Iron deficiency – a modern primer to diagnosis and management

Leo Alexandre[1, 2] and Simon S M Chan[1,2]

[1]Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, United Kingdom

[2]Department of Medicine, Norwich Medical School, University of East Anglia, Norwich, United Kingdom

Correspondence to: S S M Chan simon.chan@uea.ac.uk

Purpose of review

Iron deficiency (ID) with (IDA) and without anemia (IDWA) remain a diagnostic and management challenge. ID has a broad spectrum of causes, including gastrointestinal malignancy. The purpose of this review is to summarise the value and limitations of current methods to diagnose ID and underline the relevance of contemporaneous evidence to guide the pre-test probability of gastrointestinal disease.

Recent findings

A number of biomarkers for iron deficiency exist, and all have their caveats. Serum ferritin remains the most pragmatic means of diagnosing iron deficiency. Hepcidin holds future promise as a marker of iron status during inflammatory states. Men and post-menopausal women with IDA have the highest overall prevalence of gastrointestinal malignancy (~11%), while premenopausal women with IDA (<1.5%) and those with IDWA (<0.5%) have a very low risk. Non-invasive investigation with fecal immunochemical test (FIT) and fecal calprotectin (FC) hold promise to guide further investigations in lower risk groups.

Summary

Confirmation of ID remains a challenge. Appropriate risk stratification is the key to guiding judicious gastrointestinal investigation. Use of non-invasive tests may play an important role in lower risk groups. Risk prediction tools applicable to relevant populations are required.

Keywords: iron deficiency, anemia, risk stratification, diagnosis, management

KEY POINTS

- Iron deficiency is extremely common and is due to a diverse range of etiologies
- Ferritin is still the most pragmatic investigation to assess iron status
- Gastrointestinal cancer may be the cause of iron deficiency and endoscopic investigations must be considered especially in those with a higher risk of malignancy
- Fecal immunochemical testing and fecal calprotectin may help guide investigations for lower risk patients with iron deficiency

INTRODUCTION

Iron deficiency (ID) is the most common nutritional deficiency worldwide and can be considered a continuum from iron deficiency without anemia (IDWA) to iron deficiency with anemia (IDA). The causes of ID are diverse and include non-malignant and malignant diseases. Due to the association between IDA and gastrointestinal malignancy many national societies have provided guidance on the diagnosis and management of IDA(1-3). However, there is little consensus on the need for further investigations in those who have IDWA although a proportion of these may progress to IDA. Here we discuss a pragmatic approach to the diagnosis and management of ID in adults with and without anemia and highlight areas for further study.

EPIDEMIOLOGY

The World Health Organisation (WHO) has estimated that approximately 30% of the global population is affected by ID with and without concurrent anemia(4, 5). Reported estimates often using anemia as an indirect indicator of ID(6) as there are relatively few large robust population studies to have fully assessed the prevalence of ID. Yet based on existing population studies it is evident that the prevalence of IDWA is more common than IDA with the prevalence of ID highly dependent on the population assessed.

The National Health and Nutrition Examination Survey (NHANES I) and the NHANES I Epidemiologic Follow up Study reported that 8% (n=716) of a civilian, non-institutionalized population in the United States (n=9024) were iron deficient (transferrin saturation <15%), which included 1.6% (n=143) who also had an IDA(7). The prevalence of ID may be higher still as a more recent population-based study of 4451 adults over 50 years of age from England reported the prevalence of IDWA as 8.7% (n=389) with women having a higher prevalence of IDWA than men (10.9% versus 6.35%)(8••). Those with IDA (n=297) were excluded from this study and serum ferritin <30 μg/l was used to define ID instead of transferrin saturation. In contrast, the prevalence of ID in non-industrialised countries is higher(4) and

some studies have reported a prevalence as of >40% although small sample size and selection biases in these studies limit the generalisability of these findings to other developing countries(9, 10).

