UK National Screening Committee

Screening for hereditary haemochromatosis in adults

External review against programme appraisal criteria for the UK National Screening Committee

Version: FINAL

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The UK National Screening Committee secretariat is hosted by Public Health England.

About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes. Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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Plain English summary

Hereditary haemochromatosis is an inherited condition. It is caused by a faulty gene. It can lead to people to have too much iron in their body. This can put them at higher risk for problems with their heart, joints, and liver. Treatments to remove the extra iron from the body can lower a person's chance of having health problems.

Screening might help to find people who have hereditary haemochromatosis, but do not know that they have it. By finding people with this condition, they can get treatment sooner. This might stop the long-term problems that hereditary haemochromatosis might cause.

The last UK National Screening Committee review was published in 2015. It concluded that screening for hereditary haemochromatosis was not recommended. The key reasons were that it was not clear how many people with the faulty gene would go on to have symptoms, nor how bad the symptoms would be, or if screening would help.

The current review looked at the evidence about:

- The health outcomes of people with hereditary haemochromatosis
- Whether people with health problems were more likely to have hereditary haemochromatosis
- Whether earlier treatment for hereditary haemochromatosis is better than later treatment
- Whether screening for hereditary haemochromatosis is helpful

The review found that:

- The chances of having raised iron in the body are higher for people who have the faulty gene than those who do not
- The chances of having the faulty gene are higher in people with raised levels of iron in their body than those with normal levels of iron
- Some people with hereditary haemochromatosis will have other health problems like extreme tiredness, liver cancer, and pneumonia. But most people will not
- It is unclear if earlier treatment is better than later treatment
- It is not known if screening would be helpful to people who have hereditary haemochromatosis

Based on the current evidence, this review does not recommend screening for hereditary haemochromatosis in adults.

Executive summary

Purpose of the review

The purpose of the review was to examine (1) the proportion of people with type 1 hereditary haemochromatosis (HH) genetic mutations who develop biochemical/clinical outcomes, (2) the proportion of people with type 1 hereditary haemochromatosis-related biochemical/clinical outcomes who have type 1 hereditary haemochromatosis-associated genetic mutations in the HFE gene, (3) if earlier treatment leads to better outcomes than later treatment, and (4) if screening for type 1 HH is beneficial.

Background

Hereditary Haemochromatosis (HH) is the most common genetic predisposition disorder found in Caucasians, and one of the most common amongst people in Northern Europe. Type 1 HH is caused by the following mutations to the HFE gene: C282Y homozygosity, H63D homozygosity and C282Y/H63D compound heterozygosity. This form of haemochromatosis is the most frequent and well-defined inherited cause of iron overload. It has been associated with a range of symptoms and clinical outcomes, including extreme tiredness, joint pain, diabetes, and liver disease.

Focus of the review

This review aimed to evaluate whether the evidence base has developed substantially and a screening programme for type 1 hereditary haemochromatosis has become viable since the previous UK National Screening Committee (NSC) review was conducted in 2015. Specifically, new evidence was collected to answer the following 4 key questions, and 2 sub-questions.

1. What is the penetrance of type 1 HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity?
   Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible? (NSC criterion 1)
2. What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)?
   Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible? (NSC criterion 1)

3. Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms? (NSC criterion 9)
4. What is the effectiveness of screening to reduce HH-related morbidity and mortality? (NSC criteria 11 and 13)

This is a rapid review with prioritisation of larger studies that had control/comparator groups that meet the review inclusion criteria.

Recommendation under review

The current UK NSC recommendation is not to screen for type 1 HH. This is based on the most recent UK NSC review from 2015 which determined that a lack of evidence prevented conclusions being drawn on (1) the penetrance and expressivity of the HFE genotypes in the general population, and (2) whether there was an effective screening strategy for use in the general population.

Findings and gaps in the evidence of this review

Key question 1: What is the penetrance of type 1 HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity?

Key question 2: What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)?

Twelve prioritised studies (and 45 deprioritised articles) were identified that provided data for question 1, and 13 prioritised studies (and 46 deprioritised articles) were identified that provided data for question 2.

Penetrance

For each of the 3 genotypes, the proportion of people with elevated serum ferritin (median = 34%) and elevated transferrin saturation (median = 26%), and fatigue (34%) was generally high. While the proportion of people with clinical outcomes was generally low. For people with the homozygous C282Y mutation, cohort studies indicated that penetrance was less than 5% for rheumatoid arthritis, osteoporosis, atrial fibrillation, heart failure, liver disease, and pneumonia, 5% for fatigue, 3.2 – 6.7% for diabetes, 9.1% for myocardial infarction, 14.2% for osteoarthritis, and 15.6% for mortality. For people with the homozygous H63D mutation, cohort studies indicated that penetrance was less than 10% for diabetes, heart

failure, and myocardial infarction, 17.5% for mortality, and 47.1% for fatigue. For people with the compound heterozygous C282Y/H63D mutation, cohort studies indicated that penetrance was less than 5% for myocardial infarction, 5 – 9.9% for diabetes and heart failure, 15.5% for mortality, and 49.2% for fatigue.

Measurements of association

Homozygous C282Y mutations were associated with elevated serum ferritin, elevated transferrin saturation, hyperpigmentation, any liver disease, liver cancer, and having at least 1 clinical outcome. Inconsistent results were reported for diabetes and fatigue. Additional data from deprioritised studies may provide some clarity on their potential association with the homozygous C282Y genotype. No associations with this genotype were found for any other clinical conditions.

Homozygous H63D mutations were associated with elevated transferrin, with mixed evidence regarding elevated serum ferritin. No associations with this genotype were found for any of the clinical conditions.

Compound heterozygous C282Y/H63D mutations were associated with elevated serum ferritin, elevated transferrin saturation, and liver cancer. No associations with this genotype were reported for any of the clinical conditions.

Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?

The evidence in this review is based on studies that were typically at moderate-to-high (question 1) and high or unclear (question 2) risk of bias. In summary, there is clear and consistent evidence for an association between the 3 type 1 HH genotypes and iron overload. However, some inconsistent results were reported in relation to the association between elevated serum ferritin and the homozygous H63D genotype. Serum ferritin and transferrin saturation are extremely common outcomes in the deprioritised studies. Pooling together prioritised and deprioritised studies in a systematic review and/or meta-analysis may help to provide more refined estimates of penetrance and associations between genotypes and iron overload. In relation to the homozygous H63D mutation, a meta-analysis would also provide clarity on the mixed results of the present review and it would help to understand the potential associations between the homozygous H63D genotype and elevated serum ferritin. Nevertheless, it is worth noting that these are biochemical outcomes, which may or may not have clinical implications for individuals.

The evidence regarding clinical conditions generally does not support associations with type 1 HH genotypes. The exceptions were liver cancer (only in relation to the compound heterozygous C282Y/H63D genotype), as well as hyperpigmentation, liver disease (any or liver cancer), and 'any' clinical outcome (limited to the homozygous C282Y genotype). Inconsistent results were reported in relation to the association of diabetes and fatigue with the homozygous C282Y genotype. Additional data on diabetes and fatigue from deprioritised studies may provide some clarity on their potential association with the homozygous C282Y genotype.

Overall, potential associations between type 1 HH genotypes and biochemical and clinical outcomes have been examined in a reasonable number of studies. However, for many of the outcomes (by genotype) the data are limited to individual studies, often with limited sample size and suboptimal study designs. In particular, many papers reported clinical conditions data from studies that employed cross-sectional designs that assess outcomes at a single point in time. Prospective cohort studies with longer follow up times would be better suited for identifying health outcomes that require years to develop and manifest clinically.

UK NSC criterion 1: **MIXED (but overall, NOT MET)**

MET: serum ferritin, transferrin saturation
NOT MET: angina, arthritis, atrial fibrillation, cardiomyopathy, cirrhosis, diabetes, fatigue, heart failure, hyperpigimentation, idiopathic cardiomyopathy, liver cancer, liver disease, mortality, myocardial infarction, non-alcoholic fatty liver disease, osteoporosis, and pneumonia.

Key question 3: Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms?

One systematic review (published in 2006) and one cohort study nested in a randomised controlled trial (RCT) were identified to inform this question. The systematic review did not find any studies examining if treatment at a pre-symptomatic (or earlier) stage of type 1 HH leads to better outcomes than treatment at symptomatic (or later) stage of type 1 HH. The cohort study (nested within an RCT) examined the effectiveness of erythrocytopharesis in people with the C282Y homozygous type 1 HH genotype. A post-hoc analysis compared the effect of erythrocytapheresis on fatigue between participants who were symptomatic and asymptomatic at baseline. Mean fatigue scores were lower after treatment for both groups: asymptomatic group -6.1 points (95% CI -9.6 to -2.6), symptomatic group -8.8 points (95% CI -15.3 to -2.3 points). The authors reported no statistically significant difference between the change scores of the 2 groups (2.7 points, 95% CI -10.1 to 4.6

points). Overall, the study was judged to have unclear risks of bias, with applicability concerns as the study population, type of treatment, and end-point do not reflect UK clinical practice.

UK NSC criterion 9: **NOT MET**

Key question 4: What is the effectiveness of screening to reduce type 1 HH-related morbidity and mortality?

No eligible studies were identified which reported the benefits of screening for type 1 HH in adults.

UK NSC criteria 11 and 13: **NOT MET**

Recommendations on screening

Based on the overall synthesis of evidence against the UK NSC criteria, the current recommendation of not screening for hereditary haemochromatosis in adults should be retained.

In line with the 2015 UK NSC review and other published research, this evidence summary found that the penetrance of the type 1 HH genotypes is low. In addition, the reviewers did not identify any controlled trials examining either the benefits of screening for type 1 HH in adults or the benefits of earlier versus later treatment. On this basis, the reviewers found no reason to change the conclusion of the previous review, that systematic population screening for type 1 HH should not be recommended.

Limitations

The reviewers used a rapid evidence assessment approach. This review only included peer-reviewed journal publications in the English language. Eighty percent of assessments, extractions, and quality appraisal were conducted by a single reviewer. Study design filters were applied to the search strategy, a select number of outcomes was assessed, and a hierarchy of evidence approach was applied to studies meeting the inclusion criteria, which means that the conclusions were based on data from the highest level of evidence and the largest studies. Given that these are accepted methodological adjustments for a rapid review, and that the searches for this evidence summary covered relevant literature since

1996 (when the HFE mutation was first discovered), these limitations should not have led to the exclusion of any pivotal studies.

Evidence uncertainties

There is considerable uncertainty regarding the penetrance of type 1 HH genotypes. For example, there is evidence that some biochemical and clinical outcomes are more common amongst people with type 1 HH genotypes than those with the wild type genotype. However, the proportion of individuals with clinical outcomes was often typically low. Further, there are important gaps in the evidence in relation to a lack of (1) RCT evidence on the benefits of screening for type 1 HH in adults, and (2) controlled trials comparing treatment effects at pre-symptomatic (or earlier) versus symptomatic (or later) phases of HH.

Introduction and approach

Background

Condition

Hereditary haemochromatosis (HH) is an inherited, autosomal recessive genetic predisposition condition.[1] Four types of HH have been reported.[2] They are caused by mutations in the human haemochromatosis protein (HFE) gene (type 1 HH), hemojuvelin bone morphogenetic protein co-receptor and hepcidin antimicrobial peptide genes (type 2, or juvenile, HH), transferrin receptor 2 gene (type 3 HH), and ferroportin gene (type 4 HH).[3] In keeping with previous NSC reviews on the topic, only type 1 HH is considered here. Type 1 HH is the most common genetic predisposition disorder found in Caucasians,[4] and one of the most common amongst people in Northern Europe.[5] Homozygosity for the C282Y mutation accounts for 60 – 90% of type 1 HH cases, compound heterozygosity for the C282Y/H63D mutation for 3 – 8% of cases, and homozygosity for the H63D mutation for approximately 1% of cases.[1] Type 1 HH is associated with a deficiency of the hormone hepcidin, which controls iron regulation within the body.[6] This deficiency can cause iron overload, [4] which may lead to liver disease (for example cancer, cirrhosis of the liver), heart failure, joint pain and arthritis, hyperpigmentation, and diabetes.[7]

Type 1 HH is characterised by incomplete penetrance. This means that only a limited proportion of people with the specific genotypes will develop the associated phenotypes, that is biochemical or clinical manifestations.[1] A range of environmental and genetic factors have been proposed as modifiers of the progression from genotype to phenotype, including alcohol consumption, blood loss from menstruation or donation, comorbid diseases, diet, and sex.[8 9] Measuring penetrance in people with type 1 HH can be difficult as symptoms such as fatigue and arthralgia are common in the general population and not specific to type 1 HH.[10] The European Association for the Study of the Liver has proposed 4 stages of HH:[10]

1. HH genotype but no other ‘abnormalities’
2. Iron overload but no symptoms
3. Iron overload with symptoms (for example fatigue)
4. Iron overload with organ damage

Approaches to screening

The evidence regarding incomplete penetrance presents a challenge for population screening of type 1 HH. Two main approaches to screening have been proposed: genotypic screening and phenotypic screening.[11] In the genotypic approach, individuals would be screened for the relevant mutation (for example homozygous C282Y or H63D, or compound heterozygous C282Y/H63D mutations), with diagnoses of type 1 HH being given on the basis of iron overload and / or symptoms. In the phenotypic approach, individuals would be screened for iron overload, with diagnosis given on the basis of the presence of the C282Y or H63D homozygous, or compound heterozygous C282Y/H63D genotype. The genotypic approach might lead to overdiagnosis as many people with the type 1 HH genotypes do not go on to develop symptoms. The phenotypic approach might lead to underdetection because people with the genotypes might not have elevated iron at the point of screening. The most recent NSC review examined whether there is an effective screening strategy for identifying type 1 HH in the general adult population and determined that there was insufficient evidence on which to draw a conclusion.[12]

A small number of studies has examined the potential psychological effects, attitudes towards, and barriers to screening for type 1 HH in adults. Uncontrolled studies of genetic screening in Australia (participants self-selecting in the work-place)[13] and the USA and Canada (population screening, HEIRS)[14 15] have indicated that there are no statistically significant changes in self-reported symptoms of anxiety and depression, or perceptions of general health pre- and post-screening. There is evidence of some unfavourable psychological impact.[14 16-18] For example, a study (conducted in the US and Canada) showed decreased general health and mental wellbeing as well as increased health worry among participants with low or indeterminate risk compared to controls with normal iron levels and no HFE mutations at 6 weeks after screening.[18] This was associated with participants' belief that their results indicated they are positive for haemochromatosis or iron overload. Thus, notification of indeterminate risk may have negative psychological implications. Nevertheless, not notifying those with indeterminate risk would raise other ethical issues. However, as none of the studies included participants who were not screened, it is not possible to know the true impact that screening might have on psychological wellbeing.

Attitudes and perceptions towards screening for type 1 HH have been reported to vary by demographic characteristics, such as age and educational background,[16 19-23] and method of screening.[17 22] For example, there is some evidence that people might prefer transferrin saturation measurement (over genetic screening only) because of the information it provides about current health. In a study in Denmark, at-risk participants who were given only genetic information demonstrated negative reactions to the test result while participants who were given both genetic and biochemical (serum ferritin and transferrin saturation) information were more satisfied and demonstrated fewer negative psychological reactions.[17] This suggests that screening might be more acceptable when biochemical measurements are offered in addition to genotyping.

Practical barriers (such as lack of time, concern about having their blood drawn and lack of interest) have been reported as common reasons why people did not want to participate in screening. [15-17 19 23-25] Other potential issues include concerns about insurance and employment discrimination.[19 23] However, only one person out of 220 reported insurance as a concern in the UK study.[19] Some individuals may be concerned about their fertility desires, especially if both partners have the same diagnosis.[16 17]

Approaches to treatment

While international guidelines differ slightly in their approaches to treatment, the premise of treatment is consistent; to counteract iron overload, prevent iron deposition in tissue, and prevent organ dysfunction.[4 5 10 26] The British Society of Haematology Committee Guidelines express that the primary treatment, phlebotomy (venesection) should be initiated in all fit patients with iron overload.[26] Biochemical response is determined by assessing biochemical iron indices, transferrin saturation and ferritin concentration.[26] Clinically, the response to treatment will not be uniform amongst all individuals. This is dictated by the degree of progression of type 1 HH amongst individuals, and the nature of symptoms within individuals; some alleviated by phlebotomy, others not.[4] Active treatment of phlebotomy is followed by maintenance treatment, in the form of regular monitoring and phlebotomy as needed.[26] Adverse events from phlebotomy include anaemia, fatigue, fainting, hematomas, and injection site pain.[27] In cases where phlebotomy is contraindicated, or not tolerated, alternative treatment strategies including iron chelation (removal of excess iron from the body with medications) and erythrocytapheresis (selective withdrawal of red blood cells) amongst others have been considered.[28] A recent systematic review concluded that there is insufficient evidence to determine if erythrocytapheresis is more/less beneficial or harmful than phlebotomy, and no evidence comparing erythrocytapheresis or phlebotomy to iron chelation.[28] Depending upon genotype, and degree of iron overload, specialist evaluation for liver pathology, including fibrosis assessment and cirrhosis, may also be recommended.[4 5 10 26]

Current policy context and previous reviews

The current UK NSC recommendation is not to screen for type 1 HH in adults. This decision was determined from 2 prior NSC reviews, which determined that a lack of evidence prevented conclusions being drawn on the penetrance and expressivity of the HFE genotypes in the general population, and on whether there was an effective screening strategy for use in the general population.[12 29] The recommendation not to offer screening to the general adult population is consistent with guidance of the U.S. Preventive Services Task Force,[30] European Association for the Study of the Liver,[10] the American Association

for the Study of Liver Diseases,[4] and the recommendation of the authors of the HEmochromatosis and IRon overload Screening (HEIRS) study regarding a primary care population.[31] These decisions were based on a lack of evidence on screening and evidence of incomplete penetrance. However, cascade testing for relatives of people with type 1 HH has been advocated in America, Europe, and the UK.[4 10 26]

In the majority of cases, conclusions not to recommend screening for type 1 HH are based on evidence published up to 14 years ago. Recent research from the UK has suggested that penetrance might be higher than previously estimated for people who have the homozygous C282Y genotype.[32] This, in combination with wider use of genomics to predict and diagnose disease, interest in targeted screening, and an aim to personalise treatments and interventions, has led to some renewed interest in the condition.

Objectives

The objectives of this review were to examine evidence about the effectiveness and appropriateness of screening for type 1 HH in asymptomatic adults, to develop a comprehensive overview of the evidence base, and to identify outcomes which may benefit from systematic reviews which might be supported by a reasonable body of evidence. The review examines 4 key questions relating to the relationship between mutations in the HFE gene (C282Y, H63D) and biochemical/clinical outcomes (questions 1 and 2), whether earlier (pre-symptomatic, or early after symptomatic presentation) treatment leads to better outcomes than later (early or late symptomatic stage) treatment (question 3), and the effectiveness of screening for HH (question 4). The review appraised evidence on the questions in Table 1, which each relate to the criteria set out by the UK NSC for assessing the suitability of a screening programme.

Table 1. Key questions for the evidence summary, and relationship to UK NSC screening criteria

	Criterion	Key questions	Studies Included
	THE CONDITION		
1	The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	1	21 prioritised papers 45 deprioritised papers
		2	21 prioritised papers 46 deprioritised papers

	Criterion	Key questions	Studies Included
	THE INTERVENTION		
9	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.	3	2
	THE SCREENING PROGRAMME		
11	There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	4	0
13	The benefit gained by individuals from the screening programme should outweigh any harms for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.	4	0

Methods

The current review was conducted by the University of Warwick, in keeping with the UK National Screening Committee evidence review process. Database searches were conducted on 18 December 2019 to identify studies relevant to the questions detailed inTable 1.

Eligibility for inclusion in the review

The following review process was followed:

1. Titles and abstracts of records identified by the searches were screened by one reviewer. A second reviewer independently assessed a random 20% sample of the titles/abstracts.
2. Full-text articles were acquired for records considered potentially relevant by either reviewer.
3. Full text articles were assessed against the inclusion/exclusion criteria by one reviewer, with a random 20% sample assessed independently by a second reviewer. Disagreements were resolved by consensus, or through discussion with a third reviewer.

Eligibility criteria for each question are presented in Table 2 below.

Table 2. Inclusion and exclusion criteria for the key questions

Key question	Inclusion criteria						Exclusion criteria
	Population	**Target condition**	**Exposure/ Intervention**	**Comparator**	**Outcome**	**Study type**	
Question 1 What is the penetrance of HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity ? Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary	Adults (18 years and older) who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity and who are not being treated for HH with phlebotomy, erythrocytapheresis , or iron chelating agents	HH	Mutation to HFE gene (C282Y homozygosity, H63D homozygosity and C282Y/H63D compound heterozygosity)	A different HFE gene mutation (C282Y and/or H63D), no mutation, or no comparator	Biochemical: Elevated blood iron parameters (serum ferritin, transferrin saturation, unsaturated iron binding capacity) Clinical (any method of identification) Mortality Clinical (diagnosed): Diabetes (diagnosed according to World Health Organisation (WHO) or American Diabetes Association criteria), any	Systematic reviews, cohort studies, case-control studies	Papers published before 1996, < 18 years, studies of non-HFE types of HH, qualitative studies, < 100 participants, insufficient information for assessment of methodological quality/risk of bias, outcomes not listed in the inclusion criteria, studies where > 10% of the sample do not meet the

estimate possible?					liver disease (including cancer) not caused by bacterial/viral infections or alcoholism, cardiovascular disease (myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation Clinical (self-reported): Fatigue/weakness		inclusion criteria, articles not available in English, grey literature, publications that contain no numerical outcomes data.
Question 2 What is the association between HH-related biochemical and clinical	Adults (18 years and older) with biochemical or clinical features of HH (see exposure/intervention column)	HH	Biochemical features: Elevated blood iron parameters (that is serum ferritin, transferrin saturation, unsaturated iron binding capacity)	Healthy controls, or no comparator	Homozygous C282Y, homozygous H63D, or compound heterozygous	Systematic reviews, case-control studies, cohort studies,	Papers published before 1996, < 18 years, studies of non-HFE types of HH,

features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)? Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?		Clinical characteristics (diagnosed): Diabetes (diagnosed according to World Health Organisation or American Diabetes Association criteria), any liver disease (including cancer) not caused by bacterial/viral infections or alcoholism, cardiovascular disease (myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation Clinical characteristics (self-reported): Fatigue/weakness	C282Y/H63D mutations	cross-sectional studies	qualitative studies, < 100 participants, insufficient information for assessment of methodological quality/risk of bias, outcomes not listed in the inclusion criteria, studies where > 10% of the sample do not meet the inclusion criteria, articles not available in English, grey literature, publications that contain no numerical outcomes data.

Question 3 Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms?	Adults (18 years and older) who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity	HH	Phlebotomy, erythrocytapheresis, iron chelating agents following pre-symptomatic detection of HH (screening, cascade testing, incidental detection), or phlebotomy, erythrocytapheresis, iron chelating agents following early symptomatic detection of HH if no studies of pre-symptomatic detection of HH are available	Phlebotomy, erythrocytapheresis, iron chelating agents following symptomatic detection of HH, or phlebotomy, erythrocytapheresis, iron chelating agents following late symptomatic detection of HH if no studies of pre-symptomatic detection of HH are available, or no comparator	Biochemical: Elevated blood iron parameters (serum ferritin, transferrin saturation, unsaturated iron binding capacity): Clinical (any method of identification): Mortality Clinical (diagnosed): Diabetes (diagnosed according to World Health Organisation or American Diabetes Association criteria), any liver disease (including cancer) not caused by bacterial/viral infections or alcoholism, cardiovascular disease	Systematic reviews, RCTs, cohort studies	Papers published before 1996, < 18 years, studies of non-HFE types of HH, qualitative studies, < 100 participants, insufficient information for assessment of methodological quality/risk of bias, outcomes not listed in the inclusion criteria, studies where > 10% of the sample do not meet the inclusion criteria, articles not available in English, grey literature, publications that contain no numerical

					(myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation Clinical (self-reported): Fatigue/weakness		outcomes data.
Question 4 What is the effectiveness of screening to reduce HH-related morbidity and mortality?	Adults (18 years and older) with no symptoms or family history of HH	HH	Genotype screening strategy: genetic testing for C282Y or H63D mutations of the HFE gene followed by assessment of blood iron parameters and/or liver biopsy, and/or magnetic resonance imaging of the liver Phenotype screening strategies: measurement of	Genotype screening strategy, phenotype screening strategies, usual care, no screening	Biochemical: Elevated blood iron parameters (serum ferritin, transferrin saturation, unsaturated iron binding capacity): Clinical (any method of identification): Mortality	Systematic reviews, RCTs, non-randomised controlled trials	Papers published before 1996, < 18 years, studies of non-HFE types of HH, qualitative studies, < 100 participants, insufficient information for assessment of

		blood iron parameters, followed by genetic testing for C282Y or H63D mutations of the HFE gene	Clinical (diagnosed): Diabetes (diagnosed according to World Health Organisation or American Diabetes Association criteria), any liver disease (including cancer) not caused by bacterial/viral infections or alcoholism, cardiovascular disease (myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation	methodological quality/risk of bias, outcomes not listed in the inclusion criteria, studies where > 10% of the sample do not meet the inclusion criteria, articles not available in English, grey literature, publications that contain no numerical outcomes data.

	Clinical (self-reported): Fatigue/weakness

HH = Hereditary haemochromatosis, RCT = randomised controlled trial

Methods of analysis/synthesis

An initial search (in Medline) identified over 12,000 unique records. This volume of work was beyond the scope of a rapid review. Therefore, in keeping with rapid review methods an order of priority approach to the selection and analysis / synthesis of the papers was developed. The lists with the order of study priority are provided in Table 3. The prioritisation was based on study design and sample size, with only the most informative studies prioritised. The order of priority was applied to each outcome/biochemical or clinical factor, for example:

Example 1 (question 1): 2 studies are identified which examine fatigue in people with the homozygous C282Y mutations compared to those with the wildtype. Study A employs a cohort design, has a comparator arm, and over 1000 participants. Study B employs a case-control design, and has over 500 participants. For this question the cohort design is most appropriate, and so study A is prioritised.

Example 2 (question 1): 2 studies are identified which examine hyperpigmentation in people with homozygous C282Y muations compared to those with the wildtype. Study C employs a cohort design, with *no* comparator arm, and over 1000 participants. Study D employs a case-control design, and has over 500 participants. Here study D is prioristised, because although cohort designs are most appropriate, study C does not have a comparator arm.

A narrative synthesis and full quality assessment of studies that included the highest priority population and study design (henceforth referred to as ‘prioritised studies’) is provided. For lower priority studies (henceforth referred to as ‘deprioritised studies’), details of study characteristics, including study design, country in which the study took place, sample sizes, and list of key outcomes are provided in Appendix 2, Tables 30 and 31.

Table 3. Order of study priority

Key question	Order of priority	
	Population	**Study type**
Question 1 What is the penetrance of HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity? Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?	1. North/Western European, North American, Australian; general population, no sub-samples 2. North/Western European, North American, Australian; selected samples (for example entire sample is a blood donor, or has a particular disease) 3. Any other nationality, general population, no sub-samples 4. Any other nationality, selected samples (for example entire sample is a blood donor, or has a particular disease)	1. Systematic reviews 2. Cohort studies: comparator arm, ≥ 1000 participants in total 3. Cohort studies: comparator arm, < 1000 participants in total 4. Case-control studies: ≥ 500 participants in total 5. Case-control studies: < 500 participants in total 6. Cross-sectional studies: comparator arm, ≥ 1000 participants in total 7. Cross-sectional studies: comparator arm, ≤ 1000 participants in total 8. Cohort studies: no comparator arm, ≥ 1000 participants in total 9. Cohort studies: no comparator arm, < 1000 participants in total 10. Cross-sectional studies: no comparator arm, ≥ 1000 participants in total 11. Cross-sectional studies: no comparator arm, ≤ 1000 participants in total
Question 2 What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D	Not applicable	1. Systematic reviews 2. Case-control studies: ≥ 500 participants in total 3. Case-control studies: < 500 participants in total 4. Cohort studies: comparator arm, ≥ 1000 participants in total

homozygosity or C282Y/H63D compound heterozygosity)? Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?		5. Cohort studies: comparator arm, < 1000 participants in total 6. Cohort studies: no comparator arm, ≥ 1000 participants in total 7. Cohort studies: no comparator arm, < 1000 participants in total 8. Cross-sectional studies: comparator arm, ≥ 1000 participants in total 9. Cross-sectional studies: comparator arm, < 1000 participants in total 10. Cross-sectional studies: no comparator arm, ≥ 1000 participants in total 11. Cross-sectional studies: no comparator arm, < 1000 participants in total
Question 3. Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms?	Not applicable	1. Systematic reviews 2. RCT: pre-symptomatic versus symptomatic detection, ≥ 1000 participants in total 3. RCT: pre-symptomatic versus symptomatic detection, ≤ 1000 participants in total 4. RCT: early symptomatic versus late symptomatic detection, ≥ 1000 participants in total 5. RCT: early symptomatic versus late symptomatic detection, ≤ 1000 participants in total 6. Cohort studies: comparator arm, ≥ 1000 participants in total 7. Cohort studies: comparator arm, ≤ 1000 participants in total 8. Cohort studies: no comparator arm, ≥ 1000 participants in total 9. Cohort studies: no comparator arm, ≤ 1000 participants in total

Question 4. What is the effectiveness of screening to reduce HH-related morbidity and mortality?	Not applicable	1. Systematic reviews 2. RCT: screening versus usual care, ≥ 1000 participants in total 3. RCT: screening versus usual care, ≤ 1000 participants in total 4. RCT: genetic screening versus phenotypic screening, ≥ 1000 participants in total 5. RCT: genetic screening versus phenotypic screening ≤ 1000 participants in total 6. Non-randomised control trials: screening versus usual care, ≥ 1000 participants in total 7. Non-randomised control trials: screening versus usual care, ≤ 1000 participants in total 8. Non-randomised control trials: genetic screening versus phenotypic screening, ≥ 1000 participants in total 9. Non-randomised control trials: genetic screening versus phenotypic screening ≤ 1000 participants in total

Appraisal for quality/risk of bias tool

The following tools were used to assess the quality and risk of bias of each study included in the review:

- Quality in Prognostic Studies tool.[33] (question 1)
- Joanna Briggs Institute (JBI) Checklist for Case Control Studies.[34] (question 2)
- JBI Checklist for Analytical Cross-sectional Studies.[34] (question 2)
- Risk of Bias in Systematic Reviews tool (ROBIS).[35] (questions 2 and 3)
- JBI Checklist for Cohort Studies.[34] (question 3)

Assessment of quality appraisal and risk of bias was undertaken by one reviewer, with a random 20% checked by a second reviewer. Disagreements were resolved by consensus or through discussion with a third reviewer

Databases/sources searched

One systematic literature search was undertaken to cover all 4 review questions. A copy of the search strategy can be found in Appendix 1. The search strategy was developed in MEDLINE (Ovid) using terms relating to HH, observational study designs, randomised controlled trials (RCT), and systematic reviews. The search was adapted as appropriate for the following databases: MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); Web of Science (Ovid), and Cochrane Library: Cochrane Database of Systematic Reviews. Database searches were conducted on 18 December 2019.

The search strategy comprised the following elements:
1) Searching of electronic bibliographic databases,
2) Contacting experts in the field,
3) Scrutiny of references of included studies and relevant systematic reviews.

Database searches yielded 3,377 results, of which 678 articles were judged to be relevant to one or more questions. An additional 24 relevant articles were identified through reference list checking. In total, 36 articles were prioritised for extraction and inclusion in the review. An additional 91 articles were deprioritised for extraction based on the order of study priority outlined in table 3.

Question level synthesis

Criterion 1 — association between the risk or disease marker and serious or treatable disease

The condition should be an important health problem as judged by its frequency and/or severity. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and/or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.

Question 1 – What is the penetrance of HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity?

Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?

The current UK NSC recommendation is not to screen for type 1 HH. This is based on the most recent UK NSC review from 2015, which searched for literature published between 2009 and 2015. The review noted that due to a lack of evidence it was not possible to draw conclusions on the penetrance and expressivity of the HFE genotypes in the general population, and that it was not possible to determine if there was an effective screening strategy for use in the general population.[12]

Eligibility for inclusion in the review

Articles were included in this question if they reported the results of studies (or systematic reviews of these) of adults who had homozygous C282Y, homozygous H63D, or compound heterozygous C282Y/H63D mutations who were not being treated for HH, for example with phlebotomy, erythrocytapheresis, or iron chelating agents. The outcomes of interest were serum ferritin, transferrin saturation, unsaturated iron binding capacity, mortality, diabetes, any liver disease not caused by bacterial/viral infections or alcoholism, myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure, rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation, or fatigue/weakness. Only papers in English were included.

Papers that met any of the following criteria were excluded: participants younger than 18 years old, fewer than 100 participants, more than 10% of sample not meeting the inclusion criteria, non-HFE types of haemochromatosis, qualitative studies, insufficient information for

assessment of risk of bias, no numerical information, outcomes/exposures not listed in the inclusion criteria, grey literature (letters, reviews, editorials, communications, conference abstracts).

Description of the evidence

Full details of the number of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 4. Searches yielded 3,377 unique records, of which 678 were retained for full text assessment. An additional 12 relevant articles were identified through reference list checking. After full text assessment, a total 66 articles were included in the review: 21 were prioritised and 45 were deprioritised. Details of the prioritised studies are reported below. Summary information about the deprioritised studies is provided in Appendix 3, Table 30. A list of excluded studies (with reasons) is given in Appendix 2, Table 28.

Characteristics of included studies

Details of the 21 prioritised papers are provided in Appendix 3 Table 29. The papers reported data from 12 studies. Cross-sectional study designs were employed in 8 studies (reported in 15 papers),[36-50] prospective cohort study designs in 2 studies (reported in 4 papers),[32 51-53] mixed cross-sectional/prospective cohort study designs for 1 study (reported in 1 paper),[54] and 1 case cohort study (reported in 1 paper).[55] The studies were conducted in Australia,[40 42 47 50 54] Denmark,[44 51-53] New Zealand,[39] the UK,[32 43] the USA plus Canada,[36-38 41 46 48 49] and the USA alone.[45] Ten studies (reported in 18 papers) reported on the homozygous C282Y mutation,[32 36-41 43-46 48-53] 9 studies (reported in 15 papers) reported on the homozygous H63D mutation,[37-40 42-44 46 48 51-53 55] and 8 studies (reported in 15 papers) on the compound heterozygous C282Y/H63D mutation.[36-41 43 44 46 47 49 51-54] The biochemical outcomes of interest were serum ferritin,[37-39 41 42 44 45 47-51 53 54] transferrin saturation, [36-39 41 42 44 47-49 52-54] and unbound iron-binding capacity.[43] The clinical outcomes of interest were fatigue,[32 36 45 46] hyperpigmentation,[41 45] osteoporosis,[32] arthritis,[32 41 50] angina,[32 40 48] atrial fibrillation,[32] cardiomyopathy,[41] cirrhosis/fibrosis,[41 50] diabetes,[32 41 46] heart failure,[46] liver cancer,[41] liver disease,[32 41] myocardial infarction,[32 40 48 51] pneumonia,[32] mortality.[46]

Discussion of findings

Quality appraisal of included studies

Risk of bias in systematic reviews was assessed using the Quality in Prognostic Studies (QUIPS) tool.[33] The QUIPS comprises 6 domains: study participants, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Details of quality appraisal for the included studies are shown in Figure 1, and Appendix 3 Table 32. Two studies (reported in 4 papers) had no domains rated as being at high risk of bias.[32 51-53] High risks of bias were present in the remaining 10 studies; 5 studies (reported in 5 papers) had high risks of bias in 1 domain,[39 41 45 46 50] 4 studies (reported in 10 papers) had high risks of bias in 2 domains,[36-38 40 42 47-50 54 55] and one study (reported in 1 paper) had high risks of bias in 3 domains.[44] The domains most frequently rated as being at high risk of bias were study attrition, outcome measurement, and study confounders. Reasons for high risks were reasons for loss to follow up (and the potential impact of this) not being considered, confounders not being addressed, use of self-report measures, and different assessment measures being used with different study participants. Moderate risks of bias were present in all studies. These were present in 2 domains for one study, 3 domains for 2 studies, 4 domains for 5 studies, 5 domains for 3 studies, and 6 domains for one study.

Figure 1. Quality appraisal of included studies

Applicability of included studies to the UK screening setting

While applicability is not assessed in the QUIPS tool, applicability concerns were apparent in relation to screening for type 1 HH in the UK. Only 2 of the included studies were undertaken in the UK.[32] One of these studies included many of the outcomes of interest, but only considered the homozygous C282Y genotype.[32] The other UK study considered the homozygous C282Y and H63D, and compound heterozygous C282Y/H63D mutations, but

only reported mean values for serum ferritin, transferrin saturation, and unbound iron-binding capacity.[43] There were 2 studies (reported in 4 papers) which provided data from a North-Western European country (Denmark).[44 51-53] It was not reported in either of the studies if the participants received treatment for iron overload. Therefore, the results might not be generalisable to an untreated population.

Analysis of the evidence

The included papers reported results of people with wild-type, heterozygous, and homozygous genotypes. The present review is concerned only with the homozygous C282Y and H63D genotypes, and heterozygous C282Y/H63D genotype (plus the wild/wild genotype as a reference against which they were assessed). Therefore, data on other genotypes such as heterozygous C282Y and heterozygous H63D are not reported here.

Full study details are provided in the study-level data in Appendix 3. The results of studies that report the prevalence of outcomes are outlined in tables 4, 6, and 8 (biochemical markers), and tables 5, 7, and 9 (clinical conditions). In these tables, data in bold indicate a significant difference compared to the wild/wild genotype. Results of studies that report other statistics (for example mean scores, hazard ratios) are reported in Appendix 3, Table 29.

Homozygous C282Y

Biochemical outcomes (see Table 4)

Two cross-sectional studies provided data on homozygous C282Y mutations and serum ferritin.[39 49] Serum ferritin was reported to be elevated in 60 – 65% of people with the homozygous C282Y mutation and 2.4 – 8.4% of people with the wild type genotype.[39 49] The risk difference ranged from 56.9 – 57.6%.[39 49] People with the homozygous C282Y mutation were 7.8 – 24.6 times more likely to have elevated serum ferritin than people with the wild type genotype, with the larger study (n = 22,523) providing the lower relative risk estimate.[39 49] Subgroup analyses indicated that this effect was found for both men and women (see Appendix 3, Table 29).[49]

Two cross-sectional studies provided data on homozygous C282Y mutations and transferrin saturation.[39 49] Transferrin saturation was reported to be elevated in 54 – 100% of people with the homozygous C282Y mutation[36 39 49 56] and 1 – 3.2% of people with the wild type genotype.[39 49] The risk difference ranged from 53 – 96.8%.[39 49] People with the homozygous C282Y mutation were 28 – 53.9 times more likely to have elevated transferrin saturation than people with the wild type genotype, with the larger study (n = 22,523) providing the higher relative risk estimate.[39 49] Subgroup analyses indicated that this effect was found for both men and women (see Appendix 3, table 29).[49]

Clinical outcomes (see Table 5)

Three prospective cohort studies (mean follow up range: 7 – 24 years) provided data on homozygous C282Y mutations and clinical outcomes ('any' clinical outcome, fatigue, osteoarthritis, rheumatoid arthritis, osteoporosis, atrial fibrillation, diabetes, heart failure, liver disease, myocardial infarction, pneumonia, mortality).[32 46 51] The proportion of people with clinical outcomes ranged from 1.4 – 28.3% in people with the homozygous C282Y mutation and 0.5 – 18.2% in people with the wild type genotype. People with the homozygous C282Y mutation were at higher risk for 'any' clinical outcome, fatigue, osteoarthritis, osteoporosis, and liver disease, and lower risk for angina/myocardial infarction (combined) than people with the wild type genotype (see Appendix 3, Table 29).[32] There was no evidence of statistically significant differences in risk for rheumatoid arthritis, atrial fibrillation, pneumonia,[32] myocardial infarction,[51] heart failure or mortality[46] between the groups. The direction of the evidence was inconsistent for diabetes.[32 46] Subgroup analyses indicated that men (but not women) with the homozygous C282Y mutation had a greater risk for rheumatoid arthritis, diabetes (type 1 or 2), fatigue, liver disease, angina/myocardial infarction (combined), osteoporosis, and pneumonia than those with the wild type genotype (see Appendix 3, Table 29).[32]

Five cross-sectional studies (including one that provided both cross-sectional and prospective data)[46] provided data on homozygous C282Y mutations and clinical outcomes (fatigue, hyperpigmentation, angina, fibrosis/cirrhosis, myocardial infarction). [36 40 45 46 48] The proportion of people with clinical outcomes ranged from 0 – 44.0% in people with the homozygous C282Y mutation and 3.0 – 43.0% in people with the wild type genotype. People with the homozygous C282Y mutation were 3 times more likely to have hyperpigmentation than people with the wild type genotype.[45] There was no evidence of statistically significant differences in risk for fatigue, angina, or myocardial infarction between the groups.[36 40 46 48] Subgroup analyses indicated no difference in effect between men and women for fatigue,[36] angina or myocardial infarction.[48]

Homozygous H63D

Biochemical outcomes (see Table 6)

One cross-sectional study provided data on homozygous H63D mutations and serum ferritin.[42] Serum ferritin was elevated in 25.8% of people with the homozygous H63D mutation and 12.2% of people with the wild type genotype. The risk difference was 13.5%.[42] People with the homozygous H63D mutation were 2.1 times more likely to have elevated serum ferritin than people with the wild type genotype.[42] Subgroup analysis indicated no difference in effect between men and women (see Appendix 3, Table 29).[42]

One cross-sectional study provided data on homozygous H63D mutations and transferrin saturation.[42] Transferrin saturation was elevated in 11.3% of people with the homozygous H63D mutation and 3.5% of people with the wild type genotype. Statistical analyses produced inconsistent results: a nonsignificant risk difference 7.8% (95% CI -0.16, 15.69), but a statistically significant relative risk. People with the homozygous H63D mutation were 3.2 times more likely to have elevated transferrin saturation than people with the wild type genotype.[42] Subgroup analysis indicated no difference in effect between men and women (see Appendix 3, Table 29).[42]

Clinical outcomes (see Table 7)
Two prospective cohort studies (mean follow up range: 8 – 24 years) provided data on homozygous H63D mutations and clinical outcomes outcomes (diabetes (type unspecified), heart failure, myocardial infarction, mortality).[46 51] The proportion of people with these clinical outcomes ranged from 6.4 – 17.5% in people with the homozygous H63D mutation and 5.7 – 15.8% in people with the wild type genotype. There was no evidence of statistically significant differences in risk for any of the clinical outcomes between the groups.[46 51] Subgroup analysis of data on myocardial infarction indicated no difference in effect between men and women (see Appendix 3, table 29).[51]

Three cross-sectional studies studies (including one that provided both cross-sectional and prospective data)[46] provided data on homozygous H63D mutations and clinical outcomes (fatigue, angina, myocardial infarction). [40 46 48] The proportion of people with these clinical outcomes ranged from 4.1 – 47.1% in people with the homozygous H63D mutation and 3.2 – 43.0% in people with the wild type genotype. There was no evidence of statistically significant differences in risk for any of the clinical outcomes between the groups.[40 46 48] Subgroup analysis of data on angina and myocardial infarction indicated no difference in effect between men and women (see Appendix 3, Table 29).[48]

Compound heterozygous C282Y/H63D
Biochemical outcomes (see Table 8)
Two cross-sectional studies provided data on compound heterozygous C282Y/H63D and serum ferritin. [39 41 54] Serum ferritin was reported to be elevated in 15.8 – 33.9% of people with the compound heterozygous C282Y/H63D mutation and 2.4 – 12.8% of people with the wild type genotype. The risk difference ranged from 13.4 – 21.1%.[39 54] People with the compound heterozygous C282Y/H63D mutation were 2.7 – 6.5 times more likely to have elevated serum ferritin than people with the wild type genotype.[39 54] In one study, statistical analyses produced inconsistent results: a nonsignificant risk difference 13.4% (95% CI -3.09, 29.79); a statistically significant relative risk 6.5% (95% CI 2.06, 20.33).

Two cross-sectional studies provided data on compound heterozygous C282Y/H63D and transferrin saturation.[39 54] Transferrin saturation was elevated in 21.5 – 26.3% of people with the compound heterozygous C282Y/H63D mutation and 3.2 – 4.9% of people with the wild type genotype. The risk difference ranged from 16.7 – 23.1%.[39 54] People with the compound heterozygous C282Y/H63D mutation were 4.4 – 8.2 times more likely to have elevated transferrin saturation than people with the wild type genotype.[39 54] Subgroup analyses indicated that this effect was found for both men and women (see Appendix 3, Table 29).[47]

Clinical outcomes (see Table 9)

Two prospective cohort studies (mean follow up range: 8 – 24 years) provided data on compound heterozygous C282Y/H63D mutations and clinical outcomes diabetes (type unspecified), heart failure, myocardial infarction, mortality).[46 51] The proportion of people with clinical outcomes ranged from 3.3 – 15.5% in people with the compound heterozygous C282Y/H63D mutation and 5.7 – 15.8% in people with the wild type genotype. There was no evidence of statistically significant differences in risk for any of the clinical outcomes between the groups. Subgroup analysis of data on myocardial infarction indicated no difference in effect between men and women (see Appendix 3, Table 29).[51]

Five cross-sectional studies (including one that provided both cross-sectional and prospective data)[46] provided data on compound heterozygous C282Y/H63D mutations and clinical outcomes (fatigue, hyperpigmentation, arthritis, angina, cardiomyopathy, cirrhosis, diabetes (type unspecified), liver cancer, liver disease, myocardial infarction).[36 40 41 46 48] The proportion of people with clinical outcomes ranged from 0 – 49.2% in people with the compound heterozygous C282Y/H63D mutation and 3.2 – 43.0% in people with the wild type genotype.There was no evidence of statistically significant differences in risk for fatigue, angina, or myocardial infarction between the groups. Comparative data were not available for any of the other clinical outcomes.[41] Subgroup analysis of data on fatigue,[36] angina and myocardial infarction[48] indicated no statistically significant differences in effects between men and women (see Appendix 3, Table 29).

