Item: BMJ-UK; Article ID: stus076750;
Article Type: Standard article; TOC Heading: Practice; DOI: 10.1136/bmj-2023-076750

Bmj-2023-076750

Clinical Update

Managing raised ferritin in primary care

Stuart Stewart(https://orcid.org/0000-0002-7767-4308), academic GP and research fellow,[1] research ambassador[2]

William Evans(https://orcid.org/0000-0003-0337-1221), clinical assistant professor,[3] GP with special interest in genetics[4]

Charlotte Bradbury(https://orcid.org/0000-0001-5348-8165), consultant haematologist and senior lecturer, haemochromatosis clinical lead[5]

Iain Turnbull(https://orcid.org/0000-0002-9913-1961), clinical research fellow,[6] sessional GP

Judith Hayward(https://orcid.org/0000-0001-7137-1261), GP with special interest in genetics,[4] honorary research fellow,[7] primary care adviser to Health Education England Genomics Education Programme

Jeremy Shearman(https://orcid.org/0000-0002-7314-6233), consultant gastroenterologist and hepatologist,[8] honorary associate clinical professor[9]

[1]NIHR School for Primary Care Research, Centre for Primary Care & Health Services Research, University of Manchester

[2]Rochdale Care Organisation, part of the Northern Care Alliance, Greater Manchester

[3]NIHR School for Primary Care Research, Centre for Academic Primary Care, University of Nottingham

[4]Yorkshire Regional Genetic Service

[5]University Hospitals Bristol and Weston

[6]Nuffield Department of Population Health, University of Oxford.

[7]St George's University London

[8]University NHS Foundation Trust, South Warwickshire

[9]Warwick Medical School, Warwick

Correspondence to S Stewart stuartjstewart@gmail.com

Box start

What you need to know

- Raised levels of ferritin can be associated with several serious underlying conditions and should be investigated appropriately
- Determine whether raised ferritin reflects iron overload or another disease process
- Initial tests for investigating raised ferritin in primary care are fasting transferrin saturation, full blood count, liver blood tests, and C reactive protein

- Assess patients for organ damage associated with iron overload to determine further investigations, management, and whether the patient needs to be referred to secondary care
- Haemochromatosis is a common genetic condition that can cause iron overload, and primary care clinicians can order *HFE* gene mutation analysis to diagnose the condition

Box end

A 47 year old woman who is pre-menopausal presents to her GP feeling "tired all the time." She takes thyroxine for hypothyroidism and asks when a dose increase is indicated. She discloses drinking a bottle of wine daily and reports that her sleep is rarely unbroken. You take a blood sample, and the results show raised ferritin 500 ug/L (normal range 15-300 ug/L), alanine transaminase (ALT) 100 IU/L (1-40 IU/L), and C reactive protein 70 mg/L (0-5 mg/L). Results of other investigations are normal, including full blood count, kidney function, and thyroid function.

Serum ferritin is a commonly requested investigation in primary care.[1] Ferritin is an intracellular iron storage protein.[2] It can represent total iron stores[3] and is most often requested in primary care when investigating anaemia or associated symptoms (fatigue, restless legs, hair loss).[1] It is also commonly requested in further investigation of abnormal liver blood results[4] or to monitor patients with iron overload.[1] Low serum ferritin indicates low iron stores and is usually easy to interpret and manage; however, raised serum ferritin often presents a significant diagnostic challenge owing to multiple possible causes.

Ferritin is an acute phase reactant and rises in multiple acute inflammatory conditions and as a result of chronic inflammation.[5] Up to 10% of patients with raised ferritin may have iron overload.[3 5] Identifying the underlying cause of raised ferritin is important because of the need to assess for serious underlying disease and potential organ specific complications. General practitioners who routinely manage multisystem disease are ideally placed to consider and detect the multi-organ pathology associated with iron overload.[6] Our diagnostic approach to managing raised ferritin in primary care is underpinned by evidence on the multisystem consequences of iron overload[2 7-11] and updated European guidelines on the management of haemochromatosis.[12]

How should I explain raised ferritin to a patient?

