UK National Screening Committee

# Screening for iron deficiency anaemia in children under 5 years

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

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

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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.

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# Plain English summary

This review assesses whether children under the age of 5 should be screened for iron deficiency anaemia. This is when the child's iron levels are too low (often because of insufficient dietary intake) to support red blood cell production. It is possible that iron deficiency anaemia may affect a child's development, but this is not known for certain.

The UK National Screening Committee (NSC) does not currently recommend screening for iron deficiency anaemia in children under 5 years. This policy dates from the last review in 2012 which identified several gaps in the evidence. It was then not clear whether iron deficiency anaemia affected a child's health and development, or whether giving iron treatment to iron deficient children would improve these outcomes. Neither was there an accurate screening test that would be suitable for population screening.

The current review looks at whether evidence published over the last 6 years has answered these questions.

The evidence suggests that around 1 to 3 children in 100 in the UK may have iron deficiency anaemia, though many more may have iron deficiency without suffering from anaemia (anaemia means that the blood is carrying around less oxygen than normal because it contains fewer red blood cells or less haemoglobin). However, these figures are not certain because there is lack of agreement around the blood levels of iron that confirm iron deficiency or anaemia.

No recent studies have assessed whether iron deficiency anaemia affects later developmental or health outcomes. No studies have examined a test that could be used for population screening.

A few small studies have looked at whether giving iron treatment to children under 5 years with iron deficiency anaemia affected developmental or health outcomes. These studies did not give consistent results, and are very different from each other in terms of the study setting, children included, and treatment given. Most studies were carried

out over 25 years ago and included symptomatic children identified through hospital clinics. They may have limited relevance to a current UK child screening population, many of whom would have mild anaemia and no symptoms.

Therefore the evidence available suggests the policy not to screen for iron deficiency anaemia in children under 5 years should not be changed.

# Executive summary

## Purpose of the review

This review aimed to see whether there is evidence to support screening for iron deficiency anaemia (IDA) in children under 5 years.

## Background

IDA is the most common form of anaemia. Children under the age of 5 can be at particular risk as their diet may have insufficient iron to support haemoglobin (Hb) red blood cell production. IDA has been linked with adverse cognitive and developmental outcomes in young children, but there is limited evidence of a direct causal relationship. Iron deficiency (ID) and IDA are usually diagnosed by a blood test looking at Hb and serum ferritin (SF) levels. Universal screening could potentially lead to earlier diagnosis and treatment which may improve health outcomes for young children.

## Recommendation under review

The UK NSC does not currently recommend systematic population screening for IDA in children under 5 years.

This policy dates from the last external evidence review conducted in 2011 which found lack of evidence for a causal relationship between IDA and adverse developmental outcomes, lack of evidence that iron treatment improves health outcomes in asymptomatic children, and lack of a suitable non-invasive screen test.

## Focus of the review

This review aims to see whether evidence has been published since 2011 that addresses these uncertainties and suggests a need to reconsider the screening policy.

The review addresses 4 key questions:

1. The prevalence of ID/IDA in the UK population aged under 5 year.

2. The adverse developmental outcomes of children aged under 5 years with ID/IDA.
3. Whether there is a non-invasive, simple, safe, precise and valid screening test.
4. Whether there is evidence that treatment of asymptomatic screen-detected children improves development outcomes.

## Findings and gaps in the evidence of this review

The review did not identify the evidence needed to answer these questions:

1. Prevalence estimates for ID/IDA in UK children under 5 years are inconsistent. Most suggest an IDA prevalence of 1 to 3%, consistent with other studies in Western populations. However, UK registry data gives IDA prevalence as high as 20%, more in-keeping with estimates of iron deficiency only, which has higher prevalence.
2. No prospective studies were identified that had assessed whether ID/IDA in children under 5 is associated with later adverse health and developmental outcomes. There is also a lack of evidence on whether ID/IDA before age 5 years resolves or persists after age 5.
3. No studies were identified that had assessed a screen test for ID/IDA (invasive, non-invasive or minimally invasive) against a diagnostic reference standard in a non-selected sample representative of the general UK population aged less than 5 years.
4. Two systematic reviews identified a number of small RCTs assessing whether iron treatment improves cognitive and developmental outcomes for clinically-detected children with IDA or ID. The trials give inconsistent and inconclusive evidence. They varied in inclusion criteria, treatment given, and assessed short term outcomes in children aged less than 30 months only. Trials were also published over 25 years ago and have limited applicability to a contemporary UK screening population.

## Recommendations on screening

The findings do not indicate that the current policy not to screen for iron deficiency anaemia in children aged less than 5 years should be reversed.

Further study in the UK, or analogous Western population, may be beneficial in several areas:

- standardisation of the diagnostic criteria used to define ID and IDA
- prospective cohorts that assess whether ID/IDA in children under 5 adversely affects later cognitive and developmental outcomes
- diagnostic cohorts assessing the performance of non-invasive or minimally invasive screen tests that could be suitable for a screening programme (such as urinary hepcidin)
- high quality RCTs that assess whether iron treatment for otherwise asymptomatic children diagnosed with ID/IDA improves health outcomes

## Limitations

This was a rapid review process. Searching was limited to 3 literature databases and did not include grey literature resources. Study design filters were applied, in accordance with the protocol developed *a priori*, in order to manage the literature yield. We did not include studies only available in non-English language, and did not review abstracts, conference reports or poster presentations. We were also unable to contact study authors or review non-published material.

# Introduction and approach

## Background

Iron deficiency anaemia (IDA) is the most common form of anaemia and is associated with several adverse health outcomes. Diagnosis and management is recognised as an important clinical health issue worldwide.[1]

Babies and young children can be at risk of developing IDA when they have insufficient iron in their diet to support haemoglobin (Hb) and red blood cell production. The prevalence of IDA in children aged 1 to 5 years is estimated at between 1 and 4% in developed countries.[2]

IDA in young children has been linked with adverse cognitive and behavioural development, though evidence of a direct causal relationship is limited. For example, some observational studies have shown that young children with IDA perform poorer on cognitive, behavioural and coordination tests compared with non-IDA controls. Other studies have observed infants with IDA to have poorer motor function, sleep patterns and mother-baby interactions. However, it has not been possible to rule out the influence of confounding, such as socioeconomic factors.