Table 4. Penetrance of biochemical outcomes: homozygous C282Y versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants with wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
Elevated serum ferritin								
	Burt (1998)[39]	Cross-sectional	5	655	60.00	2.44	**57.56 (14.60, 100.51)**	**24.56 (10.35, 58.28)**
	Waalen (2002)[49]	Cross-sectional	124	22429	65.32	8.41	**56.91 (48.52, 65.29)**	**7.76 (6.78, 8.89)**
Elevated transferrin saturation								
	Burt (1998)[39]	Cross-sectional	5	655	100	3.21	**96.79 (74.64, 118.95)**	**27.97 (17.30, 45.23)**
	Waalen (2002)[49]	Cross-sectional	124	22429	54.03	1.00	**53.03 (44.26, 61.80)**	**53.86 (43.75, 66.31)**

[1] = calculated by review team, CI = confidence interval, NA = not applicable. Values in **bold** indicate statistically significant results

Table 5. Penetrance of clinical outcomes: homozygous C282Y versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
At least 1 outcome								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	28.34	18.15	**10.19 (8.54, 11.84)**	**1.56 (1.47, 1.66)**
Fatigue								
	Beutler (2002)[36]	Cross-sectional	124	22347	27.4	26.5	0.91 (-6.96, 8.79)	1.03 (0.78, 1.38)
	Pankow (2008)[46]	Cohort (baseline only)	45	6768	40.0	43.0	-3.00 (-17.36, 11.37)	0.93 (0.65, 1.33)

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	5.0	3.9	**1.05 (0.26, 1.85)**	**1.27 (1.08, 1.49)**
Hyperpigmentation								
	McLaren (2008)[45]	Cross-sectional	282	364	13.12	2.98	**8.72 (4.26, 13.19)**	**2.98 (1.70, 5.25)**
Arthritis								
Osteoarthritis	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	14.15	9.28	**4.87 (3.60, 6.15)**	**1.53 (1.39, 1.67)**
Rheumatoid	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	1.66	1.29	0.37 (-0.10, 0.84)	1.29 (0.97, 1.71)
Osteoporosis								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	2.70	1.95	**0.75 (0.16, 1.35)**	**1.39 (1.11, 1.73)**
Angina								
	Fox (2002)[40]	Cross-sectional	16	1358	0	5.2	-5.15 (-13.27, 2.96)	0.57 (0.04, 8.78)
	Waalen (2002)[48]	Cross-sectional	137	19273	2.92	4.94	-2.03 (-4.86, 0.81)	0.59 (0.22, 1.55)
Atrial fibrillation								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	1.38	1.54	-0.16 (-0.58, 0.27)	0.90 (0.66, 1.22)
Diabetes								
Type 1 or 2	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	3.18	2.32	**0.87 (0.22, 1.51)**	**1.37 (1.12, 1.68)**
Unspecified	Pankow (2008)[46]	Prospective cohort (8 years)	45	6768	6.67	8.36	-1.70 (-9.01, 5.62)	0.80 (0.27, 2.39)

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
Fibrosis/Cirrhosis								
	Wood (2017)[50]	Cross-sectional	291	NA	43.99	NA	NA	NA
Heart failure								
	Pankow (2008)[46]	Prospective cohort (15 years)	45	6768	4.44	8.33	-3.89 (-9.95, 2.17)	0.53 (0.14, 2.07)
Liver disease (any)								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	1.38	0.46	**0.92 (0.50, 1.35)**	**3.00 (2.19, 4.09)**
Myocardial infarction								
	Fox (2002)[40]	Cross-sectional	16	1358	0	7.9	-7.88 (-16.04, 0.28)	0.37 (0.02, 5.74)
	Ellervik (2005)[51]	Prospective (24 years)	22	5767	9.09	5.74	3.35 (-8.68, 15.38)	1.58 (0.42, 5.96)
	Waalen (2002)[48]	Cross-sectional	137	19273	1.46	3.22	-1.76 (-3.79, 0.26)	0.45 (0.11, 1.80)
Myocardial infarction or angina (combined)								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	4.53	5.43	**-0.89 (-1.66, -0.13)**	**0.84 (0.71, 0.99)**
Pneumonia								
	Pilling (2019)[32]	Prospective cohort (7 years)	2890	383909	2.39	1.95	0.44 (-0.12, 1.00)	1.23 (0.97, 1.55)
Mortality (all-cause)								
	Pankow (2008)[46]	Prospective cohort (15 years)	45	6768	15.56	15.75	-0.20 (-10.82, 10.43)	0.99 (0.50, 1.96)

[1] = calculated by review team, CI = confidence interval. Values in **bold** indicate statistically significant results

Table 6. Penetrance of biochemical outcomes: homozygous H63D versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants with wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
Elevated serum ferritin								
	Gochee (2002)[42]	Cross-sectional	62	1758	25.81	12.19	**13.52 (2.52, 24.52)**	**2.10 (1.35, 3.26)**
Elevated transferrin saturation								
	Gochee (2002)[42]	Cross-sectional	62	1758	11.29	3.53	7.76 (-0.16, 15.69)	**3.20 (1.53, 6.71)**

[1] = calculated by review team, CI = confidence interval. Values in **bold** indicate statistically significant results

Table 7. Penetrance of clinical outcomes: homozygous H63D versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95% CI)
Fatigue								
	Pankow (2008)[46]	Prospective cohort (baseline only)	257	6768	47.1	43.0	4.09 (-2.13, 10.30)	1.10 (0.96, 1.25)
Angina								
	Fox (2002)[40]	Cross-sectional	48	1358	6.3	5.2	1.10 (-5.85, 8.04)	1.21 (0.40, 3.71)
	Waalen (2002)[48]	Cross-sectional	137	19273	5.49	4.94	0.54 (-1.14, 2.22)	1.11 (0.82, 1.51)
Diabetes (type unspecified)								
	Pankow (2008)[46]	Prospective cohort (8 years)	45	6768	7.78	8.36	-0.58 (-3.92, 2.76)	0.93 (0.61, 1.43)

Heart failure								
	Pankow (2008)[46]	Prospective cohort (15 years)	257	6768	8.95	8.33	0.62 (-2.94, 4.17)	1.07 (0.72, 1.60)
Myocardial infarction								
	Fox (2002)[40]	Cross-sectional	48	1358	6.3	7.9	-1.63 (-8.63, 5.37)	0.79 (0.26, 2.41)
	Ellervik (2005)[51]	Prospective (24 years)	22	5767	6.38	5.74	0.64 (-3.44, 4.72)	1.11 (0.59, 2.11)
	Waalen (2002)[48]	Cross-sectional	729	19273	4.12	3.22	0.89 (-0.57, 2.36)	1.28 (0.89, 1.83)
Mortality (all-cause)								
	Pankow (2008)[46]	Prospective cohort (15 years)	257	6768	17.51	15.75	1.76 (-2.97, 6.49)	1.11 (0.85, 1.46)

[1] = calculated by review team, CI = confidence interval

Table 8. Penetrance of biochemical outcomes: compound heterozygous C282Y/H63D versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95%)
Elevated serum ferritin								
	Burt (1998)[39]	Cross-sectional	19	655	15.79	2.44	13.35 (-3.09, 29.79)	**6.46 (2.06, 20.33)**
	Olynyk (1999)[54]	Cross-sectional	65	2571	33.85	12.76	**21.09 (9.51, 32.66)**	**2.65 (1.86, 3.78)**
Elevated transferrin saturation								
	Burt (1998)[39]	Cross-sectional	19	655	26.32	3.21	**23.11 (3.26, 42.96)**	**8.21 (3.47, 19.44)**
	Olynyk (1999)[54]	Cross-sectional	65	2571	21.54	4.86	**16.68 (6.65, 26.70)**	**4.43 (2.70, 7.26)**

[1] = calculated by review team, CI = confidence interval, NA = not applicable. Values in **bold** indicate statistically significant results

Table 9. Penetrance of clinical outcomes: compound heterozygous C282Y/H63D versus wild type

Outcome	Study	Design (follow-up time)	No. participants with mutation	No. participants wild type	Proportion in mutation group %	Proportion in wild type group %	Risk difference[1] % (95% CI)	Relative risk[1] % (95% CI)
Fatigue								
	Beutler (2002)[36]	Cross-sectional	594	22347	26.43	26.50	-0.07 (-3.67, 3.52)	1.00 (0.87, 1.14)
	Pankow (2008)[46]	Prospective cohort (baseline only)	193	6788	49.22	43.00	6.23 (-0.92, 13.38)	1.14 (0.99, 1.32)
Hyperpigmentation								
	Gallego (2015)[41]	Cross-sectional	368	NA	1.90	NA	NA	NA
Arthritis (type unspecified)								
	Gallego (2015)[41]	Cross-sectional	391	NA	32.48	NA	NA	NA
Angina								
	Fox (2002)[40]	Cross-sectional	44	1358	9.1	5.2	3.94 (-4.64, 12.51)	1.76 (0.67, 4.61)
	Waalen (2002)[48]	Cross-sectional	137	19273	5.11	4.94	0.16 (-1.70, 2.03)	1.03 (0.72, 1.49)
Cardiomyopathy								
	Gallego (2015)[41]	Cross-sectional	385	NA	4.34	NA	NA	NA
Cirrhosis								
	Gallego (2015)[41]	Cross-sectional	351	NA	4.88	NA	NA	NA
Diabetes (unspecified)								
	Gallego (2015)[41]	Cross-sectional	395	NA	23.29	NA	NA	NA
	Pankow (2008)[46]	Prospective cohort (8 years)	45	6768	9.84	8.36	1.48 (-2.77, 5.74)	1.18 (0.76, 1.82)
Heart failure								

	Pankow (2008)[46]	Prospective cohort (15 years)	193	6768	8.29	8.33	-0.04 (-3.99, 3.90)	0.99 (0.62, 1.60)
Liver cancer								
	Gallego (2015)[41]	Cross-sectional	0	NA	0	NA	NA	NA
Liver disease (any)								
	Gallego (2015)[41]	Cross-sectional	NA	344	NA	20.64	NA	NA
Myocardial infarction								
	Fox (2002)[40]	Cross-sectional	44	1358	2.3	7.9	-5.61 (-10.24, -0.98)	0.29 (0.04, 2.02)
	Ellervik (2005)[51]	Prospective cohort (24 years)	123	5767	3.25	5.74	-2.49 (-5.68, 0.70)	0.57 (0.21, 1.49)
	Waalen (2002)[48]	Cross-sectional	548	19273	4.56	3.22	1.34 (-0.42, 3.10)	1.42 (0.96, 2.09)
Mortality (all-cause)								
	Pankow (2008)[46]	Prospective cohort (15 years)	193	6768	15.54	15.75	-0.20 (-10.82, 10.43)	0.99 (0.50, 1.96)

[1] = calculated by review team, CI = confidence interval, NA = not applicable

Question 2 – What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)?

Sub-question: Based on the quality and heterogeneity of the studies, is a meta-analysis or a summary estimate possible?

This question was not examined in the 2015 review of HH for the UK NSC.[12] As phenotypic screening for type 1 HH has been proposed, the aim of this question is to identify associations (odds ratios) between health problems and genotypes.

Eligibility for inclusion in the review

Articles were included in this question if they reported the results of studies (or systematic reviews of these) of adults who had any of the following biochemical or clinical features: serum ferritin, transferrin saturation, unsaturated iron binding capacity, diabetes, any liver disease not caused by bacterial/viral infections or alcoholism, myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure, rheumatoid arthritis, osteoarthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation, or fatigue/weakness. The outcomes of interest were homozygous C282Y, homozygous H63D, and compound heterozygous C282Y/H63D. Only papers in English were included.

Papers that met any of the following criteria were excluded: participants younger than 18 years old, fewer than 100 participants, more than 10% of sample not meeting the inclusion criteria, non-HFE types of haemochromatosis, qualitative studies, insufficient information for assessment of risk of bias, no numerical information, outcomes/exposures not listed in the inclusion criteria, grey literature (letters, reviews, editorials, communications, conference abstracts).

Description of the evidence

Full details of the number of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 4. Searches yielded 3,377 unique records, an additional 12 relevant articles were identified through reference list checking. In total 59 articles were included in the review: 13 were prioritised and 46 were deprioritised. Studies were prioritised based on population characteristics and study design (see Table 3). Details of the prioritised studies are reported below. Summary information about the deprioritised studies is provided in Appendix 3, Table 31. A list of excluded studies (with reasons) is given in Appendix 2, Table 28.

Characteristics of included studies

Details of the 13 prioritised papers are provided in Appendix 3, Table 29. There were 8 case control studies,[57-64] one cross-sectional study,[65] and 4 systematic reviews with meta-analyses.[66-69] One of the meta-analyses was conducted on individual participant data.[67]

Case-control studies
Case-control studies were conducted in England,[58 63] England and France,[62] Denmark,[60] Finland,[64] France,[57] Greece,[59] and Sweden.[61] Total sample sizes ranged from 193 (91 cases and 102 controls) to 9,890 (716 cases and 9,174 controls). Unmatched control groups comprised (1) healthy recipients of a free health check-up,[62] (2) adults from the general population,[60] (3) adults with iron overload,[57] healthy medical students or laboratory personnel,[64] healthy blood donors or factory workers.[63] Matched control groups comprised (1) participants in health screening programmes matched to cases on sex, age, date of health survey, screening programme, and geographic area,[61] (2) non-diabetics matched to cases for age, body mass index (BMI), and sex,[59] and individuals from general practice (GP) registers matched to cases for age, sex and GP practice.[58] The clinical factors of interest were arthralgia,[62] cardiomyopathy,[63] fatigue,[62] hyperpigimentation,[57] idiopathic cardiomyopathy,[63 64] late-onset type 1 diabetes,[60] myocardial infarction,[61] osteoporosis,[62] and type 2 diabetes.[58 59]

Cross-sectional study
The cross-sectional study was conducted in unspecified Scandinavian countries.[65] The study included 667 people (all cases). The clinical factor of interest was heart failure.

Systematic reviews
The number of studies included in the reviews ranged from 2 to 23. The number of participants included in the meta-analyses ranged from 3,843 (637 cases and 3,206 controls) to 50,670 (8,567 cases and 42,103 controls). The clinical factors of interest were arthritis,[69] cirrhosis,[66] liver cancer,[66] myocardial infarction,[67 69] and non-alcoholic fatty liver disease.[66] The biochemical factors of interest were serum ferritin,[68] and transferrin saturation.[68]

Discussion of findings

Quality appraisal of included studies

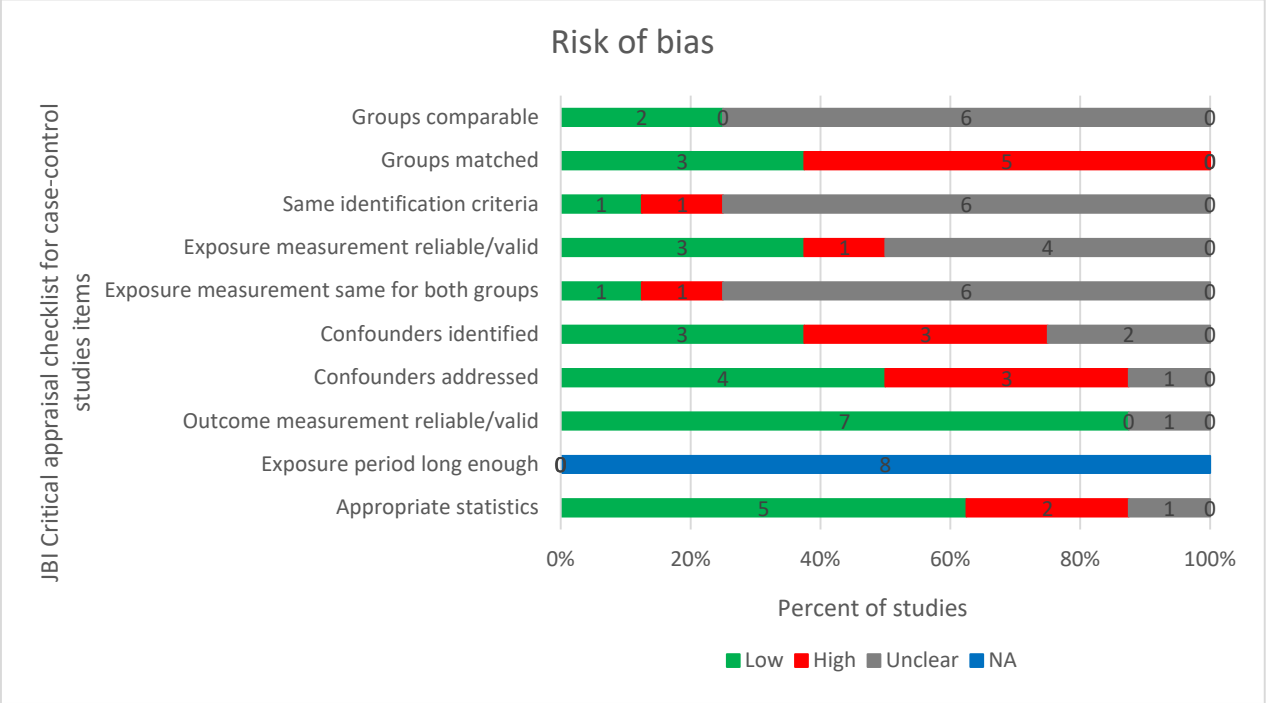
Risk of bias in systematic reviews was assessed using the ROBIS,[35] the quality of the case control studies was assessed using the JBI Checklist for Case Control Studies, [34] and the

quality of the cross-sectional study was assessed using the JBI Checklist for Analytical Cross-sectional Studies.[34] The ROBIS comprises 4 domains: study eligibility criteria, identification and selection of studies, data collection and study appraisal, and synthesis and findings. The JBI Checklist for Case Control Studies comprises 10 items: comparable groups, group matching, identification criteria, reliability and validity of exposure measurement, consistency of exposure measurement, identification of confounders, strategies to address confounders, reliability and validity of outcome measurement, period of exposure, statistical analyses. The JBI Checklist for Analytical Cross-sectional Studies comprises 8 items: clearly defined inclusion criteria, clearly described participants and settings, reliability and validity of exposure measurement, use of standard and objective measurement of condition, identification of confounders, strategies to address confounders, reliability and validity of outcome measurement, statistical analyses. For the JBI Checklists, items rated as 'yes' are referred to as low risk of bias, and items rated as 'no' are referred to as high risk of bias.

Case control studies

Details of quality appraisal for the case control studies are shown in Figure 2, and Appendix 3 Table 33. Two studies had no items rated as being at high risk of bias.[58 61] Only one study had more items rated as low risk of bias than high or unclear risk.[61] High risks of bias were present in the remaining 6 studies; one study had a risk of bias on 1 item,[63] 3 studies had high risks of bias on 2 items,[59 60 64] one study had high risks of bias on 3 items,[57] and one study had high risks of bias on 4 items.[62] The items most frequently rated as being at high risk of bias were group matching, identification of confounders, and strategies to deal with confounders (5, 3, and 3 studies, respectively). In 5 studies, no matching took place between cases and controls,[57 60 62-64] no attempts to identify confounders were reported,[57 59 60 63] and no strategies to address confounders within either the study design or statistical analyses were employed.[57 59 60] Unclear risks of bias were present in all studies. These were present in 1 item for one study,[61] 2 items for one study,[60] 3 items for one study,[64] 4 items for 3 studies,[57 59 63] and 5 items for 2 studies.[58 62]

Figure 2. Quality appraisal of case control studies



NA = not applicable

Cross-sectional study

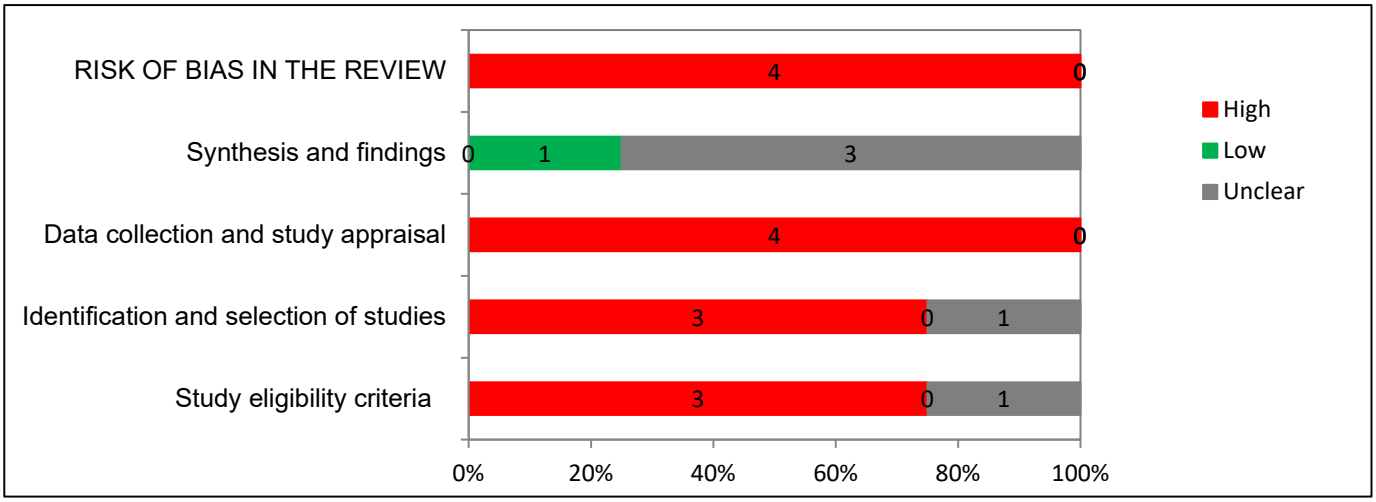
Details of quality appraisal for the cross-sectional study is shown in Appendix 3 Table 34. High risk of bias was present in 2 out of 8 domains (20%).[65] The domains were "Were confounding factors identified?" and "Were strategies to deal with confounding factors stated?" The domains were rated as high risk of bias as no attempt to identify or address confounders were reported.

Systematic reviews

Details of the risk of bias assessment for the systematic reviews are shown in Figure 3 and Appendix 3 Table 35. The overall risk of bias was high in all 4 systematic reviews. One review was at high risk of bias in one out of 4 (25%) domains,[66] and 3 reviews were at high risk of bias in 3 out of 4 (75%).[67-69] The domain most frequently rated as being at high risk of bias was 'Data collection and study appraisal' (all 4 reviews). This was because none of the reviews included an assessment of risk of bias/quality appraisal. 'Study eligibility criteria' and 'Identification and selection of studies' domains were the next most frequently rated as being at high risk of bias (3 out of 4 reviews for both domains).[66-68] The 'study eligibility' domain was at high risk of bias as the reviews did not publish protocols and provided incomplete population, intervention, comparator, outcomes (PICOs) research

strategies. The 'identification and selection of studies' domain was at high risk of bias because the systematic reviews did not provide descriptions of the review process, such as number of reviewers, whether independent assessments were conducted, or how disagreement were resolved. The final domain (Synthesis and findings) was at low risk of bias in one review,[68] and unclear in the remaining 3.[66 67 69] Only one review was rated as being at low risk of bias in any of the domains (Synthesis and findings, 1/4, 25%).[68]

Figure 3. Quality appraisal of systematic reviews



Applicability of included studies to the UK screening setting

Case control studies

While applicability is not assessed in the JBI Checklist for Case Control Studies, applicability concerns were apparent in relation to screening for type 1 HH in the UK. First, only 2 of the studies were conducted in the UK.[58 63] The remaining studies were carried out in Denmark,[60] Finland,[64] France,[57 62] and Sweden.[61] While 3 studies did recruit participants from England, the data from English participants in one of the studies was not included in the present review as they did not have any of the clinical or biochemical factors of interest.[62] Second, in the study that provided data on hyperpigmentation, all participants were recruited on the basis of having iron overload.[57] The results might not generalise to people without iron overload. And third, one study assessed the predictive value of first-time myocardial infarction to homozygous C282Y and H63D genotypes, but not the compound heterozygous genotype.[61]

Cross-sectional study

Applicability concerns are not assessed in the JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies. The single cross-sectional study has applicability concerns as it was not conducted in the UK.

Systematic reviews
Applicability is partially assessed in the ROBIS tool. All 4 systematic reviews were considered to have included studies that were relevant to the present review. However, all of the reviews combined data across countries/ethnicities with none providing subgroup analyses that were representative of the UK population,[66-69] none of the studies provided clear inclusion/exclusion criteria,[66-69] 2 reviews provided limited detail on the characteristics of included studies,[68 69] and in 2 reviews the method by which diagnoses were made was not reported,[66] or included vague diagnostic criteria (for example “clinical diagnosis”, “internationally accepted criteria”).[69]

Analysis of the evidence

The included papers reported results of people with wild-type, heterozygous, and homozygous genotypes. The present review is concerned only with the homozygous C282Y and H63D genotypes, and compound heterozygous C282Y/H63D genotype (plus the wild/wild genotype as a reference against which they were assessed). Therefore, data on other genotypes (for example, heterozygous C282Y, heterozygous H63D) are not reported here.

Full study details are provided in the study-level data in Appendix 3 Table 29. The results of studies that report the associations between biochemical markers and type 1 HH mutations are outlined in Tables 10, 12, and 14 (alongside the proportions of cases and controls who had each mutation). The studies that report the associations between clinical conditions and type 1 HH mutations are outlined in tables 11, 13, and 15 (alongside the proportions of cases and controls who had each mutation). In these tables, data in bold indicate a significant difference compared to the wild/wild genotype.

Homozygous C282Y
Biochemical markers (see Table 10)
The odds of having the homozygous C282Y mutation was significantly greater for people with elevated serum ferritin (thresholds not reported) or elevated transferrin saturation (transferrin saturation values ≥45%, ≥55%, or ≥50% for women and ≥60% for men) than for controls.[68]

Clinical conditions (see Table 11)

The odds of having the homozygous C282Y mutation were significantly greater in people with arthralgia and fatigue,[62] hyperpigmentation,[57] liver cancer,[66] and type 1 diabetes[60] than those without these conditions. There were no statistically significant differences in the odds of having the homozygous C282Y mutation between those with or without any of the other clinical conditions.[58 59 61-64 66 67 69] Ethnicity (African, Asian, Caucasian, mixed) subgroup analyses for liver disease indicated that for Caucasians only, the odds of having the homozygous C282Y mutation was significantly higher for people with non-alcoholic fatty liver disease (NAFLD) than those without.[66] There was no effect of ethnicity for liver cancer or cirrhosis.[66] Sex subgroup analyses indicated no effect of sex for first-time myocardial infaction.[61]

Homozygous H63D

Biochemical markers (see Table 12)

The odds of having the homozygous H63D mutation was significantly greater for people with elevated transferrin saturation than controls.[68] There was no evidence of a difference in the odds of having the homozygous H63D mutations between people with or without elevated serum ferritin.[68]

Clinical conditions (Table 13)

The odds of having the homozygous H63D mutation were significantly greater in people with arthralgia with fatigue than those without these conditions[62]. There were no statistically significant difference in the odds of having the homozygous H63D between those with or without any of the other clinical conditions.[57 59-64 66 67 69] Ethnicity (African, Asian, Caucasian, mixed) subgroup analyses for liver diseases indicated that for Caucasians the odds of having the homozygous H63D mutation was significantly higher for people with liver cancer than those without.[66] There was no effect of ethnicity for liver cirrhosis or NAFLD.[66] Sex subgroup analyses indicated that for women, only the odds of having the homozygous H63D mutation was significantly higher for people with first-time myocardial infarction than those without.[61]

Compound heterozygous C282Y/H63D

Biochemical markers (see Table 14)

The odds of having the compound heterozygous C282Y/H63D mutations was significantly greater for people with elevated serum ferritin or elevated transferrin saturation than for controls.[68]

Clinical conditions (see Table 15)

The odds of having the compound heterozygous C282Y/H63D mutations were significantly greater in people with arthralgia with fatigue,[62] and liver cancer[66] than those without these conditions. There were no statistically significant differences in the odds of having the

compound heterozygous C282Y/H63D mutation between those with or without any of the other clinical conditions.[57 58 60 62 66 67 69] Ethnicity (African, Asian, Caucasian, mixed) subgroup analyses for liver diseases indicated that for Caucasians, the odds of having the compound heterozygous C282Y/H63D mutation was significantly higher for people with NAFLD than those without.[66] There was no effect of ethnicity for liver cancer or cirrhosis.[66]

Table 10. Association between biochemical markers of type 1 HH and homozygous C282Y mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odds ratio % (95% CI)
Elevated serum ferritin								
	Neghina (2011)[68]	Systematic review	2	337	1568	NE	NE	**69.17 (6.99, 683.97)**
Elevated transferrin saturation								
	Neghina (2011)[68]	Systematic review	2	52	2462	17.3	0.1	**613.87 (11.73, 32125.72)**

CI = confidence interval, NE = not extractable. Values in **bold** indicate statistically significant results

Table 11. Association between clinical conditions and homozygous C282Y mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odds ratio % (95% CI)
Arthralgia and fatigue								
	Cadet (2003)[62]	Case control	NA	115	606	11.3	0.3	**38.49 (8.56, 173.09)**[1]
Hyperpigmentation								
	Moirand (1999)[57]	Case control	NA	157	185	91.3	66.3	**5.23 (2.80, 9.80)**[1]
Non-alcoholic fatty liver disease								
	Ye (2016)[66]	Systematic review	8	NE	NE	NE	NE	3.32 (0.72, 15.36)
Osteoarthritis								
	Ellervik (2007)[69]	Systematic review	6	11124	16805	NE	NE	2.40 (0.50, 13.00)[2]
Osteoporosis								
	Cadet (2003)[62]	Case control	NA	90	606	1.1	0.3	3.40 (0.31, 37.87)[1]
Cirrhosis								
	Ye (2016)[66]	Systematic review	9	NE	NE	NE	NE	0.88 (0.41, 1.91)
Heart failure								
	Møller (2016)[65]	Cross-sectional	NA	667	0	0.2	NA	NA
Idiopathic cardiomyopathy								
	Hannuksela (2005)[64]	Case control	NA	91	102	0	0	1.25 (0.03, 64.05)
	Mahon (2000)[63]	Case control	NA	207	200	0.5	0	3.62 (0.15, 89.69)
Liver cancer								
	Ye (2016)[66]	Systematic review	10	NE	NE	NE	NE	**3.16 (1.02, 9.79)**

Myocardial infarction								
	Ekblom (2011)[61]	Case control	NA	506	932	0.8	0.4	2.62 (0.59, 11.73)
	Ellervik (2007)[69]	Systematic review	12	4471	27363	NE	NE	1.10 (0.60, 2.00)[2]
	Van der (2008)[67]	Systematic review	9	3553	27554	0.9	0.7	1.01 (0.65, 1.57)
Type 1 diabetes								
	Ellervik (2001)[60]	Case control	NA	483	6158	1.9	0.4	**5.06 (2.3, 11.01)**[1]
Type 2 diabetes								
	Halsall (2003)[58]	Case control	NA	452	460	0.4	0.9	0.50 (0.09, 2.80)[1]

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable. Values in **bold** indicate statistically significant results

Table 12. Association between biochemical markers of type 1 HH and homozygous H63D mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odd ratio % (95% CI)
Elevated serum ferritin								
	Neghina (2011)[68]	Systematic review	3	273	942	1.8	1.7	2.28 (0.62, 8.31)
Elevated transferrin saturation								
	Neghina (2011)[68]	Systematic review	2	99	1494	12.2	3.3	**7.17 (1.25, 41.49)**

CI = confidence interval. Values in **bold** indicate statistically significant results

Table 13. Association between clinical conditions and homozygous H63D mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odds ratio % (95% CI)
Arthralgia and fatigue								
	Cadet (2003)[62]	Case control	NA	123	631	17.1	4.3	**4.61 (2.51, 8.46)**[1]
Hyperpigmentation								
	Moirand (1999)[57]	Case control	NA	19	73	26.3	15.1	2.01 (0.60, 6.72)[1]
Non-alcoholic fatty liver disease								
	Ye (2016)[66]	Systematic review	13	NE	NE	NE	NE	1.47 (0.97, 2.22)
Osteoarthritis								

	Ellervik (2007)[69]	Systematic review	7	5926	21197	NE	NE	1.50 (0.70, 3.00)[2]
Osteoporosis								
	Cadet (2003)[62]	Case control	NA	93	631	4.3	4.3	1.01 (0.35, 2.97)[1]
Cirrhosis								
	Ye (2016)[66]	Systematic review	23	NE	NE	NE	NE	1.07 (0.72, 1.58)
Heart failure								
	Møller (2016)[65]	Cross-sectional	NA	667	0	1.8	NA	NA
Idiopathic cardiomyopathy								
	Hannuksela (2005)[64]	Case control	NA	91	102	0	2.9	0.18 (0.01, 3.53)
	Mahon (2000)[63]	Case control	NA	207	200	1.9	3.0	0.81 (0.22, 2.93)
Liver cancer								
	Ye (2016)[66]	Systematic review	18	NE	NE	NE	NE	0.99 (0.65, 1.51)
Myocardial infarction								
	Ekblom (2011)[61]	Case control	NA	448	869	1.3	1.7	0.77 (0.30, 2.01)[1]
	Ellervik (2007)[69]	Systematic review	8	3887	25558	NE	NE	1.20 (0.90, 1.60)[2]
	Van der (2008)[67]	Systematic review	11	3649	28281	3.5	3.3	1.14 (0.92, 1.42)
Type 1 diabetes								
	Ellervik (2001)[60]	Case control	NA	489	6293	3.1	2.5	1.23 (0.72, 2.10)[1]
Type 2 diabetes								
	Habeos (2003)[59]	Case control	NA	75	76	0	0	1.01 (0.02, 51.73)[1]

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable. Values in **bold** indicate statistically significant results

Table 14. Association between biochemical markers of type 1 HH and compound heterozygous C282Y/H63D mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odds ratio % (95% CI)
Elevated serum ferritin								
	Neghina (2011)	Systematic review	2	27	696	7.4	1.0	**10.79 (1.17, 99.01)**
Elevated transferrin saturation								
	Neghina (2011)	Systematic review	1	13	1437	23.1	2.2	**13.73 (2.43, 77.75)**

CI = confidence interval. Values in **bold** indicate statistically significant results

Table 15. Association between clinical conditions and compound heterozygous C282Y/H63D mutations

Outcome	Study	Design	No. of included studies	No. cases	No. controls	Proportion with mutation in case group %	Proportion with mutation in control group %	Odds ratio % (95% CI)
Arthralgia and fatigue								
	Cadet (2003)[62]	Case control	NA	120	633	15	4.6	**3.68 (1.97, 6.86)**[1]
Hyperpigmentation								
	Moirand (1999)[57]	Case control	NA	25	102	44	39.2	1.22 (0.50, 2.95)[1]
Non-alcoholic fatty liver disease								
	Ye (2016)[66]	Systematic review	6	NE	NE	NE	NE	1.45 (0.63, 3.32)
Osteoarthritis								
	Ellervik (2007)[69]	Systematic review	7	11082	17059	NE	NE	1.20 (0.70, 2.10)[2]
Osteoporosis								
	Cadet (2003)[62]	Case control	NA	92	633	3.3	4.6	0.72 (0.21, 2.41)[1]
Cirrhosis								
	Ye (2016)[66]	Systematic review	10	NE	NE	NE	NE	0.86 (0.50, 1.48)
Heart failure								
	Møller (2016)[65]	Cross-sectional	NA	667	0	1.8	NA	NA
Idiopathic cardiomyopathy								
	Mahon (2000)[63]	Case control	NA	207	200	4.8	2	3.02 (0.92, 9.90)
Liver cancer								
	Ye (2016)[66]	Systematic review	14	NE	NE	NE	NE	**1.70 (1.03, 2.80)**
Myocardial infarction								
	Ellervik (2007)[69]	Systematic review	7	4091	26063	NE	NE	1.10 (0.90, 1.50)[2]
	Van der (2008)[67]	Systematic review	11	3641	28105	3.3	2.7	1.10 (0.88, 1.38)
Type 1 diabetes								
	Ellervik (2001)[60]	Case control	NA	482	6266	1.7	2.1	0.79 (0.38, 1.62)[1]
Type 2 diabetes								
	Halsall (2003)[58]	Case control	NA	459	459	2.0	0.7	3.05 (0.82, 11.35)[1]

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable. Values in **bold** indicate statistically significant results

Discussion of findings of questions 1 and 2

Twelve prioritised studies (and 45 deprioritised articles) were identified that sought to examine the penetrance of type 1 HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity (question 1). Thirteen prioritised studies (and 46 deprioritised articles) were identified that sought to examine associations between type 1 HH-related biochemical and clinical features and homozygous C282Y, homozygous H63D, and compound heterozygous C282Y/H63D mutations in the HFE gene (question 2).

Homozygous C282Y genotype

Twenty-two papers provided data on the homozygous C282Y genotype and biochemical or clinical outcomes.[32 39 40 45 46 48-51 57 58 60-69] These papers employed cross-sectional designs (8 papers), case-control designs (7 papers), prospective designs (2 papers), and a cross-sectional plus prospective design (one study). Four papers were systematic reviews with meta-analyses. Table 16 summarises the results of questions 1 and 2 by biochemical and clinical condition for the homozygous C282Y genotype, with a met/not met/uncertain decision provided for each. Conditions in the table are ordered as follows: (1) question 1 significant and question 2 significant, (2) question 1 significant and question 2 not significant, (3) question 1 not significant and question 2 significant, and (4) question 1 not significant and question 2 not significant.

Table 16. Summary of results for homozygous C282Y studies

C282Y homozygosity summary table							
	Q1			Q2			
Condition / outcome	Penetrance rate	Risk Difference / attributable risk	Relative Risk	Cases	Controls	Odds Ratio (95% CI)	Conclusion Met / Not / Uncertain
Elevated serum ferritin	60% 65%	**57.56 (14.60, 100.51)[1]** **56.91 (48.52, 65.29)[1]**	**24.56 (10.35, 58.28)[1]** **7.76 (6.78, 8.89)[1]**	337	1568	**69.17 (6.99, 683.97)**	Met
Elevated transferrin saturation	100% 54%	**96.79 (74.64, 118.95)[1]** **53.03 (44.26, 61.80)[1]**	**27.97 (17.30, 45.23)[1]** **53.86 (43.75, 66.31)**[1]	52	2462	**613.87 (11.73, 32125.72)**	Met
Hyperpigmentation	13%	**8.72 (4.26, 13.19)[1]**	**2.98 (1.70, 5.25)[1]**	157	185	**5.23 (2.80, 9.80)**	Not met
Osteoarthritis	14%	**4.87 (3.60, 6.15)[1]**	**1.53 (1.39, 1.67)[1]**	11124	16805	2.40 (0.50, 13.00)[2]	Not met
Osteoporosis	3%	**0.75 (0.16, 1.35)[1]**	**1.39 (1.11, 1.73)[1]**	90	606	3.40 (0.31, 37.87)[1]	Not met
Liver disease (any)	1%	**0.92 (0.50, 1.35)[1]**	**3.00 (2.19, 4.09)[1]**	NA	NA	NA	Not met
Myocardial infarction or angina (combined)	5%	**-0.89 (-1.66, -0.13)[1]**	**0.84 (0.71, 0.99)**[1]	NA	NA	NA	Not met
Arthralgia and fatigue	NA	NA	NA	115	606	**38.49 (8.56, 173.09)[1]**	Not met
Liver cancer	NA	NA	NA	NE	NE	**3.16 (1.02, 9.79)**	Not met
Diabetes Type 1 Type 2 Unspecified Any	 NA NA 7% 3%	 NA NA -1.70 (-9.01, 5.62)[1] **0.87 (0.22, 1.51)[1]**	 NA NA 0.80 (0.27, 2.39) **1.37 (1.12, 1.68)[1]**	 483 425 NA NA	 6158 460 NA NA	 **5.06 (2.3, 11.01)**[1] 0.50 (0.09, 2.80)[1] NA NA	Uncertain
Fatigue	27% 40% 5%	0.91 (-6.96, 8.79)[1] -3.00 (-17.36, 11.37)[1] **1.05 (0.26, 1.85)[1]**	1.03 (0.78, 1.38)[1] 0.93 (0.65, 1.33)[1] **1.27 (1.08, 1.49)[1]**	NA	NA	NA	Not met
Rheumatoid arthritis	2%	0.37 (-0.10, 0.84)[1]	1.29 (0.97, 1.71)[1]	NA	NA	NA	Not met
Angina	0% 3%	-5.15 (-13.27, 2.96)[1] -2.03 (-4.86, 0.81)[1]	0.57 (0.04, 8.78)[1] 0.59 (0.22, 1.55)[1]	NA	NA	NA	Not met
Atrial fibrillation	1%	-0.16 (-0.58, 0.27)[1]	0.90 (0.66, 1.22)[1]	NA	NA	NA	Not met
Fibrosis/Cirrhosis	44%	NA	NA	NE	NE	0.88 (0.41, 1.91)	Not met
Heart failure	4%	-3.89 (-9.95, 2.17)[1]	0.53 (0.14, 2.07)[1]	667	0	NA	Not met
Idiopathic cardiomyopathy	NA	NA	NA	91 207	102 200	1.25 (0.03, 64.05) 3.62 (0.15, 89.69)	Not met
Myocardial infarction	0% 6% 3%	-7.88 (-16.04, 0.28)[1] 3.35 (-8.68, 15.38)[1] -1.76 (-3.79, 0.26)[1]	0.37 (0.02, 5.74)[1] 1.58 (0.42, 5.96)[1] 0.45 (0.11, 1.80)[1]	506 4471 3553	932 27363 27554	2.62 (0.59, 11.73) 1.10 (0.60, 2.00)[2] 1.01 (0.65, 1.57)	Not met
Non-alcoholic fatty liver disease	NA	NA	NA	NE	NE	3.32 (0.72, 15.36)[2]	Not met

Pneumonia	2%	0.44 (-0.12, 1.00)[1]	1.23 (0.97, 1.55)[1]	NA	NA	NA	Not met
Mortality (all-cause)	16%	-0.20 (-10.82, 10.43)[1]	0.99 (0.50, 1.96)[1]	NA	NA	NA	Not met

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable

Biochemical manifestations

Penetrance

The proportion of people with elevated serum ferritin was 60 – 65% for people with the homozygous C282Y genotype and 2.4 – 8.4% for people with the wildtype genotype. The proportion of people with elevated transferrin saturation was 54 – 100% for people with the homozygous C282Y genotype and 1.0 – 3.2% for people with the wildtype genotype.

Measurements of association

Statistically significant associations (odds ratios, risk difference, relative risk) were observed between the homozygous C282Y genotype and the 2 key biochemical manifestations of type 1 HH: elevated serum ferritin (3 papers), and elevated transferrin saturation (4 studies).

The evidence of effect was consistent between both questions. However, a larger volume of studies was available for question 2. The evidence considered in question 1, penetrance, was limited to 2 cross sectional studies for both outcomes. A large number of deprioritised studies were identified. A meta-analysis may help provide a more refined estimate of penetrance.

Clinical conditions

Penetrance

The results of cohort and cross-sectional studies indicated that the proportion of people with clinical outcomes ranged from 0 – 44% in people with the homozygous C282Y genotype and 0.5 – 43% in people with the wild type genotype. Results from cohort studies indicated that for those with the homozygous C282Y mutation, penetrance was less than 5% for rheumatoid arthritis, osteoporosis, atrial fibrillation, diabetes, heart failure, liver disease, myocardial infarction, and pneumonia, 5% for fatigue, 14.2% for osteoarthritis, and 15.8% for all cause mortality.

Measurements of association

Statistically significant associations were observed between the homozygous C282Y genotype and 4 of the clinical manifestations: hyperpigmentation (2 studies), any liver disease (one study), liver cancer (systematic review of 10 studies), and having at least one clinical outcome (one study). However, the overall assessment is that these outcomes are still not met because of the volume, type of evidence, and risks of bias. For example, for any liver disease, only one prospective study met the criteria for inclusion in this review and it was found to be at moderate risk of bias. Similarly, for liver cancer, even though a systematic review of 10 studies was included, these were all case-control studies and the review was considered to be at high risk of bias.

No statistically significant associations were observed between the C282Y genotype and angina (2 studies), atrial fibrillation (one study), cirrhosis (systematic review of 9 studies), idiopathic cardiomyopathy (2 studies), heart failure (one study), myocardial infarction (6 studies), non-alcoholic fatty liver disease (systematic review of 8 studies), osteoarthritis (7 studies, including one systematic review), osteoporosis (one study), pneumonia (one study), rheumatoid arthritis (one study), or mortality (one study).

Inconsistent results were reported in relation to associations between genotype and fatigue (4 studies), and diabetes (4 studies). The lack of consistency between results might be derived from differences within the studies. For example, for fatigue the 2 studies that reported no association with genotype were cross-sectional, while the 2 studies that reported a significant association were a prospective (one study) and case-control study (one study). If observable features of fatigue take time to manifest, this might only be captured in longitudinal studies. Further, the method by which fatigue was identified was only reported in one study (in which fatigue was diagnosed on the basis of a 'yes' response to either of 2 questions),[36] making it difficult to draw comparisons between studies. Additional evidence on fatigue was identified in a small number of deprioritised studies (see Tables 27 and 28). Of these 2 included comparator arms, which would be helpful in terms of calculating risk difference and relative risk.[70 71] For diabetes, there were significant differences between the studies that could account for inconsistencies in results. For example, the type of diabetes was not uniform between the four studies (one study of late-onset type 1 diabetes, one study of type 2 diabetes, one study of either type 1 or type 2 diabetes, and one study in which the type of diabetes was not specified). Additional data on diabetes (predominantly type 2 diabetes) is also available in 19 deprioritised studies comprising approximately 5000 participants (see Tables 27 and 28), 12 of which include comparator arms.[72-83] Overall, the deprioritised diabetes studies are small. The purpose of a potential meta-analysis for this outcome would be to confirm the Pilling et a. 2019 study. However, this could pose some challenges because the type of diabetes assessed and how it is diagnosed are not consistent between studies (for example WHO criteria or self-reported).

Homozygous H63D genotype

Seventeen studies provided data on the homozygous H63D genotype and biochemical or clinical conditions.[40 42 46 48 51 57 59-69] These papers employed case-control designs (7 papers), cross-sectional designs (4 papers), a prospective design (one study), and a cross-sectional plus prospective designs (one study). Four papers were systematic reviews with meta-analyses. Table 17 summarises the results of questions 1 and 2 by biochemical and clinical condition for the homozygous H63D genotype, with a met/not met/uncertain decision provided for each. Conditions in the table are ordered as follows: (1) question 1 significant and question 2 significant, (2) question 1 significant and question 2 not

significant, (3) question 1 not significant and question 2 significant, and (4) question 1 not significant and question 2 not significant.

Table 17. Summary of results for homozygous H63D studies

H63D homozygosity summary table							
	Q1			Q2			
Condition / outcome	Penetrance rate	Risk Difference / attributable risk	Relative Risk	Cases	Controls	Odds Ratio	Conclusion Met / Not / Uncertain
Elevated transferrin saturation	11%	7.76 (-0.16, 15.69)[1]	**3.20 (1.53, 6.71)[1]**	99	1494	**7.17 (1.25, 41.49)**	Met
Elevated serum ferritin	26%	**13.52 (2.52, 24.52)[1]**	**2.10 (1.35, 3.26)[1]**	273	942	2.28 (0.62, 8.31)	Not met
Arthralgia and fatigue	NA	NA	NA	123	631	**4.61 (2.51, 8.46)**[1]	Not met
Hyperpigmentation	NA	NA	NA	19	73	2.01 (0.60, 6.72)[1]	Not met
Angina	6% 6%	1.10 (-5.85, 8.04)[1] 0.54 (-1.14, 2.22)[1]	1.21 (0.40, 3.71)[1] 1.11 (0.82, 1.51)[1]	NA	NA	NA	Not met
Cirrhosis	NA	NA	NA	NE	NE	1.07 (0.72, 1.58)	Not met
Diabetes Type 1 Type 2 Unspecified	 NA NA 8%	 NA NA -0.58 (-3.92, 2.76)[1]	 NA NA 0.93 (0.61, 1.43)[1]	 489 75 NA	 6293 76 NA	 1.23 (0.72, 2.10)[1] 1.01 (0.02, 51.73)[1] NA	Uncertain
Fatigue	47%	4.09 (-2.13, 10.30)[1]	1.10 (0.96, 1.25)[1]	NA	NA	NA	Not met
Heart failure	9%	0.62 (-2.94, 4.17)[1]	1.07 (0.72, 1.60)[1]	667	0	NA	Not met
Idiopathic cardiomyopathy	NA	NA	NA	91 207	102 200	0.18 (0.01, 3.53) 0.81 (0.22, 2.93)	Not met
Liver cancer	NA	NA	NA	NE	NE	0.99 (0.65, 1.51)	Not met
Myocardial infarction	6% 6% 4%	-1.63 (-8.63, 5.37)[1] 0.64 (-3.44, 4.72)[1] 0.89 (-0.57, 2.36)[1]	0.79 (0.26, 2.41)[1] 1.11 (0.59, 2.11)[1] 1.28 (0.89, 1.83)[1]	448 3887 3649	869 25558 28281	0.77 (0.30, 2.01)[1] 1.20 (0.90, 1.60)[2] 1.14 (0.92, 1.42)	Not met
Mortality (all-cause)	18%	1.76 (-2.97, 6.49)[1]	1.11 (0.85, 1.46)[1]	NA	NA	NA	Not met
Non-alcoholic fatty liver disease	NA	NA	NA	NE	NE	1.47 (0.97, 2.22)	Not met
Osteoarthritis	NA	NA	NA	5926	21197	1.50 (0.70, 3.00)[2]	Not met
Osteoporosis	NA	NA	NA	93	631	1.01 (0.35, 2.97)[1]	Not met

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable

Biochemical manifestations

Penetrance

The proportion of people with elevated serum ferritin was 25.8% for people with the homozygous H63D genotype and 12.2% for people with the wildtype genotype. The proportion of people with elevated transferrin saturation was 11.3% for people with the homozygous H63D genotype and 3.5% for people with the wildtype genotype.

Measurements of association

Statistically significant associations were observed between the homozygous H63D genotype and the elevated transferrin saturation (3 studies, including one systematic review of 2 studies). Inconsistent results were reported in relation to potential associations between the H63D genotype and elevated serum ferritin (4 studies, including one systematic review of 3 studies) in which a significant association (relative risk and risk difference)nwas observed in a single cross-sectional study,[42] but no association in a meta-analysis of 3 studies (odds ratio).[68] It is of note that in the meta-analysis the most recent of the included study was from 2007, and the 95% confidence interval was wide with the lower limit close to 1 (OR 2.28 95% CI 0.62, 8.31). The present review identified many more deprioritised studies (n = 48) on serum ferritin (see Tables 27 and 28), 34 of which included comparator arms.[70-72 84-112] An updated meta-analysis that includes relevant studies from this 34 is justified to provide clarity on the mixed results of the present review, and to aid the understanding of potential associations between the homozygous H63D genotype and serum ferritin.

Clinical condition

Penetrance

The results of cohort and cross-sectional studies indicated that the proportion of people with clinical conditions ranged from 4.1 – 47.1% in people with the homozygous H63D genotype and 3.2 – 43% in people with the wild type genotype. Results from cohort studies indicated that for those with the homozygous H63D mutation, penetrance was less than 10% for diabetes, heart failure, and myocardial infarction, 17.5% for mortality, and 47.1% for fatigue.

Measurements of association

No statistically significant associations were observed between the homozygous H63D genotype and angina (2 studies), cirrhosis (systematic review of 23 studies), diabetes (4 studies), fatigue (one study), heart failure (one study), hyperpigmentation (one study), idiopathic cardiomyopathy (2 studies), liver cancer (systematic review of 18 studies), non-alcoholic fatty liver disease (systematic review of 13 studies), myocardial infarction (6 studies), mortality (one study), osteoarthritis (systematic review of 7 studies), and osteoporosis (one study).