DIAGNOSING IRON DEFICIENCY

There is no single universal test that can readily assess for ID. Bone marrow aspirates with iron (Perl's Prussian blue) staining previously considered the gold standard for assessing iron stores are highly invasive and serum markers are now commonly used instead to assess iron status(11).

Serum ferritin, a circulating iron storage protein that is proportionate to iron stores in the body is the most widely used biomarker to assess for ID. Measurements of ferritin have been standardised internationally despite the different laboratory quantification methods that are available(12) and based on limited data and expert opinion a serum ferritin <15μg/L is often defined as the threshold that represents ID(13). This 'cut-off' is used by the WHO to define ID in adults(14•) although some advocate a higher cut-off i.e. serum ferritin <45μg/L(2) increasing sensitivity at the expense of specificity for the detection of ID and many associations/societies have set different 'thresholds' for ID taking into account the sensitivity and specificity required for their specific patient population(15). However, the correlation between ferritin and iron status becomes distorted during inflammatory processes(16) and should be interpreted cautiously in the context of raised acute phase reactants e.g. C-reactive protein. Meta-analyses report that inflammation can increase ferritin measurements by approximately 30-90%(17) and in those with chronic inflammatory conditions, one study reported a mean serum ferritin of 82.4 μg/L despite ID on bone marrow aspirates(18) implying that the presence of ID may be overlooked in those with covert inflammation. Higher 'cut-off' values for ferritin (i.e. <70 μg/L) to define ID and the application of 'correction factors' to ferritin measurements have been suggested in the context of inflammation but this is based on limited data and should be interpreted with caution until such approaches have been validated(19).

Other commonly used serum markers of ID include low iron, low transferrin saturation, and increased total iron binding capacity although these have their own limitations. For example, serum iron unlike ferritin fluctuates with dietary intake and diurnal variation(20) and whilst a low serum iron may represent low body stores of iron (absolute ID), serum iron may also be low due to iron being sequestered during infection and inflammatory conditions despite adequate stores of iron in the body (functional ID)(21). Thus, in isolation a low serum iron is of little diagnostic value and is typically evaluated in the context of transferrin saturations (T_{sat}). Transferrin is a circulating transport protein for iron that is increased during ID and can be decreased in inflammatory conditions and the T_{sat} is effectively the ratio of serum iron to the total iron capacity of transferrin. The role of transferrin saturations in the diagnosis of ID has been extensively systematically reviewed by Cacoub et al. and a threshold of T_{sat}<16% is considered diagnostic of absolute ID; with T_{sat}<20% the threshold for ID regardless of inflammation(22). However, it should be noted that T_{sat} has the same limitations as the serum markers used in its calculation, with high estrogen levels (pregnancy, medication) and certain endocrine conditions reported to alter the production of transferrin irrespective of the body's iron stores(23).

Similar to serum transferrin, the soluble transferrin receptor (sTfR) is a circulating protein that reflects erythropoiesis and is inversely proportional to the availability of tissue iron. Elevated in those with ID, some studies imply that sTfR may be a better indicator of ID in certain inflammatory conditions(24••). Others have reported that sTfR is no better than ferritin or only of use in detecting advanced ID(25) and conditions such as hemolysis and malignancy are known to falsely elevate sTfR levels(26). Regardless, sTfR is not routinely available in clinical practice due to a lack of standardised assays and reference ranges.

Due to the aforementioned limitations, novel serum markers and indices for ID are still under investigation(27). Elevated erythrocyte zinc protoporphyrin is consistent with ID as zinc is

incorporated into protoporphyrin when iron stores are low and has the potential to be investigated non-invasively(28). However, zinc protoporphyrin can be elevated in inflammatory states and lead poisoning(29). Reticulocyte hemoglobin content is available on many automated cell counters and can rapidly provide information on iron status(30); unaffected by inflammation at present the data for its role in diagnosing ID is limited(31). Hepcidin is probably the most promising upcoming marker for detecting ID. A peptide hormone that is a key regulator of iron homeostasis, its production is decreased in ID and increased during inflammation(32). However, Stoffel and colleagues have demonstrated that low iron status offsets the inflammatory stimulus on hepcidin expression implying that hepcidin may be a useful marker of iron status during inflammatory states(33••).

