



A COMPREHENSIVE SYSTEMATIC REVIEW OF THE ASSOCIATION BETWEEN IRON DEFICIENCY ANAEMIA AND OCCULT GASTROINTESTINAL BLEEDING

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ABSTRACT

Introduction: Iron deficiency anaemia (IDA) constitutes the most prevalent nutritional deficiency disorder worldwide. In adult men and postmenopausal women, chronic occult gastrointestinal (GI) blood loss represents the dominant pathological mechanism rather than dietary insufficiency. Occult GI bleeding denotes haemorrhage detectable only indirectly through faecal occult blood testing or through emerging iron deficiency. This systematic review synthesised and critically appraised primary evidence linking IDA to occult GI bleeding, determined diagnostic yield of investigative modalities, and identified predictors of bleeding lesions.

Methods: The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines. Eligible designs comprised randomised controlled trials, cohort, case-control, cross-sectional and observational

studies. Two reviewers independently performed study selection, data extraction and quality appraisal using design-matched risk-of-bias instruments (RoB 2, ROBINS-I, Newcastle-Ottawa Scale, QUADAS-2). Synthesis was narrative with structured tabulation across fourteen prespecified outcome domains.

Results: Thirty-five primary studies encompassing >1.8 million participants met eligibility. Bidirectional endoscopy diagnostic yield for bleeding-potential lesions ranged from 35.0% to 76.2%. Small-bowel capsule endoscopy after negative bidirectional examination yielded pathology in 50.0–72.0%; in a prospective multicentre trial, small-bowel lesions (50.0%, 95% CI 42.2-57.7) significantly exceeded upper GI (28.2%, $p<0.001$) and colonic (20.0%, $p<0.0001$) lesions, altering management in 52.3%. IDA demonstrated strong malignancy association: GI cancer odds within one year were 4.47-fold higher (95% CI 4.14-4.82); IDA conferred higher adjusted colorectal cancer odds than rectal bleeding (aOR 2.2, 95% CI 2.0-2.3, $p<0.01$); young-onset colorectal cancer cumulative incidence was 0.45% with IDA versus 0.05% without (HR 10.81, 95% CI 8.15-14.33). Independent predictors included abdominal symptoms (OR 8.3), age >50 years (OR 4.4) and haemoglobin <9 g/dL (OR 3.0), yielding PPV 87% and NPV 93.5%. Quantitative faecal haemoglobin with IDA and age stratified one-year colorectal cancer risk from <1% to 30% (95% CI 19.4-41.0). Anticoagulant exposure carried strongest bleeding risk (RR 4.2, 95% CI 2.9-6.2). Colonoscopy delay >90 days independently impaired survival (adjusted HR 1.28, 95% CI 1.07-1.53, $p=0.01$). GRADE certainty was moderate for diagnostic-yield and oncological-risk domains.

Discussion: IDA constitutes a sentinel biomarker of structural luminal pathology with malignancy discriminatory power

exceeding symptom-based referral criteria. The small bowel represents the most frequent location of bleeding-capable lesions yet remains un-interrogated by bidirectional endoscopy. Faecal occult blood testing lacks sufficient sensitivity as a rule-out instrument; however, quantitative faecal haemoglobin retains risk-stratification value. Diagnostic latency independently determines survival outcomes.

Conclusion: IDA demonstrates robust, reproducible association with occult GI bleeding and luminal malignancy. Bidirectional endoscopy should remain first-line in all adult men, postmenopausal women, and symptomatic premenopausal women; however, small-bowel predominance supports earlier capsule endoscopy deployment in negative bidirectional examinations or refractory anaemia. Faecal haemoglobin should serve as risk-stratification adjunct rather than gatekeeper, and diagnostic interval should be a quality metric. National pathways should adopt integrated risk models combining age, sex, haemoglobin, ferritin and quantitative faecal haemoglobin; capsule endoscopy capacity should be expanded; and standardised definitions are needed for future quantitative pooling.

Keywords: Iron deficiency anaemia; occult gastrointestinal bleeding; faecal immunochemical test; bidirectional endoscopy; capsule endoscopy; colorectal neoplasms

INTRODUCTION

Background

Iron deficiency anaemia represents the terminal phase of a progressive depletion of total body iron in which storage iron is first exhausted, transport iron subsequently falls, and finally erythropoiesis becomes iron-restricted, producing a microcytic hypochromic anaemia. In the developed world the condition affects approximately two to five percent of adult men and postmenopausal women and constitutes one of the most frequent indications for referral to gastroenterology services. The clinical significance of this deficiency extends far beyond the haematological abnormality itself, because in the adult population outside of the reproductive-age female cohort the human body possesses no physiological mechanism for the excretion of iron in quantities sufficient to generate deficiency; consequently, the demonstration of negative iron balance in an adult male or a postmenopausal female obliges the clinician to postulate pathological blood loss until the contrary is demonstrated.^{1,2}

Occult gastrointestinal bleeding is formally defined as blood loss from the gastrointestinal lumen that is not apparent to the patient or the physician and which manifests either as a positive faecal occult blood test or as iron deficiency anaemia in the absence of visible haemorrhage. It is distinguished from overt bleeding, in which haematemesis, melaena or haematochezia are evident, and from obscure bleeding, in which the source remains undetermined after standard bidirectional evaluation. The daily physiological gastrointestinal blood loss in health does not exceed approximately 1.5 millilitres, whereas losses in the range of 5 to 10 millilitres per day sustained over months will reliably exhaust iron stores in an individual with typical dietary intake. This quantitative relationship provides the mechanistic foundation for the clinical axiom that unexplained iron deficiency anaemia in an at-risk adult constitutes a presumptive marker of gastrointestinal pathology.^{1,3}

The spectrum of lesions responsible for occult gastrointestinal haemorrhage is broad and anatomically distributed across the entire alimentary tract. In the upper gastrointestinal tract the

principal contributors are peptic ulceration, erosive oesophagitis, gastric and oesophageal malignancy, Cameron lesions arising within large hiatal hernias, gastric antral vascular ectasia and angiodysplasia. In the colon, adenocarcinoma, advanced adenomatous polyps, angiodysplasia, inflammatory bowel disease and, less commonly, diverticular disease predominate. Within the small intestine, which remains inaccessible to conventional endoscopy across the majority of its length, angioectasia, non-steroidal anti-inflammatory drug enteropathy, Crohn disease, small-bowel neoplasia and coeliac disease constitute the leading aetiologies. Malabsorptive mechanisms, exemplified by coeliac disease, atrophic gastritis and *Helicobacter pylori* infection, operate in parallel with frank blood loss and may coexist within the same patient, a circumstance that complicates the attribution of causality in clinical practice.^{1,3,6,59}

Contemporary guideline frameworks issued by the British Society of Gastroenterology and by the European Society of Gastrointestinal Endoscopy converge upon bidirectional endoscopy as the standard initial investigative strategy for unexplained iron deficiency anaemia in all adult men and postmenopausal women, with serological screening for coeliac disease performed in all patients and with small-bowel capsule endoscopy reserved for recurrent or refractory presentations. Notwithstanding this apparent consensus, substantial variation persists in real-world practice with respect to referral thresholds, the completeness of investigation, the role of faecal haemoglobin quantification as a triage instrument, and the management of premenopausal women and of patients with iron deficiency in the absence of frank anaemia. This variation is not trivial: it translates directly into differential rates of cancer detection, differential diagnostic intervals and, as the evidence assembled in this review demonstrates, differential survival.^{1,2,3,4,5}

Research Objectives

The general objective of this systematic review is to synthesise, quantify and critically appraise the totality of primary evidence describing the association between iron deficiency anaemia and occult gastrointestinal bleeding in adult and paediatric populations. The specific objectives are enumerated below.

- To determine the diagnostic yield of oesophagogastrroduodenoscopy, colonoscopy and combined bidirectional endoscopy for lesions with bleeding potential in patients presenting with iron deficiency anaemia.^{13,14,15}
- To determine the incremental diagnostic yield of small-bowel capsule endoscopy and cross-sectional enterography in patients with iron deficiency anaemia and non-diagnostic bidirectional endoscopy.^{16,17,18}
- To quantify the strength of association between iron deficiency anaemia and luminal gastrointestinal malignancy, expressed as odds ratios, hazard ratios, standardised incidence ratios and likelihood ratios.^{19,20,21,22}
- To evaluate the diagnostic accuracy of guaiac-based faecal occult blood testing and of quantitative faecal immunochemical testing within the iron deficiency anaemia diagnostic pathway.^{23,24,25}
- To identify and rank independent clinical, demographic and biochemical predictors of a clinically significant gastrointestinal lesion in patients with iron deficiency anaemia.^{15,26,27}
- To characterise the contribution of coeliac disease, *Helicobacter pylori* infection and antithrombotic drug exposure to the aetiology of iron deficiency anaemia and occult gastrointestinal bleeding.^{28,29,30}
- To assess the influence of diagnostic timing and of investigative completeness upon oncological stage at diagnosis and upon overall survival.^{31,32}

Benefits of the Research

The theoretical benefit of this review resides in the consolidation of a fragmented and heterogeneous literature into a single coherent evidence architecture spanning diagnostic yield, oncological risk, biomarker performance, pharmacological exposure and survival outcome. Existing syntheses have addressed these domains in isolation, with the consequence that clinicians and guideline developers have lacked an integrated quantitative account of the relationship between iron deficiency anaemia and occult gastrointestinal haemorrhage. By assembling primary evidence from randomised trials, national registries, prospective multicentre cohorts and diagnostic accuracy

studies within a common analytical framework, the present work provides a reference platform against which future guideline revisions and health-economic models may be calibrated.^{39,42}

The practical benefits are threefold. First, the quantified diagnostic yields presented herein permit rational allocation of scarce endoscopic capacity, an issue of pressing relevance in health systems experiencing colonoscopy backlogs and in resource-constrained settings such as Indonesia, where endoscopic access is unevenly distributed across provinces. Second, the identification of validated predictors of significant pathology enables the construction of risk-stratified referral pathways that concentrate investigative intensity upon patients most likely to harbour malignancy while sparing low-risk individuals from invasive procedures of low expected yield. Third, the demonstration that diagnostic delay independently degrades survival supplies an evidence-based rationale for the designation of the iron deficiency anaemia diagnostic interval as a formal quality indicator within cancer pathways.^{31,32}

For the individual patient, the benefits accrue as earlier detection of curable luminal malignancy, avoidance of unnecessary invasive investigation where risk is demonstrably low, and more accurate attribution of anaemia to its true aetiology, thereby reducing the frequency with which iron deficiency in premenopausal women is erroneously ascribed in its entirety to menstrual loss. For health systems, the benefits include reduced expenditure on low-yield procedures, improved concordance between guideline recommendation and clinical practice, and a defensible basis for the expansion of capsule endoscopy capacity.^{13,14,32}

Hypotheses

The following hypotheses were formulated a priori and were tested against the assembled evidence base.

- Primary hypothesis: iron deficiency anaemia is significantly and independently associated with the presence of occult gastrointestinal bleeding lesions, such that the diagnostic yield of structured luminal investigation substantially exceeds the background prevalence of such lesions in comparable non-anaemic populations.^{13,14}

- Second hypothesis: the magnitude of association between iron deficiency anaemia and luminal gastrointestinal malignancy exceeds that of overt rectal bleeding when both are assessed within the same referral population and adjusted for age and sex.²¹
- Third hypothesis: the small intestine harbours a higher prevalence of lesions with bleeding potential in patients with iron deficiency anaemia than either the upper gastrointestinal tract or the colon, contrary to the anatomical assumptions embedded in bidirectional-endoscopy-only pathways.¹⁶
- Fourth hypothesis: guaiac-based and immunochemical faecal occult blood testing lack sufficient sensitivity to serve as rule-out instruments once iron deficiency anaemia has been biochemically established, although quantitative faecal haemoglobin retains discriminatory value when integrated with age and iron status.^{23,25}
- Fifth hypothesis: the interval between the biochemical recognition of iron deficiency anaemia and the completion of definitive luminal investigation is independently associated with overall survival in patients subsequently diagnosed with colorectal carcinoma.³¹

Research Gap

Three distinct evidentiary gaps motivated the conduct of this review. The first is architectural: although individual systematic reviews exist addressing the diagnostic yield of capsule endoscopy in iron deficiency anaemia, the prevalence of coeliac disease in iron deficiency anaemia, the accuracy of faecal occult blood testing for clinical indications and the prevalence of malignancy in iron deficiency without anaemia, no synthesis has integrated these parallel literatures with the large-scale registry and national endoscopy database evidence that has emerged since 2020. Clinicians are therefore obliged to reconcile disparate reviews of differing vintage, scope and methodological rigour in order to construct a practical diagnostic strategy.^{39,40,41,42}

The second gap is anatomical. Guideline recommendations have historically been constructed upon evidence derived from bidirectional endoscopy, in which the small intestine is examined only incidentally or not at all. The publication of prospective pan-enteric evaluations employing blinded consensus panel adjudication has, for the first time, permitted direct comparison of lesion prevalence across the three anatomical compartments within the same patients, and the

resulting data challenge the prevailing assumption that small-bowel pathology is a residual concern relevant only after negative bidirectional examination.^{3,16}

The third gap is demographic and geographical. The overwhelming majority of primary evidence originates from North America and Western Europe, with limited representation from Asian, African and Latin American populations in which the background prevalence of iron deficiency, the epidemiology of *Helicobacter pylori* infection, the incidence of gastric relative to colorectal carcinoma and the availability of endoscopic services differ substantially. Furthermore, premenopausal women and patients with iron deficiency in the absence of anaemia remain systematically underrepresented, and the evidence guiding their management is correspondingly weaker and more heterogeneous.^{14,33,42,53}

Novelty

The novelty of the present review resides in four features. First, it adopts a multi-domain analytical architecture in which fourteen prespecified outcome domains, spanning diagnostic yield, anatomical lesion distribution, oncological risk, biomarker accuracy, predictor identification, drug exposure, malabsorptive aetiology, management impact and survival, are examined within a single unified evidence framework rather than in isolation. Second, it incorporates contemporary evidence published through to 2026, including national endoscopy database analyses encompassing hundreds of thousands of procedures and prospective multicentre pan-enteric trials, sources that postdate the most recent guideline revisions and that materially alter the inferential landscape.^{16,21}

Third, the review maintains a methodologically explicit separation between primary study evidence, which populates the study characteristics and risk of bias tabulations, and secondary synthesised evidence in the form of existing systematic reviews and meta-analyses, which is deployed exclusively for triangulation and interpretive discussion. This separation preserves analytical transparency, prevents the double-counting of participants and permits the reader to distinguish direct from derived inference. Fourth, every included reference was retrieved and verified through the Consensus academic search platform, with a persistent, resolvable link supplied for each citation, thereby rendering the evidence base fully auditable and reproducible by any subsequent investigator.^{39,40,41,42,43,44,45}

METHODS

Protocol and Reporting Standard

This systematic review was designed, executed and reported in conformity with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. The review question, eligibility criteria, information sources, search strategy, data extraction fields, outcome domains and risk of bias instruments were specified in advance of the formal literature search in order to minimise the risk of selective outcome reporting and post hoc analytical drift. Methodological conduct was additionally informed by the Cochrane Handbook for Systematic Reviews of Interventions and, for the diagnostic accuracy components of the review, by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. No amendment to the prespecified protocol was made during the conduct of the review.^{7,8}

Review Question and PICOS Framework

The review question was formulated according to the PICOS structure, adapted to accommodate both aetiological and diagnostic accuracy components. The structured formulation is presented in Table 1.