Compound heterozygous C282Y/H63D genotype

Eighteen studies provided data on the compound heterozygous C282Y/H63D genotype and biochemical or clinical outcomes.[36 39-41 46 48 51 54 57 58 60 62 63 65-69] The papers employed cross-sectional designs (7 papers), case-control designs (5 papers), a prospective designs (one study), and a cross-sectional plus prospective design (one paper). Four papers were systematic reviews with meta-analyses. Table 18 summarises the results of questions 1 and 2 by biochemical and clinical condition for the compound heterozygous C282Y/H63D genotype, with a met/not met/uncertain decision provided for each. Conditions in the table are ordered as follows: (1) question 1 significant and question 2 significant, (2) question 1 not significant and question 2 significant, and (3) question 1 not significant and question 2 not significant.

Table 18. Summary of results for compound heterozygous C282Y/H63D studies

C282Y/H63D compound heterozygous summary table							
	Q1			Q2			
Condition / outcome	Penetrance rate	Risk Difference / attributable risk	Relative Risk	Cases	Controls	Odds Ratio	Conclusion Met / Not / Uncertain
Elevated transferrin saturation	26% 22%	**23.11 (3.26, 42.96)[1]** **16.68 (6.65, 26.70)[1]**	**8.21 (3.47, 19.44)[1]** **4.43 (2.70, 7.26)[1]**	13	1437	**13.73 (2.43, 77.75)**	Met
Elevated serum ferritin	16% 34%	13.35 (-3.09, 29.79)[1] **21.09 (9.51, 32.66)[1]**	**6.46 (2.06, 20.33)[1]** **2.65 (1.86, 3.78)[1]**	27	696	**10.79 (1.17, 99.01)**	Met
Arthralgia and fatigue	NA	NA	NA	120	633	**3.68 (1.97, 6.86)[1]**	Not met
Liver disease (any)	21%	NA	NA	NE	NE	**1.70 (1.03, 2.80)**	Not met
Hyperpigmentation	2%	NA	NA	25	102	1.22 (0.50, 2.95)[1]	Not met
Arthritis (unspecified)	3%	NA	NA	NA	NA	NA	Not met
Angina	9% 5%	3.94 (-4.64, 12.51)[1] 0.16 (-1.70, 2.03)[1]	1.76 (0.67, 4.61)[1] 1.03 (0.72, 1.49)[1]	NA	NA	NA	Not met
Cardiomyopathy	4%	NA	NA	NA	NA	NA	Not met
Cirrhosis	5%	NA	NA	NE	NE	0.86 (0.50, 1.48)	Not met
Diabetes Type 1 Type 2 Unspecified	 NA NA 23% 9%	 NA NA NA 1.48 (-2.77, 5.74)[1]	 NA NA NA 1.18 (0.76, 1.82)[1]	 482 459 NA NA	 6266 459 NA NA	 0.79 (0.38, 1.62)[1] 3.05 (0.82, 11.35)[1] NA NA	Not met
Fatigue	26% 49%	-0.07 (-3.67, 3.52)[1] 6.23 (-0.92, 13.38)[1]	1.00 (0.87, 1.14)[1] 1.14 (0.99, 1.32)[1]	NA	NA	NA	Not met
Heart failure	8%	-0.04 (-3.99, 3.90)[1]	0.99 (0.62, 1.60)[1]	667	0	NA	Not met
Idiopathic cardiomyopathy	NA	NA	NA	207	200	3.02 (0.92, 9.90)	Not met
Liver cancer	0%	NA	NA	NA	NA	NA	Not met
Myocardial infarction	2% 3% 5%	-5.61 (-10.24, -0.98)[1] -2.49 (-5.68, 0.70)[1] 1.34 (-0.42, 3.10)[1]	0.29 (0.04, 2.02)[1] 0.57 (0.21, 1.49)[1] 1.42 (0.96, 2.09)[1]	4091 3641	26063 28105	1.10 (0.90, 1.50)[2] 1.10 (0.88, 1.38)	Not met
Mortality (all-cause)	16%	-0.20 (-10.82, 10.43)[1]	0.99 (0.50, 1.96)[1]				Not met
Non-alcoholic fatty liver disease	NA	NA	NA	NE	NE	1.45 (0.63, 3.32)	Not met
Osteoarthritis	NA	NA	NA	11082	17059	1.20 (0.70, 2.10)[2]	Not met
Osteoporosis	NA	NA	NA	92	633	0.72 (0.21, 2.41)[1]	Not met

[1] = calculated by review team, [2] = 99% confidence intervals, CI = confidence interval, NA = not applicable, NE = not extractable.

Biochemical manifestations

Penetrance

The proportion of people with elevated serum ferritin was 15.8 – 33.9% for people with the compound heterozygous C282Y/H63D genotype and 2.4 – 12.8% for people with the wildtype genotype. The proportion of people with elevated transferrin saturation was 21.5 – 26.3% for people with the compound heterozygous C282Y/H63D genotype and 3.2 – 4.9% for people with the wildtype genotype.

Measurements of association

Compared to people with the wildtype genotype, people with the compound heterozygous C282Y/H63D mutation were more likely to have elevated serum ferritin (4 studies, including one systematic review), and elevated transferrin saturation (3 studies, including one systematic review).

Clinical manifestations

Penetrance

The results of cohort and cross-sectional studies indicated that the proportion of people with clinical outcomes ranged from 0 – 49.2% in people with the compound heterozygous C282Y/H63D genotype and 3.2 – 43% in people with the wild type genotype. Results from cohort studies indicated that for those with the compound heterozygous C282Y/H63D mutation, penetrance was less than 5% for myocardial infarction, 5 – 9.9% for diabetes and heart failure, 15.5% for mortality, and 49.2% for fatigue.

Measurements of association

Statistically significant associations were observed between the compound heterozygous C282Y/H63D genotype and liver cancer (systematic review of 14 studies). No statistically significant associations were observed between the compound heterozygous C282Y/H63D mutation and angina (2 studies), cirrhosis (systematic review of 10 studies), diabetes (3 studies), fatigue (2 studies), heart failure (one study), hyperpigmentation (one study), idiopathic cardiomyopathy (one study), myocardial infarction (14 studies, including 2 systematic reviews), mortality (one study), non-alcoholic fatty liver disease (systematic review of 6 studies), osteoarthritis (systematic review of 7 studies), and osteoporosis (one study).

Conclusions

In summary, there is clear and consistent evidence for an association between the 3 type 1 HH genotypes and iron overload. In question 1, the proportion of people with elevated serum ferritin was higher in people with the homozygous C282Y mutation (60 – 65%) than the homozygous H63D (26%) or compound heterozygous C282Y/H63D (16 – 34%)

mutations. The proportion of people with elevated transferrin saturation was higher in people with the homozygous C282Y mutation (54 –100%) than the homozygous H63D (11%) or compound heterozygous C282Y/H63D (22 – 26%) mutations. The increases were large in magnitude. For example, Waalen 2002 found the absolute risk of elevated serum ferritin increased by 57% (95% CI 49% to 65%) in the homozygous C282Y group (65% in comparison to 8% with elevated levels in the wild type).[49] These results were mirrored in question 2, in which the odds of having any of the 3 mutations were significantly higher in people with elevated transferrin saturation than those without. Similarly, the odds of having the homozygous C282Y and compound heterozygous C282Y/H63D genotypes were higher in individuals with increased serum ferritin. The results about potential associations between the homozygous H63D genotype and serum ferritin were inconsistent. It is worth noting that these are biochemical outcomes, which may or may not have clinical implications for individuals. Nevertheless, serum ferritin and transferrin saturation are extremely common outcomes in the deprioritised studies. A systematic review and/or meta-analysis might help to bring precision to the estimates outlined in this evidence summary. More specifically, in relation to the homozygous H63D mutation, a meta-analysis would provide clarity on the mixed results of the present review and it would help to understand the potential associations between the homozygous H63D genotype and elevated serum ferritin.

The evidence regarding health outcomes generally does not support associations with type 1 HH genotypes. The exceptions being liver cancer (only in relation to the compound heterozygous C282Y/H63D genotype), as well as hyperpigmentation, liver disease (any or liver cancer), and ‘any’ clinical outcome, though these were limited to the homozygous C282Y genotype

Summary of Findings Relevant to Criterion 1: Criterion **MIXED (but overall, NOT MET)**[*]

Twelve prioritised studies (and 45 deprioritised articles) were identified that sought to examine the penetrance of type 1 HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity (question 1). Thirteen prioritised studies (and 46 deprioritised articles) were identified that sought to examine the association between type 1 HH-related biochemical and clinical features and homozygous C282Y, homozygous H63D, and compound heterozygous C282Y/H63D mutations in the HFE gene (question 2).

Criterion 1 focuses on the importance of the health problem as judged by its frequency and severity. Two aspects of criterion 1 were considered in this review: prevalence, and the association between the disease markers (i.e. genotypes) and treatable disease.

Overall, criterion 1 is **NOT MET** because even though there is clear evidence for an association between the 3 type 1 HH genotypes and iron overload, these are biochemical outcomes, which may or may not have clinical implications for individuals. Moreover, the evidence regarding clinical conditions generally does not support associations with type 1 HH genotypes. The evidence in this review is based on studies that were typically at moderate-to-high (question 1) and high or unclear (question 2) risk of bias, and the majority of papers in question 1 reported health outcome data from cross-sectional studies. While cross-sectional studies are useful for identifying iron overload, prospective cohort studies are more appropriate for identifying many health outcomes as they take time to develop. Further, only 4 study were conducted in the UK.[32 43 58 63] One considered all 3 mutations (but only reported mean values for biochemical outcomes),[43] one only assessed type 2 diabetes,[58] one only assessed idiopathic cardiomyopathy,[63] and one only considered the homozygous C282Y genotype.[32]

Tables 16, 17, and 18 provide met, not met, uncertain decisions for individual outcomes.

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[*] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criterion 9 — Outcomes following early treatment compared to later treatment

There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care. Evidence relating to wider benefits of screening, for example those relating to family members, should be taken into account where available. However, where there is no prospect of benefit for the individual screened then the screening programme shouldn't be further considered.

Question 3 – Is there evidence that intervention at an asymptomatic phase leads to better outcomes compared to intervention following presentation of symptoms?

This question was not examined in the last review of HH for the UK NSC.[12] The aim of this question is not to address the overall efficacy of treatment(s) for type 1 HH. The aim of this question is to identify whether intervention at an asymptomatic (or earlier) stage of type 1 HH would result in better outcomes in comparison to intervention at a symptomatic (or later) stage of type 1 HH.

Eligibility for inclusion in the review

Articles were included in this question if they reported outcomes in adults over the age of 18 years with HFE haemochromatosis genotyped as C282Y homozygous, H63D homozygous, or C282Y/H63D heterozygous following asymptomatic detection, compared with adults identified following symptomatic detection. Eligible treatments for pre- and post-symptomatic detection were phlebotomy, erythrocytopharesis, or iron chelating agents. Diagnosis in asymptomatic individuals was initiated by screen detection, cascade testing or an incidental finding. In the absence of studies comparing individuals following 'asymptomatic' detection with 'symptomatic' detection; the alternative 'early' symptomatic detection with the comparator 'late' symptomatic detection would be accepted. The study definition of 'asymptomatic', and 'early' and 'late' would be accepted, and care has been taken to be transparent in reporting definitions for the respective papers.

The clinical outcomes of mortality, development of diabetes, any liver disease (including cancer) not caused by bacterial/viral infections, cardiovascular disease (myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoporosis, pneumonia, arthralgia, hyperpigmentation and self-reported symptoms of fatigue/weakness were assessed. Biochemical outcomes of serum ferritin, transferrin saturation and unsaturated iron binding capacity were also assessed.

Papers that met any of the following criteria were excluded: participants younger than 18 years old, fewer than 100 participants, more than 10% of sample not meeting the inclusion criteria, non-HFE types of haemochromatosis, qualitative studies, insufficient information for assessment of risk of bias, no numerical information, outcomes/exposures not listed in the inclusion criteria, grey literature (letters, reviews, editorials, communications, conference abstracts).

Description of the evidence

Full details of the number of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 4. After the removal of duplicated studies, 3,377 unique items were identified. Of these, 678 were suitable for full text assessment. Two of these studies met the eligibility criteria for inclusion in question 3. A list of excluded studies (with reasons) is given in Appendix 2, Table 28.

Characteristics of Included Studies

One systematic review by the United States Preventative Services Task Force (USPSTF) which was published in 2006,[30] and one post-hoc analysis from a randomised controlled study published in 2017 were included.[113] A detailed summary of data characteristics from these 2 studies is provided in Appendix 3. Data of interest from the RCT were analysed in subgroups on the basis of baseline characteristics (asymptomatic versus symptomatic) not randomisation, therefore for this review the study has been categorised as a cohort study.

The USPSTF systematic review sought to assess whether there was adequate evidence to recommend a screening programme for HH in individuals of Northern European descent with homozygosity for C282Y. No studies were identified that examined whether intervention at an earlier stage (that is pre-symptomatic) of the condition leads to better outcomes than intervention at a later stage (for example following presentation of symptoms).

The cohort study (nested within a randomised controlled trial), was conducted in Australia.[113] A total of 104 participants were included in the trial (treatment, n = 54; control, n = 50). Participants were 18 – 70 years old, had the homozygous C282Y genotype, and elevated serum ferritin (300–1000 µg/L), and transferrin saturation (threshold not specified). The number of participants included in the post-hoc analysis comparing asymptomatic (detected via family history or routine iron studies as part of a health check) and symptomatic individuals was not reported. Nor were the characteristics of the 2 groups. The outcome of interest was self-reported fatigue (as measured by the Modified Fatigue Impact Scale).[114]

Discussion of findings

Quality appraisal of included studies

The quality of the USPSTF systematic review was assessed using the ROBIS,[35] and the quality of the cohort study was assessed using the JBI Checklist for Cohort Studies.[34] For the JBI Checklist for Cohort Studies, items rated as 'yes' are referred to as low risk of bias, and items rated as 'no' are referred to as high risk of bias.

Details of quality appraisal for the cohort study is shown in Appendix 3 Table 36. A high risk of bias was identified on one item (valid and reliable measurement of outcomes), the key concern being that clinically meaningful change score has not been established for the research tool (Modified Fatigue Impact Scale). Low risk of bias was identified on 4 items, and unclear risk of bias on 5 items. Examples of reasons for unclear ratings are: lack of individual and pooled participant data, no information on the number of people in the symptomatic and asymptomatic groups, absence of power calculation for the post-hoc analysis, and lack of information on whether fatigue scores met clinical thresholds.

While applicability is not assessed in the JBI Checklist for Cohort Studies, applicability concerns for the included cohort study are apparent in relation to screening for type 1 HH in the UK. First, the study evaluated erythrocytapheresis. While erythrocytapheresis is an applicable treatment for type 1 HH, the first line treatment is phlebotomy.[26] Second, the cohort study evaluated the benefit of normalising moderately elevated serum ferritin (between 300µg/L and 1000 µg/L). This represents a specific sub-cohort of type 1 HH individuals and is not representative of the broad expressivity of elevated ferritin amongst the population of patients with type 1 HH for which treatment is advised.[26] Third, due to concerns of confounding secondary to development of iron deficiency anaemia and associated fatigue, the authors chose a serum ferritin level of less than 300µg/L as the end-point. However, this end-point does not reflect current clinical guidelines within the UK, which advises treatment until serum ferritin is approximately 20–30 µg/L.[26]

Details of the systematic review are shown in Appendix 3 Table 37. As no studies were identified by the systematic review, the domains relating to 'data collection and study appraisal', and 'synthesis and findings' were not applicable. Therefore, only 2 domains were assessed: study eligibility criteria, and identification and selection of studies. Both domains were at low risk of bias.

Analysis of the evidence

The systematic review did not identify any studies allowing for a valid comparison of the efficacy of intervention at an asymptomatic (or earlier) stage of type 1 HH versus symptomatic (or later) stage of type 1 HH. A post-hoc analysis from the cohort study compared the effect of erythrocytapheresis on fatigue between participants who were symptomatic and asymptomatic at baseline. The number of participants in the 2 groups was not reported. Mean fatigue scores were lower after treatment for both groups (asymptomatic group = 6.1 points lower, 95% CI -9.6 to -2.6 points; symptomatic group = 8.8 points lower, 95% CI -15.3 to -2.3 points). There was no statistically significant difference between the change scores of the 2 groups (2.7 points, 95% CI -10.1 to 4.6 points).

The paucity of research identified by this evidence summary prevents from drawing conclusions on whether intervention at an asymptomatic phase leads to better outcomes compared to intervention following presentation of symptoms in individuals with hereditary haemochromatosis.

Summary of Findings Relevant to Criterion 9: Criterion **NOT MET**[†]

One systematic review and one cohort study nested in an RCT were identified that sought to investigate the effects of treatments at earlier versus later stages of type 1 HH in people with the homozygous C282Y genotype. No studies were identified in relation to the homozygous H63D or compound heterozygous C282Y/H63D genotypes.

The systematic review (published in 2006) did not identify any controlled studies of phlebotomy treatment, nor an evidence base to evaluate the question of whether early versus late phlebotomy treatment affected outcomes.

A cohort study (published in 2017) evaluated the effectiveness of erythrocytopharesis in people with type 1 HH (homozygous C282Y only) and moderately elevated serum ferritin. A post-hoc analysis did not find a significant difference in self-reported fatigue scores after treatment between individuals who were asymptomatic or symptomatic at baseline. Overall, the study was judged to have unclear risks of bias. There were applicability concerns as the study population, type of treatment, and end-point do not reflect UK clinical practice.

There is insufficient evidence to inform the question and draw conclusions on whether intervention at an earlier/asymptomatic stage leads to better outcomes compared to intervention at a later/symptomatic stage in individuals with hereditary haemochromatosis. Therefore criterion 9 is **NOT MET**.

[†] **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Criteria 11 and 13 — Harms of screening and effectiveness of screening to reduce morbidity and mortality

There should be evidence from high quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (such as Down's syndrome or cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

The benefit gained by individuals from the screening programme should outweigh any harms, for example from overdiagnosis, overtreatment, false positives, false reassurance, uncertain findings and complications.

Question 4 – What is the effectiveness of screening to reduce type 1 HH-related morbidity and mortality?

This question was not examined in the last review of type 1 HH for the UK NSC.[12] The aim of this question is to examine if screening (genotypic or phenotypic) is effective in reducing mortality or morbidity related to type 1 HH, and whether the benefits of screening outweigh the harms.

Eligibility for inclusion in the review

Articles were included in this question if they reported outcomes of screening (genotype or phenotype strategies) compared to usual care, no screening, or genotype or phenotype strategies in RCT or non-randomised control trials in adults over the age of 18 years with no symptoms or family history of HH.

The clinical outcomes of mortality, development of diabetes, any liver disease (including cancer) not caused by bacterial/viral infections, cardiovascular disease (myocardial infarction, angina, atrial fibrillation, cardiomyopathy, heart failure), rheumatoid arthritis, osteoporosis, pneumonia arthralgia, hyperpigmentation and self-reported symptoms of fatigue/weakness were assessed. Biochemical outcomes of serum ferritin, transferrin saturation and unsaturated iron binding capacity were also assessed.

Papers that met any of the following criteria were excluded: participants younger than 18 years old, fewer than 100 participants, more than 10% of sample not meeting the inclusion criteria, non-HFE types of haemochromatosis, qualitative studies, insufficient information for assessment of risk of bias, no numerical information, outcomes/exposures not listed in the

inclusion criteria, grey literature (letters, reviews, editorials, communications, conference abstracts).

Description of the evidence

Full details of the number of studies included and excluded at each stage of the review are provided in Appendix 2, Figure 4. After the removal of duplicated studies, a total of 3,377 unique items were identified. Supplementation of electronic database searches by contact with subject experts and scrutiny of references from included studies and relevant systematic reviews identified 11 potentially relevant studies. Of these, 11 were suitable for full text screening. No studies met the eligibility criteria for inclusion in question 4. A list of excluded studies (with reasons) is given in Appendix 2, Table 28.

Discussion of findings

No eligible studies were identified which reported benefits of screening for type 1 HH in adults. Most studies were excluded because they were not RCTs, and/or did not have any relevant outcomes. In the absence of any included studies, a brief summary of one cohort study on the prevalence and clinical effects of iron overload and type 1 HH (known as the HEIRS study),[115] and one study which reported on the potential harms of screening is reported.[25] As these studies did not meet the eligibility criteria for the present review, formal extraction and quality appraisal were not undertaken.

The paper on the prevalence and clinical effects of iron overload and type 1 HH was a large (n = 99,711) uncontrolled cohort study conducted in Canada and the USA.[115] Participants aged 25 years and older were recruited from primary care clinics and medical blood-drawing laboratories. Participants underwent testing for levels of serum ferritin and transferrin saturation, and assessment for C282Y and H63D mutations. In addition, participants provided self-report information about history of liver disease, diabetes, arthritis, congestive heart failure, impotence, and infertility.

HH mutations were rare: C282Y/C282Y n = 299 (0.3%), H63D/H63D n = 1270 (1.3%), C282Y/H63D n = 1017 (1.0%). Assessment of iron overload indicated that elevated serum ferritin (>300µg for men, >200µg for women) was observed in the majority of participants with the C282Y/C282Y genotype, and a minority of participants with other type 1 HH genotypes or the wild type (Table 19). Amongst the people with the C282Y/C282Y genotype, elevated transferrin saturation (>50% for men, >45% for women) was reported for 84% of men and 73% of women. The number above these thresholds were not reported for any of the other genotypes or for the wild type. With the exception of people with the C282Y/C282Y genotype, mean serum ferritin and transferrin saturation levels were within

the normal ranges. Screening using the thresholds specified in the study would have failed to identify 12 – 43% of participants with the C282Y/C282Y genotype according to serum ferritin levels (and the majority of those with either the H63D/H63D or C282Y/H63D genotypes), and 16 – 27% of participants with the C282Y/C282Y genotype according to transferrin saturation levels.

Table 19. Percentage of participants with type 1 HH genotypes who had serum ferritin above threshold

Genotype	Men % above threshold (>300µg)	Women % above threshold (>200µg)
Homozygous C282Y	88	57
Homozygous H63D	32	15
Compound heterozygous C282Y/H63D	37	20
Wild type	26	13

Few differences were observed between the presence or absence of type 1 HH genotypes and self-reported health. For men, the odds of self-reported arthritis were higher amongst people with the H63D/H63D genotype compared to people with the wild type (OR 1.28, 95% CI 1.03–1.59), and the odds of any liver disease were higher amongst those with the C282Y/C282Y (OR 3.28, 95% CI 1.49–7.22) and C282Y/H63D (OR 1.65, 95% CI 1.00–2.73) genotypes compared to people with the wild type. There were no statistically significant differences in the odds of any of the other self-reported health problems. For women, no statistically significant differences in the odds of any health problems was reported between those with C282Y/C282Y, H63D/H63D, and C282Y/H63D genotypes compared to those with the wild type. In a follow up publication, the study authors concluded that population screening in a primary care population, as conducted in the HEIRS study, is not recommended.[31] In the absence of a control group, benefits and harms of screening cannot be assessed.

The paper on harms was part of a pragmatic trial that compared genotypic and phenotypic screening strategies.[25] Participants aged 30 – 70 years old were recruited from 2 general practice registers in the UK. From the initial random sample of 3,000 people contacted, 939 (31.3%) agreed to participate in the study (genotypic screening arm, n = 497; phenotypic screening arm, n = 442). Participants completed questionnaires on anxiety, depression, and perception of general health at 4 time points (at invitation, testing, when test results were given, and 6 months after participation). The study authors reported that analysis of covariance (with baseline anxiety, depression, and general health scores as covariates) indicated no statistically significant differences between the 2 strategies (1) when test results were given, or (2) at 6-month follow up. Additional analysis was conducted that adjusted for age, sex, deprivation, employment, screening outcome (screen positive, screen negative with iron overload, screen negative without iron overload), and screening strategy

(genotypic, phenotypic). There were small, statistically significant differences in the adjusted means of the 2 groups for all 3 measures, with the genotyping group having higher depression and anxiety scores (that is more depressed and anxious), and lower health perception scores (meaning worse self-reported health) than the phenotypic group (see Table 20).The study authors reported that these differences are unlikely to be clinically meaningful.

Table 20. Anxiety, depression, and general health scores by screening strategy

Screening strategy	Anxiety [a]	Depression [b]	General health [c]
	Adjusted mean (95% CI)	Adjusted mean (95% CI)	Adjusted mean (95% CI)
Genotypic	34.8 (33.9 - 35.7)	3.9 (3.8 – 4.1)	69 (68 - 70.1)
Phenotypic	32.9 (31 – 33.9)	3.4 (3.2 – 3.6)	32.9 (31 – 33.9)

[a] Scale range: 20 – 80 (high score is more anxious), [b] Scale range: 0 – 21 (higher score is more depressed), [c] Scale range 0 – 100 (higher score is better self-reported health)

Caution is warranted in drawing conclusions from this paper about the potential harms of screening for type 1 HH. First, the trial was primarily concerned with uptake of screening, with sample size calculations determined on the basis of detecting differences in uptake between the 2 screening strategies. Sample size calculations were not conducted in relation to detecting differences in anxiety, depression, or general health between the strategies. Second, there was no 'no screening/usual care comparator', preventing an assessment of the harms of screening itself. Third, few details were provided on participant anxiety, depression, and general health (that is scores were not reported for any of the time points investigated), and none of the numerical details of the results of the analysis of covariance were reported (for example change scores, test statistics and 95% confidence intervals or p-values).

Summary of Findings Relevant to Criterion 11 and 13: Criterion **NOT MET**‡

No studies met the eligibility criteria for inclusion in this review.

There is insufficient evidence to answer the question and draw conclusions on the harms of screening for hereditary haemochromatosis and on the effectiveness of screening to reduce morbidity and mortality. Therefore criteria 11 and 13 are **NOT MET**.

‡ **Met** -for example, this should be applied in circumstances in which there is a sufficient volume of evidence of sufficient quality to judge an outcome or effect which is unlikely to be changed by further research or systematic review.
Not Met - for example, this should be applied in circumstances where there is insufficient evidence to clearly judge an outcome or effect or where there is sufficient evidence of poor performance.
Uncertain -for example, this should be applied in circumstances in which the constraints of an evidence summary prevent a reliable answer to the question. An example of this may be when the need for a systematic review and meta-analysis is identified by the rapid review.

Review summary

Conclusions and implications for policy

This review examined 4 key questions relating to the effectiveness and appropriateness of screening for type 1 HH:

1. What is the penetrance of type 1 HH in untreated adults who are positive for C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity?
2. What is the association between HH-related biochemical and clinical features and mutations in the HFE gene (C282Y homozygosity, H63D homozygosity or C282Y/H63D compound heterozygosity)?
3. Is there evidence that intervention at a pre-symptomatic phase leads to better outcomes compared to intervention following presentation of symptoms?
4. What is the effectiveness of screening to reduce type 1 HH-related morbidity and mortality?

The evidence in this review is based on studies that were typically at moderate-to-high (question 1) and high or unclear (question 2) risk of bias. Questions 1 and 2 provided clear and consistent evidence for an association between homozygous C282Y and compound heterozygous C282Y/H63D mutations and iron overload (elevated serum ferritin and transferrin saturation), and evidence for a possible association for the homozygous H63D mutation. Penetrance was considerably higher for people with the homozygous C282Y mutation (elevated serum ferritin 60 – 65%; elevated transferrin saturation 54 – 100%) than those with homozygous H63D (elevated serum ferritin 26%; elevated transferrin saturation 11%) or compound heterozygous C282Y/H63D (elevated serum ferritin 16 – 34%; elevated transferrin saturation 22 – 26%) mutations. The evidence of effect was consistent between both question 1 and 2. A large number of deprioritised studies were identified. Pooling prioritised and deprioritised studies together may help to provide more refined estimates of penetrance and potential associations between genotypes and iron overload. In relation to the homozygous H63D mutation, a meta-analysis would provide clarity on the mixed results of the present review and it would help to understand the potential associations between the homozygous H63D genotype and elevated serum ferritin. However, it is worth noting that these are biochemical outcomes, which may or may not have clinical implications for individuals.

The evidence regarding health outcomes generally does not support associations with type 1 HH genotypes. The exceptions were liver cancer (only in relation to the compound heterozygous C282Y/H63D genotype), as well as hyperpigmentation, liver disease (any or

liver cancer), and ‘any’ clinical outcome (limited to the homozygous C282Y genotype). Inconsistent results were reported in relation to the association of diabetes and fatigue with the homozygous C282Y genotype. Additional data on on these 2 outcomes is available in some of the deprioritised studies and may provide some clarity on their potential association with the homozygous C282Y genotype.

Overall, potential associations between type 1 HH genotypes and biochemical and clinical outcomes have been examined in a reasonable number of studies. Nevertheless, for many of the outcomes (by genotype), there is limited data from individual studies, often characterised by small sample sizes and suboptimal study designs, for example cross-sectional designs, which assess outcomes at a single point in time. Prospective cohort studies with longer follow up times would be better suited for identifying health outcomes that require years to develop and manifest clinically.

For questions 3 and 4, there was insufficient evidence on which to draw conclusion about the effects of earlier compared to later treatment for iron overload in people with type 1 HH or whether screening for type 1 HH would lead to reduction in morbidity or mortality.

In keeping with the conclusions of the previous UK NSC review, the evidence from this review does not support screening for type 1 HH in adults. This is driven by a lack of evidence for associations between the type 1 HH genotypes and clinical outcomes, incomplete penetrance, and important gaps in the evidence in relation to the lack of (1) RCT evidence on the benefits of screening for type 1 HH in adults, and (2) controlled trials comparing treatment effects at pre-symptomatic (or earlier) versus symptomatic (or later) phases of type 1 HH.

Strengths and limitations

The major strength of this review is the large volume of research that was identified, exploring a wide range of clinical outcomes. This can form the basis of future work. For example, where systematic review evidence is warranted to refine estimates of association between genotypes and clinical outcomes, and identifying particular clinical conditions that require additional primary research (e.g. diabetes, fatigue).

This review has a number of limitations. Only English language papers were included. Study design filters were applied to the searches, and studies that met the review inclusion criteria were divided into prioritised/deprioritised categories (on the basis of study design, sample size, and applicability to the UK) with only the prioritised studies being considered in detail for the review. Further, a single reviewer conducted the majority of the review process

alone (that is searching titles and abstracts, assessing full text papers, extracting data, and appraising study risk of bias), with a second review carrying out independent assessment or checking for only 20% of review tasks. Given that these are accepted methodological adjustments for a rapid review, and that the searches for this evidence summary covered relevant literature since 1996 (when the HFE mutation was first discovered), these limitations should not have led to the exclusion of any pivotal studies.

Appendix 1 — Search strategy

Electronic databases

The search strategy included searches of the databases shown in Table .

Table 21. Summary of electronic database searches and dates

Database	Platform	Searched on date	Date range of search
MEDLINE, MEDLINE In-Process, MEDLINE Daily, Epub Ahead of Print	Ovid SP	18.12.19	1946 to December Week 1 2019
Embase	Ovid SP	18.12.19	1947 to 2019 Week 50
The Cochrane Library, including: - Cochrane Database of Systematic Reviews (CDSR) - Cochrane Central Register of Controlled Trials (CENTRAL) - Database of Abstracts of Reviews of Effects (DARE)	Wiley Online	18.12.19	All
Web of Science	OVID SP	18.12.19	1996 to present

Search Terms

Search terms included combinations of free text and subject headings grouped into the following categories:

- disease area: **type 1 hereditary haemochromatosis**
- study design: **randomised controlled trials, case control, cohort, cross-sectional**
- other term group: **exclusions, database**

Search terms for MEDLINE are shown in Table 22, search terms for Embase are shown in Table 23, search terms for MEDLINE Daily updates and MEDLINE Epub Ahead of Print and In-Process & Other Non-Indexed Citations are shown in Table 24, search terms for the Cochrane Library database are shown in Table 25, and search terms for Web of Science are shown in Table 26.

Table 22. Search strategy for MEDLINE

Term Group	#	Search terms	Results
Study design	1	exp Meta Analysis/	(107911)
Study design	2	((meta adj analy$) or metaanalys$).tw.	(128420)
Study design	3	(systematic adj (review$1 or overview$1)).tw.	(120326)
Study design	4	systematic review.pt.	(116819)
Study design	5	or/1-4	(224194)
Other	6	cancerlit.ab.	(599)
Other	7	cochrane.ab.	(61918)

Other	8	embase.ab.	(66292)
Other	9	(psychlit or psyclit).ab.	(877)
Other	10	(psychinfo or psycinfo).ab.	(24926)
Other	11	(cinahl or cinhal).ab.	(20944)
Other	12	science citation index.ab.	(2714)
Other	13	bids.ab.	(428)
Other	14	or/6-13	(108558)
Other	15	reference lists.ab.	(13992)
Other	16	bibliograph$.ab.	(14945)
Other	17	hand-search$.ab.	(5616)
Other	18	manual search$.ab.	(3578)
Other	19	relevant journals.ab.	(1018)
Other	20	or/15-19	(35131)
Other	21	data extraction.ab.	(15974)
Other	22	selection criteria.ab.	(26911)
Other	23	21 or 22	(40780)
Other	24	review.pt.	(2400730)
Other	25	23 and 24	(27390)
Other	26	letter.pt.	(1003578)
Other	27	editorial.pt.	(456019)
Other	28	animal/	(6518679)
Other	29	human/	(18147763)
Other	30	28 not (28 and 29)	(4615802)
Other	31	or/26-27,30	(6028289)
Other	32	5 or 14 or 20 or 25	(265438)
Other	33	32 not 31	(255598)
Study design	34	Randomized controlled trials as Topic/	(128846)
Study design	35	Randomized controlled trial/	(495358)
Study design	36	Random allocation/	(101363)
Study design	37	Double blind method/	(154931)
Study design	38	Single blind method/	(27714)
Study design	39	Clinical trial/	(519407)
Study design	40	exp Clinical Trials as Topic/	(333932)
Study design	41	or/34-40	(1145119)
Study design	42	(clinic$ adj trial$1).tw.	(295776)
Study design	43	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.	(151966)
Study design	44	Placebos/	(34618)
Study design	45	Placebo$.tw.	(189971)
Study design	46	Randomly allocated.tw.	(23069)
Study design	47	(allocated adj2 random).tw.	(745)
Study design	48	or/42-47	(533669)
Study design	49	41 or 48	(1331234)
Other	50	Case report.tw.	(237106)
Other	51	Letter/	(1003578)
Other	52	Historical article/	(355469)

Other	53	Review of reported cases.pt.	(0)
Other	54	Review, multicase.pt.	(0)
Other	55	or/50-54	(1581387)
Other	56	49 not 55	(1298374)
Study design	57	Epidemiologic studies/	(8156)
Study design	58	exp case control studies/	(1037553)
Study design	59	exp cohort studies/	(1928801)
Study design	60	Case control.tw.	(104839)
Study design	61	(cohort adj (study or studies)).tw.	(156575)
Study design	62	Cohort analy$.tw.	(6249)
Study design	63	(Follow up adj (study or studies)).tw.	(44087)
Study design	64	(observational adj (study or studies)).tw.	(79904)
Study design	65	Longitudinal.tw.	(194241)
Study design	66	Retrospective.tw.	(417546)
Study design	67	Cross sectional.tw.	(266622)
Study design	68	Cross-sectional studies/	(311409)
Study design	69	or/57-68	(2659125)
Study design	70	33 or 56 or 69	(3808304)
Disease	71	exp Hemochromatosis/	(7832)
Disease	72	exp Hemochromatosis Protein/	(2069)
Disease	73	hemochromatosis.mp.	(9729)
Disease	74	haemochromatosis.mp.	(1711)
Disease	75	hfe.mp.	(3265)
Disease	76	hhc.mp.	(546)
Disease	77	c282y.mp.	(1451)
Disease	78	h63d.mp.	(942)
Disease	79	bronze diabetes.mp.	(27)
Disease	80	bronzed cirrhosis.mp.	(3)
Disease	81	iron storage disorder.mp.	(8)
Disease	82	pigmentary cirrhosis.mp.	(39)
Disease	83	(troisier-hanot-chauffard or troisier hanot chauffard).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(0)
Disease	84	(recklehausen-applebaum or recklehausen applebaum).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(0)
Disease	85	71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84	(11045)
Disease, study design	86	70 and 85	(1426)
Other	87	limit 86 to (english language and yr="1996 -Current")	(1230)

Table 23. Search strategy for Embase Classic+Embase (Searched via the OVID platform)

Term Group	#	Search terms	Results
Study design	1	exp Meta Analysis/	(176893)
Study design	2	((meta adj analy$) or metaanalys$).tw.	(211710)
Study design	3	(systematic adj (review$1 or overview$1)).tw.	(194837)
Study design	4	or/1-3	(358811)
Other	5	cancerlit.ab.	(728)
Other	6	cochrane.ab.	(99882)
Other	7	embase.ab.	(106373)
Other	8	(psychlit or psyclit).ab.	(994)
Other	9	(psychinfo or psycinfo).ab.	(29734)
Other	10	(cinahl or cinhal).ab.	(30734)
Other	11	science citation index.ab.	(3497)
Other	12	bids.ab.	(661)
Other	13	or/5-12	(166305)
Other	14	reference lists.ab.	(18511)
Other	15	bibliograph$.ab.	(26085)
Other	16	hand-search$.ab.	(8095)
Other	17	manual search$.ab.	(5114)
Other	18	relevant journals.ab.	(1363)
Other	19	or/14-18	(53642)
Other	20	data extraction.ab.	(24321)
Other	21	selection criteria.ab.	(35585)
Other	22	20 or 21	(57750)
Other	23	review.pt.	(2556996)
Other	24	22 and 23	(28111)
Other	25	letter.pt.	(1088348)
Other	26	editorial.pt.	(634319)
Other	27	animal/	(1943056)
Other	28	human/	(21507596)
Other	29	27 not (27 and 28)	(1475626)
Other	30	or/25-26,29	(3181234)
Other	31	4 or 13 or 19 or 24	(429629)
Other	32	31 not 30	(418338)
Study design	33	Clinical trial/	(980453)
Study design	34	Randomized controlled trial/	(583395)
Study design	35	Randomization/	(85276)
Study design	36	Single blind procedure/	(37347)
Study design	37	Double blind procedure/	(170148)
Study design	38	Crossover procedure/	(61788)
Study design	39	Placebo/	(354027)
Study design	40	Randomi?ed controlled trial$.tw.	(216786)
Study design	41	Rct.tw.	(35086)
Study design	42	Random allocation.tw.	(2043)
Study design	43	Randomly allocated.tw.	(34152)

Study design	44	Allocated randomly.tw.	(2523)
Study design	45	(allocated adj2 random).tw.	(970)
Study design	46	Single blind$.tw.	(24152)
Study design	47	Double blind$.tw.	(209824)
Study design	48	((treble or triple) adj blind$).tw.	(1113)
Study design	49	Placebo$.tw.	(305357)
Study design	50	Prospective study/	(570052)
Study design	51	or/33-50	(2167883)
Other	52	Case study/	(74981)
Other	53	Case report.tw.	(425175)
Other	54	Abstract report/ or letter/	(1119939)
Other	55	or/52-54	(1610054)
Other	56	51 not 55	(2115082)
Study design	57	Clinical study/	(168711)
Study design	58	Case control study/	(149654)
Study design	59	Family study/	(27016)
Study design	60	Longitudinal study/	(134442)
Study design	61	Retrospective study/	(861431)
Study design	62	Prospective study/	(570052)
Study design	63	Randomized controlled trials/	(170607)
Study design	64	62 not 63	(564171)
Study design	65	Cohort analysis/	(530781)
Study design	66	(Cohort adj (study or studies)).mp.	(284867)
Study design	67	(Case control adj (study or studies)).tw.	(128515)
Study design	68	(follow up adj (study or studies)).tw.	(66976)
Study design	69	(observational adj (study or studies)).tw.	(156451)
Study design	70	(epidemiologic$ adj (study or studies)).tw.	(107179)
Study design	71	(cross sectional adj (study or studies)).tw.	(203196)
Study design	72	or/57-61,64-71	(2582369)
Study design	73	32 or 56 or 72	(4247447)
Disease	74	exp hemochromatosis/	(14237)
Disease	75	exp hemochromatosis protein/	(373)
Disease	76	hemochromatosis.mp.	(15694)
Disease	77	haemochromatosis.mp.	(3093)
Disease	78	hfe.mp.	(4977)
Disease	79	hhc.mp.	(884)
Disease	80	c282y.mp.	(2211)
Disease	81	h63d.mp.	(1482)
Disease	82	bronze diabetes.mp.	(51)
Disease	83	bronzed cirrhosis.mp.	(5)
Disease	84	iron storage disorder.mp.	(22)
Disease	85	pigmentary cirrhosis.mp.	(77)
Disease	86	(troisier-hanot-chauffard or troisier hanot chauffard).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade	(0)

		name, keyword, floating subheading word, candidate term word]	
Disease	87	(recklehausen-applebaum or recklehausen applebaum).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	(0)
Disease	88	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87	(18208)
Study design, disease	89	73 and 88	(2008)
Other	90	limit 89 to (english language and yr="1996 -Current")	(1820)

Table 24. Search strategy for MEDLINE Daily Update, MEDLINE Epub Ahead of Print and In-Process & Other Non-Indexed Citations (Searched via the OVID platform)

Term Group	#	Search terms	Results
Disease	1	exp Hemochromatosis/	(7)
Disease	2	exp Hemochromatosis Protein/	(2)
Disease	3	hemochromatosis.mp.	(430)
Disease	4	haemochromatosis.mp.	(99)
Disease	5	hfe.mp.	(305)
Disease	6	hhc.mp.	(100)
Disease	7	c282y.mp.	(81)
Disease	8	h63d.mp.	(50)
Disease	9	bronze diabetes.mp.	(3)
Disease	10	bronzed cirrhosis.mp.	(0)
Disease	11	iron storage disorder.mp.	(1)
Disease	12	pigmentary cirrhosis.mp.	(1)
Disease	13	(troisier-hanot-chauffard or troisier hanot chauffard).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(0)
Disease	14	(recklehausen-applebaum or recklehausen applebaum).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	(0)
Disease	15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	(789)
Other	16	limit 15 to yr="1996 -Current"	(732)

Table 25. Search strategy for the Cochrane Library

Term Group	#	Search terms	Results
Disease	1	MeSH descriptor: [Hemochromatosis] explode all trees	(39)

Disease	2	MeSH descriptor: [Hemochromatosis Protein] explode all trees	(15)
Disease	3	(hemochromatosis):ti,ab,kw	(176)
Disease	4	(haemochromatosis):ti,ab,kw	(176)
Disease	5	(hfe or hhc or c282y or h63d):ti,ab,kw	(123)
Disease	6	(bronzed cirrhosis):ti,ab,kw	(0)
Disease	7	("bronze diabetes"):ti,ab,kw	(0)
Disease	8	(iron storage disorder):ti,ab,kw	(9)
Disease	9	(pigmentary cirrhosis):ti,ab,kw	(1)
Disease	10	(troisier-hanot-chauffard or troisier hanot chauffard):ti,ab,kw	(0)
Disease	11	(recklehausen-applebaum or recklehausen applebaum):ti,ab,kw	(0)
Disease	12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11	(264)

Table 26. Search strategy Web of Science

Term Group	#	Search terms	Results
Disease	1	**TOPIC:** ((Hemochromatosis or "Hemochromatosis Protein" or haemochromatosis) OR TOPIC: (hfe or hhc or c282y or h63d) OR TOPIC: ("bronze diabetes" or "bronzed cirrhosis" or "iron storage disorder" or "pigmentary cirrhosis" or "troisier-hanot-chauffard" or "troisier hanot chauffard" or "recklehausen-applebaum" or "recklehausen applebaum"))	10,860
Study design	2	**TOPIC:** ("Randomi?ed controlled trial*" or "Random allocat*" or "Double blind method" or "Single blind method" or "Clinical trial*" or placebo*) *OR* **TOPIC:** ((clinic* near/3 trial*)) *OR* **TOPIC:** (((singl* or doubl* or treb* or tripl*) near/3 (blind* or mask*))) *OR* **TOPIC:** ("Epidemiologic stud*" or "case control stud*" or "cohort stud*" or "case control" or "cohort analys*" or "cross sectional" or "cross-sectional" or retrospective or longitudinal or "observational stud*" or "follow-up stud*" or "follow up stud*") *OR* **TOPIC:** ("Meta Analys*" or metaanalys* or "meta-analys*" or "systematic review*")	2,493,208
Disease, study design		#1 AND #2	725
Other	3	**Refined by: PUBLICATION YEARS:** (2019 OR 2011 OR 2003 OR 2018 OR 2010 OR 2017 OR 2009 OR 2001 OR 2016 OR 2008 OR 2000 OR 2015 OR 2007 OR 1999 OR 2014 OR 2006 OR 1998 OR 2013 OR 2005 OR 1997 OR 2012 OR 2004 OR 1996)	662
Other	4	#1 AND #2 **Refined by: PUBLICATION YEARS:** (2019 OR 2011 OR 2003 OR 2018 OR 2010 OR 2017 OR 2009 OR 2001 OR 2016 OR 2008 OR 2000 OR 2015 OR 2007 OR 1999 OR 2014 OR 2006 OR 1998 OR 2013 OR 2005 OR 1997 OR 2012 OR 2004 OR 1996) AND **DOCUMENT TYPES:** (ARTICLE OR REVIEW OR EARLY ACCESS)	621

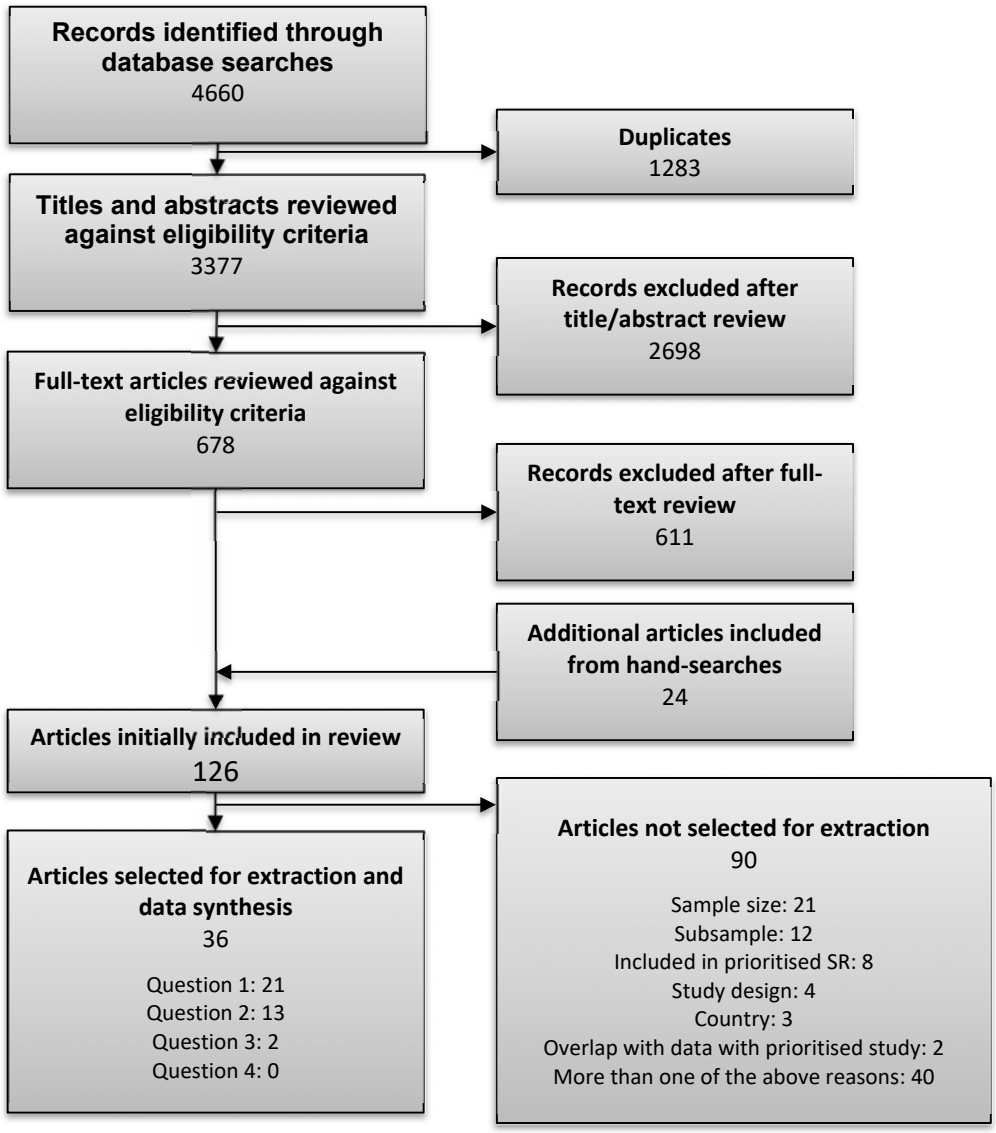
Results were imported into EndNote and de-duplicated.