It is also unknown whether any adverse health effects of IDA are more detrimental for young children than they would be for older children or adults, for example.

If there was evidence that IDA in children aged less than 5 years directly affected growth and development, then screening with earlier identification and treatment could potentially improve these outcomes.

## Current policy context and previous reviews

The UK National Screening Committee (NSC) does not currently recommend systematic population screening for IDA in children under 5 years.

This policy dates from the last external evidence review[3] which considered evidence published between 2006 and 2011. It identified several key uncertainties:

- lack of evidence for a causal relationship between IDA and adverse developmental outcomes
- lack of a non-invasive screening test that would be suitable for universal screening
- lack of evidence whether iron supplementation for asymptomatic children improves health outcomes in children

The review concluded that in the absence of evidence for screening, emphasis should be placed on primary prevention through good diet.

This recommendation does not refer to the management of symptomatic children under the care of paediatricians.

## Objectives

The current review considers whether new evidence has been published in the 6 years since January 2011 to suggest that the decision not to screen children aged under 5 years should be reconsidered.

Four key questions will be addressed to cover the uncertainties raised by the last external evidence review.

**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. | Q1: What is the UK prevalence or incidence of ID or IDA in children under 5 years? | 3 studies (1 registry data, 1 systematic review, 1 cohort) |
| | | Q2: What are the adverse developmental outcomes of ID or IDA in children under 5 years? | 0 |
| | **THE TEST** | | |

| | Criterion | Key questions | Studies Included |
|---|---|---|---|
| **4** | There should be a simple, safe, precise and validated screening test. | Q3: Is there a non-invasive, simple, safe, precise and validated screening test for ID/IDA in children under 5 years? | 0 |
| | **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 should not be further considered. | Q4: What is the effect of iron supplementation on developmental complications of ID/IDA in asymptomatic children identified through screening? | 2 systematic reviews |

## Methods

The current review was conducted by Bazian, in keeping with the UK NSC evidence review process. Database searches were conducted on 23 March 2017 to identify studies relevant to the questions detailed in Table 1.

### Eligibility for inclusion in the review

A systematic literature search of 3 databases was performed for studies published between January 2011 and March 2017.

After de-duplication the search yielded 2,759 references addressing IDA. These studies were further filtered at title and abstract level by 2 information specialists, and 187 studies were considered to be of relevance to IDA screening in children aged ≤5 years.

These abstracts were then further reviewed against the inclusion criteria by one main reviewer. Studies of relevance, or those where applicability was uncertain from the abstract, were selected for full text appraisal to ensure that all potentially relevant studies were captured.

Forty studies were selected for full text appraisal. Each full text article was reviewed against the inclusion/exclusion criteria by one main reviewer, who determined whether the article was relevant to one or more of the review questions. Any uncertainties around inclusion/exclusion were resolved through input from a second independent reviewer, followed by further discussion with UK NSC evidence team as needed.

Eligibility criteria for each question are presented in Table 2 below. Any refinements to these criteria (for example, the need to move down the hierarchy of evidence), and further information on the evidence selection process for each key question, is discussed in the evidence description for each criterion in the report below.

**Table 2. Inclusion and exclusion criteria for the key ques**

| Key question | Inclusion criteria | | | | | | | Exclusion criteria |
|---|---|---|---|---|---|---|---|---|
| | **Population** | **Target condition** | **Intervention** | **Reference Standard** | **Comparator** | **Outcome** | **Study type** | |
| 1 | Children aged ≤5 years from the general UK population, or otherwise analogous Western populations | ID or IDA | NA | NA | NA | NA | Cross sectional, cohorts, registry data or SRs of these studies | Studies with sample size <500; no data specific to children aged <5 years; conference abstracts; non-English language studies. |
| 2 | Children aged ≤5 years with ID/IDA from the UK or analogous population (screen or clinically detected) | ID or IDA | NA | NA | Healthy children without ID/IDA | Adverse developmental outcomes (motor or neuro-development, behaviour, physical growth).<br><br>Spontaneous resolution of IDA | Prospective cohorts comparing children with and without ID/IDA. Alternatively case controls by developmental outcome with retrospective ID/IDA data. SRs of these studies. | Cross sectional studies; baseline assessment of ID/IDA aged >5 years; studies with sample size <20; conference abstracts; non-English language studies; animal studies. |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 3 | General population of children aged ≤5 years from the UK or other analogous population | ID or IDA | Non-invasive or minimally invasive screening test | Serum haemoglobin haematocrit serum ferritin or transferrin saturation levels | NA | Test accuracy, validity outcomes: sensitivity, specificity, PPV, NPV, likelihood ratios (+/-) | Diagnostic cohorts with performance data available (or where this can be calculated). SRs of these studies. | Studies in non-consecutive samples (for example, high risk); children aged >5 years; studies with sample size <20; conference abstracts; non-English language studies; animal studies. |
| 4 | Children ≤5 years with ID/IDA, ideally screen-detected otherwise clinical-detected | ID or IDA | Iron supplementation | NA | No iron supplementation or placebo. Possible alternative intervention | Resolution of ID/IDA<br><br>Effect on long-term developmental outcomes | RCTs or SRs of these studies. Comparative cohorts considered if this data is not available. | Treatment >5 years of age; studies with sample size <20; conference abstracts; non-English language studies; animal studies. |

## Appraisal for quality

Each criterion was summarised as ‘met’, ‘not met’ or ‘uncerta
considering the results of the included studies in light of the v
quality, consistency and applicability of the body of evidence.

Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the evidence extraction tables in Appendix 3.

If identified, diagnostic accuracy studies considered for criterion 4 were to be assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool. This quality assessment focused on 4 main domains: patient selection, the index test, the reference standard, and flow and timing of index test and reference standard. Each domain would be assessed for risk of bias and applicability to a potential UK screening programme population. However, no diagnostic studies met inclusion criteria.

## Databases searched

Searches for the 4 key questions were performed in MEDLINE and Embase databases (Embase.com) on 23 March 2017, and The Cochrane Library (Wiley Online) on 27 March 2017. The full search strategy is presented in Appendix 1.

Appendix 2 contains a full PRISMA flow diagram (Figure 1), along with a table of the included publications and details of which questions these publications were identified as being relevant to (Table 8).

