Factors Associated with Delayed Diagnosis of Crohn's Disease: A Systematic Review and Meta-Analysis

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Research Article

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Abstract

BACKGROUND

Delayed diagnosis is a major barrier to the effective management of Crohn's disease (CD). Several studies have investigated factors responsible for delays in diagnosis, but no meta-analyses have systematically assessed the impact of these factors.

AIM

To assess the impact of various factors on the delayed diagnosis of CD.

METHODS

PubMed, EMBASE, and Web of Science databases were searched to identify observational studies published before April 2022 that assessed factors associated with delays in CD diagnosis. We excluded review articles, case reports, or commentaries without original data. We pooled effect sizes as odds ratios (OR) using random effects models for each risk factor examined in at least three distinct samples. We assessed study quality on the basis of the Newcastle-Ottawa Scale and examined between-study heterogeneity. A funnel plot was used for visual assessment of publication bias. The study protocol was registered with PROSPERO, CRD42022322251.

RESULTS

A total of 18 studies were included in the paper, covering 13 countries. The study sample consisted of 9,669 cases. Ileal CD (OR =1.46, 95% CI =1.21–1.76), smoking at the time of diagnosis (OR =1.19, 95% CI =1.02–1.38), and use of NSAIDs (OR =1.34, 95% CI =1.04–1.72) were significantly associated with a delay in CD diagnosis.

CONCLUSION

The findings suggest that ileal CD, use of NSAIDs, and smoking are risk factors for the delayed diagnosis of CD. Education of patients and primary care providers about these risk factors should be increased.

Introduction

Crohn's disease (CD) is a chronic and recurrent inflammatory bowel illness[1]. Patients may experience diarrhea, abdominal pain, weight loss, vomiting, and other symptoms during the onset of disease[2]. While the specific cause of CD is unknown, it is thought to arise from a combination of genetic, immunological, environmental, and microbial factors[3].

CD has a high incidence and prevalence in Western countries[4], with 0.3–12.7 per 100,000 individuals living with CD in Europe, and 0–20.2 per 100,000 individuals diagnosed living with CD in North
In several newly industrialized countries in Asia and South America, the incidence and frequency have risen dramatically in recent decades. This rise has resulted in an increase in the population burden of CD, making it one of the most urgent public health issues worldwide. The clinical symptoms of CD, however, are similar to those of other gastrointestinal disorders such as irritable bowel syndrome, allergic gastroenteritis, and infectious gastroenteritis, meaning that it is frequently misdiagnosed. According to a study by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA), 24.1% of patients had experienced CD symptoms for 5 years prior to seeing a gastroenterologist. There is growing evidence that delays in CD diagnosis reduce quality of life and increase the probability of complications and a need for surgery.

Several existing cohort studies have analyzed factors influencing the delay in CD diagnosis. However, to the best of our knowledge, no meta-analyses have specifically described these factors to date. Thus, there remains a need for a systematic analysis of factors influencing the delay in CD diagnosis to inform methods of reducing the time from disease onset to diagnosis.

**Methods**

**Inclusion and exclusion criteria**

Studies were included in the analysis if they met the following criteria: (1) they included patients with CD, (2) investigated factors that were associated with a delay in CD diagnosis, (3) were designed as observational studies, and (4) provided enough information to calculate the odds ratio (OR) and 95% confidence intervals (CI). Studies were excluded if they (1) were duplicate studies, (2) did not investigate factors associated with CD, or (3) were review articles, case reports, or commentaries without original data.

The titles and abstracts of the papers that were initially included were separately examined by two authors to determine their eligibility based on the inclusion and exclusion criteria. Whenever a disagreement arose about the appropriateness of a study, the reviewers discussed the study until they came to an agreement about whether or not to include it.

**Search Strategy**

A search of Pubmed, EMBASE, and Web of Science was conducted to identify papers published before May 2022 on factors associated with delays in CD diagnosis. The MeSH headings used were “Crohn Disease” and “Delayed Diagnosis”. If it was unclear whether a study was eligible, the full text was reviewed. The PubMed search strategy is shown in Table 1.
Table 1
PubMed database search terms and strategy.