Appendix 2 — Included and excluded studies

PRISMA flowchart

Figure 4 summarises the volume of publications included and excluded at each stage of the review. One hundred and twenty-six publications were ultimately judged to be relevant to one or more review questions and were considered for extraction. Publications that were included or excluded after the review of full-text articles are detailed below.

Figure 4. Summary of publications included and excluded at each stage of the review



SR = systematic review

Publications included after review of full-text articles

The 36 prioritised publications included after review of full-texts are summarised in 26 below. The 90 deprioritised papers are outlined in Tables 30 and 31. Publications not selected for extraction and data synthesis are clearly detailed in 28 below.

Table 27. Summary of publications included after review of full-text articles, and the question(s) each publication was identified as being relevant to

	Study	The condition	The test	The intervention	The screening programme	Implementation criteria
1.	**Andersen (2004)**[53]	Q1	-	-	-	-
2.	**Beutler (2000)**[38]	Q1	-	-	-	-
3.	**Beutler (2002)**[36]	Q1	-	-	-	-
4.	**Beutler (2003)**[37]	Q1	-	-	-	-
5.	**Burt (1998)**[39]	Q1	-	-	-	-
6.	**Cadet (2003)**[62]	Q2	-	-	-	-
7.	**Cobbaert (2012)**[55]	Q1	-	-	-	-
8.	**Ekblom (2011)**[61]	Q2	-	-	-	-
9.	**Ellervik (2001)**[60]	Q2	-	-	-	-
10.	**Ellervik (2005)**[51]	Q1	-	-	-	-
11.	**Ellervik (2007)**[52]	Q1	-	-	-	-
12.	**Ellervik (2007)**[69]	Q2				
13.	**Fox (2002)**[40]	Q1	-	-	-	-
14.	**Gallego (2015)**[41]	Q1	-	-	-	-
15.	**Gochee (2002)**[42]	Q1	-	-	-	-
16.	**Greenwood (2005)**[43]	Q1	-	-	-	-
17.	**Habeos (2003)**[59]	Q2	-	-	-	-
18.	**Halsall (2003)**[58]	Q2	-	-	-	-
19.	**Hannuksela (2005)**[64]	Q2	-	-	-	-
20.	**Henriksen (2016)**[44]	Q1	-	-	-	-
21.	**Mahon (2000)**[63]	Q2	-	-	-	-
22.	**Moirand (1999)**[57]	Q2	-	-	-	-
23.	**Møller (2010)**[65]	Q2	-	-	-	-
24.	**McLaren (2008)**[116]	Q1	-	-	-	-
25.	**Neghina (2011)**[68]	Q2	-	-	-	-
26.	**Olynyk (1999)**[54]	Q1	-	-	-	-
27.	**Ong (2017)**[113]	-	-	Q3	-	-
28.	**Pankow (2008)**[46]	Q1	-	-	-	-
29.	**Pilling (2019)**[32]	Q1	-	-	-	-
30.	**Rossi (2001)**[47]	Q1	-	-	-	-
31.	**Van der (2008)**[67]	Q2	-	-	-	-

32.	**Waalen (2002)**[48]	Q1	-	-	-	-
33.	**Waalen (2002)**[49]	Q1	-	-	-	-
34.	**Wood (2017)**[50]	Q1	-	-	-	-
35.	**Whitlock (2006)**[30]	-	-	Q3	-	-
36.	**Ye (2016)**[66]	Q2	-	-	-	-

Publications excluded after review of full-text articles

Of the 678 publications included after the review of titles and abstracts, 576 were ultimately judged not to be relevant to this review. These publications, along with reasons for exclusion, are listed in Table 28.

Table 28. Publications excluded after review of full-text articles

	Reference	Reason for exclusion
1.	**Aamodt AH, Stovner LJ, Thorstensen K, Lydersen S, White LR, Aasly JO. Prevalence of haemochromatosis gene mutations in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2007;78:315-7.**	Ineligible outcome
2.	**Aarsand AK, Boman H, Sandberg S. Familial and sporadic Porphyria cutanea tarda: Characterization and diagnostic strategies. *Clin Chem* 2009;55:795-803.**	Ineligible starting condition: PCT
3.	**Abhishek A, Doherty S, Maciewicz R, Muir K, Zhang W, Doherty M*, et al.* The association between ANKH promoter polymorphism and chondrocalcinosis is independent of age and osteoarthritis: results of a case-control study. *Arthritis Res Ther* 2014;16:R25. 3**	Not hereditary haemochromatosis
4.	**Abraham BK, Justenhoven C, Pesch B, Harth V, Weirich G, Baisch C*, et al.* Investigation of genetic variants of genes of the hemochromatosis pathway and their role in breast cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1102-7.**	Ineligible disease outcome
5.	**Abraham D, Rogers J, Gault P, Kushner JP, McClain DA. Increased insulin secretory capacity but decreased insulin sensitivity after correction of iron overload by phlebotomy in hereditary haemochromatosis. *Diabetologia*. 2006;49(11):2546-2551.**	Fewer than 100 participants.
6.	**Acton RT, Barton JC. HFE genotype frequencies in consecutive reference laboratory specimens: comparisons among referral sources and association with initial diagnosis. *Genet Test* 2001;5:299-306.**	Starting condition prior to genotyping missing. Referral source not starting condition.
7.	**Acton RT, Barton JC, Snively BM, McLaren CE, Adams PC, Harris EL*, et al.* Geographic and racial/ethnic differences in HFE mutation frequencies in the Hemochromatosis and Iron Overload Screening (HEIRS) Study. *Ethnicity & disease* 2006;16:815-21.**	No outcomes.
8.	**Acton RT, Barton JC, Passmore LV, et al. Accuracy of family history of hemochromatosis or iron overload: the hemochromatosis and iron overload screening study. Clin Gastroenterol Hepatol. 2008;6(8):934-938.**	HH group was C282Y or iron overload. No separation of results
9.	**Adams PC, Agnew S. Alcoholism in hereditary hemochromatosis revisited: prevalence and clinical consequences among homozygous siblings. *Hepatology*. 1996;23(4):724-727**	No extractable data

10.	**Adams LA, Angulo P, Abraham SC, Torgerson H, Brandhagen D. The effect of the metabolic syndrome, hepatic steatosis and steatohepatitis on liver fibrosis in hereditary hemochromatosis. *Liver Int* 2006;26:298-304.**	Fewer than 100 participants.
11.	**Adams PC, Barton JC, Guo H, Alter D, Speechley M. Serum ferritin is a biomarker for liver mortality in the Hemochromatosis and Iron Overload Screening Study. *Ann Hepatol*. 2015;14(3):348-353.**	>10% treated for iron overload
12.	**Adams PC, Bradley C, Henderson AR. Evaluation of the hepatic iron index as a diagnostic criterion for genetic hemochromatosis. *J Lab Clin Med* 1997;130:509-14.**	Fewer than 100 participants.
13.	**Adams PC, Campion ML, Gandon G, LeGall JY, David V, Jouanolle AM. Clinical and family studies in genetic hemochromatosis: Microsatellite and HFE studies in five atypical families. *Hepatology* 1997;26:986-90.**	Fewer than 100 participants.
14.	**Adams PC, Deugnier Y, Moirand R, Brissot P. The relationship between iron overload, clinical symptoms, and age in 410 patients with genetic hemochromatosis. *Hepatology* 1997;25:162-6.**	No genotyping and no screening. Ineligible population.
15.	**Adams PC, Reboussin DM, Leiendecker-Foster C, Moses GC, McLaren GD, McLaren CE*, et al.* Comparison of the unsaturated iron-binding capacity with transferrin saturation as a screening test to detect C282Y homozygotes for hemochromatosis in 101,168 participants in the hemochromatosis and iron overload screening (HEIRS) study. *Clin Chem* 2005;51:1048-52.**	No extractable data about outcomes of interest.
16.	**Adams PC, Speechley M. The effect of arthritis on the quality of life in hereditary hemochromatosis. *J Rheumatol* 1996;23:707-10.**	Fewer than 100 participants.
17.	**Adhoute X, Foucher J, Laharie D, et al. Diagnosis of liver fibrosis using FibroScan and other noninvasive methods in patients with hemochromatosis: a prospective study. *Gastroenterol Clin Biol*. 2008;32(2):180-187.**	No treatment
18.	**Adris N, Hazeldine S, Bentley P, et al. Detection of HFE Haemochromatosis in the clinic and community using standard erythrocyte tests. *Blood Cells Mol Dis*. 2019;74:18-24.**	>10% treated for iron overload
19.	**Agudo A, Bonet C, Sala N, Munoz X, Aranda N, Fonseca-Nunes A*, et al.* Hemochromatosis (HFE) gene mutations and risk of gastric cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Carcinogenesis* 2013;34:1244-50**	Ineligible starting condition: Gastric cancer
20.	**Aguilar-Martinez P, Bismuth M, Picot MC, Thelcide C, Pageaux GP, Blanc F*, et al.* Variable phenotypic presentation of iron overload in H63D homozygotes: are genetic modifiers the cause? *Gut* 2001;48:836-42.**	Fewer than 100 participants.
21.	**Akesson A, Stal P, Vahter M. Phlebotomy increases cadmium uptake in hemochromatosis. *Environmental Health Perspectives* 2000;108:289-91.**	Fewer than 100 participants.
22.	**Akin K, Beyler AR, Kaya M, Erden E. The importance of iron and copper accumulation in the pathogenesis of non-alcoholic steatohepatitis. *Turk J Gastroenterol* 2003;14:228-33.**	Fewer than 100 participants.

23.	**Aleman S, Endalib S, Stal P, Loof L, Lindgren S, Sandberg-Gertzen H*, et al.* Health check-ups and family screening allow detection of hereditary hemochromatosis with less advanced liver fibrosis and survival comparable with the general population. *Scandinavian Journal of Gastroenterology* 2011;46:1118-26.**	No genotyping by outcomes. Ineligible population.
24.	**Alfred T, Ben-Shlomo Y, Cooper R, Hardy R, Deary IJ, Elliott J*, et al.* Genetic variants influencing biomarkers of nutrition are not associated with cognitive capability in middle-aged and older adults. *J Nutr* 2013;143:606-12.**	Ineligible condition
25.	**Alizadeh BZ, Njajou OT, Houwing-Duistermaat JJ, de Jong G, Vergeer JM, Hofman A*, et al.* Does bilirubin protect against hemochromatosis gene (HFE) related mortality? *Am J Med Genet A* 2004;129A:39-43.**	Outcome not reported by genotype
26.	**Alizadeh BZ, Njajou OT, Millan MR, Hofman A, Breteler MM, van Duijn CM. HFE variants, APOE and Alzheimer's disease: findings from the population-based Rotterdam study. *Neurobiology of Aging* 2009;30:330-2.**	Ineligible outcomes: Alzheimer's disease.
27.	**Allen KJ, Bertalli NA, Osborne NJ, et al. HFE Cys282Tyr homozygotes with serum ferritin concentrations below 1000 microg/L are at low risk of hemochromatosis. *Hepatology*. 2010;52(3):925-933.**	>10% treated for iron overload
28.	**Altes A, Ruiz A, Martinez C, et al. The relationship between iron overload and clinical characteristics in a Spanish cohort of 100 C282Y homozygous hemochromatosis patients. *Ann Hematol*. 2007;86(11):831-835.**	>10% treated for iron overload
29.	**Altes A, Bach V, Ruiz A, Esteve A, Felez J, Remacha AF*, et al.* Mutations in HAMP and HJV genes and their impact on expression of clinical hemochromatosis in a cohort of 100 Spanish patients homozygous for the C282Y mutation of HFE gene. *Annals of Hematology* 2009;88:951-5.**	Ineligible outcomes.
30.	**Alustiza JM, Artetxe J, Castiella A, Agirre C, Emparanza JI, Otazua P*, et al.* MR Quantification of Hepatic Iron Concentration. *Radiology* 2004;230:479-84.**	No genotyping.
31.	**Alves LN, Santos EV, Stur E, Silva Conforti AM, Louro ID. Molecular epidemiology of HFE gene polymorphic variants (C282Y, H63D and S65C) in the population of Espirito Santo, Brazil. *Genet Mol Res* 2016;15:27.**	No outcomes.
32.	**Anderson RT, Press N, Tucker DC, Snively BM, Wenzel L, Ellis SD*, et al.* Patient acceptability of genotypic testing for hemochromatosis in primary care. *Genetics in Medicine* 2005;7:557-63.**	Ineligible study type: qualitative study
33.	**Anderson RT, Wenzel L, Walker AP, Ruggiero A, Acton RT, Hall MA*, et al.* Impact of hemochromatosis screening in patients with indeterminate results: the hemochromatosis and iron overload screening study. *Genetics in Medicine* 2006;8:681-7.**	Ineligible study type: qualitative study
34.	**Andrikovics H, Meggyesi N, Szilvasi A, Tamaska J, Halm G, Lueff S*, et al.* HFE C282Y mutation as a genetic modifier influencing disease susceptibility for chronic myeloproliferative disease. *Cancer Epidemiology Biomarkers and Prevention* 2009;18:929-34.**	Ineligible population: blood cancer.
35.	**Annichino-Bizzacchi JM, Saad ST, Arruda VR, et al. C282Y mutation in the HLA-H gene is not a risk factor for patients with myocardial infarction. *J Cardiovasc Risk*. 2000;7(1):37-40. doi:10.1177/204748730000700107**	Carriers, not C282Y/C282Y, H63D/H63D, or C282Y/H63D

36.	**Arena R, Shizukuda Y, Bolan CD, Tripodi DJ, Yau YY, Smith KP*, et al.* Heart rate recovery is lower following supine exercise in asymptomatic hereditary hemochromatosis subjects compared with healthy controls. *J Mol Signal* 2007;27:157-60.**	Fewer than 100 participants. Ineligible outcomes: exercise based heart outcomes
37.	**Asberg A, Tretli S, Hveem K, Bjerve KS. Benefit of population-based screening for phenotypic hemochromatosis in young men. *Scandinavian Journal of Gastroenterology* 2002;37:1212-9.**	Ineligible study type: Modelling study
38.	**Asif S, Begemann M, Raza S. Polycythemia in Patients With Hereditary Hemochromatosis: Real or Myth?. *J Clin Med Res*. 2019;11(6):422-427. doi:10.14740/jocmr3816**	Ineligible outcome
39.	**Assy N, Adams PC. Predictive value of family history in diagnosis of hereditary hemochromatosis. *Dig Dis Sci* 1997;42:1312-5.**	Only reported as homozygous, and not clear what the reported is homozygous for.
40.	**Bacon BR. Screening for hemochromatosis. *Curr Gastroenterol Rep* 2006;8:5-6.**	Ineligible publication type: Abstract and comment
41.	**Bacon BR, Sadiq SA. Hereditary hemochromatosis: presentation and diagnosis in the 1990s. *American Journal of Gastroenterology* 1997;92:784-9.**	Fewer than 100 participants.
42.	**Balasubbu S, Sundaresan P, Rajendran A, Ramasamy K, Govindarajan G, Perumalsamy N*, et al.* Association analysis of nine candidate gene polymorphisms in Indian patients with type 2 diabetic retinopathy. *BMC Medical Genetics* 2010;11:158.**	Ineligible type of study: cohort of diabetic patients, not case control study. Looking at SNPs not genotyping
43.	**Barale C, Senkeev R, Napoli F, De Gobbi M, Guerrasio A, Morotti A*, et al.* Transferrin Saturation Inversely Correlates with Platelet Function. *Thrombosis and Haemostasis* 2019;119:766-78.**	Fewer than 100 participants.
44.	**Bardou-Jacquet E, Laine F, Guggenbuhl P, Morcet J, Jezequel C, Guyader D*, et al.* Worse Outcomes of Patients With HFE Hemochromatosis With Persistent Increases in Transferrin Saturation During Maintenance Therapy. *Clin Gastroenterol Hepatol* 2017;15:1620-7.**	Ineligible population: treated.
45.	**Bardou-Jacquet E, Morandeau E, Anderson GJ, et al. Regression of Fibrosis Stage With Treatment Reduces Long-Term Risk of Liver Cancer in Patients With Hemochromatosis Caused by Mutation in HFE [published online ahead of print, 2019 Oct 14]. *Clin Gastroenterol Hepatol*. 2019;S1542-3565(19)31109-7. doi:10.1016/j.cgh.2019.10.010**	Ineligible population: all C282Y/C282Y plus fibrosis
46.	**Bardou-Jacquet E, Morcet J, Manet G, et al. Decreased cardiovascular and extrahepatic cancer-related mortality in treated patients with mild HFE hemochromatosis. J Hepatol. 2015;62(3):682-689. doi:10.1016/j.jhep.2014.10.025**	No separation of data for screen detected and symptomatically detected participants.

47.	**Bardou-Jacquet E, Philip J, Lorho R, Ropert M, Latournerie M, Houssel-Debry P*, et al.* Liver transplantation normalizes serum hepcidin level and cures iron metabolism alterations in HFE hemochromatosis. *Hepatology* 2014;59:839-47.**	No genotyping information
48.	**Barisani D, Ceroni S, Del Bianco S, Meneveri R, Bardella MT. Hemochromatosis gene mutations and iron metabolism in celiac disease. *Haematologica* 2004;89:1299-305.**	Ineligible starting disease: celiacs
49.	**Barros RK, Cotrim HP, Daltro CH, Oliveira YA. Hyperferritinemia in patients with nonalcoholic fatty liver disease. *Rev Assoc Med Bras* 2017;63:284-9.**	Ineligible condition: SR of those with NFA liver disease, hereditary hemochromatosis diagnosis was excluded
50.	**Bartolo C, McAndrew PE, Sosolik RC, Cawley KA, Balcerzak SP, Brandt JT*, et al.* Differential diagnosis of hereditary hemochromatosis from other liver disorders by genetic analysis: gene mutation analysis of patients previously diagnosed with hemochromatosis by liver biopsy. *Arch Pathol Lab Med* 1998;122:633-7.**	Fewer than 100 participants.
51.	**Barton EH, West PA, Rivers CA, Barton JC, Acton RT. Transferrin receptor-2 (TFR2) mutation Y250X in Alabama Caucasian and African American subjects with and without primary iron overload. *Blood Cells Mol Dis* 2001;27:279-84.**	Ineligible HFE mutation
52.	**Barton, J.C., Wiener, H.W., Acton, R.T. *et al.* Total blood lymphocyte counts in hemochromatosis probands with *HFE*C282Y homozygosity: relationship to severity of iron overload and HLA-A and -B alleles and haplotypes. *BMC Hematol* 5, 5 (2005)**	>10% treated for iron overload
53.	**Barton JC, Acton RT, Leiendecker-Foster C, Lovato L, Adams PC, Eckfeldt JH*, et al.* Characteristics of participants with self-reported hemochromatosis or iron overload at HEIRS Study initial screening. *American Journal of Hematology* 2008;83:126-32.**	Fewer than 100 participants.
54.	**Barton JC, Barton JC, Acton RT, So J, Chan S, Adams PC. Increased risk of death from iron overload among 422 treated probands with HFE hemochromatosis and serum levels of ferritin greater than 1000 mug/L at diagnosis. *Clin Gastroenterol Hepatol* 2012;10:412-6.**	Ineligible population: treated. Analysis by genotype. No information whether participants are symptomatic or not at diagnosis
55.	**Barton JC, Bertoli LF, Acton RT. HFE C282Y and H63D in adults with malignancies in a community medical oncology practice. *BMC Cancer* 2004;4:6.**	Ineligible starting condition: Non liver based cancers
56.	**Barton JC, Wiener HW, Acton RT, Go RC. Total blood lymphocyte counts in hemochromatosis probands with HFE C282Y homozygosity: relationship to severity of iron overload and HLA-A and -B alleles and haplotypes. *BMC Blood Disord*. 2005;5:5.**	>10% treated for iron overload

57.	**Barton JC, Barton JC, Acton RT. Insulin Resistance and Metabolic Syndrome: Clinical and Laboratory Associations in African Americans Without Diabetes in the Hemochromatosis and Iron Overload Screening Study. *Metab Syndr Relat Disord*. 2018;16(6):267-273.**	>10% treated for iron overload
58.	**Barton JC, Clayborn Barton J, Adams PC. Prevalence and characteristics of anti-HCV positivity and chronic hepatitis C virus infection in HFE p.C282Y homozygotes. *Annals of Hepatology* 2019;18:354-9.**	Ineligible outcome: hep C. No other outcomes of interest
59.	**Barton JC, Lafreniere SA, Leiendecker-Foster C, Li H, Acton RT, Press RD*, et al.* HFE, SLC40A1, HAMP, HJV, TFR2, and FTL mutations detected by denaturing high-performance liquid chromatography after iron phenotyping and HFE C282Y and H63D genotyping in 785 HEIRS Study participants. *American Journal of Hematology* 2009;84:710-4.**	Ineligible HFE mutations
60.	**Barton JC, Leiendecker-Foster C, Reboussin DM, Adams PC, Acton RT, Eckfeldt JH*, et al.* Thyroid-stimulating hormone and free thyroxine levels in persons with HFE C282Y homozygosity, a common hemochromatosis genotype: the HEIRS study. *Thyroid* 2008;18:831-8.**	Ineligible outcomes: hyperthyroidism
61.	**Barton JC, Barton JC. Dupuytren's Contracture in Alabama HFE Hemochromatosis Probands. *Clin Med Insights Arthritis Musculoskelet Disord*. 2012;5:67-75.**	>10% treated for iron overload
62.	**Barton JC, McLaren CE, Chen WP, et al. Cirrhosis in Hemochromatosis: Independent Risk Factors in 368 HFE p.C282Y Homozygotes. *Ann Hepatol*. 2018;17(5):871-879.**	Study does not include participants with HH genotypes
63.	**Bartzokis G, Lu PH, Tingus K, Peters DG, Amar CP, Tishler TA*, et al.* Gender and iron genes may modify associations between brain iron and memory in healthy aging. *Neuropsychopharmacology* 2011;36:1375-84.**	Ineligible outcomes. Genotyping healthy individuals.
64.	**Barut G, Balci H, Bozdayi M, Hatemi I, Ozcelik D, Senturk H. Screening for iron overload in the Turkish population. *Digestive Diseases* 2003;21:279-85.**	Fewer than 100 participants.
65.	**Bastarache L, Hughey JJ, Hebbring S, Marlo J, Zhao W, Ho WT*, et al.* Phenotype risk scores identify patients with unrecognized mendelian disease patterns. *Science* 2018;359:1233-9.**	Fewer than 100 participants.
66.	**Bathum L, Christiansen L, Nybo H, Ranberg KA, Gaist D, Jeune B*, et al.* Association of mutations in the hemochromatosis gene with shorter life expectancy. *Arch Intern Med* 2001;161:2441-4.**	Prevalence of mutations in a healthy pop. No outcomes reported
67.	**Beaton MD, Adams PC. Prognostic factors and survival in patients with hereditary hemochromatosis and cirrhosis. *Can J Gastroenterol* 2006;20:257-60.**	Fewer than 100 participants.
68.	**Beste LA, Leipertz SL, Green PK, Dominitz JA, Ross D, Ioannou GN. Trends in burden of cirrhosis and hepatocellular carcinoma by underlying liver disease in US veterans, 2001-2013. *Gastroenterology*. 2015;149(6):1471-e18. doi:10.1053/j.gastro.2015.07.056**	Haemochromatosis genotype not specified

69.	**Bharath V, Kahn SR, Lazo-Langner A. Genetic polymorphisms of vein wall remodeling in chronic venous disease: a narrative and systematic review. *Blood* 2014;124:1242-50.**	Ineligible starting condition: varicous veins
70.	**Bi M, Li B, Li Q. Correlation of hemochromatosis gene mutations and cardiovascular disease in hemodialysis patients. *Ann Saudi Med*. 2013;33(3):223-228. doi:10.5144/0256-4947.2013.223**	No eligible clinical feature
71.	**Bialek SR, Redd JT, Lynch A, et al. Chronic liver disease among two American Indian patient populations in the southwestern United States, 2000-2003. Journal of Clinical Gastroenterology. 2008 Aug;42(7):949-954. DOI: 10.1097/mcg.0b013e318054492a.**	Not about diseases in haemochromatosis
72.	**Biasiotto G, Belloli S, Ruggeri G, et al. Identification of new mutations of the HFE, hepcidin, and transferrin receptor 2 genes by denaturing HPLC analysis of individuals with biochemical indications of iron overload. *Clin Chem*. 2003;49(12):1981-1988.**	Clinical factor was elevated serum ferritin or transferrin saturation. No separation of data.
73.	**Blanco-Rojo R, Baeza-Richer C, Lopez-Parra AM, Perez-Granados AM, Brichs A, Bertoncini S*, et al.* Four variants in transferrin and HFE genes as potential markers of iron deficiency anaemia risk: an association study in menstruating women. *Nutr Metab (Lond)* 2011;8:69.**	Ineligible group - reporting variants, not genotypes
74.	**Blanco-Rojo R, Toxqui L, Lopez-Parra AM, Baeza-Richer C, Perez-Granados AM, Arroyo-Pardo E*, et al.* Influence of diet, menstruation and genetic factors on iron status: a cross-sectional study in Spanish women of childbearing age. *Int* 2014;15:4077-87.**	Reports SNPs, not genotyping
75.	**Bonkovsky HL, Jawaid Q, Tortorelli K, LeClair P, Cobb J, Lambrecht RW*, et al.* Non-alcoholic steatohepatitis and iron: increased prevalence of mutations of the HFE gene in non-alcoholic steatohepatitis. *Journal of Hepatology* 1999;31:421-9.**	Fewer than 100 participants.
76.	**Bonkovsky HL, Naishadham D, Lambrecht RW, Chung RT, Hoefs JC, Nash SR*, et al.* Roles of iron and HFE mutations on severity and response to therapy during retreatment of advanced chronic hepatitis C. *Gastroenterology* 2006;131:1440-51.**	Ineligible cohort: hep C
77.	**Borie C, Gasparini F, Verpillat P, Bonnet AM, Agid Y, Hetet G*, et al.* Association study between iron-related genes polymorphisms and Parkinson's disease. *J Neurol* 2002;249:801-4.**	Ineligible outcomes and cohort: Parkinson's disease cohort
78.	**Borot N, Roth MP, Malfroy L, Demangel C, Vinel JP, Pascal JP*, et al.* Mutations in the MHC class I-like candidate gene for hemochromatosis in French patients. *Immunogenetics* 1997;45:320-4.**	Fewer than 100 participants.
79.	**Botsford E, George J, Buckley EE. Parkinson's disease and metal storage disorders: A systematic review. *Brain Sciences* 2018;8.**	Ineligible condition: Parkinson's disease cohort.
80.	**Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: a unifying analysis of published intervention trials. *Journal of Medical Screening* 1996;3:178-84.**	Meta- analysis of papers up to 1995.

81.	**Bradley LA, Haddow JE, Palomaki GE. Population screening for haemochromatosis: expectations based on a study of relatives of symptomatic probands. *Journal of Medical Screening* 1996;3:171-7.**	Literature review of papers up to 1995.
82.	**Bradley LA, Johnson DD, Palomaki GE, Haddow JE, Robertson NH, Ferrie RM. Hereditary haemochromatosis mutation frequencies in the general population. *Journal of Medical Screening* 1998;5:34-6.**	Ineligible outcomes.
83.	**Bralet MP, Regimbeau JM, Pineau P, Dubois S, Loas G, Degos F*, et al.* Hepatocellular carcinoma occurring in nonfibrotic liver: epidemiologic and histopathologic analysis of 80 French cases. *Hepatology* 2000;32:200-4.**	No genetic analysis undertaken. Not defined what kind of HH mutation participants have
84.	**Branco CC, Gomes CT, De Fez L, Bulhoes S, Brilhante MJ, Pereirinha T*, et al.* Carriers of the Complex Allele HFE c.[187C>G;340+4T>C] Have Increased Risk of Iron Overload in Sao Miguel Island Population (Azores, Portugal). *PLoS ONE* 2015;10:e0140228.**	Fewer than 100 participants.
85.	**Brandao M, Oliveira JC, Bravo F, Reis J, Garrido I, Porto G. The soluble transferrin receptor as a marker of iron homeostasis in normal subjects and in HFE-related hemochromatosis. *Haematologica* 2005;90:31-7.**	Fewer than 100 participants.
86.	**Brissot P, Moirand R, Jouanolle AM, et al. A genotypic study of 217 unrelated probands diagnosed as "genetic hemochromatosis" on "classical" phenotypic criteria. *J Hepatol*. 1999;30(4):588-593.**	>10% treated for iron overload
87.	**Broedbaek K, Poulsen HE, Weimann A, Kom GD, Schwedhelm E, Nielsen P*, et al.* Urinary excretion of biomarkers of oxidatively damaged DNA and RNA in hereditary hemochromatosis. *Free Radic Biol Med* 2009;47:1230-3.**	Fewer than 100 participants.
88.	**Brown K, Luddington R, Taylor SA, Lillicrap DP, Baglin TP. Risk of venous thromboembolism associated with the common hereditary haemochromatosis Hfe gene (C282Y) mutation. *Br J Haematol* 1999;105:95-7.**	Ineligible starting condition: venous thromboembolism then genotyped
89.	**Bruckl D, Kamhieh-Milz S, Kamhieh-Milz J, Salama A. Efficacy and safety of erythrocytapheresis and low-dose erythropoietin for treatment of hemochromatosis. *J Clin Apheresis* 2017;32:170-4.**	Fewer than 100 participants.
90.	**Bryant J, Cooper K, Picot J, et al. A systematic review of the clinical validity and clinical utility of DNA testing for hereditary haemochromatosis type 1 in at-risk populations. *J Med Genet*. 2008;45(8):513-518.**	More recent systematic review
91.	**Bryant J, Cooper K, Picot J, et al. Diagnostic strategies using DNA testing for hereditary haemochromatosis in at-risk populations: a systematic review and economic evaluation. *Health Technol Assess*. 2009;13(23):iii-126.**	More recent systematic review
92.	**Buchanan DD, Silburn PA, Chalk JB, Le Couteur DG, Mellick GD. The Cys282Tyr polymorphism in the HFE gene in Australian Parkinson's disease patients. *Neurosci Lett* 2002;327:91-4.**	Ineligible starting condition: Parkinson's disease

93.	**Bugianesi E, Leone N, Vanni E, Marchesini G, Brunello F, Carucci P*, et al.* Expanding the natural history of nonalcoholic steatohepatitis: from cryptogenic cirrhosis to hepatocellular carcinoma. *Gastroenterology* 2002;123:134-40.**	Fewer than 100 participants.
94.	**Bulaj ZJ, Griffen LM, Jorde LB, Edwards CQ, Kushner JP. Clinical and biochemical abnormalities in people heterozygous for hemochromatosis. *N Engl J Med* 1996;335:1799-805.**	No report on the genotypes or information by genotype, only reported as heterozygotes
95.	**Buretic-Tomljanovic A, Vlastelic I, Radojcic Badovinac A, Starcevic-Cizmarevic N, Nadalin S, Ristic S. The impact of hemochromatosis mutations and transferrin genotype on gonadotropin serum levels in infertile men. *Fertil Steril* 2009;91:1793-800.**	Ineligible starting condition: infertility. Ineligible outcomes.
96.	**Burke W, Imperatore G, McDonnell SM, Baron RC, Khoury MJ. Contribution of different HFE genotypes to iron overload disease: a pooled analysis. *Genet Med*. 2000;2(5):271-277. doi:10.1097/00125817-200009000-0000**	More recent systematic review
97.	**Buysschaert M, Paris I, Selvais P, Hermans MP. Clinical aspects of diabetes secondary to idiopathic haemochromatosis in French-speaking Belgium. *Diabetes Metab* 1997;23:308-13.**	No genotyping
98.	**Buzzetti E, Kalafateli M, Thorburn D, Davidson BR, Tsochatzis E, Gurusamy KS. Interventions for hereditary haemochromatosis: an attempted network meta-analysis. *Cochrane Database Syst Rev* 2017;3:CD011647.**	Ineligible population: treated. No screening.
99.	**Byrne D, Walsh JP, Daly C, McKiernan S, Norris S, Murphy RT*, et al.* Improvements in cardiac function detected using echocardiography in patients with hereditary haemochromatosis. *Ir J Med Sci* 2019;20:20.**	Fewer than 100 participants.
100.	**Cabezas Arteaga JE, Vieira FMJ, Silva dos Reis VM. Experience in management of porphyria cutanea tarda in a tertiary referral Brazilian hospital from 2002 to 2017. *International Journal of Dermatology* 2019;58:925-32.**	Ineligible starting condition. No genotype, no screening.
101.	**Cade JE, Moreton JA, O'Hara B, Greenwood DC, Moor J, Burley VJ*, et al.* Diet and genetic factors associated with iron status in middle-aged women. *Am J Clin Nutr* 2005;82:813-20.**	Ineligible outcomes.
102.	**Cadet E, Capron D, Gallet M, Omanga-Leke ML, Boutignon H, Julier C*, et al.* Reverse cascade screening of newborns for hereditary haemochromatosis: A model for other late onset diseases? *Journal of Medical Genetics* 2005;42:390-5.**	No measure of genes. Ineligible patient group: newborns.
103.	**Campbell S, George DK, Robb SD, Spooner R, McDonagh TA, Dargie HJ*, et al.* The prevalence of haemochromatosis gene mutations in the West of Scotland and their relation to ischaemic heart disease. *Heart* 2003;89:1023-6.**	Ineligible starting condition.
104.	**Campos WN, Massaro JD, Martinelli ALC, Halliwell JA, Marsh SGE, Mendes-Junior CT*, et al.* HFE gene polymorphism defined by sequence-based typing of the Brazilian population and a standardized nomenclature for HFE allele sequences. *Hla* 2017;90:238-42.**	No info relevant to any question

105.	**Cancado R, Melo MR, de Moraes Bastos R, Santos PCJL, Guerra-Shinohara EM, Chiattone C*, et al.* Deferasirox in patients with iron overload secondary to hereditary hemochromatosis: Results of a 1-yr Phase 2 study. *European Journal of Haematology* 2015;95:545-50.**	Fewer than 100 participants.
106.	**Cancado RD, Guglielmi AC, Vergueiro CS, Rolim EG, Figueiredo MS, Chiattone CS. Analysis of HFE gene mutations and HLA-A alleles in Brazilian patients with iron overload. *Sao Paulo Med J* 2006;124:55-60.**	Fewer than 100 participants.
107.	**Candore G, Balistreri CR, Lio D, Mantovani V, Colonna-Romano G, Chiappelli M*, et al.* Association between HFE mutations and acute myocardial infarction: a study in patients from Northern and Southern Italy. *Blood Cells Mol Dis* 2003;31:57-62.**	Reported by allele rather than genotype, information unavailable.
108.	**Cardoso CS, Oliveira P, Porto G, Oberkanins C, Mascarenhas M, Rodrigues P*, et al.* Comparative study of the two more frequent HFE mutations (C282Y and H63D): Significant different allelic frequencies between the North and South of Portugal. *European Journal of Human Genetics* 2001;9:843-8.**	Ineligible patient group: newborn study.
109.	**Cardoso C, Porto G, Lacerda R, et al. T-cell receptor repertoire in hereditary hemochromatosis: a study of 32 hemochromatosis patients and 274 healthy subjects. *Hum Immunol*. 2001;62(5):488-499.**	>10% treated for iron overload
110.	**Carpenter JP, Grasso AE, Porter JB, Shah F, Dooley J, Pennell DJ. On myocardial siderosis and left ventricular dysfunction in hemochromatosis. *J Cardiovasc Magn Reson* 2013;15:24.**	Fewer than 100 participants.
111.	**Carroll GJ. Precocious bilateral hip joint osteoarthritis is a "form-fruste" of the arthropathy of hereditary haemochromatosis. *Med Hypotheses* 2010;74:719-21.**	Fewer than 100 participants.
112.	**Cascales A, Sanchez-Vega B, Navarro N, Pastor-Quirante F, Corral J, Vicente V*, et al.* Clinical and genetic determinants of anthracycline-induced cardiac iron accumulation. *Int J Cardiol* 2012;154:282-6.**	Fewer than 100 participants.
113.	**Cash WJ, O'Neill S, O'Donnell ME, McCance DR, Young IS, McEneny J*, et al.* Disordered vascular compliance in haemochromatosis. *Ir J Med Sci* 2014;183:303-9.**	Fewer than 100 participants.
114.	**Cash WJ, O'Neill S, O'Donnell ME, McCance DR, Young IS, McEneny J*, et al.* Endothelial function, antioxidant status and vascular compliance in newly diagnosed HFE C282Y homozygotes. *Adv Med Sci* 2014;59:28-33.**	Fewer than 100 participants.
115.	**Cassiman D, Vannoote J, Roelandts R, Libbrecht L, Roskams T, Van den Oord J*, et al.* Porphyria cutanea tarda and liver disease. A retrospective analysis of 17 cases from a single centre and review of the literature. *Acta Gastroenterol Belg* 2008;71:237-42.**	Ineligible condition: PCT. Fewer than 100 participants.
116.	**Castiella A, Mugica F, Zapata E, Zubiaurre L, Iribarren A, de Juan MD*, et al.* Gender and plasma iron biomarkers, but not HFE gene mutations, increase the risk of colorectal cancer and polyps. *Tumour Biol* 2015;36:6959-63.**	Ineligible starting condition: CRC
117.	**Castiella A, Zapata E, Zubiaurre L, Ma Alustiza J, De Juan MD, Iribarren A*, et al.* Impact of H63D mutations, magnetic resonance and metabolic syndrome among outpatient referrals for elevated serum ferritin in the Basque Country. *Annals of Hepatology* 2015;14:333-9.**	Ineligible starting condition: hyperferrienemia.

118.	**Castiglione A, Ciorba A, Aimoni C, Orioli E, Zeri G, Vigliano M*, et al.* Sudden sensorineural hearing loss and polymorphisms in iron homeostasis genes: new insights from a case-control study. *Biomed Res Int* 2015;2015:834736.**	Ineligible starting condition: Sudden hearing loss.
119.	**Chan AT, Ma J, Tranah GJ, Giovannucci EL, Rifai N, Hunter DJ*, et al.* Hemochromatosis gene mutations, body iron stores, dietary iron, and risk of colorectal adenoma in women. *J Natl Cancer Inst* 2005;97:917-26.**	Ineligible starting population: colorectal adenoma.
120.	**Chen VL, Chen Y, Du X, Handelman SK, Speliotes EK. Genetic variants that associate with liver cirrhosis have pleiotropic effects on human traits. *Liver International* 2019;09:09.**	Participants with cirrhosis. Not reporting on genotype only SNPs.
121.	**Chen W, Zhao H, Li T, Yao H. HFE gene C282Y variant is associated with colorectal cancer in Caucasians: a meta-analysis. *Tumour Biol* 2013;34:2255-9.**	SR on ineligible starting condition: CRC.
122.	**Cheng R, Barton JC, Morrison ED, et al. Differences in hepatic phenotype between hemochromatosis patients with HFE C282Y homozygosity and other HFE genotypes. *J Clin Gastroenterol*. 2009;43(6):569-573.**	>10% treated for iron overload
123.	**Chiaverini C, Halimi G, Ouzan D, Halfon P, Ortonne JP, Lacour JP. Porphyria cutanea tarda, C282Y, H63D and S65C HFE gene mutations and hepatitis C infection: a study from southern France. *Dermatology* 2003;206:212-6.**	Ineligible outcome: hep C. Fewer than 100 participants.
124.	**Chio A, Mora G, Sabatelli M, Caponnetto C, Lunetta C, Traynor BJ*, et al.* HFE p.H63D polymorphism does not influence ALS phenotype and survival. *Neurobiology of Aging* 2015;36:2906.e7-.e11.**	Ineligible starting condition: ALS patients
125.	**Chitturi S, Weltman M, Farrell GC, McDonald D, Kench J, Liddle C*, et al.* HFE mutations, hepatic iron, and fibrosis: ethnic-specific association of NASH with C282Y but not with fibrotic severity. *Hepatology* 2002;36:142-9.**	Fewer than 100 participants.
126.	**Choi SJ, Min WK, Chun S, et al. Frequencies of C282Y and H63D mutations and transferrin saturation indices in the Korean population. *Clin Chem Lab Med*. 2002;40(7):689-692. doi:10.1515/CCLM.2002.118**	Ineligible population (participants had any level of serum ferritin, not elevated)
127.	**Christiansen AL, Brock A, Bygum A, Rasmussen LM, Jepsen P. Increased mortality in patients with porphyria cutanea tarda - a nationwide cohort study. *Journal of the American Academy of Dermatology* 2019;30.**	Ineligible starting condition: PCT
128.	**Ciesielski TH, Schwartz J, Bellinger DC, Hauser R, Amarasiriwardena C, Sparrow D*, et al.* Iron-processing genotypes, nutrient intakes, and cadmium levels in the Normative Aging Study: Evidence of sensitive subpopulations in cadmium risk assessment. *Environ Int* 2018;119:527-35.**	Ineligible outcomes: Calcadium and hemoglobin
129.	**Connor JR, Milward EA, Moalem S, Sampietro M, Boyer P, Percy ME*, et al.* Is hemochromatosis a risk factor for Alzheimer's disease? *J Alzheimers Dis* 2001;3:471-7.**	Ineligible publication type: Review. Ineligible starting condition: Alzheimers

130.	**Constantine CC, Anderson GJ, Vulpe CD, McLaren CE, Bahlo M, Yeap HL*, et al.* A novel association between a SNP in CYBRD1 and serum ferritin levels in a cohort study of HFE hereditary haemochromatosis. *Br J Haematol* 2009;147:140-9.**	Ineligible outcomes.
131.	**Conte D, Manachino D, Colli A, Guala A, Aimo G, Andreoletti M*, et al.* Prevalence of genetic hemochromatosis in a cohort of Italian patients with diabetes mellitus. *Ann Intern Med* 1998;128:370-3.**	No genotyping.
132.	**Cooper K, Bryant J, Picot J, Clegg A, Roderick PR, Rosenberg WM*, et al.* A decision analysis model for diagnostic strategies using DNA testing for hereditary haemochromatosis in at risk populations. *Qjm* 2008;101:631-41.**	Ineligible study type: Cost analysis, no applicable data.
133.	**Coppin H, Bensaid M, Fruchon S, Borot N, Blanche H, Roth MP. Longevity and carrying the C282Y mutation for haemochromatosis on the HFE gene: case control study of 492 French centenarians. *Bmj* 2003;327:132-3.**	Ineligible outcomes.
134.	**Corley DA, Kubo A, Levin TR, Block G, Habel L, Rumore GJ*, et al.* Hemochromatosis gene status as a risk factor for Barrett's esophagus. *Dig Dis Sci* 2008;53:3095-102.**	Ineligible starting conditions: Reflux and oesophogal cancer.
135.	**Costa-Matos L, Batista P, Monteiro N, Henriques P, Girao F, Carvalho A. Hfe mutations and iron overload in patients with alcoholic liver disease. *Arq Gastroenterol* 2013;50:35-41.**	Ineligible starting condition: alcoholic liver disease.
136.	**Couto AR, Peixoto MJ, Garrett F, Laranjeira F, Cipriano T, Armas JB. Linkage disequilibrium between S65C HFE mutation and HLA A29-B44 haplotype in Terceira Island, Azores. *Human Immunology* 2003;64:625-8.**	Ineligible outcomes.
137.	**Crawford DH, Jazwinska EC, Cullen LM, Powell LW. Expression of HLA-linked hemochromatosis in subjects homozygous or heterozygous for the C282Y mutation. *Gastroenterology*. 1998;114(5):1003-1008**	>10% treated for iron overload
138.	**Crawford DH, Fletcher LM, Hubscher SG, Stuart KA, Gane E, Angus PW*, et al.* Patient and graft survival after liver transplantation for hereditary hemochromatosis: Implications for pathogenesis. *Hepatology* 2004;39:1655-62.**	Fewer than 100 participants. Unclear whether participants were genotyped.
139.	**Cribier B, Chiaverini C, Dali-Youcef N, Schmitt M, Grima M, Hirth C*, et al.* Porphyria cutanea tarda, hepatitis C, uroporphyrinogen decarboxylase and mutations of HFE gene. A case-control study. *Dermatology* 2009;218:15-21.**	Ineligible starting condition: porphyria cutanea tarda and hepatitis C.
140.	**Crooks CJ, West J, Solaymani-Dodaran M, Card TR. The epidemiology of haemochromatosis: a population-based study. *Aliment Pharmacol Ther* 2009;29:183-92.**	No genotyping. No screening or treatment.
141.	**Cruz E, Melo G, Lacerda R, Almeida S, Porto G. The CD8+ T-lymphocyte profile as a modifier of iron overload in HFE hemochromatosis: an update of clinical and immunological data from 70 C282Y homozygous subjects. *Blood Cells Mol Dis* 2006;37:33-9.**	Fewer than 100 participants.

142.	**Dallos T, Sahinbegovic E, Aigner E, Axmann R, Schoniger-Hekele M, Karonitsch T, *et al.* Validation of a radiographic scoring system for haemochromatosis arthropathy. *Ann Rheum Dis* 2010;69:2145-51.**	Ineligible population: treated.
143.	**Dar FS, Faraj W, Zaman MB, Bartlett A, Bomford A, O'Sullivan A, *et al.* Outcome of liver transplantation in hereditary hemochromatosis. *Transpl Int* 2009;22:717-24.**	Fewer than 100 participants.
144.	**Datz C, Haas T, Rinner H, Sandhofer F, Patsch W, Paulweber B. Heterozygosity for the C282Y mutation in the hemochromatosis gene is associated with increased serum iron, transferrin saturation, and hemoglobin in young women: a protective role against iron deficiency? *Clin Chem* 1998;44:2429-32. https://doi.org/10.1093/clinchem/44.12.2429**	Ineligible genotype
145.	**Davidsen ES, Hervig T, Omvik P, Gerdts E. Left ventricular long-axis function in treated haemochromatosis. *Int J Cardiovasc Imaging* 2009;25:237-47.**	Ineligible population: treated (with phlebotomy). No information of stage of treatment to discuss early vs late. No genotyping
146.	**Davidsen ES, Liseth K, Omvik P, Hervig T, Gerdts E. Reduced exercise capacity in genetic haemochromatosis. *Eur J Cardiovasc Prev Rehabil* 2007;14:470-5.**	No genotyping information. Ineligible outcomes of interest. No screening or treatment
147.	**Davidsen ES, Omvik P, Hervig T, Gerdts E. Left ventricular diastolic function in patients with treated haemochromatosis. *Scand Cardiovasc J* 2009;43:32-8.**	No genotyping. Ineligible population: treated.
148.	**Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. *Gut* 2005;54:533-9.**	No determination of how they have HH or genotyping
149.	**Davis TM, Peters KE, Bruce DG, Davis WA. Prevalence, incidence, and prognosis of hepatobiliary disease in community-based patients with type 2 diabetes: the Fremantle Diabetes Study. *J Clin Endocrinol Metab* 2012;97:1581-8.**	No genotyping
150.	**De Falco L, Tortora R, Imperatore N, Bruno M, Capasso M, Girelli D, *et al.* The role of TMPRSS6 and HFE variants in iron deficiency anemia in celiac disease. *American Journal of Hematology* 2018;93:383-93.**	Ineligible starting condition: coeliacs.
151.	**de Graaff B, Neil A, Sanderson K, Si L, Yee KC, Palmer AJ. A Systematic Review and Narrative Synthesis of Health Economic Studies Conducted for Hereditary Haemochromatosis. *Appl Health Econ Health Policy* 2015;13:469-83.**	Ineligible study type: Cost study.
152.	**de Graaff B, Neil A, Sanderson K, Yee KC, Palmer AJ. Costs associated with hereditary haemochromatosis in Australia: a cost-of-illness study. *Aust Health Rev* 2017;41:254-67.**	Ineligible study type: Cost study.