# Question level synthesis

## *Criterion 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.*

*Question 1 – What is the UK prevalence or incidence of ID or IDA in children under 5 years?*

### Eligibility for inclusion in the review

The 2012 UK NSC external review[3] noted a lack of data on UK prevalence of IDA in children aged under 5 years.

The current review aimed to identify cross-sectional studies, cohorts or registry data containing a representative sample of the general UK child population aged less than 5 years. A sample size of 500 or more was selected in order to increase reliability of prevalence estimates.

Studies within the UK population were to be prioritised but studies from analogous Western populations would also be reviewed. Studies from non-Organisation for Economic Cooperation and Development (OECD) countries were excluded. The aim was to prioritise studies including general (non-selected) child samples, but studies including specific UK samples (for example, by sociodemographic) would also be considered.

### Description of the evidence

After an initial appraisal at title and abstract level 37 studies were judged to be relevant to this question. After further review against the set inclusion/exclusion criteria outlined above, 14 studies were selected for full text appraisal.

Exclusions at abstract level included studies reviewing IDA in pregnancy or high risk newborns (for example, preterm/low birthweight) and several

studies in immigrant/refugee populations. Studies reporting other nutrient deficiencies or assessing the frequency/prevalence of consumption of iron-rich foods were also excluded.

Additional exclusions at full text appraisal were predominantly for reasons of lack of relevant data specific to children ≤5 years; small sample size; or being a selective sample not representative of the general population.

Three studies were ultimately included for this key question,[4-6] all of which provided data relevant to the UK and Ireland. The results of these studies are summarised in table 3.

Appendix 2 contains a summary of the studies included and excluded at full text appraisal. A summary of data extracted from each of the 3 included publications is presented below and appraisal of individual studies in Appendix 3.

In Appendix 3, publications are stratified by question.

## Summary of findings

**Table 3: Summary of UK prevalence data**

| Study | Setting | Population | Prevalence | |
|---|---|---|---|---|
| | | | ID | IDA |
| Global Burden of Disease Pediatrics Collaboration, 2016[4] | UK data from global review of registries | Children <5 years (2013) | NA | 20.2% (771,753 cases, unclear cut-offs) |
| Eussen et al 2015[5] | Systematic review identifying 5 UK studies | 18 to 54 months (1992 to 2003, n=727) | 31% (SF <12) | 3.4% (SF<10, Hb<110) |
| | | 8 to 12 months (1993 to 2004, n≈850) | 2 to 7% at 8 months<br>3 to 11% 12 months (SF<16) | NA |
| | | 18 months (1994, n=709) | 4% (SF<12) | 1.7% (SF<12, Hb<110) |
| | | 4 to 24 months (1996 to 2008, n=278) | 0% at 4 months<br>4.2% at 12 months<br>2.8% at 24 months | NA |

| Study | Setting | Population | Prevalence | |
|---|---|---|---|---|
| | | | ID | IDA |
| | | | (SF<10) | |
| | | 13 months (n=414, unclear year) | 7.7% (SF<10) | NA |
| McCarthy et al 2016[6] | Cork, Ireland. Prospective birth cohort | 24 months (n=729) | 1.8 to 20.8% (depending on SF cut-off) | 0.2 to 1.3% (depending on SF and Hb cut-offs) |

Abbreviations: Hb, haemoglobin (in g/l); NA, not applicable; SF, serum ferritin (in µg/l)

These 3 studies show the evidence available to date on the prevalence of ID and IDA in UK and Irish children under the age of 5 years. It highlights some of the difficulties in getting definite prevalence figures.

The quantity of evidence is overall quite small because the studies have varied in whether they have assessed ID and/or IDA prevalence. The age of assessment has also varied giving a mixed body of evidence.

Most of the studies had sufficient sample size (>500), but some studies in the Eussen et al review[5] had smaller samples. These studies also analysed smaller subgroups, such as by age or infant feeding method, which could give unreliable prevalence estimates.

The prevalence findings are overall inconsistent. This may be partly due to the variations in sample size and age group, as prevalence will vary by dietary iron exposure. However, much of the variability may be explained by differences in diagnostic criteria used for ID/IDA.

The most recent estimate from the Global Collaboration[4] gives a 20% prevalence of IDA among all UK children aged <5 years in 2013. This prevalence figure is very high when compared with other studies[5, 6] which give estimates of around 1 to 3% more in-keeping with recent US estimates.[2] However, the Global study does not state which UK registries were used to provide data, and therefore it is unclear whether the estimate covers the whole of the UK or only selected areas. Diagnostic criteria used for ID/IDA may have varied considerably across health

regions. Some of these cases may actually have been iron deficiency, rather than anaemia, which could fit with a higher prevalence.

The other studies estimate ID prevalence at anywhere between 2 and 30%, but the SF threshold used to define ID varied from <10 to 16µg/l. Similarly, while Hb <110g/l is most often used as the cut-off for anaemia, some studies used 105g/l, and also reduced the SF cut-off used to define ID when defining IDA. Overall this highlights the need for consensus and standardisation around the diagnostic criteria used for ID/IDA.

Looking at other aspects of quality and applicability, all but one of the studies included in the Eussen et al review[5] was reported to be in nationally representative (non-selected) samples. However, as the review used previously collected data, the method of recruitment to the 5 studies and potential limitations of representation are not known. It is notable that several of these studies assessed children during the 1990s. These may not give a reliable indication of ID/IDA prevalence today as dietary exposures may differ.

The Irish birth cohort[6] gives data within the past 10 years and the study authors state that this is the largest study of this kind in European toddlers. The birth cohort included a non-selected sample of newborns. However, only one third of the birth cohort provided blood samples at 2 years for assessment of ID/IDA prevalence. There may be sociodemographic differences between those who did and did not complete follow-up. Additionally about 1 in 5 children in this study were taking iron-supplemented food. It is uncertain whether iron intake and status of children from Cork could differ from children elsewhere in Ireland or the UK.

The Global Collaboration[4] is expected to give a national estimate, though as previously stated, representation and diagnostic criteria used are not clear.

Overall these collective uncertainties make it difficult to give a definite estimate on prevalence.

There were no studies identified that reported incidence figures.

*Question 2 – What are the adverse developmental outcomes of ID or IDA in children under 5 years?*

## Eligibility for inclusion in the review

The 2012 UK NSC external review[3] highlighted that although a causal association had not been demonstrated, many previous observational studies (with potential for bias) had found a strong association between IDA and adverse developmental outcomes in young children. The last review identified no studies published between 2006 and 2011 addressing this question.