In summary, serum ferritin is probably the most widely available and useful marker to initially assess iron status with other serum markers sometimes required to provide the best assessment.

MANAGEMENT

The overwhelming focus on the management of patients with ID is on the diagnostic approach. Treatment of the cause, iron supplementation and monitoring (hemoglobin and iron indices), are also important, however, these are not within the scope of this review. The causes of ID can be divided into three categories: insufficient dietary intake, decreased absorption and blood loss (Table 1). Whilst ID is associated with many diseases, healthy individuals with dietary restrictions (e.g. vegetarians) and/or increased iron requirements (e.g. adolescents, menstruating women of child-bearing age, pregnancy and intense physical activity) are also at risk of ID(34-38). A thorough clinical history together with clinical examination is important to refine a relevant list of differential diagnoses, risk stratify for gastrointestinal (GI) malignancy, and permit appropriate selection of onward investigations.

Emphasis on investigation of the GI tract is predicated on an increased relative and absolute risk of prevalent GI malignancy observed in iron deficient states (see Figure 1). The observational research which underlies the current evidence-base, includes studies which vary by healthcare setting (e.g. primary and secondary care), geographical location, demography (with differing age and gender distributions) and symptomatology; with resultant substantial heterogeneity in estimates(39•, 40••). Given this, the optimal approach to GI investigation is likely best tailored by taking into account the pre-test probability of GI disease in the local at-risk population group. It should also be noted that non-malignant GI diseases are also relevant and their pre-test probability may also guide investigation(41). Non-invasive tests for coeliac disease and *helicobacter pylori* should be considered as part of the initial diagnostic work up. With regards to endoscopic investigation, the following factors deserve consideration: the pre-test probability of GI disease, the risks of endoscopic investigation, patient preference, endoscopic capacity and cost. Based on current evidence and its inherent uncertainties we propose a pragmatic approach to guide investigation in patients with ID (Figure 2). In the highest risk groups for GI cancer, urgent investigation with both upper and lower GI endoscopy is likely justifiable: a recent meta-analysis of the prevalence of GI cancer in men and postmenopausal women with IDA demonstrated colorectal cancer (CRC) in 8.9% (95% CI 8.3-9.5%) and upper GI cancer in 1.96% (95% CI 1.7-2.3%)(40). Included studies comprised populations with and without symptoms, and while it is unclear the extent to which risk of GI cancer varies between these groups, the absolute risk of GI cancer in these groups is still likely to elevated, based on population-based research(7). The benefit of endoscopic investigation is less clear in lower risk groups, where the prevalence of CRC and upper GI cancer in premenopausal women with IDA was 0.95% (0.3-1.9%) and 0.24% (95% CI 0-0.9%), respectively.

The evidence-base informing the prevalence of GI malignancy in patients with IDWA is more limited (Figure 1) and restricted to five observational studies, summarised in a recent systematic review(40). A single population-based study from the US estimated prevalence of GI malignancy in men and post-

menopausal women (expected to be predominantly asymptomatic) with IDWA to be 0.9% (95% CI 0.11-3.2%)(7), however, in older patients in three studies including men and women aged ≥50 years, the pooled prevalence was to 2.58% (95% CI 0-8.77%). In pre-menopausal women(7) or younger men and women (<50 years)(7, 42, 43), the pooled prevalence of GI malignancy in both groups was 0%. Although the prevalence of GI cancer in patients with IDWA is lower than equivalent groups with IDA, given the paucity of studies in the former, there remain uncertainties about the magnitude of risk. As the amount of evidence in lower risk groups (pre-menopausal women with IDA and those <50 years with IDWA) is limited, accordingly there is a lack of consistency in recommended diagnostic approach in these groups. Developments in non-invasive screening tests could play an important role in these lower risk groups as triaging tools for colonoscopy.