153.	**de Graaff B, Si L, Neil AL, Yee KC, Sanderson K, Gurrin LC*, et al.* Population Screening for Hereditary Haemochromatosis in Australia: Construction and Validation of a State-Transition Cost-Effectiveness Model. *Pharmacoeconom Open* 2017;1:37-51.**	Ineligible study type: Cost study.
154.	**de Greef BTA, Hoeijmakers JGJ, Gorissen-Brouwers CML, Geerts M, Faber CG, Merkies ISJ. Associated conditions in small fiber neuropathy - a large cohort study and review of the literature. *European Journal of Neurology* 2018;25:348-55.**	Ineligible starting condition: small giber neuropathy.
155.	**De Marco F, Liguori R, Giardina MG, D'Armiento M, Angelucci E, Lucariello A*, et al.* High prevalence of non-HFE gene-associated haemochromatosis in patients from southern Italy. *Clin Chem Lab Med* 2004;42:17-24.**	Fewer than 100 participants.
156.	**De Souza GF, Ribeiro HL, Jr., De Sousa JC, Heredia FF, De Freitas RM, Martins MR*, et al.* HFE gene mutation and oxidative damage biomarkers in patients with myelodysplastic syndromes and its relation to transfusional iron overload: an observational cross-sectional study. *BMJ Open* 2015;5:e006048.**	Ineligible starting condition: MDS.
157.	**de Valk B, Witlox, van der Schouw YT, Marx. Biochemical expression of heterozygous hereditary hemochromatosis. *Eur* 2000;11:317-21.**	Fewer than 100 eligible participants.
158.	**Desgrippes R, Lainé F, Morcet J, et al. Decreased iron burden in overweight C282Y homozygous women: Putative role of increased hepcidin production. *Hepatology*. 2013;57(5):1784-1792.**	>10% treated for iron overload
159.	**Deguti MM, Sipahi AM, Gayotto LC, Palacios SA, Bittencourt PL, Goldberg AC*, et al.* Lack of evidence for the pathogenic role of iron and HFE gene mutations in Brazilian patients with nonalcoholic steatohepatitis. *Braz J Med Biol Res* 2003;36:739-45.**	Fewer than 100 participants.
160.	**Dereure O, Aguilar-Martinez P, Bessis D, Perney P, Vallat C, Guillot B*, et al.* HFE mutations and transferrin receptor polymorphism analysis in porphyria cutanea tarda: a prospective study of 36 cases from southern France. *Br J Dermatol* 2001;144:533-9.**	Fewer than 100 participants.
161.	**Deugnier Y, Morcet J, Lainé F, et al. Reduced phenotypic expression in genetic hemochromatosis with time: Role of exposure to non-genetic modifiers. *J Hepatol*. 2019;70(1):118-125.**	>10% treated for iron overload
162.	**Dereure O, Jumez N, Bessis D, Gallix B, Guillot B. Measurement of liver iron content by magnetic resonance imaging in 20 patients with overt porphyria cutanea tarda before phlebotomy therapy: a prospective study. *Acta Derm Venereol* 2008;88:341-5.**	Fewer than 100 participants.
163.	**Dever JB, Mallory MA, Mallory JE, Wallace D, Kowdley KV. Phenotypic characteristics and diagnoses of patients referred to an iron overload clinic. *Dig Dis Sci*. 2010;55(3):803-807. doi:10.1007/s10620-009-1080-1**	HH genotype numbers not reported for eligible clinical factor
164.	**Dhillon BK, Das R, Garewal G, et al. Frequency of primary iron overload and HFE gene mutations (C282Y, H63D and S65C) in chronic liver disease patients in north India. *World J Gastroenterol*. 2007;13(21):2956-2959. doi:10.3748/wjg.v13.i21.2956**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)

165.	**Dhillon BK, Prakash S, Chandak GR, Chawla YK, Das R. H63D mutation in HFE gene is common in Indians and is associated with the European haplotype. *J Genet* 2012;91:229-32.**	No genotype information - Allelle study of SNPs.
166.	**Dietrich S, Jacobs S, Zheng JS, Meidtner K, Schwingshackl L, Schulze MB. Gene-lifestyle interaction on risk of type 2 diabetes: A systematic review. *Obesity Reviews* 2019;20:1557-71.**	Reporting on alleles rather than genotypes.
167.	**Dijck-Brouwer DA, Hepkema BG, van der Dijs FP, Steward HN, de Windt-Hol JM, Muskiet FA. Curacao patients with coronary artery disease have a higher prevalence of the HFE C282Y mutation. *West Indian Med J* 2004;53:143-6.**	Ineligible starting condition: CAD
168.	**Donnelly SC, Joshi NG, Thorburn D, Cooke A, Reid G, Neilson M*, et al.* Prevalence of genetic haemochromatosis and iron overload in patients attending rheumatology and joint replacement clinics. *Scott Med J* 2010;55:14-6.**	Unknown starting condition.
169.	**Dostalikova-Cimburova M, Balusikova K, Kratka K, Chmelikova J, Hejda V, Hnanicek J*, et al.* Role of duodenal iron transporters and hepcidin in patients with alcoholic liver disease. *J Cell Mol Med* 2014;18:1840-50.**	Ineligible condition: alcoholic liver disease.
170.	**Dostalikova-Cimburova M, Kratka K, Stransky J, Putova I, Cieslarova B, Horak J. Iron overload and HFE gene mutations in Czech patients with chronic liver diseases. *Dis Markers* 2012;32:65-72.**	Fewer than 100 eligible participants.
171.	**Duan C, Wang M, Zhang Y, Wei X, Huang Y, Zhang H*, et al.* C282Y and H63D Polymorphisms in Hemochromatosis Gene and Risk of Parkinson's Disease: A Meta-Analysis. *Am J Alzheimers Dis Other Demen* 2016;31:201-7.**	Ineligible starting condition: Parkinson's disease.
172.	**Dulger AC, Esen R, Mete R, Begenik H, Aytemiz E, Tasdemir M*, et al.* The prevalence of hereditary hemochromatosis in some men from the Eastern part of Turkey and the effects of H63D mutations on iron studies. *Clin Chem Lab Med* 2012;0:1-4.**	Paper could not be obtained.
173.	**Dunn T, Blankenship D, Beal N, et al. HFE mutations in heart disease. *Heart Vessels*. 2008;23(5):348-355. doi:10.1007/s00380-008-1047-8**	Data not reported for C282Y/C282Y, H63D/H63D, or C282Y/H63D genotypes
174.	**Duseja A, Das A, Das R, Dhiman RK, Chawla Y, Bhansali A*, et al.* The clinicopathological profile of Indian patients with nonalcoholic fatty liver disease (NAFLD) is different from that in the West. *Dig Dis Sci* 2007;52:2368-74.**	Ineligible publication type: Letter to the editor
175.	**Ekblom K, Hultdin J, Stegmayr B, Johansson I, Van Guelpen B, Hallmans G*, et al.* Iron stores and HFE genotypes are not related to increased risk of ischemic stroke. A prospective nested case-referent study. *Cerebrovasc Dis* 2007;24:405-11.**	Ineligible starting condition: stroke.
176.	**Ekblom K, Marklund SL, Palmqvist R, Guelpen BV, Hallmans G, Weinehall L*, et al.* Iron biomarkers in plasma, HFE genotypes, and the risk for colorectal cancer in a prospective setting. *Diseases of the Colon and Rectum* 2012;55:337-44.**	Ineligible starting condition: colorectal cancer.

177.	**El Osta R, Grandpre N, Monnin N, Hubert J, Koscinski I. Hypogonadotropic hypogonadism in men with hereditary hemochromatosis. *Basic clin* 2017;27:13.**	Ineligible study type. Ineligible outcomes: Hypogonadotropic hypogonadism, male infertility.
178.	**ElAoud S, Kamoun A, Mahfoudh N, Charfi A, Snoussi M, Hachicha H*, et al.* Beyond Human Leukocyte Antigen Class I Antigens: Hereditary Hemochromatosis Gene Mutations in Recurrent Aphthous Oral Ulcers and Behcet Disease in the South of Tunisia. *Medical Principles and Practice* 2017;26:427-32.**	Ineligible starting condition: recurrent aphthous oral ulcers and Behçet disease.
179.	**Ellervik C, Tybjaerg-Hansen A, Appleyard M, Ibsen H, Nordestgaard BG. Haemochromatosis genotype and iron overload: association with hypertension and left ventricular hypertrophy. *J Intern Med* 2010;268:252-64.**	No outcomes of interest
180.	**Ellervik C, Tybjaerg-Hansen A, Nordestgaard BG. Risk of cancer by transferrin saturation levels and haemochromatosis genotype: population-based study and meta-analysis. *J Intern Med* 2012;271:51-63.**	Ineligible outcomes.
181.	**Ellervik C, Andersen HU, Tybjærg-Hansen A, et al. Total mortality by elevated transferrin saturation in patients with diabetes. *Diabetes Care*. 2013;36(9):2646-2654. doi:10.2337/dc12-2032**	Same data as Ellervik 2001
182.	**Elmberg M, Hultcrantz R, Ebrahim F, Olsson S, Lindgren S, Loof L*, et al.* Increased mortality risk in patients with phenotypic hereditary hemochromatosis but not in their first-degree relatives. *Gastroenterology* 2009;137:1301-9.**	No HFE genotypes reported, patients with phenotypic HH only. Unclear if untreated.
183.	**Elmberg M, Hultcrantz R, Ekbom A, Brandt L, Olsson S, Olsson R*, et al.* Cancer risk in patients with hereditary hemochromatosis and in their first-degree relatives. *Gastroenterology* 2003;125:1733-41.**	No HFE genotypes reported. No diagnosis of HH according to International Classification of Disease [ICD-7, 289.23; ICD-8, 273.20; ICD-9, 275A; ICD-10, E83.1]) between 1964 and December 31, 1999. Unclear if population treated.
184.	**Elmberg M, Hultcrantz R, Simard JF, Carlsson A, Askling J. Increased risk of arthropathies and joint replacement surgery in patients with genetic hemochromatosis: a study of 3,531 patients and their 11,794 first-degree relatives. *Arthritis Care Res (Hoboken)* 2013;65:678-85.**	No HFE genotype reported. Patients with phenotypic haemochromatosis; unclear if treated.

185.	**Elmberg M, Hultcrantz R, Simard JF, Stal P, Pehrsson K, Askling J. Risk of ischaemic heart disease and cardiomyopathy in patients with haemochromatosis and in their first-degree relatives: a nationwide, population-based study. *J Intern Med* 2012;272:45-54.**	Ineligible patient group: phenotypic haemochromatosis. No HFE genotype measured. Treatment of HH unclear.
186.	**Elsaid MI, John T, Li Y, Koduru S, Ali SZ, Catalano C*, et al.* Health Care Utilization and Economic Burdens of Hemochromatosis in the United States: A Population-Based Claims Study. *Journal of managed care & specialty pharmacy* 2019;25:1377-86.**	No information on HFE genotype (primary and secondary haemochromatosis included). Ineligible outcomes.
187.	**Elsass P, Pedersen P, Husum K, Milman N. Assessment of the psychological effects of genetic screening for hereditary hemochromatosis. *Ann Hematol*. 2008;87(5):397-404. doi:10.1007/s00277-007-0415-2**	No eligible outcome
188.	**El-Serag HB, Richardson PA, Everhart JE. The role of diabetes in hepatocellular carcinoma: a case-control study among United States Veterans. *American Journal of Gastroenterology* 2001;96:2462-7.**	No HFE genotypes determined.
189.	**Elstob A, Ejindu V, Heron CW, Kiely PDW. MRI ankle and subtalar characteristics in haemochromatosis arthropathy: a case-control study. *Clin Radiol* 2018;73:323.e1-.e8.**	Ineligible study design.
190.	**Emery J, Rose P, Harcourt J, Livesey K, Merryweather-Clarke A, Pointon JJ*, et al.* Pilot study of early diagnosis of hereditary haemochromatosis through systematic case finding in primary care. *Community Genet* 2002;5:262-5.**	Fewer than 100 participants.
191.	**Engberink MF, Povel CM, Durga J, Swinkels DW, de Kort WL, Schouten EG*, et al.* Hemochromatosis (HFE) genotype and atherosclerosis: Increased susceptibility to iron-induced vascular damage in C282Y carriers? *Atherosclerosis* 2010;211:520-5.**	Ineligible genotype
192.	**Erhardt A, Maschner-Olberg A, Mellenthin C, Kappert G, Adams O, Donner A*, et al.* HFE mutations and chronic hepatitis C: H63D and C282Y heterozygosity are independent risk factors for liver fibrosis and cirrhosis. *Journal of Hepatology* 2003;38:335-42.**	Ineligible starting condition: hepatitis C.
193.	**Eum KD, Seals RM, Taylor KM, Grespin M, Umbach DM, Hu H*, et al.* Modification of the association between lead exposure and amyotrophic lateral sclerosis by iron and oxidative stress related gene polymorphisms. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 2015;16:72-9.**	Ineligible starting condition. Ineligible outcomes: lead concentrations.
194.	**Evers D, Kerkhoffs JL, Van Egmond L, Schipperus MR, Wijermans PW. The efficiency of therapeutic erythrocytapheresis compared to phlebotomy: a mathematical tool for predicting response in hereditary hemochromatosis, polycythemia vera, and secondary erythrocytosis. *J Clin Apheresis* 2014;29:133-8.**	Ineligible biochemical and clinical outcomes.

195.	**Ewald N, Kaufmann C, Raspe A, Kloer HU, Bretzel RG, Hardt PD. Prevalence of diabetes mellitus secondary to pancreatic diseases (type 3c). *Diabetes Metab Res Rev* 2012;28:338-42.**	No HFE genotype reported. Unclear how HH defined.
196.	**Ezzikouri S, Rebbani K, Mostafa A, El Feydi AE, Afifi R, Brahim I*, et al.* Influence of mutation of the HFE gene on the progression of chronic viral hepatitis B and C in Moroccan patients. *J Med Virol* 2011;83:2096-102. h**	Ineligible starting condition: hepatitis B and C.
197.	**Fallon KE. Utility of hematological and iron-related screening in elite athletes. *Clin J Sport Med* 2004;14:145-52.**	Ineligible outcomes.
198.	**Fang Y, Lin H, Wang J, Su X, Wang F, You P*, et al.* Association between H63D polymorphism and alcoholic liver disease risk: A meta-analysis. *International Journal of Clinical and Experimental Medicine* 2017;10:69-78.**	Ineligible starting condition: alcoholic liver disease.
199.	**Fargion S, Fracanzani AL, Romano R, Cappellini MD, Fare M, Mattioli M*, et al.* Genetic hemochromatosis in Italian patients with porphyria cutanea tarda: possible explanation for iron overload. *Journal of Hepatology* 1996;24:564-9.**	Ineligible starting condition: PCT. Ineligible outcomes: prevalence of HLA-A3.
200.	**Fargion S, Mattioli M, Fracanzani AL, et al. Hyperferritinemia, iron overload, and multiple metabolic alterations identify patients at risk for nonalcoholic steatohepatitis. *Am J Gastroenterol*. 2001;96(8):2448-2455. doi:10.1111/j.1572-0241.2001.04052.x**	Unclear reporting of results for C282Y/C282Y, H63D/H63D, and C282Y/H63D genotypes
201.	**Farrell CP, Overbey JR, Naik H, Nance D, McLaren GD, McLaren CE*, et al.* The D519G Polymorphism of Glyceronephosphate O-Acyltransferase Is a Risk Factor for Familial Porphyria Cutanea Tarda. *PLoS ONE* 2016;11:e0163322.**	Ineligible clinical feature: familial and sporadic porphyria cutanea tarda.
202.	**Fashir B, Sivasubramaniam V, Al Momen S, Assaf H. Pattern of liver disease in a Saudi patient population: a decade of experience at security forces hospital, Riyadh, KSA. *Saudi j* 1996;2:50-2.**	Ineligible population: various reasons. Ineligible outcomes. No HFE genotype determined.
203.	**Fassio E, Miguez C, Soria S, Palazzo F, Gadano A, Adrover R*, et al.* Etiology of hepatocellular carcinoma in Argentina: Results of a multicenter retrospective study. *Acta Gastroenterologica Latinoamericana* 2009;39:47-52.**	Ineligible outcomes. No HFE genotypes reported.
204.	**Felipoff AL, Fleischman SJ, Donadio ML, Sebastiano V, Castro M, Vellicce A*, et al.* Iron intake and HFE gen in male adults from Buenos Aires. *Medicina-Buenos Aires* 2017;77:458-64.**	Language (full text in Spanish).
205.	**Felitti VJ. Hemochromatosis Update. *Perm* 2004;8:39-44.**	Ineligible publication type: Review.

206.	**Fernandez-Real JM, Equitani F, Moreno JM, Manco M, Ortega F, Ricart W. Study of circulating prohepcidin in association with insulin sensitivity and changing iron stores. *J Clin Endocrinol Metab* 2009;94:982-8.**	Ineligible outcomes: insulin sensitivity. Ineligible population. Ineligible outcomes. Fewer than 100 participants.
207.	**Ferrari M, Werner GS, Rieber J, Richartz BM, Sigusch HH, Brandstadt A*, et al.* No influence of hemochromatosis-related gene mutations on restenosis rate in a retrospective study of 137 patients after coronary stent implantation. *International Journal of Cardiovascular Interventions* 2001;4:181-6**	Ineligible population.
208.	**Festa F, Kumar R, Sanyal S, Unden B, Nordfors L, Lindholm B*, et al.* Basal cell carcinoma and variants in genes coding for immune response, DNA repair, folate and iron metabolism. *Mutat Res* 2005;574:105-11.**	Ineligible starting condition: skin cancer.
209.	**Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol* 2007;5:513-20.**	No HFE genotype reported.
210.	**Flais J, Bardou-Jacquet E, Deugnier Y, Coiffier G, Perdriger A, Chales G*, et al.* Hyperferritinemia increases the risk of hyperuricemia in HFE-hereditary hemochromatosis. *Joint Bone Spine* 2017;84:293-7.**	Ineligible outcomes.
211.	**Floreani A, Navaglia F, Rizzotto ER, Basso D, Chiaramonte M, Padoan A*, et al.* Mass spectrometry measurement of plasma hepcidin for the prediction of iron overload. *Clinical Chemistry and Laboratory Medicine* 2011;49:197-206.**	Ineligible population. No information on treatment.
212.	**Fonseca-Nunes A, Jakszyn P, Agudo A. Iron and cancer risk--a systematic review and meta-analysis of the epidemiological evidence. *Cancer Epidemiol Biomarkers Prev* 2014;23:12-31.**	Ineligible exposure: no HFE mutation determined. Ineligible outcomes.
213.	**Fracanzani AL, Conte D, Fraquelli M, Taioli E, Mattioli M, Losco A*, et al.* Increased cancer risk in a cohort of 230 patients with hereditary hemochromatosis in comparison to matched control patients with non-iron-related chronic liver disease. *Hepatology* 2001;33:647-51.**	Ineligible population: treated.
214.	**Fracanzani AL, Fargion S, Stazi MA, et al. Association between heterozygosity for HFE gene mutations and hepatitis viruses in hepatocellular carcinoma. *Blood Cells Mol Dis*. 2005;35(1):27-32. doi:10.1016/j.bcmd.2005.03.007**	Data not reported for C282Y/C282Y, H63D/H63D, or C282Y/H63D genotypes
215.	**Fracanzani AL, Piperno A, Valenti L, et al. Hemochromatosis in Italy in the last 30 years: role of genetic and acquired factors. *Hepatology*. 2010;51(2):501-510. doi:10.1002/hep.23333**	Ineligible clinical factor (mixed definition of iron overload)
216.	**Franco RF, Zago MA, Trip MD, et al. Prevalence of hereditary haemochromatosis in premature atherosclerotic vascular disease. *Br J Haematol*. 1998;102(5):1172-1175. doi:10.1046/j.1365-2141.1998.00898.x**	Ineligible clinical factor (premature

		atherosclerotic vascular disease)
217.	**French JK, Van de Water NS, Sutton TM, et al. Potential thrombophilic mutations/polymorphisms in patients with no flow-limiting stenosis after myocardial infarction. *Am Heart J*. 2003;145(1):118-124. doi:10.1067/mhj.2003.29**	No data for C282Y/C282Y, H63D/H63D, or C282Y/H63D genotypes
218.	**Gabrikova D, Boronova I, Bernasovsky I, Behulova R, Macekova S, Bozikova A*, et al.* Hemochromatosis gene mutations in the general population of Slovakia. *Central European Journal of Medicine* 2011;6:148-51.**	Ineligible HFE mutations, not associated with relevant outcomes.
219.	**Galesloot TE, Geurts-Moespot AJ, den Heijer M, Sweep FC, Fleming RE, Kiemeney LA*, et al.* Associations of common variants in HFE and TMPRSS6 with iron parameters are independent of serum hepcidin in a general population: a replication study. *Journal of Medical Genetics* 2013;50:593-8.**	Ineligible exposure: allele frequency in population not on individual level
220.	**Ganesh SK, Tragante V, Guo W, Guo Y, Lanktree MB, Smith EN*, et al.* Loci influencing blood pressure identified using a cardiovascular gene-centric array. *Human Molecular Genetics* 2013;22:1663-78.**	Ineligible outcomes: hypertension / blood pressure.
221.	**Gangaidzo IT, Moyo VM, Saungweme T, Khumalo H, Charakupa RM, Gomo ZA*, et al.* Iron overload in urban Africans in the 1990s. *Gut* 1999;45:278-83.**	Fewer than 100 participants.
222.	**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. *Archives of Medical Research* 2018;49:405-17. https://doi.org/10.1016/j.arcmed.2018.12.005**	Ineligible outcome: HFE genotype not assessed
223.	**Garewal G, Das R, Ahluwalia J, Marwaha RK. Prevalence of the H63D mutation of the HFE in north India: its presence does not cause iron overload in beta thalassemia trait. *European Journal of Haematology* 2005;74:333-6.**	Ineligible starting condition: beta-thalassemia. Fewer than 100 participants. No relevant outcomes reported
224.	**Gazzina S, Premi E, Zanella I, Biasiotto G, Archetti S, Cosseddu M*, et al.* Iron in Frontotemporal Lobar Degeneration: A New Subcortical Pathological Pathway? *Neurodegener* 2016;16:172-8.**	Ineligible population: co-morbidity. Ineligible starting condition: FTLD
225.	**Geier A, Reugels M, Weiskirchen R, Wasmuth HE, Dietrich CG, Siewert E*, et al.* Common heterozygous hemochromatosis gene mutations are risk factors for inflammation and fibrosis in chronic hepatitis C. *Liver International* 2004;24:285-94.**	Ineligible population: co-morbidity.

		Ineligible starting disease: hepatitis C
226.	**Geier D, Hebert B, Potti A. Risk of primary non-hepatocellular malignancies in hereditary hemochromatosis. *Anticancer Res* 2002;22:3797-9.**	Fewer than 100 participants.
227.	**Gelatti U, Donato F, Tagger A, Fantoni C, Portolani N, Ribero ML*, et al.* Etiology of hepatocellular carcinoma influences clinical and pathologic features but not patient survival. *American Journal of Gastroenterology* 2003;98:907-14.**	No HFE genotype information.
228.	**Gemmati D, Tognazzo S, Catozzi L, et al. Influence of gene polymorphisms in ulcer healing process after superficial venous surgery. *J Vasc Surg*. 2006;44(3):554-562. doi:10.1016/j.jvs.2006.05.011**	Ineligible clinical factor (leg ulcer), sample size, study design
229.	**Gemmati D, Federici F, Catozzi L, Gianesini S, Tacconi G, Scapoli GL*, et al.* DNA-array of gene variants in venous leg ulcers: detection of prognostic indicators. *J Vasc Surg* 2009;50:1444-51.**	Ineligible starting condition: chronic venous disease or venous leg ulcers.
230.	**George DK, Goldwurm S, MacDonald GA, Cowley LL, Walker NI, Ward PJ*, et al.* Increased hepatic iron concentration in nonalcoholic steatohepatitis is associated with increased fibrosis. *Gastroenterology* 1998;114:311-8.**	Fewer than 100 participants.
231.	**George PM, Conaghan C, Angus HB, Walmsley TA, Chapman BA. Comparison of histological and biochemical hepatic iron indexes in the diagnosis of genetic haemochromatosis. *J Clin Pathol* 1996;49:159-63.**	Fewer than 100 participants.
232.	**Geramizadeh B, Ghazanfari Y, Nikeghbalian S, Malekhosseini S-A. A Single Center Study Comparing the Stainable Iron Depositions in 1000 Explanted Cirrhotic Livers of Different Causes. *Hepatitis Monthly* 2015;15:e33710.**	Ineligible clinical feature: patients with cirrhosis not caused by primary and secondary hemochromatosis
233.	**Gerayli S, Pasdar A, Shakeri MT, Sepahi S, Hoseini SM, Ahadi M*, et al.* Haplotype analysis of hemochromatosis gene polymorphisms in chronic hepatitis C virus infection: A case control study. *Iranian Red Crescent Medical Journal* 2016;18.**	Ineligible starting condition: hepatitis C.
234.	**Ghaziani T, Alavian S-M, Zali MR, Shahraz S, Agah M, Jensen KP*, et al.* Serum measures of iron status and HFE gene mutations in patients with hepatitis B virus infection. *Hepatology Research* 2007;37:172-8.**	Ineligible starting condition: Hepatitis B virus infection.
235.	**Giampietro PF, Greenlee RT, McPherson E, Benetti LL, Berg RL, Wagner SF. Acute health events in adult patients with genetic disorders: The Marshfield Epidemiologic Study Area. *Genetics in Medicine* 2006;8:474-90.**	Unclear haemochromatosis definition. No HFE genotypes reported.

236.	**Gichohi-Wainaina WN, Tanaka T, Towers GW, Verhoef H, Veenemans J, Talsma EF*, et al.* Associations between common variants in iron-related genes with haematological traits in populations of african ancestry. *PLoS ONE* 2016;11.**	Ineligible population: 1237/2151= 58% children.
237.	**Gill D, Benyamin B, Moore LSP, Monori G, Zhou A, Koskeridis F*, et al.* Associations of genetically determined iron status across the phenome: A mendelian randomization study. *PLoS Med* 2019;16:e1002833.**	Ineligible exposure: allele frequency in population not individual level
238.	**Gill D, Del Greco MF, Walker AP, Srai SKS, Laffan MA, Minelli C. The Effect of Iron Status on Risk of Coronary Artery Disease: A Mendelian Randomization Study-Brief Report. *Arterioscler Thromb Vasc Biol* 2017;37:1788-92.**	Study examines the effect of the allele without discriminating between homozygosity (2 alleles) vs heterozygosity (1 allele).
239.	**Gleeson D, Evans S, Bradley M, Jones J, Peck RJ, Dube A*, et al.* HFE genotypes in decompensated alcoholic liver disease: Phenotypic expression and comparison with heavy drinking and with normal controls. *American Journal of Gastroenterology* 2006;101:304-10.**	Ineligible starting condition: decompensated alcoholic liver disease.
240.	**Gordon AS, Rosenthal EA, Carrell DS, Amendola LM, Dorschner MO, Scrol A*, et al.* Rates of Actionable Genetic Findings in Individuals with Colorectal Cancer or Polyps Ascertained from a Community Medical Setting. *Am J Hum Genet* 2019;105:526-33.**	Ineligible starting condition: CRC or polyps.
241.	**Graff RE, Cho E, Lindstrom S, Kraft P, Willett WC, Eliassen AH. Premenopausal plasma ferritin levels, HFE polymorphisms, and risk of breast cancer in the nurses' health study II. *Cancer Epidemiol Biomarkers Prev* 2014;23:516-24.**	Ineligible starting condition: breast cancer. Association of HFE genotype and ferritin levels is reported but study not designed to answer that question.
242.	**Grashow R, Sparrow D, Hu H, Weisskopf MG. Cumulative lead exposure is associated with reduced olfactory recognition performance in elderly men: The Normative Aging Study. *Neurotoxicology* 2015;49:158-64.**	Ineligible on outcomes.
243.	**Greco V, De Marco EV, Rocca FE, Annesi F, Civitelli D, Provenzano G*, et al.* Association study between four polymorphisms in the HFE, TF and TFR genes and Parkinson's disease in southern Italy. *Neurol Sci* 2011;32:525-7.**	Ineligible starting condition: PD. Ineligible outcomes.
244.	**Grosse SD, Gurrin LC, Bertalli NA, Allen KJ. Clinical penetrance in hereditary hemochromatosis: estimates of the cumulative incidence of severe liver disease among HFE C282Y homozygotes. *Genetics in Medicine* 2018;20:383-9.**	Ineligible study design: not a systematic review.

245.	**Guerreiro RJ, Bras JM, Santana I, Januario C, Santiago B, Morgadinho AS*, et al.* Association of HFE common mutations with Parkinson's disease, Alzheimer's disease and mild cognitive impairment in a Portuguese cohort. *BMC Neurol* 2006;6:24.**	Ineligible starting condition: Alzheimer, Parkinsons, cognitive impairment. Ineligible outcomes reported.
246.	**Gunel-Ozcan A, Alyilmaz-Bekmez S, Guler EN, Guc D. HFE H63D mutation frequency shows an increase in Turkish women with breast cancer. *BMC Cancer* 2006;6:37.**	Ineligible starting condition: breast cancer. Ineligible outcomes.
247.	**Gunn IR, Maxwell FK, Gaffney D, McMahon AD, Packard CJ. Haemochromatosis gene mutations and risk of coronary heart disease: a west of Scotland coronary prevention study (WOSCOPS) substudy. *Heart*. 2004;90(3):304-306. doi:10.1136/hrt.2003.015149**	Ineligible clinical factor (mixed myocardial infarction/ revascularisation procedure)
248.	**Gunnarsdottir SA, Olsson R, Olafsson S, Cariglia N, Westin J, Thjodleifsson B*, et al.* Liver cirrhosis in Iceland and Sweden: Incidence, aetiology and outcomes. *Scandinavian Journal of Gastroenterology* 2009;44:984-93.**	Ineligible outcomes. Unclear definition of haemochromatosis.
249.	**Gunton JE, Gates F, Fulcher GR, Clifton-Bligh PB. Bone Mineral Density in Postmenopausal Women Heterozygous for the C282Y HFE Mutation. *J Osteoporos* 2016;2016:5638273.**	Ineligible population. Ineligible outcomes.
250.	**Guyader D, Gandon Y, Sapey T, Turlin B, Mendler MH, Brissot P*, et al.* Magnetic resonance iron-free nodules in genetic hemochromatosis. *American Journal of Gastroenterology* 1999;94:1083-6.**	Study was undertaken before the discovery of the HFE gene, C282Y genotyping was not available.
251.	**Haddow JE, Palomaki GE, McClain M, Craig W. Hereditary haemochromatosis and hepatocellular carcinoma in males: A strategy for estimating the potential for primary prevention. *Journal of Medical Screening* 2003;10:11-3.**	Hypothetic cohort only.
252.	**Halling J, Petersen MS, Grandjean P, Weihe P, Brosen K. Genetic predisposition to Parkinson's disease: CYP2D6 and HFE in the Faroe Islands. *Pharmacogenet Genomics* 2008;18:209-12.**	Ineligible starting condition: PD.
253.	**Halme L, Heliö T, Mäkinen J, et al. HFE haemochromatosis gene mutations in liver transplant patients. *Scand J Gastroenterol*. 2001;36(8):881-885.**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)

254.	**Hamdi-Rozé H, Beaumont-Epinette MP, Ben Ali Z, et al. Rare HFE variants are the most frequent cause of hemochromatosis in non-c282y homozygous patients with hemochromatosis. *Am J Hematol*. 2016;91(12):1202-1205. doi:10.1002/ajh.24535**	Ineligible clinical factor (mixed definition of iron overload)
255.	**Hamdi-Roze H, Ben Ali Z, Ropert M, Detivaud L, Aggoune S, Simon D*, et al.* Variable expressivity of HJV related hemochromatosis: "Juvenile" hemochromatosis? *Blood Cells, Molecules, and Diseases* 2019;74:30-3.**	Ineligible population: patients with non-HFE hemochromatosis with elevated transferrin saturation.
256.	**Harty LC, Lai D, Connor S, Dunne A, Ali M, Ryan J*, et al.* Prevalence and progress of joint symptoms in hereditary hemochromatosis and symptomatic response to venesection. *J* 2011;17:220-2.**	Unclear HH definition. no HFE genotype reported. Ineligible population: Treated.
257.	**Hatunic M, Finucane FM, Brennan AM, Norris S, Pacini G, Nolan JJ. Effect of iron overload on glucose metabolism in patients with hereditary hemochromatosis. *Metabolism* 2010;59:380-4.**	Fewer than 100 participants. Ineligible outcomes
258.	**Haukeland JW, Lorgen I, Schreiner LT, Frigstad SO, Brandsaeter B, Bjoro K*, et al.* Incidence rates and causes of cirrhosis in a Norwegian population. *Scandinavian Journal of Gastroenterology* 2007;42:1501-8.**	Fewer than 100 participants.
259.	**He X, Lu X, Hu J, Xi J, Zhou D, Shang H*, et al.* H63D polymorphism in the hemochromatosis gene is associated with sporadic amyotrophic lateral sclerosis in China. *European Journal of Neurology* 2011;18:359-61. https://doi.org/10.1111/j.1468-1331.2010.03158.x**	Ineligible starting condition: ALS.
260.	**Henninger B, Rauch S, Zoller H, Plaikner M, Jaschke W, Kremser C. R2 -relaxometry of the pancreas in patients with human hemochromatosis protein associated hereditary hemochromatosis. *Eur J Radiol* 2017;89:149-55.**	Fewer than 100 participants.
261.	**He M, Workalemahu T, Manson JE, Hu FB, Qi L. Genetic determinants for body iron store and type 2 diabetes risk in US men and women. *PLoS One*. 2012;7(7):e40919. doi:10.1371/journal.pone.0040919**	No data for C282Y/C282Y, H63D/H63D, or C282Y/H63D genotypes
262.	**Hetet G, Elbaz A, Gariepy J, Nicaud V, Arveiler D, Morrison C, et al. Association studies between haemochromatosis gene mutations and the risk of cardiovascular diseases. Eur J Clin Invest 2001;31:382-8.**	Ineligible genotype
263.	**Hicken BL, Tucker DC, Barton JC. Patient compliance with phlebotomy therapy for iron overload associated with hemochromatosis. *American Journal of Gastroenterology* 2003;98:2072-7.**	Ineligible outcomes. Haemochromatosis definition/diagnosis not based on genotyping.

264.	**Holmström P, Marmur J, Eggertsen G, Gåfvels M, Stål P. Mild iron overload in patients carrying the HFE S65C gene mutation: a retrospective study in patients with suspected iron overload and healthy controls. *Gut*. 2002;51(5):723-730. doi:10.1136/gut.51.5.723**	Ineligible clinical factor (mixed definition of iron overload)
265.	**Hramiak IM, Finegood DT, Adams PC. Factors affecting glucose tolerance in hereditary hemochromatosis. *Clin Invest Med* 1997;20:110-8.**	Fewer than 100 participants.
266.	**Hucl T, Kylanpaa-Back ML, Witt H, Kunzli B, Lempinen M, Schneider A*, et al.* HFE genotypes in patients with chronic pancreatitis and pancreatic adenocarcinoma. *Genetics in Medicine* 2007;9:479-83.**	Ineligible population: subset of the patients (n = 157, 16%) were children. Ineligible starting condition.
267.	**Hunt JR, Zeng H. Iron absorption by heterozygous carriers of the HFE C282Y mutation associated with hemochromatosis. *Am J Clin Nutr* 2004;80:924-31.**	Fewer than 100 participants.
268.	**Husing-Kabar A, Meister T, Kohler M, Domschke W, Kabar I, Wilms C*, et al.* Is de novo hepatocellular carcinoma after transjugular intrahepatic portosystemic shunt increased? *United European Gastroenterology Journal* 2018;6:413-21.**	No definition of "haemochromatosis" provided. No HFE genotype reported.
269.	**Hutchinson C, Bomford A, Geissler CA. The iron-chelating potential of silybin in patients with hereditary haemochromatosis. *Eur J Clin Nutr* 2010;64:1239-41.**	Fewer than 100 participants.
270.	**Iancu TC, Deugnier Y, Halliday JW, Powell LW, Brissot P. Ultrastructural sequences during liver iron overload in genetic hemochromatosis. *Journal of Hepatology* 1997;27:628-38.**	Fewer than 100 participants.
271.	**Iqbal S, Ruknuddin A. Liver cirrhosis in North-West Frontier Province of Pakistan. *Journal of the College of Physicians and Surgeons Pakistan* 2002;12:289-91.**	No information on HFE genotype or definition of "primary haemochromatosis".
272.	**Ishizu Y, Katano Y, Honda T, Hayashi K, Ishigami M, Itoh A*, et al.* Clinical impact of HFE mutations in Japanese patients with chronic hepatitis C. *J Gastroenterol Hepatol* 2012;27:1112-6.**	Ineligible starting condition: viral.
273.	**Ismail AA, Ismail A, Ismail Y. Diagnosis of hereditary haemochromatosis. *Annals of Clinical Biochemistry* 2019;**	Ineligible publication type: Letter.
274.	**Jablonska J, Cielecka-Kuszyk J, Mikula T, Kozlowska J, Wiercinska-Drapalo A. Hepatopathy of unknown etiology - is liver biopsy a good tool in differential diagnosis? *Arch* 2019;15:1462-7.**	Fewer than 100 participants.
275.	**Jacobs EM, Hendriks JC, Marx JJ, van Deursen CT, Kreeftenberg HG, de Vries RA*, et al.* Morbidity and mortality in first-degree relatives of C282Y homozygous probands with clinically detected haemochromatosis compared with the general population: the HEmochromatosis FAmily Study (HEFAS). *Neth J Med* 2007;65:425-33.**	Ineligible population: HH was symptomatic and treated.

276.	**Jacobs EM, Meulendijks CF, Elving L, van der Wilt GJ, Swinkels DW. Impact of the introduction of a guideline on the targeted detection of hereditary haemochromatosis. *Neth J Med* 2005;63:205-14.**	Fewer than 100 participants.
277.	**Jalil S, Grady JJ, Lee C, Anderson KE. Associations among behavior-related susceptibility factors in porphyria cutanea tarda. *Clin Gastroenterol Hepatol* 2010;8:297-302, .e1.**	Ineligible starting condition: PCT.
278.	**Jezequel P, Bargain M, Lellouche F, Geffroy F, Dorval I. Allele frequencies of hereditary hemochromatosis gene mutations in a local population of west Brittany. *Hum Genet* 1998;102:332-3.**	No associations of genotype and outcomes reported.
279.	**Jia X, Yang Y, Chen Y, Cheng Z, Du Y, Xia Z*, et al.* Multivariate analysis of genome-wide data to identify potential pleiotropic genes for five major psychiatric disorders using MetaCCA. *Journal of Affective Disorders* 2019;242:234-43.**	Ineligible starting conditions.
280.	**Jin F, Qu LS, Shen XZ. Association between C282Y and H63D mutations of the HFE gene with hepatocellular carcinoma in European populations: a meta-analysis. *J Exp Clin Cancer Res*. 2010;29(1):18. Published 2010 Mar 2. doi:10.1186/1756-9966-29-18**	More recent systematic review
281.	**Jones NR, Ashmore JH, Lee SY, Richie JP, Lazarus P, Muscat JE. Association Studies of HFE C282Y and H63D Variants with Oral Cancer Risk and Iron Homeostasis Among Whites and Blacks. *Cancers (Basel)* 2015;7:2386-96.**	Ineligible starting condition: oral cancer.
282.	**Jouanolle AM, Fergelot P, Raoul ML, Gandon G, Roussey M, Deugnier Y*, et al.* Prevalence of the C282Y mutation in Brittany: penetrance of genetic hemochromatosis? *Ann Genet* 1998;41:195-8.**	Ineligible population: 100% <18 years of age.
283.	**Julian-Serrano S, Yu K, Yuan F, Wheeler W, Karimi P, Amundadottir L*, et al.* A Pathway Analysis of Hereditary Hemochromatosis-related Genes and Pancreatic Ductal Adenocarcinoma Risk (FS11-05-19). *Curr* 2019;3.**	Ineligible publication type: Abstract.
284.	**Juzėnas S, Kupčinskas J, Valantienė I, et al. Association of HFE gene C282Y and H63D mutations with liver cirrhosis in the Lithuanian population. *Medicina (Kaunas)*. 2016;52(5):269-275. doi:10.1016/j.medici.2016.09.004**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)
285.	**Kallianpur AR, Hall LD, Yadav M, Christman BW, Dittus RS, Haines JL*, et al.* Increased prevalence of the HFE C282Y hemochromatosis allele in women with breast cancer. *Cancer Epidemiol Biomarkers Prev* 2004;13:205-12.**	Ineligible starting condition: breast cancer or hematological cancer.
286.	**Kaltwasser JP, Werner E, Schalk K, Hansen C, Gottschalk R, Seidl C. Clinical trial on the effect of regular tea drinking on iron accumulation in genetic haemochromatosis. *Gut* 1998;43:699-704.**	Fewer than 100 participants.
287.	**Kamble RT, Selby GB, Mims M, Kharfan-Dabaja MA, Ozer H, George JN. Iron overload manifesting as apparent exacerbation of hepatic graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2006;12:506-10.**	Fewer than 100 participants.

288.	**Kaur G, Rapthap CC, Xavier M, Saxena R, Choudhary VP, Reuben SK*, et al.* Distribution of C282Y and H63D mutations in the HFE gene in healthy Asian Indians and patients with thalassaemia major. *Natl Med J India* 2003;16:309-10.**	Ineligible starting condition: thalassaemia. Ineligible outcomes.
289.	**Kauwe JS, Bertelsen S, Mayo K, et al. Suggestive synergy between genetic variants in TF and HFE as risk factors for Alzheimer's disease. *Am J Med Genet B Neuropsychiatr Genet*. 2010;153B(4):955-959. doi:10.1002/ajmg.b.31053**	Ineligible clinical factor (Alzheimer's disease)
290.	**Kelleher T, Ryan E, Barrett S, O'Keane C, Crowe J. DMT1 genetic variability is not responsible for phenotype variability in hereditary hemochromatosis. *Blood Cells Mol Dis* 2004;33:35-9.**	Ineligible outcomes.
291.	**Ko C, Siddaiah N, Berger J, Gish R, Brandhagen D, Sterling RK*, et al.* Prevalence of hepatic iron overload and association with hepatocellular cancer in end-stage liver disease: Results from the National Hemochromatosis Transplant Registry. *Liver International* 2007;27:1394-401.**	Ineligible population. Ineligible outcomes. HFE mutation status in the study subjects was unknown.
292.	**Kohan A, Niborski R, Daruich J, Rey J, Bastos F, Amerise G*, et al.* Erythrocytapheresis with recombinant human erythropoietin in hereditary hemochromatosis therapy: A new alternative. *Vox Sanguinis* 2000;79:40-5.**	Fewer than 100 participants.
293.	**Koller DL, Imel EA, Lai D, Padgett LR, Acton D, Gray A*, et al.* Genome-wide association study of serum iron phenotypes in premenopausal women of European descent. *Blood Cells, Molecules, and Diseases* 2016;57:50-3.**	Ineligible population.
294.	**Kom GD, Schwedhelm E, Nielsen P, Böger RH. Increased urinary excretion of 8-iso-prostaglandin F2alpha in patients with HFE-related hemochromatosis: a case-control study. *Free Radic Biol Med*. 2006;40(7):1194-1200. doi:10.1016/j.freeradbiomed.2005.11.004**	Fewer than 100 participants
295.	**Kong X, Xie L, Zhu H, Song L, Xing X, Yang W*, et al.* Genotypic and phenotypic spectra of hemojuvelin mutations in primary hemochromatosis patients: A systematic review. *Orphanet Journal of Rare Diseases* 2019;14.**	Ineligible mutations
296.	**Kowdley KV, Trainer TD, Saltzman JR, Pedrosa M, Krawitt EL, Knox TA*, et al.* Utility of hepatic iron index in american patients with hereditary hemochromatosis: A multicenter study. *Gastroenterology* 1997;113:1270-7.**	No HFE genotyping performed.
297.	**Kowdley KV, Brandhagen DJ, Gish RG, et al. Survival after liver transplantation in patients with hepatic iron overload: the national hemochromatosis transplant registry. *Gastroenterology*. 2005;129(2):494-503. doi:10.1016/j.gastro.2005.05.004**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)
298.	**Kratka K, Dostalikova-Cimburova M, Michalikova H, Stransky J, Vranova J, Horak J. High prevalence of HFE gene mutations in patients with porphyria cutanea tarda in the Czech Republic. *Br J Dermatol* 2008;159:585-90.**	Fewer than 100 participants. Ineligible starting condition: PCT.

299.	**Krayenbuehl PA, Hersberger M, Truninger K, Mullhaupt B, Maly FE, Bargetzi M*, et al.* Toll-like receptor 4 gene polymorphism modulates phenotypic expression in patients with hereditary hemochromatosis. *Eur J Gastroenterol Hepatol* 2010;22:835-41.**	Fewer than 100 participants.
300.	**Kroner PT, Mareth KF, Wijarnpreecha K, Palmer WC. Hereditary hemochromatosis is associated with increased use of joint replacement surgery: Results of a nationwide analysis. *Semin Arthritis Rheum* 2019;11:11.**	No information on HFE genotype and treatment in HH patients.
301.	**Kumar N, Rizek P, Sadikovic B, Adams PC, Jog M. Movement Disorders Associated With Hemochromatosis. *Can J Neurol Sci* 2016;43:801-8.**	Fewer than 100 participants.
302.	**Ladero JM, Ropero P, Ortega L, Taxonera C, Gonzalez FA, Lopez-Alonso G*, et al.* [HFE gene mutations, hepatic iron content, and histological severity in hepatitis C virus-induced chronic hepatitis]. *Rev Esp Enferm Dig* 2003;95:829-36.**	Ineligible starting condition: hepatitis C virus. Ineligible outcomes.
303.	**Lagergren K, Wahlin K, Mattsson F, Alderson D, Lagergren J. Haemochromatosis and gastrointestinal cancer. *Int J Cancer* 2016;139:1740-3.**	Ineligible outcomes. Diagnosis of HH unclear.
304.	**Lamoril J, Andant C, Gouya L, Malonova E, Grandchamp B, Martasek P*, et al.* Hemochromatosis (HFE) and transferrin receptor-1 (TFRC1) genes in sporadic porphyria cutanea tarda (sPCT). *Cell Mol Biol (Noisy-le-grand)* 2002;48:33-41.**	Ineligible starting condition: PCT. Ineligible outcomes.
305.	**Lanktree MB, Lanktree BB, Pare G, Waye JS, Sadikovic B, Crowther MA. Examining the clinical use of hemochromatosis genetic testing. *Can J Gastroenterol Hepatol* 2015;29:41-5.**	Fewer than 100 participants. Individual symptoms by genotype were not reported.
306.	**Laursen AH, Bjerrum OW, Friis-Hansen L, Hansen TO, Marott JL, Magnussen K. Causes of iron overload in blood donors - a clinical study. *Vox Sanguinis* 2018;113:110-9.**	Fewer than 100 participants.
307.	**Lawrence EM, Pooler BD, Pickhardt PJ. Opportunistic Screening for Hereditary Hemochromatosis With Unenhanced CT: Determination of an Optimal Liver Attenuation Threshold. *AJR Am J Roentgenol* 2018;211:1206-11.**	Ineligible outcomes.
308.	**Lawrence SP, Caminer SJ, Yavorski RT, Borosky BD, Rak KM, Merenich JA*, et al.* Correlation of liver density by magnetic resonance imaging and hepatic iron levels. A noninvasive means to exclude homozygous hemochromatosis. *J Clin Gastroenterol* 1996;23:113-7.**	Fewer than 100 participants.
309.	**Lebray P, Zylberberg H, Hue S, Poulet B, Carnot F, Martin S*, et al.* Influence of HFE gene polymorphism on the progression and treatment of chronic hepatitis C. *J Viral Hepat* 2004;11:175-82.**	Ineligible starting condition: chronic hepatitis C.