The current review aimed to identify prospective cohorts comparing children aged ≤5 years with and without ID/IDA and assessed adverse developmental outcomes or resolution of ID/IDA. If these were not available, case control studies by disease outcome that included retrospective childhood data on ID/IDA would also be considered.

Cohorts that reported outcomes of children with ID/IDA but that included no comparison group would be excluded. Cross sectional studies that measured ID/IDA in children presenting with adverse outcomes (such as seizures) would also be excluded as these cannot demonstrate temporality of the relationship and prove cause and effect.

Studies within the UK population were to be prioritised but studies from analogous Western populations would also be reviewed, excluding non-OECD countries.

## Description of the evidence

After an initial appraisal at title and abstract level 52 studies were assessed to be relevant to this question. After further review against the set inclusion/exclusion criteria outlined above, 12 studies were selected for full text appraisal.

Additional exclusions at abstract level included studies reviewing IDA in pregnancy and studies in high risk samples, for example preterm/low birthweight infants, exclusively breastfeeding and immigrant/refugee populations. Studies that were not a fit to the question were also excluded. This included studies assessing whether child dietary intake,

rather than ID/IDA, was linked with adverse outcomes, or studies looking at whether childhood ID/IDA was associated with outcomes such as drug sensitivity in later life, rather than health outcomes.

At full text appraisal no studies were identified that contained data relevant to this key question.

No studies had prospectively studied children with and without ID/IDA and assessed later iron status or developmental outcomes. Neither had any case control studies included clear historic data on ID/IDA status in those with adverse outcomes. Excluded studies included those assessing samples of children with conditions such as febrile seizures and ADHD but where the ID/IDA assessment was cross sectional so causation and temporality of the association could not be known with certainty. Other studies assessed whether nutritional status or dietary intake was associated with adverse developmental outcomes, but not ID/IDA.

Appendix 2 contains a summary of the studies excluded at full text appraisal.

## Summary of Findings Relevant to Criterion 1: Criterion not met.

Q1 Prevalence of ID/IDA: estimates for the UK and Ireland are inconsistent. Most studies suggest prevalence of IDA among UK children <5 years of around 1 to 3%, which is consistent with other estimates from Western countries. However, recent registry data for the UK reports IDA prevalence of 20% in this age group. It is possible that some of these recorded cases could have been for iron deficiency only, as other studies estimate ID prevalence in this group of up to 30%. Overall the widely differing estimates are likely to be explained by the lack of standardisation around the SF and Hb levels that define ID and IDA.

Q2 Adverse outcomes of ID/IDA: no prospective studies were identified that had assessed whether ID/IDA in children <5 years is associated with later adverse health and developmental outcomes. Neither had any studies assessed whether ID/IDA in children <5 years is likely to persist or resolve after 5 years.

## *Criterion 4 – There should be a simple, safe, precise and validated screening test.*

*Question 3 – Is there a non-invasive, simple, safe, precise and validated screening test for ID/IDA in children under 5 years?*

## Eligibility for inclusion in the review

The 2012 UK NSC external review[3] identified previous guidance from the World Health Organisation (WHO) and a 2006 recommendation from the US Preventative Services Task Force (USPSTF) reporting that measurement of Hb and haematocrit (Hct) may be useful for screening for anaemia. However, this cannot distinguish IDA from other causes and also could not identify ID without anaemia.

The previous review discussed various diagnostic markers of iron status, such as SF and blood reticulocyte Hb concentration, but a simple non-invasive or minimally invasive test that would be suitable to screen for ID/IDA was not identified. An invasive blood test is unlikely to be acceptable as a universal screen test for children under 5.

Future screening possibilities in development included measurement of urinary hepcidin, a regulator of iron absorption from the gut.

The current review therefore aimed to identify diagnostic cohorts comparing the performance accuracy of a non-invasive or minimally invasive screen test, such as urinary hepcidin, against a valid reference standard for identification of ID/IDA, such as serum Hb, Hct, SF, or transferrin saturation.

Eligible cohorts would include a non-selected (e.g. consecutively enrolled) sample representative of the general child population aged ≤5 years, from the UK or other analogous Western population.

Any diagnostic cohorts assessing an invasive screen test would also be reviewed.

## Description of the evidence

Fifty studies were considered relevant to this question at initial appraisal and 9 were selected for full text appraisal.

Exclusions at abstract and full text level included case control studies comparing potential new laboratory analysers or diagnostic markers in selected samples with and without anaemia/IDA. This included several studies using discarded blood samples from hospital laboratories. Studies screening select population groups such as preterm babies or those with chronic kidney disease were also excluded.

Only a single study analysing urinary hepcidin was identified. However, this was a case control study from a non-Western population (Egypt) so was excluded at abstract level.

One other diagnostic cohort of a minimally invasive screen test (capillary Hb) was identified. However, this was conducted in a selected sample of low-income toddlers from the mid-US with a high prevalence of anaemia (14 to 25%) who were taking part in a separate study (the Supplemental Nutrition Program for Women, Infants and Children). Performance data was expected to have limited applicability to the general UK child population and therefore this study was excluded.

No other eligible cohorts were identified.

The 2015 updated systematic review[2] and accompanying recommendation statement from the USPSTF[7] on screening for IDA in young children was also identified.

The USPSTF[7] concluded that there is currently insufficient evidence to assess the balance and harms of screening for IDA in children aged 6 to 24 months. They state that measurement of serum Hb or Hct is usually the first step in diagnosis of IDA, but found insufficient evidence to recommend specific screen tests. Any diagnostic studies referenced by these papers all pre-date 2011. The USPSTF also found no studies evaluating the benefits or harms of screening programmes for asymptomatic children.

A 2015 systematic review of European and US guidelines on the diagnosis and treatment of ID[1] was also identified. This review stated that all guidelines recommend measurement of SF in the diagnosis of iron deficiency, with over half also recommending transferrin saturation as an alternative test. However, these guidelines do not mention screening tests.

Therefore since 2011 no further studies have been published assessing non-invasive or invasive screening tests for IDA in children ≤5 years.

Appendix 2 contains a summary of the studies excluded at full text appraisal.