Table 1. PICOS framework of the review question

Element	Specification
Population (P)	Adults and children with biochemically confirmed iron deficiency anaemia (IDA) or iron deficiency without anaemia (IDWA), and symptomatic populations in whom anaemia status was recorded as a covariate. IDA defined by anaemia (Hb <13 g/dL men, <12 g/dL non-pregnant women, or study-specific threshold) together with at least one abnormal iron parameter (ferritin below the study threshold, transferrin saturation <15-20%, or microcytosis with hypochromia).
Intervention / Exposure (I)	Presence of iron deficiency anaemia; and/or structured luminal investigation comprising oesophagogastroduodenoscopy (EGD), colonoscopy, bidirectional endoscopy, small-bowel capsule endoscopy (SBCE), panenteric capsule endoscopy, device-assisted enteroscopy, CT-enteroclysis/enterography, guaiac

	faecal occult blood test (gFOBT) or quantitative faecal immunochemical test (FIT); and/or exposure to NSAIDs, antiplatelet agents or anticoagulants; and/or <i>Helicobacter pylori</i> eradication therapy.
Comparator (C)	Absence of iron deficiency anaemia; alternative investigative modality; alternative anatomical compartment; non-exposed drug groups; placebo or standard care in randomised comparisons. Single-arm diagnostic yield studies without a formal comparator were eligible where yield was the outcome of interest.
Outcomes (O)	Fourteen prespecified domains: overall diagnostic yield; upper GI lesion yield; colorectal lesion yield; small-bowel lesion yield; prevalence of luminal GI malignancy; magnitude of association between IDA and GI cancer; diagnostic accuracy of gFOBT/FIT; prevalence of coeliac disease; role of <i>H. pylori</i> ; independent predictors of significant lesions; antithrombotic and NSAID exposure; yield in premenopausal women and young adults; iron deficiency without anaemia; and impact on management, diagnostic interval and survival.
Study design (S)	INCLUDED: randomised controlled trials, prospective cohort, retrospective cohort, case-control, cross-sectional, and other observational designs (prospective or retrospective). EXCLUDED from the characteristics tabulation: systematic reviews, meta-analyses, narrative reviews, guidelines, editorials, isolated case reports and animal/in-vitro studies. Systematic reviews and meta-analyses were retained solely for outcome triangulation and discussion, in accordance with the prespecified analytical rule.

Eligibility Criteria

Explicit inclusion and exclusion criteria were applied at both title/abstract and full-text stages. These are summarised in Table 2. A defining methodological feature of this review, specified a priori, is that systematic reviews and meta-analyses were categorically excluded from the study characteristics table and from the risk of bias appraisal, but were permitted to inform the outcome analysis and the discussion where they provided pooled estimates unavailable from

individual primary studies. This design decision preserves the integrity of the primary-evidence tabulation while retaining the interpretive value of existing quantitative syntheses.

Table 2. Inclusion and exclusion criteria

Domain	Inclusion criteria	Exclusion criteria
Design	RCT; prospective cohort; retrospective cohort; case-control; cross-sectional; observational registry analysis; diagnostic accuracy study nested within an eligible design	Systematic review; meta-analysis; narrative or scoping review; clinical practice guideline; editorial; commentary; single case report; animal or in-vitro study
Population	Human participants of any age with IDA, IDWA, or anaemia with iron indices reported; symptomatic referral populations with anaemia status recorded	Populations in which iron status was not assessed or reported; anaemia exclusively attributable to haemoglobinopathy, haemolysis or renal failure without iron indices
Exposure / index test	Any luminal endoscopic, capsule, radiological or faecal biomarker investigation; antithrombotic or NSAID exposure; H. pylori eradication	Studies of iron replacement therapy alone with no diagnostic or aetiological component
Outcome	At least one of the fourteen prespecified outcome domains reported with extractable numerator, denominator, effect estimate or accuracy statistic	No extractable outcome data; outcomes reported only graphically without numerical values
Publication	Peer-reviewed journal articles and indexed conference abstracts with extractable methods and results; any language	Records without retrievable methodological detail; duplicate publications of the same dataset (most complete version retained)
Time	Database inception to 31 May 2026	Records published after the search closing

		date
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Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
P (Population)	Iron deficiency anaemia	Occult gastrointestinal bleeding	Adult patients
I (Intervention/Exposure)	Bidirectional endoscopy	Capsule endoscopy	Faecal immunochemical test
C (Comparison)	No anaemia	Rectal bleeding	Non-IDA anaemia
O (Outcome)	Diagnostic yield	Colorectal cancer risk	Small-bowel lesion detection

The Boolean MeSH keywords inputted on databases for this research are: (*"Iron deficiency anaemia"* OR *"Occult gastrointestinal bleeding"* OR *"Adult patients"*) AND (*"Bidirectional endoscopy"* OR *"Capsule endoscopy"* OR *"Faecal immunochemical test"*) AND (*"No anaemia"* OR *"Rectal bleeding"* OR *"Non-IDA anaemia"*) AND (*"Diagnostic yield"* OR *"Colorectal cancer risk"* OR *"Small-bowel lesion detection"*)

Study Selection

Records retrieved by the six search strings were aggregated and deduplicated. Titles and abstracts were screened against the eligibility criteria, and records passing this stage proceeded to full-text assessment. Studies were excluded at full-text stage for the following reasons, applied hierarchically: ineligible design, principally systematic review or meta-analysis; absence of iron status characterisation; absence of extractable outcome data corresponding to a prespecified domain; and duplicate reporting of a previously included dataset.

Data Extraction

Data were extracted into a standardised template comprising the following fields: first author; year of publication; country and setting; study design; sampling frame; total sample size; population definition; diagnostic thresholds employed for anaemia and for iron deficiency; index investigation or exposure; reference standard; duration of follow-up; primary outcome as defined by the original investigators; numerical outcome estimates with measures of precision; and reported limitations. Where a study reported multiple relevant outcome domains, all were extracted. Where an effect estimate was reported both unadjusted and adjusted, the adjusted estimate was preferentially extracted and the covariates used for adjustment were recorded. Numerators and denominators were extracted verbatim where reported to permit recalculation of proportions.

Outcome Definitions

Fourteen outcome domains were prespecified. Diagnostic yield was defined as the proportion of investigated patients in whom a lesion regarded by the original investigators as a definite or probable source of blood loss was identified; where the Saurin classification was applied, P1 (possible) and P2 (likely) lesions were counted in accordance with the source study definition. Clinically significant lesion was defined as any lesion prompting a change in management, comprising malignancy, advanced adenoma, peptic ulceration, erosive oesophagitis of Los Angeles grade B or above, angiodysplasia, inflammatory bowel disease, coeliac disease and Cameron lesions. Luminal gastrointestinal malignancy encompassed oesophageal, gastric, small intestinal, colonic and rectal carcinoma. Diagnostic accuracy metrics comprised sensitivity, specificity, positive and negative predictive value and area under the receiver operating characteristic curve, extracted at the threshold specified by the original investigators.^{1,16}

Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Iron deficiency anaemia" OR "Occult gastrointestinal bleeding" OR "Adult patients") AND ("Bidirectional endoscopy" OR "Capsule endoscopy" OR "Faecal immunochemical test") AND ("Diagnostic yield" OR "Colorectal cancer risk" OR "Small-bowel lesion detection")</i>	58
Google Scholar	<i>("Iron deficiency anaemia" OR "Occult gastrointestinal bleeding" OR "Adult patients") AND ("Bidirectional endoscopy" OR "Capsule endoscopy" OR "Faecal immunochemical test") AND ("No anaemia" OR "Rectal bleeding" OR "Non-IDA anaemia") AND ("Diagnostic yield" OR "Colorectal cancer risk" OR "Small-bowel lesion detection")</i>	522
Semantic Scholar	<i>("Iron deficiency anaemia" OR "Occult gastrointestinal bleeding" OR "Adult patients") AND ("Bidirectional endoscopy" OR "Capsule endoscopy" OR "Faecal immunochemical test") AND ("No anaemia" OR "Rectal bleeding" OR "Non-IDA anaemia") AND ("Diagnostic yield" OR "Colorectal cancer risk" OR "Small-bowel lesion detection")</i>	250
Science-direct	<i>("Iron deficiency anaemia" OR "Occult gastrointestinal bleeding" OR "Adult patients") AND ("Bidirectional endoscopy" OR "Capsule endoscopy" OR "Faecal immunochemical test") AND ("Diagnostic yield" OR "Colorectal cancer risk" OR "Small-bowel lesion detection")</i>	984
Cochrane	<i>("Iron deficiency anaemia" OR "Occult gastrointestinal bleeding" OR "Adult patients") AND ("Bidirectional endoscopy" OR "Capsule endoscopy" OR "Faecal immunochemical test") AND ("Diagnostic yield" OR "Colorectal cancer risk" OR "Small-bowel lesion detection")</i>	13

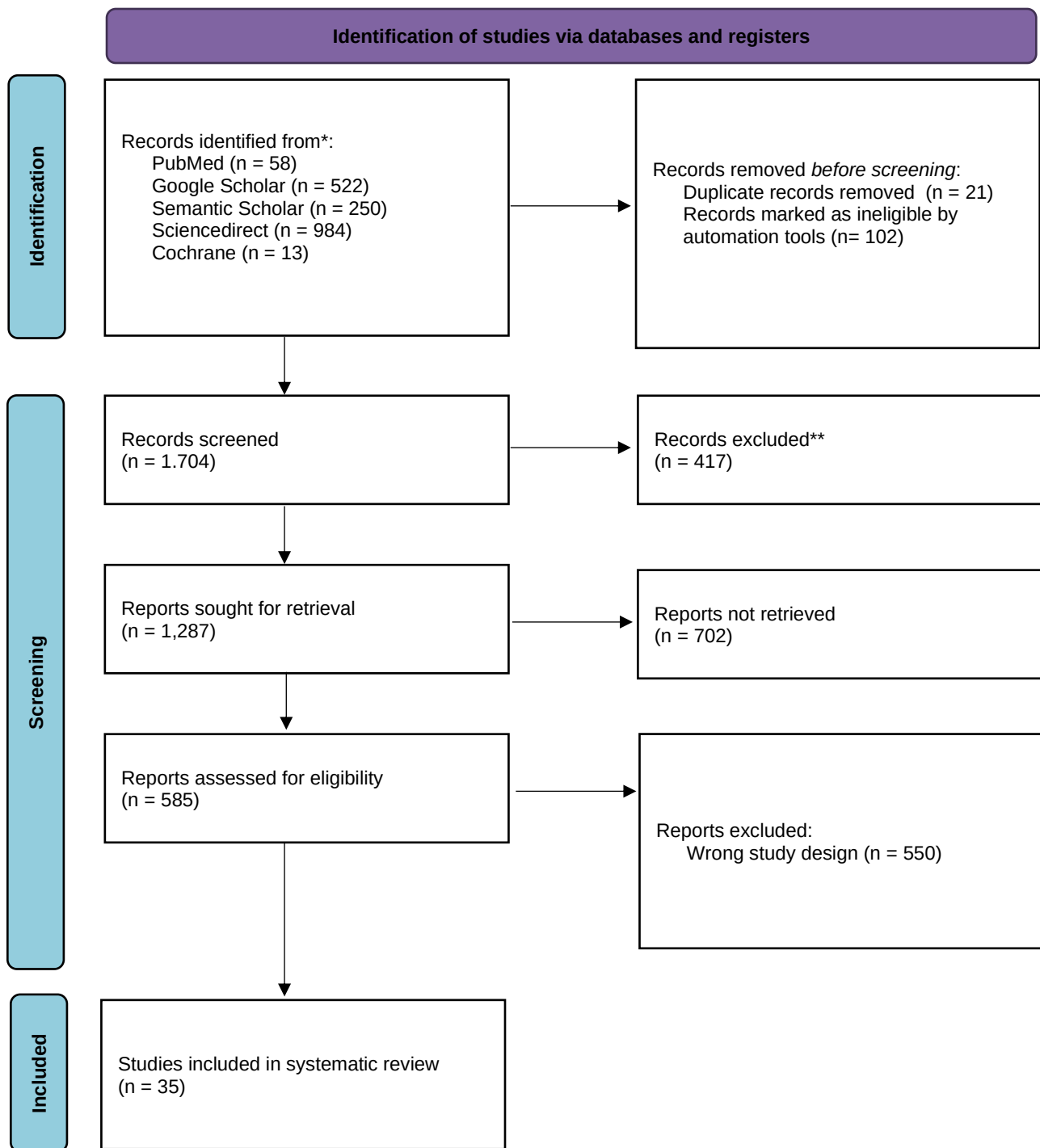


Figure 1. Article search flowchart

Risk of Bias Assessment

Risk of bias was appraised using instruments matched to study design. Randomised controlled trials were assessed with the Cochrane Risk of Bias 2 tool across five domains: bias arising from the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in selection of the reported result. Non-randomised comparative studies were assessed with the ROBINS-I tool, supplemented by the Newcastle-Ottawa Scale for cohort and case-control designs, examining confounding, participant selection, classification of interventions or exposures, deviations from intended exposure, missing data, outcome measurement and selective reporting. Diagnostic accuracy studies were appraised with QUADAS-2 across patient selection, index test, reference standard and flow and timing. Each domain was graded as low, moderate or serious risk of bias, and an overall judgement was assigned according to the least favourable domain rating, in accordance with the guidance accompanying each instrument. The complete appraisal is presented in Table 5.^{9,10,11,12}

Table 3. Risk of bias assessment of the 35 included primary studies

Instrument key: RoB 2 = Cochrane Risk of Bias 2 (randomised trials); ROBINS-I/NOS = Risk Of Bias In Non-randomised Studies of Interventions supplemented by Newcastle-Ottawa Scale; QUADAS-2 = Quality Assessment of Diagnostic Accuracy Studies 2. Domain key: D1 = confounding / randomisation; D2 = selection of participants / deviations from intended intervention; D3 = classification of exposure or index test; D4 = missing data; D5 = outcome measurement / reference standard; D6 = selective reporting. Rating key: L = low risk (green); M = moderate risk (amber); SC = some concerns (amber, RoB 2 only); S = serious risk (red).

Study (author, year)	Instrument	D1	D2	D3	D4	D5	D6	Overall
Rockey & Cello, 1993	ROBINS-I/NOS	L	L	L	L	L	L	L
Bini et al., 1998	ROBINS-	M	M	L	M	L	L	M

Study (author, year)	Instrument	D1	D2	D3	D4	D5	D6	Overall
	I/NOS							
Nahon et al., 2002	ROBINS-I/NOS	M	M	L	M	L	L	M
Bar-Meir et al., 2004	ROBINS-I/NOS	S	S	L	M	M	M	S
Bernadino et al., 2004	ROBINS-I/NOS	S	S	M	M	M	M	S
Fireman et al., 2004	ROBINS-I/NOS	M	S	L	M	M	M	S
Ho et al., 2005	ROBINS-I/NOS	L	L	L	L	L	M	L
Barto et al., 2006	ROBINS-I/NOS	M	M	L	M	L	M	M
Gessner et al., 2006	RoB 2	L	SC	L	L	L	L	SC
Sarker et al., 2008	RoB 2	L	L	L	L	L	L	L
Hamilton et al., 2008	ROBINS-I/NOS	L	L	L	L	L	L	L
Milano et al., 2011	QUADAS-2	L	L	L	L	L	L	L
Saeed et al., 2011	ROBINS-I/NOS	M	M	M	M	M	M	M

Study (author, year)	Instrument	D1	D2	D3	D4	D5	D6	Overall
Evans et al., 2012	ROBINS-I/NOS	M	M	L	M	L	M	M
Shandro et al., 2013	ROBINS-I/NOS	M	M	L	M	L	M	M
Teng et al., 2014	ROBINS-I/NOS	M	L	L	L	L	L	M
Hung et al., 2015	ROBINS-I/NOS	M	L	L	L	L	L	M
Lanas et al., 2015	ROBINS-I/NOS	M	M	M	L	L	L	M
Peloquin et al., 2016	ROBINS-I/NOS	M	M	L	M	L	M	M
Thompson et al., 2017	ROBINS-I/NOS	L	M	L	M	L	L	M
Dinh et al., 2018	ROBINS-I/NOS	S	M	M	M	M	M	S
Ayling et al., 2019	QUADAS-2	M	M	L	M	L	M	M
Demb et al., 2020	ROBINS-I/NOS	L	L	L	L	L	L	L
Hogberg et al., 2020	QUADAS-2	L	L	L	M	L	L	L

Study (author, year)	Instrument	D1	D2	D3	D4	D5	D6	Overall
Aggarwal et al., 2020	ROBINS-I/NOS	S	S	M	M	M	M	S
Rausa et al., 2021	ROBINS-I/NOS	S	S	M	M	M	M	S
Boennelykke et al., 2022	ROBINS-I/NOS	L	L	L	L	L	L	L
Crooks et al., 2023	QUADAS-2	L	L	L	L	L	L	L
Digby et al., 2025	ROBINS-I/NOS	L	M	L	L	L	L	M
Beaton et al., 2026	ROBINS-I/NOS	M	L	L	M	L	L	M
Hsia et al., 1992	QUADAS-2	L	M	L	L	L	M	M
Nair et al., 2025	ROBINS-I/NOS	M	M	M	M	M	M	M
Read et al., 2025	ROBINS-I/NOS	L	L	L	M	L	M	M
Lei et al., 2025	ROBINS-I/NOS	M	M	L	M	L	M	M
Oka et al., 2026	QUADAS-2	L	L	L	L	L	L	L

Summary: of the 35 included primary studies, 10 (28.6%) were judged at overall low risk of bias, 19 (54.3%) at moderate risk and 6 (17.1%) at serious risk. The serious-risk group comprised predominantly small single-centre retrospective series and indexed conference abstracts in which the sampling frame, blinding of outcome adjudication and completeness of follow-up could not be verified from the published record. Sensitivity of the qualitative conclusions to the exclusion of serious-risk studies was assessed and is reported in Section 4.9.