The faecal immunochemical test (FIT) uses an immune-assay to target the globulin component of hemoglobin and is specific to lower GI cancers(44). FIT could play a role in the diagnostic pathway for pre-menopausal women with IDA or those <50 years with IDWA, given its established diagnostic accuracy for CRC in low-risk populations(45••) (e.g. for ≥10 µg Hb/g FIT threshold, for CRC, sensitivity 90.5%, specificity 91.3%, positive predictive value 10.1% and negative predictive value 99.9%), with little evidence of age or gender affecting performance(45, 46). Furthermore, sensitivity and specificity have been shown to be similar between those presenting with IDA and those referred with other symptoms(47). Importantly, in patients with IDA specifically, FIT has a high negative predictive value (98.4%) with a ≥10 µg Hb/g threshold(48••). There is no evidence that early repeat FIT in those at high risk of CRC, or that two sample FIT in screening populations improves diagnostic accuracy(49, 50).

IDA and IDWA can herald a diagnosis of inflammatory bowel disease (IBD), particularly in younger patients(41, 42). Faecal calprotectin (FC) is a non-invasive marker of disease activity in inflammatory bowel disease, which correlates with histological evidence of inflammation(51). A cohort study conducted in UK primary care, including symptomatic young adults without alarm symptoms (18-46

years old) established the diagnostic accuracy of FC for IBD (versus functional bowel disease) with a threshold of ≥100 μg/g (sensitivity 83%, specificity 91%, positive predictive value 27% and negative predictive value 99%)(52). The accuracy of FC in aiding diagnosis of IBD is asymptomatic patients with ID is unclear.

The development of personalised risk prediction tools in patients with ID could guide clinical decision-making in the future. The derivation and validation of the IDIOM score, a risk prediction tool developed in secondary care in patients in predominantly older patients with IDA to predict GI malignancy, is a welcome development(53•, 54). In addition to age and sex, the variables hemoglobin and mean corpuscular volume provide additional independent predictive value. The model's current clinical application is restricted to identifying a very low-risk group: those assigned predicted <1.5% risk (accounting for 10% of the validation cohort), where no GI cancers were found (NPV 100%). The model demonstrated predictive value for higher risk categories, however this was at the expense of sensitivity, precluding use in this context. Future risk scores, developed and validated in populations representative of patient cohorts separately in primary and secondary care, in broad adult age-groups are urgently required.

CONCLUSIONS

ID is the most common nutritional deficiency worldwide. Serum ferritin remains the most pragmatic and widely available means of diagnosing ID, but should be interpreted in context (such as systemic inflammation). IDA and IDWA are of direct clinical relevance, given their association with prevalent GI malignancy. Non-malignant GI causes of ID deserve consideration. Diagnostic strategy is predicated on the pre-test probability of malignant and non-malignant GI disease. Patients at highest risk of GI malignancy (for example men and post-menopausal women with IDA or those ≥50 years with IDWA) will most likely require upper and lower GI endoscopy. Lower risk groups, such as those <50 years with

IDWA or premenopausal women with IDA could be triaged for colonoscopy with non-invasive tools such as FIT and FC. Further research is needed to establish precise estimates of the prevalence of malignant and non-malignant GI disease in patients with IDWA. The development of risk prediction tools for GI disease in patients with ID could shape future clinical practice.