## Summary of Findings Relevant to Criterion 4: Criterion not met.

No studies were identified that have assessed a non-invasive or minimally invasive (or invasive) screening test for ID/IDA in a non-selected sample of children aged <5 years from the UK or analogous Western population.

*Criterion 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 should not be further considered.*

*Question 4 – What is the effect of iron supplementation on developmental complications of ID/IDA in asymptomatic children identified through screening?*

## Eligibility for inclusion in the review

The 2012 UK NSC external review[3] concluded that although iron treatment improves iron status in young children, there is conflicting evidence whether it has any effect of longer term health or developmental outcomes such as cognition. There was some evidence that outcomes are better for children identified and treated early, but this was from observational studies without an untreated control group.

The current review aimed to see if evidence has been published since 2011 to answer whether iron treatment has an effect on developmental outcomes. The aim was to identify randomised controlled trials (RCTs) or systematic reviews of these studies comparing iron treatment with placebo/no treatment in children aged ≤5 years with ID/IDA.

Studies would be analogous to a UK population, ideally screen-detected asymptomatic children. Trials in clinically-detected children would also be reviewed.

## Description of the evidence

After an initial appraisal at title and abstract level 48 studies were judged to be relevant to this question, and 18 were selected for full text appraisal.

Studies not exclusively looking at the child population aged ≤5 years diagnosed with ID or IDA were excluded at abstract or full text. This

included studies of pregnant women, preterm/low birthweight infants, and mixed age groups (unless there was separate analysis of the target age group). Studies assessing iron treatment regardless of ID/IDA status (treatment or prevention studies) were also excluded.

Two systematic reviews met inclusion criteria. The updated Cochrane review by Wang et al (2013)[8] assessed the effect of iron therapy for children aged ≤3 years with IDA on developmental and cognitive outcomes. Abdullah et al (2013)[9] assessed the effect of iron therapy on developmental outcomes in pre-school children with non-anaemic iron deficiency (NAID).

One recent RCT[10] was also identified, but this was not prioritised for inclusion as it was considered to provide minimal relevant information. It included iron deficient children aged 1 to 2 years who had been exclusively breastfed for the first 9 months, and compared iron therapy with iron plus vitamin E. It found that additional vitamin E made no difference to serum iron response at 8 weeks, but increased the abundance of certain intestinal bacteria. The trial was not further analysed as it did not assess the effect of iron therapy, and did not look at longer term health or developmental outcomes.

Also of relevance to this key question, were the updated USPSTF recommendations on screening and supplementation[2, 7] and the systematic review of guidelines on diagnosis and treatment of ID.[1]

The USPSTF review[2] found no clear evidence that iron supplementation improved growth outcomes. However, their research question was to look at the effect of routine supplementation (that is, for prevention and not restricted to children with diagnosed ID/IDA), and therefore, provided no further information to this review.

The systematic review of guidelines[1] reported that most guidelines report oral iron supplementation as the first-line treatment of iron deficiency and provide haematological targets for treatment. Treatment of asymptomatic or screen-detected children is not covered. Therefore this review provided no further information of relevance.

Appendix 2 contains a summary of the studies included and excluded at full text appraisal. A study-level summary of data extracted from the 2

included publications is presented in the summary and appraisal of individual studies in Appendix 3. In Appendix 3, publications are stratified by question.

## Summary of findings

**Table 4: Summary of systematic review findings**

| Study | Population | Intervention | Comparator | Outcomes (mean difference, 95% CI) |
|---|---|---|---|---|
| Wang et al 2013[8] SR and MA | Children ≤3 years with IDA<br>8 RCTs (n=385) | Iron<br>(n=4 oral, n=3 IM, n=1 mixed) | Placebo (or vitamin C alone) | Bayley PDI at 30 days<br>-1.25 (-4.56 to 2.06)<br>(5 studies, n=162, $I^2$ 33%)<br>Bayley MDI at 30 days<br>+1.04 (-1.30 to 3.39)<br>(5 studies, n=164, $I^2$ 31%)<br>Bayley PDI >30 days<br>*+18.4 (95% CI 10.16 to 26.64)*<br>(1 study, n=47)<br>Bayley MDI >30 days:<br>*+18.8 (95% CI 10.17 to 27.43)*<br>(1 study, n=47) |
| Abdullah et al 2012[9] SR | Children 1 to 5 years with NAID<br>2 RCTs (Akman, n=40; Idjradinata, n=29) | Oral iron | Placebo/no treatment | Bayley PDI post-treatment:<br>Akman: -0.23 (-7.07 to 6.61)<br>Idjradinata: +1.20 (-5.99 to 8.39)<br>Bayley MDI post-treatment:<br>*Akman: +6.26 (1.54 to 10.98)*<br>Idjradinata: -1.60 (-9.38 to 6.18)<br>(Both studies post-treatment improvements in SF; 1 study improvement in Hb) |

Abbreviations: CI, confidence interval; intramuscular, IM; MA, meta-analysis; MDI, mental development index; PDI, psychomotor development index; SR, systematic review.

The overall body of evidence is limited and does not provide sufficient evidence that iron treatment for children <5 years with ID/IDA improves developmental and cognitive outcomes.

Both systematic reviews were of good quality with clearly defined research question and search methods. They both identified RCTs only, but conclusions were limited by the quantity and consistency of the evidence identified.

The Wang et al [8] review included meta-analyses of 5 studies with moderate heterogeneity and found no evidence for an effect on mental or psychomotor development at 30 days. There was evidence for an improvement after 30 days, but this was the finding of 1 small study only.

The studies identified by the Wang et al[8] review were of small sample size, varied in their method of iron delivery (oral or intramuscular), and have limited applicability to a UK screen-detected population. Only 2 of the studies came from the UK, several were conducted in non-Western countries, and recruitment varied from community and paediatric clinics to an orphanage in one study. No studies appear to have been in screen-detected populations. Clinically-detected children may have more severe ID/IDA than screen-detected children, and it is possible that neither baseline function nor treatment effects are applicable. They were also all published around 25 to 40 years ago so may not be generalizable to children or treatment practices today.