310.	**Le Gac G, Ka C, Gourlaouen I, et al. HFE-Related Hemochromatosis: The Haptoglobin 2-2 Type Has a Significant but Limited Influence on Phenotypic Expression of the Predominant p.C282Y Homozygous Genotype. *Adv Hematol*. 2009;2009:251701. doi:10.1155/2009/251701**	>10% treated for iron overload
311.	**Lee SY, Slagle-Webb B, Sheehan JM, et al. HFE polymorphisms affect survival of brain tumor patients. *J Neurooncol*. 2015;122(1):97-104. doi:10.1007/s11060-014-1681-1**	Ineligible clinical factor (brain tumour)
312.	**Legros L, Bardou-Jacquet E, Latournerie M, Guillygomarc'h A, Turlin B, Le Lan C*, et al.* Non-invasive assessment of liver fibrosis in C282Y homozygous HFE hemochromatosis. *Liver International* 2015;35:1731-8.**	Fewer than 100 participants.
313.	**Leitman SF, Browning JN, Yau YY, Mason G, Klein HG, Conry-Cantilena C*, et al.* Hemochromatosis subjects as allogeneic blood donors: a prospective study. *Transfusion* 2003;43:1538-44.**	Ineligible population: Treated. Ineligible outcomes.
314.	**Leone PE, Giménez P, Collantes JC, Paz-y-Miño C. Analysis of HFE gene mutations (C282Y, H63D, and S65C) in the Ecuadorian population. *Ann Hematol*. 2005;84(2):103-105. doi:10.1007/s00277-004-0966-4**	No eligible outcome
315.	**Levstik A, Stuart A, Adams PC. GNPAT variant (D519G) is not associated with an elevated serum ferritin or iron removed by phlebotomy in patients referred for C282Y-linked hemochromatosis. *Ann Hepatol*. 2016;15(6):907-910.**	No extractable data
316.	**Leyden J, Kelleher B, Ryan E, Barrett S, O'Keane JC, Crowe J. The celtic coincidence--the frequency and clinical characterisation of hereditary haemochromatosis in patients with coeliac disease. *Ir J Med Sci*. 2006;175(1):32-36. doi:10.1007/BF03168997**	Ineligible clinical factor (coeliac disease)
317.	**Li M, Wang L, Wang W, Qi XL, Tang ZY. Mutations in the HFE gene and sporadic amyotrophic lateral sclerosis risk: a meta-analysis of observational studies. *Braz J Med Biol Res* 2014;47:215-22.**	Ineligible starting condition: ALS.
318.	**Li SH, Zhao H, Ren YY, Liu YZ, Song G, Ding P*, et al.* The H63D mutation of the hemochromatosis gene is associated with sustained virological response in chronic hepatitis C patients treated with interferon-based therapy: a meta-analysis. *Tohoku J Exp Med* 2012;226:293-9.**	Ineligible outcomes: SVR in chronic hepatitis C patients.
319.	**Lian J, Xu L, Huang Y, et al. Meta-analyses of HFE variants in coronary heart disease. *Gene*. 2013;527(1):167-173. doi:10.1016/j.gene.2013.06.034**	Ineligible clinical factor (coronary heart disease)
320.	**Lim EM, Rossi E, De Boer WB, Reed WD, Jeffrey GP. Hepatic iron loading in patients with compound heterozygous HFE mutations. *Liver International* 2004;24:631-6.**	Ineligible outcomes. Fewer than 100 participants.
321.	**Lin TJ, Lin CL, Wang CS, Liu SO, Liao LY. Prevalence of HFE mutations and relation to serum iron status in patients with chronic hepatitis C and patients with nonalcoholic fatty liver disease in Taiwan. *World J Gastroenterol*. 2005;11(25):3905-3908. doi:10.3748/wjg.v11.i25.3905**	Data not reported for C282Y/C282Y, H63D/H63D, or C282Y/H63D genotypes

322.	**Lin M, Zhao L, Fan J, Lian XG, Ye JX, Wu L*, et al.* Association between HFE polymorphisms and susceptibility to Alzheimer's disease: a meta-analysis of 22 studies including 4,365 cases and 8,652 controls. *Mol Biol Rep* 2012;39:3089-95.**	Ineligible starting condition: AD.
323.	**Livesey KJ, Wimhurst VL, Carter K, Worwood M, Cadet E, Rochette J*, et al.* The 16189 variant of mitochondrial DNA occurs more frequently in C282Y homozygotes with haemochromatosis than those without iron loading. *Journal of Medical Genetics* 2004;41:6-10.**	Ineligible outcomes.
324.	**Lobbes H, Gladine C, Mazur A, Pereira B, Duale C, Cardot JM*, et al.* Effect of procyanidin on dietary iron absorption in hereditary hemochromatosis and in dysmetabolic iron overload syndrome: A crossover double-blind randomized controlled trial. *Clinical Nutrition* 2019;**	Fewer than 100 participants.
325.	**Looker AC, Johnson CL. Prevalence of elevated serum transferrin saturation in adults in the United States. *Ann Intern Med* 1998;129:940-5.**	Ineligible outcomes: biochemical markers not reported by HFE mutation.
326.	**Lorenz M, Kletzmayr J, Huber A, Horl WH, Sunder-Plassmann G, Fodinger M. Iron overload in kidney transplants: prospective analysis of biochemical and genetic markers. *Kidney Int* 2005;67:691-7.**	Fewer than 100 participants.
327.	**Lu X, Wang L, Lin X, Huang J, Charles Gu C, He M*, et al.* Genome-wide association study in Chinese identifies novel loci for blood pressure and hypertension. *Human Molecular Genetics* 2015;24:865-74.**	Ineligible starting condition: hypertension.
328.	**Lucijanic M, Pejsa V, Mitrovic Z, Stoos-Veic T, Livun A, Jaksic O*, et al.* Hemochromatosis gene mutations may affect the survival of patients with myelodysplastic syndrome. *Hematol* 2015;04:04.**	Fewer than 100 participants. Ineligible starting condition: myelodysplastic syndrome.
329.	**Lucijanic M, Pejsa V, Mitrovic Z, Stoos-Veic T, Livun A, Jaksic O*, et al.* Hemochromatosis gene mutations may affect the survival of patients with myelodysplastic syndrome. *Hematol* 2016;21:170-4.**	Fewer than 100 participants. Ineligible starting condition in cases: myelodysplastic syndrome.
330.	**Lucotte G. Frequency analysis and allele map in favor of the celtic origin of the C282Y mutation of hemochromatosis. *Blood Cells Mol Dis* 2001;27:549-56.**	Ineligible outcomes: no association of HFE genotype and biochemical or clinical features.
331.	**Lucotte G, Dieterlen F. A European allele map of the C282Y mutation of hemochromatosis: Celtic versus Viking origin of the mutation? *Blood Cells Mol Dis* 2003;31:262-7.**	Ineligible outcome: no association of HFE genotype and

		biochemical or clinical features.
332.	**Ludvigsson JF, Murray JA, Adams PC, Elmberg M. Does hemochromatosis predispose to celiac disease? A study of 29,096 celiac disease patients. *Scandinavian Journal of Gastroenterology* 2013;48:176-82.**	Ineligible starting condition: CD. No HFE genotype reported.
333.	**Lunn JV, Gallagher PM, Hegarty S, Kaliszer M, Crowe J, Murray P*, et al.* The role of hereditary hemochromatosis in aseptic loosening following primary total hip arthroplasty. *J Orthop Res* 2005;23:542-8.**	Ineligible starting condition.
334.	**Luszczyk M, Kaczorowska-Hac B, Milosz E, Adamkiewicz-Drozynska E, Ziemann E, Laskowski R*, et al.* Reduction of Skeletal Muscle Power in Adolescent Males Carrying H63D Mutation in the HFE Gene. *Biomed Res Int* 2017;2017:5313914.**	Fewer than 100 participants. Ineligible population: adolescents.
335.	**Lv YF, Chang X, Hua RX, et al. The risk of new-onset cancer associated with HFE C282Y and H63D mutations: evidence from 87,028 participants. *J Cell Mol Med*. 2016;20(7):1219-1233. doi:10.1111/jcmm.12764**	More comprehensive systematic review available
336.	**Lv T, Zhang W, Xu A, Li Y, Zhou D, Zhang B*, et al.* Non-HFE mutations in haemochromatosis in China: combination of heterozygous mutations involving HJV signal peptide variants. *Journal of Medical Genetics* 2018;55:650-60. h**	Fewer than 100 participants.
337.	**Maatta KM, Nikkari ST, Kunnas TA. Genetic variant coding for iron regulatory protein HFE contributes to hypertension, the TAMRISK study. *Medicine (Baltimore)* 2015;94:e464.**	No numerical outcomes data
338.	**Madani HA, Afify RA, Abd El-Aal AA, Salama N, Ramy N. Role of HFE gene mutations on developing iron overload in beta-thalassaemia carriers in Egypt. *East Mediterr Health J* 2011;17:546-51.**	Ineligible population.
339.	**Mah YH, Kao JH, Liu CJ, Chen CL, Chen PJ, Lai MY*, et al.* Prevalence and clinical implications of HFE gene mutations (C282Y and H63D) in patients with chronic hepatitis B and C in Taiwan. *Liver International* 2005;25:214-9.**	Ineligible population.
340.	**Maia ML, Pereira CS, Melo G, Pinheiro I, Exley MA, Porto G*, et al.* Invariant Natural Killer T Cells are Reduced in Hereditary Hemochromatosis Patients. *J Clin Immunol* 2015;35:68-74.**	Fewer than 100 participants.
341.	**Mainous AG, 3rd, King DE, Pearson WS, Garr DR. Is an elevated serum transferrin saturation associated with the development of diabetes? *J* 2002;51:933-6.**	Ineligible outcomes.
342.	**Mainous AG, 3rd, Knoll ME, Everett CJ, Matheson EM, Hulihan MM, Grant AM. Uric acid as a potential cue to screen for iron overload. *J Am Board Fam Med* 2011;24:415-21.**	Ineligible outcomes.
343.	**Malecki MT, Klupa T, Walus M, Czogala W, Greenlaw P, Sieradzki J. A search for association between hereditary hemochromatosis HFE gene mutations and type 2 diabetes mellitus in a Polish population. *Med Sci Monit* 2003;9:BR91-5.**	No numerical outcome data.

344.	**Malton K, Turnock D. A short report: reflective testing in the diagnosis of hereditary haemochromatosis: results of a short retrospective study. *Annals of Clinical Biochemistry* 2019;56:408-10.**	Fewer than 100 participants.
345.	**Mamta P. Sumi, Sameer Ahmad Guru, Samantak Sahu, Bazila Khan, Girish Mp, Alpana Saxena, "Role of HFE gene in coronary artery disease" – A study from India, Clinical Epidemiology and Global Health, Volume 8, Issue 2, 2020, Pages 469-472,**	Ineligible clinical characteristic
346.	**Manet G, Bardou-Jacquet E, Perrin M, Morcet J, Sinteff JP, Laine F*, et al.* The iron reabsorption index: a new phenotypic and pathophysiological descriptor in HFE hemochromatosis. *Eur J Gastroenterol Hepatol* 2013;25:1321-9.**	Ineligible population: treated.
347.	**Marginean EC, Bennick M, Cyczk J, Robert ME, Jain D. Gastric siderosis: patterns and significance. *Am J Surg Pathol* 2006;30:514-20.**	Ineligible outcomes.
348.	**Mariani S, Ventriglia M, Simonelli I, Bucossi S, Siotto M, Donno S*, et al.* Association between sex, systemic iron variation and probability of Parkinson's disease. *Int J Neurosci* 2016;126:354-60.**	Ineligible outcomes.
349.	**Martinelli AL, Filho AB, Franco RF, Tavella MH, Ramalho LN, Zucoloto S*, et al.* Liver iron deposits in hepatitis B patients: association with severity of liver disease but not with hemochromatosis gene mutations. *J Gastroenterol Hepatol* 2004;19:1036-41.**	Ineligible outcomes.
350.	**Martinelli AL, Zago MA, Roselino AM, Filho AB, Villanova MG, Secaf M*, et al.* Porphyria cutanea tarda in Brazilian patients: association with hemochromatosis C282Y mutation and hepatitis C virus infection. *American Journal of Gastroenterology* 2000;95:3516-21.**	Ineligible population.
351.	**Martinelli ALC, Filho R, Cruz S, Franco R, Tavella M, Secaf M*, et al.* Hereditary hemochromatosis in a Brazilian university hospital in Sao Paulo State (1990-2000). *Genetics and Molecular Research* 2005;4:31-8.**	Fewer than 100 participants.
352.	**Martinelli N, Garcia-Heredia A, Roca H, Aranda N, Arija V, Mackness B*, et al.* Paraoxonase-1 status in patients with hereditary hemochromatosis. *J Lipid Res* 2013;54:1484-92.**	Ineligible population.
353.	**Mast AE, Lee TH, Schlumpf KS, Wright DJ, Johnson B, Carrick DM*, et al.* The impact of HFE mutations on haemoglobin and iron status in individuals experiencing repeated iron loss through blood donation. *Br J Haematol* 2012;156:388-401.**	Ineligible outcomes.
354.	**McCrossin I. Porphyria cutanea tarda in south-east New South Wales. *Australas J Dermatol* 2002;43:285-8.**	Fewer than 100 participants.
355.	**McCullen MA, Fletcher LM, Dimeski G, Pink A, Powell LW, Crawford DH*, et al.* Patient-focused outcomes following detection in a hospital-based screening programme for C282Y haemochromatosis. *Intern Med J* 2008;38:651-6.**	Ineligible population: treated.

356.	**McCune CA, Al-Jader LN, May A, Hayes SL, Jackson HA, Worwood M. Hereditary haemochromatosis: only 1% of adult HFEC282Y homozygotes in South Wales have a clinical diagnosis of iron overload. *Hum Genet* 2002;111:538-43.**	Ineligible population: treated.
357.	**McLaren GD, Gordeuk VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. *Hematology Am Soc Hematol Educ Program*. 2009;195-206. doi:10.1182/asheducation-2009.1.195**	Summary of study
358.	**McLaren CE, Barton JC, Eckfeldt JH, McLaren GD, Acton RT, Adams PC*, et al.* Heritability of serum iron measures in the hemochromatosis and iron overload screening (HEIRS) family study. *American Journal of Hematology* 2010;85:101-5.**	No numerical outcome data.
359.	**McLaren CE, Chen WP, Bertalli NA, Delatycki MB, Giles GG, English DR*, et al.* Bivariate mixture models for the joint distribution of repeated serum ferritin and transferrin saturation measured 12 years apart in a cohort of healthy middle-aged Australians. *PLoS ONE* 2019;14.**	No numerical outcome data.
360.	**McLaren CE, Emond MJ, Subramaniam VN, Phatak PD, Barton JC, Adams PC*, et al.* Exome sequencing in HFE C282Y homozygous men with extreme phenotypes identifies a GNPAT variant associated with severe iron overload. *Hepatology* 2015;62:429-39.**	Fewer than 100 participants.
361.	**McLaren CE, Li KT, McLaren GD, Gordeuk VR, Snively BM, Reboussin DM*, et al.* Mixture models of serum iron measures in population screening for hemochromatosis and iron overload. *Translational Research* 2006;148:196-206.**	No numerical outcome data.
362.	**McLaren GD, Gordeuk VR. Hereditary hemochromatosis: insights from the Hemochromatosis and Iron Overload Screening (HEIRS) Study. *Hematology / the Education Program of the American Society of Hematology* 2009;American Society of Hematology. Education Program.:195-206.**	No numerical outcome data.
363.	**McNamee AP, Sabapathy S, Singh I, Horobin J, Guerrero J, Simmonds MJ. Acute Free-Iron Exposure Does Not Explain the Impaired Haemorheology Associated with Haemochromatosis. *PLoS ONE* 2016;11:e0146448.**	Fewer than 100 participants.
364.	**McPhail MJW, Khorsandi SE, Abbott L, Al-Kadhimi G, Kane P, Karani J*, et al.* Modern Outcomes Following Treatment of Hepatocellular Carcinoma in Hereditary Hemochromatosis: A Matched Cohort Study. *American Journal of Clinical Oncology: Cancer Clinical Trials* 2019;42:918-23.**	Ineligible outcomes.
365.	**Mehrany K, Drage LA, Brandhagen DJ, Pittelkow MR. Association of porphyria cutanea tarda with hereditary hemochromatosis. *J Am Acad Dermatol* 2004;51:205-11.**	Fewer than 100 participants.
366.	**Meidtner K, Podmore C, Kroger J, van der Schouw YT, Bendinelli B, Agnoli C*, et al.* Interaction of Dietary and Genetic Factors Influencing Body Iron Status and Risk of Type 2 Diabetes Within the EPIC-InterAct Study. *Diabetes Care* 2018;41:277-85.**	No numerical outcome data.

367.	**Meier P, Schuff-Werner P, Steiner M. Hemochromatosis gene HFE Cys282Tyr mutation analysis in a cohort of Northeast German hospitalized patients supports assumption of a North to South allele frequency gradient throughout Germany. *Clin Lab* 2005;51:539-43.**	No numerical outcome data.
368.	**Meiser B, Dunn S, Dixon J, Powell LW. Psychological adjustment and knowledge about hereditary hemochromatosis in a clinic-based sample: a prospective study. *J Genet Couns* 2005;14:453-63.**	No numerical outcome data.
369.	**Mendez M, Rossetti MV, Del CBAM, Parera VE. The role of inherited and acquired factors in the development of porphyria cutanea tarda in the Argentinean population. *J Am Acad Dermatol* 2005;52:417-24.**	Ineligible outcomes.
370.	**Menghini M, Prunte C, Krayenbuehl PA, Nowak A. Assessment of drusen and other retinal degenerative changes in patients with hereditary hemochromatosis. *Retina* 2018;38:594-9.**	No numerical outcome data.
371.	**Merono T, Brites F, Dauteuille C, Lhomme M, Menafra M, Arteaga A*, et al.* Metabolic alterations, HFE gene mutations and atherogenic lipoprotein modifications in patients with primary iron overload. *Clin Sci (Colch)* 2015;128:609-18.**	Fewer than 100 participants.
372.	**Mikhailova SV, Babenko VN, Ivanoshchuk DE, Gubina MA, Maksimov VN, Solovjova IG*, et al.* Haplotype analysis of the HFE gene among populations of Northern Eurasia, in patients with metabolic disorders or stomach cancer, and in long-lived people. *BMC Genetics* 2016;17.**	No numerical outcomes data
373.	**Milet J, Le Gac G, Scotet V, Gourlaouen I, Theze C, Mosser J*, et al.* A common SNP near BMP2 is associated with severity of the iron burden in HFE p.C282Y homozygous patients: a follow-up study. *Blood Cells Mol Dis* 2010;44:34-7.**	Ineligible population: treated.
374.	**Milman N, Pedersen P, a Steig T, Byg KE, Graudal N, Fenger K. Clinically overt hereditary hemochromatosis in Denmark 1948-1985: epidemiology, factors of significance for long-term survival, and causes of death in 179 patients. *Annals of Hematology* 2001;80:737-44.**	Ineligible population.
375.	**Milman N, Pedersen P, Ovesen L, Melsen GV, Fenger K. Frequency of the C282Y and H63D mutations of the hemochromatosis gene (HFE) in 2501 ethnic Danes. *Annals of Hematology* 2004;83:654-7.**	Ineligible outcomes.
376.	**Milman N, Pedersen P, Steig TA, Melsen GV. Frequencies of the hereditary hemochromatosis allele in different populations. Comparison of previous phenotypic methods and novel genotypic methods. *International Journal of Hematology* 2003;77:48-54.**	No numerical outcome data.
377.	**Milman N, Steig TA, Koefoed P, Pedersen P, Fenger K, Nielsen FC. Frequency of the hemochromatosis HFE mutations C282Y, H63D, and S65C in blood donors in the Faroe Islands. *Annals of Hematology* 2005;84:146-9.**	Ineligible outcomes.
378.	**Moen IW, Bergholdt HKM, Mandrup-Poulsen T, Nordestgaard BG, Ellervik C. Increased Plasma Ferritin Concentration and Low-Grade Inflammation-A Mendelian Randomization Study. *Clin Chem*. 2018;64(2):374-385. doi:10.1373/clinchem.2017.276055**	Summary of included studies
379.	**Moirand R, Adams PC, Bicheler V, Brissot P, Deugnier Y. Clinical features of genetic hemochromatosis in women compared with men. *Ann Intern Med* 1997;127:105-10.**	Ineligible population.

380.	**Moller DV, Pecini R, Gustafsson F, Hassager C, Hedley P, Jespersgaard C*, et al.* Hereditary Hemochromatosis (HFE) genotypes in heart failure: Relation to etiology and prognosis. *BMC Medical Genetics* 2010;11.**	No numerical outcomes data
381.	**Molzer G, Finsterer J, Krugluger W, Stanek G, Stollberger C. Possible causes of symptoms in suspected coronary heart disease but normal angiograms. *Clin Cardiol* 2001;24:307-12.**	Fewer than 100 participants.
382.	**Montgomery KD, Williams JR, Sculco TP, DiCarlo E. Clinical and pathologic findings in hemochromatosis hip arthropathy. *Clin Orthop* 1998:179-87.**	Fewer than 100 participants.
383.	**Moodie SJ, Ang L, Stenner JM, et al. Testing for haemochromatosis in a liver clinic population: relationship between ethnic origin, HFE gene mutations, liver histology and serum iron markers. *Eur J Gastroenterol Hepatol*. 2002;14(3):223-229. doi:10.1097/00042737-200203000-00004**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)
384.	**Moretti D, van Doorn GM, Swinkels DW, Melse-Boonstra A. Relevance of dietary iron intake and bioavailability in the management of HFE hemochromatosis: a systematic review. *Am J Clin Nutr* 2013;98:468-79.**	Ineligible outcomes.
385.	**Morgan TM, Xiao L, Lyons P, Kassebaum B, Krumholz HM, Spertus JA. Investigation of 89 candidate gene variants for effects on all-cause mortality following acute coronary syndrome. *Bmc Medical Genetics* 2008;9. https://doi.org/10.1186/1471-2350-9-66**	No numerical outcome data.
386.	**Moris W, Verhaegh P, Jonkers D, Deursen CV, Koek G. Hyperferritinemia in Nonalcoholic Fatty Liver Disease: Iron Accumulation or Inflammation? *Seminars in Liver Disease* 2019;39:476-82.**	No numerical outcome data.
387.	**Morrison ED, Brandhagen DJ, Phatak PD, Barton JC, Krawitt EL, El-Serag HB*, et al.* Serum ferritin level predicts advanced hepatic fibrosis among U.S. patients with phenotypic hemochromatosis. *Ann Intern Med* 2003;138:627-33.**	No numerical outcome data.
388.	**Mousavi SA, Mahmood F, Aandahl A, Knutsen TR, Llohn AH. Relationship of Baseline Hemoglobin Level with Serum Ferritin, Postphlebotomy Hemoglobin Changes, and Phlebotomy Requirements among HFE C282Y Homozygotes. *Biomed Res Int* 2015;2015:241784.**	Ineligible population: treated.
389.	**Muncunill J, Vaquer P, Galmes A, Obrador A, Parera M, Bargay J*, et al.* In hereditary hemochromatosis, red cell apheresis removes excess iron twice as fast as manual whole blood phlebotomy. *J Clin Apheresis* 2002;17:88-92.**	Fewer than 100 participants.
390.	**Murtagh LJ, Whiley M, Wilson S, Tran H, Bassett ML. Unsaturated iron binding capacity and transferrin saturation are equally reliable in detection of HFE hemochromatosis. *American Journal of Gastroenterology* 2002;97:2093-9.**	No numerical outcome data.
391.	**Nahon P, Sutton A, Rufat P, Ziol M, Thabut G, Schischmanoff PO*, et al.* Liver iron, HFE gene mutations, and hepatocellular carcinoma occurrence in patients with cirrhosis. *Gastroenterology* 2008;134:102-10.**	Ineligible population.

392.	**Nct. Erythrocyte Apheresis Versus Phlebotomy in Hemochromatosis. *https://clinicaltrialsgov/show/NCT00509652* 2007.**	Grey Literature
393.	**Nct. Clinical Management of Hereditary Hemochromatosis: phlebotomy vs. Erythrocytoapheresis. *https://clinicaltrialsgov/show/NCT00440986* 2007.**	Grey Literature
394.	**Nct. Erythrocytapheresis Versus Phlebotomy as Maintenance Therapy in Hereditary Hemochromatosis (HH) Patients. *https://clinicaltrialsgov/show/NCT01398644* 2011.**	Grey Literature
395.	**Nct. Treatment of Iron Overload With Deferasirox (Exjade) in Hereditary Hemochromatosis and Myelodysplastic Syndrome. *https://clinicaltrialsgov/show/NCT01892644* 2013.**	Grey Literature
396.	**Nct. A Two-year Study to Evaluate the Efficacy and Safety of Deferasirox Film-coated Tablet Versus Phlebotomy in Patients With Hereditary Hemochromatosis. *https://clinicaltrialsgov/show/NCT03203850* 2017.**	Grey Literature
397.	**Nct. A Study of LJPC-401 for the Treatment of Iron Overload in Adult Patients With Hereditary Hemochromatosis. *https://clinicaltrialsgov/show/NCT03395704* 2018.**	Grey Literature
398.	**Nct. Inhibiting Dietary Iron Absorption in Subjects With Hereditary Hemochromatosis by a Natural Polyphenol Supplement. *https://clinicaltrialsgov/show/NCT03990181* 2019.**	Grey Literature
399.	**Nearman ZP, Szpurka H, Serio B, Warshawksy I, Theil K, Lichtin A*, et al.* Hemochromatosis-associated gene mutations in patients with myelodysplastic syndromes with refractory anemia with ringed sideroblasts. *American Journal of Hematology* 2007;82:1076-9.**	Ineligible outcomes
400.	**Nell-Duxneuner V, Axmann R, Husar-Memmer E, Dallos T, Datz C, Stadlmayr A*, et al.* VCAM-1 serum levels are associated with arthropathy in hereditary haemochromatosis. *Ann Rheum Dis* 2013;72:2006-10.**	Ineligible population: treated.
401.	**Nelson RL, Persky V, Davis F, Becker E. Risk of disease in siblings of patients with hereditary hemochromatosis. *Digestion* 2001;64:120-4.**	Ineligible population.
402.	**Nelson RL, Persky V, Davis F, Becker E. Is hereditary hemochromatosis a balanced polymorphism: an analysis of family size among hemochromatosis heterozygotes. *Hepatogastroenterology* 2001;48:523-6.**	Ineligible outcomes.
403.	**Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107-19.**	Ineligible population.
404.	**Nieves-Santiago P, Cancel D, Canales D, Toro DH. Presence of hemochromatosis-associated mutations in Hispanic patients with iron overload. *P R Health Sci J* 2011;30:135-8.**	Fewer than 100 participants.
405.	**Njajou OT, Hollander M, Koudstaal PJ, Hofman A, Witteman JC, Breteler MM*, et al.* Mutations in the hemochromatosis gene (HFE) and stroke. *Stroke* 2002;33:2363-6.**	Ineligible outcomes.
406.	**Njajou OT, Houwing-Duistermaat J, Osborne RH, et al. A population-based study of the effect of the HFE C282Y and H63D mutations on iron metabolism. *European Journal of Human Genetics* 2003;11(3):225-31.**	C282Y/C282Y, H63D/H63D,

		C282Y/H63D not reported for controls
407.	**Nkontchou G, Tran Van Nhieu J, Ziol M, Tengher I, Mahmoudi A, Roulot D*, et al.* Peripheral intrahepatic cholangiocarcinoma occurring in patients without cirrhosis or chronic bile duct diseases: epidemiology and histopathology of distant nontumoral liver in 57 White patients. *Eur J Gastroenterol Hepatol* 2013;25:94-8.**	Fewer than 100 participants.
408.	**Nowak A, Giger RS, Krayenbuehl PA. Higher age at diagnosis of hemochromatosis is the strongest predictor of the occurrence of hepatocellular carcinoma in the Swiss hemochromatosis cohort: A prospective longitudinal observational study. *Medicine (Baltimore)*. 2018;97(42):e12886. doi:10.1097/MD.0000000000012886**	>10% treated for iron overload
409.	**O'Glasser AY, Scott DL, Corless CL, Zaman A, Sasaki A, Gopal DV*, et al.* Hepatic and cardiac iron overload among patients with end-stage liver disease referred for liver transplantation. *Clin Transplant* 2010;24:643-51.**	No numerical outcome data.
410.	**Oliveira VC, Caxito FA, Gomes KB, Castro AM, Pardini VC, Ferreira ACS. Frequency of the S65C mutation in the hemochromatosis gene in Brazil. *Genetics and Molecular Research* 2009;8:794-8.**	Ineligible outcomes.
411.	**Olsson KS, Konar J, Dufva IH, Ricksten A, Raha-Chowdhury R. Was the C282Y mutation an Irish Gaelic mutation that the Vikings helped disseminate? HLA haplotype observations of hemochromatosis from the west coast of Sweden. *European Journal of Haematology* 2011;86:75-82.**	Ineligible outcomes.
412.	**Olsson KS, Ritter B, Raha-Chowdhury R. HLA-A3-B14 and the origin of the haemochromatosis C282Y mutation: founder effects and recombination events during 12 generations in a Scandinavian family with major iron overload. *European Journal of Haematology* 2010;84:145-53.**	Ineligible outcomes. Fewer than 100 participants.
413.	**Olsson KS, Vaisanen M, Konar J, Bruce A. The effect of withdrawal of food iron fortification in Sweden as studied with phlebotomy in subjects with genetic hemochromatosis. *Eur J Clin Nutr* 1997;51:782-6.**	Fewer than 100 participants.
414.	**Olynyk JK, Hagan SE, Cullen DJ, Beilby J, Whittall DE. Evolution of untreated hereditary hemochromatosis in the Busselton population: a 17-year study. *Mayo Clin Proc* 2004;79:309-13.**	Fewer than 100 participants.
415.	**Olynyk JK, Knuiman MW, Divitini ML, Bartholomew HC, Cullen DJ, Powell LW. Effects of HFE gene mutations and alcohol on iron status, liver biochemistry and morbidity. *J Gastroenterol Hepatol* 2005;20:1435-41.**	Ineligible outcomes.
416.	**Ong SY, Dolling L, Dixon JL, Nicoll AJ, Gurrin LC, Wolthuizen M*, et al.* Should HFE p.C282Y homozygotes with moderately elevated serum ferritin be treated? A randomised controlled trial comparing iron reduction with sham treatment (Mi-iron). *BMJ Open* 2015;5:e008938.**	No numerical outcome data.
417.	**O'Reilly FM, Darby C, Fogarty J, Tormey W, Kay EW, Leader M*, et al.* Screening of patients with iron overload to identify hemochromatosis and porphyria cutanea tarda. *Arch Dermatol* 1997;133:1098-101.**	No numerical outcome data.
418.	**Osborne NJ, Gurrin LC, Allen KJ, Constantine CC, Delatycki MB, McLaren CE*, et al.* HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. *Hepatology* 2010;51:1311-8.**	Ineligible outcomes

419.	**Osterreicher CH, Datz C, Stickel F, Hellerbrand C, Penz M, Hofer H*, et al.* TGF-beta1 codon 25 gene polymorphism is associated with cirrhosis in patients with hereditary hemochromatosis. *Cytokine* 2005;31:142-8.**	Ineligible outcomes.
420.	**Pacal L, Husa P, Znojil V, Kankova K. HFE C282Y gene variant is a risk factor for the progression to decompensated liver disease in chronic viral hepatitis C subjects in the Czech population. *Hepatology Research* 2007;37:740-7.**	Ineligible population.
421.	**Padula MC, Martelli G, Larocca M, Rossano R, Olivieri A. A novel homozygous stop-codon mutation in human HFE responsible for nonsense-mediated mRNA decay. *Blood Cells Mol Dis* 2014;53:138-43.**	Fewer than 100 participants.
422.	**Pardo Silva MC, Njajou OT, Alizadeh BZ, Hofman A, Witteman JC, van Duijn CM*, et al.* HFE gene mutations increase the risk of coronary heart disease in women. *Eur J Epidemiol* 2010;25:643-9.**	No numerical outcome data.
423.	**Park SK, O'Neill MS, Wright RO, Hu H, Vokonas PS, Sparrow D*, et al.* HFE genotype, particulate air pollution, and heart rate variability: a gene-environment interaction. *Circulation* 2006;114:2798-805.**	No numerical outcome data.
424.	**Parkash O, Akram M. Hereditary Hemochromatosis. *J Coll Physicians Surg Pak* 2015;25:644-7.**	Fewer than 100 participants.
425.	**Patch C, Roderick P, Rosenberg W. Comparison of genotypic and phenotypic strategies for population screening in hemochromatosis: assessment of anxiety, depression, and perception of health. *Genet Med* 2005;7:550-6.**	Ineligible outcome: psychological effects of screening.
426.	**Patch C, Roderick P, Rosenberg W. Factors affecting the uptake of screening: a randomised controlled non-inferiority trial comparing a genotypic and a phenotypic strategy for screening for haemochromatosis. *J Hepatol* 2005;43:149-55.**	Ineligible outcomes: predictors of uptake.
427.	**Patch C, Roderick P, Rosenberg WM. Psychological effects of genetic and biochemical population screenign for hemochromatosis. *Hepatology (baltimore, md)* 2004;40:576A.**	Ineligible publication type: Abstract only.
428.	**Pawlowski M, Latute F, Bardou-Jacquet E, Latournerie M, Zerrouki S, Bendavid C*, et al.* Portable hemoglobinometer is a reliable technology for the follow-up of venesections tolerance in hemochromatosis. *Clin Res Hepatol Gastroenterol* 2015;39:570-5.**	Ineligible outcomes.
429.	**Pedersen P, Melsen GV, Milman N. Frequencies of the haemochromatosis gene (HFE) variants C282Y, H63D and S65C in 6,020 ethnic Danish men. *Annals of Hematology* 2008;87:735-40.**	Ineligible outcomes.
430.	**Pedersen P, Milman N. Extrinsic factors modifying expressivity of the HFE variant C282Y, H63D, S65C phenotypes in 1,294 Danish men. *Annals of Hematology* 2009;88:957-65.**	Ineligible outcomes.
431.	**Pelucchi S, Galimberti S, Greni F, Rametta R, Mariani R, Pelloni I*, et al.* Proprotein convertase 7 rs236918 associated with liver fibrosis in Italian patients with HFE-related hemochromatosis. *J Gastroenterol Hepatol* 2016;31:1342-8.**	Ineligible outcomes.

432.	**Percy M, Somerville MJ, Hicks M, Garcia A, Colelli T, Wright E, *et al.* Risk factors for development of dementia in a unique six-year cohort study. I. An exploratory, pilot study of involvement of the E4 allele of apolipoprotein E, mutations of the hemochromatosis-HFE gene, type 2 diabetes, and stroke. *J Alzheimers Dis* 2014;38:907-22.**	Ineligible outcomes.
433.	**Pericole FV, Alves MA, Saad ST, Costa FF. Hemochromatosis (HFE) gene mutations in Brazilian chronic hemodialysis patients. *Braz J Med Biol Res* 2005;38:1321-4.**	Ineligible population: treated.
434.	**Perkins JD. Hemochromatosis and liver transplant survival. *Liver Transpl* 2006;12:322.**	Grey Literature
435.	**Petrick JL, Yang BY, Altekruse SF, Van Dyke AL, Koshiol J, Graubard BI, *et al.* Risk factors for intrahepatic and extrahepatic cholangiocarcinoma in the United States: A population-based study in SEER-Medicare. *Plos One* 2017;12. https://doi.org/10.1371/journal.pone.0186643**	No numerical outcome data.
436.	**Phatak P, Brissot P, Wurster M, Adams PC, Bonkovsky HL, Gross J, *et al.* A phase 1/2, dose-escalation trial of deferasirox for the treatment of iron overload in HFE-related hereditary hemochromatosis. *Hepatology* 2010;52:1671-779.**	Fewer than 100 participants.
437.	**Phatak PD, Barton JC. Phlebotomy-mobilized iron as a surrogate for liver iron content in hemochromatosis patients. *Hematol* 2003;8:429-32.**	Fewer than 100 participants.
438.	**Phatak PD, Ryan DH, Cappuccio J, Oakes D, Braggins C, Provenzano K, *et al.* Prevalence and penetrance of HFE mutations in 4865 unselected primary care patients. *Blood Cells Mol Dis* 2002;29:41-7.**	Fewer than 100 participants.
439.	**Phatak PD, Sham RL, Raubertas RF, Dunnigan K, O'Leary MT, Braggins C, *et al.* Prevalence of hereditary hemochromatosis in 16031 primary care patients. *Ann Intern Med* 1998;129:954-61.**	No numerical outcome data.
440.	**Pichler I, Del Greco MF, Gogele M, Lill CM, Bertram L, Do CB, *et al.* Serum iron levels and the risk of Parkinson disease: a Mendelian randomization study. *PLoS Med* 2013;10:e1001462.**	Ineligible outcomes.
441.	**Picot J, Bryant J, Cooper K, Clegg A, Roderick P, Rosenberg W, *et al.* Psychosocial aspects of DNA testing for hereditary hemochromatosis in at-risk individuals: a systematic review. *Genet Test Mol Biomarkers* 2009;13:7-14.**	Ineligible publication type: Review.
442.	**Pinheiro T, Fleming R, Goncalves A, Neres M, Alves LC, Silva JN, *et al.* Imaging iron in skin and liver: Non-invasive tools for hemochromatosis therapy. *Nuclear Instruments & Methods in Physics Research Section B-Beam Interactions with Materials and Atoms* 2009;267:2140-3. https://doi.org/10.1016/j.nimb.2009.03.064**	Fewer than 100 participants.
443.	**Pleass H, Garden OJ. Early diagnosis of hepatocellular carcinoma in haemochromatosis influences surgical management. *Scott Med J* 1998;43:114-5.**	Fewer than 100 participants.
444.	**Power MC, Weisskopf MG, Alexeeff SE, Wright RO, Coull BA, Spiro A, 3rd, *et al.* Modification by hemochromatosis gene polymorphisms of the association between traffic-related air pollution and cognition in older men: a cohort study. *Environ Health* 2013;12:16.**	Ineligible outcomes.
445.	**Praline J, Blasco H, Vourc'h P, Rat V, Gendrot C, Camu W, *et al.* Study of the HFE gene common polymorphisms in French patients with sporadic amyotrophic lateral sclerosis. *J Neurol Sci* 2012;317:58-61.**	Ineligible outcomes.

446.	**Pratiwi R, Fletcher LM, Pyper WR, Do KA, Crawford DHG, Powell LW*, et al.* Linkage disequilibrium analysis in Australian haemochromatosis patients indicates bipartite association with clinical expression. *Journal of Hepatology* 1999;31:39-46.**	Fewer than 100 participants.
447.	**Press RD, Eickelberg G, McDonald TJ, Halley J, Long T, Tafe LJ*, et al.* Highly accurate molecular genetic testing for HFE hereditary hemochromatosis: results from 10 years of blinded proficiency surveys by the College of American Pathologists. *Genetics in medicine* 2016;18:1206-13. https://doi.org/10.1038/gim.2016.34**	Ineligible outcomes.
448.	**Przygodzki RM, Goodman ZD, Rabin L, Centeno JA, Liu Y, Hubbs AE*, et al.* Hemochromatosis (HFE) gene sequence analysis of formalin-fixed, paraffin-embedded liver biopsy specimens. *Mol Diagn* 2001;6:227-32.**	Fewer than 100 participants.
449.	**Raffield LM, Louie T, Sofer T, Jain D, Ipp E, Taylor KD*, et al.* Genome-wide association study of iron traits and relation to diabetes in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL): Potential genomic intersection of iron and glucose regulation? *Human Molecular Genetics* 2017;26:1966-78.**	No numerical outcome data.
450.	**Rainero I, Rivoiro C, Rubino E, Milli V, Valfre W, De Martino P*, et al.* Prevalence of HFE (hemochromatosis) gene mutations in patients with cluster headache. *Headache* 2005;45:1219-23.**	Ineligible outcomes.
451.	**Rainero I, Rubino E, Rivoiro C, Valfre W, Binello E, Zampella E*, et al.* Haemochromatosis gene (HFE) polymorphisms and migraine: an association study. *Cephalalgia* 2007;27:9-13.**	Ineligible outcomes.
452.	**Rametta R, Dongiovanni P, Pelusi S, Francione P, Iuculano F, Borroni V*, et al.* Hepcidin resistance in dysmetabolic iron overload. *Liver International* 2016;36:1540-8.**	Fewer than 100 participants.
453.	**Rasmussen ML, Folsom AR, Catellier DJ, Tsai MY, Garg U, Eckfeldt JH. A prospective study of coronary heart disease and the hemochromatosis gene (HFE) C282Y mutation: the Atherosclerosis Risk in Communities (ARIC) study. *Atherosclerosis* 2001;154:739-46.**	No numerical outcomes data
454.	**Raszeja-Wyszomirska J, Kurzawski G, Zawada I, Suchy J, Lubinski J, Milkiewicz P. HFE gene mutations in patients with alcoholic liver disease. A prospective study from northwestern Poland. *Pol Arch Med Wewn* 2010;120:127-31.**	Ineligible outcomes.
455.	**Rauber MR, Pilger DA, Cecconello DK, Falcetta FS, Marcondes NA, Faulhaber GAM. Hepcidin is a useful biomarker to evaluate hyperferritinemia associated with metabolic syndrome. *An Acad Bras Cienc* 2019;91:e20180286.**	Fewer than 100 participants.
456.	**Remacha AF, Carrasco M, Sarda MP, Barcelo MJ, Blesa I, Baiget M. Screening for iron overload and HFE mutations in a university hospital. *Haematologica* 2000;85:873-4.**	Fewer than 100 participants.
457.	**Rhodes SL, Buchanan DD, Ahmed I, Taylor KD, Loriot MA, Sinsheimer JS*, et al.* Pooled analysis of iron-related genes in Parkinson's disease: association with transferrin. *Neurobiol Dis* 2014;62:172-8.**	Ineligible outcomes.
458.	**Richardson A, Prideaux A, Kiely P. Haemochromatosis: unexplained metacarpophalangeal or ankle arthropathy should prompt diagnostic tests: findings from two UK observational cohort studies. *Scand J Rheumatol* 2017;46:69-74.**	No numerical outcome data.

459.	**Richette P, Ottaviani S, Vicaut E, Bardin T. Musculoskeletal complications of hereditary hemochromatosis: a case-control study. *J Rheumatol* 2010;37:2145-50.**	Ineligible outcomes. No numerical outcome data.
460.	**Ristic S, Lovrecic L, Brajenovic-Milic B, Starcevic-Cizmarevic N, Jazbec SS, Sepcic J*, et al.* Mutations in the hemochromatosis gene (HFE) and multiple sclerosis. *Neurosci Lett* 2005;383:301-4.**	Ineligible outcomes.
461.	**Robertson DM. Hemochromatosis and ovarian cancer. *Womens Health (Lond Engl)* 2011;7:525-7.**	Ineligible outcomes.
462.	**Robinson JP, Johnson VL, Rogers PA, Houlston RS, Maher ER, Bishop DT*, et al.* Evidence for an association between compound heterozygosity for germ line mutations in the hemochromatosis (HFE) gene and increased risk of colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1460-3.**	Ineligible outcomes.
463.	**Robson KJ. The U. A simple genetic test identifies 90% of UK patients with haemochromatosis. The UK Haemochromatosis Con-sortium. Gut. 1997;41(6):841-844. doi:10.1136/gut.41.6.841**	Ineligible starting condition
464.	**Robson KJ, Lehmann DJ, Wimhurst VL, Livesey KJ, Combrinck M, Merryweather-Clarke AT*, et al.* Synergy between the C2 allele of transferrin and the C282Y allele of the haemochromatosis gene (HFE) as risk factors for developing Alzheimer's disease. *Journal of Medical Genetics* 2004;41:261-5.**	Ineligible outcomes.
465.	**Rodriguez AMF, Gascon LH, La Orden IG, Santos JP, Samper RG, Letosa RM*, et al.* C282Y hemochromatosis gene mutation and iron parameters in dialysis patients. *Clinical Nephrology* 2011;75:328-35.**	Ineligible population: treated.
466.	**Rodriguez LM, Giraldo MC, Velasquez LI, Alvarez CM, Garcia LF, Jimenez-Del-Rio M*, et al.* Ancestral association between HLA and HFE H63D and C282Y gene mutations from northwest Colombia. *Genet* 2015;38:8-13.**	Ineligible outcomes.
467.	**Rodriguez-Lopez R, Donoso M, Fernandez-Cavada M, Gonzalez LM, Margallo A, Corral C*, et al.* Diagnostic utility of HFE variants in Spanish patients: association with HLA alleles and role in susceptibility to acute lymphoblastic leukemia. *Gene* 2013;514:31-5.**	Ineligible population.
468.	**Roe MA, Heath AL, Oyston SL, Macrow C, Hoogewerff JA, Foxall R*, et al.* Iron absorption in male C282Y heterozygotes. *Am J Clin Nutr* 2005;81:814-21.**	Fewer than 100 participants.
469.	**Roe MA, Spinks C, Heath AL, Harvey LJ, Foxall R, Wimperis J*, et al.* Serum prohepcidin concentration: no association with iron absorption in healthy men; and no relationship with iron status in men carrying HFE mutations, hereditary haemochromatosis patients undergoing phlebotomy treatment, or pregnant women. *Br J Nutr* 2007;97:544-9.**	No numerical outcome data.
470.	**Roest M, van der Schouw YT, de Valk B, Marx JJ, Tempelman MJ, de Groot PG*, et al.* Heterozygosity for a hereditary hemochromatosis gene is associated with cardiovascular death in women. *Circulation* 1999;100:1268-73.**	No numerical outcome data.
471.	**Roest M, Van der Schouw YT, Voorbij HAM, Marx JJM, Grobbee DE. Hereditary hemochromatosis: A risk factor for cardiovascular disease. *Cardiovascular Reviews and Reports* 2001;22:656-7+92.**	Ineligible population: hereditary haemochromatosis carriers

472.	**Romanowski T, Sikorska K, Bielawski KP. UGT1A1 gene polymorphism as a potential factor inducing iron overload in the pathogenesis of type 1 hereditary hemochromatosis. *Hepatology Research* 2009;39:469-78.**	Fewer than 100 participants.
473.	**Rombout-Sestrienkova E, Koek GH, Neslo R, van Kraaij M, Menheere PP, Masclee A*, et al.* Course of iron parameters in HFE-hemochromatosis patients during initial treatment with erythrocytapheresis compared to phlebotomy. *J Clin Apheresis* 2016;31:564-70.**	Fewer than 100 participants.
474.	**Rombout-Sestrienkova E, Nieman FH, Essers BA, van Noord PA, Janssen MC, van Deursen CT*, et al.* Erythrocytapheresis versus phlebotomy in the initial treatment of HFE hemochromatosis patients: results from a randomized trial. *Transfusion* 2012;52:470-7.**	Fewer than 100 participants.
475.	**Rombout-Sestrienkova E, Noord PAHv, Reuser E, Heeremans J, Deursen CTBMv, Janssen M*, et al.* Therapeutic Erythrocytapheresis (TE) versus Phlebotomy (P) in the treatment of Hereditary Hemochromatosis (HH) patients: Preliminary results from an ongoing randomized clinical trial (NCT 00202436). *Transfusion and Apheresis Science* 2009;40:135-6.**	Fewer than 100 participants.
476.	**Rombout-Sestrienkova E, Winkens B, Essers BA, Nieman FH, Noord PA, Janssen MC*, et al.* Erythrocytapheresis versus phlebotomy in the maintenance treatment of HFE hemochromatosis patients: results from a randomized crossover trial. *Transfusion* 2016;56:261-70.**	Fewer than 100 participants
477.	**Rong Y, Bao W, Rong S, Fang M, Wang D, Yao P*, et al.* Hemochromatosis gene (HFE) polymorphisms and risk of type 2 diabetes mellitus: a meta-analysis. *Am J Epidemiol* 2012;176:461-72.**	No numerical outcome data.
478.	**Rozwadowska K, Danilowicz-Szymanowicz L, Fijalkowski M, Sikorska K, Galaska R, Kozlowski D*, et al.* Can two-dimensional speckle tracking echocardiography be useful for left ventricular assessment in the early stages of hereditary haemochromatosis? *Echocardiography* 2018;35:1772-81.**	Fewer than 100 participants.
479.	**Rozwadowska K, Raczak G, Sikorska K, Fijalkowski M, Kozlowski D, Danilowicz-Szymanowicz L. Influence of hereditary hemochromatosis on left ventricular wall thickness: does iron overload exacerbate cardiac hypertrophy? *Folia Morphol (Warsz)* 2019;05:05.**	Fewer than 100 participants.
480.	**Ryan E, O'Keane C, Crowe J. Hemochromatosis in Ireland and HFE. *Blood Cells Mol Dis* 1998;24:428-32.**	No numerical outcome data.
481.	**Sahinbegovic E, Dallos T, Aigner E, et al. Musculoskeletal disease burden of hereditary hemochromatosis. *Arthritis Rheum*. 2010;62(12):3792-3798**	>10% treated for iron overload
482.	**Sahinbegovic E, Dallos T, Aigner E, Axmann R, Engelbrecht M, Schoniger-Hekele M*, et al.* Hereditary hemochromatosis as a risk factor for joint replacement surgery. *Am J Med* 2010;123:659-62.**	Ineligible population: Treated. No HFE genotype reported for healthy subjects.

483.	**Salinas IP, Limon AM, Flores VR, Fernandez-Mosteirin N, Garcia-Erce JA. Predictive factors of response to erytrhocytapheresis in patients with biochemical iron overload with or without hereditary hemochromatosis type 1. *Medicina Clinica* 2014;142:187-91. https://doi.org/10.1016/j.medcli.2013.05.043**	Fewer than 100 participants.
484.	**Saliou P, Le Gac G, Mercier AY, et al. Evidence for the high importance of co-morbid factors in HFE C282Y/H63D patients cared by phlebotomies: results from an observational prospective study. *PLoS One*. 2013;8(12):e81128. Published 2013 Dec 5. doi:10.1371/journal.pone.0081128**	>10% treated for iron overload
485.	**Sanchez-Luna SA, Brown KE. Clinical burden of liver disease from hemochromatosis at an academic medical center. *Hepatol* 2017;1:453-9.**	Fewer than 100 participants. No information on HH treatment.
486.	**Sanchez-Pablo MA, Gonzalez-Garcia V, del Castillo-Rueda A. Study of total stimulated saliva flow and hyperpigmentation in the oral mucosa of patients diagnosed with hereditary hemochromatosis. Series of 25 cases. *Med Oral Patol Oral Cir Bucal* 2012;17:e45-9.**	Fewer than 100 participants.
487.	**Sangiuolo F, Puxeddu E, Pezzuto G, Cavalli F, Longo G, Comandini A*, et al.* HFE gene variants and iron-induced oxygen radical generation in idiopathic pulmonary fibrosis. *Eur Respir J* 2015;45:483-90.**	Ineligible starting condition: idiopathic pulmonary fibrosis.
488.	**Sangwaiya A, Manglam V, Busbridge M, Thursz M, Arnold J. Blunted increase in serum hepcidin as response to oral iron in HFE-hemochromatosis. *Eur J Gastroenterol Hepatol* 2011;23:721-4.**	Fewer than 100 participants.
489.	**Saracco GM, Evangelista A, Fagoonee S, Ciccone G, Bugianesi E, Caviglia GP*, et al.* Etiology of chronic liver diseases in the Northwest of Italy, 1998 through 2014. *World J Gastroenterol* 2016;22:8187-93.**	No HFE genotypes reported.
490.	**Sarigianni M, Liakos A, Vlachaki E, Paschos P, Athanasiadou E, Montori VM*, et al.* Accuracy of magnetic resonance imaging in diagnosis of liver iron overload: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015;13:55-63.e5.**	Ineligible outcomes.
491.	**Schiepers OJ, van Boxtel MP, de Groot RH, et al. Serum iron parameters, HFE C282Y genotype, and cognitive performance in older adults: results from the FACIT study. *J Gerontol A Biol Sci Med Sci*. 2010;65(12):1312-1321.**	Carriers, not C282Y/C282Y, H63D/H63D, or C282Y/H63D
492.	**Schiepers OJ, van Boxtel MP, de Groot RH, Jolles J, de Kort WL, Swinkels DW*, et al.* Serum iron parameters, HFE C282Y genotype, and cognitive performance in older adults: results from the FACIT study. *J Gerontol A Biol Sci Med Sci* 2010;65:1312-21.**	Ineligible genotype.
493.	**Schmitt B, Golub RM, Green R. Screening primary care patients for hereditary hemochromatosis with transferrin saturation and serum ferritin level: systematic review for the American College of Physicians. *Ann Intern Med* 2005;143:522-36.**	Ineligible population. Ineligible definition of HH.

