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# Systematic review with meta-analysis: Time to diagnosis and the impact of delayed diagnosis on clinical outcomes in inflammatory bowel disease

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## Summary

**Background:** The impact of diagnostic delay on the clinical course of inflammatory bowel disease (IBD) remains uncertain.

**Aim:** To perform a systematic review of time to diagnosis and the impact of delayed diagnosis on clinical outcomes in Crohn's disease (CD) and ulcerative colitis (UC).

**Methods:** We searched EMBASE and Medline from inception to 30th November 2022 for studies reporting diagnostic interval, from symptom onset to IBD diagnosis. We calculated the median, interquartile range (IQR) and pooled weighted median, of median diagnostic intervals of eligible studies. We defined delayed diagnosis as individuals above the 75th centile of longest time to diagnosis in each study. Using random effects meta-analysis, we pooled odds ratios (ORs) with 95% confidence intervals (CI) for studies reporting clinical outcomes, according to delayed diagnosis.

**Results:** One hunderd and one studies representing 112,194 patients with IBD (CD = 59,359; UC = 52,835) met inclusion criteria. The median of median times to diagnosis was 8.0 (IQR: 5.0–15.2) and 3.7 months (IQR: 2.0–6.7) in CD and UC, respectively. In high-income countries, this was 6.2 (IQR: 5.0–12.3) and 3.2 months (IQR: 2.2–5.3), compared with 11.7 (IQR: 8.3–18.0) and 7.8 months (IQR: 5.2–21.8) in low-middle-income, countries, for CD and UC respectively. The pooled weighted median was 7.0 (95% CI: 3.0–26.4) and 4.6 (95% CI: 1.0–96.0) months, for CD and UC respectively. Eleven studies, representing 6164 patients (CD = 4858; UC = 1306), were included in the meta-analysis that examined the impact of diagnostic delay on clinical outcomes. In CD, delayed diagnosis was associated with higher odds of stricturing (OR = 1.88; CI: 1.35–2.62), penetrating disease (OR = 1.64; CI: 1.21–2.20) and intestinal surgery (OR = 2.24; CI: 1.57–3.19). In UC, delayed diagnosis was associated with higher odds of colectomy (OR = 4.13; CI: 1.04–16.40).

As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr Y Yuan.

The Handling Editor for this article was Professor Alexander Ford, and it was accepted for publication after full peer-review.

**Conclusion:** Delayed diagnosis is associated with disease progression in CD, and intestinal surgery in both CD and UC. Strategies are needed to achieve earlier diagnosis of IBD.

## 1 | INTRODUCTION

Inflammatory bowel diseases, Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing conditions with a rising global prevalence now approaching 1% in some countries.[1] These conditions often develop at a young age and may require immunosuppressive medical therapy and hospitalisation. The cumulative inflammatory burden can result in progressive damage to the gastrointestinal tract, potentially resulting in strictures, penetrating disease and dysplasia.[2] These complications result in 50% and 15% of individuals with CD and UC, respectively, requiring surgery within 10 years of diagnosis.[3] Poor clinical outcomes may also adversely impact psychological well-being, quality of life and work productivity, at considerable cost to the individual and the economy.[3,4]

The diagnosis of IBD can be challenging and protracted, with more than one in 10 patients presenting with symptoms at least 5 years before a diagnosis is established.[5] Furthermore, damage to the bowel may be subclinical, preceding the onset of symptoms.[6] When symptoms occur they may be intermittent, particularly in the early stages of disease, and can be mistaken for more common conditions.[7,8] More timely diagnosis and treatment may offer the opportunity to alter the natural history of inflammatory bowel disease (IBD).[9] Current therapeutic interventions in IBD treat active inflammation, but may not reverse the cumulative inflammatory burden that has accrued before diagnosis.[10] Earlier diagnosis and treatment may therefore lead to improved long-term outcomes in IBD.[6]

Time to diagnosis describes the time interval from IBD-related symptom onset until IBD is diagnosed. Diagnosis is not possible until a patient initiates contact with a healthcare professional, is investigated and referred onto specialist care. Delayed diagnosis can therefore be separated into a patient-related interval (from symptom onset to the first visit of a physician) and a healthcare-related interval (from first clinical contact until IBD diagnosis is established).

Reported estimates of time to diagnosis vary widely, which may reflect differences in healthcare settings, methods of data collection and how time to diagnosis is defined, whether from the point of symptom onset or initial consultation.[11–14] Delayed diagnosis may potentially impact disease progression and subsequent clinical outcomes, although the current evidence is conflicting. Some studies report an association between the time from symptom onset to diagnosis and risk of disease progression or intestinal surgery in both CD and UC, while others do not.[11,14–18] Uncertainty remains about the length of time to diagnosis and the impact of delayed diagnosis on subsequent clinical outcomes in IBD. There are no previous published systematic reviews or meta-analyses on this topic in adult-onset IBD, leaving an important gap in the available evidence base.

We therefore conducted a systematic review and meta-analysis of studies firstly, to identify the time from symptom onset to diagnosis of CD and UC, and secondly, report the impact of delayed diagnosis on subsequent clinical outcomes including disease progression, the need for medical or surgical treatment, and healthcare utilisation. We hypothesised that delayed diagnosis is associated with adverse clinical outcomes in adult IBD.

## 2 | METHODS

This systematic review has been conducted as per the guidance provided by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) group.

### 2.1 | Search strategy and selection criteria

We used, EMBASE and Medline, accessed via Ovid, to search systematically the medical literature, from inception to 30th of November 2022, and identify studies reporting on the time to diagnosis from symptom onset among patients diagnosed with IBD. For our secondary aim, we further identified longitudinal follow-up studies examining the associated impact of delayed diagnosis on the clinical course of the disease.

We developed a search strategy using a combination of free text terms and medical subject headings (MeSH) or equivalents from each database (Table S1). Two academic librarians, with the authors, helped conduct the literature search.

Inclusion criteria were defined prospectively. Studies were selected for inclusion if they reported the time to IBD diagnosis from symptom onset, and/or examined the impact of delayed diagnosis on the clinical disease course of IBD. Both prospective and retrospective studies were considered. All studies included patients with an IBD diagnosis based on established clinical, endoscopic, histological and/or radiographic criteria. We excluded studies that were not in English and studies examining only paediatric-onset IBD, defined as age <16 years.

### 2.2 | Study outcomes

Our study outcomes were firstly, the median, interquartile range (IQR) and pooled weighted median of the median times to diagnosis, reported in months, and secondly, the impact of delayed diagnosis on the subsequent clinical outcomes in CD and UC.

We defined total time to diagnosis as the reported time from symptom onset to the diagnosis of CD and UC. We also examined potential sources of delay in the diagnostic pathway by identifying three time intervals namely, the patient-related interval,

healthcare-related interval and total time to diagnosis as illustrated in Figure 1.[17,18] Since time to diagnosis intervals are usually not normally distributed, studies that reported only the mean for the time intervals, rather than median or interquartile range, were reported separately and not included in the main finding (Tables S2 and S3).

To examine the impact of delayed diagnosis on clinical outcomes, at the point of or after diagnosis, we defined the following outcomes: IBD phenotype (stricturing or penetrating disease), disease severity quantified with clinical scoring tools, IBD-related medical therapy, IBD-related surgery and healthcare utilisation following IBD diagnosis defined as hospitalisation and emergency department attendance related to IBD activity.