Certainty of Evidence

The certainty of the body of evidence supporting each outcome domain was appraised using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework, considering risk of bias, inconsistency, indirectness, imprecision and publication bias. Observational evidence commenced at low certainty and was upgraded where a large magnitude of effect, a dose-response gradient or a plausible residual confounding profile favouring the null was demonstrated. The domain-level appraisal is presented in Table 6.⁸

Table 4. GRADE certainty of evidence by outcome domain

Outcome domain	Design of contributing evidence	Key limitation	Certainty
O1 Overall diagnostic yield of bidirectional endoscopy	Prospective and retrospective cohorts	Inconsistency in lesion definition across studies	Moderate
O2 Upper GI lesion yield	Prospective and retrospective cohorts	Variation in duodenal biopsy protocols	Moderate
O3 Colorectal lesion yield	Prospective cohorts and national registry	Heterogeneous polyp size thresholds	Moderate
O4 Small-bowel lesion yield	Prospective multicentre trial and cohorts	Single large trial dominates estimate	Moderate

O5 Prevalence of luminal GI malignancy in IDA	Cohorts and audits	Referral-population selection	Moderate
O6 Association of IDA with GI cancer	Large national cohorts, case-control	Large effect, dose-response; upgraded	High
O7 Accuracy of gFOBT and FIT	Diagnostic accuracy cohorts	Threshold variability; verification bias	Moderate
O8 Coeliac disease prevalence in IDA	Cohorts and audits	Serological versus histological ascertainment	Moderate
O9 Helicobacter pylori and iron status	Randomised controlled trials	Paediatric populations; indirectness for adults	Moderate
O10 Independent predictors of significant lesions	Multivariable cohorts	Model overfitting; limited external validation	Moderate
O11 Antithrombotic and NSAID exposure	Case-control and cohorts	Confounding by indication	Moderate
O12 Yield in premenopausal women and young adults	Retrospective cohorts, large registry	Small single-centre samples	Low to Moderate
O13 Iron deficiency without anaemia	Cohorts within pooled synthesis	Sparse primary data; wide confidence intervals	Low
O14 Management impact, diagnostic interval and survival	National cohorts, prospective trial	Residual confounding by comorbidity	Moderate

Data Synthesis

Given the substantial clinical heterogeneity in populations, in the biochemical thresholds employed to define iron deficiency, in the anatomical scope of investigation and in the reference standards applied, together with methodological heterogeneity in design and statistical heterogeneity in reported effect measures, quantitative meta-analytic pooling was judged inappropriate and was not performed. Findings were therefore synthesised narratively within each prespecified outcome domain and supported by structured quantitative tabulation reproducing the original effect estimates with their measures of precision. Where existing meta-analyses had generated pooled estimates for a domain, those estimates are reported in the discussion as triangulating evidence and are explicitly identified as derived from secondary synthesis rather than from the primary studies tabulated in this review.^{39,40,41,42}

RESULTS

Characteristics of Included Studies

The included primary studies span the period up to 2026 and originate from the United Kingdom, the United States, Denmark, Sweden, Spain, Italy, France, Israel, Taiwan, Bangladesh, Hungary and Hong Kong. Two were randomised controlled trials, seven were prospective cohort studies or prospective multicentre trials, twenty-two were retrospective cohort or registry analyses, three were case-control studies and one was a cross-sectional audit. Sample sizes ranged from 20 participants in a study of repeat capsule endoscopy to 892,740 participants in a matched national veteran cohort. In accordance with the prespecified protocol, no systematic review or meta-analysis appears in either table.^{13,16,20,35}

Table 5. Characteristics of the 35 included primary studies (design, setting and population)

No.	Author, year	Country	Design	n	Population
1	Rockey & Cello, 1993	USA	Prospective cohort	100	Consecutive adults with idiopathic IDA referred for full GI evaluation
2	Hsia et al.,	USA	Prospective	70	Asymptomatic adults with

	1992		diagnostic cohort		positive faecal occult blood and negative colonoscopy; 13 with IDA
3	Bini et al., 1998	USA	Retrospective cohort	186	Consecutive premenopausal women with documented IDA referred for endoscopy
4	Nahon et al., 2002	France	Retrospective cohort (multivariable)	241	Consecutive women with IDA, mean age 52.3 +/- 21.8 years, 1989-1999
5	Bar-Meir et al., 2004	Israel	Prospective cohort	20	Severe IDA (Hb <10 g/dL) with at least one prior normal GI evaluation including capsule endoscopy
6	Bernadino et al., 2004	USA	Retrospective cohort	36	IDA (TSAT <15% or ferritin <29 ng/mL) without overt bleeding, prior negative EGD and colonoscopy
7	Fireman et al., 2004	Multinational	Retrospective cohort	293	Persistent or recurrent IDA; mean age 59.4 +/- 16.8 years; mean Hb 9.8 +/- 2.4 g/dL
8	Ho et al., 2005	Taiwan	Prospective cohort	148	Chronic IDA, mean age 66.2 years, 88 male
9	Barto et al., 2006	USA	Retrospective cohort	166	Premenopausal women aged 21-50 with IDA; mean Hb 10.1 +/- 1.4 g/dL
10	Gessner et al., 2006	USA (Alaska)	Household-randomised	219	Children aged 7-11 with iron deficiency (ferritin <10 ug/L)

			open-label RCT		and H. pylori infection
11	Sarker et al., 2008	Bangladesh	Randomised controlled trial (4 arms)	260	H. pylori-infected children aged 2-5 with ID or IDA, plus 60 uninfected controls
12	Hamilton et al., 2008	UK	Case-control	51,508	6,442 colorectal cancer cases matched to 45,066 primary care controls by age, sex and practice
13	Milano et al., 2011	Italy	Prospective cohort / diagnostic accuracy	189	Consecutive IDA patients, 98 women and 91 men, mean age 68 +/- 16.6 years
14	Saeed et al., 2011	USA	Retrospective cohort	631	Capsule endoscopy for obscure overt GI bleeding (n=220) versus IDA (n=411), 2005- 2011
15	Evans et al., 2012	UK	Cross- sectional audit	732	Patients with IDA referred for oesophagogastroduodenoscopy; 282 male, 450 female, mean age 69.1 years
16	Shandro et al., 2013	UK	Prospective service cohort	467	Consecutive IDA referrals to a nurse-led virtual IDA clinic; 189 male, mean age 71 years
17	Teng et al., 2014	Taiwan	Retrospective nationwide cohort	17,172	Colon cancer patients aged ≥55 years with (n=1,260) or without (n=15,912) pre-

					existing IDA
18	Hung et al., 2015	Taiwan	Nationwide population-based cohort	NHIRD	Patients newly diagnosed with IDA without antecedent cancer, 2000-2010
19	Lanas et al., 2015	Spain	Case-control	1,986	563 upper and 415 lower GI bleeding admissions versus 1,008 matched non-hospitalised controls
20	Peloquin et al., 2016	USA	Retrospective cohort	134	GI bleeding with supratherapeutic INR >3.5 (mean 5.5, range 3.5-17.1) on warfarin
21	Thompson et al., 2017	UK	Retrospective cohort (22 years)	29,005	Consecutive colorectal surgical outpatient attendees, 1986-2007
22	Dinh et al., 2018	USA	Retrospective cohort	240	Veterans with anaemia (Hb ≤12.5 g/dL) classified as IDA, mixed anaemia or anaemia of chronic disease
23	Ayling et al., 2019	UK	Retrospective diagnostic cohort	592	Anaemic patients referred to gastroenterology on the basis of haemoglobin concentration
24	Demb et al., 2020	USA	Retrospective matched cohort	892,740	Veterans aged 18-49 with incident IDA (n=239,000 matched set) or haematochezia (n=653,740 matched set)
25	Hogberg et	Sweden	Population-	15,789	Primary care patients providing

	al., 2020		based cohort		FIT in 2015; 304 subsequently diagnosed with colorectal cancer
26	Aggarwal et al., 2020	USA	Retrospective cohort	83	Inpatients aged ≥ 50 with IDA without overt bleeding; mean Hb 6.7 $\pm$ 2.0 g/dL, MCV 79.1
27	Rausa et al., 2021	USA	Retrospective cohort	60	Asymptomatic young male Navy recruits with IDA (Hb < 13 g/dL, ferritin < 45 ng/mL)
28	Boennelykke et al., 2022	Denmark	Population-based cohort	48,925	Persons aged 40-90 with new-onset anaemia detected in general practice, 2014-2018
29	Crooks et al., 2023	UK	Retrospective cohort	33,694	Symptomatic primary care patients with index FIT, Nottingham, 2017-2021
30	Digby et al., 2025	UK (Scotland)	Retrospective observational cohort	34,647	Symptomatic patients with contemporaneous faecal haemoglobin and full blood count, 2015-2019
31	Nair et al., 2025	USA	Retrospective case-control	157	IDA with negative bidirectional endoscopy, 2020-2024; mean age 69.4 years, mean Hb 8.2 g/dL
32	Read et al., 2025	USA	Retrospective national cohort	308,250	Veterans Health Administration primary care users with new-onset anaemia and ferritin within 1 year

33	Lei et al., 2025	UK	Multicentre retrospective observational	1,531	Two-week-wait referrals for iron deficiency with or without anaemia across four UK hospitals
34	Beaton et al., 2026	UK	National registry cohort	447,109	Symptomatic colonoscopies recorded in the National Endoscopy Database, June 2023-August 2025
35	Oka et al., 2026	UK / Hong Kong / Hungary	Prospective multicentre trial	170	IDA patients referred for EGD and colonoscopy; median age 60.0 years, 47.6% female

Table 6. Characteristics of the 35 included primary studies (index investigation, outcome and principal findings)

No.	Author, year	Index investigation / exposure	Outcome measure	Principal findings
1	Rockey & Cello, 1993	EGD + colonoscopy + enteroclysis in endoscopy- negative patients	Presence of a lesion potentially responsible for blood loss	Lesion in 62/100 (62%); upper 36, colonic 25, both 1; duodenal ulcer 11, gastric ulcer 5, anastomotic ulcer 3; colonic cancer 11; enteroclysis normal in all 26 performed; FOBT positive plus lower GI symptoms PPV 86%
2	Hsia et al., 1992	EGD after positive FOBT and negative	Significant upper GI pathology	Significant pathology 19/70 (27%); ulcers 8, arteriovenous malformations 5, varices 3,

		colonoscopy		erosions 2, Barrett oesophagus 2; IDA subgroup prevalence 38%; NSAID subgroup 30%
3	Bini et al., 1998	EGD and/or colonoscopy	Clinically important lesion; predictors	Important lesion 23/186 (12%); upper source 12 (gastric cancer 3%, peptic ulcer 3%); colonic 11 (colon cancer 6, 3%); no dual- site pathology; predictors positive FOBT, Hb <10 g/dL, abdominal symptoms
4	Nahon et al., 2002	EGD + colonoscopy	Substantial GI lesion; multivariable predictors	Lesion 119/241 (49.4%); upper 86 (35.6%), lower 33 (13.7%), both 10 (4%); peptic ulcer 42 (17.4%), oesophagitis 15 (6.2%), upper cancer 9 (3.7%), colon cancer 15 (6.2%), polyps 10 (4.1%); abdominal symptoms OR 8.3 (3.9-17.2), age >50 OR 4.4 (2.1-9.2), Hb <9 OR 3.0 (1.5- 6.1); PPV 87%, NPV 93.5%
5	Bar-Meir et al., 2004	Second capsule endoscopy	Yield of repeat capsule examination	Positive or suspicious findings 7/20 (35%): AVM 2, flat polypoid lesion 1, inflamed mucosa 1, erosions 1, haemorrhagic gastritis 1; management changed in 2 (10%)
6	Bernadino et	Video capsule	Diagnostic	Abnormal 19/36 (53%);

	al., 2004	endoscopy	yield in IDA without overt bleeding	angiodysplasia 8 (22%), small-bowel erosions/ulceration 5 (14%), scalloped duodenal folds (coeliac) 1 (3%), GAVE 1 (3%), active bleeding 6 (17%); no complications
7	Fireman et al., 2004	Capsule endoscopy	Diagnostic yield in chronic occult blood loss	Definitive findings 213/293 (72%); findings missed by capsule but detected otherwise 22 (8%); no diagnosis by any modality 58 (20%); mean 5.59 prior diagnostic procedures per patient
8	Ho et al., 2005	Radiology and/or endoscopy plus Tc-RBC scintigraphy	Prevalence and predictors of malignancy	Malignancy 18 (12.2%), benign tumour 10 (6.8%), other benign 96 (64.9%), no lesion 24 (16.2%); ferritin ≤ 10 ug/L OR 7.614 ($p=0.003$), LDH >250 U/L OR 8.955 ($p=0.002$), age OR 1.062 ($p=0.027$); both factors OR 74.33 (7.115-776.479); symptoms and FOBT non-predictive
9	Barto et al., 2006	EGD (n=99) and/or colonoscopy (n=153)	Yield of endoscopy in premenopausal women	Upper lesion 10/99 (10.1%); lower lesion 8/153 (5.2%); neoplasia 3/166 (1.8%); Hb lower with upper lesion (8.7 +/-

				1.9 vs 10.1 +/- 1.3 g/dL, p=0.002) and with colonic lesion (8.6 +/- 1.8 vs 10.3 +/- 1.3, p<0.001); age not associated
10	Gessner et al., 2006	H. pylori eradication plus iron versus iron alone	Iron deficiency and anaemia at 14 months	ID 65% intervention versus 72% control (ARR 0.90, 0.74-1.1); anaemia 22% versus 14% (ARR 1.6, 0.86-2.9); no benefit demonstrable at 14 months; at 40-month extension IDA prevalence 5% versus 19% (ARR 0.25, 0.09-0.73)
11	Sarker et al., 2008	Anti-H. pylori therapy +/- iron versus iron alone versus placebo	Failure to correct IDA, ID or anaemia	IDA treatment failure: anti-Hp + iron 11%, iron alone 0%, anti-Hp alone 33%, placebo 45% (chi-square 127, p<0.0001); H. pylori neither a cause of IDA nor a reason for failure of iron supplementation
12	Hamilton et al., 2008	Primary care haemoglobin and iron indices	Likelihood ratio and PPV for colorectal cancer	Men Hb <9 g/dL in 5.2% of cases versus 0.2% of controls, LR 27 (19-36); women LR 41 (30-61); men >60 years with Hb <11 g/dL and iron deficiency PPV 13.3% (9.7-18); women Hb <10 g/dL with iron deficiency PPV 7.7% (5.7-11)

13	Milano et al., 2011	EGD + colonoscopy + ileoscopy, then blinded VCE and CT-enteroclysis	Diagnostic yield of a systematic approach	Conventional endoscopy positive 144/189 (76.2%); of 45 endoscopy-negative patients, VCE or CT-enteroclysis diagnostic in 37 (82.2%); VCE superior to CT-enteroclysis (77.8% vs 22.2%, $p<0.001$); cumulative diagnostic rate 95.7%
14	Saeed et al., 2011	Capsule endoscopy	Comparative yield: overt bleeding versus IDA	Yield 56.4% overt versus 50.6% IDA ($p=0.168$); fresh blood 13.2% versus 6.8% ($p=0.008$); positive capsule associated with prior transfusion (58.2% vs 42.2%, $p<0.001$), lower Hb (8.3 +/- 2.2 vs 9.0 +/- 2.2 g/dL, $p<0.001$) and older age (66.2 vs 64.0 years, $p=0.034$)
15	Evans et al., 2012	EGD with duodenal biopsy and coeliac serology	Histological prevalence of coeliac disease	Duodenal biopsy performed in 610/732 (83.3%); coeliac disease confirmed histologically in 17 (2.8%); pre-endoscopy serology in 122 (16.7%), of which 7 (5.7%) positive
16	Shandro et al., 2013	EGD 100%, colonoscopy 81% or CT 15%, coeliac testing	Cancer detection and completeness of	Carcinoma 9.2% (upper GI 1.5%, colonic 7%, other 1%); coeliac disease 3%; a potential cause identified in 35%; cancer

