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Factors associated with delayed diagnosis of Crohn's disease: A systematic review and meta-analysis

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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. Further, we excluded review articles, case reports, or commentaries without original data. We pooled effect siee distinct samples. The assessment of study quality was performed utilizing the Newcastle-Ottawa Scale, while the presence of between-study heterogeneity was investigated. For a visual appraisal of potential publication bias, a funnel plot was employed. 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 9669 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. However, no significant associations were observed between diagnostic delay and sex, age, endoscopic ileocolonoscopy, or diarrhea. Funnel plot analysis, indicating potential risks of publication bias, suggested the existence of unpublished or unreported study findings.
Conclusion: The findings suggest that ileal CD, use of NSAIDs, and smoking are risk factors for the delayed diagnosis of CD. Enhancing education of patients and primary care providers about these factors is warranted.

1. 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 America [5,6]. In several newly industrialized countries in Asia

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and South America, the incidence and frequency have risen dramatically in recent decades [7–9]. 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 [10]. 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 [11]. There is growing evidence that delays in CD diagnosis reduce quality of life and increase the probability of complications and a need for surgery [12,13].

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.

2. Methods

2.1. Search strategy

This study selection was processed using the PRISMA 2020 flowchart [14]. A systematic search was conducted across Pubmed, EMBASE, and Web of Science databases to identify relevant studies published prior to May 2022, focusing on factors linked to delays in the diagnosis of CD. MeSH headings employed included "Crohn Disease" and "Delayed Diagnosis". In instances where study eligibility was uncertain, a comprehensive review of the full text was performed. The detailed PubMed search strategy is presented in S1 Table. Prior to the literature search, we registered our study protocol with the National Institute for Health Research International prospective register of systematic reviews (PROSPERO, #CRD42022322251).

2.2. 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.

2.3. Study description

Study relied on the Montreal Classification for disease localization, behavior, and age grouping [15,16]. 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 [17]. 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.

2.4. 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 [18].

2.5. 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.

2.6. 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). Moreover, Egger tests representing funnel plots

were used to assess the publication bias.

3. Results

3.1. 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.

3.2. Characteristics and quality scores of the included studies

The 18 papers included in this study were published between 2012 and 2021, originating from 13 different countries. The total study sample included 9669 cases. Among the 18 papers, 12 presented cohort studies, 5 presented retrospective studies, and 1 presented a cross-sectional study. In terms of quality assessment, 11 studies achieved a score of 5, two scored 6, four attained a score of 7, and one reached a score of 8. The primary rationale underlying lower scores was attributed to the inability to meet the mandated follow-up rate and duration (Table 1).