Delayed diagnosis in IBD was defined as individuals above the 75th centile of longest time to diagnosis in each study cohort, as previously described.[18,19] Patient and healthcare-related sub-intervals were similarly defined for these respective sub-intervals. We used the above definition of delayed diagnosis to identify studies for inclusion in the meta-analysis, where we examined the pooled impact of delayed diagnosis on the defined clinical outcomes.

## 2.3 | Data extraction and synthesis

Two investigators (NJ and SB) reviewed titles and abstracts independently and retrieved those relevant for further eligibility assessment. Any discrepancy was resolved by a third reviewer (RP). We extracted data from included studies on: year of study, country, income status of country stratified according to World Bank economic class (high, middle and low income), study design, data source (questionnaire or electronic records), setting (primary, secondary or tertiary care, multicentre, regional or national registry), population size and characteristics (age and sex), IBD subtype (CD or UC), time to diagnosis interval and sub-intervals with duration in months and the impact of delayed diagnosis on clinical outcomes related to IBD activity at diagnosis or during longitudinal follow-up (Tables S4 and S5).

We extracted the adjusted odds ratio (OR), with 95% confidence intervals (CI), for each of the events of interest. If these were unavailable, we extracted raw data where possible. For studies where adjusted ORs or raw data were not reported, we used unadjusted ORs (Table S6). To report on the quality of research evidence in this area, each of the final studies included were appraised for quality and bias using the Joanna Briggs Institute critical appraisal tool checklist. This appraisal tool is designed to assess the methodological quality and determine the extent to which each study has addressed the possibility of bias in its design, conduct and analysis. There are no standardised instruments to assess the methodological quality of studies on diagnostic delays. We adapted and used the Joanna Briggs Institute critical appraisal tool checklist for cross-sectional studies to assess the quality of studies reporting the time to diagnosis intervals in CD and UC. The appraisal tool checklist for cohort studies was used to assess the quality of studies that reported the impact of diagnostic delay in CD and UC. Both reviewers (NJ and SB) independently scored the studies against 8 and 11 criteria, for studies reporting on the time to diagnosis interval and those examining the impact of delayed diagnosis respectively (Tables S7–S10).[20]

## 2.4 | Statistical analysis

We presented the median and IQR for each critical diagnostic time interval from each study, where available. We calculated the median, IQR and pooled weighted median, of the median times for each diagnostic interval (total time to diagnosis, patient, and healthcare sub-intervals).

We used the weighted median of the reported study-specific medians as our pooled median estimate and constructed an approximate 95% CI around the weighted median.[21] This analysis was performed using R Statistical Software (v4.1.2; R Core Team 2021), using the wtd.quantile function in the Hmisc package.[22] Similarly, for those studies reporting means rather than medians, a weighted mean and standard deviation (SD) were calculated using the wtd.mean function in the same package (Tables S2 and S3).[21]

We performed a meta-analysis to examine the impact of delayed diagnosis on the subsequent clinical outcomes in IBD. We calculated pooled OR with 95% CI using the log OR and standard error. We used the adjusted OR where available.[23] We analysed CD and UC separately. We pooled data using the inverse variance method and a random effects model to provide conservative estimates of the impact of delayed diagnosis on the examined clinical outcomes. The Dersimonian–Laird random effects model was used to calculate the pooled OR as it is unclear if there was a single effect that underpins all of the studies.[24] We assessed heterogeneity between studies using the $I^2$ statistic with values of 0%–24%, 25%–49%, 50%–74% and ≥75%, considered very low, low, moderate and high levels respectively.

We predicted a priori that the following variables may contribute to heterogeneity: studies conducted in high-income versus the lower and middle-income countries, era of study (pre-2010, 2010–2015

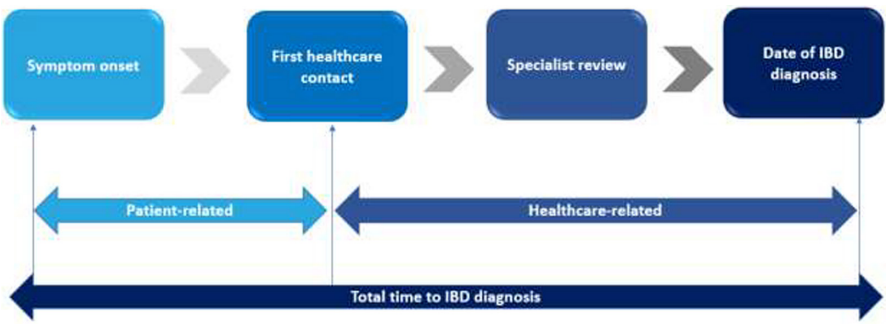


FIGURE 1 Time intervals from onset of symptoms to diagnosis.

and post-2015) and study quality. The impact of these variables on heterogeneity was examined by conducting separate sub-group analyses. We planned to assess for the evidence of publication bias by applying Egger's test to funnel plots of odds ratios (ORs), or other small study effects, where ≥10 studies were present, in line with published recommendations.[25] The meta-analysis was performed using Review Manager (RevMan) Version 5.4.1 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

## 3 | RESULTS

### 3.1 | Time to diagnosis

The literature search identified 15,538 citations, of which 383 were obtained for further review (Figure 2). In all, 101 studies were published between 1971 and 30 November 2022 representing 112,194 patients diagnosed with IBD that reported on the time to diagnosis interval (CD 86 studies, *n* = 59,359: UC 61 studies, *n* = 52,835) (Figure 2 and Tables S4 and S5).[7,11–19,26–115] Fifty-four studies were published from Europe, eight from North America, four from South America, 30 from Asia, one from Australia, one from Africa and three reported from multiple nations (Tables S4 and S5). Agreement was complete between reviewers with respect to studies deemed suitable for inclusion.

Sixty-one studies published between 1971 and 30th November 2022 met our inclusion criteria, reporting the median and/or IQR of the total time to diagnosis interval, representing a total of 54,183 patients diagnosed with IBD (CD = 33,736 and UC = 20,447) (Figure 2). Almost all studies were conducted in a single country, except for two, one of which reported on IBD patients from Eastern and Western Europe, and the second reported on patients with IBD surveyed from Finland, Italy, France, Canada, Germany, UK, Spain and Sweden.[42,63] Thirty-eight studies originated from Europe, five