ACKNOWLEDGEMENTS

None

FINANCIAL SUPPORT AND SPONSORSHIP

None

CONFLICTS OF INTEREST

None

REFERENCES

• of special interest

•• of outstanding interest

1. Goddard AF, James MW, McIntyre AS, Scott BB, British Society of G. Guidelines for the management of iron deficiency anaemia. Gut. 2011;60(10):1309-16.
2. Ko CW, Siddique SM, Patel A, Harris A, Sultan S, Altayar O, et al. AGA Clinical Practice Guidelines on the Gastrointestinal Evaluation of Iron Deficiency Anemia. Gastroenterology. 2020.
3. Sinclair M. Clinical Update: Iron deficiency. Gastroenterological Society of Australia; Updated 2015.
4. Kassebaum NJ, Jasrasaria R, Naghavi M, Wulf SK, Johns N, Lozano R, et al. A systematic analysis of global anemia burden from 1990 to 2010. Blood. 2014;123(5):615-24.
5. WHO/UNICEF/UNU. Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers. Geneva: World Health Organization; 2001.
6. WHO. Serum ferritin concentrations for the assessment of iron status and iron deficiency in populations. Geneva: WHO; 2011.
7. Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. Am J Med. 2002;113(4):276-80.
8. •• Philip KEJ, Sadaka AS, Polkey MI, Hopkinson NS, Steptoe A, Fancourt D. The prevalence and associated mortality of non-anaemic iron deficiency in older adults: a 14 years observational cohort study. Br J Haematol. 2020;189(3):566-72. Contemporaneous cohort study on the prevalence of iron deficiency
9. Phatlhane DV, Zemlin AE, Matsha TE, Hoffmann M, Naidoo N, Ichihara K, et al. The iron status of a healthy South African adult population. Clin Chim Acta. 2016;460:240-5.
10. Shalini T, Sivaprasad M, Balakrishna N, Madhavi G, Radhika MS, Kumar BN, et al. Micronutrient intakes and status assessed by probability approach among the urban adult population of Hyderabad city in South India. Eur J Nutr. 2019;58(8):3147-59.
11. Camaschella C. Iron deficiency. Blood. 2019;133(1):30-9.
12. Garcia-Casal MN, Pena-Rosas JP, Urrechaga E, Escanero JF, Huo J, Martinez RX, et al. Performance and comparability of laboratory methods for measuring ferritin concentrations in human serum or plasma: A systematic review and meta-analysis. PLoS One. 2018;13(5):e0196576.
13. Garcia-Casal MN, Pena-Rosas JP, Pasricha SR. Rethinking ferritin cutoffs for iron deficiency and overload. Lancet Haematol. 2014;1(3):e92-4.
14. • WHO. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. Geneva: WHO; 2020. World Health Organization guidance on use of ferritin to assess iron deficiency
15. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. Am J Clin Nutr. 2015;102(6):1585-94.
16. Blake DR, Waterworth RF, Bacon PA. Assessment of iron stores in inflammation by assay of serum ferritin concentrations. Br Med J (Clin Res Ed). 1981;283(6300):1147-8.
17. Thurnham DI, McCabe LD, Haldar S, Wieringa FT, Northrop-Clewes CA, McCabe GP. Adjusting plasma ferritin concentrations to remove the effects of subclinical inflammation in the assessment of iron deficiency: a meta-analysis. Am J Clin Nutr. 2010;92(3):546-55.
18. Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Pena-Rosas JP. Are Current Serum and Plasma Ferritin Cut-offs for Iron Deficiency and Overload Accurate and Reflecting Iron Status? A Systematic Review. Arch Med Res. 2018;49(6):405-17.