The Abdullah et al[9] review was more limited in scope. Only 2 trials on the management of iron deficiency without anaemia were identified. However, neither of these trials was designed to assess the effects of treatment in children with NAID specifically, and these analyses came from very small subgroups only. The 2 trials were too heterogeneous to pool in meta-analysis. One (Akman) was a Turkish trial from 2004 and the other (Idjradinata) an Indonesian trial from 1993. They differed in child age, inclusion criteria and dose and duration of iron treatment. The Turkish trial found a significant improvement in mental development index score, while no other effects on psychomotor development index were observed. However, this is insufficient evidence to make firm conclusions about treatment effects in NAID as the trials were likely underpowered to assess effects in these small subsamples.

Other quality and applicability aspects related to both reviews:

1. In general all included trials were of moderate quality with uncertain bias around randomisation/allocation and blinding.
2. Study populations differed in terms of SF and Hb status defining IDA and NAID. This could have affected both treatment effects and also influenced group allocation if this was not concealed.
3. The trials in both reviews include children aged less than 30 months only. There is no evidence for the treatment of older children up to 5

years. The effect of iron treatment may differ by age group, which could also account for some of the heterogeneity in trial results.

4. Development and cognitive outcomes were assessed in the relatively short term only, after 2 to 3 months' treatment. There is no assessment of development outcomes or resolution of ID/IDA in the longer term. However, with limited evidence on natural history, it is not known whether ID/IDA could be more pertinent to psychomotor development in the immediate/short term rather than longer term.
5. The 2 reviews provide no evidence on adverse effects of iron treatment.

Overall the evidence has limited applicability to a contemporary UK asymptomatic screen-detected population.

## Summary of Findings Relevant to Criterion 9: Criterion not met.

Two systematic reviews have identified a small number of trials that give inconsistent and inconclusive evidence on whether iron treatment for children aged <5 with ID/IDA affects developmental or cognitive outcomes. The trials were heterogeneous in terms of inclusion criteria (recruitment, child age and diagnostic criteria), method of iron administration (oral or intramuscular), dose and duration of treatment. Small sample sizes may also mean the study is underpowered to detect differences in these outcomes.

All trials have assessed children aged <30 months and looked at outcomes in the short-term only, though with the limited evidence on natural history it is not known whether treatment effects in the short term could be most relevant. Most trials were conducted over 25 years ago and come from non-Western populations which limits applicability to the UK. Studies were also conducted in clinically-detected children who may not be representative of asymptomatic, screen-detected populations, either for baseline function or potential treatment effects.

# Review summary

## Conclusions and implications for policy

The findings do not indicate that the current policy not to screen for iron deficiency anaemia in children aged less than five years should be reversed.

The review identified several gaps to the evidence:

1. UK prevalence estimates vary widely and highlight the need for standardisation around the diagnostic criteria for iron deficiency with and without anaemia.
2. There is a lack of prospective studies looking at whether ID/IDA in children under 5 years is associated with risk of later adverse developmental or cognitive outcomes. There is also a lack of evidence on whether ID/IDA before age 5 years resolves or persists after age 5.
3. There is a lack of evidence assessing a suitable screen test. No studies have assessed the performance of a potential screen test against a validated reference standard in a non-selected sample who would be representative of the general UK child population eligible for universal screening. In particular future studies assessing non-invasive or minimally invasive screen tests that could be suitable for a screening programme (such as urinary hepcidin) would be valuable.
4. A small number of heterogeneous trials with various methodological limitations provide inconsistent evidence whether iron supplements affect short-term developmental or cognitive outcomes in clinically-detected children with ID/IDA. The evidence has limited applicability to a contemporary UK screening population. Large, high quality RCTs that assess treatment of otherwise asymptomatic children diagnosed with ID/IDA from the UK, or other analogous population, would be valuable.

## Limitations

This was a rapid evidence review process. Searching was limited to 3 bibliographic databases and did not include grey literature sources. Study design filters were applied, in accordance with the protocol developed *a*

*priori*, in order to manage the literature yield within the timeframe of this rapid review.

Literature search and first pass appraisal were undertaken by 2 information specialists. Second pass appraisal and study selection was then conducted by a third analyst. Any decisions on study inclusions, queries or scope refinement were then resolved in a meeting between analyst and in discussion with UK NSC as needed. Systematic reviews, RCTs and prospective controlled studies were prioritised (according to research question) before moving down through the lower hierarchy of evidence.

We did not include studies only available in non-English language, and did not review abstracts, conference reports or poster presentations. We were also unable to contact study authors or review non-published material.

# Appendix 1 — Search strategy

## Electronic databases

The search strategy below is for the MEDLINE and Embase databases (Embase.com). The strategy was informed by the one used in the previous UK NSC review published in 2012. The strategy was developed for the Embase.com search interface and uses text words and the preferred EMTREE indexing terms.

The strategies below address the 4 research questions for this update. Due to the large volume of literature (9,502 results) methodological study filters were used as per inclusion criteria for each question, using search filters developed by the Scottish Intercollegiate Guidelines Network (SIGN).

The combined searches for the 4 questions retrieved 2,692 results for the period 2011-2017. The Cochrane Library search retrieved 259 records. After de-duplication there were 2,759 records. The search strategy included searches of the databases shown in Table 5.

**Table 5. Summary of electronic database searches and dates**

| Database | Platform | Searched on date | Date range of search |
|---|---|---|---|
| MEDLINE, Embase | Embase.com | 23/03/2017 | 2011 to present |
| The Cochrane Library, including:<br>- Cochrane Database of Systematic Reviews (CDSR)<br>- Cochrane Central Register of Controlled Trials<br>- Database of Abstracts of Reviews of Effects (DARE)<br>- Health Technology Assessment (HTA) database | Wiley Online | 27/03/2017 | 2011 to present<br>CDSR: Issue 3 of 12, March 2017 |

## Search Terms

Search terms included combinations of free text and subject headings (EMTREE terms for Embase), grouped into the following concepts:

1. Iron deficiency anaemia in children under 5 years of age (disease area).
2. Developmental outcomes (question 1).
3. Prevalence/Incidence (question 2).
4. Screening test (question 3).
5. Treatment – iron supplementation (question 4).

Study design filters used: Systematic reviews, RCTs, observational studies (comparative), diagnostic accuracy and epidemiologic studies

Search terms for Embase.com are shown in Table 6, and search terms for the Cochrane Library databases are shown in Table 7.

Results were imported into EndNote and de-duplicated.

