 862 | NR | 576 | 38±36.8 | NR |
| Liu [27] | 2022 | China | RC | NR | Dyslipidemia n=229 | NR | NR | |
| | | | | | Remission n=2 | | | 9.6 (8.2-) |
| | | | | | Mild n=29 | | | 10.6±3.2 |
| | | | | | Moderate n=107 | | | 22.7±7.1 |
| | | | | | Severe n=91 | | | 12.8±5.1 |
| | | | | | Normal Lipid n=179 | | | |
| | | | | | Remission n=41 | | | 12.7±4.3 |
| | | | | | Mild n=72 | | | 13.5±4.1 |
| | | | | | Moderate n=63 | | | 10.4±1.6 |
| | | | | | Severe n=3 | | | 17.1 (10.1-) |
| Rodríguez-Hernández [28] | 2023 | Spain | CS | 130 | 67 208 | 208 | NR | NR |

IBD, inflammatory bowel disease; Lp (a), lipoprotein (a); CD, Crohn's disease; UC, ulcerative colitis; CC, case-control; PC, prospective cohort; RC, retrospective cohort; CS, cross-sectional; NR, not reported

a lower risk of bias. Studies that fulfilled most criteria were considered to have a low risk of bias, moderate scores indicated some concerns, and studies with many unmet criteria were classified as having a high risk of bias.

### Statistical analysis

When adequate data were available and outcome measures were comparable across studies, meta-analyses were performed to generate a quantitative summary. Lp(a) values reported in mmol/L were converted to mg/dL when necessary. For studies (Hudson *et al*, Lu *et al*) presenting data as median/interquartile range (IQR), values were converted to mean ± standard deviation (SD) using the method proposed by McGrath *et al* (DOI: 10.1177/0962280219889080), which assumes approximate normality and may introduce minor bias in skewed Lp(a) distributions, though its validation minimizes impact on pooled estimates. Pooled estimates were treated as continuous variables. Based on the degree of heterogeneity, either a fixed-effects or random-effects model was utilized. Mean differences (MD) with corresponding 95% confidence intervals (CI) were calculated for continuous outcomes. All

statistical analyses were conducted using Review Manager (RevMan), version 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008), with statistical significance set at P<0.05.

### Heterogeneity analysis

Statistical heterogeneity among the included studies was assessed using the $I^2$ statistic. An $I^2$ value below 25% was considered indicative of low heterogeneity, values around 50% as moderate, and values above 75% were classified as high. A P-value less than 0.10 was interpreted as evidence of significant heterogeneity, in which case a random-effects model was employed; otherwise, a fixed-effects model was used. Additionally, heterogeneity between studies was evaluated using both the Q test and the $I^2$ statistic.

## Results

### Study selection

The study selection process is illustrated in the PRISMA flow diagram (Fig. 1). An initial database search yielded 66 articles. Following the removal of duplicates, 53 articles were excluded during the title and abstract screening as they did not meet the predefined inclusion criteria. Upon full-text evaluation, 11 studies [18-28] were deemed eligible for inclusion in the systematic review; of these, 6 studies [18-21,24,26] met the criteria for inclusion in the meta-analysis.