<table>
<thead>
<tr>
<th>Search terms and strategy</th>
</tr>
</thead>
</table>
| (("Crohn Disease"[Mesh]) AND ((((((((Crohn's Enteritis>Title/Abstract)) OR (Regional Enteritis>Title/Abstract)) OR (Crohn's Disease>Title/Abstract)) OR (Crohns Disease>Title/Abstract)) OR (Inflammatory Bowel Disease 1>Title/Abstract)) OR (Enteritis, Granulomatous>Title/Abstract)) OR (Granulomatous Enteritis>Title/Abstract)) OR (Enteritis, Regional>Title/Abstract)) OR (Ileocolitis>Title/Abstract)) OR (Colitis, Granulomatous>Title/Abstract)) OR (Granulomatous Colitis>Title/Abstract)) OR (Colitis, Terminal>Title/Abstract)) OR (Terminal Ileitis>Title/Abstract)) OR (Ileitis, Regional>Title/Abstract)) OR (Regional Ileitides>Title/Abstract)) OR (Regional Ileitis>Title/Abstract)) AND ("Delayed Diagnosis"[Mesh]) OR (((Delayed Diagnoses>Title/Abstract)) OR (Diagnosis, Delayed>Title/Abstract)) OR (Late Diagnosis>Title/Abstract)) OR (Diagnosis, Late>Title/Abstract)) OR (Late Diagnoses>Title/Abstract)) OR (Late Diagnoses>Title/Abstract)))

Study Description

Study relied on the Montreal Classification for disease localization, behavior, and age grouping\textsuperscript{[14–15]}. The time of diagnosis was defined as the time interval between the first appearance of CD-related symptoms until CD diagnosis was made. A stratification was performed into an interval between the appearance of the first CD-related symptoms until CD diagnosis was established. A delay was defined as a number of days between diagnosis and onset of greater than or equal to the third quartile. Without delayed diagnosis was used to describe the time of diagnosis laying from in the first to the third quartile. Extraintestinal manifestations (EIMS) are common in CD patients and include ankylosing spondylitis, aphthous stomatitis, episcleritis, erythema nodosum, peripheral arthritis, primary sclerosing cholangitis, noma suppurativa, and uveitis\textsuperscript{[16]}. Referring to the Montreal classification, we divided the age of patients into two categories. patients over 40 years of age were defined as older and the remainder as younger.

Study quality evaluation

The quality of all included studies was rated using the Newcastle Ottawa Quality Assessment Scale (NOS) for non-randomized studies in meta-analyses\textsuperscript{[17]}. Data Extraction

Two authors extracted data from eligible studies separately. Disagreements were handled through a consensus-building process among the reviewers. Authors, year of publication, study region, study design, sample characteristics, dependent variable measurements, data sources, and findings were retrieved from each study.

Statistical Analysis

The overall impact of factors associated with delays in the diagnosis of CD was assessed by a meta-analysis of ORs and 95% confidence intervals (CIs). If ORs and 95% CIs were not reported in the original article but sufficient data was provided, the Review Manager software 5.2 calculator was used to determine them. The included studies were tested for heterogeneity using the Homogeneity Test and $I^2$
values. We used random-effects model in the results and perform fixed-effect mode as sensitivity analysis. Funnel plots were used to test for publication bias (only for factors with \( \geq 10 \) included studies).

**Results**

**Study search results**

A total of 565 documents related to delays in CD diagnosis were retrieved. After eliminating 80 duplicates and evaluating the titles and abstracts, 430 publications that were not closely linked to the issue or were the wrong type of study were excluded, leaving a total of 55 papers for the first screening. The whole text of these papers was evaluated to eliminate those that did not investigate factors impacting delays in CD diagnosis or did not contain CD subgroups, leaving 18 studies. A flow chart of the literature search is shown in Fig. 1.

**Characteristics and quality scores of the included studies**

The 18 papers included in this study were published between 2012 and 2021 and covered 13 countries. The total study sample included 9,669 cases. Cohort studies were described in 11 of the 18 papers. Of the included studies, 11 received a quality score of 5, two received a score of 6, four received a score of 7, and one received a score of 8. The primary reason for lower scores was the failure to reach the required follow-up rate and duration (Table 2).
Table 2
Characteristics of the 18 included studies.