Before explaining the result, we recommend reviewing the initial reason the test was requested and how the result may or may not be in line with the initial thought process. We suggest explaining:

- Ferritin is a marker of iron stores in the body, and raised ferritin can be caused by many conditions
- Why ferritin was requested (ie, suspicion of anaemia or iron deficiency)
- Raised ferritin levels should be further investigated—this may be because of a condition the patient already knows about or an undiagnosed condition, such as alcohol excess with fatty liver disease. Common causes of raised ferritin are outlined in the infographic.
- A transient rise in ferritin is seen during acute illness and is not always a concern.

How should I investigate raised ferritin?

The infographic shows an algorithm for the management of raised ferritin in primary care, based on the European Association for the Study of the Liver Clinical Practice Guidelines for the management of haemochromatosis 2022.[12] The algorithm comprises three stages.

Step 1: Initial clinical assessment

Some clinical information will already be known prior to identifying raised ferritin. Step 1 reiterates the key information which supports clinicians in determining the underlying cause. This includes assessing alcohol consumption, other risk factors for liver disease, acute illness, family history, and red flags for malignancy. Clinical examination includes looking for signs of chronic liver disease. This step is increasingly important because clinicians often review and manage investigations in patients they have not seen, and the clinical considerations of the reviewing clinician may differ from those of the requesting clinician (eg, ferritin is most frequently requested when iron deficiency is suspected).[1] Although no established guidelines exist on repeat testing, in our experience, we recommend re-testing serum ferritin six weeks after an acute illness to inform the need for further investigation, including assessment of iron overload.

Step 2: Assess for iron overload

Initial assessment of iron overload (step 2) is determined by measuring morning serum transferrin saturation (TSAT).[7 12] TSAT levels can fluctuate considerably because of diurnal variation,[13] dietary iron intake,[13] and menstruation,[3] and morning/fasting measurements reduce some of this variation. Borderline TSAT results should be repeated and a morning fasting TSAT considered.[3] Normal TSAT threshold is <45% in women and <50% in men[5]; our algorithm adopts a widely used combined threshold of 45% for both sexes.[12] Serum levels above these thresholds may indicate iron overload. A TSAT >45% has high sensitivity in detecting homozygous *p*C282Y[7] (94% in men and 74% in women).

Step 3: Assess for serious underlying disease

After determining presence (or absence) of iron overload, assess the patient for underlying disease (step 3). For patients with isolated hyperferritinaemia (raised ferritin, TSAT <45%), important causes to be considered are highlighted in the infographic. For patients with raised ferritin with TSAT >45% (possible iron overload) an important and frequently underdiagnosed[1 6 10-12] cause is haemochromatosis (box 1).[5 7] Other less frequent causes include transfusion related iron overload[25] and primary bone marrow disorders.[7] Clinicians can confidently diagnose haemochromatosis with targeted mutation testing of the *HFE* gene. This is widely available in primary care in the UK[26] and internationally. Ferritin >1000 ug/L is associated with serious underlying disease including iron overload (ref: Ogilive, O'Cullis). Refer all patients with unexplained persistent ferritin >1000ug/L to a hepatologist (ref: O'Cullis, EASL).

Table 1 Summary of system complications of iron overload[2 4 7-12 14-19]

System	Complications	Assessment of complications
Liver	Chronic liver disease Liver fibrosis/cirrhosis Hepatocellular carcinoma	Primary care: Liver blood tests C reactive protein and clotting studies Fibrosis-4 (FIB-4, non-alcoholic fatty liver disease (NAFLD) fibrosis score, or enhanced liver fibrosis (ELF) score Liver ultrasound scan. Referral to secondary care for consideration of: Liver fibroscan (elastography) Liver magnetic resonance imaging (MRI) scan Liver biopsy
Musculoskeletal	Arthropathies Osteoporosis	Primary care: Plan film x ray image of affected joints Dual energy x ray absorptiometry (DEXA) scan Fracture risk assessment (FRAX). Referral to secondary care for consideration of joint MRI scan
Endocrine and metabolic	Diabetes Hypogonadism Hypopituitarism	Primary care: HbA_{1c} Fasting glucose Thyroid stimulating hormone Follicle stimulating hormone, luteinising hormone, sex hormone binding globulin, testosterone, free testosterone, oestradiol. Referral to secondary care for consideration of brain/pituitary MRI scan
Reproductive	Infertility	Primary care:

	Subfertility Low libido Erectile dysfunction	Fertility: in addition to sex hormone analysis, clinicians can request semen analysis for men. Referral to secondary care for consideration of female fertility assessment
Cardiovascular	Cardiomyopathy Heart failure Arrhythmia Increased cardiovascular risk	Primary care: Electrocardiograph Echocardiogram Assessment of cardiovascular risk using QRISK2 or QRISK3. Referral to secondary care for consideration of cardiac MRI scan
Neurological	Dementia Movement disorders Acceleration of existing neurological conditions	Referral to secondary care for consideration of brain MRI scan, further specialist investigations
Psychological	Low mood Anxiety Fatigue	Primary care: Screening for depression, anxiety, fatigue

Box start

Box 1 Haemochromatosis

In northern Europe, haemochromatosis is the most common disease caused by a single pathogenic variant, with one in 150-220 individuals in the UK homozygous for the *p*C282Y variant[7] (and one in 385 individuals in the US[20]). Patients with other genotypes (including compound heterozygote *p*C282Y/H63D) are less likely to develop iron overload and significant morbidity.[12]

Variable penetrance means that many individuals do not develop severe iron overload and/or "classic" haemochromatosis. A large prospective cohort study in Australia found that 35% of male versus 6% of female *p*C282Y homozygotes developed serious iron overload (defined as ferritin levels >1000 ug/L).[21] For individuals who do develop iron overload, the clinical effects of this condition are insidious, frequently resulting in late diagnosis when organ damage has already occurred.[7 12] Iron overload in haemochromatosis is associated with many potentially irreversible health consequences and reduced life expectancy.[13 18 22] Early diagnosis and treatment with venesection can prevent liver cirrhosis, hepatocellular carcinoma, diabetes, arthropathy, and other complications, and patients often have a normal life expectancy.[12]

Differences between sexes

Although haemochromatosis is an autosomal recessive condition, clinical manifestation is often later in women because of iron loss from menstruation, pregnancy, and lactation.[7 23] Overall, men are generally at a greater risk of developing iron overload, associated complications,[7] and death.[24]

Who should be tested?

Adults who present with fatigue, joint pain, arthritis, osteoporosis, diabetes, chronic liver disease, primary liver cancer, reproductive or sexual dysfunction, and/or a family history of haemochromatosis should be tested for haemochromatosis with *HFE* gene mutation analysis.[12]

What information should I give to patients?

Iron overload is associated with many long term health consequences. Lifelong monitoring and treatment are needed to manage haemochromatosis. This includes venesection and regular blood

tests. Once venesection has helped lower a patient's ferritin level to within a normal range (induction phase) they are potentially eligible to be a blood donor to manage their haemochromatosis (maintenance phase). Abstinence from alcohol is recommended in patients with evidence of iron overload and/or liver cirrhosis. All patients should avoid iron supplements. First degree relatives should be screened for haemochromatosis.
Box end

How should I assess someone with iron overload?

In primary care, assess patients with iron overload to determine whether they have organ dysfunction. Some patients may show clear signs of organ involvement from existing clinical information (eg, liver dysfunction identified from abnormal blood test results). For others, a more proactive assessment is needed (eg, inquiring about family planning and sexual dysfunction) which is summarised in table 1.

Liver

The liver is the largest store of iron in the body and the organ most at risk of iron overload.[2] Liver iron deposition can result in inflammation (hepatitis), chronic liver disease, cirrhosis (8% of women; 25% of men with haemochromatosis[7]), and hepatocellular carcinoma.[7 25]

To assess for liver injury, initial investigations include liver blood tests, C reactive protein, and clotting studies. A review of alcohol consumption is essential for determining contributing factors and management advice. If liver blood test results are abnormal, investigate further with a liver ultrasound scan, testing for HbA_{1c} and autoantibodies, and screening for hepatitis B and C, as well as other investigations according to local pathways. These include non-invasive measures of liver fibrosis, which are increasingly available in primary care (fibrosis-4 (FIB-4), non-alcoholic fatty liver disease (NAFLD) fibrosis score, and enhanced liver fibrosis (ELF) score).[4 14]