19. Namaste SM, Rohner F, Huang J, Bhushan NL, Flores-Ayala R, Kupka R, et al. Adjusting ferritin concentrations for inflammation: Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia (BRINDA) project. Am J Clin Nutr. 2017;106(Suppl 1):359S-71S.
20. Nguyen LT, Buse JD, Baskin L, Sadrzadeh SMH, Naugler C. Influence of diurnal variation and fasting on serum iron concentrations in a community-based population. Clin Biochem. 2017;50(18):1237-42.
21. Nairz M, Weiss G. Iron in infection and immunity. Mol Aspects Med. 2020:100864.
22. Cacoub P, Vandewalle C, Peoc'h K. Using transferrin saturation as a diagnostic criterion for iron deficiency: A systematic review. Crit Rev Clin Lab Sci. 2019;56(8):526-32.
23. Matsubara M, Koyanagawa Y, Odagaki E, Nakagawa K. Plasma transferrin levels in abnormal endocrine states. II. The changes in various endocrine states. Horm Metab Res. 1989;21(6):334-7.
24. •• Daude S, Remen T, Chateau T, Danese S, Gastin I, Baumann C, et al. Comparative accuracy of ferritin, transferrin saturation and soluble transferrin receptor for the diagnosis of iron deficiency in inflammatory bowel disease. Aliment Pharmacol Ther. 2020;51(11):1087-95. Comparison of the accuracy of different biomarkers to assess iron status in inflammatory conditions
25. Choi JW. Sensitivity, specificity, and predictive value of serum soluble transferrin receptor at different stages of iron deficiency. Ann Clin Lab Sci. 2005;35(4):435-9.
26. Metzgeroth G, Schultheis B, Kuhn C, Dorn-Beineke A, LaRosee P, Hehlmann R, et al. The soluble transferrin receptor reflects tumor load in chronic lymphocytic leukemia. Clin Chem Lab Med. 2007;45(10):1313-8.
27. Ginzburg YZ. New diagnostic tools for delineating iron status. Hematology Am Soc Hematol Educ Program. 2019;2019(1):327-36.
28. Hennig G, Homann C, Teksan I, Hasbargen U, Hasmuller S, Holdt LM, et al. Non-invasive detection of iron deficiency by fluorescence measurement of erythrocyte zinc protoporphyrin in the lip. Nat Commun. 2016;7:10776.
29. Magge H, Sprinz P, Adams WG, Drainoni ML, Meyers A. Zinc protoporphyrin and iron deficiency screening: trends and therapeutic response in an urban pediatric center. JAMA Pediatr. 2013;167(4):361-7.
30. Brugnara C, Schiller B, Moran J. Reticulocyte hemoglobin equivalent (Ret He) and assessment of iron-deficient states. Clin Lab Haematol. 2006;28(5):303-8.
31. Urrechaga E, Hoffmann J, Bernal A, Arevalo JA, Cabriada JL. Reticulocyte hemoglobin content (MCHr) in the assessment of iron deficient erythropoiesis in inflammatory bowel disease. Dig Liver Dis. 2018;50(11):1178-82.
32. Pagani A, Nai A, Silvestri L, Camaschella C. Hepcidin and Anemia: A Tight Relationship. Front Physiol. 2019;10:1294.
33. •• Stoffel NU, Lazrak M, Bellitir S, Mir NE, Hamdouchi AE, Barkat A, et al. The opposing effects of acute inflammation and iron deficiency anemia on serum hepcidin and iron absorption in young women. Haematologica. 2019;104(6):1143-9. Study suggesting that hepcidin may have promise as a future marker of iron status in inflammatory conditions
34. Coates A, Mountjoy M, Burr J. Incidence of Iron Deficiency and Iron Deficient Anemia in Elite Runners and Triathletes. Clin J Sport Med. 2017;27(5):493-8.
35. Haider LM, Schwingshackl L, Hoffmann G, Ekmekcioglu C. The effect of vegetarian diets on iron status in adults: A systematic review and meta-analysis. Crit Rev Food Sci Nutr. 2018;58(8):1359-74.
36. Harvey LJ, Armah CN, Dainty JR, Foxall RJ, John Lewis D, Langford NJ, et al. Impact of menstrual blood loss and diet on iron deficiency among women in the UK. Br J Nutr. 2005;94(4):557-64.
37. Mei Z, Cogswell ME, Looker AC, Pfeiffer CM, Cusick SE, Lacher DA, et al. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999-2006. Am J Clin Nutr. 2011;93(6):1312-20.
38. Milman NT. Dietary Iron Intake in Women of Reproductive Age in Europe: A Review of 49 Studies from 29 Countries in the Period 1993-2015. J Nutr Metab. 2019;2019:7631306.