<table>
<thead>
<tr>
<th>Studies</th>
<th>Location</th>
<th>Study design</th>
<th>Sample</th>
<th>NOS score</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banerjee, R201818</td>
<td>India</td>
<td>Retrospective study</td>
<td>N = 334, 41.6% were male, median age was 32 years</td>
<td>6</td>
<td>Male, age (younger), ileum, NSAIDS intake, smoking</td>
</tr>
<tr>
<td>Li, Y 2015[19]</td>
<td>China</td>
<td>Retrospective study</td>
<td>N = 343, 70% were male, the average age at diagnosis was 31.8 years</td>
<td>6</td>
<td>Male, age (younger), ileum, family history of IBD, EIMS, smoking, NSAIDS intake</td>
</tr>
<tr>
<td>Nahon, S 2013[20]</td>
<td>France</td>
<td>Cross sectional study</td>
<td>N = 314, 40.8% were male, age at enrolment was 41 years</td>
<td>5</td>
<td>Family history of IBD, EIMS</td>
</tr>
<tr>
<td>Maconi, G 2015[21]</td>
<td>Italy</td>
<td>Cohort study</td>
<td>N = 83, 49.4% were male, median age was 31 years</td>
<td>5</td>
<td>Male, ileum</td>
</tr>
<tr>
<td>Nahon, S 2016[22]</td>
<td>France</td>
<td>Cohort study</td>
<td>N = 497, 46.4% were male, median age at diagnosis was 25.6 years</td>
<td>5</td>
<td>Male, age (younger), ileum, smoking</td>
</tr>
<tr>
<td>El Mouzan, M. I 2019[23]</td>
<td>Saudi Arabia</td>
<td>Retrospective study</td>
<td>N = 240, 60% were male, median delays in diagnosis were 8 years</td>
<td>5</td>
<td>Male, family history of IBD, ileum</td>
</tr>
<tr>
<td>Hong, Z 2017[24]</td>
<td>China</td>
<td>Retrospective study</td>
<td>N = 342, 71.2% were male, average age at diagnosis was 32.7 years</td>
<td>5</td>
<td>Male, age (younger), ileum, smoking</td>
</tr>
<tr>
<td>Lee, Dong-won 2017[25]</td>
<td>Korea</td>
<td>Retrospective study</td>
<td>N = 165, 76.4% were male, mean age at diagnosis was 28.2 years</td>
<td>5</td>
<td>Male, age (younger), ileum, family history of IBD, diarrhea</td>
</tr>
<tr>
<td>Chang, Mo-Moon 2015[26]</td>
<td>Korea</td>
<td>Cohort study</td>
<td>N = 1047, 72.3% were male, mean age at first diagnosis was 27.7 years</td>
<td>7</td>
<td>Male, age (younger), family history of IBD</td>
</tr>
<tr>
<td>Nahon, S 2014[27]</td>
<td>France</td>
<td>Cohort study</td>
<td>N = 364, 40.8% were male, median age was 29.2 years</td>
<td>7</td>
<td>Male, age (younger), ileum, family history of IBD, EIMS, smoking, diarrhea</td>
</tr>
<tr>
<td>Ricciuto, A 2020[28]</td>
<td>Canada</td>
<td>Cohort study</td>
<td>N = 898, 60% were male, age at diagnosis was 12.9 years</td>
<td>5</td>
<td>Male, ileum, family history of IBD, EIMS, smoking, diarrhea</td>
</tr>
<tr>
<td>Studies</td>
<td>Location</td>
<td>Study design</td>
<td>Sample</td>
<td>NOS score</td>
<td>Risk factors</td>
</tr>
<tr>
<td>-------------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Takeyama, E 2021[29]</td>
<td>Japan</td>
<td>Cohort study</td>
<td>N = 528, 76.9% were male, mean age at diagnosis was 31.5 years</td>
<td>7</td>
<td>Male, diarrhea</td>
</tr>
<tr>
<td>Vavricka, Stephan. R 2012[30]</td>
<td>Switzerland</td>
<td>Cohort study</td>
<td>N = 932, 47% were male, median age was 41 years</td>
<td>5</td>
<td>Male, age (younger), family history of IBD, EIMS, smoking, NSAIDS intake</td>
</tr>
<tr>
<td>Yamamoto-Furusho, J. K 2021[31]</td>
<td>Mexico</td>
<td>Cohort study</td>
<td>N = 843, 52.7% were male</td>
<td>5</td>
<td>Male, ileum, family history of IBD, EIMS, smoking, diarrhea</td>
</tr>
<tr>
<td>Zaharie, R 2016[32]</td>
<td>Romania</td>
<td>Cohort study</td>
<td>N = 478, 47.9% were male, median age at diagnosis was 33 years</td>
<td>5</td>
<td>Male, age (younger), family history of IBD, EIMS, smoking</td>
</tr>
<tr>
<td>Nguyen, V. Q. 2017[33]</td>
<td>American</td>
<td>Cohort study</td>
<td>N = 110, 41% were male, average age at diagnosis was 38 years</td>
<td>8</td>
<td>Male, age (younger), ileum, family history of IBD, EIMS, smoking, NSAIDS intake</td>
</tr>
<tr>
<td>Cantoro, L 2017[34]</td>
<td>Italy</td>
<td>Cohort study</td>
<td>N = 1246, 49.8% were male, age at diagnosis was 40 years</td>
<td>7</td>
<td>Male, age (younger)</td>
</tr>
<tr>
<td>Schoepfer, A. M 2013[35]</td>
<td>Switzerland</td>
<td>Cohort study</td>
<td>N = 905, 46.6% were male, median age at diagnosis 26 years</td>
<td>5</td>
<td>Male, age (younger), ileum, smoking, NSAIDS intake</td>
</tr>
</tbody>
</table>