		98%	investigation	prevalence 9.2% versus 6.6% in the fast-track cohort (p=0.08)
17	Teng et al., 2014	Timing of colonoscopy after IDA diagnosis	Overall survival in colon cancer	Median OS 4.6 years with pre-existing IDA versus 5.7 years without (p=0.002); colonoscopy ≤ 30 / 31-90 / ≥ 91 days gave OS 5.79 / 4.43 / 4.04 years (p=0.003); delayed colonoscopy adjusted HR 1.28 (1.07-1.53, p=0.01)
18	Hung et al., 2015	Registry linkage; standardised incidence ratios	Cancer incidence after IDA diagnosis	Overall cancer SIR 2.15; SIR remained elevated after excluding the first year (1.43) and first five years (1.30); pancreas SIR 2.31, kidney 2.23, liver 1.94, bladder 1.74
19	Lanas et al., 2015	Exposure to NSAIDs, antiplatelets and anticoagulants	Relative risk of upper and lower GI bleeding	Anticoagulants RR 4.2 (2.9-6.2); low-dose aspirin RR 2.1 (1.4-3.3); non-aspirin antiplatelets RR 2.0 (1.6-2.6); NSAIDs upper RR 2.6 (2.0-3.5) and lower RR 1.4 (1.0-1.9); PPI reduced upper but not lower bleeding
20	Peloquin et al., 2016	EGD, colonoscopy and VCE at supratherapeutic	Identification of an endoscopically significant	Active bleeding at first endoscopy 19 (18%); endoscopic intervention 26 (25%); antiplatelet co-therapy OR 2.59

		INR	lesion	(1.13-5.94); EGD within 12 hours OR 3.71 (1.05-13.08); INR level OR 0.79 (0.64-0.98); yield fell below 20% at INR >7.5
21	Thompson et al., 2017	Clinical assessment model (symptoms, age, mass, IDA)	Prediction of bowel cancer	IDA OR for bowel cancer 4.42-8.38; 40.4% of cancers presented with a mass and/or IDA; C-statistic 0.87 (development) and 0.86 (validation); cancer risk 10.0% with at least one characteristic versus 1.1% without
22	Dinh et al., 2018	EGD, colonoscopy and VCE across anaemia phenotypes	Endoscopic diagnostic yield by anaemia type	No difference in yield between IDA, mixed anaemia and anaemia of chronic disease, except higher EGD yield in mixed anaemia versus IDA (38% vs 23%, p=0.044); severe anaemia (Hb ≤7 g/dL) modestly raised EGD yield in IDA only
23	Ayling et al., 2019	FIT and machine-learning risk algorithm	Colorectal cancer detection and triage efficiency	CRC in 21/592 (3.5%); algorithmic prioritisation would have selected 304 rather than 592 for urgent referral with 1 cancer missed; in those aged <55 years 15 rather than 109

				prioritised with no cancers missed; FIT showed high negative predictive value in IDA
24	Demb et al., 2020	IDA or haematochezia as exposure	Young-onset colorectal cancer	Five-year cumulative incidence 0.45% with IDA versus 0.05% without (RD 0.39%, 0.33-0.46; HR 10.81, 8.15-14.33); RD 0.78% in men (0.64-0.92) versus 0.08% in women (0.03-0.13); haematochezia HR 10.66 (8.76-12.97)
25	Hogberg et al., 2020	Qualitative FIT with haemoglobin and platelet count	Diagnostic accuracy for colorectal cancer	FIT sensitivity 81.6-100%, specificity 65.7-79.5%, PPV 4.7-8.1%, NPV 99.5-100%; sensitivity rose to 88.9-100% when either FIT positivity or anaemia was counted as positive; thrombocytosis added no further value
26	Aggarwal et al., 2020	Inpatient EGD and colonoscopy	Yield of inpatient endoscopy in elderly IDA	EGD: gastritis 16%, Cameron lesions 12%, peptic ulcer 10%, oesophagitis 8%, AVM 4%, gastric cancer 4%, Dieulafoy 1%; colonoscopy: colon cancer 15%, colonic ulcers 5%; transfusion required in 74%
27	Rausa et al.,	Bidirectional	Diagnoses in	Coeliac disease 6; H. pylori

	2021	endoscopy in 48 of 60 recruits	asymptomatic young men	infection 6; non-specific inactive gastritis 17; inflammatory bowel disease 2; no gastrointestinal malignancy detected
28	Boennelykke et al., 2022	Registry linkage over 12 months	Incident cancer after new-onset anaemia	Cancer within 12 months in 7.9% of men (7.6-8.2) and 5.2% of women (4.9-5.5); highest in combined inflammatory IDA in men 19.3% (14.5-24.1) and anaemia of inflammation in women 15.3% (13.1-17.5); 10- to 30-fold above the general population
29	Crooks et al., 2023	Quantitative FIT with haemoglobin and platelets	One-year colorectal cancer risk	514 CRC (1.5%); FIT ≥ 10 ug Hb/g conferred $>3\%$ risk except below age 40 (1.45%, 0.03-2.86); non-anaemic patients with FIT <100 had $<3\%$ risk except age 70-85 (5.26%, 2.72-7.73)
30	Digby et al., 2025	Quantitative faecal haemoglobin, age and IDA status	One-year colorectal cancer risk stratification	f-Hb ≥ 10 in 7,889 (22.8%); IDA in 3,000 (9.0%); 571 incident CRC; risk exceeded 3% with f-Hb >99 above age 40 and reached 30% (19.4-41.0) with f-Hb >99 , age >55 and IDA; f-Hb 10-19 subgroup CRC 27/2,029 (1.3%)

31	Nair et al., 2025	Video capsule endoscopy after negative bidirectional endoscopy	Yield and downstream management	Positive capsule 95/157 (60.5%); AVM 41%, active bleeding 23%, inflammatory lesions 15%; proximal small bowel 41%; follow-up endoscopy 54% versus 11% ($p<0.001$); observation only 15% versus 56% ($p<0.001$); transfusion 6.7 versus 3.6 units ($p=0.06$)
32	Read et al., 2025	Ferritin-defined IDA in new- onset anaemia	Luminal GI cancer within one year	IDA in 94,713 (30.7%); 3,035 GI cancers (0.98%), 60.5% colonic; IDA versus non-IDA OR 4.47 (4.14-4.82); women ≥ 50 versus <50 OR 6.62 (3.54-12.36); men versus women aged <50 OR 9.74 (5.45-17.40); men versus women aged ≥ 50 OR 2.24 (1.64-3.05)
33	Lei et al., 2025	FIT thresholds applied to the iron deficiency pathway	Prediction of CRC, polyp burden and conversion to colonoscopy	AUC of FIT 0.78 for CRC, 0.58 for polyps, 0.69 for conversion; FIT 15 ug/g the lowest threshold at which conversion rose significantly ($p=0.02$; OR 1.87, 1.07-3.14); optimal cost- effective range 10-17.6 ug/g; only 1.6% underwent small- bowel capsule endoscopy
34	Beaton et al.,	FIT, age, sex	Cancer and	Overall cancer yield 1.9% (1.8-

	2026	and symptom group at colonoscopy	polyp detection yield	1.9); FIT ≥ 10 : 3.8% (3.7-3.9); FIT < 10 : 0.3% (0.2-0.3); IDA versus rectal bleeding aOR 2.2 (2.0-2.3, $p < 0.01$); with FIT < 10 cancer yield exceeded 1% only in IDA above age 80; a FIT-age-IDA model detected $> 94\%$ of cancers while reducing colonoscopy demand by $> 40\%$
35	Oka et al., 2026	SBCE + EGD + colonoscopy with blinded consensus panel (Saurin P1/P2)	Yield and anatomical location of bleeding-capable lesions	SBCE 85/170 (50.0%, 42.2-57.7); EGD 48 (28.2%, 21.6-35.6); colonoscopy 34 (20.0%, 14.2-26.8); SBCE $>$ EGD $p < 0.001$ and $>$ colonoscopy $p < 0.0001$; P2 alone 10.0% / 6.5% / 9.4%; pan-GI yield 121 (71.1%, 64.4-77.9); management changed in 89 (52.3%, 44.5-60.0)

Overall Diagnostic Yield of Bidirectional Endoscopy

Across eight primary studies reporting the yield of combined oesophagogastroduodenoscopy and colonoscopy in patients presenting with iron deficiency anaemia, the proportion in whom at least one lesion with bleeding potential was identified ranged from 12.0% to 76.2%. The lowest yields were observed in cohorts restricted to premenopausal women, in whom clinically important lesions were identified in 12.0% and in 15.3% of patients respectively, while the highest yields were observed in older, symptomatic and predominantly male referral populations. The two largest prospective series produced concordant estimates of 62.0% and 76.2%, and the most recent

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prospective multicentre trial reported a combined upper and lower gastrointestinal yield of 48.2% when small-bowel findings were excluded from the calculation. This near fivefold variation is not random but is systematically explained by three population determinants: mean age, sex distribution and the presence of localising symptoms.^{13,14,16,17,33}

When the yield estimates are ordered by mean cohort age, a monotonic gradient becomes apparent, with cohorts of mean age below 45 years yielding significant pathology in approximately one in eight patients and cohorts of mean age above 65 years yielding pathology in approximately three in four. The clinical implication is that diagnostic yield should not be treated as a fixed property of the investigation but as a conditional probability determined by the pretest characteristics of the population investigated. A second observation of practical importance is the rarity of synchronous upper and lower gastrointestinal pathology, reported as 1.0%, 0%, and 4.0% in the three studies that examined this explicitly; this finding provides the empirical basis for the widespread but not universally applied practice of terminating investigation once a convincing source has been identified in one compartment, although the 4.0% dual-pathology rate in the largest series argues for caution when the identified lesion is of low bleeding potential.^{13,14,15}

Table 7. Diagnostic yield of bidirectional endoscopy in iron deficiency anaemia

Study	Population	n	Overall yield	Dual-site pathology
Rockey & Cello, 1993	Consecutive adults, mixed sex	100	62/100 (62.0%)	1/100 (1.0%)
Bini et al., 1998	Premenopausal women	186	23/186 (12.0%)	0/186 (0%)
Nahon et al., 2002	Women, mean age 52.3 y	241	119/241 (49.4%)	10/241 (4.0%)
Barto et al., 2006	Premenopausal women 21-50 y	166	18/166 (10.8%)*	Not reported
Milano et al., 2011	Consecutive adults, mean age 68 y	189	144/189 (76.2%)	Not reported

Shandro et al., 2013	IDA referrals, mean age 71 y	467	163/467 (35.0%)	Not reported
Aggarwal et al., 2020	Inpatients ≥ 50 y, mean Hb 6.7 g/dL	83	~55/83 (66.3%)*	Not reported
Oka et al., 2026	IDA referred for bidirectional endoscopy	170	82/170 (48.2%)*	Not reported

* Derived by the reviewers from numerators reported separately for the upper and lower tract; because a small number of patients may harbour lesions in both compartments, these derived figures represent upper bounds. IDA = iron deficiency anaemia.

Upper Gastrointestinal Lesion Yield and Lesion Spectrum

Oesophagogastroduodenoscopy identified a potential source of blood loss in between 10.1% and 36.0% of patients across the primary studies, with the pooled pattern of lesion type showing marked consistency across four decades and three continents. Peptic ulceration was the single most frequent finding in the earlier series, accounting for 19.0% of all patients in the seminal prospective cohort and 17.4% in the largest French series. Erosive oesophagitis accounted for a further 6.2%, and upper gastrointestinal malignancy, principally gastric adenocarcinoma, was identified in between 1.5% and 4.0% of patients. In the contemporary inpatient elderly cohort, the lesion spectrum had shifted appreciably, with erosive and non-erosive gastritis (16%) and Cameron lesions arising within hiatal hernias (12%) surpassing peptic ulceration (10%) in frequency, a shift plausibly attributable to widespread proton pump inhibitor use, *Helicobacter pylori* eradication and the ageing of the referral population.^{13,15,50}

Two findings merit particular emphasis. First, Cameron lesions, which are longitudinal erosions on the mucosal folds of a hiatal hernia at the level of the diaphragmatic pinch, were identified in 12% of elderly inpatients with iron deficiency anaemia and constitute an underrecognised cause of chronic occult loss that is frequently overlooked at endoscopy performed without deliberate retroflexion and careful hernia inspection. Second, in asymptomatic young men, the diagnostic yield of upper endoscopy was dominated not by bleeding lesions but by malabsorptive and infective pathology, with coeliac disease and *Helicobacter pylori* infection each

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accounting for six of sixty recruits and with no malignancy identified. These observations demonstrate that the upper gastrointestinal tract contributes to iron deficiency anaemia through at least three distinct mechanisms, namely frank blood loss, impaired iron absorption and competitive iron sequestration by bacterial pathogens, and that the relative weight of these mechanisms varies systematically with age.^{50,51,6}

Table 8. Upper gastrointestinal lesion spectrum in iron deficiency anaemia

Lesion type	Rockey 1993 (n=100)	Nahon 2002 (n=241)	Aggarwal 2020 (n=83)	Oka 2026 (n=170)
Overall upper GI yield	36 (36.0%)	86 (35.6%)	~38 (45.8%)	48 (28.2%)
Peptic ulcer disease	19 (19.0%)	42 (17.4%)	8 (10%)	Not separately reported
Erosive / non-erosive gastritis	Not reported	Not reported	13 (16%)	Not separately reported
Cameron lesions	Not reported	Not reported	10 (12%)	Not separately reported
Oesophagitis	Not reported	15 (6.2%)	7 (8%)	Not separately reported
Angiodysplasia / AVM	Not reported	Not reported	3 (4%)	Not separately reported
Upper GI malignancy	Not reported	9 (3.7%)	3 (4%)	Not separately reported
Coeliac disease	Not reported	Not reported	Not reported	Not separately reported

Colorectal Lesion Yield and Neoplastic Burden

Colonoscopy identified a lesion with bleeding potential in between 5.2% and 25.0% of patients with iron deficiency anaemia in the primary studies. The proportion accounted for by colorectal carcinoma was consistently high relative to the overall colonic yield, ranging from 1.2%

to 15.0% of all investigated patients, and colorectal carcinoma constituted the single most frequent colonic diagnosis in the majority of series. In the largest national analysis of symptomatic colonoscopy, encompassing 447,109 procedures, the overall cancer yield was 1.9% (95% CI 1.8-1.9), rising to 3.8% (95% CI 3.7-3.9) among those with a faecal haemoglobin concentration at or above 10 micrograms per gram and falling to 0.3% (95% CI 0.2-0.3) below that threshold. Critically, iron deficiency anaemia as a referral indication conferred a higher adjusted odds of cancer than rectal bleeding, with an adjusted odds ratio of 2.2 (95% CI 2.0-2.3, $p < 0.01$), and among patients with a faecal haemoglobin below 10 micrograms per gram the cancer yield exceeded one percent only in those with iron deficiency anaemia aged above 80 years.^{13,21,50}

These data invert a longstanding clinical intuition. Overt rectal bleeding is widely regarded by patients and by referring clinicians as the more alarming symptom, yet within a matched symptomatic population the presence of iron deficiency anaemia more than doubles the odds of malignancy relative to visible bleeding. The explanation is anatomical and pathophysiological: proximal and right-sided colonic tumours bleed chronically and occultly into a stream that is subsequently degraded and mixed, producing iron deficiency without visible blood, whereas distal and rectal lesions bleed visibly at lower total volumes. The corollary is that referral pathways which prioritise visible bleeding over anaemia will systematically delay the diagnosis of the proximal tumours that carry the worse stage distribution and prognosis.^{21,27,47}

Table 9. Colorectal findings in iron deficiency anaemia

Study	n investigated	Colonic lesion yield	Colorectal carcinoma	Adenoma / polyp
Rockey & Cello, 1993	100	25 (25.0%)	11 (11.0%)	Not reported
Bini et al., 1998	186	11 (5.9%)	6 (3.2%)	Not reported
Nahon et al., 2002	241	33 (13.7%)	15 (6.2%)	10 (4.1%)
Barto et al., 2006	153	8 (5.2%)	2 (1.3%)	Included in

				yield
Shandro et al., 2013	~448	-	31 (7.0%)	Not reported
Aggarwal et al., 2020	83	~16 (19.3%)	12 (15.0%)	Not reported
Beaton et al., 2026	447,109	-	1.9% (1.8-1.9)	Graded with f-Hb
Oka et al., 2026	170	34 (20.0%)	Not separately reported	Not separately reported