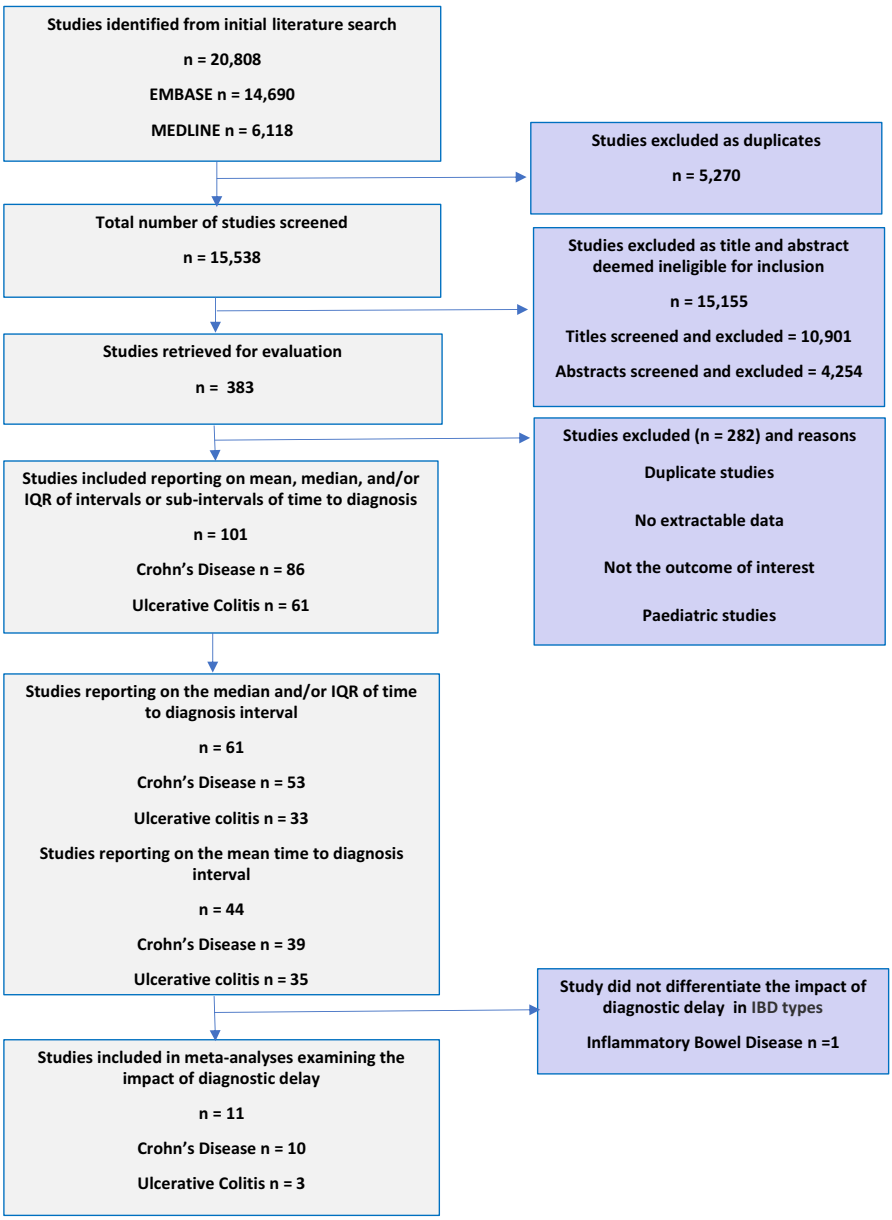


FIGURE 2 Flow diagram of assessment of studies identified in the systematic review and meta-analysis.

from North America, one from South America, 16 from Asia and one from multiple nations across both Europe and North America as described above. The majority were retrospective cohort studies with data collected from electronic patient records. On the Joanna Briggs Institute quality assessment tool, these studies reporting on the time to diagnosis interval scored a median of 6 out of 8 points for CD (ranging from 4 to 8), and 6 points for UC (ranging from 4 to 8). The quality of each study is reported in Tables S9 and S10. Studies that reported the mean time to diagnosis alone ($n = 44$) were not included in the main analyses and are presented separately in Tables S2 and S3.

Fifty-three studies reported the median and/or IQR duration of one or more of the described time intervals for CD (Table 1). The median time to diagnosis among these studies ranged from 2 to 84 months. The median of the median times to diagnosis was 8.0 months for the total time to diagnosis interval (IQR: 5.0–15.2 months, $n = 33{,}736$). The pooled weighted median of the median times to diagnosis was 7.0 months (95% CI: 3.0–26.4). Seven studies reported the patient-related interval and eight the healthcare-related interval in CD (Table 1).

Thirty-three studies reported the median and/or IQR duration of one or more of the described time intervals for UC (Table 2). The median time to diagnosis among these studies ranged from 2 to 114 months. The median of the median times to diagnosis was 3.7 months for the total time to diagnosis interval (IQR: 2.0–6.7 months, $n = 20{,}357$). The pooled weighted median of the median times to diagnosis was 4.6 months (95% CI: 1.0–96.0). Five studies reported the patient-related interval and six the healthcare-related interval in UC (Table 2).

In the sub-group analysis, for high-income countries, the median of the median times to diagnosis was 6.2 months (IQR: 5.0–12.3) for the total time to diagnosis interval for CD, and 3.2 months (IQR: 2.2–5.3) for UC, compared with 11.7 months (IQR: 8.3–18.0) and 7.8 months (IQR: 2.0–21.8) for CD and UC, respectively, for low- and middle-income countries. For high-income countries, the pooled weighted median of the median times to diagnosis was 6.0 months (95% CI: 3.0–26.4) for CD and 4.0 months (95% CI: 2.0–12.0) for UC, compared with 18.0 months (95% CI: 3.0–24.0) and 24.0 months (95% CI: 1.0–96.0) for CD and UC, respectively, for low- and middle-income countries.

For CD and UC, six and three studies, respectively, reported the median of the total time to diagnosis interval with data collated from population-based registry cohorts. For CD, the median of the median times to diagnosis was 8.7 months (IQR: 6.0–13.7) and 7.6 months (IQR: 5.0–15.2) among studies from population-based registry cohorts compared with those from referral centre cohorts respectively. For UC, the median of the median times to diagnosis was 4.8 months (IQR: 4.8–12.0) and 3 months (2.0–6.0) among studies from population-based registry cohorts compared with those from referral centre cohorts respectively.

For both CD and UC, we did not identify any clear trend in the median of the median times to diagnosis by different era (Table S11). Eleven and six studies examined the differences between the total time to diagnosis among males and females in CD and UC respectively (Table S13).

## 3.2 | Impact of delayed diagnosis on clinical outcomes

Eleven studies, published from 2012 to 2020, met the inclusion criteria for our second outcome reporting the impact of delayed diagnosis on the subsequent clinical course of IBD, representing a total of 6164 patients diagnosed with IBD (CD; $n = 4858$ and UC; $n = 1306$).[11,13,16,18,19,56,74,75,98,107,113] Five studies originated from Europe, one from North America and five from Asia. In total, 10 studies examined the impact of delayed diagnosis in CD and three studies examined the impact of delayed diagnosis in UC. Studies examining the impact of delayed diagnosis on clinical outcomes in IBD scored from 7 to 10 points out of 11 for CD, and 7 to 9 for UC, using the Joanna Briggs Institute quality assessment tool (Tables S7 and S8). One study reported the impact of delayed diagnosis in IBD, but did not differentiate IBD subtype and was therefore not included in the meta-analysis (Figure 2).[17] Among studies included in the meta-analysis, the impact of era, study quality and income status of country on heterogeneity were examined by conducting separate subgroup analyses (Tables S14 and S15).

## 3.3 | Crohn's disease

Ten studies reported the association between delayed diagnosis on the subsequent clinical outcomes related to disease activity among 4858 patients diagnosed with CD.[11,13,18,19,56,74,75,98,107,113] Eight studies reported the association between delayed diagnosis with CD phenotype (stricturing or penetrating disease).[11,18,19,56,74,75,98,113] Pooled analysis showed an association between delayed diagnosis with a stricturing disease phenotype at or following diagnosis (OR = 1.88, 95% CI: 1.35–2.62) with moderate heterogeneity between studies ($I^2 = 61\%$) (Figure 3A). Pooled analysis of OR also showed an association between delayed diagnosis and the odds of developing penetrating disease phenotype at or following diagnosis (OR = 1.64, 95% CI: 1.21–2.20), with low heterogeneity between studies ($I^2 = 38\%$) (Figure 3B).