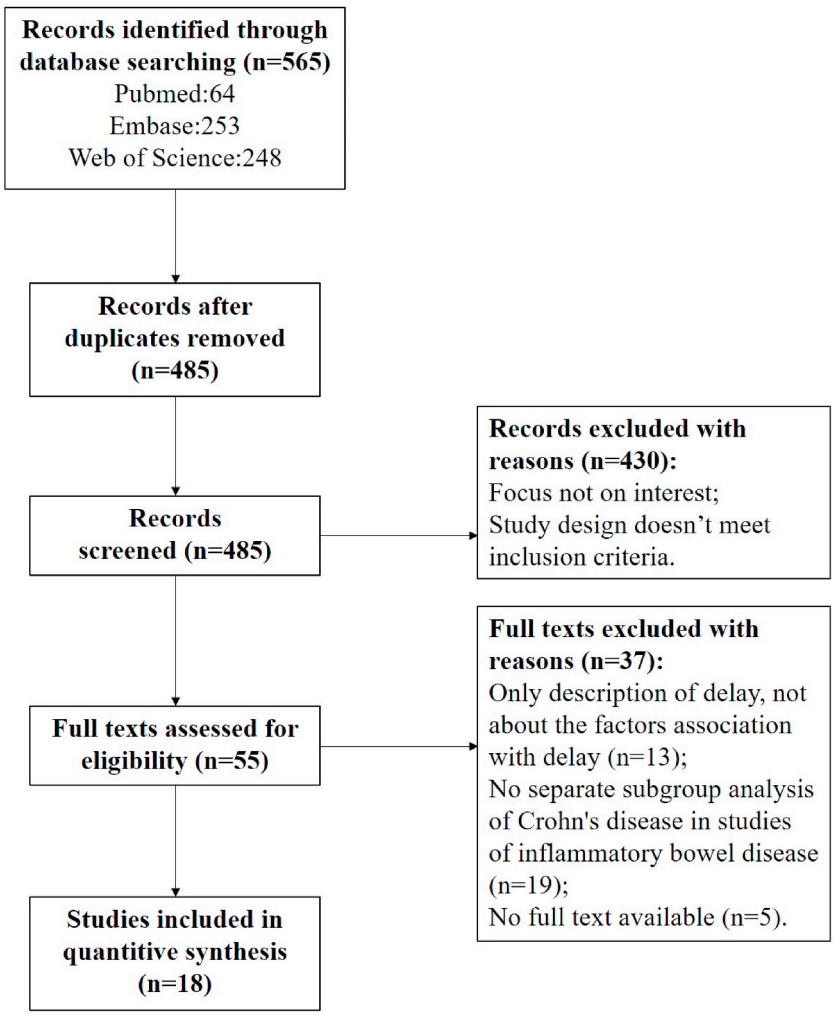

Fig. 1. Flow Chart of literature search.

Table 1
Characteristics of the 18 included studies.

Studies	Location	Study design	Sample	NOS score	Risk factors
Banerjee, R2018 [19]	India	Retrospective study	N = 334, 41.6 % were male, median age was 32 years	6	Male, age (younger), ileum, NSAIDS intake, smoking
Li, Y 2015 [20]	China	Retrospective study	N = 343, 70 % were male, the average age at diagnosis was 31.8 years	6	Male, age (younger), ileum, family history of IBD, EIMS, smoking, NSAIDS intake
Nahon, S 2013 [21]	France	Cross sectional study	N = 314, 40.8 % were male, age at enrolment was 41 years	5	Family history of IBD, EIMS
Maconi, G 2015 [22][j]	Italy	Cohort study	N = 83, 49.4 % were male, median age was 31 years	5	Male, ileum
Nahon, S 2016 [23]	France	Cohort study	N = 497, 46.4 % were male, median age at diagnosis was 25.6 years	5	Male, age (younger), ileum, smoking
El Mouzan, M. I 2019 [24][j]	Saudi Arabia	Retrospective study	N = 240, 60 % were male, median delays in diagnosis were 8 years	5	Male, family history of IBD, ileum
Hong, Z 2017 [25]	China	Retrospective study	N = 342, 71.2%were male, average age at diagnosis was 32.7 years	5	Male, age (younger), ileum, smoking
Lee, Dong-won 2017 [26]	Korea	Retrospective study	N = 165, 76.4 % were male, mean age at diagnosis was 28.2 years	5	Male, age (younger), ileum, family history of IBD, diarrhea
Chang, Mo-Moon 2015 [27]	Korea	Cohort study	N = 1047, 72.3 % were male, mean age at first diagnosis was 27.7 years	7	Male, age (younger), family history of IBD
Nahon, S 2014 [28]	France	Cohort study	N = 364, 40.8 % were male, median age was 29.2 years	7	Male, age (younger), ileum, family history of IBD, EIMS, smoking, diarrhea
Ricciuto, A 2020 [29]	Canada	Cohort study	N = 898, 60 % were male, age at diagnosis was 12.9 years	5	Male, ileum, family history of IBD, EIMS, smoking, diarrhea
Takeyama, E 2021 [30]	Japan	Cohort study	N = 528, 76.9 % were male, mean age at diagnosis was 31.5 years	7	Male, diarrhea
Vavricka, Stephan. R 2012 [31]	Switzerland	Cohort study	N = 932, 47 % were male, median age was 41 years	5	Male, age (younger), family history of IBD, EIMS, smoking, NSAIDS intake
Yamamoto-Furusho, J. K 2021 [32]	Mexico	Cohort study	N = 843, 52.7 % were male	5	Male, ileum, family history of IBD, EIMS, smoking, diarrhea
Zaharie, R 2016 [33]	Romania	Cohort study	N = 478, 47.9 % were male, median age at diagnosis was 33 years	5	Male, age (younger), family history of IBD, EIMS, smoking
Nguyen, V. Q. 2017 [34]	American	Cohort study	N = 110, 41 % were male, average age at diagnosis was 38 years	8	Male, age (younger), ileum, family history of IBD, EIMS, smoking, NSAIDS intake
Cantoro, L 2017 [35]	Italy	Cohort study	N = 1246, 49.8 % were male, age at diagnosis was 40 years	7	Male, age (younger)
Schoepfer, A. M 2013 [36]	Switzerland	Cohort study	N = 905, 46.6 % were male, median age at diagnosis 26 years	5	Male, age (younger), ileum, smoking, NSAIDS intake