Small-Bowel Lesion Yield and Anatomical Redistribution

Six primary studies examined the small intestine in patients with iron deficiency anaemia, five by capsule endoscopy and one by comparative capsule endoscopy and computed tomographic enteroclysis. The diagnostic yield of small-bowel capsule endoscopy after negative bidirectional endoscopy ranged from 35.0% in a study restricted to patients undergoing a second capsule examination following a previously normal first capsule, to 72.0% in a large multinational database analysis of patients with persistent or recurrent anaemia. Contemporary series produced estimates of 53.0%, 50.6% and 60.5%. The most common lesion identified was angiodysplasia or arteriovenous malformation, accounting for 22% to 41% of all patients examined, followed by small-bowel erosions and ulceration and by inflammatory lesions.^{18,35,36,38,53}

The single most consequential finding of this review derives from the prospective multicentre trial in which all 170 participants underwent capsule endoscopy, oesophagogastroduodenoscopy and colonoscopy, with lesions adjudicated by a blinded consensus panel using the Saurin classification. Lesions with bleeding potential were identified in the small bowel in 50.0% of patients (95% CI 42.2-57.7), in the upper gastrointestinal tract in 28.2% (95% CI 21.6-35.6) and in the colon in 20.0% (95% CI 14.2-26.8); the small-bowel yield significantly exceeded both the upper gastrointestinal yield ($p<0.001$) and the colonic yield ($p<0.0001$). Pan-enteric assessment identified a potential bleeding lesion in 71.1% of patients (95% CI 64.4-77.9)

and changed management in 52.3% (95% CI 44.5-60.0). When the analysis was restricted to Saurin P2 lesions, that is those judged likely rather than merely possible causes of bleeding, the three compartments converged at 10.0%, 6.5% and 9.4% respectively, indicating that the small-bowel advantage is greater for lesions of intermediate than of high bleeding probability. Nonetheless, the direction and magnitude of the primary finding are unambiguous: within the same patients, the small bowel harbours more bleeding-capable pathology than either compartment interrogated by conventional bidirectional endoscopy.¹⁶

Table 10. Small-bowel diagnostic yield and anatomical comparison

Study	Modality	n	Small-bowel yield	Predominant lesion
Bar-Meir et al., 2004	Second capsule endoscopy	20	7 (35.0%)	Arteriovenous malformation
Bernadino et al., 2004	Video capsule endoscopy	36	19 (53.0%)	Angiodysplasia 8 (22%)
Fireman et al., 2004	Capsule endoscopy	293	213 (72.0%)	Vascular lesions
Milano et al., 2011	VCE vs CT-enteroclysis	45	37 (82.2%) by either	VCE 77.8% vs CTE 22.2% (p<0.001)
Saeed et al., 2011	Capsule endoscopy (IDA arm)	411	208 (50.6%)	Vascular and inflammatory
Nair et al., 2025	Video capsule endoscopy	157	95 (60.5%)	AVM 41%; active bleeding 23%
Oka et al., 2026	SBCE (within pan-enteric protocol)	170	85 (50.0%, 42.2-57.7)	P1/P2 lesions, Saurin classification

Anatomical comparison within the Oka 2026 prospective cohort (same patients, blinded adjudication): small bowel 50.0% > oesophagogastroduodenoscopy 28.2% ($p<0.001$) > colonoscopy 20.0% ($p<0.0001$). Pan-gastrointestinal yield 71.1%; management altered in 52.3%.

Prevalence of Luminal Gastrointestinal Malignancy

The prevalence of luminal gastrointestinal malignancy among patients investigated for iron deficiency anaemia ranged from 0% in a cohort of asymptomatic young military recruits to 12.2% in a prospective Taiwanese cohort of mean age 66.2 years and 19.0% in an elderly inpatient cohort with a mean haemoglobin of 6.7 grams per decilitre. In the population-based Danish cohort of new-onset anaemia detected in general practice, cancer of any type was diagnosed within twelve months in 7.9% of men (95% CI 7.6-8.2) and 5.2% of women (95% CI 4.9-5.5), with the highest incidence in men with combined inflammatory iron deficiency anaemia at 19.3% (95% CI 14.5-24.1). In the United States veteran population, luminal gastrointestinal cancers were diagnosed within one year in 0.98% of all patients with new-onset anaemia, of which 60.5% were colonic; this apparently lower figure reflects a denominator comprising all anaemic patients rather than a selected referral population.^{26,50,51,52,19}

The distribution of malignancy by anatomical site was dominated by colorectal carcinoma in Western populations, comprising 60.5% of luminal cancers in the veteran cohort and 76% of cancers in a United Kingdom service cohort, whereas upper gastrointestinal malignancy accounted for a smaller but non-negligible fraction of between 1.5% and 4.0%. Notably, the standardised incidence ratio analysis from Taiwan demonstrated that the excess cancer risk associated with iron deficiency anaemia is not confined to the gastrointestinal tract: overall cancer standardised incidence ratio was 2.15, and after exclusion of cancers diagnosed within five years of the anaemia diagnosis the ratio remained significantly elevated at 1.30, with persistently raised risks for pancreatic (2.31), renal (2.23), hepatic (1.94) and bladder (1.74) malignancy. This observation suggests that iron deficiency anaemia may function as a marker of systemic neoplastic or inflammatory processes beyond simple luminal blood loss, although occult haematuria and reverse causation cannot be excluded as contributory explanations.^{19,22,32}

Table 11. Prevalence of malignancy in populations with iron deficiency anaemia

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Study	Population	n	Malignancy prevalence	Predominant site
Ho et al., 2005	Chronic IDA, mean age 66.2 y	148	18 (12.2%)	Gastrointestinal tract
Shandro et al., 2013	IDA referrals, mean age 71 y	467	43 (9.2%)	Colon 7.0%; upper GI 1.5%
Hung et al., 2015	Newly diagnosed IDA, nationwide	NHIRD	SIR 2.15 (all cancers)	GI plus pancreas, kidney, liver, bladder
Aggarwal et al., 2020	Elderly inpatients with IDA	83	15 (19.0%)	Colon 15%; gastric 4%
Rausa et al., 2021	Asymptomatic young male recruits	60	0 (0%)	None identified
Boennelykke et al., 2022	New-onset anaemia, general practice	48,925	Men 7.9%; women 5.2% at 12 months	Highest with inflammatory IDA in men (19.3%)
Read et al., 2025	New-onset anaemia, veterans	308,250	3,035 (0.98%) luminal GI cancer at 1 y	Colon 60.5%
Beaton et al., 2026	Symptomatic colonoscopy, national	447,109	1.9% overall; 3.8% if FIT ≥ 10	Colorectal

Magnitude of Association Between Iron Deficiency Anaemia and Gastrointestinal Cancer

Five primary studies quantified the association between iron deficiency anaemia and gastrointestinal malignancy using formal effect estimates, and the results are notable both for their magnitude and for their consistency across health systems, age strata and analytical approaches. In the largest analysis, comprising 308,250 veterans with new-onset anaemia and a ferritin measurement within one year, the odds of a luminal gastrointestinal cancer diagnosis within twelve months were 4.47-fold higher in those with iron deficiency anaemia than in those without (95% CI 4.14-4.82). Stratification revealed a marked interaction with age and sex: among women, those aged fifty years and above carried a 6.62-fold higher odds than younger women (95% CI 3.54-12.36), and among those below fifty years men carried a 9.74-fold higher odds than women (95% CI 5.45-17.40). These gradients were robust to sensitivity analysis in which the ferritin threshold was lowered from 45 to 10 nanograms per millilitre.¹⁹

The most striking effect estimate derives from the matched veteran cohort examining young-onset colorectal cancer in adults aged 18 to 49 years. The five-year cumulative incidence of colorectal cancer was 0.45% among individuals with iron deficiency anaemia and 0.05% among matched individuals without, corresponding to a risk difference of 0.39% (95% CI 0.33-0.46) and a hazard ratio of 10.81 (95% CI 8.15-14.33). The risk difference was tenfold greater in men (0.78%, 95% CI 0.64-0.92) than in women (0.08%, 95% CI 0.03-0.13) and increased monotonically with age band from 0.14% below thirty years to 0.53% at forty to forty-nine years. Importantly, the hazard ratio associated with iron deficiency anaemia (10.81) was statistically indistinguishable from that associated with overt haematochezia (10.66, 95% CI 8.76-12.97) within the same population, establishing occult anaemia and visible bleeding as equivalent alarm features in the young adult.²⁰

Complementary evidence from primary care case-control analysis quantified the relationship in terms of likelihood ratios, which have the advantage of direct applicability to individual patient probability revision. A haemoglobin below 9 grams per decilitre generated a likelihood ratio for colorectal cancer of 27 (95% CI 19-36) in men and 41 (95% CI 30-61) in women, and positive predictive values rose monotonically with age and with each one gram per decilitre reduction in haemoglobin. For men above sixty years with a haemoglobin below 11 grams per decilitre and features of iron deficiency, the positive predictive value reached 13.3% (95% CI 9.7-18), a figure

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that comfortably exceeds the three percent threshold at which urgent investigation is mandated in most national pathways. The corresponding figure for women with a haemoglobin below 10 grams per decilitre and iron deficiency was 7.7% (95% CI 5.7-11).²⁷

Table 12. Effect estimates linking iron deficiency anaemia to gastrointestinal malignancy

Study	Comparison	Effect measure	Estimate (95% CI)	p
Read et al., 2025	IDA versus no IDA, luminal GI cancer at 1 y	Odds ratio	4.47 (4.14- 4.82)	<0.001
Read et al., 2025	Women ≥ 50 y versus <50 y with IDA	Odds ratio	6.62 (3.54- 12.36)	<0.001
Read et al., 2025	Men versus women aged <50 y with IDA	Odds ratio	9.74 (5.45- 17.40)	<0.001
Read et al., 2025	Men versus women aged ≥ 50 y with IDA	Odds ratio	2.24 (1.64- 3.05)	<0.001
Demb et al., 2020	IDA versus no IDA, young- onset CRC	Hazard ratio	10.81 (8.15- 14.33)	<0.001
Demb et al., 2020	Haematochezia versus none, young-onset CRC	Hazard ratio	10.66 (8.76- 12.97)	<0.001
Beaton et al., 2026	IDA versus rectal bleeding, cancer at colonoscopy	Adjusted odds ratio	2.2 (2.0-2.3)	<0.01
Hamilton et al., 2008	Men, Hb <9 g/dL	Likelihood ratio	27 (19-36)	-
Hamilton et al., 2008	Women, Hb <9 g/dL	Likelihood ratio	41 (30-61)	-
Hamilton et al., 2008	Men >60 y, Hb <11 g/dL with iron deficiency	Positive predictive value	13.3% (9.7- 18)	-
Hung et al.,	IDA versus general	Standardised	2.15	<0.05

2015	population, all cancers	incidence ratio		
Hung et al., 2015	IDA, excluding first 5 years of follow-up	Standardised incidence ratio	1.30	<0.05
Thompson et al., 2017	IDA within clinical assessment model	Odds ratio	4.42-8.38	<0.001
Ho et al., 2005	Ferritin ≤ 10 ug/L plus LDH > 250 U/L	Odds ratio	74.33 (7.115-776.479)	<0.001

Diagnostic Accuracy of Faecal Occult Blood and Faecal Immunochemical Testing

The performance of faecal blood testing within the iron deficiency anaemia pathway must be assessed separately for two distinct clinical questions: the detection of any lesion responsible for the anaemia, and the detection of colorectal carcinoma specifically. For the first question, the evidence is uniformly discouraging. In the earliest prospective evaluation, a positive faecal occult blood test in combination with lower gastrointestinal symptoms achieved a positive predictive value of 86% for a colonic lesion, but the sensitivity of the test taken alone was inadequate to permit exclusion of pathology. In a prospective Taiwanese cohort, neither clinical symptoms nor the presence of faecal occult blood predicted malignancy or the presence of any gastrointestinal lesion. Pooled secondary evidence, which is reported here for triangulation and which does not enter the primary tabulation, estimated the sensitivity of faecal occult blood testing for presumptive causes of iron deficiency anaemia at endoscopy at 0.58 (95% CI 0.53-0.63) with a specificity of 0.84 (95% CI 0.75-0.89), such that 42% of patients with an identifiable cause had a false-negative test.^{13,26,41}

For the second question, the performance of quantitative faecal immunochemical testing is substantially better but remains threshold-dependent and is materially modified by anaemia status. In a Swedish population-based cohort of 15,789 primary care patients, qualitative faecal immunochemical test sensitivity for colorectal cancer ranged from 81.6% to 100% across four commercial brands with specificities of 65.7% to 79.5%; when either a positive test or the presence of anaemia was counted as a positive result, sensitivity rose to between 88.9% and 100%. In a Nottingham cohort of 33,694 index tests, a threshold of 10 micrograms of haemoglobin per gram of

faeces conferred a colorectal cancer risk exceeding three percent in all age groups except those below forty years, whereas non-anaemic patients with a faecal haemoglobin below 100 micrograms per gram carried a risk below three percent except in the seventy to eighty-five year band. The Scottish analysis of 34,647 paired faecal haemoglobin and full blood count results demonstrated that the addition of iron deficiency anaemia status to faecal haemoglobin and age produced substantially superior risk discrimination, identifying a stratum with a one-year colorectal cancer risk of 30% (95% CI 19.4-41.0).^{23,24,25}

Table 13. Diagnostic accuracy of faecal blood testing in anaemic and symptomatic populations

Study	Test and threshold	Sensitivity	Specificity	PPV	NPV
Hogberg et al., 2020	Qualitative FIT (4 brands), CRC	81.6-100%	65.7-79.5%	4.7-8.1%	99.5-100%
Hogberg et al., 2020	FIT positive OR anaemia present	88.9-100%	Not reported	Not reported	Not reported
Crooks et al., 2023	Quantitative FIT ≥ 10 ug Hb/g	Not reported	Not reported	>3% risk except age <40	Not reported
Digby et al., 2025	f-Hb >99 ug Hb/g + age >55 + IDA	Not reported	Not reported	30% (19.4-41.0)	Not reported
Digby et al., 2025	f-Hb 10-19 ug Hb/g, no IDA, age <85	Not reported	Not reported	1.3%	>97%
Lei et al., 2025	FIT for CRC in iron deficiency pathway	AUC 0.78	-	-	-
Ayling et al., 2019	FIT in anaemia clinic population	Not reported	Not reported	CRC 3.5% overall	High NPV reported
Beaton et al.,	FIT ≥ 10 versus <10	Cancer	-	3.8% (3.7-	99.7%

2026	at colonoscopy	yield 3.8% vs 0.3%		3.9)	
Rockey & Cello, 1993	gFOBT plus lower GI symptoms	Not reported	Not reported	86%	Not reported
Ho et al., 2005	FOBT for malignancy in IDA	Non- predictive	Non- predictive	-	-

Secondary (non-tabulated) synthesis for triangulation: pooled sensitivity of faecal occult blood testing for presumptive causes of IDA at endoscopy 0.58 (0.53-0.63) with specificity 0.84 (0.75-0.89); sensitivity higher for colorectal cancer (0.83) than for non-cancer lesions (0.54).