Hepatic iron overload should be assessed in secondary care in patients with raised ferritin, raised transferrin saturation, and abnormal liver blood test results, or in those with an unclear cause of hyperferritinaemia.[12] Specialist investigations may be needed, including magnetic resonance imaging (MRI) of the liver, measurement of iron concentration, liver elastography (FibroScan) to assess for fibrosis, and potentially liver biopsy.[12] Patients with cirrhosis are at an increased risk of hepatocellular carcinoma and require surveillance by a specialist.[12]

Musculoskeletal

Joint disease is a common presenting symptom in patients with haemochromatosis (affecting 24%).[7 12] This can mimic osteoarthritis[7 12] but with an earlier age of onset, and affects both

weight bearing and non-weight bearing joints such as the ankle and the second and third metacarpophalangeal joints.[27] A lesser known consequence of iron overload is osteoporosis,[11 27] with prevalence estimates ranging from 25.3% to 34.2% which may be independent of cirrhosis and hypogonadism.[27-30] Osteoporosis and fracture risk are assessed in primary care using dual energy x ray absorptiometry (DEXA) imaging and calculation of FRAX (fracture risk assessment) score, respectively.[15] Refer patients to a rheumatologist for further evaluation and management of joint disease.

Endocrine and metabolic

Diabetes is the most common endocrinopathy (23% prevalence) associated with iron overload caused by haemochromatosis.[8] Although historical descriptions report iron deposition in pancreatic β cells resulting in insulin deficiency, hepatocellular iron also causes insulin resistance and impaired glucose tolerance.[2] Hypogonadism is the second most common endocrinopathy[8] in haemochromatosis, caused by pituitary iron deposition and/or primary gonadal failure.[8] Mixed quality epidemiological data in a general adult population of men show hypogonadism prevalence ranging from 2.1% to 38.7%, indicating that the condition is potentially under investigated and under diagnosed.[16]

Initial investigations include thyroid stimulating hormone, HbA_{1c}, fasting glucose, follicle stimulating hormone, luteinising hormone, sex hormone binding globulin, morning total testosterone, free testosterone, and oestradiol. Testing of sex hormone levels should be repeated after four weeks to determine if the thresholds for further investigation and treatment are met. Refer patients with abnormal results or if clinically concerned to an endocrinologist for further assessment.

Reproductive and sexual functioning

The role of iron in reproductive and sexual functioning is complex, with both iron deficiency and iron overload contributing to dysfunction via different mechanisms.[26] Specifically, iron overload may increase the risk of infertility, subfertility,[8 26] and sexual dysfunction (low libido, erectile dysfunction, amenorrhoea)[12] through hypopituitarism, hypogonadism, direct sex organ dysfunction, and increased oxidative stress on gametes.[8 12 26 31] Self-reported survey data from patients with haemochromatosis show sexual dysfunction symptom prevalence ranges from 25.8%[17] to 57.3%,[18] supporting the international recommendations to screen for reproductive and sexual dysfunction.[12]

Clinicians in primary care should inquire about family planning, difficulties conceiving, and sexual function. In addition to sex hormone analysis, clinicians can request semen analysis for men, with onward referral to a fertility specialist. Refer women who have iron overload and report difficulties conceiving to a fertility specialist.

Cardiovascular

Cardiomyopathy, although rare in haemochromatosis,[7] is a more frequent manifestation of secondary or transfusional iron overload. A large, retrospective cohort study of patients with predominantly transfusional iron overload showed that nearly 30% of patients had experienced one or more features of cardiovascular disease (conduction disorders, arrhythmias, congestive heart failure, pulmonary hypertension, and non-ischaemic cardiomyopathy).[32] Patients with haemochromatosis may also have an increased prevalence of such cardiovascular disease (odds ratio, OR, 1.24, 95% confidence interval, CI, 1.03 to 1.48, P<0.05) and, in particular, supraventricular arrhythmia (OR 1.59, 95% CI 1.28 to 1.96, P<0.001).[32] These data[32] may represent disease association rather than a feature of cardiac iron, but they serve to highlight important cardiovascular diagnoses, which may be preventable or reversible with early diagnosis and treatment.[12 19]

Initial investigations for cardiovascular disease include lipid profile, electrocardiogram, echocardiography, and assessment of overall cardiovascular risk using QRISK2 or QRISK3.[19] Refer patients with iron overload and signs and symptoms of cardiovascular disease to a cardiologist for further assessment.[12]