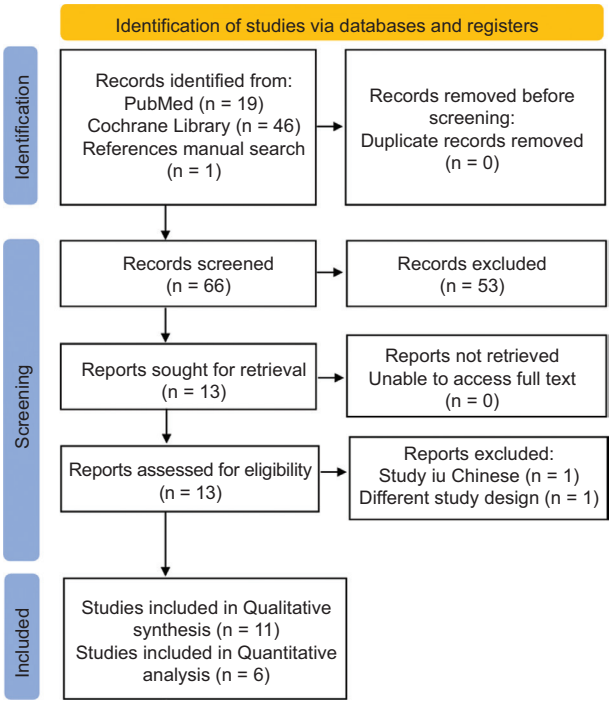


**Figure 1** PRISMA flow chart used for literature search and study selection

### Study characteristics

A total of 11 studies [18-28], published between 1996 and 2023 were included in the qualitative synthesis. Detailed characteristics of each study are summarized in Table 1. Of these, 6 were case–control studies, 2 were cross-sectional, 2 were prospective cohort studies and 1 was a retrospective cohort study. Geographically, 2 studies were conducted in Turkey, 2 in China and 2 in Greece, while the rest took place in the UK, Canada, India, Poland and Spain. Collectively, the above-mentioned 11 studies included 2687 participants, of whom 1574 were patients with IBD. All included studies matched participants by age and sex. Seven studies [18,21-25,28] included patients with either CD or UC, 2 studies [19,26] included only patients with CD, and 2 studies [20,27] focused exclusively on patients with UC. Additionally, 3 studies [19,20,27] reported disease activity by categorizing patients into active and inactive disease groups, while 2 studies [20,27] assessed the extent of disease involvement. Lastly, 2 studies [19,24] included pediatric populations. In 2 studies [18,26] we converted median/IQR to mean ± SD regarding Lp(a) values by using the McGrath's method, as mentioned above.

### Study outcomes – meta-analysis

In total, 6 studies (5 with adult and 1 with pediatric population) with 1978 participants were included in this meta-analysis: of these, 1196 were IBD patients and 782 were HC. All studies reported Lp(a) levels, with individual values ranging from 11-97 mg/dL. The mean Lp(a) levels were 33.8 mg/dL in CD patients, 27.5 mg/dL in UC patients and 17.8 mg/dL in HC. Comparative analyses of Lp(a) levels were conducted between CD patients and HC, UC patients and HC, CD and UC patients, as well as between active and inactive disease states within both CD and UC patient populations. Pooled results from the included studies are summarized in Fig. 2-4 and Supplementary Fig. 1-5. Regarding differences in Lp(a) between CD patients and HC, a pooled analysis from 4 studies showed that CD patients had significantly higher Lp(a) levels compared to HC (MD 18.36 mg/dL, 95% CI 14.53-22.20; P<0.001; $I^2$=15%) (Fig. 2). Similarly, a pooled analysis from 4 studies showed that UC patients had higher Lp(a) levels compared to HC (MD 7.32 mg/dL, 95% CI 2.85-11.79; P=0.001; $I^2$=0%) (Fig. 3). Comparison of Lp(a) levels between CD and UC patients, from a pooled analysis of 3 studies, revealed a non-significant difference, although Lp(a) levels were higher in CD patients (MD 6.40 mg/dL, 95% CI -1.80 to 14.60; P=0.13; $I^2$=0%) (Fig. 4). In subgroup analyses based on disease activity, the pooled synthesis of 2 studies showed that CD patients with active disease exhibited significantly higher Lp(a) levels compared to those with inactive disease (MD 32.91 mg/dL, 95% CI 17.74-48.09; P<0.001; $I^2$=0%) (Supplementary Fig. 1). Lastly, no significant difference was observed from the pooled synthesis of 2 studies among UC patients stratified by disease activity (MD 4.46 mg/dL, 95% CI -4.64 to 13.57; P=0.34; $I^2$=0%) (Supplementary Fig. 2). Nevertheless, these observations are constrained by the inclusion of only two studies for CD [19, 21]