**A meta-analysis of factors influencing delays in CD diagnosis**

A total of nine potential factors influencing delays in CD diagnosis were discussed. Results of the meta-analysis showed that ileal CD (OR = 1.46, 95% CI = 1.21–1.76; Fig. 2), smoking at the time of diagnosis (OR = 1.19, 95% CI = 1.02–1.38; Fig. 3), and NSAID use (OR = 1.34, 95% CI = 1.04–1.72; Fig. 4) were risk factors for delayed CD diagnosis. Male (OR = 0.93, 95% CI = 0.84–1.02; Fig. 5), age at diagnosis < 40 years (OR = 0.80, 95% CI = 0.59–1.06; Fig. 6), family history of IBD (OR = 0.90, 95% CI = 0.62–1.30; Fig. 7), diarrhea (OR = 1.07, 95% CI = 0.71–1.62; Fig. 8), and EIMS at presentation (OR = 1.24, 95% CI = 0.95–1.61; Fig. 9) had no significant effect on time to CD diagnosis. Other factors could not be evaluated because the data were lacking in some or all studies (Table 3).
Table 3
Results of the meta-analyses and the test for heterogeneity.

<table>
<thead>
<tr>
<th>Variable</th>
<th>K</th>
<th>OR (95%CI)</th>
<th>Heterogeneity between studies</th>
<th>Test for overall effect (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>P-value</td>
<td>$\chi^2$</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>0.93 (0.84–1.02)</td>
<td>0.21</td>
<td>21%</td>
</tr>
<tr>
<td>Age (younger)</td>
<td>12</td>
<td>0.80 (0.59–1.06)</td>
<td>&lt; 0.00001</td>
<td>79%</td>
</tr>
<tr>
<td>Smoking</td>
<td>11</td>
<td>1.19 (1.02–1.38)</td>
<td>0.55</td>
<td>0%</td>
</tr>
<tr>
<td>Ileum</td>
<td>13</td>
<td>1.46 (1.21–1.76)</td>
<td>0.07</td>
<td>40%</td>
</tr>
<tr>
<td>Family history of IBD</td>
<td>11</td>
<td>0.90 (0.62–1.30)</td>
<td>0.07</td>
<td>42%</td>
</tr>
<tr>
<td>EIMS</td>
<td>8</td>
<td>1.24 (0.95–1.61)</td>
<td>0.10</td>
<td>42%</td>
</tr>
<tr>
<td>NSAID intake</td>
<td>5</td>
<td>1.34 (1.04–1.72)</td>
<td>0.27</td>
<td>23%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>1.07 (0.71–1.62)</td>
<td>0.05</td>
<td>58%</td>
</tr>
</tbody>
</table>

Sensitivity analysis and publication bias evaluation

A comparative analysis of the nine included factors was performed using a fixed-effects and a random-effects model. Except for two factors, younger age and extraintestinal manifestation, the remaining variables were stable in both models. According to the funnel plot analysis, the scatter distribution was largely uniform and symmetrical on both sides of the axis. This indicated that there was no publication bias in the manuscripts used in this study (Fig. 10–14).