3.3. 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), smoking at the time of diagnosis (OR = 1.19, 95 % CI = 1.02–1.38), and NSAID use (OR = 1.34, 95 % CI = 1.04–1.72) were risk factors for delayed CD diagnosis. Male (OR = 0.93, 95 % CI = 0.84–1.02), age at diagnosis <40 years (OR = 0.80, 95 % CI = 0.59–1.06), family history of IBD (OR = 0.90, 95 % CI = 0.62–1.30), diarrhea (OR = 1.07, 95 % CI = 0.71–1.62), and EIMS at presentation (OR = 1.24, 95 % CI = 0.95–1.61) had no significant effect on time to CD diagnosis (Fig. 2). Other factors could not be evaluated because the data were lacking in some or all studies (Table 2).

3.4. 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, and Egger's test was not statistically significant for all subgroups ($p \leq 0.01$). These indicated that there was no publication bias in the manuscripts used in this study (S1–S5 Figures).

4. 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 [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 [20]. Additionally, smoking increases the likelihood of a delayed diagnosis. As noted by Laaksonen et al. [37], smoking tend to be more prevalent among

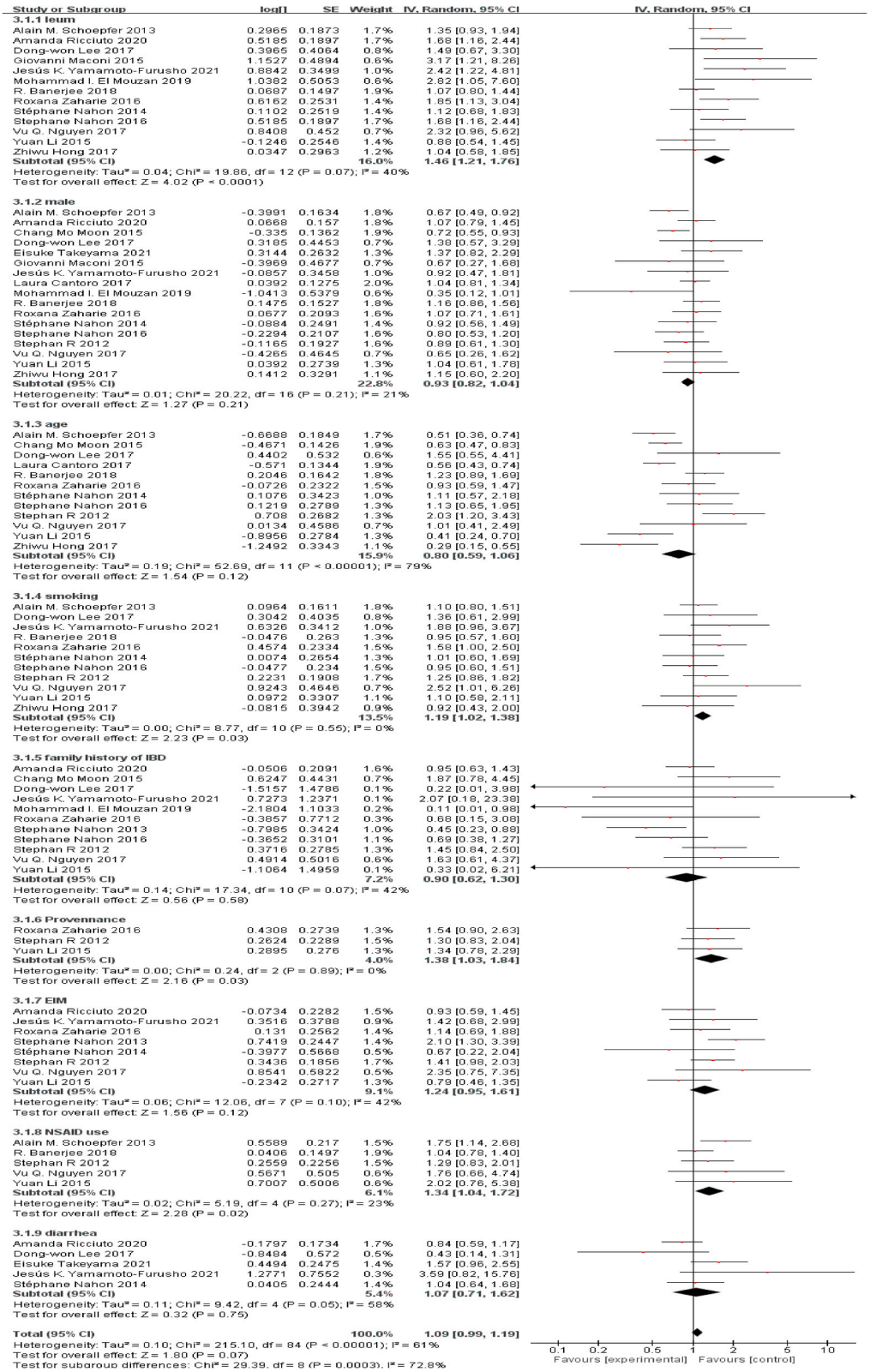

Fig. 2. Meta-analysis forest plot for each subgroup.

Table 2
Results of the meta-analyses and the test for heterogeneity.

Variable	K	OR (95%CI)	Heterogeneity between studies		Test for overall effect (P)
			P-value	I^2	
Male	17	0.93 (0.84–1.02)	0.21	21 %	0.13
Age (younger)	12	0.80 (0.59–1.06)	<0.00001	79 %	0.12
Smoking	11	1.19 (1.02–1.38)	0.55	0 %	0.03
Ileum	13	1.46 (1.21–1.76)	0.07	40 %	<0.0001
Family history of IBD	11	0.90 (0.62–1.30)	0.07	42 %	0.58
EIMS	8	1.24 (0.95–1.61)	0.10	42 %	0.12
NSAID intake	5	1.34 (1.04–1.72)	0.27	23 %	0.01
Diarrhea	5	1.07 (0.71–1.62)	0.05	58 %	0.75

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 similarties between NSAID side effects and CD symptoms. This could reduce patient awareness of the disease and increase the risk of a misdiagnosis. Howerer, 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 [38,39]. In addition, genetic risk varies by subtype, and these factors may reduce patient vigilance to some extent [40]. 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 [41]. 