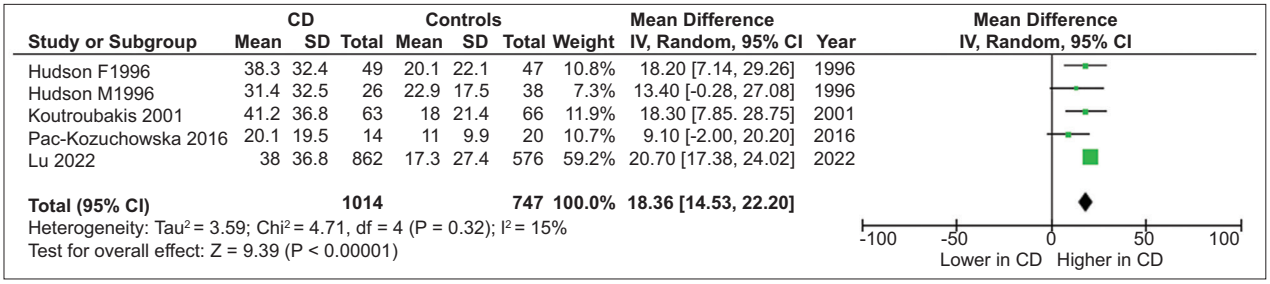


**Figure 2** Forest plot of comparison: CD vs. HC for Lp(a) [18,21,24,26]
*CD, Crohn's disease; HC, healthy controls; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*

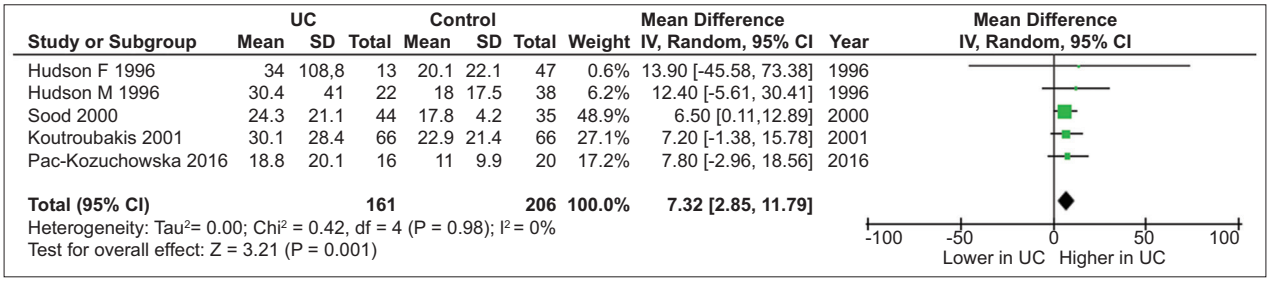


**Figure 3** Forest plot of comparison: UC vs. HC for Lp(a) [18,20,21,24]
*UC, ulcerative colitis; HC, healthy controls; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*

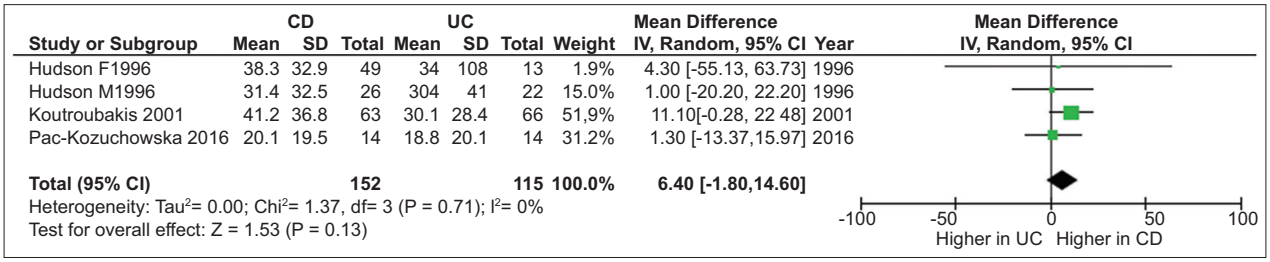


**Figure 4** Forest plot of comparison: CD vs. UC for Lp(a) [18,21,24]
*CD, Crohn's disease; UC, ulcerative colitis; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*

and UC [20,21], thereby limiting statistical power, precluding robust assessment of heterogeneity or publication bias, and heightening susceptibility to confounding factors.