Discussion

Identifying factors influencing the delay in the diagnosis of CD is important to define areas of priority for action to reduce diagnostic delay. This meta-analysis reviewed factors associated with delays in CD diagnosis in order to inform recommendations for shortening the time to diagnosis. The results suggest that ileal CD is a risk factor for delayed diagnosis. This could be because patients with ileal illness are less likely to experience severe warning signals like blood in the stool\textsuperscript{33}. Another reason ileal CD is a risk factor is that it frequently manifests as stomach pain without diarrhea, which can be misinterpreted with irritable bowel syndrome\textsuperscript{20}. Additionally, smoking increases the likelihood of a delayed diagnosis. As noted by Laaksonen et al. \textsuperscript{36}, smoking tend to be more prevalent among individuals in lower socioeconomic positions. The link between smoking and delayed diagnosis may correlate with the lower socioeconomics of this patient population. People who smoked at the time of diagnosis were more likely to have delayed diagnosis as a result of financial constraints, such as a lack of health insurance. The extent to which lower socioeconomic position explains the relationship between smoking at diagnosis and delays in diagnosis still requires further research. The association between NSAID use and delays in
diagnosis may be related to similarities between NSAID side effects and CD symptoms. This could reduce patient awareness of the disease and increase the risk of a misdiagnosis. However, NSAID use and smoking at the time of diagnosis are not solid results according to OR and sample numerosity. Surprisingly, a family history of inflammatory bowel disease was not a protective factor against a delay in CD diagnosis. This may relate to the difficulty of identifying inflammatory bowel disease subtypes. While a family history of inflammatory bowel disease is predictive of an increased risk of CD, only 10–25% of patients have a first-degree relative with the disease. In addition, genetic risk varies by subtype, and these factors may reduce patient vigilance to some extent. No association was found between diagnostic delay and any of sex, age, and diarrhea.

To improve the time to CD diagnosis, medical facilities should provide easy access to colonoscopy and ileoscopy for patients. The governments should raise awareness and knowledge about CD, especially among low-income people. In addition, general practitioners, family practitioners, and general pediatricians should also be educated to ensure early referral to gastroenterologists. Examine the referral system to ensure that patients are referred to concerned gastroenterologists as soon as possible. Finally, promote easy-to-use Crohn's disease diagnostic tools such as the 'Red Flags Index for Suspected Crohn's Disease' to help clinicians identify the symptoms of Crohn's disease more easily and accurately, thereby reducing the time to diagnosis. Furthermore, a recent study found that fecal calprotectin appeared to be clinically useful in ruling out CD. Fecal calprotectin and a clinical index of suspicion can work well together to identify people who should be sent quickly to a specialist for a CD diagnosis.

The studies included in this meta-analysis were predominantly retrospective cohort studies. Compared to randomized controlled trials, this study type is more prone to recall bias, resulting in greater heterogeneity in particular impact factors. The notable heterogeneity of the methodologies used by the studies included in our review is one of the work's limitations. In addition, some of the studies had a very small sample size, some risk factors were only measured by a few studies, and some risk factor definitions were not consistent across the studies.

**Conclusion**

This meta-analysis revealed that ileal CD, the use of NSAIDs, and smoking at the time of diagnosis were all risk factors for delays in CD diagnosis. Education of patients and primary care providers about these risk factors should be increased. This study had some limitations, however. Future meta-analyses including more and higher-quality studies that investigate other perspectives on factors associated with delays in CD diagnosis are needed to support the findings of this study.

**Declarations**

**Data sharing**

Study data are available on request to the authors.
Ethical Approval

Not applicable.

Competing interests

The authors deny any conflict of interest.

Authors' contributions

Miaofeng C acquisition of data, analysis and interpretation of data, drafting the article, final approval; Wenrui W acquisition of data, analysis and interpretation of data; Rong S conception and design of the study, critical revision, final approval; Jinping X conception and design of the study, critical revision, final approval.

Funding

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Availability of data and materials

The authors stated that all information provided in this article could be shared.

PRISMA 2021 Checklist statement: The authors have read the PRISMA 2021 Checklist, and the manuscript was prepared and revised according to the PRISMA 2021 Checklist.