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 [42]. Furthermore, a recent study found that fecal calprotectin appeared to be clinically useful in ruling out CD [43]. The amalgamation of fecal calprotectin with a clinical suspicion index can prove exceptionally efficacious in pinpointing individuals warranting expeditious referral to a specialist for a CD diagnosis. This approach streamlines the diagnostic procedure, guaranteeing swift and precise assessments for patients. It may be considered for practical application.

This study has several limitations that need further discussion. Firstly, despite our extensive search across multiple databases, there may still be studies that were not included in the analysis, resulting in missing data on certain potential factors. Secondly, the studies included in this research were predominantly retrospective cohort studies, which are susceptible to recall bias. This bias may have an impact on specific impact factors and introduce heterogeneity in the results. Additionally, some of the included studies in this research had small sample sizes, which may limit the statistical power and generalizability of the results. Moreover, certain risk factors were only measured by a few studies, and there was inconsistency in the definition of risk factors across the studies, which may contribute to inconsistencies and uncertainties in the results.

5. Conclusion

This meta-analysis demonstrated that ileal CD, alongside the utilization of NSAIDs and smoking at the time of diagnosis, emerged as risk factors associated with delays in Crohn's Disease (CD) diagnosis. Therefore, there is a clear imperative to enhance the education of both patients and primary care providers regarding these identified risk factors.

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Data availability

No. Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

Jinping Xie: Conceptualization, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing, Formal analysis. **Miaofeng Chen:** Data curation, Formal analysis, Validation, Visualization, Writing – original draft, Writing – review &

editing, Investigation. **Wenrui Wang:** Data curation, Investigation. **Rong Shao:** Methodology, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e20863.

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