39. • Alexandre L, Manning C, Chan SSM. Prevalence of gastrointestinal malignancy in iron deficiency without anaemia: A systematic review and meta-analysis. Eur J Intern Med. 2020;72:27-33. Contemporaneous meta-analysis of prevalence of GI cancer in IDWA
40. •• Rockey DC, Altayar O, Falck-Ytter Y, Kalmaz D. AGA Technical Review on Gastrointestinal Evaluation of Iron Deficiency Anemia. Gastroenterology. 2020;159(3):1097-119. Contemporaneous meta-analysis of prevalence of GI cancer in IDA
41. Park JS, Park DI, Park SK, Choi JS, Kim YH, Chang DK, et al. Endoscopic evaluation of significant gastrointestinal lesions in patients with iron deficiency with and without anaemia: a Korean Association for the Study of Intestinal Disease study. Intern Med J. 2009;39(7):441-6.
42. Carter D, Bardan E, Derazne E, Tzur D, Avidan B. The incidence of gastrointestinal pathology and subsequent anemia in young men presenting with iron deficiency without anemia. Eur J Gastroenterol Hepatol. 2016;28(10):1126-9.
43. Garcia Garcia de Paredes A, Teruel Sanchez-Vegazo C, Hernanz Ruiz N, Ferre Aracil C, Rodriguez de Santiago E, Aguilera Castro L, et al. Do patients with iron deficiency without anemia benefit from an endoscopic examination? J Dig Dis. 2017;18(7):416-24.
44. Nicholson BD, Thompson M, Price CP, Heneghan C, Pluddemann A. Home-use faecal immunochemical testing: primary care diagnostic technology update. Br J Gen Pract. 2015;65(632):156-8.
45. •• Nicholson BD, James T, Paddon M, Justice S, Oke JL, East JE, et al. Faecal immunochemical testing for adults with symptoms of colorectal cancer attending English primary care: a retrospective cohort study of 14 487 consecutive test requests. Aliment Pharmacol Ther. 2020. Favourable diagnostic accuracy of FIT for detection of CRC in a low risk population.
46. Selby K, Levine EH, Doan C, Gies A, Brenner H, Quesenberry C, et al. Effect of Sex, Age, and Positivity Threshold on Fecal Immunochemical Test Accuracy: A Systematic Review and Meta-analysis. Gastroenterology. 2019;157(6):1494-505.
47. Cunin L, Khan AA, Ibrahim M, Lango A, Klimovskij M, Harshen R. FIT negative cancers: A right-sided problem? Implications for screening and whether iron deficiency anaemia has a role to play. Surgeon. 2020.
48. •• Ayling RM, Lewis SJ, Cotter F. Potential roles of artificial intelligence learning and faecal immunochemical testing for prioritisation of colonoscopy in anaemia. Br J Haematol. 2019;185(2):311-6. Diagnostic accuracy of FIT in patients with IDA
49. Schreuders EH, Grobbee EJ, Nieuwenburg SAV, Kapidzic A, van Roon AHC, van Vuuren AJ, et al. Multiple rounds of one sample versus two sample faecal immunochemical test-based colorectal cancer screening: a population-based study. Lancet Gastroenterol Hepatol. 2019;4(8):622-31.
50. Turvill J, Mellen S, Jeffery L, Bevan S, Keding A, Turnock D. Diagnostic accuracy of one or two faecal haemoglobin and calprotectin measurements in patients with suspected colorectal cancer. Scand J Gastroenterol. 2018;53(12):1526-34.
51. D'Amico F, Bonovas S, Danese S, Peyrin-Biroulet L. Review article: faecal calprotectin and histologic remission in ulcerative colitis. Aliment Pharmacol Ther. 2020;51(7):689-98.
52. Walker GJ, Moore L, Heerasing N, Hendy P, Perry MH, McDonald TJ, et al. Faecal calprotectin effectively excludes inflammatory bowel disease in 789 symptomatic young adults with/without alarm symptoms: a prospective UK primary care cohort study. Aliment Pharmacol Ther. 2018;47(8):1103-16.
53. • Almilaji O, Smith C, Surgenor S, Clegg A, Williams E, Thomas P, et al. Refinement and validation of the IDIOM score for predicting the risk of gastrointestinal cancer in iron deficiency anaemia. BMJ Open Gastroenterol. 2020;7(1). Study validation of a predictive model for GI cancer in patients with IDA
54. Silva AC, Sheppard ZA, Surgenor SL, Williams EJ, Thomas PW, Snook JA. Clinical risk factors for underlying gastrointestinal malignancy in iron deficiency anaemia: the IDIOM study. Frontline Gastroenterol. 2014;5(4):237-42.