References


**Figures**
Figure 1

Flow Chart of literature search.
Figure 2

Meta-analysis forest plot of ileal CD.

Figure 3

Meta-analysis forest plot of smoking at time of diagnosis.
Figure 4

Meta-analysis forest plot of NSAID use.

Figure 5

Meta-analysis forest plot of male sex.
### Figure 6

**Meta-analysis forest plot of age <40 years at diagnosis.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alain M. Schaeffer 2013</td>
<td>-0.5688</td>
<td>0.1849</td>
<td>9.9%</td>
<td>0.51 [0.38, 0.74]</td>
<td>0.1849</td>
<td>9.9%</td>
<td>0.51 [0.38, 0.74]</td>
</tr>
<tr>
<td>Chang Mo Moon 2015</td>
<td>-0.4671</td>
<td>0.1426</td>
<td>10.5%</td>
<td>0.63 [0.47, 0.83]</td>
<td>0.1426</td>
<td>10.5%</td>
<td>0.63 [0.47, 0.83]</td>
</tr>
<tr>
<td>Dong-won Lee 2017</td>
<td>0.4402</td>
<td>0.532</td>
<td>4.7%</td>
<td>1.55 [0.55, 4.41]</td>
<td>0.532</td>
<td>4.7%</td>
<td>1.55 [0.55, 4.41]</td>
</tr>
<tr>
<td>Laura Cantoro 2017</td>
<td>-0.571</td>
<td>0.1344</td>
<td>10.6%</td>
<td>0.56 [0.43, 0.74]</td>
<td>0.1344</td>
<td>10.6%</td>
<td>0.56 [0.43, 0.74]</td>
</tr>
<tr>
<td>R. Banerjee 2011</td>
<td>0.2046</td>
<td>0.1642</td>
<td>10.2%</td>
<td>1.23 [0.89, 1.69]</td>
<td>0.1642</td>
<td>10.2%</td>
<td>1.23 [0.89, 1.69]</td>
</tr>
<tr>
<td>Roxana Zaharie 2016</td>
<td>-0.0726</td>
<td>0.2322</td>
<td>9.1%</td>
<td>0.93 [0.59, 1.47]</td>
<td>0.2322</td>
<td>9.1%</td>
<td>0.93 [0.59, 1.47]</td>
</tr>
<tr>
<td>Stéphane Nahon 2014</td>
<td>0.1070</td>
<td>0.3423</td>
<td>7.2%</td>
<td>1.11 [0.57, 2.18]</td>
<td>0.3423</td>
<td>7.2%</td>
<td>1.11 [0.57, 2.18]</td>
</tr>
<tr>
<td>Stéphane Nahon 2016</td>
<td>0.1219</td>
<td>0.2789</td>
<td>8.3%</td>
<td>1.13 [0.65, 1.96]</td>
<td>0.2789</td>
<td>8.3%</td>
<td>1.13 [0.65, 1.96]</td>
</tr>
<tr>
<td>Stephen R 2012</td>
<td>0.708</td>
<td>0.2882</td>
<td>8.4%</td>
<td>2.03 [1.20, 3.43]</td>
<td>0.2882</td>
<td>8.4%</td>
<td>2.03 [1.20, 3.43]</td>
</tr>
<tr>
<td>Vu Q. Nguyen 2017</td>
<td>0.0134</td>
<td>0.4586</td>
<td>5.5%</td>
<td>1.01 [0.41, 2.49]</td>
<td>0.4586</td>
<td>5.5%</td>
<td>1.01 [0.41, 2.49]</td>
</tr>
<tr>
<td>Yuan Li 2015</td>
<td>-0.8958</td>
<td>0.2784</td>
<td>8.3%</td>
<td>0.41 [0.24, 0.70]</td>
<td>0.2784</td>
<td>8.3%</td>
<td>0.41 [0.24, 0.70]</td>
</tr>
<tr>
<td>Zhiwu Hong 2017</td>
<td>-1.2492</td>
<td>0.3343</td>
<td>7.3%</td>
<td>0.29 [0.15, 0.55]</td>
<td>0.3343</td>
<td>7.3%</td>
<td>0.29 [0.15, 0.55]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: $\tau^2 = 0.19$; $\chi^2 = 52.69$, $df = 11$ ($P < 0.00001$); $I^2 = 79$