Finally, sensitivity analyses excluding the study by Pac-Kożuchowska [24] were conducted with the exclusion of pediatric patients. The results were similar to the original meta-analyses. In brief, MDs in Lp(a) levels between CD vs. HC, UC vs. HC and CD vs. UC were 19.98 mg/dL (95% CI 17.01-22.95; P<0.001; $I^2$=0%), 7.22 mg/dL (95% CI 2.31-12.13; P=0.004; $I^2$=0%) and 8.72 mg/dL (95% CI -1.17 to 18.60; P=0.08; $I^2$=0%), respectively (Supplementary Fig. 3-5).

### Quality appraisal and risk of bias

The quality assessment of the observational studies included in this review, using the JBI tool, showed a mean score of 6.5 out of 10 for the 6 case-control studies, indicating overall moderate methodological quality, as seen in Supplementary Table 2. A mean score of 6.7 out of 11 for the 3 cohort studies reflected moderate methodological quality, as detailed in Supplementary Table 3. Lastly, a mean score of 7 out of 8 for the 2 cross-sectional studies reflected high methodological quality, as detailed in Supplementary Table 4.

## Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis studying the impact of IBD on Lp(a) levels. Our meta-analysis suggests that Lp(a) levels are significantly higher in both IBD subgroups compared to HC, with CD patients presenting higher Lp(a) levels than those with UC. These findings translate into clinically meaningful elevations in ASCVD risk, especially for patients with an already high baseline cardiovascular risk. Furthermore, according to our analysis, active disease was associated with higher Lp(a) levels in patients with CD, but not UC. Given that the production of apo(a), and

hence Lp(a), is triggered by the effect of interleukin (IL)-6, a marker of systemic inflammation, on several response elements of the LPA gene, the above findings possibly reflect the difference in inflammatory burden between the 2 entities [29]. This is highlighted by significant differences in serum inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate and IL-6, which tend to be higher in CD [30-32]. The more pronounced systemic component of CD compared with UC is further attested by a higher prevalence of extraintestinal manifestations that are associated with genetic variants implicating tumor necrosis factor, JAK-STAT and IL-6 signaling pathways, as identified by genome-wide association studies [29,33,34].

In contrast to the rest of the studies included in the present systematic review, Rodriguez *et al* [28] demonstrated greater Lp(a) levels in HC vs. IBD patients, which could potentially be attributed to the higher rate of statin use in the HC group [35]. Statins, although having strong hypolipidemic effects, may increase Lp(a) levels—even in a dose-dependent manner—as described by Agouridis *et al* in their studies [36,37]. Moreover, tocilizumab, an IL6 receptor antagonist, has been reported to lower Lp(a) concentrations by approximately 30-40% in rheumatoid arthritis, probably via suppression of IL-6–responsive elements within the LPA promoter that govern apo(a) production [38]. Nevertheless, the impact of anti-tumor necrosis factor (TNF) biologics, such as adalimumab, etanercept and infliximab, on Lp(a) remains unclear, as existing studies largely report changes only in conventional lipids and apolipoproteins, rather than in Lp(a) itself [39]. Lastly, as was demonstrated in a comparative study, in patients receiving total parenteral nutrition, serum apo A-IV concentrations are markedly and disproportionately lower compared with healthy controls, underscoring a pronounced dependence of apo A-IV on intact enteral nutrient delivery [40]. A similar sensitivity to loss of enteral feeding could conceivably apply to Lp(a) concentrations, although this has not been directly demonstrated.