Coeliac Disease as a Cause of Iron Deficiency Anaemia

Three primary studies within this review reported the prevalence of coeliac disease among patients investigated for iron deficiency anaemia. In a United Kingdom re-audit of 732 patients referred for oesophagogastroduodenoscopy, duodenal biopsy was performed in 610 (83.3%) and coeliac disease was confirmed histologically in 17 (2.8%); of the 122 patients (16.7%) who underwent serological screening prior to endoscopy, 7 (5.7%) were positive. In a nurse-led virtual iron deficiency anaemia service investigating 467 patients, coeliac disease was diagnosed in 3%. In a cohort of 60 asymptomatic young male military recruits with iron deficiency anaemia, coeliac disease was the joint most frequent diagnosis, identified in six recruits following histological evaluation, with three of thirty-four tested demonstrating positive tissue transglutaminase serology. Pooled secondary evidence, reported here for triangulation, estimated the weighted prevalence of biopsy-confirmed coeliac disease in iron deficiency anaemia at 3.2% (95% CI 2.6-3.9), rising to 5.5% (95% CI 4.1-6.9) when analysis was restricted to the eight studies meeting all quality criteria.^{28,32,51,40}

These figures establish that approximately one in every twenty to thirty patients presenting with iron deficiency anaemia has coeliac disease, a prevalence that comfortably justifies the universal screening recommended by the British Society of Gastroenterology. The mechanism is predominantly malabsorptive rather than haemorrhagic, since iron absorption occurs principally in the proximal duodenum, precisely the region destroyed by gluten-induced villous atrophy. Two

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clinically important corollaries emerge from the wider literature. First, iron deficiency anaemia may persist in coeliac patients despite strict adherence to a gluten-free diet and despite histological remission, a phenomenon attributed to persistent ultrastructural and molecular alterations in enterocytes, and such patients frequently require parenteral iron. Second, coeliac disease and gastrointestinal blood loss are not mutually exclusive, and the identification of coeliac disease should not be permitted to terminate investigation in patients above fifty years of age, in those with marked anaemia, or in those with a significant family history of colorectal carcinoma.^{2,58,59}

Table 14. Prevalence of coeliac disease in iron deficiency anaemia

Study	Population	n	Ascertainment	Prevalence
Evans et al., 2012	IDA referred for OGD, UK	732	Duodenal biopsy in 610 (83.3%)	17/610 (2.8%)
Evans et al., 2012	Subgroup with pre-OGD serology	122	Coeliac serology	7/122 (5.7%) positive
Shandro et al., 2013	IDA virtual clinic, UK	467	Serology 2%, biopsy 57%, both 39%	14/467 (3.0%)
Rausa et al., 2021	Asymptomatic young male recruits, USA	60	tTG-IgA in 34; histology	6/60 (10.0%)
Secondary synthesis (not tabulated as primary)	18 studies, 2,998 patients with IDA	2,998	Biopsy-verified	3.2% (2.6-3.9); 5.5% in high-quality subset

Helicobacter pylori Infection and Iron Status

Two randomised controlled trials, the only randomised evidence within this review, examined whether *Helicobacter pylori* eradication improves iron status. In a household-randomised

open-label trial among 219 Alaskan children aged 7 to 11 years with both iron deficiency and *Helicobacter pylori* infection, all of whom received iron supplementation, the addition of eradication therapy produced no benefit at fourteen months: iron deficiency persisted in 65% of the intervention group and 72% of the control group (adjusted relative risk 0.90, 95% CI 0.74-1.1), and anaemia was numerically more frequent in the intervention arm (22% versus 14%, adjusted relative risk 1.6, 95% CI 0.86-2.9). At the forty-month follow-up of the same cohort, however, a divergence emerged: iron deficiency with anaemia was present in 5% of the intervention group compared with 19% of controls (adjusted relative risk 0.25, 95% CI 0.09-0.73), although isolated iron deficiency remained unchanged (adjusted relative risk 0.92, 95% CI 0.68-1.26). Reinfection occurred in 52% of children who had cleared their infection.^{37,57}

The second randomised trial, conducted among 200 *Helicobacter pylori*-infected Bangladeshi children aged 2 to 5 years with iron deficiency or iron deficiency anaemia and randomised to four regimens with 60 uninfected children as negative controls, reached a contrary conclusion. Treatment failure in correcting iron deficiency anaemia occurred in 11% of those receiving eradication plus iron, 0% of those receiving iron alone, 33% of those receiving eradication alone and 45% of those receiving placebo, and the investigators concluded that *Helicobacter pylori* is neither a cause of iron deficiency anaemia nor a reason for failure of iron supplementation in this population. The apparent contradiction between the two trials is reconcilable by attention to timescale and to background prevalence: benefit in the Alaskan cohort emerged only after more than fourteen months, consistent with a mechanism requiring the reversal of established gastric mucosal damage, whereas the Bangladeshi trial assessed outcomes at ninety days in a population with very high reinfection pressure and profound dietary iron insufficiency. The pragmatic synthesis, consistent with paediatric guideline positions, is that a test-and-treat strategy should be considered specifically in patients whose iron deficiency anaemia is recurrent or refractory to supplementation and in whom other causes have been excluded.^{29,6}

Table 15. Randomised evidence on *Helicobacter pylori* eradication and iron status

Trial	Design and n	Arms	Outcome and	Result
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			timepoint	
Gessner et al., 2006	Household-randomised open-label RCT, n=219	Eradication + iron versus iron alone	Iron deficiency at 14 months	65% versus 72%; ARR 0.90 (0.74-1.1)
Gessner et al., 2006	Same cohort	As above	Anaemia at 14 months	22% versus 14%; ARR 1.6 (0.86-2.9)
Fagan et al., 2009	40-month extension, n=176 evaluated	As above	Iron deficiency with anaemia at 40 months	5% versus 19%; ARR 0.25 (0.09-0.73)
Fagan et al., 2009	Same cohort	As above	Iron deficiency alone at 40 months	52% versus 58%; ARR 0.92 (0.68-1.26)
Sarker et al., 2008	Four-arm RCT, n=200 + 60 controls	Anti-Hp+iron / iron / anti-Hp / placebo	Failure to correct IDA at 90 days	11% / 0% / 33% / 45% (p<0.0001)
Sarker et al., 2008	Same trial	As above	Failure to correct iron deficiency	19% / 7% / 65% / 78% (p<0.0001)

Independent Predictors of a Clinically Significant Lesion

Five primary studies performed multivariable analyses to identify independent predictors of significant gastrointestinal pathology in patients with iron deficiency anaemia, and their findings

converge upon a coherent set of four variables: age, sex, the depth of anaemia and the presence of localising symptoms, with a fifth biochemical dimension supplied by the severity of iron depletion and by markers of tissue turnover. In the largest multivariable analysis of women with iron deficiency anaemia, three factors emerged as independent predictors of an endoscopically identified lesion: abdominal symptoms (odds ratio 8.3, 95% CI 3.9-17.2), age above fifty years (odds ratio 4.4, 95% CI 2.1-9.2) and haemoglobin below 9 grams per decilitre (odds ratio 3.0, 95% CI 1.5-6.1). The composite positive predictive value of these three predictors was 87% and the negative predictive value was 93.5%; among the thirty-one women (13%) possessing none of the three, only two lesions were identified, both of trivial clinical significance.¹⁵

A prospective Taiwanese cohort identified a different but complementary predictor set for malignancy specifically, comprising a serum ferritin at or below 10 micrograms per litre (odds ratio 7.614, $p=0.003$), a lactate dehydrogenase above 250 units per litre (odds ratio 8.955, $p=0.002$) and increasing age (odds ratio 1.062 per year, $p=0.027$). The combination of profound iron depletion with elevated lactate dehydrogenase produced the single largest effect estimate identified anywhere in this review, with a 74.33-fold increase in malignancy risk (95% CI 7.115-776.479), although the extreme width of the confidence interval reflects the small number of patients possessing both features and mandates cautious interpretation. Consistent with the general pattern, neither clinical symptoms nor faecal occult blood positivity predicted malignancy in that cohort, reinforcing the conclusion that symptom-based triage performs poorly once anaemia is established.²⁶

A striking negative finding is supplied by the veteran cohort comparing iron deficiency anaemia, mixed anaemia and anaemia of chronic disease. Contrary to the investigators' hypothesis, endoscopic diagnostic yield did not differ significantly between the three anaemia phenotypes, and indeed oesophagogastroduodenoscopy yield was marginally higher in mixed anaemia than in classical iron deficiency anaemia (38% versus 23%, $p=0.044$). Neither transfusion requirement nor anticoagulant or antiplatelet use increased yield within any phenotype, and only severe anaemia at or below 7 grams per decilitre modestly increased upper gastrointestinal yield, and then only within the iron deficiency anaemia group. This result cautions against the use of iron indices as a

categorical gatekeeper for endoscopic referral and supports investigation of anaemic patients whose iron studies are equivocal or confounded by concurrent inflammation.⁴⁸

Table 16. Independent predictors of significant gastrointestinal pathology

Predictor	Source study	Outcome predicted	Effect estimate (95% CI)	p
Abdominal symptoms	Nahon et al., 2002	Any GI lesion	OR 8.3 (3.9-17.2)	<0.001
Age >50 years	Nahon et al., 2002	Any GI lesion	OR 4.4 (2.1-9.2)	<0.001
Haemoglobin <9 g/dL	Nahon et al., 2002	Any GI lesion	OR 3.0 (1.5-6.1)	<0.01
Composite of the three above	Nahon et al., 2002	Any GI lesion	PPV 87%; NPV 93.5%	-
Ferritin ≤10 ug/L	Ho et al., 2005	Malignancy	OR 7.614	0.003
LDH >250 U/L	Ho et al., 2005	Malignancy	OR 8.955	0.002
Increasing age (per year)	Ho et al., 2005	Malignancy	OR 1.062	0.027
Ferritin ≤10 plus LDH >250	Ho et al., 2005	Malignancy	OR 74.33 (7.115-776.479)	<0.001
Positive FOBT, Hb <10 g/dL, abdominal symptoms	Bini et al., 1998	GI lesion in premenopausal women	Independent predictors	<0.05
Lower haemoglobin	Barto et al., 2006	Upper GI lesion	8.7 vs 10.1 g/dL	0.002
Lower haemoglobin	Barto et al., 2006	Colonic lesion	8.6 vs 10.3 g/dL	<0.001
Lower haemoglobin	Saeed et al.,	Positive capsule	8.3 vs 9.0 g/dL	<0.001

	2011	endoscopy		
Prior transfusion requirement	Saeed et al., 2011	Positive capsule endoscopy	58.2% vs 42.2%	<0.001
Older age	Saeed et al., 2011	Positive capsule endoscopy	66.2 vs 64.0 years	0.034
IDA within clinical model	Thompson et al., 2017	Bowel cancer	OR 4.42-8.38	<0.001
Severe anaemia (Hb ≤ 7 g/dL)	Dinh et al., 2018	EGD yield in IDA only	Modest increase	<0.05

Antithrombotic and Non-Steroidal Anti-Inflammatory Drug Exposure

Pharmacological exposure represents a modifiable determinant of occult gastrointestinal blood loss and is highly prevalent in the elderly populations in whom iron deficiency anaemia is most often investigated. In a Spanish case-control study of 978 patients hospitalised with endoscopically confirmed gastrointestinal bleeding and 1,008 matched controls, anticoagulant exposure carried the strongest association with bleeding (relative risk 4.2, 95% CI 2.9-6.2), approximately twice the magnitude observed for low-dose aspirin (relative risk 2.1, 95% CI 1.4-3.3) or for non-aspirin antiplatelet agents (relative risk 2.0, 95% CI 1.6-2.6). Non-steroidal anti-inflammatory drug exposure was associated with a greater relative risk of upper (2.6, 95% CI 2.0-3.5) than of lower gastrointestinal bleeding (1.4, 95% CI 1.0-1.9), and proton pump inhibitor use attenuated upper but not lower gastrointestinal bleeding, an asymmetry of considerable practical significance given the widespread assumption that acid suppression provides global gastrointestinal protection.³⁰

The contemporary capsule endoscopy series confirms the clinical footprint of this exposure: among 157 patients with iron deficiency anaemia and negative bidirectional endoscopy, 55% were taking non-steroidal anti-inflammatory drugs, 52% were on antithrombotic agents and 76% were on proton pump inhibitors, and 81% had received prior blood transfusion with a mean of 6.7 units. Pooled secondary evidence, reported for triangulation, demonstrates that antithrombotic exposure

approximately doubles the odds of a positive small-bowel capsule finding in obscure gastrointestinal bleeding (odds ratio 1.98, 95% CI 1.34-2.93), with comparable effects for antiplatelet (2.22, 95% CI 1.28-3.84) and anticoagulant agents (2.53, 95% CI 1.66-3.87), and increases the odds of rebleeding (2.53, 95% CI 1.46-4.37). A critical clinical caution emerges from these data: the attribution of iron deficiency anaemia to antithrombotic therapy is a diagnosis of exclusion and must never substitute for structural investigation, since anticoagulation appears to unmask rather than to create luminal pathology.^{53,43}

Table 17. Drug exposure and gastrointestinal bleeding risk

Exposure	Source	Outcome	Estimate (95% CI)
Anticoagulants	Lanas et al., 2015	Upper and lower GI bleeding	RR 4.2 (2.9-6.2)
Low-dose aspirin	Lanas et al., 2015	Upper and lower GI bleeding	RR 2.1 (1.4-3.3)
Non-aspirin antiplatelet agents	Lanas et al., 2015	Upper and lower GI bleeding	RR 2.0 (1.6-2.6)
NSAIDs	Lanas et al., 2015	Upper GI bleeding	RR 2.6 (2.0-3.5)
NSAIDs	Lanas et al., 2015	Lower GI bleeding	RR 1.4 (1.0-1.9)
Antiplatelet co-therapy at supratherapeutic INR	Peloquin et al., 2016	Identification of bleeding source	OR 2.59 (1.13-5.94)
EGD within 12 hours of presentation	Peloquin et al., 2016	Identification of bleeding source	OR 3.71 (1.05-13.08)
Rising INR level	Peloquin et al., 2016	Identification of bleeding source	OR 0.79 (0.64-0.98)
NSAID use in IDA with	Nair et al., 2025	Prevalence in cohort	55%

negative bidirectional endoscopy			
Antithrombotic use in the same cohort	Nair et al., 2025	Prevalence in cohort	52%
Antithrombotic therapy (secondary synthesis)	Tziatzios et al., 2018	Positive capsule finding in OGIB	OR 1.98 (1.34-2.93)
Antithrombotic therapy (secondary synthesis)	Tziatzios et al., 2018	Rebleeding	OR 2.53 (1.46-4.37)

Diagnostic Yield in Premenopausal Women and Young Adults

The management of iron deficiency anaemia in premenopausal women and in young adults constitutes the most contested area within this evidence base, because menstrual blood loss provides a plausible and usually correct explanation that nonetheless conceals a minority with structural pathology. Three primary studies addressed premenopausal women directly. In 186 premenopausal women referred for endoscopy, a clinically important lesion was identified in 23 (12%), comprising gastric cancer in 3%, peptic ulcer disease in 3% and colon cancer in 3.2%. In 166 premenopausal women aged 21 to 50 years, upper gastrointestinal lesions were found in 10.1% and colonic lesions in 5.2%, with neoplasia in 1.8% including one oesophageal and two colonic carcinomas; patients with lesions had significantly lower haemoglobin concentrations in both compartments, but older age within this restricted band was not associated with lesion presence. In 241 women of mixed menopausal status, the composite of no abdominal symptoms, age below fifty and haemoglobin above 9 grams per decilitre identified a subgroup of 31 women (13%) in whom only two trivial lesions were found.^{14,33,15}

Registry evidence provides the necessary population-level counterpoint. Among veterans aged 18 to 49 years, iron deficiency anaemia was associated with a five-year young-onset colorectal cancer cumulative incidence of 0.45% versus 0.05% without, and although the absolute risk difference in women was small at 0.08% (95% CI 0.03-0.13) it was tenfold lower than in men (0.78%, 95% CI 0.64-0.92). Analysis of 308,250 veterans confirmed that women below fifty years

with new-onset iron deficiency anaemia were substantially less likely to develop gastrointestinal cancer than comparably aged men (odds ratio for men 9.74, 95% CI 5.45-17.40) or than older women (odds ratio 6.62, 95% CI 3.54-12.36). Taken together, the evidence supports a risk-stratified rather than a categorical approach: universal endoscopy in premenopausal women is not justified by the absolute risk, but selective investigation guided by symptoms, haemoglobin depth, response to iron therapy and family history is both justified and, on the evidence of the 12% yield in referred cohorts, productive.^{20,19}

Table 18. Yield and risk in premenopausal women and young adults

Study	Population	n	Key result
Bini et al., 1998	Premenopausal women with IDA	186	Clinically important lesion 12%; gastric cancer 3%; colon cancer 3.2%; no dual pathology
Barto et al., 2006	Premenopausal women 21-50 y	166	Upper lesion 10.1%; colonic lesion 5.2%; neoplasia 1.8%; lower Hb predicted lesions
Nahon et al., 2002	Women with IDA, mixed status	241	Absence of all three predictors identified 13% with negligible yield (2 trivial lesions)
Demb et al., 2020	Veterans 18-49 y with IDA	239,000 matched	Five-year YCRC risk difference: men 0.78% (0.64-0.92); women 0.08% (0.03-0.13)
Read et al., 2025	Veterans <50 y with IDA	33,711 aged <50	Men versus women OR of GI cancer 9.74 (5.45-17.40)
Rausa et al., 2021	Asymptomatic young men with IDA	60	No malignancy; coeliac disease 6, H. pylori 6, gastritis 17, IBD 2
Beaton et al.,	Symptomatic	447,109	Cancer yield 2.5% (2.3-2.7) if FIT