Nine studies reported the association between delayed diagnosis and the odds of IBD-related surgery among individuals diagnosed with CD (intestinal surgery $n = 9$; perianal surgery $n = 4$; any CD-related surgery: $n = 5$; emergency surgery related to CD $n = 1$; fistula surgery $n = 1$).[11,13,18,19,56,74,75,98,113] Pooled analysis of OR showed an association between delayed diagnosis and higher odds of CD-related intestinal surgery (OR = 2.24, 95% CI: 1.57–3.19) with moderate heterogeneity between studies ($I^2 = 61\%$) (Figure 4A).[11,13,18,19,56,74,75,98,113]

Pooled analysis of four studies showed no statistically significant association between delayed diagnosis and the subsequent odds of CD-related perianal surgery following diagnosis (OR = 1.23, 95%

**TABLE 1** Studies reporting time to diagnosis intervals in Crohn's disease

| Diagnostic interval | Study | Year | Country | Time to diagnosis (months) | |
|---|---|---|---|---|---|
| | | | | Median | (IQR) |
| Total time to diagnosis | Kyle et al[69] | 1971 | Scotland | 6 | NR |
| | Lind[a] et al[78] | 1985 | Norway | 36 | – |
| | Lind[a] et al[78] | 1985 | Norway | 24 | – |
| | Lind[a] et al[78] | 1985 | Norway | 24 | – |
| | Foxworthy[a] et al[53] | 1986 | UK | 16 | – |
| | Foxworthy[a] et al[53] | 1986 | UK | 5 | – |
| | Segal et al[99] | 1988 | South Africa | 36 | NR |
| | Loftus et al[80] | 1998 | USA | 3 | – |
| | Timmer et al[106] | 1999 | Germany | 20 | – |
| | Timmer et al[106] | 1999 | Germany | 5 | – |
| | Pilar et al[90] | 2002 | Spain | 3 | – |
| | Piront[a] et al[96] | 2002 | France | 7.5 | NR |
| | Piront[a] et al[96] | 2002 | France | 6 | NR |
| | Edouard et al[51] | 2005 | West indies | 2 | NR |
| | Vind et al[108] | 2006 | Denmark | 8.3 | – |
| | Burgmann et al[7] | 2006 | Canada | 84 | NR |
| | Abakar-Mahamat et al[27] | 2007 | France | 5 | – |
| | Tine[a] et al[65] | 2007 | Denmark | 26.4 | NR |
| | Tine[a] et al[65] | 2007 | Denmark | 6 | NR |
| | Tine[a] et al[65] | 2007 | Denmark | 8.4 | NR |
| | Albert et al[30] | 2008 | Germany | 13 | NR |
| | Romberg-Camps et al[12] | 2009 | Netherlands | 3 | (0–480) |
| | Munkholm et al[87] | 2009 | Denmark | 26.4 | NR |
| | Guariso et al[60] | 2010 | Italy | 4 | NR |
| | Vavricka et al[107] | 2012 | Switzerland | 9 | (3–24) |
| | Goel[b] et al[58] | 2013 | India | 24 | (6–240) |
| | Schoepfer et al[98] | 2013 | Switzerland | 9 | (3–24) |
| | Pezerovic et al[94] | 2013 | Croatia | 6 | NR |
| | Burisch et al[42] | 2014 | Eastern Europe | 4.6 | NR |
| | Burisch et al[42] | 2014 | Western Europe | 3.4 | NR |
| | Furfaro et al[54] | 2014 | Italy | 7 | (1.03–26.4) |
| | Sjoberg et al[102] | 2014 | Sweden | 6 | (2–15) |
| | Can[b] et al[43] | 2014 | Turkey | 8.3 | NR |
| | Nahon et al[11] | 2014 | France | 5 | (2–12) |
| | Pellino et al[14] | 2015 | Italy | 11 | (1–163) |
| | Mickael et al[83] | 2015 | France | 3 | (NR–7) |
| | Li[b] et al[75] | 2015 | China | 10 | (2–34) |
| | Maconi et al[81] | 2015 | Spain | 14.2 | (5–38.5) |
| | Basaranoglu[b] et al[37] | 2015 | Turkey | 2 | NR |
| | Zaharie et al[113] | 2016 | Romania | 5 | (NR[b]–8) |
| | Cantoro et al | 2017 | Italy | 7.1 | (1–26) |
| | Hong[b] et al[13] | 2017 | China | NR | (NR–34) |

TABLE 1 (Continued)

| Diagnostic interval | Study | Year | Country | Time to diagnosis (months) | |
|---|---|---|---|---|---|
| | | | | Median | (IQR) |
| | Nguyen et al[19] | 2017 | USA | 9.5 | (3.8–25.6) |
| | Lee et al[74] | 2017 | South Korea | 6.2 | (NR[b]–21.4) |
| | Szanto et al[104] | 2018 | Hungary | 2.1 | (0–8.6) |
| | Banerjee[b] et al[34] | 2018 | India | 18 | (6–36) |
| | Irving et al[63] | 2018 | Multiple[c] | 12 | NR |
| | Song[a] et al[103] | 2019 | South Korea | 15.5 | (4.4–43.1) |
| | Song[a] et al[103] | 2019 | South Korea | 5.9 | (24.5–66) |
| | Song[a] et al[103] | 2019 | South Korea | 17.4 | (5.4–94.9) |
| | Novacek et al[33] | 2019 | Austria | 6 | (2–23) |
| | Ghosh et al[56] | 2019 | Bangladesh | 18 | (1–180) |
| | Chaisidhivej[a,b] et al[45] | 2019 | Thailand | 15.8 | NR |
| | Chaisidhivej[a,b] et al[45] | 2019 | Thailand | 10.1 | NR |
| | Chaisidhivej[a,b] et al[45] | 2019 | Thailand | 11.7 | NR |
| | Qiao[b] et al[71] | 2019 | China | 11 | (0–220) |
| | Schoepfer et al[18] | 2019 | Switzerland | 6 | (1–24) |
| | Yzet et al[112] | 2020 | France | 7.6 | (2.7–26.1) |
| | Banerjee[a,b] et al[35] | 2020 | India | 24 | (9–60) |
| | Banerjee[a,b] et al[35] | 2020 | India | 12 | (1–288) |
| | Walker et al[17] | 2020 | UK | 7.6 | (3.1–15) |
| | Gomes[b] et al[59] | 2021 | Brazil | 20 | (6.5–48) |
| | Chaparro et al[46] | 2021 | Spain | 5 | NR |
| | Alourifi et al[31] | 2022 | Saudi Arabia | 5 | (2–51) |
| | Robles[a] et al[101] | 2022 | Spain | 12.6 | (3.8–31) |
| | Robles[a] et al[101] | 2022 | Spain | 4.5 | (2.2–9.8) |
| | Median of medians (IQR) | | | 8 (5.0–15.2) | |
| | Median of medians (IQR) | | | 6.2 (5.0–12.3) | |
| | Median of medians (IQR) Low- and middle-income countries | | | 11.2 (8.3–18.0) | |
| | Pooled weighted median of medians (95% CI) High-income countries | | | 7.0 (3.0–26.4) | |
| | Pooled weighted median of medians (95% CI) High-income countries | | | 6.0 (3.0–26.4) | |
| | Pooled weighted median of medians (95% CI) Low- and middle-income countries | | | 18 (3.0–24.0) | |
| Patient interval[d] | Vavricka et al[107] | 2012 | Switzerland | 2 | (0–6) |
| | Maconi et al[81] | 2015 | Spain | 1 | (0.5–2) |
| | Nguyen et al[19] | 2017 | USA | 1 | (0.2–4.9) |
| | Schoepfer et al[18] | 2019 | Switzerland | 2 | (1–6) |
| | Qiao[b] et al[71] | 2019 | China | 1 | (0–154) |
| | Walker et al[17] | 2020 | UK | 3 | (0.9–6.7) |
| | Robles[a] et al[101] | 2022 | Spain | 0.6 | (0.2–8) |
| | Robles[a] et al[101] | 2022 | Spain | 0.9 | (0.2–1.6) |
| | Median of medians (IQR) | | | 1 (1.0–2.0) | |
| | Pooled weighted median of medians (95% CI) | | | 2.0 (0.9–3.0) | |