Although IBD is an independent risk factor for thromboembolic events (especially venous), high disease activity and severity further enhance that risk [41]. The rise in Lp(a) levels during active disease phases observed in our pooled analysis may partly explain this hypercoagulable state: because of its structural resemblance to plasminogen, Lp(a) tends to interfere with fibrinolysis [21]. Specifically, the apo(a) moiety of Lp(a) blocks plasminogen activators, and antagonizes plasminogen and plasmin binding to fibrin clots [42]. In addition, Lp(a) also has significant proinflammatory, and thus pro-atherogenic properties, mediated by its high content of oxidized phospholipids [7,8,10].

Interestingly, the association between IBD and ASCVD appears despite a seemingly favorable lipid profile characterized by low total cholesterol, high-density lipoprotein cholesterol (HDL-C) and LDL-C levels, which often show an increase in response to anti-inflammatory treatment [43,44]. The so-called "lipid paradox" is explained by catabolism of LDL-C within the inflammatory milieu, and has been also described in other chronic immune-mediated diseases, including rheumatoid arthritis and axial spondylarthritis [45,46].

IBD pathogenesis involves genetic and environmental factors that lead to intestinal barrier disruption and consequent bacterial translocation. As a result, resident immune cells, including macrophages, T cells and innate lymphoid cells, are activated, and produce a series of proinflammatory cytokines, such as IL-1, IL-6, IL-12, IL-23, IL-21, interferon-γ and TNF-α, which promote chronic inflammation [47]. The potential Lp(a)-lowering properties of disease-modifying anti-inflammatory agents targeting these cytokines were evaluated in a study by Koutroubakis *et al* [23], which showed that anti-TNF agent administration did not significantly alter Lp(a) levels in patients with IBD. On the other hand, Sleutjes *et al* demonstrated a reduction in Lp(a) levels in IBD patients who received thiopurines [48]. Moreover, studies on rheumatoid arthritis populations have demonstrated Lp(a) reductions in patients receiving methotrexate, with or without anti-TNF [49], as well as with Janus kinase inhibitors [50], drugs also approved for IBD. Finally, despite the protective role of IL-6 in intestinal homeostasis, IL-6 (receptor) inhibitors have shown promise against CD, while also reducing Lp(a) levels by capitalizing on the aforementioned pathophysiological link between the IL-6 axis and apo(a) [8,51].

The present study has some notable merits. It is the first systematic review and meta-analysis to assess the association between IBD and Lp(a) levels. Methodologically, it adhered to the PRISMA guidelines, ensuring outcome reproducibility. Thorough quality assessment via the JBI tool indicated good overall study quality and, consequently, a relatively moderate risk of bias. Finally, our meta-analysis has low heterogeneity, indicating robust statistical associations. However, the relatively small number of included studies, especially in sub-analyses, mean that the study's statistical power is relatively low, rendering heterogeneity tests and publication bias measures less reliable. Moreover, Lp(a) concentrations, which are typically rightskewed, were extracted as reported in the primary studies and pooled on the mean ± SD scale without additional normality assessment, which may not fully capture the underlying distribution of Lp(a). In addition, given the paucity of relevant data, a comprehensive synthesis of confounding factors potentially contributing to the observed Lp(a) changes in the IBD population was not performed.

Overall, our results suggest that Lp(a) levels are significantly increased in both CD and UC patients, with the former presenting higher Lp(a) levels than the latter. Active disease status seems to correlate with greater elevations in Lp(a) levels; however, larger studies are required to better determine this association.