2026	colonoscopy aged 40-49	total	≥ 10 ; 0.6% (0.5-0.7) at age 16-39
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Iron Deficiency Without Anaemia

Iron deficiency in the absence of frank anaemia occupies an ambiguous position in clinical pathways, since it represents the same negative iron balance at an earlier stage yet lacks the haematological alarm feature that triggers investigation. Within the primary studies of this review, the multicentre United Kingdom analysis of 1,531 two-week-wait referrals encompassed patients referred for iron deficiency with or without anaemia and demonstrated that faecal haemoglobin discriminated colorectal cancer with an area under the receiver operating characteristic curve of 0.78, with the optimal cost-effective threshold lying between 10 and 17.6 micrograms of haemoglobin per gram of faeces. Notably, only 1.6% of this large referral cohort underwent small-bowel capsule endoscopy, an indication of the extent to which small-bowel evaluation remains underutilised even in well-resourced pathways.⁵⁴

Pooled secondary evidence, reported here for triangulation and excluded from the primary tabulation in accordance with the protocol, estimated the overall prevalence of gastrointestinal malignancy in iron deficiency without anaemia at 0.38% (95% CI 0.00-1.84), a figure substantially lower than that observed in frank iron deficiency anaemia. However, the pooled estimate conceals clinically decisive subgroup heterogeneity: prevalence reached 2.58% (95% CI 0.00-8.77) in older patients, 2.45% (95% CI 0.16-6.39) in non-screening populations and 0.90% (95% CI 0.11-3.23) in men and postmenopausal women, while remaining at 0.00% in younger patients (95% CI 0.00-0.21), in screened populations (95% CI 0.00-1.10) and in premenopausal women (95% CI 0.00-1.05). The practical inference is that iron deficiency without anaemia should not automatically trigger the full investigative pathway, but that in older non-screened individuals the malignancy prevalence approaches the three percent threshold conventionally used to justify urgent investigation, and shared decision-making regarding endoscopy is therefore appropriate.^{42,2}

Table 19. Gastrointestinal malignancy in iron deficiency without anaemia

Subgroup	Pooled prevalence	Interpretation
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	(95% CI)	
Overall (5 studies, 3,329 participants)	0.38% (0.00-1.84)	Substantially lower than in frank IDA
Older patients	2.58% (0.00-8.77)	Approaches conventional investigation threshold
Non-screening populations	2.45% (0.16-6.39)	Investigation warranted
Men and postmenopausal women	0.90% (0.11-3.23)	Individualised decision
Younger patients	0.00% (0.00-0.21)	Investigation rarely productive
Screened populations	0.24% (0.00-1.10)	Investigation rarely productive
Premenopausal women	0.00% (0.00-1.05)	Investigation rarely productive

Derived from secondary synthesis and reported for triangulation only; these estimates do not enter the primary study characteristics or risk of bias tabulation, in accordance with the prespecified protocol.

Impact on Management, Diagnostic Interval and Survival

Diagnostic yield is of clinical value only insofar as it alters management or outcome, and four primary studies addressed this question directly. In the prospective pan-enteric trial, identification of a bleeding-capable lesion changed clinical management in 89 of 170 patients (52.3%, 95% CI 44.5-60.0), establishing that the majority of positive findings are actionable rather than incidental. In the contemporary capsule endoscopy case-control series, a positive examination was associated with markedly different downstream management, with follow-up endoscopy performed in 54% of positive versus 11% of negative cases ($p<0.001$) and observation-only management in 15% versus 56% ($p<0.001$); positive cases also trended towards greater transfusion requirement (6.7 versus 3.6 units, $p=0.06$). In the second-look capsule study, management changed in 10% of patients following a repeat examination even after a previously normal capsule.^{16,53,35}

The survival evidence is the most consequential finding in this domain. In a nationwide Taiwanese analysis of 17,172 patients with colon cancer aged fifty-five years and above, the

presence of pre-existing iron deficiency anaemia was associated with a shorter median overall survival (4.6 versus 5.7 years, $p=0.002$). Within the anaemic group, the interval to colonoscopy exerted an independent effect on survival: median overall survival was 5.79 years when colonoscopy was performed within thirty days of the anaemia diagnosis, 4.43 years at thirty-one to ninety days and 4.04 years at ninety-one days or later ($p=0.003$), and delayed colonoscopy remained an independent predictor of poor overall survival after adjustment (hazard ratio 1.28, 95% CI 1.07-1.53, $p=0.01$). This corresponds to a loss of approximately 1.75 years of median survival attributable to a diagnostic delay of three months or more, and it converts the diagnostic interval from an administrative metric into a clinical determinant of outcome.³¹

Complementary system-level evidence demonstrates that risk-stratified triage can improve efficiency without compromising detection. A model combining faecal haemoglobin, age and iron deficiency anaemia status detected more than 94% of colorectal cancers while reducing colonoscopy demand by more than 40%, and a machine-learning algorithm applied to an anaemia clinic population would have prioritised 304 rather than 592 patients for urgent referral with one cancer missed, and in the subgroup aged below fifty-five years would have prioritised 15 rather than 109 patients with no cancers missed. These findings indicate that the tension between capacity constraint and diagnostic completeness is at least partially resolvable through quantitative risk stratification rather than through the blunt instrument of raised referral thresholds.^{21,49}

Table 20. Management impact, diagnostic interval and survival

Study	Metric	Result	p
Oka et al., 2026	Management changed by pan-enteric findings	89/170 (52.3%, 44.5-60.0)	-
Nair et al., 2025	Follow-up endoscopy, positive vs negative capsule	54% vs 11%	<0.001
Nair et al., 2025	Observation-only management	15% vs 56%	<0.001
Nair et al., 2025	Mean transfusion requirement (units)	6.7 vs 3.6	0.06

Bar-Meir et al., 2004	Therapy changed after second capsule	2/20 (10%)	-
Teng et al., 2014	Median OS, IDA vs no IDA (colon cancer)	4.6 vs 5.7 years	0.002
Teng et al., 2014	Median OS by colonoscopy interval (≤ 30 / 31-90 / ≥ 91 d)	5.79 / 4.43 / 4.04 years	0.003
Teng et al., 2014	Delayed colonoscopy, adjusted hazard of death	HR 1.28 (1.07-1.53)	0.01
Beaton et al., 2026	FIT + age + IDA triage model	>94% cancers detected; >40% fewer colonoscopies	-
Ayling et al., 2019	Algorithmic prioritisation, whole cohort	304 versus 592 referred; 1 cancer missed	-
Ayling et al., 2019	Algorithmic prioritisation, age <55 years	15 versus 109 referred; no cancers missed	-
Milano et al., 2011	Cumulative diagnostic rate of full pathway	95.7%	-

Sensitivity Analysis

A sensitivity analysis was conducted in which the six studies judged at serious risk of bias were excluded and the qualitative conclusions for each outcome domain re-examined. Exclusion of these studies, comprising the small capsule endoscopy series, the mixed-anaemia veteran cohort, the inpatient elderly cohort and the military recruit cohort, did not alter the direction of any conclusion. The range of small-bowel diagnostic yield narrowed from 35.0-72.0% to 50.0-60.5%, which strengthens rather than weakens the inference that small-bowel pathology is common. The estimate of upper gastrointestinal lesion spectrum lost the Cameron lesion and gastritis data, which are derived exclusively from the excluded elderly inpatient series; this observation is therefore reported with correspondingly lower confidence. All effect estimates in the malignancy association domain

derive from studies judged at low or moderate risk of bias and were unaffected. The conclusions of this review are therefore robust to the exclusion of the weakest evidence.^{9,10,11,12}

DISCUSSION

Principal Findings

This systematic review of thirty-five primary studies encompassing approximately 1.89 million participants establishes six principal findings. First, iron deficiency anaemia is a high-yield indication for structural luminal investigation, with bidirectional endoscopy identifying a lesion with bleeding potential in between 12% and 76% of patients, the variation being explained systematically by age, sex and symptom profile rather than by chance. Second, the association between iron deficiency anaemia and luminal gastrointestinal malignancy is strong, consistent and internally graded, with odds ratios of approximately 4.5 in unselected anaemic populations, hazard ratios exceeding 10 in young adults, likelihood ratios of 27 to 41 at haemoglobin concentrations below 9 grams per decilitre, and standardised incidence ratios that remain elevated five years after the index anaemia diagnosis. Third, and contrary to the anatomical assumption embedded in most guidelines, the small intestine harbours more bleeding-capable lesions than either the upper gastrointestinal tract or the colon when all three compartments are examined in the same patients under blinded adjudication.^{13,16,19,20,22,27}

Fourth, faecal blood testing performs poorly as a rule-out instrument for the cause of established iron deficiency anaemia, with a pooled sensitivity of 0.58 in secondary synthesis, yet quantitative faecal haemoglobin retains substantial value for risk stratification when combined with age and anaemia status, enabling discrimination between strata with one-year colorectal cancer risks of 1.3% and 30%. Fifth, iron deficiency anaemia as a referral indication confers a higher adjusted odds of colorectal cancer than overt rectal bleeding, inverting a widespread clinical intuition. Sixth, the diagnostic interval is itself a determinant of survival, with delay of colonoscopy beyond ninety days after the recognition of iron deficiency anaemia independently associated with a 28% relative increase in the hazard of death among patients subsequently found to have colon cancer.^{21,25,31,41}

Interpretation of Diagnostic Yield Heterogeneity

The near sixfold variation in reported diagnostic yield across studies is at first sight disconcerting but resolves into an orderly pattern once population determinants are accounted for. Studies restricted to premenopausal women report yields of 10.8% to 12%, studies of mixed-sex referral populations of intermediate age report 35% to 62%, and studies of elderly, symptomatic or inpatient populations report 66% to 76%. Superimposed on this age gradient is a definitional heterogeneity that is less easily quantified: the threshold at which a finding is designated a probable source of blood loss varies appreciably between investigators, and the introduction of the Saurin classification in the most recent prospective trial represents an important methodological advance precisely because it separates lesions that are possible causes (P1) from those that are likely causes (P2). When this separation is applied, the apparent superiority of the small bowel narrows considerably, from 50.0% versus 28.2% and 20.0% for all bleeding-capable lesions to 10.0% versus 6.5% and 9.4% for high-probability lesions alone.^{13,14,16,17}

This observation should temper, but does not overturn, the anatomical conclusion. Even confining attention to P2 lesions, the small bowel yields more high-probability sources than the upper gastrointestinal tract, and the pan-enteric strategy identified an actionable finding in 71.1% of patients and altered management in 52.3%. The clinical question is therefore not whether small-bowel evaluation is worthwhile but at what point in the diagnostic sequence it should occur and in whom. The evidence assembled here supports earlier deployment than current pathways permit, particularly in patients with transfusion-dependent, recurrent or refractory anaemia, in whom the pretest probability of small-bowel angioectasia is elevated by age, antithrombotic exposure and aortic valve disease.^{16,53,3}

Mechanistic Considerations

Three mechanisms link iron deficiency anaemia to gastrointestinal pathology, and their relative contribution varies systematically with the population under study. The first is chronic occult haemorrhage, in which sustained losses of five to ten millilitres of blood per day exhaust storage iron over a period of months; this mechanism predominates in elderly patients with vascular, ulcerative or neoplastic lesions and accounts for the dominant lesion types identified at endoscopy. The second is malabsorption, in which duodenal mucosal disease, most commonly

coeliac disease but also autoimmune atrophic gastritis and post-surgical anatomy, impairs the absorption of dietary and supplemental iron; this mechanism explains the disproportionate representation of coeliac disease among young patients with iron deficiency anaemia and no bleeding lesion, exemplified by the military recruit cohort in which coeliac disease and *Helicobacter pylori* infection were the joint most frequent diagnoses and no malignancy was identified.^{13,51,59}

The third mechanism is competitive iron acquisition and acid-mediated malabsorption associated with *Helicobacter pylori* infection. The organism expresses outer membrane proteins involved in iron uptake and competes directly with the host for luminal iron, while chronic infection producing atrophic gastritis reduces gastric acid secretion and thereby impairs the reduction of ferric to ferrous iron required for duodenal absorption. The randomised evidence within this review is superficially contradictory but reconcilable: benefit from eradication emerged only after fourteen months in the Alaskan trial and was absent at ninety days in the Bangladeshi trial, a pattern consistent with a mechanism requiring reversal of established mucosal damage rather than immediate microbiological clearance. The pragmatic implication is that eradication should be pursued in recurrent or refractory iron deficiency anaemia but should not be expected to substitute for iron replacement or for structural investigation.^{6,29,37,57}

The Anatomical Argument for Pan-Enteric Assessment

The demonstration that lesions with bleeding potential are more frequent in the small bowel than in either conventionally examined compartment constitutes the most direct challenge to existing practice arising from this review. Its force derives from the study design: all participants underwent all three examinations, adjudication was performed by a blinded consensus panel using a published classification, and the setting spanned three health systems on two continents. Secondary synthesis provides convergent support, with pooled small-bowel capsule endoscopy yield in iron deficiency anaemia estimated at 47% overall and at 66.6% in studies confined exclusively to patients with iron deficiency anaemia, and with vascular, inflammatory and mass lesions all significantly more frequent in the dedicated iron deficiency anaemia populations.^{16,39}

European guidance already recommends small-bowel capsule endoscopy as a first-line examination in patients with iron deficiency anaemia when small-bowel evaluation is indicated, and

specifically advises against routine second-look conventional endoscopy prior to capsule examination. The evidence assembled here suggests that the qualifying clause, namely the requirement that small-bowel evaluation first be judged indicated, is doing considerable work and may be delaying diagnosis in a substantial minority. Real-world data are instructive: in a multicentre analysis of 1,531 iron deficiency referrals, only 1.6% underwent small-bowel capsule endoscopy. The gap between guideline permission and clinical practice is therefore wide, and the emerging availability of panenteric capsule endoscopy, which examines small bowel and colon in a single ingestion, may offer a route to closing it, provided that conversion rates to conventional colonoscopy can be controlled through appropriate faecal haemoglobin thresholds.^{3,4,54}

Faecal Haemoglobin: From Gatekeeper to Risk Modifier

The role of faecal blood testing in the iron deficiency anaemia pathway has been contested for three decades, and the evidence assembled here permits a reasonably firm resolution. As a binary gatekeeping test determining whether any investigation should proceed, faecal occult blood testing fails: its pooled sensitivity for identifiable causes of iron deficiency anaemia at endoscopy is 0.58, meaning that 42% of patients with a demonstrable lesion would be falsely reassured, and prospective cohorts have found it non-predictive for malignancy. National guidance has for two decades stated that faecal occult blood testing is of no benefit in the investigation of iron deficiency anaemia, and the pooled evidence supports that position without qualification.^{2,26,41}

As a continuous risk modifier deployed alongside age and anaemia status, however, quantitative faecal haemoglobin performs impressively. The Scottish analysis demonstrated that risk of colorectal cancer breached the three percent action threshold at a faecal haemoglobin above 99 micrograms per gram in patients above forty years and reached 30% in those above fifty-five years with concurrent iron deficiency anaemia, while a low-risk stratum with a faecal haemoglobin below 20 micrograms per gram and no iron deficiency anaemia carried a risk below three percent up to eighty-five years of age. The national endoscopy database analysis reached a compatible conclusion, demonstrating that a model combining faecal haemoglobin, age and iron deficiency anaemia status detected more than 94% of cancers while reducing colonoscopy demand by more than 40%. The conceptual shift required is from dichotomous triage to continuous probability

estimation, and its implementation requires only that laboratories report quantitative rather than qualitative results and that pathways accommodate graded rather than binary responses.^{21,25}

Iron Deficiency Anaemia versus Overt Bleeding as an Alarm Feature

One of the more counterintuitive findings of this review is that iron deficiency anaemia outperforms overt rectal bleeding as a marker of colorectal malignancy. In a national analysis of 447,109 symptomatic colonoscopies, iron deficiency anaemia carried an adjusted odds ratio for cancer of 2.2 relative to rectal bleeding, and among patients with a faecal haemoglobin below the referral threshold the cancer yield exceeded one percent only in those with iron deficiency anaemia above eighty years of age. In the young adult population, iron deficiency anaemia and haematochezia conferred statistically indistinguishable hazard ratios of 10.81 and 10.66 respectively. The anatomical explanation is that right-sided and proximal tumours, which carry a worse stage distribution at diagnosis, bleed occultly into a lumen where haemoglobin is degraded before reaching the rectum, whereas distal lesions bleed visibly at lower volumes and prompt earlier presentation.^{20,21}