Table 1: Important causes of iron deficiency

Insufficient dietary intake	Decreased absorption	Blood loss
Malnourishment Vegetarian Vegan	Autoimmune gastritis Bariatric surgery Coeliac disease Gastrectomy *H. pylori* Inflammatory disorders of the gastrointestinal tract e.g. inflammatory bowel disease Inherited disorders Medications e.g. Proton pump inhibitors	Bleeding disorders Blood donation Colorectal polyps Gastrointestinal cancers Gastrointestinal inflammation e.g. inflammatory bowel disease Gastrointestinal ulceration e.g. inflammatory bowel disease, gastric ulcer, duodenal ulcer Intense physical activity e.g. marathon running Medications e.g. NSAIDs, anti-coagulants Menorrhagia Surgery

Figure 1. Summary meta-estimates of prevalent gastrointestinal cancer in patients with iron deficiency with and without anaemia. Source data from Alexandre et al, 2020 (39), Ioannou et al, 2002 (7)and Rockey et al, 2020 (40).

Group	Studies	Total	Events	Proportion (%)	Proportion (95% CI)	I^2 (%)
Iron deficiency anemia						
Lower GI cancer						
Men and Post-menopausal women	16	8210	769		8.88 (8.26-9.52)	86
Pre-menopausal women	9	910	14		0.95 (0.30-1.86)	19
Upper GI cancer						
Men and Post-menopausal women	16	9632	228		1.96 (1.67-2.27)	76
Pre-menopausal women	9	910	8		0.24 (0.00-0.87)	35
Iron deficiency without anemia						
Lower GI cancer						
Men and Post-menopausal women	1	2	223		0.90 (0.11-3.20)	-
Pre-menopausal women	1	350	0		0.00 (0.00-1.05)	-
Men and women	4	3086	3		0.03 (0.00-0.39)	62
Upper GI cancer						
Men and Post-menopausal women	1	0	223		0.00 (0.00-1.64)	-
Pre-menopausal women	1	350	0		0.00 (0.00-1.05)	-
Men and women	3	2974	4		0.07 (0.00-0.59)	78
Any GI cancer						
Men and Post-menopausal women	1	350	2		0.90 (0.11-3.20)	-
Men and women	5	3329	13		0.38 (0.00-1.84)	88
Men and women (≥ 50 years)	3	252	6		2.58 (0.00-8.77)	68
Men and women (< 50 years)	3	2308	1		0.00 (0.00-0.21)	62

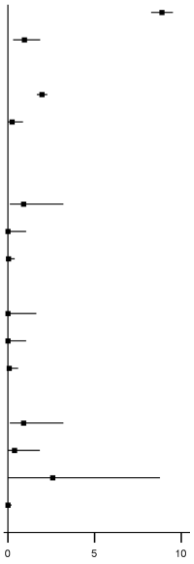

Figure 2. Proposed diagnostic algorithm for patients with confirmed iron deficiency.

Abbreviations: GI, gastrointestinal; Hb, hemoglobin; IDA, iron deficiency anemia; IDWA, iron deficiency without anemia; FC, fecal calprotectin; FIT, Fecal immunochemical test; TTG, Tissue transglutaminase; VCE, video capsule endoscopy