**Summary Box**

**What is already known:**

- Inflammatory bowel disease (IBD) is associated with increased atherosclerotic cardiovascular disease risk. Cardiovascular IBD manifestations include venous and arterial thromboembolic events
- An altered classic lipid profile is observed in IBD, whose main characteristics are low total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol levels
- Lipoprotein(a) [Lp(a)], a genetically determined LDL-like lipoprotein bound to apo(a) which has pro-inflammatory, proatherogenic and prothrombotic properties, may represent a novel link between inflammation and atherosclerosis in IBD population

**What the new findings are:**

- To the best of our knowledge this is the first systematic review with meta-analysis studying the impact of IBD on Lp(a) levels
- Lp(a) levels are significantly increased in both IBD subgroups, Crohn's disease (CD) and ulcerative colitis (UC), compared with healthy controls
- Active disease was associated with increased Lp(a) levels in patients with CD, but not in patients with UC

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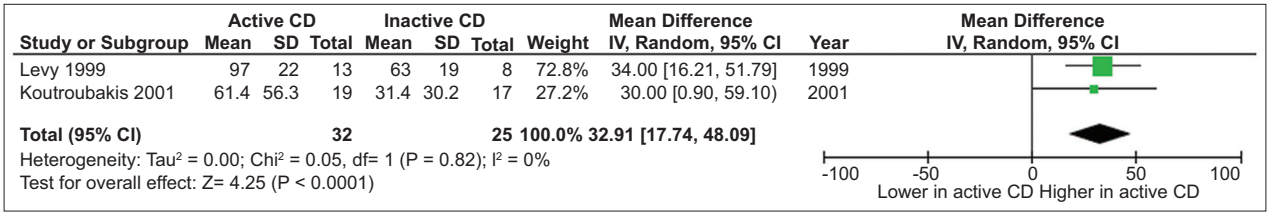
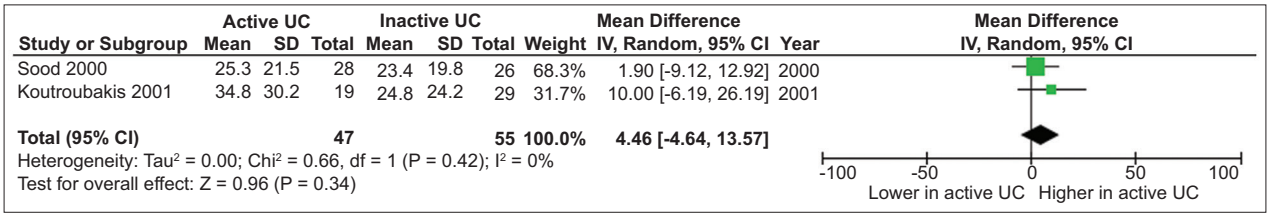
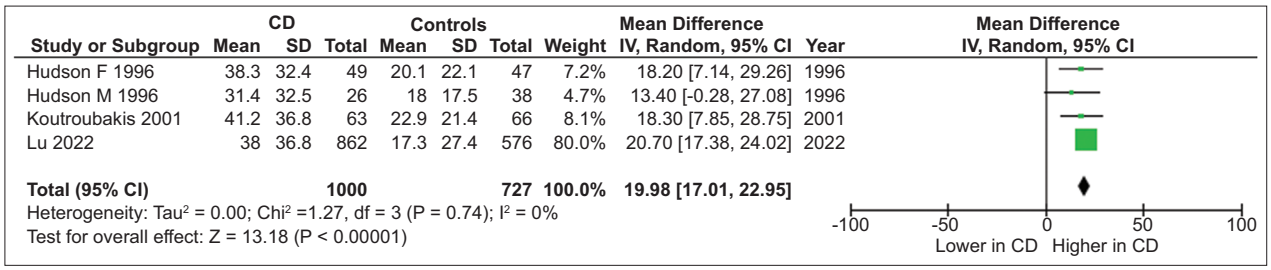
## Supplementary material