(Continues)

TABLE 1 (Continued)

| Diagnostic interval | Study | Year | Country | Time to diagnosis (months) | |
|---|---|---|---|---|---|
| | | | | Median | (IQR) |
| Healthcare interval[d] | Vavricka et al[107] | 2012 | Switzerland | 4 | (0–18) |
| | Maconi et al[81] | 2015 | Spain | 3 | (1.5–8) |
| | Benchimol et al[40 ¥] | 2016 | Canada | 0.6 | (0–8.6) |
| | Benchimol et al[40 Ω] | 2016 | Canada | 0.2 | (0–7.9) |
| | Nguyen et al[19] | 2017 | USA | 3.5 | (1.2–20.5) |
| | Schoepfer et al[18] | 2019 | Switzerland | 2 | (1–17) |
| | Qiao[b] et al[71] | 2019 | China | 4 | (0–227) |
| | Walker et al[17] | 2020 | UK | 0.3 | (0–1.2) |
| | Robles et[a]al[101] | 2022 | Spain | 5.9 | (2.3–15.6) |
| | Robles[a] et al[101] | 2022 | Spain | 3.3 | (0.9–8.7) |
| | Median of medians (IQR) | | | 3 (0.6–4.0) | |
| | Pooled weighted median of medians (95% CI) | | | 0.2 (0.2–4.0) | |

Abbreviations: NR, not reported; IQR, Interquartile range; ¥, represents non-immigrant population in study; Ω, represents immigrant population in study.

[a]Data from different population groups in study.

[b]Represents low- and middle-income countries.

[c]Finland, Italy, France, Canada, Germany, UK, Spain and Sweden.

[d]Data may not be available for complete study cohort.

CI: 0.90–1.68; $I^2$ =0%).[11,18,75,113] Pooled analysis of OR from five studies showed an association between delayed diagnosis and any CD-related surgery (OR = 1.90, 95% CI: 1.42–2.53) with very low heterogeneity between studies ($I^2$ =8%).[18,19,74,75,113]

One study reported a higher odds of emergency surgery among individuals who had a delayed diagnosis of CD, which showed a significant association (OR = 5.32; 95% CI: 2.04–13.91).[13] Pooled analysis showed no statistically significant association between delayed diagnosis and disease location at diagnosis[11,13,19,74,75,98] or CD-related medical treatment.[11,18,75] One study examined the association between delayed diagnosis and frequency of CD-related healthcare utilisation, with no statistically significant association found (Table S16).[74]

### 3.4 | Ulcerative colitis

Three studies examined the association between delayed diagnosis and subsequent clinical outcomes among 1306 patients diagnosed with UC.[16,74,107] Two studies reported the association between delayed diagnosis and the subsequent odds of colectomy.[16,74] Pooled analysis showed an association between delayed diagnosis and the higher odds of colectomy (OR = 4.13, 95% CI: 1.04–16.40) with no heterogeneity between studies ($I^2$ =0%) (Figure 4B).

Three studies evaluated the association between delayed diagnosis and disease extent at the time of UC diagnosis.[16,74,107] Two studies reported the association between delayed diagnosis and disease severity, healthcare utilisation, UC-related hospitalisation and frequency of hospital admissions.[16,74] Pooled analysis of ORs showed no significant association between delayed diagnosis of UC with disease extent,[16,74,107] disease severity [16,74] or healthcare utilisation (Table S16).[16,74] One study reported an association between delayed diagnosis and the odds of anti-TNF (anti-tumour necrosis factor) use (OR = 2.60, 95% CI: 1.01–6.71).[16] One study reported the association between delayed diagnosis and the subsequent clinical disease course of IBD in a combined analysis and was therefore not included in the meta-analyses of this study.[17] We were unable to examine the impact of publication bias due to the inadequate number of studies eligible for each analysis, although bias is probable given the small number of studies for some of our outcomes of interest.

## 4 | DISCUSSION

This is the first systematic review and meta-analysis to examine time to diagnosis and the impact of delayed diagnosis on clinical outcomes in IBD, comprising 101 studies representing over 100,000 patients. The time to IBD diagnosis from symptom onset may be prolonged, with a longer delay in CD than in UC and among patients living in low- and middle-income versus patients in high-income countries.

Among individuals who had a delayed diagnosis of CD, the odds of progressing to stricturing and penetrating disease at the time of diagnosis, or thereafter, were 88% and 64% higher respectively. Delayed diagnosis was also associated with a two- and fourfold

**TABLE 2** Studies reporting time to diagnosis intervals in ulcerative colitis

| Diagnostic interval | Study | Year | Country | Time to diagnosis (months) | |
|---|---|---|---|---|---|
| | | | | Median | (IQR) |
| Total time to diagnosis | Langholz et al[72] | 1991 | Denmark | 12 | NR |
| | Stewenius et al[105] | 1996 | Sweden | 2 | – |
| | Park et al[93] | 1996 | Korea | 1 | NR |
| | Timmer[b] et al[106] | 1999 | Germany | 2 | – |
| | Timmer[b] et al[106] | 1999 | Germany | 9 | – |
| | Yang et al[111] | 2000 | Korea | 6 | – |
| | Ling et al[79] | 2002 | Singapore | 1 | – |
| | Piront[b] et al[96] | 2002 | France | 5 | NR |
| | Piront[b] et al[96] | 2002 | France | 8.5 | NR |
| | Edouard[a] et al[51] | 2005 | West indies | 2 | – |
| | Vind et al[108] | 2006 | Denmark | 4.5 | – |
| | Burgmann et al[7] | 2006 | Canada | 114 | NR |
| | Abakar-Mahamat et al[27] | 2007 | France | 5 | – |
| | Tine[b] et al[65] | 2007 | Denmark | 12 | NR |
| | Tine[b] et al[65] | 2007 | Denmark | 4.8 | NR |
| | Tine[b] et al[65] | 2007 | Denmark | 4.8 | NR |
| | Romberg-Camps et al[12] | 2009 | Netherlands | 3 | (0–180) |
| | Moum et al[86] | 2009 | Norway | 4 | (2–8.5) |
| | Guariso et al[60] | 2010 | Italy | 2 | – |
| | Vavricka et al[107] | 2012 | Switzerland | 4 | (1–12) |
| | Pezerovic et al[94] | 2013 | Croatia | 3 | NR |
| | Burisch[b] et al[42] | 2014 | Eastern Europe | 2.2 | NR[a] |
| | Burisch[b] et al[42] | 2014 | Western Europe | 2 | NR[a] |
| | Basaranoglu[a] et al[37] | 2015 | Turkey | 2 | NR |
| | Zaharie et al[113] | 2016 | Romania | 1 | (NR[a]–3) |
| | Cantoro et al[44] | 2017 | Italy | 2 | (0–7) |
| | Nguyen et al[19] | 2017 | USA | 3.1 | (1.1–9.6) |
| | Lee et al[74] | 2017 | South Korea | 2.4 | (NR–6.2) |
| | Szanto et al[104] | 2018 | Hungary | 4.6 | (0–10.3) |
| | Irving et al[63] | 2018 | Multiple[c] | 12 | NR |
| | Novacek et al[33] | 2019 | Austria | 3 | (1–10) |
| | Kang et al[16] | 2019 | South Korea | 2.3 | (NR[a]–6.5) |
| | Ghosh[a] et al[56] | 2019 | Bangladesh | 21 | (1–300) |
| | Banerjee[a,b] et al[35] | 2020 | India | 24 | (7–48) |
| | Banerjee[a,b] et al[35] | 2020 | India | 96 | (1–456) |
| | Walker et al[17] | 2020 | Walker | 3.3 | (1.9–7.3) |
| | Gomes[a] et al[59] | 2021 | Brazil | 11 | (4–29) |
| | Chaparro et al[46] | 2021 | Spain | 2 | NR |
| | Robles[b] et al[101] | 2022 | Spain | 6.1 | (3–11.2) |
| | Robles[b] et al[101] | 2022 | Spain | 2.7 | (1.5–5.6) |
| | Median of median (IQR) | | | 3.7 (2–6.7) | |
| | Median of medians (IQR) High-income countries | | | 3.2 (2.2–5.3) | |