Neurological

Although evidence is currently limited and of varying quality, there is increasing interest in an association of iron overload with neurological conditions such as dementia[9] and movement disorders.[10] Recent cohort studies using UK biobank data found incident diagnoses of dementia were more common in male *p*C282Y homozygotes (hazard ratio, HR, 1.83)[9] versus female, and an increased prevalence of movement disorders in male *p*C282Y homozygotes (OR 1.80; 95% CI 1.28 to 2.55; P=0.001) but not in female *p*C282Y homozygotes (OR 1.09; 95% CI 0.7 to 1.73; P=0.69).[10] Refer to a neurologist if clinically concerned.

Psychological

The psychological impact of iron overload secondary to haemochromatosis is little understood and is recommended as a research priority.[18] Self-reported survey data of 2851

individuals (62% male; 99% white ethnicity) with haemochromatosis from 20 countries highlights 20.8% reported symptoms of depression, with 40.8% reporting improvements in depression symptoms after venesection treatment.[17] Further data of 1998 patients with haemochromatosis report that 73% experience psychological and cognitive difficulties.[18] Despite the inherent limitations of self-reported data, this suggests a large degree of co-existing psychological burden.[18] Inquire about the psychological impact of iron overload and for symptoms of psychological disease, eg, depression and anxiety.

When should I refer?

For patients with raised ferritin and without iron overload (TSAT <45%), refer to a specialist when the cause of the raised ferritin is uncertain, and/or for further management advice regarding potentially underlying disease.[12] Generalists may repeat ferritin and TSAT tests to determine trends while considering causes detailed in the infographic.

All patients receiving a diagnosis of iron overload should have *HFE* genotyping performed in primary care (with appropriate counselling) prior to referral. Patients who are *p*C282Y homozygous with iron overload should be referred to a physician with an interest in haemochromatosis for consideration of venesection, and should also be referred to a hepatologist for assessment of liver fibrosis. Patients who are not *p*C282Y homozygous with iron overload (unexplained biochemical iron overload) should be referred for further assessment and management according to local pathways.

Clinical vignette revisited

After asking further key clinical questions to help determine the underlying cause of the raised ferritin, ALT, and C reactive protein (step 1), you perform fasting TSAT (step 2), which comes back borderline at 45%. *HFE* gene mutation analysis shows the patient is not homozygous for *p*C282Y and is therefore at low risk of a genetic cause of iron overload. You consider this to be “unexplained biochemical iron overload” and refer to a hepatologist for assessment of increased liver iron (step 3). Ultrasound imaging reveals a bright echotexture consistent with fatty change. After advice and support resulting in reduced alcohol consumption, the patient’s ferritin, ALT, and C reactive protein normalise, and her sleep disturbance improves.

Box start

Education into practice

• How often do you request transferrin saturation after identifying a patient with raised ferritin?

• How would you discuss the possible organ complications of iron overload with patients?

Box end

Box start

How patients were involved in the creation of this article

• Author Stuart Stewart is a patient (and GP) with haemochromatosis who has experienced organ dysfunction resulting from iron overload. Experiences as a patient and GP managing the diagnostic dilemma of raised ferritin helped shape the systematic approach to investigating patients with iron overload in primary care.

Box end

Box start

Future recommendations for research

• Given the prevalence of *p*C282Y homozygosity, research should focus on the disease expression and the contribution of excess iron to chronic liver disease, joint disease, and diabetes.

• National screening for haemochromatosis is not recommended currently. Further evidence needs to inform future screening considerations.

• Research should seek to understand the barriers to systematic and comprehensive assessment of iron overload in primary care.

Box end

<graphic>stus076750.f1</graphic>

Web extra BMJ infographic

Supplementary materials

file: stus076750.ww1

Contributorship: SS and JS wrote the paper based on discussions amongst all authors. All authors reviewed and contributed to each draft. We acknowledge the contribution of Howard Don, patient and president of Haemochromatosis International.

Competing interests: none disclosed.

Provenance and peer review: commissioned, based on an idea from the author; externally peer reviewed.