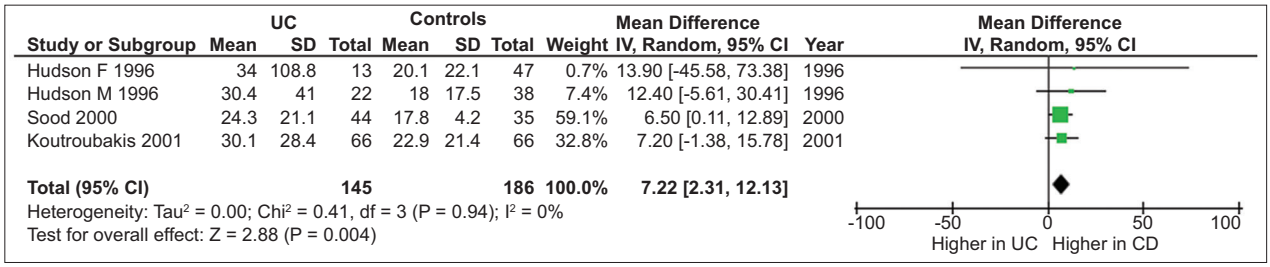

**Supplementary Figure 1** Forest plot of comparison: active vs. inactive CD for Lp(a) [19,21]
*CD, Crohn's disease; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*



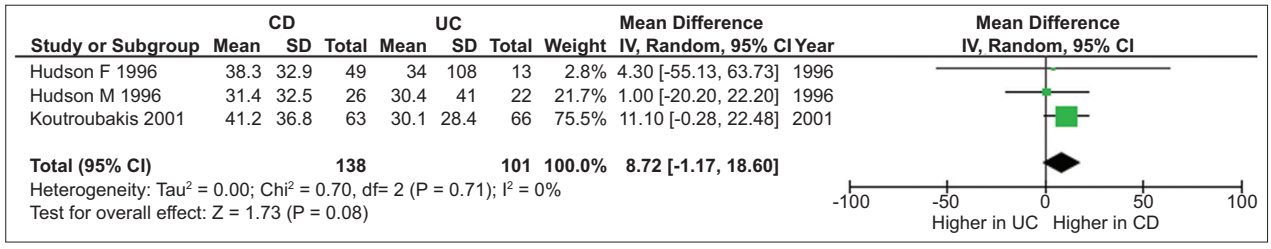

**Supplementary Figure 2** Forest plot of comparison: active vs. inactive UC for Lp(a) [20,21]
*UC, ulcerative colitis; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*




**Supplementary Figure 3** Forest plot of comparison: CD vs. HC for Lp(a) in adults [18,21,26]
*CD, Crohn's disease; HC, healthy controls; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*




**Supplementary Figure 4** Forest plot of comparison: UC vs. HC for Lp(a) in adults [18,20,21]
*UC, ulcerative colitis; HC, healthy controls; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*




**Supplementary Figure 5** Forest plot of comparison: CD vs. UC for Lp(a) in adults [18,21]
*CD, Crohn's disease; UC, ulcerative colitis; Lp(a), lipoprotein (a); SD, standard deviation; CI, confidence interval*

**Supplementary Table 1** PRISMA checklist

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | TITLE | |
| Title | 1 | Identify the report as a systematic review. | p. 1 |
| | | ABSTRACT | |
| Abstract | 2 | See the PRISMA 2020 for Abstracts checklist. | p. 3 |
| | | INTRODUCTION | |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | p. 5 |
| Objectives | 4 | Provide an explicit statement of the objective (s) or question (s) the review addresses. | p. 6 |
| | | METHODS | |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | p. 7-8 |
| 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. | p. 6 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | p. 6 |
| 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. | p. 7-8 |
| 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. | p. 7-8 |
| 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. | p. 7-8 |
| | 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. | p. 7-8 |
| 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. | p. 8 |
| 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. | p. 8-9 |
| 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)). | p. 7-8 |
| | 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | p. 9 |
| | 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | p. 8-9 |
| | 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. | p. 9-10 |
| | 13e | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression). | p. 9 |
| | 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | p. 12 |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | p. 9-10 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | N/A |

(*Contd...*)