494.	**Scotet V, Mérour MC, Mercier AY, et al. Hereditary hemochromatosis: effect of excessive alcohol consumption on disease expression in patients homozygous for the C282Y mutation. *Am J Epidemiol*. 2003;158(2):129-134**	>10% treated for iron overload
495.	**Scotet V, Le Gac G, Mérour MC, et al. Impact of HFE genetic testing on clinical presentation of hereditary hemochromatosis: new epidemiological data. *BMC Med Genet*. 2005;6:24.**	>10% treated for iron overload
496.	**Scott J. Symposium on 'The challenge of translating nutrition research into public health nutrition'. Session 2: Personalised nutrition. Genetic variation and disease risk: new advances. *Proc Nutr Soc* 2009;68:113-21.**	Ineligible publication type: symposium.
497.	**Sendi H, Mehrab-Mohseni M. HFE Gene Mutations in Cryptogenic Cirrhosis Patients. *Hepatitis Monthly* 2012;12:48-9.**	Ineligible publication type: letter.
498.	**Seravalle G, Piperno A, Mariani R, Pelloni I, Facchetti R, Dell'Oro R*, et al.* Alterations in sympathetic nerve traffic in genetic haemochromatosis before and after iron depletion therapy: a microneurographic study. *Eur Heart J* 2016;37:988-95.**	Fewer than 100 participants.
499.	**Settin A, El-Bendary M, Abo-Al-Kassem R, El Baz R. Molecular analysis of A1AT (S and Z) and HFE (C282Y and H63D) gene mutations in Egyptian cases with HCV liver cirrhosis. *J* 2006;15:131-5.**	Ineligible starting condition: viral C cirrhosis (HCV).
500.	**Severson TJ, Besur S, Bonkovsky HL. Genetic factors that affect nonalcoholic fatty liver disease: A systematic clinical review. *World J Gastroenterol*. 2016;22(29):6742-6756. doi:10.3748/wjg.v22.i29.6742**	More recent systematic review and meta-analysis
501.	**Shaheen NJ, Bacon BR, Grimm IS. Clinical characteristics of hereditary hemochromatosis patients who lack the C282Y mutation. *Hepatology* 1998;28:526-9.**	Fewer than 100 participants.
502.	**Sham RL, Ou CY, Cappuccio J, Braggins C, Dunnigan K, Phatak PD. Correlation between genotype and phenotype in hereditary hemochromatosis: analysis of 61 cases. *Blood Cells Mol Dis* 1997;23:314-20.**	Fewer than 100 participants.
503.	**Shen LL, Gu DY, Zhao TT, Tang CJ, Xu Y, Chen JF. Implicating the H63D polymorphism in the HFE gene in increased incidence of solid cancers: a meta-analysis. *Genet Mol Res*. 2015;14(4):13735-13745. Published 2015 Oct 29. doi:10.4238/2015.October.28.36**	More recent systematic review
504.	**Shi Y, Zhou L, Huang LH, et al. Plasma ferritin levels, genetic variations in HFE gene, and coronary heart disease in Chinese: a case-control study. *Atherosclerosis*. 2011;218(2):386-390. doi:10.1016/j.atherosclerosis.2011.05.040**	Ineligible clinical factor (coronary heart disease)
505.	**Shizukuda Y, Bolan CD, Tripodi DJ, Sachdev V, Nguyen TT, Botello G*, et al.* Does oxidative stress modulate left ventricular diastolic function in asymptomatic subjects with hereditary hemochromatosis? *Echocardiography* 2009;26:1153-8.**	Fewer than 100 participants.
506.	**Shizukuda Y, Bolan CD, Tripodi DJ, Yau YY, Smith KP, Arena R*, et al.* Exercise capacity of cardiac asymptomatic hereditary hemochromatosis subjects. *Med Sci Sports Exerc* 2007;39:3-7.**	Fewer than 100 participants.

507.	**Shizukuda Y, Smith KP, Tripodi DJ, Arena R, Yau YY, Bolan CD*, et al.* Changes in exercise capacity in subjects with cardiac asymptomatic hereditary hemochromatosis during a follow-up after 5 yrs. *Am J Phys Med Rehabil* 2012;91:418-24.**	Fewer than 100 participants.
508.	**Shizukuda Y, Tripodi DJ, Zalos G, Bolan CD, Yau YY, Leitman SF*, et al.* Incidence of cardiac arrhythmias in asymptomatic hereditary hemochromatosis subjects with C282Y homozygosity. *Am J Cardiol* 2012;109:856-60.**	Fewer than 100 participants.
509.	**Shukla P, Julka S, Bhatia E, Shah S, Nagral A, Aggarwal R. HFE, hepcidin and ferroportin gene mutations are not present in Indian patients with primary haemochromatosis. *Natl Med J India* 2006;19:20-3.**	Fewer than 100 participants.
510.	**Sikorska K, Romanowski T, Stalke P, Iżycka-Świeszewska E, Bielawski KP. Iron overload and HFE gene mutations in Polish patients with liver cirrhosis. *Hepatobiliary Pancreat Dis Int*. 2011;10(3):270-275. doi:10.1016/s1499-3872(11)60045-3**	>10% with ineligible clinical factor (liver disease caused by viral infection or alcohol)
511.	**Sikorska K. Association of HFE Gene Mutations With Liver Cirrhosis Depends on Induction of Iron Homeostasis Disturbances. *Hepatitis Monthly* 2012;12:213-4.**	Ineligible publication type: letter.
512.	**Sikorska K, Stalke P, Izycka-Swieszewska E, Romanowski T, Bielawski KP. The role of iron overload and HFE gene mutations in the era of pegylated interferon and ribavirin treatment of chronic hepatitis C. *Med Sci Monit* 2010;16:CR137-43.**	Ineligible starting condition: viral liver disease.
513.	**Sini M, Sorbello O, Civolani A, Demelia L. Hemochromatosis gene mutations: prevalence and effects on pegylated-interferon and ribavirin therapy response in chronic hepatitis C in sardinia. *J* 2012;2:211-7.**	Fewer than 100 participants. Ineligible starting condition: viral liver disease.
514.	**Sokolova EA, Shadrina AS, Sevost'ianova KS, Shevela AI, Soldatsky EY, Seliverstov EI*, et al.* HFE p.C282Y gene variant is associated with varicose veins in Russian population. *Clin Exp Med* 2016;16:463-70.**	Ineligible starting condition: primary varicose veins.
515.	**Solanas-Barca M, Mateo-Gallego R, Calmarza P, Jarauta E, Bea AM, Cenarro A*, et al.* Mutations in HFE causing hemochromatosis are associated with primary hypertriglyceridemia. *J Clin Endocrinol Metab* 2009;94:4391-7.**	Ineligible starting condition: HTG.
516.	**Speechley M, Alter D, Guo H, Harrison H, Adams PC. Effect of ambiguous hemochromatosis gene test results on physician utilization. *Med Care* 2012;50:394-8.**	Ineligible outcomes.
517.	**Steinberg KK, Cogswell ME, Chang JC, Caudill SP, McQuillan GM, Bowman BA*, et al.* Prevalence of C282Y and H63D mutations in the hemochromatosis (HFE) gene in the United States. *Jama* 2001;285:2216-22.**	Ineligible outcomes
518.	**Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States - Prognostic features, treatment outcome, and survival. *Cancer* 1996;77:2217-22.**	No HFE genotypes reported.

519.	**Su XWW, Lee SY, Mitchell RM, Stephens HE, Simmons Z, Connor JR. H63D HFE polymorphisms are associated with increased disease duration and decreased muscle superoxide dismutase-1 expression in amyotrophic lateral sclerosis patients. *Muscle & Nerve* 2013;48:242-6. https://doi.org/10.1002/mus.23740**	Fewer than 100 participants. Ineligible starting condition: ALS.
520.	**Sucak GT, Yasar DG, Yegin ZA, Ergun MA, Ozkurt ZN, Aki SZ, *et al.* The prognostic role of hemochromatosis H63D allele in allogeneic hematopoietic stem cell transplantation. *Annals of Hematology* 2012;91:1281-7.**	Ineligible starting condition.
521.	**Sukiennicki GM, Marciniak W, Muszynska M, Baszuk P, Gupta S, Bialkowska K, *et al.* Iron levels, genes involved in iron metabolism and antioxidative processes and lung cancer incidence. *PLoS ONE* 2019;14:e0208610.**	Ineligible starting condition: lung cancer.
522.	**Sundic T, Hervig T, Hannisdal S, Assmus J, Ulvik RJ, Olaussen RW, *et al.* Erythrocytapheresis compared with whole blood phlebotomy for the treatment of hereditary haemochromatosis. *Blood Transfus* 2014;12 Suppl 1:s84-9.**	Fewer than 100 participants.
523.	**Sutedja NA, Sinke RJ, Van Vught PW, Van der Linden MW, Wokke JH, Van Duijn CM, *et al.* The association between H63D mutations in HFE and amyotrophic lateral sclerosis in a Dutch population. *Arch Neurol* 2007;64:63-7.**	Ineligible starting condition: ALS.
524.	**Swinkels DW, Aalbers N, Elving LD, Bleijenberg G, Swanink CM, van der Meer JW. Primary haemochromatosis: a missed cause of chronic fatigue syndrome? *Neth J Med* 2002;60:429-33.**	Fewer than 100 participants.
525.	**Syrjakoski K, Fredriksson H, Ikonen T, Kuukasjarvi T, Autio V, Matikainen MP, *et al.* Hemochromatosis gene mutations among Finnish male breast and prostate cancer patients. *Int J Cancer* 2006;118:518-20.**	Ineligible starting condition: male breast cancer or prostate cancer.
526.	**Tamosauskaite J, Atkins JL, Pilling LC, et al. Hereditary Hemochromatosis Associations with Frailty, Sarcopenia and Chronic Pain: Evidence from 200,975 Older UK Biobank Participants. *J Gerontol A Biol Sci Med Sci*. 2019;74(3):337-342. doi:10.1093/gerona/gly270**	No eligible outcomes
527.	**Tarao K, Nozaki A, Ikeda T, Sato A, Komatsu H, Komatsu T, *et al.* Real impact of liver cirrhosis on the development of hepatocellular carcinoma in various liver diseases-meta-analytic assessment. *Cancer Medicine* 2019;8:1054-65.**	No HFE genotypes reported.
528.	**Thakur V, Guptan RC, Hashmi AZ, Sakhuja P, Malhotra V, Sarin SK. Absence of hemochromatosis associated Cys282Tyr HFE gene mutation and low frequency of hemochromatosis phenotype in nonalcoholic chronic liver disease patients in India. *J Gastroenterol Hepatol*. 2004;19(1):86-90. doi:10.1111/j.1440-1746.2004.03262.x**	No HFE genotypes reported.
529.	**Thakkar DN, Palugulla S, Selvarajan S, Dubashi B. Frequency distribution of BLMH, XPO5 and hfe gene polymorphisms in the south indian population and their association with hodgkin lymphoma. *International Journal of Biological Markers* 2018;33:514-9.**	Ineligible starting condition: Hodgkin lymphoma.
530.	**Thorburn D, Curry G, Spooner R, Spence E, Oien K, Halls D, *et al.* The role of iron and haemochromatosis gene mutations in the progression of liver disease in chronic hepatitis C. *Gut* 2002;50:248-52.**	Ineligible starting condition: viral liver disease.

531.	**Tisato V, Zuliani G, Vigliano M, Longo G, Franchini E, Secchiero P*, et al.* Gene-gene interactions among coding genes of iron-homeostasis proteins and APOE-alleles in cognitive impairment diseases. *PLoS ONE* 2018;13.**	Ineligible starting condition: dementia.
532.	**Toll A, Celis R, Ozalla MD, Bruguera M, Herrero C, Ercilla MG. The prevalence of HFE C282Y gene mutation is increased in Spanish patients with porphyria cutanea tarda without hepatitis C virus infection. *J Eur Acad Dermatol Venereol* 2006;20:1201-6.**	Ineligible starting condition: PCT.
533.	**Torres FR, Souza-Neiras WC, D'Almeida Couto AA, D'Almeida Couto VS, Cavasini CE, Rossit AR*, et al.* Frequency of the HFE C282Y and H63D polymorphisms in Brazilian malaria patients and blood donors from the Amazon region. *Genet Mol Res* 2008;7:60-4.**	Ineligible starting condition: Malaria.
534.	**Tsui WM, Lam PW, Lee KC, Ma KF, Chan YK, Wong MW*, et al.* The C282Y mutation of the HFE gene is not found in Chinese haemochromatotic patients: multicentre retrospective study. *Hong Kong Med* 2000;6:153-8.**	Fewer than 100 participants.
535.	**Tuomainen TP, Kontula K, Nyyssönen K, Lakka TA, Heliö T, Salonen JT. Increased risk of acute myocardial infarction in carriers of the hemochromatosis gene Cys282Tyr mutation: a prospective cohort study in men in eastern Finland. *Circulation*. 1999;100(12):1274-1279.**	No extractable data
536.	**Turkmen E, Yildirim T, Yilmaz R, Hazirolan T, Eldem G, Yilmaz E*, et al.* HFE gene mutation is a risk factor for tissue iron accumulation in hemodialysis patients. *Hemodial* 2017;21:359-66.**	Fewer than 100 participants. Ineligible starting condition: hemodialysis patients with chronic renal failure.
537.	**Valenti L, Conte D, Piperno A, et al. The mitochondrial superoxide dismutase A16V polymorphism in the cardiomyopathy associated with hereditary haemochromatosis. *J Med Genet*. 2004;41(12):946-950.**	Outcomes not reported by genotype
538.	**Valenti L, Fracanzani AL, Rossi V, Rampini C, Pulixi E, Varenna M*, et al.* The hand arthropathy of hereditary hemochromatosis is strongly associated with iron overload. *J Rheumatol* 2008;35:153-8.**	Fewer than 100 participants.
539.	**Valenti L, Girelli D, Valenti GF, Castagna A, Como G, Campostrini N*, et al.* HFE mutations modulate the effect of iron on serum hepcidin-25 in chronic hemodialysis patients. *Clin J Am Soc Nephrol* 2009;4:1331-7.**	Ineligible starting condition: chronic hemodialysis.
540.	**Valenti L, Valenti G, Como G, Burdick L, Santorelli G, Dongiovanni P*, et al.* HFE gene mutations and oxidative stress influence serum ferritin, associated with vascular damage, in hemodialysis patients. *Am J Nephrol* 2007;27:101-7.**	Ineligible starting condition: hemodialysis.
541.	**Valenti L, Valenti G, Como G, Santorelli G, Dongiovanni P, Rametta R*, et al.* HFE genotype influences erythropoiesis support requirement in hemodialysis patients: a prospective study. *Am J Nephrol* 2008;28:311-6.**	Fewer than 100 participants. Ineligible starting condition: hemodialysis patients.
542.	**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.**	Fewer than 100 participants.

543.	**Valenti L, Fracanzani AL, Rametta R, et al. Effect of the A736V TMPRSS6 polymorphism on the penetrance and clinical expression of hereditary hemochromatosis. *J Hepatol*. 2012;57(6):1319-1325. doi:10.1016/j.jhep.2012.07.041**	Ineligible clinical factor (phenotypically-expressing haemochromatosis)
544.	**van Aerts RM, van Deursen CT, Koek GH. Proton Pump Inhibitors Reduce the Frequency of Phlebotomy in Patients With Hereditary Hemochromatosis. *Clin Gastroenterol Hepatol* 2016;14:147-52.**	Fewer than 100 participants.
545.	**Van Aken MO, De Craen AJ, Gussekloo J, et al. No increase in mortality and morbidity among carriers of the C282Y mutation of the hereditary haemochromatosis gene in the oldest old: the Leiden 85-plus study. *Eur J Clin Invest*. 2002;32(10):750-754.**	Carriers, not C282Y/C282Y, H63D/H63D, or C282Y/H63D
546.	**Van Der A DL, Marx JJM, Grobbee DE, Kamphuis MH, Georgiou NA, van Kats-Renaud JH*, et al.* Non-transferrin-bound iron and risk of coronary heart disease in postmenopausal women. *Circulation* 2006;113:1942-9. https://doi.org/10.1161/circulationaha.105.545350**	Ineligible genotype.
547.	**van der A DL, Peeters PH, Grobbee DE, et al. HFE mutations and risk of coronary heart disease in middle-aged women. *Eur J Clin Invest*. 2006;36(10):682-690. doi:10.1111/j.1365-2362.2006.01711.x**	Fewer than 100 for participants for eligible outcome (myocardial infarction)
548.	**van der A DL, Peeters PH, Grobbee DE, Roest M, Voorbij HA, van der Schouw YT. Mutations in the HFE gene and cardiovascular disease risk: an individual patient data meta-analysis of 53 880 subjects . *Nutr Metab Cardiovasc Dis*. 2006;16(1):60-68.**	Carriers, not C282Y/C282Y, H63D/H63D, or C282Y/H63D
549.	**van Rheenen W, Diekstra FP, van Doormaal PT, Seelen M, Kenna K, McLaughlin R*, et al.* H63D polymorphism in HFE is not associated with amyotrophic lateral sclerosis. *Neurobiology of Aging* 2013;34:1517.e5-7.**	Ineligible starting condition: ALS.
550.	**Van Vlierberghe H, Delanghe JR, De Bie S, Praet M, De Paepe A, Messiaen L*, et al.* Association between Cys282Tyr missense mutation and haptoglobin phenotype polymorphism in patients with chronic hepatitis C. *Eur J Gastroenterol Hepatol* 2001;13:1077-81.**	Ineligible starting condition: viral liver disease.
551.	**Vanclooster A, van Deursen C, Jaspers R, Cassiman D, Koek G. Proton Pump Inhibitors Decrease Phlebotomy Need in HFE Hemochromatosis: Double-Blind Randomized Placebo-Controlled Trial. *Gastroenterology* 2017;153:678-80.e2.**	Fewer than 100 participants.
552.	**Venat L, Loustaud-Ratti V, Liozon E, Soria P, Nadalon S, Gissot V*, et al.* Characteristic dysmetabolic hepatosiderosis in 51 patients. *Presse Medicale* 2003;32:400-5.**	Fewer than 100 participants.
553.	**Verhaegh PL, Moris W, Koek GH, van Deursen CT. The modified iron avidity index: a promising phenotypic predictor in HFE-related haemochromatosis. *Liver International* 2016;36:1535-9.**	Fewer than 100 participants.

554.	**Vitrano A, Sacco M, Rosso R, Quota A, Fiorino D, Oliva E*, et al.* Longitudinal changes in LIC and other parameters in patients receiving different chelation regimens: Data from LICNET. *European Journal of Haematology* 2018;100:124-30.**	Ineligible population. Ineligible outcomes.
555.	**Voicu PM, Cojocariu C, Petrescu-Danila E, Stanciu C, Covic M, Rusu M*, et al.* Hereditary hemochromatosis in north-eastern Romania. *Revista medico-chirurgicala a Societatii de Medici si Naturalisti din Iasi* 2010;114:982-7.**	2 studies reported in this article: 1) No relevant associations between HFE genotype and phenotype reported. 2) Fewer than 100 participants.
556.	**Wang FT, Hu H, Schwartz J, et al. Modifying effects of the HFE polymorphisms on the association between lead burden and cognitive decline. *Environ Health Perspect*. 2007;115(8):1210-1215**	Outcomes not reported by genotype
557.	**Wang X, Leiendecker-Foster C, Acton RT, et al. Heme carrier protein 1 (HCP1) genetic variants in the Hemochromatosis and Iron Overload Screening (HEIRS) Study participants. *Blood Cells Mol Dis*. 2009;42(2):150-154. doi:10.1016/j.bcmd.2008.11.003**	Ineligible outcome (Heme carrier protein 1 genetic variants)
558.	**Willis G, Wimperis JZ, Smith K, Fellows IW, Jennings BA. HFE mutations in the elderly. *Blood Cells Mol Dis* 2003;31:240-6.**	No relevant genotype/phenotype associations reported.
559.	**Wise M, Finelli L, Sorvillo F. Prognostic factors associated with hepatitis C disease: a case-control study utilizing U.S. multiple-cause-of-death data. *Public Health Rep* 2010;125:414-22.**	Ineligible starting condition: hepatitis C.
560.	**Wojcik JP, Speechley MR, Kertesz AE, Chakrabarti S, Adams PC. Natural history of C282Y homozygotes for hemochromatosis. *Can J Gastroenterol*. 2002;16(5):297-302.**	>10% treated for iron overload
561.	**Wouthuis SF, van Deursen CT, te Lintelo MP, Rozeman CA, Beekman R. Neuromuscular manifestations in hereditary haemochromatosis. *J Neurol* 2010;257:1465-72.**	Fewer than 100 participants.
562.	**Wright RO, Silverman EK, Schwartz J, Tsaih SW, Senter J, Sparrow D*, et al.* Association between hemochromatosis genotype and lead exposure among elderly men: the normative aging study. *Environmental Health Perspectives* 2004;112:746-50.**	Ineligible outcomes.
563.	**Xu YY, Tang YH, Guo XP, Wang J, Yao P. HFE genetic variability and risk of alcoholic liver disease: A meta-analysis. *J Huazhong Univ Sci Technolog Med Sci* 2016;36:626-33.**	Ineligible starting condition: alcoholic liver disease.

564.	**Yamashita C, Adams PC. Natural history of the C282Y homozygote for the hemochromatosis gene (HFE) with a normal serum ferritin level. *Clin Gastroenterol Hepatol* 2003;1:388-91.**	Fewer than 100 participants.
565.	**Yen AA, Simpson EP, Henkel JS, Beers DR, Appel SH. HFE mutations are not strongly associated with sporadic ALS. *Neurology* 2004;62:1611-2.**	Fewer than 100 participants. Ineligible starting condition: ALS.
566.	**Yenson PR, Yoshida EM, Li CH, Chung HV, Tsang PW. Hyperferritinemia in the Chinese and Asian community: a retrospective review of the University of British Columbia experience. *Can J Gastroenterol* 2008;22:37-40.**	Fewer than 100 participants.
567.	**Young M, Dick ML, O'Rourke P. Haemochromatosis--a future focus for continuing education in general practice. *Aust Fam Physician* 2004;33:1041-4.**	Ineligible outcomes.
568.	**Yu XY, Wang BB, Xin ZC, Liu T, Ma K, Jiang J*, et al.* An association study of HFE gene mutation with idiopathic male infertility in the Chinese Han population. *Asian J Androl* 2012;14:599-603.**	Ineligible starting condition: infertility.
569.	**Zaahl MG, Merryweather-Clarke AT, Kotze MJ, van der Merwe S, Warnich L, Robson KJ. Analysis of genes implicated in iron regulation in individuals presenting with primary iron overload. *Hum Genet* 2004;115:409-17.**	Ineligible outcomes.
570.	**Zaloumis SG, Allen KJ, Bertalli NA, Turkovic L, Delatycki MB, Nicoll AJ*, et al.* Natural history of HFE simple heterozygosity for C282Y and H63D: a prospective 12-year study. *J Gastroenterol Hepatol* 2015;30:719-25.**	Ineligible population. Compares simple heterozygotes with people with no HFE mutation.
571.	**Zamani F, Bagheri Z, Bayat M, Fereshtehnejad SM, Basi A, Najmabadi H*, et al.* Iranian hereditary hemochromatosis patients: baseline characteristics, laboratory data and gene mutations. *Med Sci Monit* 2012;18:CR622-9.**	Fewer than 100 participants.
572.	**Zamboni P, Tognazzo S, Izzo M, Pancaldi F, Scapoli GL, Liboni A*, et al.* Hemochromatosis C282Y gene mutation increases the risk of venous leg ulceration. *J Vasc Surg* 2005;42:309-14.**	Ineligible starting condition: severe chronic venous disease.
573.	**Zamin I, Jr., Mattos AA, Mattos AZ, Migon E, Bica C, Alexandre CO. Prevalence of the hemochromatosis gene mutation in patients with nonalcoholic steatohepatitis and correlation with degree of liver fibrosis. *Arq Gastroenterol* 2006;43:224-8.**	Fewer than 100 participants.
574.	**Zanella A, Bianchi P, Iurlo A, Boschetti C, Taioli E, Vercellati C*, et al.* Iron status and HFE genotype in erythrocyte pyruvate kinase deficiency: study of Italian cases. *Blood Cells Mol Dis* 2001;27:653-61.**	Fewer than 100 participants. Ineligible starting condition: pyruvate kinase deficiency.

575.	**Zhao Z, Li C, Hu M, Li J, Liu R. Plasma ferritin levels, HFE polymorphisms, and risk of pancreatic cancer among Chinese Han population. *Tumour Biol* 2014;35:7629-33.**	Ineligible starting condition: pancreatic cancer.
576.	**Zoller H, Cox TM. Hemochromatosis: Genetic testing and clinical practice. *Clinical Gastroenterology and Hepatology* 2005;3:945-58.**	Ineligible publication type: narrative review.

Appendix 3 — Summary and appraisal of individual studies

Data Extraction

Table 29. Studies relevant to criteria 1 and 9

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
	Question 1				
1.	**Andersen 2004**[53]	Prospective cohort	Country: Denmark 9174 people from general population 25 years follow up Copenhagen City Heart Study	**Serum ferritin** NR **Transferrin saturation** NR	**Serum ferritin,** **Whole sample** **C282Y/C282Y 492.8**[2] H63D/H63D 180.0[2] C282Y/H63D 242.5[2] Wild/wild 194.4[2] **Men** **C282Y/C282Y 473.6**[2] H63D/H63D 246.9[2] C282Y/H63D 280.3[2] Wild/wild 199.4[2] **Women** **C282Y/C282Y 329.3**[2] H63D/H63D 77.6[2] C282Y/H63D 137.9[2] Wild/wild 141.4[2]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					Transferrin saturation, mean % **Whole sample** **C282Y/C282Y 69.8**[2] **H63D/H63D 38.2**[2] **C282Y/H63D 43.6**[2] Wild/wild 29.3 **Men** **C282Y/C282Y 77.7**[2] **H63D/H63D 40.8**[2] **C282Y/H63D 45.5**[2] Wild/wild 28.4[2] **Women** **C282Y/C282Y 66.6**[2] H63D/H63D 38.0[2] **C282Y/H63D 43.9**[2] Wild/wild 30.7
2.	**Beutler 2000**[38]	Cross-sectional	Country: USA 10198 primary care patients Kaiser Permanente	NA	**Serum ferritin, mean µg/L** **Men** C282Y/C282Y 313.97 (164.8, 598.0) H63D/H63D 132.97 (111.3, 158.9)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					C282Y/H63D 187.25 (158.4, 221.3) Wild/wild 106.79 (103.3, 110.4) **Women** C282Y/C282Y 146.39 (90.4, 237.2) H63D/H63D 70.55 (58.9, 84.5) C282Y/H63D 73.76 (56.5, 96.3) Wild/wild 54.87 (53.0, 56.8) **Transferrin saturation, mean %** **Men** C282Y/C282Y 54.43 (44.2, 64.6) H63D/H63D 33.41 (31.2, 35.6) C282Y/H63D 40.05 (36.9, 43.2) Wild/wild 26.25 (25.9, 26.7) **Women** C282Y/C282Y 49.13 (40.0, 58.2) H63D/H63D 28.09 (26.1, 30.1) C282Y/H63D 31.90 (28.8, 35.0) Wild/wild 22.33 (22.0, 22.7)
3.	**Beutler 2002[36]**	Cross-sectional	Country: USA Kaiser Permanente	**Fatigue** **Whole sample** C282Y/C282Y, n = 34/124 (27.4%)	**Fatigue** **Whole sample** RD[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/H63D, n = 157/594 (26.4%) Wild/wild, n = 5923/22347 (26.5) **Men** C282Y/C282Y, n = 12/56 (21.4%) C282Y/H63D, n = 62/292 (21.2%) Wild/wild, n = 2286/10889 (21.0%) **Women** C282Y/C282Y, n = 22/68 (32.4%) C282Y/H63D, n = 95/301 (31.6%) Wild/wild, n = 3637/11458 (31.7%) **Serum ferritin** Deprioritised **Transferrin saturation** Deprioritised	C282Y/C282Y 0.91 (-6.96, 8.79) C282Y/H63D -0.07 (-3.67, 3.52) RR[1] C282Y/C282Y 1.03 (0.78, 1.38) C282Y/H63D 1.00 (0.87, 1.14) **Men** RD[1] C282Y/C282Y 0.43 (-10.34, 11.21) C282Y/H63D 0.24 (-4.51, 4.99) RR[1] C282Y/C282Y 1.02 (0.62, 1.69) C282Y/H63D 1.01 (0.81 , 1.27) **Women** RD[1] C282Y/C282Y 0.61 (-10.54, 11.76) C282Y/H63D -0.18 (-5.50, 5.14) RR[1] C282Y/C282Y 1.02 (0.72, 1.44) C282Y/H63D 0.99 (0.84, 1.18)
4.	**Beutler 2003**[37]	Cross-sectional	Country: USA	NA	**Serum ferritin, mean µg/L**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			23681 primary care patients (white) Kaiser Permanente		**Men** **C282Y/C282Y 419 (262, 670)** **H63D/H63D 147 (133, 162)** **C282Y/H63D 330 (178, 219)** Wild/wild 122 (119, 124) **Women** **C282Y/C282Y 157 (106, 233)** **H63D/H63D 63 (57, 70)** **C282Y/H63D 76 (67, 86)** Wild/wild 55 (54, 56) **Transferrin saturation, % (SD)** **Men** **C282Y/C282Y 66 (20)** **H63D/H63D 34 (11)** **C282Y/H63D 39 (13)** Wild/wild 27 (9) **Women** **C282Y/C282Y 46 (21)** **H63D/H63D 29 (10)** **C282Y/H63D 29 (10)** Wild/wild 29 (10)
5.	**Burt 1998**[39]	Cross-sectional	Country: New Zealand 1064 community sample	**Serum ferritin, men >428 µg/l, women >302 µg/l**	**Serum ferritin** RD[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = 3/5 (60%) H63D/H63D, n = NR C282Y/H63D, n = 3/19 (15.8%) Wild/wild, n = 16/655 (2.4%) **Transferrin saturation, >50.5%** C282Y/C282Y, n = 5/5 (100%) H63D/H63D, n = NR C282Y/H63D, n = 5/19 (26.3%) Wild/wild, n = 21/655 (3.2%)	**C282Y/C282Y 57.56 (14.60, 100.51)** C282Y/H63D 13.35 (-3.09, 29.79) RR[1] **C282Y/C282Y 24.56 (10.35, 58.28)** **C282Y/H63D 6.46 (2.06, 20.33)** **Transferrin saturation** RD[1] **C282Y/C282Y 96.79 (74.64, 118.95)** **C282Y/H63D 23.11 (3.26, 42.96)** RR[1] **C282Y/C282Y 27.97 (17.30, 45.23)** **C282Y/H63D 8.21 (3.47, 19.44)**
6.	**Cobbaert 2012[55]**	Case cohort	Country: Netherlands 9 – 13 year follow up Monitoring Project on Cardiovascular Disease Risk Factors	**Cardiovascular mortality** **Whole sample** C282Y/C282Y, n = NR H63D/H63D, n = NR Wild/wild, n = NR **Men** C282Y/C282Y, n = NR H63D/H63D, n = NR	**Cardiovascular mortality** **Whole sample** Not examined **C282Y/C282Y** Not examined **H63D/H63D** **Whole sample** HR 1.80 (0.88, 3.21)[a]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Wild/wild, n = NR **Women** C282Y/C282Y, n = NR H63D/H63D, n = NR Wild/wild, n = NR	**HR 2.38 (1.04, 5.47)**[b] **HR 2.71 (2.09, 6.73)**[c] **Men** HR 1.32 (0.54, 3.21) HR (1.90 (0.75, 5.17) HR 2.14 (0.70, 6.48) **Women** HR 1.80 (0.88, 3.67) **HR 5.89 (1.52, 22.9)** **HR 8.45 (2.30, 3.11)** [a] unadjusted [b] adjusted for age, sex, town [c] adjusted for age, sex, town, smoking status, body madd index, total cholesterol, HDL-cholesterol, systolic blood pressure, diastolic blood pressure
7.	**Ellervik 2005**[51]	Prospective cohort	Country: Denmark 23 year follow up (median) Copenhagen City Heart Study	**Myocardial infarction** **Whole sample** C282Y/C282Y, n = 2/22 (9.1%) H63D/H63D, n = 9/141 (6.4%) C282Y/H63D, n = 4/123 (3.3%) Wild/wild, n = 331/5767 (5.7%) **Men**	**Myocardial infarction** **Whole sample** RD[1] C282Y/C282Y 3.35 (-8.68, 15.38) H63D/H63D 0.64 (-3.44, 4.72) C282Y/H63D -2.49 (-5.68, 0.70) RR[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = 1/6 (16.7%) H63D/H63D, n = 7/58 (12.1%) C282Y/H63D, n = 2/47 (4.3%) Wild/wild, n = 213/2530 (8.4%) **Women** C282Y/C282Y, n = 1/16 (6.3%) H63D/H63D, n = 2/83 (2.4%) C282Y/H63D, n = 2/76 (2.6%) Wild/wild, n = 118/3237 (3.7%) **Serum ferritin** See Andersen 2004 **Transferrin saturation** See Andersen 2004	C282Y/C282Y 1.58 (0.42, 5.96) H63D/H63D 1.11 (0.59, 2.11) C282Y/H63D 0.57 (0.21, 1.49) **Men** RD[1] C282Y/C282Y -2.17 (-14.08, 9.74) H63D/H63D 3.65 (-4.80, 12.10) C282Y/H63D -4.16 (-10.03, 1.71) RR[1] C282Y/C282Y 0.74 (0.11, 4.97) H63D/H63D 1.43 (0.71, 2.91) C282Y/H63D 0.51 (0.13, 1.97) **Women** RD[1] C282Y/C282Y 2.60 (-9.27, 14.48) H63D/H63D -1.24 (-4.60, 2.13) C282Y/H63D -1.01 (-4.67, 2.64) RR[1] C282Y/C282Y 1.71 (0.25, 11.53) H63D/H63D 0.66 (0.17, 2.63) C282Y/H63D 0.72 (0.18, 2.87)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					Serum ferritin, median µg/L (IQR) **Whole sample** **C282Y/C282Y 410 (158, 603)** H63D/H63D 65 (36, 136) C282Y/H63D 95 (51, 172) Wild/wild 62 (32, 125) **Men** **C282Y/C282Y 603 (355, 1162)** H63D/H63D 144 (103, 308) C282Y/H63D 159 (136, 275 Wild/wild 107 (34, 200) **Women** **C282Y/C282Y 236 (135, 584)** H63D/H63D 51 (33, 70) C282Y/H63D 73 (34, 108) Wild/wild 51 (26, 95)
8.	**Ellervik 2005**[52]	Prospective cohort	Country: Denmark 9178 community sample 23 year follow up (median) Copenhagen City Heart Study	**Transferrin saturation** See Andersen 2004	See Andersen 2004
9.	**Fox 2002**[40]	Cross-sectional	Country: Australia 2326 community sample Busselton study	**Angina** **Whole sample** C282Y/C282Y, n = 0/16 (0%)	**Angina** **Whole sample** RD[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				H63D/H63D, n = 3/48 (6.3%) C282Y/H63D, n = 4/44 (9.1%) Wild/wild, n = 70/1358 (5.2%) **Myocardial infarction** **Whole sample** C282Y/C282Y, n = 0/16 (0%) H63D/H63D, n = 3/48 (6.3%) C282Y/H63D, n = 1/44(2.3%) Wild/wild, n = 107/1358 (7.9%)	C282Y/C282Y -5.15 (-13.27, 2.96) H63D/H63D 1.10 (-5.85, 8.04) C282Y/H63D 3.94 (-4.64, 12.51) RR[1] C282Y/C282Y 0.57 (0.04, 8.78) H63D/H63D 1.21 (0.40, 3.71) C282Y/H63D 1.76 (0.67, 4.61) **Myocardial infarction** **Whole sample** RD[1] C282Y/C282Y -7.88 (-16.04, 0.28) H63D/H63D -1.63 (-8.63, 5.37) C282Y/H63D -5.61 (-10.24, -0.98) RR[1] C282Y/C282Y 0.37 (0.02, 5.74) H63D/H63D 0.79 (0.26, 2.41) C282Y/H63D 0.29 (0.04, 2.02)
10.	**Gallego 2015[41]**	Cross-sectional	Country: USA 496 DNA biorepository sample	**Arthritis** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 127/391 (32.5%)	NA

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Men C282Y/C282Y, = NA C282Y/H63D, n = 61/173 (35.3%) **Women** C282Y/C282Y, n = 13/50 (26.0%) C282Y/H63D, n = 66/218 (30.3%) **Cardiomyopathy** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 17/392 (4.3%) **Men** C282Y/C282Y, = NA C282Y/H63D, n = 13/174 (7.50%) **Women** Homozygous C282Y, n = 2/49 (4.1%) C282Y/H63D, n = 4/218 (1.8%) **Cirrhosis** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 18/369 (4.9%) **Men** C282Y/C282Y, n = NA	

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/H63D, n = 8/166 (4.8%) **Women** C282Y/C282Y, n = 1/40 (2.5%) C282Y/H63D, n = 10/203 (4.9%) **Diabetes (unspecified)** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 92/395 (23.3%) **Men** C282Y/C282Y, n = NA C282Y/H63D, n = 49/175 (28.0%) **Women** C282Y/C282Y, n = 6/50 (12.0%) C282Y/H63D, n = 43/220 (19.5%) **Heart failure** Deprioritised **Hyperpigmentation** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 7/368 (1.9%) **Men**	

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = NA C282Y/H63D, n = 2/167 (1.2%) **Women** C282Y/C282Y, n = 1/42 (2.4%) C282Y/H63D, n = 5/201 (2.5%) **Liver cancer** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 71/344 (29.6%) **Men** C282Y/C282Y, n = NA C282Y/H63D, n = 29/199 (24.4%) **Women** C282Y/C282Y, n = 9/32 (29.0%) Compound, n = 42/145 (29.0%) **Liver disease** **Whole sample** C282Y/C282Y, n = NA C282Y/H63D, n = 0/387 (%) **Men** C282Y/C282Y, n = NA C282Y/H63D, n = 0/169 (0%)	