<jrn<jrn>1 Ogilvie C, Fitzsimons K, Fitzsimons EJ. Serum ferritin values in primary care: are high values overlooked? *J Clin Pathol* 2010;63:1124-6. PubMed doi:10.1136/jcp.2010.083188</jrn</jrn>

<jrn<jrn>2 Fernández-Real JM, Manco M. Effects of iron overload on chronic metabolic diseases. *Lancet Diabetes Endocrinol* 2014;2:513-26. PubMed doi:10.1016/S2213-8587(13)70174-8</jrn</jrn>

<jrn<jrn>3 Cullis JO, Fitzsimons EJ, Griffiths WJ, Tsochatzis E, Thomas DW; British Society for Haematology. Investigation and management of a raised serum ferritin. *Br J Haematol* 2018;181:331-40. PubMed doi:10.1111/bjh.15166</jrn</jrn>

<jrn<jrn>4 Newsome PN, Cramb R, Davison SM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018;67:6-19. PubMed doi:10.1136/gutjnl-2017-314924</jrn</jrn>

<jrn<jrn>5 Koperdanova M, Cullis JO. Interpreting raised serum ferritin levels. *BMJ* 2015;351:h3692. PubMed doi:10.1136/bmj.h3692</jrn</jrn>

<jrn<jrn>6 Sood R, Bakashi R, Hegade VS, Kelly SM. Diagnosis and management of hereditary haemochromatosis. *Br J Gen Pract* 2013;63:331-2. PubMed doi:10.3399/bjgp13X668410</jrn</jrn>

<edb<edb>7 Olynyk JK, Ramm GA. Hemochromatosis. *N Engl J Med* 2022;387:2159-70.</edb</edb>

<jrn<jrn>8 Pelusi C, Gasparini DI, Bianchi N, Pasquali R. Endocrine dysfunction in hereditary hemochromatosis. *J Endocrinol Invest* 2016;39:837-47. PubMed doi:10.1007/s40618-016-0451-7</jrn</jrn>

<jrn<jrn>9 Atkins JL, Pilling LC, Heales CJ, et al. Hemochromatosis mutations, brain iron imaging, and dementia in the UK Biobank cohort. *J Alzheimers Dis* 2021;79:1203-11. PubMed doi:10.3233/JAD-201080</jrn</jrn>

<jrn<jrn>10 Loughnan R, Ahern J, Tompkins C, et al. Association of genetic variant linked to hemochromatosis with brain magnetic resonance imaging measures of iron and movement disorders. *JAMA Neurol* 2022;79:919-28. PubMed doi:10.1001/jamaneurol.2022.2030</jrn</jrn>

<jrn<jrn>11 Pilling LC, Tamosauskaite J, Jones G, et al. Common conditions associated with hereditary haemochromatosis genetic variants: cohort study in UK Biobank. *BMJ* 2019;364:k5222. PubMed doi:10.1136/bmj.k5222</jrn</jrn>

<jrn<jrn>12 Zoller H, Schaefer B, Vanclooster A, et al; European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL clinical practice guidelines on haemochromatosis. *J Hepatol* 2022;77:479-502. PubMed doi:10.1016/j.jhep.2022.03.033</jrn</jrn>

<jrn<jrn>13 Elsayed ME, Sharif MU, Stack AG. Transferrin saturation. *Adv Clin Chem* 2016;75:71-97. PubMed doi:10.1016/bs.acc.2016.03.002</jrn</jrn>

<jrn<jrn>14 European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015;63:237-64. PubMed doi:10.1016/j.jhep.2015.04.006</jrn</jrn>

<jrn<jrn>15 Gregson CL, Armstrong DJ, Bowden J, et al. UK clinical guideline for the prevention and treatment of osteoporosis. *Arch Osteoporos* 2022;17:58. PubMed doi:10.1007/s11657-022-01061-5</jrn</jrn>

<jrn<jrn>16 Defeudis G, Mazzilli R, Gianfrilli D, Lenzi A, Isidori AM. The CATCH checklist to investigate adult-onset hypogonadism. *Andrology* 2018;6:665-79. PubMed doi:10.1111/andr.12506</jrn</jrn>

<unknown<unknown>17. McDonnell SM, Preston BL, Jewell SA, et al. A survey of 2851 patients with hemochromatosis: symptoms and response to treatment. 1999;106:619-24.</unknown</unknown>