Test for overall effect: $Z = 1.54$ ($P = 0.12$)

### Figure 7

**Meta-analysis forest plot of IBD family history.**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log(Odds Ratio)</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
<th>SE</th>
<th>Weight</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amanda Ricciuto 2020</td>
<td>-0.0506</td>
<td>0.2091</td>
<td>20.2%</td>
<td>0.95 [0.63, 1.43]</td>
<td>0.2091</td>
<td>20.2%</td>
<td>0.95 [0.63, 1.43]</td>
</tr>
<tr>
<td>Chang Mo Moon 2015</td>
<td>0.8247</td>
<td>0.4431</td>
<td>10.9%</td>
<td>1.87 [0.78, 4.46]</td>
<td>0.4431</td>
<td>10.9%</td>
<td>1.87 [0.78, 4.46]</td>
</tr>
<tr>
<td>Dong-won Lee 2017</td>
<td>-1.5157</td>
<td>1.4786</td>
<td>1.8%</td>
<td>0.22 [0.01, 3.96]</td>
<td>1.4786</td>
<td>1.8%</td>
<td>0.22 [0.01, 3.96]</td>
</tr>
<tr>
<td>Jesús K. Yamamoto-Furusho 2021</td>
<td>0.7232</td>
<td>1.2371</td>
<td>2.2%</td>
<td>2.06 [1.16, 3.62]</td>
<td>1.2371</td>
<td>2.2%</td>
<td>2.06 [1.16, 3.62]</td>
</tr>
<tr>
<td>Mohammad I. El Mouzan 2019</td>
<td>-2.1804</td>
<td>1.1033</td>
<td>2.7%</td>
<td>0.11 [0.01, 0.98]</td>
<td>1.1033</td>
<td>2.7%</td>
<td>0.11 [0.01, 0.98]</td>
</tr>
<tr>
<td>Roxana Zaharie 2016</td>
<td>-0.3857</td>
<td>0.7712</td>
<td>4.9%</td>
<td>0.68 [0.15, 3.08]</td>
<td>0.7712</td>
<td>4.9%</td>
<td>0.68 [0.15, 3.08]</td>
</tr>
<tr>
<td>Stéphane Nahon 2013</td>
<td>-0.7985</td>
<td>0.3424</td>
<td>14.3%</td>
<td>0.45 [0.23, 0.88]</td>
<td>0.3424</td>
<td>14.3%</td>
<td>0.45 [0.23, 0.88]</td>
</tr>
<tr>
<td>Stéphane Nahon 2014</td>
<td>-0.3652</td>
<td>0.3101</td>
<td>15.6%</td>
<td>0.69 [0.38, 1.27]</td>
<td>0.3101</td>
<td>15.6%</td>
<td>0.69 [0.38, 1.27]</td>
</tr>
<tr>
<td>Stephan R 2012</td>
<td>0.3716</td>
<td>0.2785</td>
<td>16.9%</td>
<td>1.45 [0.84, 2.50]</td>
<td>0.2785</td>
<td>16.9%</td>
<td>1.45 [0.84, 2.50]</td>
</tr>
<tr>
<td>Vu Q. Nguyen 2017</td>
<td>0.4914</td>
<td>0.5016</td>
<td>9.3%</td>
<td>1.63 [0.61, 4.37]</td>
<td>0.5016</td>
<td>9.3%</td>
<td>1.63 [0.61, 4.37]</td>
</tr>
<tr>
<td>Yuan Li 2015</td>
<td>-1.1064</td>
<td>1.4898</td>
<td>1.5%</td>
<td>0.33 [0.02, 6.21]</td>
<td>1.4898</td>
<td>1.5%</td>
<td>0.33 [0.02, 6.21]</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

Heterogeneity: $\tau^2 = 0.14$; $\chi^2 = 17.34$, $df = 10$ ($P = 0.07$); $I^2 = 42$

Test for overall effect: $Z = 0.56$ ($P = 0.58$)
Figure 8

Meta-analysis forest plot of diarrhea.

Figure 9

Meta-analysis forest plot of EIMS.
Figure 10

Funnel plot of male sex.
Figure 11

Funnel plot of male sex.
Figure 12

Funnel plot of male sex.
Figure 13

Funnel plot of smoking.
Figure 14

Funnel plot of ileal CD.