(Continues)

TABLE 2 (Continued)

| Diagnostic interval | Study | Year | Country | Time to diagnosis (months) | |
|---|---|---|---|---|---|
| | | | | Median | (IQR) |
| Patient interval[d] | Median (IQR) of medians Low- and middle-income countries | | | 7.8 (2–21.8) | |
| | Pooled weighted median of medians (95% CI) | | | 4.6 (1.0–96.0) | |
| | Pooled weighted median of medians (95% CI) High-income countries | | | 4.0 (2.0–12.0) | |
| | Pooled weighted median of medians (95% CI) Low- and middle-income countries | | | 24 (1.0–96.0) | |
| Patient interval[d] | Vavricka et al[107] | 2012 | Switzerland | 1 | (0–4) |
| | Nguyen et al[19] | 2017 | USA | 0.7 | (0.3–3) |
| | Kang et al[16] | 2019 | South Korea | 1.3 | – |
| | Walker et al[17] | 2020 | UK | 2.1 | (0.9–3.9) |
| | Robles[b] et al[101] | 2022 | Spain | 1.0 | (0.43–3) |
| | Robles[b] et al[101] | 2022 | Spain | 0.6 | (0.3–2.1) |
| | Median of medians (IQR) | | | 1.0 (0.8–1.2) | |
| | Pooled weighted median of medians (95% CI) | | | 1.0 (0.6–2.1) | |
| Healthcare interval[d] | Vavricka et al[107] | 2012 | Switzerland | 1 | (0–5) |
| | Benchimol et al[39] ¥ | 2016 | Canada | 0 | (0–1.6) |
| | Benchimol et al[39] Ω | 2016 | Canada | 0 | (0–0.0) |
| | Nguyen et al[19] | 2017 | USA | 1.1 | (0.4–5.4) |
| | Kang et al[16] | 2019 | South Korea | 0.3 | – |
| | Walker et al[17] | 2020 | UK | 0.2 | (0–0.8) |
| | Robles[b] et al[101] | 2022 | Spain | 3.4 | (1.2–6.9) |
| | Robles[b] et al[101] | 2022 | Spain | 1.9 | (0.8–4.1) |
| | Median of medians (IQR) | | | 0.7 (1.2–1.3) | |
| | Pooled weighted median of medians (95% CI) | | | 0.0 (0.0–1.0) | |

Abbreviations: NR, not reported; IQR, Interquartile range; ¥, represents non-immigrant population in study; Ω, represents immigrant population in study.

[a]Represents low- and middle-income countries.

[b]Data from different population groups in study.

[c]Finland, Italy, France, Canada, Germany, UK, Spain and Sweden.

[d]Data may not be available for complete study cohort.

higher odds of intestinal surgery for CD and UC, respectively, at or following diagnosis. These findings support the hypothesis that delayed diagnosis is associated with adverse clinical outcomes in adult patients with IBD.

We found time to diagnosis was longer among patients diagnosed with CD compared with UC, consistent with much of the literature.[19,42,107] This is likely explained, at least in part, by the fact that individuals with UC often present with rectal bleeding, a symptom concerning to both patients and healthcare professionals, which may trigger an expedited review and investigations.[5] Conversely, depending on disease location, CD is more frequently associated with symptoms of bowel frequency, abdominal bloating and pain.[107] These symptoms may be confused with irritable bowel syndrome, potentially leading to delays in referral and investigation.[5,8]

We found the time to diagnosis was longer among studies from low- and middle-income countries when compared with those from high-income countries alone, which may relate to differences in healthcare provision. In addition, difficulty in differentiating between IBD and more prevalent infectious diseases has been highlighted by clinicians from low- and middle-income countries. A commonly reported challenge is distinguishing between CD and intestinal tuberculosis due to the higher prevalence, overlap of symptoms and similar endoscopic features.[116] There have also been

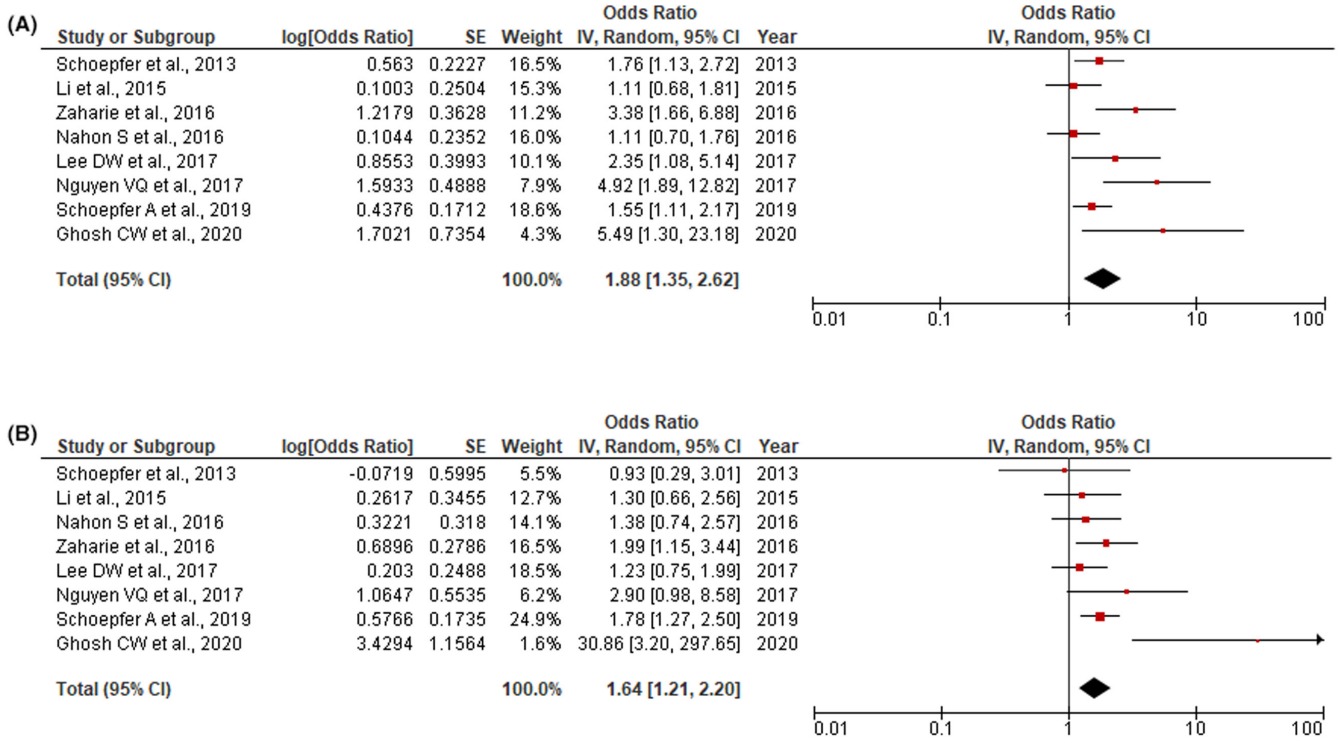


FIGURE 3 (A) Forest plot for the odds of developing stricturing disease phenotype among patients with a delayed diagnosis of Crohn's disease. (B) Forest plot for the odds of developing penetrating disease phenotype among patients with a delayed diagnosis of Crohn's disease. OR, odds ratio.