<bok<bok>18 Smith KJ, Griffiths W, Fife-Schaw C, Dibb B. *Living with the impact of iron overload.* 2018.</bok</bok>

<eref<eref>19 National Institute for Health and Care Excellence. Clinical Knowledge Summaries. Scenario: CVD risk assessment. Management. CVD risk assessment and

management. 2022. https://cks.nice.org.uk/topics/cvd-risk-assessment-management/management/cvd-risk-assessment/</eref</eref>

<jrn<jrn>20 Steinberg KK, Cogswell ME, Chang JC, et al. Prevalence of C282Y and H63D mutations in the hemochromatosis (*HFE*) gene in the United States. *JAMA* 2001;285:2216-22. PubMed doi:10.1001/jama.285.17.2216</jrn</jrn>

<jrn<jrn>21 Allen KJ, Gurrin LC, Constantine CC, et al. Iron-overload-related disease in *HFE* hereditary hemochromatosis. *N Engl J Med* 2008;358:221-30. PubMed doi:10.1056/NEJMoa073286</jrn</jrn>

<eref<eref>22 Haemochromatosis UK. Genetic haemochromatosis—a quick guide for GPs. 2021. https://www.haemochromatosis.org.uk/genetic-haemochromatosis-a-quick-guide-for-gps</eref</eref>

<jrn<jrn>23 Olynyk JK, Cullen DJ, Aquilia S, Rossi E, Summerville L, Powell LW. A population-based study of the clinical expression of the hemochromatosis gene. *N Engl J Med* 1999;341:718-24. PubMed doi:10.1056/NEJM199909023411002</jrn</jrn>

<jrn<jrn>24 Atkins JL, Pilling LC, Masoli JAH, et al. Association of hemochromatosis *HFE* p.C282Y homozygosity with hepatic malignancy. *JAMA* 2020;324:2048-57. PubMed doi:10.1001/jama.2020.21566</jrn</jrn>

<jrn<jrn>25 Sandnes M, Ulvik RJ, Vorland M, Reikvam H. Hyperferritinemia—a clinical overview. *J Clin Med* 2021;10:2008. PubMed doi:10.3390/jcm10092008</jrn</jrn>

<jrn<jrn>26 Li X, Duan X, Tan D, et al. Iron deficiency and overload in men and woman of reproductive age, and pregnant women. *Reprod Toxicol* 2023;118:108381. PubMed doi:10.1016/j.reprotox.2023.108381</jrn</jrn>

<jrn<jrn>27 Powell LW, Seckington RC, Deugnier Y. Haemochromatosis. *Lancet* 2016;388:706-16. PubMed doi:10.1016/S0140-6736(15)01315-X</jrn</jrn>

<jrn<jrn>28 Sinigaglia L, Fargion S, Fracanzani AL, et al. Bone and joint involvement in genetic hemochromatosis: role of cirrhosis and iron overload. *J Rheumatol* 1997;24:1809-13. PubMed</jrn</jrn>

<jrn<jrn>29 Guggenbuhl P, Deugnier Y, Boisdet JF, et al. Bone mineral density in men with genetic hemochromatosis and HFE gene mutation. *Osteoporos Int* 2005;16:1809-14. PubMed doi:10.1007/s00198-005-1934-0</jrn</jrn>

<jrn<jrn>30 Valenti L, Varenna M, Fracanzani AL, Rossi V, Fargion S, Sinigaglia L. Association between iron overload and osteoporosis in patients with hereditary hemochromatosis. *Osteoporos Int* 2009;20:549-55. PubMed doi:10.1007/s00198-008-0701-4</jrn</jrn>

<jrn<jrn>31 El Osta R, Grandpre N, Monnin N, Hubert J, Koscinski I. Hypogonadotropic hypogonadism in men with hereditary hemochromatosis. *Basic Clin Androl* 2017;27:13. PubMed doi:10.1186/s12610-017-0057-8</jrn</jrn>

<jrn<jrn>32 Udani K, Chris-Olaiya A, Ohadugha C, Malik A, Sansbury J, Paari D. Cardiovascular manifestations in hospitalized patients with hemochromatosis in the United States. *Int J Cardiol* 2021;342:117-24. PubMed doi:10.1016/j.ijcard.2021.07.060</jrn</jrn>