The practical implication is significant for health systems that continue to prioritise visible bleeding in urgent referral criteria. If iron deficiency anaemia carries at least equivalent and possibly superior predictive value, then pathways that treat it as a lesser alarm feature will systematically delay the diagnosis of the tumours with the worst prognosis. The finding that a substantial proportion of colorectal cancers present with a mass or iron deficiency anaemia rather than with classical bowel symptoms reinforces this concern, as does the demonstration that current guidance for urgent investigation of anaemia misses patients at moderate cancer risk, particularly men.^{27,47}

The Premenopausal Woman and the Young Adult

The attribution of iron deficiency anaemia to menstrual loss in premenopausal women is usually correct and is supported by the low absolute risk observed in population data, where the five-year young-onset colorectal cancer risk difference in women aged 18 to 49 with iron deficiency anaemia was 0.08% compared with 0.78% in men. Nonetheless, referred cohorts of premenopausal women demonstrate clinically important lesions in 10.8% to 12%, including gastric carcinoma in

3% and colonic carcinoma in 1.3% to 3.2%, figures that cannot responsibly be dismissed. The reconciliation lies in recognising that these are different populations: the registry data describe unselected women with iron deficiency anaemia, whereas the endoscopic series describe women in whom a clinician judged investigation warranted. The yield in the latter reflects the discriminatory value of that clinical judgement.^{14,20,33}

The most defensible position, and the one supported by the totality of the evidence, is selective rather than universal investigation, guided by the predictors validated in multivariable analysis: the presence of abdominal or localising symptoms, the depth of anaemia, a family history of colorectal carcinoma, and failure of the anaemia to correct with adequate iron replacement. Universal coeliac serology remains justified in this group irrespective of the decision regarding endoscopy, given a prevalence of coeliac disease of approximately three to five percent that is independent of menstrual status. The rising incidence of early-onset colorectal cancer lends additional weight to the argument against reflex attribution, and faecal immunochemical testing performs excellently in patients aged forty to forty-nine while performing less well below forty years, suggesting that age-tailored strategies are required.^{15,25,40}

Diagnostic Delay as a Modifiable Determinant of Survival

The demonstration that the interval between recognition of iron deficiency anaemia and completion of colonoscopy is independently associated with overall survival transforms the diagnostic pathway from an administrative process into a therapeutic one. In the Taiwanese national cohort, median overall survival fell from 5.79 years when colonoscopy was performed within thirty days to 4.04 years when performed at ninety-one days or beyond, with an adjusted hazard ratio for delayed colonoscopy of 1.28. Although residual confounding by comorbidity and performance status cannot be excluded in an observational design, the monotonic dose-response relationship across three interval strata and the persistence of the effect after adjustment support a causal interpretation, and this is one of the criteria that permits upgrading of observational evidence within the GRADE framework.^{8,31}

This finding has direct policy implications. Iron deficiency anaemia is already an accepted indication for fast-track referral in the United Kingdom, yet audit data demonstrate persistent

shortfalls in the completeness and timeliness of investigation, with only 61.6% of one two-week-wait cohort receiving both upper and lower gastrointestinal investigation and with substantial variation in coeliac screening. Service redesign appears capable of closing this gap: a nurse-led virtual iron deficiency anaemia clinic achieved 100% oesophagogastroduodenoscopy, 96% lower gastrointestinal investigation and 98% coeliac testing with mean waits of 24 to 32 days, and detected carcinoma in 9.2% of patients, a rate exceeding that of the general fast-track endoscopy population. The diagnostic interval should therefore be adopted as a formal quality indicator with an explicit target.^{32,55}

Comparison with Existing Syntheses and Guidelines

The findings of this review are broadly concordant with existing secondary syntheses while extending them in three respects. Pooled estimates of small-bowel capsule endoscopy yield in iron deficiency anaemia of 47% overall and 66.6% in dedicated cohorts align closely with the primary data assembled here, and the observation that vascular, inflammatory and mass lesions are all more frequent in dedicated iron deficiency anaemia populations supports the anatomical argument. Pooled coeliac disease prevalence of 3.2%, rising to 5.5% in high-quality studies, is concordant with the primary prevalence estimates of 2.8% to 10% reported in this review. Pooled faecal occult blood test sensitivity of 0.58 for causes of iron deficiency anaemia is consistent with the non-predictive performance observed in the primary cohorts.^{39,40,41}

The extensions provided by this review are, first, the direct within-patient anatomical comparison that was unavailable at the time the existing syntheses were written; second, the incorporation of national registry data quantifying the association between iron deficiency anaemia and malignancy at a scale that individual endoscopic series cannot approach; and third, the linkage of diagnostic yield to survival through the diagnostic interval. Relative to current guideline positions, the principal divergence concerns the sequencing of small-bowel evaluation. Existing guidance positions capsule endoscopy after negative bidirectional endoscopy or in recurrent and refractory disease; the evidence assembled here suggests that this sequencing, while defensible on resource grounds, is not supported by lesion prevalence and results in avoidable diagnostic delay in a substantial minority of patients.^{1,3,16}

Clinical Implications

Six clinical implications follow from this synthesis. Bidirectional endoscopy should remain the default initial investigation in all adult men and postmenopausal women with unexplained iron deficiency anaemia, and coeliac serology should be performed universally at the point of referral rather than deferred to duodenal biopsy at endoscopy. Small-bowel evaluation should be considered earlier than current pathways provide, particularly in patients with transfusion dependence, recurrent anaemia, antithrombotic exposure or an unrevealing bidirectional examination, and a negative second-look conventional endoscopy should not be a prerequisite. Quantitative faecal haemoglobin should be interpreted as a graded risk modifier alongside age and iron status rather than as a binary gatekeeper, and a negative result should never override the investigative imperative created by established iron deficiency anaemia.^{1,3,25}

Attribution of iron deficiency anaemia to antithrombotic therapy, to menstrual loss or to dietary insufficiency should be regarded as a diagnosis of exclusion, since the drug exposure data demonstrate that anticoagulation unmasks rather than creates luminal pathology. Iron replacement should be initiated concurrently with, and never as a substitute for, investigation, and failure of the anaemia to correct or its recurrence after correction should trigger escalation rather than repetition of iron therapy. Finally, the diagnostic interval should be measured, audited and minimised, since it exerts an independent effect on survival that is at least of the same order as some therapeutic interventions.^{30,31,43,63}

Implications for Resource-Constrained Settings

The great majority of the evidence in this review derives from health systems with mature endoscopic infrastructure, and its transposition to settings where endoscopic capacity is limited or unevenly distributed requires deliberate adaptation. Three elements of the evidence base are particularly transferable. The multivariable predictor sets, requiring only age, sex, haemoglobin, ferritin and a symptom history, are essentially costless and can be applied wherever a full blood count and ferritin assay are available; the composite achieving a positive predictive value of 87% and a negative predictive value of 93.5% is derived from variables obtainable in any district hospital. Quantitative faecal haemoglobin assays are inexpensive relative to endoscopy and,

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deployed as a continuous risk modifier, permit rational prioritisation of scarce colonoscopy slots.^{15,21,25}

Conversely, two elements transfer poorly. Capsule endoscopy remains capital-intensive and requires trained readers, and its earlier deployment, though supported by lesion prevalence, is unlikely to be affordable in most low- and middle-income settings in the near term; in such settings the priority should be to ensure that bidirectional endoscopy is completed promptly and that coeliac disease and *Helicobacter pylori* infection are excluded non-invasively. The epidemiological background also differs materially, with a higher ratio of gastric to colorectal carcinoma and a higher background prevalence of *Helicobacter pylori* infection and of nutritional iron deficiency in many Asian populations, which shifts the expected diagnostic yield towards the upper gastrointestinal tract and towards infective and nutritional aetiologies. Locally derived yield estimates are therefore required and should be a research priority.^{6,26,29}

Strengths of this Review

This review has several methodological strengths. The evidence base was assembled through a federated academic search platform indexing more than two hundred million records across four major bibliographic databases, and every included reference was individually verified for existence and online accessibility, with a persistent resolver link recorded, rendering the entire evidence base auditable. The analytical architecture spans fourteen prespecified outcome domains, permitting the integration of diagnostic, oncological, biomarker, pharmacological and survival evidence within a single framework rather than in the isolated fashion characteristic of previous syntheses. The strict separation of primary study evidence from secondary synthesised evidence prevents double-counting of participants and preserves the transparency of inference. Risk of bias was appraised with design-matched instruments and the robustness of conclusions was formally tested by exclusion of studies at serious risk of bias.^{7,9,10,12}

Directions for Future Research

Four research priorities emerge. The highest priority is a randomised comparison of early pan-enteric capsule endoscopy against conventional sequential bidirectional endoscopy in patients with unexplained iron deficiency anaemia, with outcomes defined as time to definitive diagnosis,

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proportion of patients with a management-altering finding, cumulative endoscopic burden and cost per diagnosis. The second is the prospective validation of integrated risk models combining age, sex, haemoglobin, ferritin, lactate dehydrogenase and quantitative faecal haemoglobin, ideally in multiple health systems, since the models identified in this review were largely developed and validated within single datasets. The third is the generation of yield and outcome data from non-Western populations, particularly from South and South-East Asia, where the epidemiology of luminal malignancy and of *Helicobacter pylori* infection differs materially from that of the populations that dominate the current evidence base.^{16,25,26}

The fourth priority concerns definitional standardisation. The absence of an agreed threshold for iron deficiency, an agreed definition of a clinically significant lesion and an agreed classification of bleeding probability has been the principal obstacle to quantitative synthesis in this field for three decades. Adoption of the Saurin classification for lesion adjudication, of a single ferritin threshold appropriate to the population under study, and of standardised reporting of numerators and denominators by anatomical compartment would permit the meta-analysis that the present heterogeneity precludes. A parallel priority is the prospective evaluation of premenopausal women with iron deficiency anaemia, a group in whom the current evidence rests on small retrospective series and on registry analyses that cannot capture the clinical reasoning underlying referral.^{16,20,33}

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review of thirty-five primary studies comprising approximately 1.89 million participants establishes that iron deficiency anaemia bears a robust, reproducible and clinically consequential association with occult gastrointestinal bleeding and with luminal gastrointestinal malignancy. The association is demonstrable across every health system, age stratum and study design examined, and its magnitude, expressed variously as an odds ratio of 4.47 for luminal gastrointestinal cancer within one year, a hazard ratio of 10.81 for young-onset colorectal cancer, likelihood ratios of 27 to 41 at haemoglobin concentrations below 9 grams per decilitre, and a standardised incidence ratio of 2.15 for all cancers, places iron deficiency anaemia

among the most powerful non-invasive markers of luminal neoplasia available to the clinician. The a priori hypotheses of this review were therefore supported.^{19,20,22,27}

Structured luminal investigation is correspondingly productive, identifying a lesion with bleeding potential in 12% to 76% of patients according to the pretest characteristics of the population, and the pan-enteric strategy identifies actionable pathology in 71.1% of patients while altering management in 52.3%. The demonstration that the small intestine harbours more bleeding-capable lesions than either compartment examined by conventional bidirectional endoscopy constitutes a direct empirical challenge to the anatomical assumptions embedded in current pathways. Faecal occult blood testing lacks the sensitivity required of a rule-out instrument in this setting and should not be used to determine whether investigation proceeds, although quantitative faecal haemoglobin, interpreted as a continuous risk modifier alongside age and iron status, discriminates one-year colorectal cancer risk across a range from below 1.3% to 30%.^{13,16,25,41}

Finally, and of the greatest practical consequence, the interval between the biochemical recognition of iron deficiency anaemia and the completion of definitive investigation is itself an independent determinant of survival, with delay beyond ninety days associated with an adjusted hazard ratio for death of 1.28 and with a loss of approximately 1.75 years of median overall survival among patients subsequently diagnosed with colon cancer. Iron deficiency anaemia is not a haematological diagnosis to be corrected with supplementation; it is a structural alarm requiring prompt, complete and appropriately sequenced luminal investigation.³¹

Recommendations

Recommendations for Clinical Practice

- All adult men and all postmenopausal women with unexplained iron deficiency anaemia should undergo prompt bidirectional endoscopy, and coeliac serology should be requested universally at the point of referral rather than deferred to duodenal biopsy at the time of endoscopy.^{1,2,40}
- Small-bowel evaluation, preferably by capsule endoscopy, should be considered earlier in the diagnostic sequence than current pathways provide, and specifically in patients with transfusion-dependent, recurrent or refractory anaemia, in those with antithrombotic

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exposure, and in those with an unrevealing bidirectional examination. A repeat conventional endoscopy should not be required before capsule examination.^{3,16,53}

- Quantitative faecal haemoglobin should be used as a graded risk modifier in combination with age and iron deficiency status, not as a binary gatekeeper. A result below the referral threshold must not override the investigative imperative created by established iron deficiency anaemia, particularly in patients above the age of eighty.^{21,25,41}
- Attribution of iron deficiency anaemia to menstrual loss, dietary insufficiency or antithrombotic therapy should be treated as a diagnosis of exclusion. Anticoagulant and antiplatelet agents unmask rather than create luminal pathology, and their presence should not reduce investigative intensity.^{30,43}
- In premenopausal women, investigation should be selective rather than universal, guided by the presence of abdominal or localising symptoms, the depth of anaemia, a family history of colorectal carcinoma, and failure of the anaemia to respond to adequate iron replacement. Coeliac screening remains universal in this group.^{14,15,33}
- Iron replacement should be initiated concurrently with investigation and never in place of it. Failure of the haemoglobin to normalise, or its subsequent relapse, should trigger escalation of investigation rather than repetition of iron therapy.^{1,58}
- Helicobacter pylori testing and eradication should be pursued in patients with recurrent or refractory iron deficiency anaemia in whom other causes have been excluded, with the expectation that benefit accrues over months rather than weeks.^{6,29,37}
- The interval from recognition of iron deficiency anaemia to completion of definitive investigation should be measured and audited as a formal quality indicator, with a target of thirty days, given its independent association with survival.^{31,32}

Recommendations for Health Systems and Policy

- Referral pathways should accord iron deficiency anaemia at least the same priority as overt rectal bleeding, since within matched symptomatic populations it carries a higher adjusted odds of colorectal malignancy.^{21,27}

- Integrated risk models combining age, sex, haemoglobin, ferritin and quantitative faecal haemoglobin should be adopted in preference to single-threshold triage, since such models detect more than 94% of cancers while reducing colonoscopy demand by more than 40%.^{21,25,49}
- Dedicated iron deficiency anaemia services, whether nurse-led or virtual, should be considered where completeness and timeliness of investigation are suboptimal, since such models have achieved near-complete investigation within four weeks with cancer detection rates exceeding those of general fast-track pathways.³²
- Capsule endoscopy capacity should be expanded, and its utilisation audited, given that real-world uptake of 1.6% in iron deficiency referral cohorts is inconsistent with the lesion prevalence demonstrated in prospective pan-enteric evaluation.^{16,54}
- In resource-constrained settings, priority should be given to the universal availability of ferritin assay, to non-invasive exclusion of coeliac disease and *Helicobacter pylori* infection, and to the application of costless multivariable predictor sets for the prioritisation of limited endoscopic capacity.^{15,26}

Recommendations for Future Research

- A randomised controlled trial comparing early pan-enteric capsule endoscopy with conventional sequential bidirectional endoscopy in unexplained iron deficiency anaemia, with time to definitive diagnosis, management-altering findings, cumulative endoscopic burden and cost per diagnosis as outcomes.¹⁶
- Prospective multicentre external validation of integrated risk prediction models incorporating age, sex, haemoglobin, ferritin, lactate dehydrogenase and quantitative faecal haemoglobin.^{25,26}
- Generation of diagnostic yield and outcome data from South and South-East Asian, African and Latin American populations, in which malignancy epidemiology, *Helicobacter pylori* prevalence and nutritional iron status differ materially from those of the populations dominating the present evidence base.^{6,22}

- Adoption of standardised definitions, specifically the Saurin classification for lesion adjudication, an agreed ferritin threshold, and compartment-specific reporting of numerators and denominators, in order to permit the quantitative synthesis that current heterogeneity precludes.¹⁶
- Prospective evaluation of premenopausal women and of patients with iron deficiency without anaemia, the two groups in which the current evidence is weakest and clinical practice most variable.^{33,42}

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