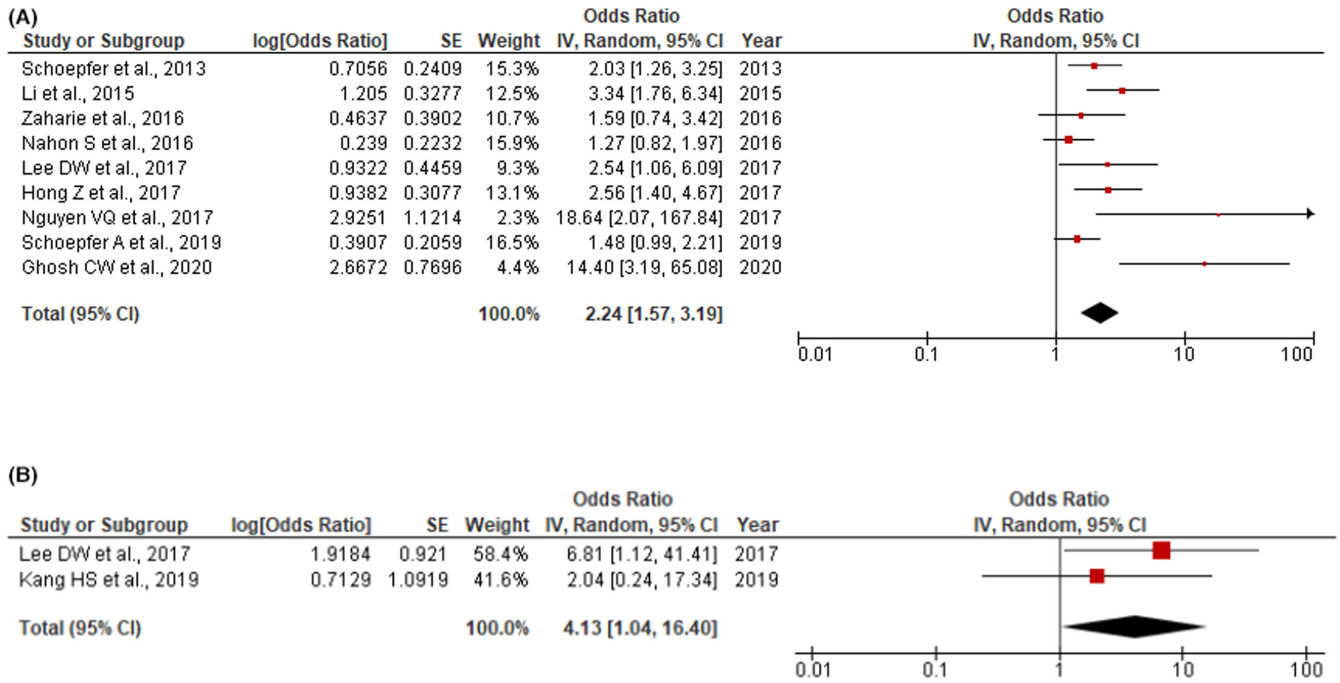


FIGURE 4 (A) Forest plot for the odds of intestinal surgery among patients with a delayed diagnosis of Crohn's disease. (B) Forest plot for the odds of colectomy among patients with a delayed diagnosis of ulcerative colitis. OR, odds ratio.

reports in difficulties differentiating between UC and intestinal tuberculosis. Enteric pathogens, such as *Shigella* species, *Salmonella* species and *Entamoeba histolytica*, more commonly cause bloody diarrhoea in low- and middle-income countries, increasing the likelihood of IBD misdiagnosis, thus contributing to diagnostic delays.[117] A further reported barrier to accurate diagnosis of IBD in

low- and middle-income countries is the perceived rarity of IBD and consequent lack of clinical awareness leading to a lower index of suspicion.[116]

We found that few studies reported the relative contribution of patient- and healthcare-related interval to the overall time to diagnosis. The findings from these studies are inconsistent and presumably this relates to the difficulty in estimating the relative contribution of these intervals retrospectively. Our findings indicate the median of the healthcare-related interval was longer than the patient-related interval in CD. Whereas, the median of the patient-related interval was found to be longer among patients diagnosed with UC.

While there are no comparable published reviews of the adult IBD population, previous systematic reviews of delayed diagnosis in the paediatric population report an increased risk of complications, specifically; growth failure and delayed puberty, more extensive disease, a poorer response to medical treatment an increased need of surgery and decreased health-related quality of life.[118,119] However, unlike our findings, they do not report an increase in the risk of colectomy in patients with UC.[118,119]

Similar to reviews from the paediatric population, factors reported to be associated with diagnostic delay among the adult population varied and, in some cases, conflicted between studies. This is likely due to different study populations examined, differences in disease behaviour, the healthcare setting and country in which the study was conducted.[11,75,107,113] Adding to the risk of diagnostic delay has been the impact of the recent COVID-19 pandemic.[120] No studies reported time to diagnosis during the pandemic; it seems likely that it may have significantly increased IBD diagnostic delay, and needs further evaluation.

In our analysis, we evaluated studies that used the most common definition of delayed diagnosis (individuals above the 75th centile of longest delay within each study cohort), but there remains a lack of consensus about the most appropriate definition.[33,42,74] Other studies, despite using different definitions of delay, also report an association between delay and subsequent adverse clinical outcomes in IBD.[14,42] One previous study, which was not eligible for inclusion in our meta-analysis, since it did not differentiate IBD type, did not report an association between delayed diagnosis and adverse clinical outcomes whereas emergency consultation prior to diagnosis was associated.[17] It is possible individuals with a more aggressive or fulminant disease phenotype,[121] may present with more frequent or emergency clinical attendances in the lead up to diagnosis, whereas those with a more indolent phenotype may have milder symptoms that are tolerated for a longer period before presentation.

We used an exhaustive search strategy and rigorous inclusion criteria to ensure that we were able to accurately assess time to diagnosis, and the association between delayed diagnosis and clinical outcomes in IBD. Our analyses examining the impact of diagnostic delay incorporated data from a number of relatively small and conflicting studies,[11,13,17] allowing us to pool data for less common events, such as surgery, which were examined in previous studies but likely underpowered for these end points. We used a random effects model to pool data in all our analyses in order not to overestimate the impact of delayed diagnosis.