**Supplementary Table 1** (*Continued*)

| Section and Topic | Item # | Checklist item | Location where item is reported |
|---|---|---|---|
| | | 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. | p. 10, Figure 1 |
| | 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | p. 11-12 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | p. 10, Table 1 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | p. 12 Supplementary Tables 2-4 |
| 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. | p. 11-12, Figures 2-4 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | p. 11-12, Table 2 |
| | 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. | p. 12-13, Figures 2-4 |
| | 20c | Present results of all investigations of possible causes of heterogeneity among study results. | p. 11-12 |
| | 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | p. 12 Supplementary Figure 3 and 5 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | N/A |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | N/A |
| | | DISCUSSION | |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | p. 12-13 |
| | 23b | Discuss any limitations of the evidence included in the review. | p. 15 |
| | 23c | Discuss any limitations of the review processes used. | p. 15 |
| | 23d | Discuss implications of the results for practice, policy, and future research. | p. 15 |
| | | 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. | p. 6 |
| | 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | p. 6 |
| | 24c | Describe and explain any amendments to information provided at registration or in the protocol. | N/A |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | p. 2 |
| Competing interests | 26 | Declare any competing interests of review authors. | p. 2 |
| 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. | N/A |

*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/

**Supplementary Table 2** Joanna Briggs Institute (JBI) critical appraisal checklist for case-control studies

| First author [ref.] | Were the groups comparable other than the presence of disease in cases or the absence of disease in controls? | Were cases and controls matched appropriately? | Were the same criteria used for identification of cases and controls? | Was exposure measured in a standard, valid and reliable way? | Was exposure measured in the same way for cases and controls? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were outcomes assessed in a standard, valid and reliable way for cases and controls? | Was the exposure period of interest long enough to be meaningful? | Was appropriate statistical analysis used? | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hudson [18] | Yes | Yes | Partially | Yes | Yes | No | Yes | No | Yes | Yes | 6/10 |
| Levy [19] | Yes | Yes | Yes | Yes | Partially | No | Yes | No | Yes | Yes | 7/10 |
| Sood [20] | Yes | Yes | Yes | Yes | Partially | No | Yes | No | Yes | Yes | 7/10 |
| Koutroubakis [21] | Yes | Yes | Yes | Yes | Yes | Partially | No | Yes | Unclear | Yes | 7/10 |
| Pac-Kożuchowska [24] | Yes | Partially | Yes | Yes | Yes | Partially | No | Yes | No | Yes | 6/10 |
| Üstün [25] | Yes | Partially | Yes | Yes | Yes | Partially | No | Yes | No | Yes | 6/10 |

**Supplementary Table 3** Joanna Briggs Institute (JBI) critical appraisal checklist for cohort studies

| First author [ref.] | Were the two groups similar and recruited from the same population? | Were the exposures measured similarly to assign people to both exposed and unexposed groups? | Was the exposure measured in a valid and reliable way? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)? | Were the outcomes measured in a valid and reliable way? | Was the follow up time reported and sufficient to be long enough for outcomes to occur? | Was follow up complete, and if not, were the reasons to loss to follow up described and explored? | Were strategies to address incomplete follow up utilized? | Was appropriate statistical analysis used? | Total Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Liu [27] | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | No | Yes | 9/11 |
| Koutroubakis [23] | N/A | No | Yes | Partially | No | Yes | Yes | Yes | Yes | N/A | Yes | 6/11 |
| Eren [22] | No | Yes | Yes | No | No | Unclear | Yes | Yes | Unclear | No | Yes | 5/11 |

**Supplementary Table 4** Joanna Briggs Institute (JBI) critical appraisal checklist for cross-sectional studies

| First author [ref.] | Were the criteria for inclusion in the sample clearly defined? | Were the study subjects and the setting described in detail? | Was the exposure measured in a valid and reliable way? | Were objective, standard criteria used for measurement of the condition? | Were confounding factors identified? | Were strategies to deal with confounding factors stated? | Were the outcomes measured in a valid and reliable way? | Was appropriate statistical analysis used? | Total Score |
|---|---|---|---|---|---|---|---|---|---|
| Lu [26] | Yes | Yes | Yes | Yes | Partially | Partially | Yes | Yes | 6/8 |
| Rodríguez-Hernández [28] | Yes | No | Yes | Yes | Yes | Yes | Yes | Yes | 8/8 |