Table 6. Search strategy all questions. Embase.com (MEDLINE and Embase)

| Term Group | # | Search terms | Results |
|---|---|---|---|
| IDA in children | #1 | 'infant'/exp | 979,285 |
| IDA in children | #2 | 'newborn'/de | 523,852 |
| IDA in children | #3 | 'child'/exp | 2,417,949 |
| IDA in children | #4 | neonat*:ab,ti | 287,771 |
| IDA in children | #5 | newborn*:ab,ti | 175,833 |
| IDA in children | #6 | child*:ab,ti | 1,470,974 |
| IDA in children | #7 | infant*:ab,ti | 421,255 |
| IDA in children | #8 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 | 3,022,325 |
| IDA in children | #9 | 'iron deficiency anemia'/de | 23,842 |
| IDA in children | #10 | anemi*:ab,ti OR anaemi*:ab,ti | 179,307 |
| IDA in children | #11 | 'iron deficien*':ab,ti | 24,703 |
| IDA in children | #12 | #9 OR #10 OR #11 | 194,433 |
| Developmental outcomes | #13 | 'developmental disorder'/exp | 32,770 |
| Developmental outcomes | #14 | 'child development'/de | 41,433 |
| Developmental outcomes | #15 | 'nerve cell differentiation'/de | 31,829 |
| Developmental outcomes | #16 | 'motor development'/de | 4,932 |
| Developmental outcomes | #17 | 'behavior disorder'/exp | 373,923 |
| Developmental outcomes | #18 | 'body growth'/exp | 89,501 |
| Developmental outcomes | #19 | 'cognition'/exp | 1,708,484 |
| Developmental outcomes | #20 | 'educational status'/de | 54,230 |
| Developmental outcomes | #21 | development*:ab,ti AND (assessment:ab,ti OR motor:ab,ti OR psychomotor:ab,ti OR delay*:ab,ti OR outcome*:ab,ti OR impair*:ab,ti OR general:ab,ti OR mental:ab,ti OR quotient*:ab,ti) | 560,502 |
| Developmental outcomes | #22 | 'cognitive function':ab,ti | 35,303 |
| Developmental outcomes | #23 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 | 2,605,976 |
| Q1 | #24 | #8 AND #12 AND #23 | 4,621 |
| Prevalence/Incidence | #25 | epidemiolog*:ab,ti OR inciden*:ab,ti OR prevalen*:ab,ti | 1,919,202 |

| Term Group | # | Search terms | Results |
|---|---|---|---|
| Prevalence/Incidence | #26 | 'epidemiology'/de | 204,473 |
| Prevalence/Incidence | #27 | 'prevalence'/de | 512,907 |
| Prevalence/Incidence | #28 | 'incidence'/de | 261,467 |
| Prevalence/Incidence | #29 | #25 OR #26 OR #27 OR #28 | 2,197,231 |
| Q2 | #30 | #8 AND #12 AND #29 | 9,854 |
| Screening test | #31 | 'mass screening'/de | 51,627 |
| Screening test | #32 | 'newborn screening'/de | 14,959 |
| Screening test | #33 | screen*:ab,ti | 773,972 |
| Screening test | #34 | detect*:ab,ti | 2,360,195 |
| Screening test | #35 | test:ab,ti OR tests:ab,ti OR testing:ab,ti | 2,475,187 |
| Screening test | #36 | 'diagnostic accuracy'/de | 209,356 |
| Screening test | #37 | 'sensitivity and specificity'/de | 259,240 |
| Screening test | #38 | sensitivity:ab,ti OR specificity:ab,ti | 1,043,561 |
| Screening test | #39 | #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 | 5,649,832 |
| Q3 | #40 | #8 AND #12 AND #39 | 11,220 |
| Treatment – iron supplementation | #41 | 'diet supplementation'/de | 75,411 |
| Treatment – iron supplementation | #42 | 'dietary supplement'/de | 1,727 |
| Treatment – iron supplementation | #43 | (iron NEAR/2 supplement*):ab,ti | 6,629 |
| Treatment – iron supplementation | #44 | (iron NEAR/2 diet*):ab,ti | 3,585 |
| Treatment – iron supplementation | #45 | #41 OR #42 OR #43 OR #44 | 85,526 |
| Q4 | #46 | #8 AND #12 AND #45 | 2,552 |
| Observational studies | #47 | 'clinical study'/de | 145,498 |
| Observational studies | #48 | 'case control study'/de | 107,558 |
| Observational studies | #49 | 'family study'/de | 20,794 |
| Observational studies | #50 | 'longitudinal study'/de | 94,588 |
| Observational studies | #51 | 'retrospective study'/de | 508,246 |
| Observational studies | #52 | 'prospective study'/de | 360,458 |
| Observational studies | #53 | 'randomized controlled trial (topic)'/de | 116,12 |
| Observational studies | #54 | #52 NOT #53 | 357,092 |
| Observational studies | #55 | 'cohort analysis'/de | 276,015 |
| Observational studies | #56 | (cohort NEAR/1 (study OR studies)):ab,ti | 194,192 |
| Observational studies | #57 | ('case control' NEAR/1 (study OR studies)):ab,ti | 100,815 |
| Observational studies | #58 | ('follow up' NEAR/1 | 56,247 |