The meta-analysis of the impact of delayed diagnosis on clinical outcomes was comprised of relatively few studies, although quality of included studies was good, thus findings need to be interpreted with some caution. This particularly relates to surgery in UC since only two studies met the inclusion criteria, the observed association between delayed diagnosis and colectomy must therefore be considered uncertain and further research in this regard is required.[16,74] There were few studies that reported the impact of delayed diagnosis on the endoscopic and histological severity of disease, and none examined the risk of dysplasia or colorectal malignancy, and more research in this regard is required.[16,107,113] Among studies included in the meta-analyses, longitudinal follow-up time was not reported in the majority of studies, making it difficult to ascertain the time scales within which the clinical outcomes were measured. Only two studies reported that adverse clinical outcomes were recorded as those that had occurred at the time of diagnosis. Studies with a longer follow-up duration are more likely to have captured the clinical outcomes reported compared with those that had a shorter duration of follow-up or reported outcomes at diagnosis.

The majority of studies relied upon retrospective estimates of symptom onset before IBD diagnosis, some of which collated data using patient questionnaires. Therefore, both patient-related and total time to diagnosis-reported intervals are subject to recall bias which may likely have resulted in inaccurate estimates of delay. Thus, recall bias may distort the measure of association between the exposure and clinical disease outcomes, which is difficult to predict.[122]

Furthermore, the majority of studies included in the meta-analysis collated data from secondary or tertiary healthcare settings. Bias may occur as a result of systematic selection of patients from referral centres for inclusion in studies, since such patients are likely to have a more severe disease phenotype compared to those followed largely in primary care or other community settings.

We did not identify any clear trend in the median of median times to diagnosis according to era of publication. It might have been anticipated that there would be an improving trend of a shorter time to diagnosis in more recent times. However, multiple factors including study duration, country of study, differing healthcare settings, data source and populations examined may have potentially masked such an association making it difficult to identify any clear-cut temporal trend.

Since delay was defined as individuals above the 75th centile with the longest time to diagnosis in each study cohort, the absolute time duration of delay beyond which adverse clinical outcomes are more likely to occur is hard to estimate. There were moderate levels of global statistical heterogeneity in some of our analyses. Variation in diagnostic pathways and available facilities may have contributed.[123] We were however unable to determine the impact of publication bias in our analyses due to the relatively small number of eligible studies. Lack of resource meant studies that were not published in English could not be included in our review, meaning certain populations, in particular low- and middle-income countries, may be

under-represented.[124] Set against this, our systematic review included studies conducted in 42 different countries, across six continents, in a variety of healthcare and economic settings, including 24 studies from low- and middle-income countries. We also performed a sub-group analysis for countries income status according to World Bank criteria and found the observed association between delayed diagnosis and higher odds of surgical intervention in CD persisted. Likewise, real-world data regarding time from specialist referral to diagnosis and time from diagnosis to treatment is lacking and warrants further evaluation.

Our findings suggest that earlier IBD diagnosis is associated with better clinical outcomes, which has important implications for future policy and diagnostic strategies. Emphasis needs to be placed on developing and implementing approaches to mitigate diagnostic delay. Symptoms at first presentation of IBD are non-specific and may be difficult to interpret. A number of studies report a lack of knowledge about IBD, among both members of the general public and patients themselves.[125–127] This may impact outcomes for patients, where late medical consultation could be a consequence. Mass media and education campaigns may enhance public awareness of IBD, as it has done so for other chronic diseases, to help facilitate earlier diagnosis.[128,129]

Studies report that more than a third of primary care physicians lacked confidence identifying the key symptoms of IBD.[130,131] Timely diagnosis can be challenging since symptoms overlap with more prevalent diagnoses such as IBS and haemorrhoids, and access to specialist resources may be limited.[8,132] The development and implementation of tools to help clinicians identify patients at high risk of IBD is one approach to enable timely diagnosis.[133] A validation study found an index, based on a questionnaire developed by the International Organization for IBD on symptoms and signs alone, had only a 50% and 58% sensitivity and specificity respectively. However, when used in conjunction with faecal calprotectin, a validated non-invasive biomarker of intestinal inflammation, the sensitivity and specificity rose substantially.[134] Despite the introduction of faecal calprotectin to facilitate fast track investigation and diagnosis of IBD, national and international uptake remains relatively limited and inconsistent.[135] The introduction of diagnostic pathways using faecal calprotectin in primary care is of proven value in supporting primary care physicians in their risk assessments, leading to improvements in the time to diagnosis, as well as achieving resource and cost savings.[136] Timely assessment and diagnosis may also be facilitated with the introduction of more convenient home and point-of-care faecal calprotectin testing.[137,138]

There is also a growing incentive to develop and implement accurate multidimensional predictive tools that may be applied to target populations in order to effectively identify those at risk of developing IBD; allowing risk stratification of individuals who may require closer surveillance, predict treatment response and apply future prevention strategies.[6,139,140]

Timely specialist review is clearly a priority, with one previous report indicating less than half of patients receive specialist review within 18 months of presenting with chronic gastrointestinal symptoms.[5] The recent introduction of a novel direct-access endoscopy pathway reported a 86% reduction in referral to treatment time while also being associated with an increased diagnostic yield, when compared to individuals who were first triaged to an outpatient clinic.[141]

In the United Kingdom, even following diagnosis, one-fifth of patients wait longer than 4 weeks to commence treatment, falling short of proposed national standards.[141,142] Previous studies have shown that timely initiation of immunomodulators and biologics to treat CD may reduce the risk of disease progression and the need for surgery.[9,143] Although the evidence for the impact of early treatment escalation in UC is not yet fully evaluated.[144] Irrespective of this, timely diagnosis and treatment of UC and CD are associated with improved quality of life,[145] and a reduced healthcare burden in the years before diagnosis.[146] Our findings demonstrate earlier diagnosis is linked to reduced disease progression and improvements in the natural course of IBD. Earlier diagnosis may allow a window of opportunity to initiate disease modifying therapy before irreversible bowel damage has occurred. Beyond delay in diagnosis, consultation frequency and emergency attendances prior to diagnosis may also be proxies of disease severity, as is the case in other conditions, and requires evaluation with respect to IBD.[147,148] Further research is needed to confirm our findings, identify underpinning reasons for delayed diagnosis and those at highest risk.

Time to IBD diagnosis may be prolonged, with a quarter of individuals waiting longer than 7 and 15 months for a diagnosis of UC and CD, respectively, taking longest in low- and middle-income countries. Delayed diagnosis is associated with adverse clinical outcomes, most notably an increased risk of intestinal surgery. Our findings highlight the need for targeted diagnostic strategies to achieve earlier diagnosis.

## AUTHORSHIP

The POP-IBD study group is a collaboration between St George's University of London, Imperial College London, University College London and King's College London, conducting population-based studies in the field of inflammatory bowel disease. NJ, SB, JB, SS and RP conceived and designed this study. NJ, SB and JB prepared the data and carried out statistical analysis overseen by IP and AB. All authors contributed to the development of the analysis, interpreting data and preparing the manuscript. RP will act as the guarantor for the article.

## AUTHOR CONTRIBUTIONS

**Nishani Jayasooriya:** Conceptualization (lead); data curation (equal); formal analysis (lead); methodology (lead); writing – original draft (lead). **Samantha Baillie:** Conceptualization (lead); data curation (lead); formal analysis (supporting); methodology (equal); writing – review and editing (supporting). **Jonathan Blackwell:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); writing – review and editing (supporting). **Alex**

**Bottle:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting). **Hanna Creese:** Conceptualization (supporting). **Irene Petersen:** Formal analysis (supporting); methodology (supporting). **Sonia Saxena:** Conceptualization (supporting); formal analysis (supporting); methodology (supporting); supervision (lead); writing – review and editing (lead). **Richard Pollok:** Conceptualization (equal); formal analysis (supporting); methodology (equal); supervision (lead); writing – review and editing (lead).

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## CONFLICT OF INTEREST

None declared.

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## SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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