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Women C282Y/C282Y, n = 0/50 (0%) C282Y/H63D, n = 0/218 (0%) **Serum ferritin** Deprioritised **Transferrin saturation** Deprioritised Note. 19.6% of C282Y/C282Y men were treated (exclusion criteria) so data not included	
11.	**Gochee 2002**[42]	Cross-sectional	Country: Australia 2531 community sample (white) Busselton study	**Serum ferritin, >300 ng/mL** **Whole sample** H63D/H63D, n = 16/62 (25.8%) Wild/wild, n = 216/1758 (12.3%) **Men** H63D/H63D, n = 12/33 (36.4%) Wild/wild, n = 177/887 (20.0%) **Women** H63D/H63D, n = 4/29 (13.8%) Wild/wild, n = 39/871 (4.5%)	**Serum ferritin** **Whole sample** **RD 13.52 (2.52, 24.52)**[1] **RR 2.10 (1.35, 3.26)**[1] **Men** RD 16.41 (-0.21, 33.03)[1] **RR 1.82 (1.14, 2.92)**[1] **Women** RD 9.32 (-3.31, 21.94)[1] **RR 3.08 (1.18, 8.05)**[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Transferrin saturation, >45% **Whole sample** H63D/H63D, n = 7/62 (11.3%) Wild/wild, n = 62/1758 (3.5%) **Men** H63D/H63D, n = 5/33 (15.2%) Wild/wild, n = 43/887 (4.9%) **Women** H63D/H63D, n = 2/29 (6.9%) Wild/wild, n = 19/871 (2.2%)	**Transferrin saturation** **Whole sample** RD 7.76 (-0.16, 15.69)[1] **RR 3.20 (1.53, 6.71)**[1] **Men** RD 10.30 (-2.01, 22.62)[1] **RR 3.13 (1.32, 7.37)**[1] **Women** RD 4.72 (-4.56, 13.99)[1] RR 3.16 (0.77, 12.94)[1]
12.	**Greenwood 2005**[43]	Cross-sectional	Country: UK 2528 UK Women's Cohort Study	NA	**Unbound iron-binding capacity, mean µmol/L (95% CI)** **Whole sample** Reference range: 23 – 65 C282Y/C282Y 13 (10, 16) H63D/H63D 32 (29, 36) C282Y/H63D 26 (25, 28) Wild/wild: 36 (35, 36) (from women genotyped for C282Y mutations) 35 (34, 35) (from women genotyped for H63D mutations)
13.	**Henriksen 2016**[44]	Cross-sectional	Country: Denmark	NA	**Serum ferritin, mean µg/l (SD)**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			20261 community sample Danish General Suburban Population Study		**Men** C282Y/C282Y 719.18 (709.59) H63D/H63D 241.33 (176.62) C282Y/H63D 299.41 (233.68) Wild/wild 207.50 (186.2) **Women** C282Y/C282Y 462.03 (1082.84) H63D/H63D 140.70 (225.18) C282Y/H63D 142.9 (129.72) Wild/wild 103.39 (90.00) **Transferrin saturation, %** **Men** C282Y/C282Y 52.00 (24.48) H63D/H63D 28.31 (8.45) C282Y/H63D 34.24 (11.04) Wild/wild 21.69 (7.14) **Women** C282Y/C282Y 47.69 (17.82) H63D/H63D 25.18 (8.83) C282Y/H63D 28.59 (9.60) Wild/wild 18.31 (6.64)
14.	**McLaren 2008**[116]	Cross-sectional	Country: Canada, USA 646 community sample (white)	**Fatigue** C282Y/C282Y, n = 119/282 (42.2%)	**Hyperpigmentation** **RD 8.72 (4.26, 13.19)**[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			HEIRS study	Wild/wild, n = 86/364 (23.6%) **Hyperpigmentation** C282Y/C282Y, n = 37/282 (13.1%) Wild/wild, n = 16/364 (4.4%) **Serum ferritin, men >300µg/L, women >200µg/L** Newly diagnosed C282Y/C282Y, n = 131/195 (66.8%) Wild/wild, n = not reported	**RR 2.98 (1.70, 5.25)**[1]
15.	**Olynyk 1999**[54]	Cross-sectional, prospective cohort	Country: Australia 3011 community sample (white) 4 years follow up Busselton study	**Serum ferritin, >300ng/mL** C282Y/C282Y, n = not extractable (4/16 treated) C282Y/H63D, n = 22/65 (33.9%) Wild/wild, n = 328/2571 (12.8%) **Transferrin saturation, ≥45%** C282Y/C282Y, n = not extractable (4/16 treated) C282Y/H63D, n = 14/65 (21.5%) Wild/wild, n = 125/2571 (4.9%)	**Serum ferritin** RD[1] **C282Y/H63D 21.09 (9.51, 32.66)** RR[1] **C282Y/H63D 2.65 (1.86, 3.78)** **Transferrin saturation** RD[1] **C282Y/H63D 16.68 (6.65, 26.70)** RR[1] **C282Y/H63D 4.43 (2.70, 7.26)**
16.	**Pankow 2008**[46]	Cross-sectional,	Country: USA 7263 community sample	**Diabetes (unspecified)** C282Y/C282Y, n = 3/45 (6.7%)	**Diabetes** RD[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
		prospective cohort	15 years follow up (mean)	H63D/H63D, n = 20/257 (7.8%) C282Y/H63D, n = 19/193 (9.8%) Wild/wild, n = 566/6768 (8.4%) **Fatigue** C282Y/C282Y, n = 18/45 (40%) H63D/H63D, n = 121/257 (47.1%) C282Y/H63D, n = 95/193 (49.2%) Wild/wild, n = 2910/6768 (43%) **Heart failure** C282Y/C282Y, n = 2/45 (4.4%) H63D/H63D, n = 23/257 (8.9%) C282Y/H63D, n = 16/193 (8.3%) Wild/wild, n = 564/6768 (8.3%) **Mortality** C282Y/C282Y, n = 7/45 (15.6%) H63D/H63D, n = 45/257 (17.5%) C282Y/H63D, n = 30/193 (15.5%) Wild/wild, n = 1066/6768 (15.8%)	C282Y/C282Y -1.70 (-9.01, 5.62) H63D/H63D -0.58 (-3.92, 2.76) C282Y/H63D 1.48 (-2.77, 5.74) RR[1] C282Y/C282Y 0.80 (0.27, 2.39) H63D/H63D 0.93 (0.61, 1.43) C282Y/H63D 1.18 (0.76, 1.82) **Fatigue** RD[1] C282Y/C282Y -3.00 (-17.36, 11.37) H63D/H63D 4.09 (-2.13, 10.30) C282Y/H63D 6.23 (-0.92, 13.38) RR[1] C282Y/C282Y 0.93 (0.65, 1.33) H63D/H63D 1.10 (0.96, 1.25) C282Y/H63D 1.14 (0.99, 1.32) **Heart failure** RD[1] C282Y/C282Y -3.89 (-9.95, 2.17) H63D/H63D 0.62 (-2.94, 4.17) C282Y/H63D -0.04 (-3.99, 3.90)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					RR[1] C282Y/C282Y 0.53 (0.14, 2.07) H63D/H63D 1.07 (0.72, 1.60) C282Y/H63D 0.99 (0.62, 1.60) **Mortality** RD[1] C282Y/C282Y -0.20 (-10.82, 10.43) H63D/H63D 1.76 (-2.97, 6.49) C282Y/H63D -0.21 (-5.39, 4.98) RR[1] C282Y/C282Y 0.99 (0.50, 1.96) H63D/H63D 1.11 (0.85, 1.46) C282Y/H63D 0.99 (0.71, 1.38)
17.	**Pilling 2019[32]**	Prospective cohort	Country: UK 451243 volunteers 7 years follow up (mean)	**Any/at least 1 outcome** **Whole sample** C282Y/C282Y, n = 819/2890 (28.3%) Wild/wild, n = 69674/383909 (18.2%) **Men** C282Y/C282Y, n = 421/1294 (32.5%) Wild/wild, n = 28143/175539 (16.0%) **Women** C282Y/C282Y, n = 398/1596 (24.9%)	**Any/at least 1 outcome** **Whole sample** **RD 10.19 (8.54, 11.84)**[1] **RR 1.56 (1.47, 1.66)**[1] **Men** **RD 16.50 (13.94, 19.06)**[1] **RR 2.03 (1.87, 2.20)**[1] **Women** **RD 5.01 (2.88, 7.14)**[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Wild/wild, n = 41531/208370 (19.9%)	**RR 1.25 (1.15, 1.36)**[1]
				Atrial fibrillation	**Atrial fibrillation**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 40/2890 (1.4%)	RD -0.16 (-0.58, 0.27)[1]
				Wild/wild, n = 5917/383909 (1.5%)	RR 0.90 (0.66, 1.22)[1]
				Men	**Men**
				C282Y/C282Y, n = 27/1294 (2.1%)	RD -0.29 (-1.07, 0.50)[1]
				Wild/wild, n = 4166/175539 (2.4%)	RR 0.88 (0.60, 1.28)[1]
				Women	**Women**
				C282Y/C282Y, n = 13/1596 (0.8%)	RD -0.03 (-0.47, 0.42)[1]
				Wild/wild, n = 1751/208370 (0.8%)	RR 0.97 (0.56, 1.67)[1]
				Diabetes (types 1 or 2)	**Diabetes (type 1 or 2)**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 92/2890 (3.2%)	RD 0.87 (0.22, 1.51)[1]
				Wild/wild, n = 8894/383909 (2.3%)	**RR 1.37 (1.12, 1.68)**[1]
				Men	**Men**
				C282Y/282Y, n = 61/1294 (4.7%)	RD 1.57 (0.41, 2.73)[1]
				Wild/wild, n = 5523/175539 (3.2%)	**RR 1.50 (1.17, 1.92)**[1]
				Women	**Women**
				C282Y/C282Y, n = 31/1596 (1.9%)	RD 0.32 (-0.35, 1.00)[1]
				Wild/wild, n = 3371/208370 (1.6%)	RR 1.20 (0.85, 1.70)[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Fatigue	**Fatigue**
				Whole sample	**Whole sample**
				C282Y/ C282Y, n = 144/2890 (5.0%)	RD 1.05 (0.26, 1.85)[1]
				Wild/wild, n = 15085/383909 (3.9%)	**RR 1.27 (1.08, 1.49)**[1]
				Men	**Men**
				C282Y/ C282Y, n = 68/1294 (5.3%)	RD 1.58 (0.36, 2.80)[1]
				Wild/wild, n = 6455/175539 (3.7%)	**RR 1.43 (1.13, 1.80)**[1]
				Women	**Women**
				C282Y/C282Y, n = 76/1596 (4.8%)	RD 0.62 (-0.43, 1.67)[1]
				Wild/wild, n = 8630/208370 (4.1%)	RR 1.15 (0.92, 1.43)[1]
				Liver disease	**Liver disease (any)**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 40/2890 (1.4%)	RD 0.92 (0.50, 1.35)[1]
				Wild/wild, n = 1774/383909 (0.5%)	**RR 3.00 (2.19, 4.09)**[1]
				Men	**Men**
				C282Y/C282Y, n = 31/1294 (2.4%)	**RD 1.88 (1.04, 2.71)**[1]
				Wild/wild, n = 910/175539 (0.5%)	**RR 4.62 (3.24, 6.58)**[1]
				Women	**Women**
				C282Y/C282Y, n = 9/1596 (0.6%)	RD 0.15 (-0.22, 0.52)[1]
				Wild/wild, n = 864/208370 (0.4%)	RR 1.36 (0.71, 2.62)[1]
				Myocardial infarction *or* angina	**Myocardial infarction *or* angina**
				Whole sample	**Whole sample**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = 131/2890 (4.5%)	**RD -0.89 (-1.66, -0.13)**[1]
				Wild/wild, n = 20836/383909 (5.4%)	**RR 0.84 (0.71, 0.99)**[1]
				Men	**Men**
				C282Y/C282Y, n = 84/1294 (6.5%)	**RD -1.68 (-3.03, -0.33)**[1]
				Wild/wild, n = 14341/175539 (8.2%)	**RR 0.79 (0.65, 0.98)**[1]
				Women	**Women**
				C282Y/C282Y, n = 47/1596 (2.9%)	RD -0.17 (-1.00, 0.66)[1]
				Wild/wild, n = 6495/208370 (3.1%)	RR 0.94 (0.71, 1.25)[1]
				Osteoarthritis	**Osteoarthritis**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 409/2890 (14.2%)	**RD 4.87 (3.60, 6.15)**[1]
				Wild/wild, n = 35627/383909 (9.3%)	**RR 1.53 (1.39, 1.67)** [1]
				Men	**Men**
				C282Y/C282Y, n = 182/1294 (14.1%)	**RD 6.60 (4.70, 8.50)** [1]
				Wild/wild, n = 13105/175539 (7.5%)	**RR 1.88 (1.64, 2.16)** [1]
				Women	**Women**
				C282Y/C282Y, n = 227/1596 (14.2%)	**RD 3.41 (1.70, 5.13)** [1]
				Wild/wild, n = 22522/208370 (10.8%)	**RR 1.32 (1.17, 1.49)** [1]
				Osteoporosis	**Osteoporosis**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 78/2890 (2.7%)	**RD 0.75 (0.16, 1.35)** [1]
				Wild/wild, n = 7469/383909 (2.0%)	**RR 1.39 (1.11, 1.73)** [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Men	**Men**
				C282Y/C282Y, n = 21/1294 (1.6%)	RD 0.96 (0.27, 1.65)[1]
				Wild/wild, n = 1164/175539 (0.7%)	**RR 2.45 (1.60, 3.76)** [1]
				Women	**Women**
				C282Y/C282Y, n = 57/1596 (3.6%)	RD 0.55 (-0.37, 1.46)[1]
				Wild/wild, n = 6305/208370 (3.0%)	RR 1.18 (0.91, 1.52)[1]
				Pneumonia	**Pneumonia**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 69/2890 (2.4%)	RD 0.44 (-0.12, 1.00)[1]
				Wild/wild, n = 7470/383909 (2.0%)	RR 1.23 (0.97, 1.55)[1]
				Men	**Men**
				C282Y/C282Y, n = 45/1294 (3.5%)	RD 1.29 (0.29, 2.29)[1]
				Wild/wild, n = 3844/175539 (2.2%)	**RR 1.59 (1.19, 2.12)** [1]
				Women	**Women**
				C282Y/C282Y, n = 24/1596 (1.5%)	RD -0.24 (-0.84, 0.36)[1]
				Wild/wild, n = 3626/208370 (1.7%)	RR 0.86 (0.58, 1.29)[1]
				Rheumatoid arthritis	**Rheumatoid arthritis**
				Whole sample	**Whole sample**
				C282Y/C282Y, n = 48/2890 (1.7%)	RD 0.37 (-0.10, 0.84)[1]
				Wild/wild, n = 4951/383909 (1.3%)	RR 1.29 (0.97, 1.71)[1]
				Men	**Men**
				C282Y/C282Y, n = 26/1294 (2%)	RD 1.13 (0.36, 1.89)[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				Wild/wild, n = 1552/175539 (0.9%) **Women** C282Y/C282Y, n = 22/1596 (1.4%) Wild/wild, n = 3399/208370 (1.6%)	**RR 2.27 (1.55, 3.34)** [1] **Women** RD -0.25 (-0.83, 0.32)[1] RR 0.85 (0.56, 1.28)[1]
18.	**Rossi 2001** [47]	Cross-sectional	Country: Australia 3010 community sample Busselton study	**Serum ferritin** **Whole sample** See Olynyk 1999[54] **Men** Not reported **Women** Not reported **Transferrin saturation** **Whole sample** See Olynyk 1999[54] **Men, >45%** C282Y/H63D, n = 7/33 (21.2%) Wild/wild, n = 90/1295 (6.9%) **Women, >45%** C282Y/H63D, n = 7/32 (21.9%) Wild/wild, n = 32/1268 (2.5%)	**Serum ferritin, mean µg/L** **Whole sample** See Olynyk 1999[54] **Men** **C282Y/H63D 323 (193, 457)** Wild/wild 177 (108, 277) **Women** C282Y/H63D 65 (35, 124) Wild/wild 63 (45, 164) **Transferrin saturation** **Whole sample** See Olynyk 1999[54] **Men** **RD 14.26 (0.25, 28.28)**[1] **RR 3.05 (1.54, 6.07)**[1] **Women** **RD 19.35 (5.00, 33.70)**[1] **RR 8.67 (4.14, 18.14)**[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					Transferrin saturation **Whole sample** See Olynyk 1999[54] **Men** **Women**
19.	**Waalen 2002**[48]	Cross-sectional	Country: USA 22553 primary care patients (white/Hispanic) Kaiser Permanente	**Serum ferritin** **Whole sample** C282Y/C282Y, n = 81/124 (65.3%) Wild/wild, n = 1887/22429 (8.4%) **Men, >250µg/L** C282Y/C282Y, n = 45/56 (80.4%) Wild/wild, n = 1403/10925 (12.8%) **Women, >200µg/L** C282Y/C282Y, n = 36/68 (52.9%) Wild/wild, n = 484/11504 (4.2%) **Transferrin saturation** **Whole sample**	**Serum ferritin** **Whole sample** **RD 56.91 (48.52, 65.29)** [1] **RR 7.76 (6.78, 8.89)** [1] **Men** **RD 67.52 (57.09, 77.94)** [1] **RR 6.26 (5.45, 7.19)** [1] **Women** **RD 48.73 (36.86, 60.60)** [1] **RR 12.58 (9.89, 16.00)** [1] **Transferrin saturation** **Whole sample**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = 67/124 (54.0%) Wild/wild, n = 225/22429 (1.0%) **Men, >55%** C282Y/C282Y, n = 35/56 (62.5%) Wild/wild, n = 77/10925 (0.7%) **Women, >45%** C282Y/C282Y, n = 32/68 (47.1%) Wild/wild, n = 148/11504 (1.3%)	**RD 53.03 (44.26, 61.80)** [1] **RR 53.86 (43.75, 66.31)** [1] **Men** **RD 61.80 (49.11, 74.48)** [1] **RR 88.68 (65.62, 119.84)** [1] **Women** **RD 45.77 (33.91, 57.64)** [1] **RR 36.58 (27.14, 49.31)** [1]
20.	**Waalen 2002**[49]	Cross-sectional	Country: USA 30916 primary care patients (white) Kaiser Permanente	**Angina** **Whole sample** C282Y/C282Y, n = 4/137 (2.9%) H63D/H63D, n = 40/729 (5.5%) C282Y/H63D, n = 28/548 (5.1%) Wild/wild, n = 953/19273 (5.0%) **Men** C282Y/C282Y, n = 1/68 (1.5%) H63D/H63D, n = 18/357 (5%) C282Y/H63D, n = 15/262 (5.7%) Wild/wild, n = 512/9566 (5.4%) **Women** C282Y/C282Y, n = 3/69 (4.4%) H63D/H63D, n = 22/372 (5.9%) C282Y/H63D, n = 13/286 (4.6%) Wild/wild, n = 441/9707 (4.5%)	**Angina** **Whole sample** RD C282Y/C282Y -2.03 (-4.86, 0.81) [1] H63D/H63D 0.54 (-1.14, 2.22) [1] C282Y/H63D 0.16 (-1.70, 2.03) [1] RR C282Y/C282Y 0.59 (0.22, 1.55)[1] H63D/H63D 1.11 (0.82, 1.51)[1] C282Y/H63D 1.03 (0.72, 1.49) [1] **Men** RD C282Y/C282Y -3.88 (-6.78, -0.99) [1] H63D/H63D -0.31 (-2.62, 2.00) [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					C282Y/H63D 0.37 (-2.48, 3.22) [1]
				Myocardial infarction	RR
				Whole sample	C282Y/C282Y 0.27 (0.04, 1.93) [1]
				C282Y/C282Y, n = 2/137 (1.5%)	H63D/H63D 0.94 (0.60, 1.49) [1]
				H63D/H63D, n = 30/729 (4.1%)	C282Y/H63D 1.07 (0.65, 1.76) [1]
				C282Y/H63D, n = 25/548 (4.6%)	**Women**
				Wild/wild, n = 621/19273 (3.2%)	RD
				Men	C282Y/C282Y -0.20 (-5.02, 4.63) [1]
				C282Y/C282Y, n = 2/68 (2.9%)	H63D/H63D 1.37 (-1.06, 3.80) [1]
				H63D/H63D, n = 22/357 (6.2%)	C282Y/H63D 0.00 (-2.45, 2.45) [1]
				C282Y/H63D, n = 21/262 (8.0%)	RR
				Wild/wild, n = 466/9566 (4.9%)	C282Y/C282Y 0.96 (0.32, 2.91) [1]
				Women	H63D/H63D 1.30 (0.86, 1.97) [1]
				C228Y/C282Y, n = 0/69 (0%)	C282Y/H63D 1.00 (0.58, 1.71) [1]
				H63D/H63D, n = 8/372 (2.2%)	
				C282Y/H63D, n = 4/286 (1.4%)	**Myocardial infarction**
				Wild/wild, n = 155/9707 (1.6%)	**Whole sample**
					RD
					C282Y/C282Y -1.76 (-3.79, 0.26) [1]
					H63D/H63D 0.89 (-0.57, 2.36) [1]
					C282Y/H63D 1.34 (-0.42, 3.10) [1]
					RR
					C282Y/C282Y 0.45 (0.11, 1.80) [1]
					H63D/H63D 1.28 (0.89, 1.83) [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					C282Y/H63D 1.42 (0.96, 2.09) [1] **Men** RD C282Y/C282Y -1.93 (-5.97, 2.11) [1] H63D/H63D 1.29 (-1.24,3.82) [1] C282Y/H63D 3.14 (-0.17, 6.46) [1] RR C282Y/C282Y 0.60 (0.15, 2.37) [1] H63D/H63D 1.27 (0.84, 1.91) [1] **C282Y/H63D 1.65 (1.08, 2.50)** [1] **Women** RD C282Y/C282Y -1.60 (-3.59, 0.39) [1] H63D/H63D 0.55 (-0.94, 2.05) [1] C282Y/H63D -0.20 (-1.58, 1.19) [1] RR C282Y/C282Y 0.45 (0.03, 7.09) [1] H63D/H63D 1.35 (0.67, 2.72) [1] C282Y/H63D 0.88 (0.33, 2.35) [1] **Serum ferritin, mean ng/mL** **Men** C282Y/C282Y 369 (265, 513) H63D/H63D 139 (128, 152)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					C282Y/H63D 186 (169, 205) Wild/wild 186 (169, 205) **Women** C282Y/C282Y 175 (126, 245) H63D/H63D 61 (55, 67) C282Y/H63D 71 (63, 79) Wild/wild 53 (52, 54) **Transferrin saturation, % (SD)** **Men** C282Y/C282Y 63 (21) H63D/H63D 34 (11) C282Y/H63D (39 (13) Wild/wild 27 (9) **Women** C282Y/C282Y 52 (22) H63D/H63D 29 (11) C282Y/H63D 33 (13) Wild/wild 23 (9)
21.	**Wood 2017**[50]	Cross-sectional	Country: Australia 291 Canberra Hospital, Royal Brisbane and Women's Hospital, the QIMR Berghofer Medical	**Fibrosis/cirrhosis** **Whole sample** C282Y/C282Y Stage 0, n = 163/291 (56.0%) Stage 1, n = 40 (13.8%)	**NA**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			Research Institute, Brisbane, Australia	Stage 2, n = 32 (11.0) Stage 3, n = 17 (5.8%) Stage 4 (cirrhosis), n = 39 (13.4%0 Wild/wild, n = NA **Arthritis** Deprioritised	
	Question 2				
1.	**Cadet 2003**[62]	Case control	Country: France Cases, n = 159 (osteoporosis), 227 (fatigue & arthralgia); diagnosis of osteoporosis based on radiographical analysis, diagnosis method for fatigue/arthralgia not reported Controls, n = 992	**Osteoporosis (n = 159)** C282Y/C282Y, n = 1 (0.6%) H63D/H63D, n = 4 (2.5%) C282Y/H63D, n = 3 (1.9%) Wild/wild, n = 89 (56%) Other, n = 62 (39%) **Fatigue/arthralgia (n = 227)** C282Y/C282Y, n = 13 (5.7%) H63D/H63D, n = 21 (9.3%) C282Y/H63D, n = 18 (7.9%) Wild/wild, n = 102 (44.9%) Other, n = 73 (32.2%) **Controls (n = 991)**	**Osteoporosis** C282Y/C282Y, OR 3.40 (0.31, 37.87) [1] H63D/H63D, OR 1.01 (0.35, 2.97) [1] C282Y/H63D, OR 0.72 (0.21, 2.41) [1] **Fatigue/arthralgia** **C282Y/C282Y, OR 38.49 (8.56, 173.09)** [1] **H63D/H63D, OR 4.61 (2.51, 8.46)** **C282Y/H63D, OR 3.68 (1.97, 6.86)** [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y/C282Y, n = 2 (0.2%) H63D/H63D, n = 27 (2.7%) C282Y/H63D, n = 29 (2.9%) Wild/wild, n = 604 (60.9%) Other, n = 329 (33.2%)	
2.	**Ekblom 2011**[61]	Case control	Country: Sweden Cases, n = 618; diagnosis method ICD-9 410, ICD-10 I21-3, "Suspected events were screened according to WHO-MONICA criteria and validated using hospital records, general practitioner's reports, death certificates, and, when available, autopsy reports." Controls, n = 1184	**Myocardial infarction, tested for C282Y (n = 587)** C282Y/C282Y, n = 4 (0.7%) Wild/wild, n = 502 (85.6%) Other, n = 81 (13.8%) **Controls, tested for C282Y (n = 1094)** C282Y/C282Y, n = 4 (0.4%) Wild/wild, n = 928 (84.8%) Other, n = 162 (14.8%) **Myocardial infarction, tested for H63D (n = 577)** H63D/H63D, n = 6 (1.0%) Wild/wild, n = 442 (76.7%) Other, n = 129 (22.4%) **Controls, tested for H63D (n = 1097)**	**Whole sample** C282Y/C282Y, OR 2.62 (0.59, 11.73) H63D/H63D, OR 2.02 (0.96, 4.25) **Men** H63D/H63D, OR 1.26 (0.48, 3.28) **Women** **H63D/H63D, OR 4.76 (1.23, 18.45)**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				H63D/H63D, n = 15 (1.4%) Wild/wild, n = 854 (77.9%) Other, n = 228 (20.8%) **Myocardial infarction, tested for C282Y, men vs women (n = 587)** Men (n = 427) C282Y/C282Y, n = 3 (0.7%) Wild/wild, n = 366 (85.7%) Other, n = 58 (13.6) Women (n = 160) C282Y / C282Y, n = 1 (0.6%) Wild/wild, n = 136 (85.0%) Other, n = 23 (14.4) **Controls, tested for C282Y, men vs women (n = 1094)** Men (n = 798) C282Y/C282Y, n = 3 (0.4%) Wild/wild, n = 674 (84.5%) Other, n = 121 (15.2%) Women (n = 296)	

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				C282Y / C282Y, n = 1 (0.3%) Wild/wild, n = 254 (85.1%) Other, n = 41 (18.9%) **Myocardial infarction, tested for H63D, men vs women (n = 585)** Men (n = 425) H63D/H63D, n = 7 (1.6%) Wild/wild, n = 327 (76.9%) Other, 91 (21.4%) Women (n = 160) H63D/H63D, n = 7 (4.4%) Wild/wild, n = 115 (71.9%) Other, n = 38 (23.8%) **Controls, tested for H63D, men vs women (n = 939)** Men (n = 642) H63D/H63D, n = 12 (1.9%) Wild/wild, n = 623 (97.0%) Other, n = 7 (1.1%) Women (n = 297)	

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
				H63D/H63D, n = 3 (1.0%) Wild/wild, n = 231 (77.8%) Other, n = 63 (21.2%)	
3.	**Ellervik 2001**[60]	Case control	Country: Denmark Cases, n = 716; WHO criteria Controls, n = 9,174	**Late-onset type 1 diabetes (n = 716)** C282Y/C282Y, n = 9 (1.3%) H63D/H63D, n = 15 (2.1%) C282Y/H63D, n = 8 (1.1%) Wild/wild, n = 474 (66.2%) Other, n = 210 (29.3%) **Controls (n = 9174)** C282Y/C282Y, n = 23 (0.3%) H63D/H63D, n = 158 (1.7%) C282Y/H63D, n = 131 (1.4%) Wild/wild, n = 6135 (66.9%) Other, n = 2727 (29.7%)	**C282Y/C282Y, OR 4.60 (2.10, 10.10)** [1] H63D/H63D, OR 1.20 (0.70, 2.10) [1] C282Y/H63D, OR 0.80 (0.40, 1.70) [1]
4.	**Ellervik 2007**[69]	Systematic review	**Arthritis** Cases, n = 15,371; diagnosis methods self-report (diagnosis or symptoms), “clinical diagnosis”, “internationally accepted criteria”, criteria of The American Rheumatism Association, American College of Rheumatology 1987 revised criteria, radiographic findings,	Not reported	**Arthritis** C282Y/C282Y, OR 2.40 (0.50, 13.00) H63D/H63D, OR 1.50 (0.70, 3.00) C282Y/H63D, OR 1.20 (0.70, 2.10)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			radiological, operative, and histological findings Controls, n = 27,016 **Myocardial infarction** Cases, n = 8,567; diagnosis methods not reported Controls, n = 42,103		**Myocardial infarction** C282Y/C282Y, OR 1.10 (0.60, 2.00) H63D/H63D, OR 1.20 (0.90, 1.60) C282Y/H63D, OR 1.10 (0.90, 1.50)
5.	**Habeos 2003**[59]	Case control	Country: Greece Cases, n = 100; diagnosis method not reported Controls, n = 100	**Type 2 diabetes group (n = 100)** C282Y/C282Y, n = 0 (0%) H63D/H63D, n = 0 (0%) C282Y/H63D, n = 0 (0%) Wild/wild, n = 75 (75%) Other, n = 25 (25%) **Controls (n = 100)** C282Y/C282Y, n = 0 (0%) H63D/H63D, n = 0 (0%) C282Y/H63D, n = 0 (0%) Wild/wild, n = 76 (76%) Other, n = 24 (24%)	C282Y/C282Y, OR 1.01 (0.02, 51.73) H63D/H63D, OR 1.01 (0.02, 51.73) C282Y/H63D, OR 1.01 (0.02, 51.73)
6.	**Halsall 2003**[58]	Case control	Country: England Cases, n = 512; diagnosis method not reported	**Type 2 diabetes group (n = 512)** C282Y/C282Y, n = 2 (0.4%) C282Y/H63D, n = 9 (1.8%)	C282Y/C282Y, OR 0.50 (0.09, 2.80) [1] C282Y/H63D, OR 3.05 (0.82, 11.35) [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			Controls, n = 508	Wild/wild, n = 450 (87.9%) Other, n = 51 (9.9%) **Controls (n = 508)** C282Y/C282Y, n = 4 (0.8%) C282Y/H63D, n = 3 (0.6%) Wild/wild, n = 456 (89.8%) Other, n = 45 (8.9%)	
7.	**Hannuksela 2005[64]**	Case control	Country: Finland Cases, n = 91; diagnosis method "dilated cardiomyopathy (left ventricular ejection fraction (LVEF)<45% and left ventricular end diastolic diameter (LVEDD) > 27 mm/m2) and exclusion of secondary causes of DCM" Controls, n = 102	**Cases (n = 91)** C282Y/C282Y, n = 0 (0%) H63D/H63D, n = 0 (0%) Wild/wild, n = 32 (35.2%) Other, n = 59 (64.8%) **Controls (n = 102)** C282Y/C282Y, n = 0 (0%) H63D/H63D, n = 3 (2.9%) Wild/wild, n = 74 (72.6%) Other, n = 25 (24.5%)	C282Y/C282Y, OR 1.25 (0.03, 64.05)[1] H63D/H63D, OR 0.18 (0.01, 3.53)[1]
8.	**Mahon 2000[63]**	Case control	Country: UK Cases: n = 207; diagnosis method "dilated cardiomyopathy by World Health Organization criteria"	**Cardiomyopathy (n = 207)** C282Y/C282Y, n = 1 (0.5%) H63D/H63D, n = 4 (1.9%) C282Y/H63D, n = 10 (4.8%)	C282Y/C282Y, OR 3.62 (0.15, 89.69)[1] H63D/H63D, OR 0.81 (0.22, 2.93)[1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			Controls, n = 200	Wild/wild, n = 102 (49.3%) Other, n = 90 (43.5%) **Controls (n = 200)** C282Y/C282Y, n = 0 (0%) H63D/H63D, n = 6 (3%) C282Y/H63D, n = 4 (2%) Wild/wild, n = 123 (61.5%) Other, n = 67 (33.5%)	C282Y/H63D, OR 3.02 (0.92, 9.90)[1]
9.	**Moirand 1999**[57]	Case control	Country: France Cases, n = NR; diagnosis method "documented on history and physical examination" Controls, n = NR	**Hyperpigmentation group (n = NE)** C282Y/C282Y, n = 144 (NC%) H63D/H63D, n = 5 (NC%) C282Y/H63D, n = 11 (NC%) Wild/wild, n = 14 (NC%) Other, n = NE (NC%) **No hyperpigmentation group (n = NE)** C282Y/C282Y, n = 122 (NC%) H63D/H63D, n = 11 (NC%) C282Y/H63D, n = 40 (NC%) Wild/wild, n = 62 (NC%) Other, n = NE (NC%)	**C282Y/C282Y, OR 5.23 (2.80, 9.80)** [1] H63D/H63D, OR 2.01 (0.60, 6.72) [1] C282Y/H63D, OR 1.22 (0.50, 2.96) [1]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
10.	**Møller 2010**[65]	Cross-sectional	**Heart failure** Cases, n = 667; depressed left ventricular function corresponding to wall motion index (WMI) ≤ 1.2 Controls, n = NA	**Heart failure** C282Y/C282Y, n = 3 (0.4%) H63D/H63D, n = 12 (1.8%) C282Y/H63D, n = 12 (1.8%) Wild/wild, n = 436 (65.4%) Other, n = 204 (30.6%)	NA
11.	**Neghina 2011**[68]	Systematic review	**Serum ferritin** Cases, n = 637; >200 ng/mL, >200 µg/L in women and >300 µg/L in men, and ≥300 µg/L Controls, n = 3,206 **Transferrin saturation** Cases, n = unclear; ≥45%, ≥50% in women and ≥60% in men, and ≥55% Controls, n = unclear	Not reported	**Serum ferritin** **C282Y/C282Y (2 studies), OR 69.17 (6.99, 683.97)** H63D/H63D (3 studies), OR 2.28 (0.62, 8.31) **C282Y/H63D (2 studies), OR 10.79 (1.17, 99.01)** **Transferrin saturation** **C282Y/C282Y (2 studies), OR 613.87 (11.73, 32125.72)** **H63D/H63D (2 studies), OR 7.17 (1.25, 41.29)** **C282Y/H63D (1 study), OR 13.73 (2.43, 77.75)**
12.	**Van der 2008**[67]	Systematic review	Cases: n = 5724; diagnosis ICD-9 code 410 or ICD-10 codes I21 and I22	**Acute myocardial infarction (n = 5724)** C282Y/C282Y, n = 33 (0.6%) H63D/H63D, n = 129 (2.3%)	C282Y/C282Y OR 1.01 (0.65, 1.57)[a] OR 0.97 (0.58, 1.64)[b] OR 1.12 (0.71, 1.77)[c]

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
			Controls: n = 43366	C282Y/H63D, n = 121 (2.1%) Wild/wild, n = 3520 (61.5%) Other, n = 1921 (33.6%) **Controls (n = 43366)** C282Y/C282Y, n = 193 (0.5%) H63D/H63D, n = 920 (2.1%) C282Y/H63D, n = 744 (1.7%) Wild/wild, n = 27,361 (63.1%) Other, n = 14,148 (32.6%)	OR 0.94 (0.50, 1.76)[d] <u>H63D/H63D</u> OR 1.14 (0.92, 1.42)[a] OR 1.13 (0.90, 1.42)[b] OR 1.16 (0.93, 1.44)[c] OR 1.12 (0.88, 1.42)[d] <u>C282Y/H63D</u> OR 1.10 (0.88, 1.38)[a] OR 1.10 (0.87, 1.41)[b] OR 1.09 (0.86, 1.38)[c] OR 1.15 (0.88, 1.50)[d] [a] Adjusted for study [b] Excluding studies by Candore et al and Hetet et al [c] Adjusted for study, age, and sex: [d] Adjusted for study, age, sex, current smoking, hypertension, hypercholesterolemia, type 2 diabetes
13.	**Ye 2016**[66]	Systematic review	Cases, n = unclear Controls, n = unclear	Not reported	**Cirrhosis** C282Y/C282Y (studies, n = 9), OR 0.88 (0.41, 1.91)

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					H63D/H63D (studies, n = 23), OR 1.07 (0.72, 1.58) C282Y/H63D (studies, n = 10), OR 0.86 (0.50, 1.48) **Liver cancer** **C282Y/C282Y (studies, n = 10), OR 3.16 (1.02, 9.79)** H63D/H63D (studies, n = 18), OR 0.99 (0.65, 1.51) **C282Y/H63D (studies, n = 14), OR 1.70 (1.03, 2.80)** **NAFLD** C282Y/C282Y (studies, n = 8), OR 3.32 (0.72, 15.36) H63D/H63D (studies, n = 13), OR 1.47 (0.97, 2.22) C282Y/H63D (studies, n = 6), OR 1.45 (0.63, 3.32)
	Question 3				
	Ong 2017[113]	Cohort	Country: Australia Asymptomatic, n = not reported Symptomatic, n = not reported	Not applicable	Mean fatigue scores after treatment **Asymptomatic group, -6.1 points, (-9.6, -2.6)** **Symptomatic group, -8.8 points (-15.3, -2.3)**

No.	Study reference, review questions	Study design	Population characteristics	Prevalence and incidence outcomes	Measure of risk, association, difference, mean values (95% confidence interval, unless otherwise stated)
					Between group difference, 2.7 points (-10.1, 4.6)
	Whitlock 2006[30]	Systematic review	Not applicable, no studies identified	Not applicable	Not applicable

Note. Figures in **bold** are significantly different compared to the wild/wild genotype
[1] calculated by review team, [2] extracted by review team using WebPlotDigitizer (https://apps.automeris.io/wpd/)
HR = hazard ratio, IQR = interquartile range, n = number, NC = not calculable, NE = not extractable, NR = not reported, OR = odds ratio, RD = risk difference, RR = relative risk

Table 30. Question 1 deprioritised studies

	Author, year	Country	Study design	Total no. participants	No. with disease	No. without disease	Primary outcome(s)	Reason for deprioritisation
1.	Adams 2001[109]	Canada	Case control	100	22	78	Serum ferritin, transferrin saturation	Sample size
2.	Adams 2005[56]	Canada, USA	Cross-sectional	227	227	0	Serum ferritin, transferrin saturation	Sample size, study design
3.	Al Abbas 2014[110]	US	Cohort	101	101	NA	Serum ferritin	Sample size
4.	Alizadeh 2006[117]	Netherlands	Cohort	1339	21	1318	Osteoarthritis	Subsample (>55 years only)
5.	Bacon 1999[111]	US	Cross-sectional	198	66	132	Serum ferritin, transferrin saturation, fibrosis (only assessed in 9 participants)	Sample size
6.	Barton 2015[112]	US	Retrospective study	235	35	200	Serum ferritin, transferrin saturation	Sample size
7.	Barton 2016[72]	Canada, US	Cohort	248	26	222	Serum ferritin, transferrin saturation, diabetes	Sample size

8.	Barton 2016[106]	Canada, US	Cohort	672	223	449	Serum ferritin, transferrin saturation	Sample size
9.	Barton 2017[118]	Canada	Cohort	373	373	0	Liver disease	Sample size, study design, subsample (African-American only)
10.	Beaton 2002[119]	Canada	Cohort	193	193	0	Serum ferritin, transferrin saturation, diabetes, arrhythmia, arthritis	Sample size
11.	Carter 2003[107]	UK	Cohort	438	173	265	Serum ferritin, transferrin saturation	Sample size
12.	Cassanelli 2001[108]	Italy	Cohort	2100	54	2046	Serum ferritin, transferrin saturation	Subsample (blood donors)
13.	Castiella 2010[102]	Spain	Case control	210	54	116	Serum ferritin, transferrin saturation	Sample size
14.	Chambers 2003[103]	UK	Cross-sectional study	6261 blood donors	280	5981	Unsaturated iron binding capacity, serum ferritin	Subsample (blood donors, men only)
15.	Dawkins 2007[104]	US	Cross-sectional	27224	70	27154	Serum ferritin, transferrin saturation	Subsample (Afrian-American only)
16.	Deugnier 2002[71]	Canada, France	Cohort	9396	54	9342	Chronic fatigue, serum ferritin, transferrin saturation	Subsample (age)
17.	Distante 1999[105]	Norway	Cohort	505 healthy subjects	2 (C282Y/C282Y)	503	Serum ferritin , Transferrin saturation,	Sample size
18.	Gerhard 2011[101]	US	Cohort	1064	33	1031	Serum ferritin, transferrin saturation (mentions iron binding capacity, but does not specify form)	Subsample (obese, white, undergoing gastric by-pass surgery)
19.	Gordeuk 2012[120]	Canada, US	Cohort	213	213	0	Serum ferritin	Sample size, study design
20.	Gordeuk 2017[100]	Canada, US	Cross-sectional	21975	55	20512 (wild type) 1408 (heterozygous)	Serum ferritin, transferrin saturation	Subsample (women only)

21.	Greni 2017[99]	Italy	Cohort	467	298	169	Serum ferritin, transferrin saturation	Sample size
22.	Gurrin 2008[121]	Australia	Cohort	203	203	0	Serum ferritin, transferrin saturation	Sample size, study design
23.	Gurrin 2009[98]	Australia	Cohort	510	180	330	Serum ferritin, transferrin saturation	Sample size
24.	Hannuksela 2003[97]	Finland	Cross-sectional	137	32	105	Serum ferritin, transferrin saturation	Sample size
25.	Jackson 2001[96]	UK	Cross-sectional	10556	574	9982	Serum ferritin, transferrin saturation, unsaturated iron binding capacity	Subsample (blood donors)
26.	Kanková 2002[78]	Czech Republic	Cross-sectional	113	108	5	Type 2 diabetes	Country, sample size
27.	Kelley 2014[122]	Canada	Cohort	170	170	0	Serum ferritin, transferrin saturation	Sample size, study design
28.	Lee 2009[95]	Korea	Cohort	484	41	443	Serum ferritin, transferrin saturation	Sample size
29.	McCune 2006[123]	UK	Cohort	286	286	0	Serum ferritin, transferrin saturation	Sample size, study design
30.	Mohammad 2013[124]	Republic of Ireland	Cross-sectional	395	395	0	Fatigue, serum ferritin, transferrin saturation	Sample size, stud design
31.	Pelucchi 2012[125]	Italy	Case control	306	306	0	Serum ferritin, transferrin saturation	Sample size, study design
32.	Powell 2006[126]	Australia	Cohort	672	672	0	Serum ferritin, transferrin saturation, hepatomegaly, fibrosis	Overlap with Wood (2017)
33.	Ramakrishna 2013[94]	Australia	Case control	194	104	90	Serum ferritin, transferrin saturation	Sample size, study design
34.	Rossi 1999[93]	Australia	Cohort	141	72	69	Serum ferritin, transferrin saturation	Sample size

35.	Rossi 2000[91]	Australia	Cross-sectional	1327	35	1143	Serum ferritin, transferrin saturation	Subsample (women only)
36.	Rossi 2004[92]	Australia	Cohort	1352	29	1165	Serum ferritin, transferrin saturation	Subsample (women ≥70 years only)
37.	Ryan 2002[127]	Ireland	Cohort	109	109	0	Serum ferritin, transferrin saturation, fatigue	Sample size, study design
38.	Ryan 2015[70]	Ireland	Cohort	105	70	35	Serum ferritin, transferrin saturation, fatigue,	Sample size
39.	Salonen 2000[81]	Finland	Cohort	555	35	520	Diabetes	Sample size, subsample (men only)
40.	Samara sena [88]2006	Canada	Cohort	820	170	371	Serum ferritin, transferrin saturation	Sample size
41.	Trieß 2012[128]	Germany	Cross-sectional	414	414	0	Serum ferritin, transferrin saturation (study includes cirrhosis, but assessed in fewer than 100 participants)	Study size, study design
42.	van der 2006[89]	Netherlands	Cohort	1611	49	1035	Serum ferritin, transferrin saturation	Subsample (women ≥ 70 years only)
43.	Vizzi 2005[90]	Venezuela	Cross-sectional study	214	52	162	Serum ferritin	Sample size, subsample (majority blood donors)
44.	Walsh 2006[129]	Australia	Cross-sectional	574	574	0	Fibrosis/cirrhosis, serum ferritin, Transferrin saturation	Overlap with Wood (2017)
45.	Wood 2012[130]	Australia	Cohort	291	291	0	Serum ferritin, transferrin saturation, diabetes (but included self-reported diabetes)	Sample size, study design

Table 31. Question 2 deprioritised studies

	Author, year	Country	Study design	Eligible disease	Sample size	No. with/without disease		Reason for deprioritisation
						With disease	Without disease	
1.	Aigner 2007[131]	Austria	Case control	Rheumatoid arthritis	193	31	162	Sample size
2.	Alkhateeb 2009[73]	Jordan	Case control	Type 2 diabetes	293	89	204	Country
3.	Altes 2003[84]	Spain	Cohort	Serum ferritin	150	129	21	Sample size, study design
				Transferrin saturation	150	143	7	
4.	Balistreri 2002[85]	Italy	Case control	Liver disease	198	92	106	Sample size
				Serum ferritin	130	24	106	
5.	Baptista-Gonzalez 2007[86]	Mexico	Cross-sectional	Iron overload (serum ferritin)	492	246	246	Country, sample size.
6.	Battiloro 2000[132]	Italy	Case control	Myocardial infarction	362	175	187	Included in Ye 2016 review
7.	Boige 2005[133]	France	Cohort	Liver cancer	233	133	100	Sample size, study design
8.	Bugianesi 2004[134]	Italy	Cohort	Non-alcoholic fatty liver disease	263	263	0	Sample size, study design,

9.	Calado 2000[135]	Brazil	Case-control	Acute myocardial infarction	320	160	160	Sample size, country
10.	Carroll 2006[136]	Australia	Cohort	Primary osteoarthritis	20	20	0	Sample size
11.	Castiella 2017[137]	Spain	Cohort	Iron overload (serum ferritin)	132	132	0	Study design, sample size
12.	Cauza 2003[138]	Austria	Case control	Liver cancer	649	162	487	Study design, sample size
13.	Claeys 2002[139]	Switzerland	Case control	Myocardial infarction	206	117	89	Included in Ellervik 2005 review
14.	Colli 2011[74]	Brazil	Case control	Type 2 diabetes	723	519	204	Country
15.	Davis 2008[75]	Australia	Cohort	Type 2 diabetes	1245	1245	0	Study design
16.	Ellervik 2005[51]	Denmark	Case control	Myocardial infarction	9193	1113	8080	Included in Ellervik 2007 review
17.	Ezzikouri 2008[140]	Morocco	Case control	Liver cancer	318	96	222	Country, study design

18.	Florkowski 1999[76]	New Zealand	Case control	Type 2 diabetes	1294	230	1064	Country
19.	Funakoshi 2016[141]	France	Cohort	Liver cancer	234	234	0	Sample size, study design
20.	Gomes 2009[77]	Brazil	Case control	Type 2 diabetes	144	72	72	Country, sample size
21.	Hagen 2002[142]	Norway	Cross-sectional	Iron overload (serum ferritin)	496	496	0	Sample size, study design
22.	Hellerbrand 2003[143]	Germany	Case control	Liver cancer	263	137	126	Included in Ye 2016 systematic review
23.	Jowkar 2011[144]	Iran	Case control	Cirrhosis	150	100	50	Country, sample size
24.	Kanková 2002[78]	Czech Republic	Case control	Type 2 diabetes	326	162	164	Country, sample size
25.	Kennish 2014[145]	USA	Case control	Osteoarthritis	147	127	20	Sample size, study design
26.	Kirk 2009[79]	Ireland	Case control	Diabetes (types 1 and 2)	489	249	249	Sample size
27.	Kwan 1998[146]	Canada	Cohort	Type 1 diabetes	103	103	0	Sample size, study design (for both diseases)
				Type 2 diabetes	105	105	0	

28.	Lee 2010[147]	South Korea	Case control	Non-alcoholic fatty liver disease	346	125	221	Country, sample size, study design
29.	McGrath 2002[116]	Canada, France	Cohort	Iron overload (serum ferritin, transferrin saturation)	8572	8572	0	Study design
30.	Nassar 1998[148]	Canada	Cross-sectional	Angina or myocardial infarction (combined)	300	300	0	Study design, sample size
31.	Nelson 2007[149]	Canada, USA	Cohort	Nonalcoholic steatohepatitis/ non-alcoholic fatty liver disease	126	126	0	Sample size, study design
32.	Oliva 2004[150]	Spain	Cross-sectional	Type 2 diabetes	225	225	0	Study design, sample size
33.	Oppl 2018[151]	Austria	Cross-sectional	Osteoarthritis	1880	940	940	Study design, subsample (surgery patients)
34.	Panigrahi 2006[152]	India	Case control	Cirrhosis	105	31	74	Country, sample size
35.	Peterlin 2003[153]	Slovenia	Cross-sectional	Type 2 diabetes	223	223	0	Study design, sample size

36.	Piperno 1998[87]	Italy	Case control	Iron overload (serum ferritin, transferrin saturation)	327	188	139	Included in Neghina 2011 systematic review
37.	Poullis 2003[154]	UK	Cohort	Transferrin saturation	377	156	221	Sample size, study design
38.	Qi 2005[80]	US	Case control	Type 2 diabetes	1834	714	1120	Subsample (women only)
39.	Ross 2003[155]	USA	Case control	Osteoarthritis	2314	176	2138	Included in Ellervik 2007 systematic review
40.	Sampson 2000[82]	UK	Case control	Type 2 diabetes	440	220	220	Subsample (men only), sample size
41.	Sharifi 2008[83]	Iran	Case control	Type 2 diabetes	202	101	101	Country, sample size
42.	Valenti 2010[156]	Italy	Case control	Non-alcoholic fatty liver disease	771	587	184	Include in Ye 2016 systematic review
43.	Wang 2012[157]	Australia	Cohort	Osteoarthritis	27848	27848	0	Study design
44.	Willis 2000[158]	UK	Case control	Liver disease (cirrhosis, cancer)	924	224	700	Include in Ye 2016 systematic review

45.	Willis 2005[159]	UK	Cross-sectional	Liver cancer	144	144	0	Sample size, study design
46.	Wong 2006[160]	Canada	Cohort	Serum ferritin	482	482	0	Study design

HH = hereditary haemochromatosis, NA = not applicable, NE = not extractable, NR = not reported

Appraisal for quality and risk of bias

Quality assessments of included studies are reported below.

Table 32. Question 1 quality appraisal of included studies

Study	Risk of bias domains					
	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Andersen 2004;[53] Ellervik 2005;[51] Ellervik 2007[52]	Moderate	Moderate	Low	Low	Moderate	Moderate
Beutler 2000;[38] Beutler 2002;[36] Beutler 2003;[37] Waalen 2002;[48] Waalen 2002[49]	Moderate	High	Low	High	Moderate	Moderate
Burt 1998[39]	Moderate	High	Moderate	Moderate	Moderate	Moderate
Cobbaert 2002[55]	Moderate	High	Moderate	Moderate	High	Moderate
Gallego 2015[41]	Moderate	Moderate	Moderate	High	Moderate	Moderate
Greenwood	Moderate	High	Moderate	Moderate	High	Moderate
Henriksen 2016[44]	High	High	Moderate	Low	High	Moderate
McLaren 2008[45]	Moderate	Moderate	Moderate	High	Moderate	Moderate
Olynyk 1999;[54] Gochee 2002[42]; Fox 2002; Rossi 2001	Moderate	High	Moderate	Moderate	High	Moderate
Pankow 2008[46]	Moderate	High	Moderate	Moderate	Moderate	Moderate
Pilling 2019[32]	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Wood 2017[50]	Moderate	High	Moderate	Moderate	Low	Low

Table 33. Question 2 quality appraisal of case control studies

Study	Risk of bias domains									
	Groups comparable	Groups matched	Same identification criteria	Exposure measurement standard, reliable, and valid	Exposure measurement same for groups	Confounder identified	Confounders addressed	Outcomes assessed in a standard, valid and reliable way	Exposure period long enough	Appropriate statistics
Cadet 2003[62]	Unclear	High	Unclear	Unclear	Unclear	High	High	Unclear	NA	High
Ekblom 2011[61]	Low	Low	Unclear	Low	Low	Low	Low	Low	NA	Low
Ellervik 2001[60]	Unclear	High	High	High	High	Unclear	Low	Low	NA	Low
Habeos 2003[59]	Unclear	Low	Unclear	Unclear	Unclear	High	High	Low	NA	Low
Halsall 2003[58]	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Low	NA	Low
Hannuksela 2005[64]	Unclear	High	Unclear	Low	Unclear	Low	Low	Low	NA	High
Mahon 2000[63]	Unclear	High	Unclear	Low	Unclear	Low	Low	Low	NA	Low
Moirand 1999[57]	Unclear	High	Low	Unclear	Unclear	High	High	Low	NA	Unclear

NA = not applicable

Table 34. Question 2 quality appraisal of cross-sectional study

	Risk of bias							
Study	Inclusion criteria clearly defined	Participants and setting clearly described	Exposure measurement standard, reliable, and valid	Condition measured using objective, standard criteria	Confounder identified	Confounders addressed	Outcomes assessed in a standard, valid and reliable way	Appropriate statistics
Møller 2010[65]	Low	Low	Low	Low	High	High	Low	Low

Table 35. Question 2 quality appraisal of systematic reviews

Study	Risk of bias domains				
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings	RISK OF BIAS IN THE REVIEW
Ellervik 2007	Unclear	Unclear	High	Unclear	High
Neghina 2011	High	High	High	Low	High
Van der 2008	High	High	High	Unclear	High
Ye 2016	High	High	High	Unclear	High

Table 36. Question 3 quality appraisal of cohort study

Study	Risk of bias domains										
	Groups comparable	Similar measure of exposure between groups	Exposure measurement valid and reliable	Confounders identified	Confounders addressed	Participants free of outcomes at baseline	Outcome measurement valid and reliable	Follow up long enough	Follow up complete/loss to follow up explored	Strategies to address missing data	Appropriate statistics
Ong 2017[113]	Unclear	Low	Unclear	Low	Low	Unclear	High	Unclear	Unclear	Unclear	Low

Table 37. Question 3 quality appraisal of systematic review

Study	Risk of bias domains			
	Study eligibility criteria	Identification and selection of studies	Data collection and study appraisal	Synthesis and findings
Whitlock 2006[30]	Low	Low	NA	NA

NA = not applicable

Appendix 4 – UK NSC reporting checklist for evidence summaries

All items on the UK NSC Reporting Checklist for Evidence Summaries have been addressed in this report. A summary of the checklist, along with the page or pages where each item can be found in this report, is presented in Table .

Table 38. UK NSC reporting checklist for evidence summaries

	Section	Item	Page no.
1.	TITLE AND SUMMARIES		
1.1	Title sheet	Identify the review as a UK NSC evidence summary.	Title page
1.2	Plain English summary	Plain English description of the executive summary.	5
1.3	Executive summary	Structured overview of the whole report. To include: the purpose/aim of the review; background; previous recommendations; findings and gaps in the evidence; recommendations on the screening that can or cannot be made on the basis of the review.	6
2.	INTRODUCTION AND APPROACH		
2.1	Background and objectives	Background – Current policy context and rationale for the current review – for example, reference to details of previous reviews, basis for current recommendation, recommendations made, gaps identified, drivers for new reviews	12
		Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, criteria they address, and number of studies included per question, description of the overall results of the literature search.	15

		Method – briefly outline the rapid review methods used.	
2.2	Eligibility for inclusion in the review	State all criteria for inclusion and exclusion of studies to the review clearly (PICO, dates, language, study type, publication type, publication status etc.) To be decided *a priori*.	17
2.3	Appraisal for quality/risk of bias tool	Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR.	29
3.	SEARCH STRATEGY AND STUDY SELECTION (FOR EACH KEY QUESTION)		
3.1	Databases/ sources searched	Give details of all databases searched (including platform/interface and coverage dates) and date of final search.	29
3.2	Search strategy and results	Present the full search strategy for at least one database (usually a version of Medline), including limits and search filters if used. Provide details of the total number of (results from each database searched), number of duplicates removed, and the final number of unique records to consider for inclusion.	81 89
3.3	Study selection	State the process for selecting studies – inclusion and exclusion criteria, number of studies screened by title/abstract and full text, number of reviewers, any cross checking carried out.	17
4.	STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION)		
4.1	Study level reporting, results and risk of bias assessment	For each study, produce a table that includes the full citation and a summary of the data relevant to the question (for example, study size, PICO, follow-up period, outcomes reported, statistical analyses etc.). Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available. For each study, present the results of any assessment of quality/risk of bias.	Study level reporting: Question 1 – 143 Question 2 – 172 Question 3 – 182 Question 4 – not applicable Quality assessment:

			Question 1 – 193 Question 2 – 194-195 Question 3 – 195-196 Question 4 – not applicable
5.	QUESTION LEVEL SYNTHESIS		
5.1	Description of the evidence	For each question, give numbers of studies screened, assessed for eligibility, and included in the review, with summary reasons for exclusion.	Question 1 – 31 Question 2 – 44 Question 3 – 70 Question 4 – 75
5.2	Combining and presenting the findings	Provide a balanced discussion of the body of evidence which avoids over reliance on one study or set of studies. Consideration of four components should inform the reviewer's judgement on whether the criterion is 'met', 'not met' or 'uncertain': quantity; quality; applicability and consistency.	Question 1 – 31 Question 2 – 45 Question 3 – 70 Question 4 – 75
5.3	Summary of findings	Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion. Summarise the main findings including the quality/risk of bias issues for each question. Have the criteria addressed been 'met', 'not met' or 'uncertain'?	Question 1 – 68 Question 2 – 68 Question 3 – 73 Question 4 – 77
6.	REVIEW SUMMARY		
6.1	Conclusions and implications for policy	Do findings indicate whether screening should be recommended? Is further work warranted? Are there gaps in the evidence highlighted by the review?	78

6.2	Limitations	Discuss limitations of the available evidence and of the review methodology if relevant.	79

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