| Term Group | # | Search terms | Results |
|---|---|---|---|
| | | (study OR studies)):ab,ti | |
| Observational studies | #59 | (observational NEAR/1 (study OR studies)):ab,ti | 103,032 |
| Observational studies | #60 | (epidemiologic* NEAR/1 (study OR studies)):ab,ti | 89,876 |
| Observational studies | #61 | cross:ab,ti AND (sectional NEAR/1 (study OR studies)):ab,ti | 133,313 |
| Observational studies | #62 | ('cross sectional' NEAR/1 (study OR studies)):ab,ti | 133,709 |
| Observational studies | #63 | #47 OR #48 OR #49 OR #50 OR #51 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 | 1,730,741 |
| Q1 Observational studies, no date limit | #64 | #24 AND #63 | 809 |
| Q1 Observational studies | #65 | #24 AND #63 AND [2011-2017]/py | 533 |
| Q2 Observational studies, no date limit | #66 | #30 AND #63 | 2,531 |
| Q2 Observational studies | #67 | #30 AND #63 AND [2011-2017]/py | 1,495 |
| Diagnostic studies | #68 | 'sensitivity and specificity'/de | 260,231 |
| Diagnostic studies | #69 | sensitivity:ab,ti OR specificity:ab,ti | 1,045,527 |
| Diagnostic studies | **#70** | (('pre test' OR pretest) NEAR/1 probability):ab,ti | 2,857 |
| Diagnostic studies | #71 | 'post-test probability':ab,ti | 607 |
| Diagnostic studies | #72 | 'predictive value':ab,ti | 103,590 |
| Diagnostic studies | #73 | 'likelihood ratio':ab,ti | 11,443 |
| Diagnostic studies | #74 | 'diagnostic accuracy'/mj | 7,457 |
| Diagnostic studies | #75 | #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 | 1,217,462 |
| Q3 Diagnostic studies, no date limit | #76 | #40 AND #75 | 1,214 |
| Q3 Diagnostic studies | #77 | #40 AND #75 AND [2011-2017]/py | 545 |
| Q4 Treatment-observational, no date limit | #78 | #46 AND #63 | 363 |
| Q4 Treatment-observational | #79 | #46 AND #63 AND [2011-2017]/py | 211 |
| RCTs | #80 | 'clinical trial'/de | 839,017 |

| Term Group | # | Search terms | Results |
|---|---|---|---|
| RCTs | #81 | 'randomized controlled trial'/de | 363,892 |
| RCTs | #82 | 'randomization'/de | 65,267 |
| RCTs | #83 | 'single blind procedure'/de | 19,556 |
| RCTs | #84 | 'double blind procedure'/de | 120,392 |
| RCTs | #85 | 'crossover procedure'/de | 42,039 |
| RCTs | #86 | 'placebo'/de | 268,029 |
| RCTs | #87 | 'randomized controlled trial':ab,ti | 47,600 |
| RCTs | #88 | 'randomised controlled trial':ab,ti | 15,415 |
| RCTs | #89 | rct:ab,ti | 16,711 |
| RCTs | #90 | 'random allocation':ab,ti | 1,429 |
| RCTs | #91 | 'randomly allocated':ab,ti | 22,234 |
| RCTs | #92 | 'allocated randomly':ab,ti | 2,018 |
| RCTs | #93 | (allocated NEAR/2 random):ab,ti | 802 |
| RCTs | #94 | single:ab,ti OR double:ab,ti OR triple:ab,ti OR treble:ab,ti | 1,762,202 |
| RCTs | #95 | blind*:ab,ti | 291,292 |
| RCTs | #96 | #94 AND #95 | 182,543 |
| RCTs | #97 | placebo*:ab,ti | 216,672 |
| RCTs | #98 | 'prospective study'/de | 279,194 |
| RCTs | #99 | #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #96 OR #97 OR #98 OR #99 | 1,438,470 |
| RCTs | #100 | 'case study'/de | 33,193 |
| RCTs | #101 | 'case report':ab,ti | 288,905 |
| RCTs | #102 | 'abstract report'/de | 89,647 |
| RCTs | #103 | 'letter'/de | 843,967 |
| RCTs | #104 | #100 OR #101 OR #102 OR #103 | 1,249,486 |
| RCTs | #105 | #99 NOT #104 | 1,635,215 |
| Q4 Treatment RCTs, no date limit | #106 | #46 AND #105 | 722 |
| Q4 Treatment RCTs | #107 | #46 AND #105 AND [2011-2017]/py | 272 |
| Q1 - Q4 no filters | #108 | #24 OR #30 OR #40 OR #46 | 20,875 |
| Systematic reviews | #109 | 'meta analysis (topic)'/de | 23,354 |
| Systematic reviews | #110 | 'meta analysis'/exp | 101,273 |
| Systematic reviews | #111 | meta:ab,ti AND | 111,022 |

| Term Group | # | Search terms | Results |
|---|---|---|---|
| | | analy*:ab,ti | |
| Systematic reviews | #112 | 'meta-analysis':ab,ti OR 'meta-analyses':ab,ti OR 'meta-analytic':ab,ti | 105,685 |
| Systematic reviews | #113 | 'metaanalysis':ab,ti | 4,355 |
| Systematic reviews | #114 | (systematic NEAR/2 (review* OR overview*)):ab,ti | 95,444 |
| Systematic reviews | #115 | 'systematic review'/de | 100,089 |
| Systematic reviews | #116 | 'systematic review (topic)'/de | 13,734 |
| Systematic reviews | #117 | cochrane:ab OR embase:ab OR psychlit:ab OR psyclit:ab OR psychinfo:ab OR psycinfo:ab OR cinahl:ab OR cinhal:ab OR bids:ab | 76,808 |
| Systematic reviews | #118 | 'science citation index':ab | 2,495 |
| Systematic reviews | #119 | 'reference list':ab OR bibliograph*:ab OR 'hand searching':ab OR 'hand search':ab OR 'relevant journals':ab OR (manual NEAR/1 search*):ab | 23,118 |
| Systematic reviews | #120 | #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 | 271,242 |
| Systematic reviews | #121 | 'selection criteria':ab OR 'data extraction':ab | 35,837 |
| Systematic reviews | #122 | review:it | 2,080,441 |
| Systematic reviews | #123 | #121 AND #122 | 17,362 |
| Systematic reviews | #124 | letter:it OR editorial:it | 1,389,774 |
| Systematic reviews | #125 | 'animal'/exp | 21,013,295 |
| Systematic reviews | #126 | 'human'/exp | 16,447,832 |
| Systematic reviews | #127 | #125 NOT (#125 AND #126) | 4,565,463 |
| Systematic reviews | #128 | #124 OR #127 | 5,924,325 |
| Systematic reviews | #129 | #120 OR #123 | 275,226 |
| Systematic reviews | #130 | #129 NOT #128 | 319,205 |
| Q1 - Q4 Systematic reviews, no date limit | #131 | #108 AND #130 | 423 |
| Q1 - Q4 Systematic reviews | #132 | #108 AND #130 AND [2011-2017]/py | 274 |
| Q1 - Q4 All eligible study types | #133 | #65 OR #67 OR #77 OR #79 OR #107 OR | 2,692 |

| Term Group | # | Search terms | Results |
|---|---|---|---|
| | | #132 | |

**Table 7. Search strategy for the Cochrane Library Databases (Searched via the Wiley Online platform)**

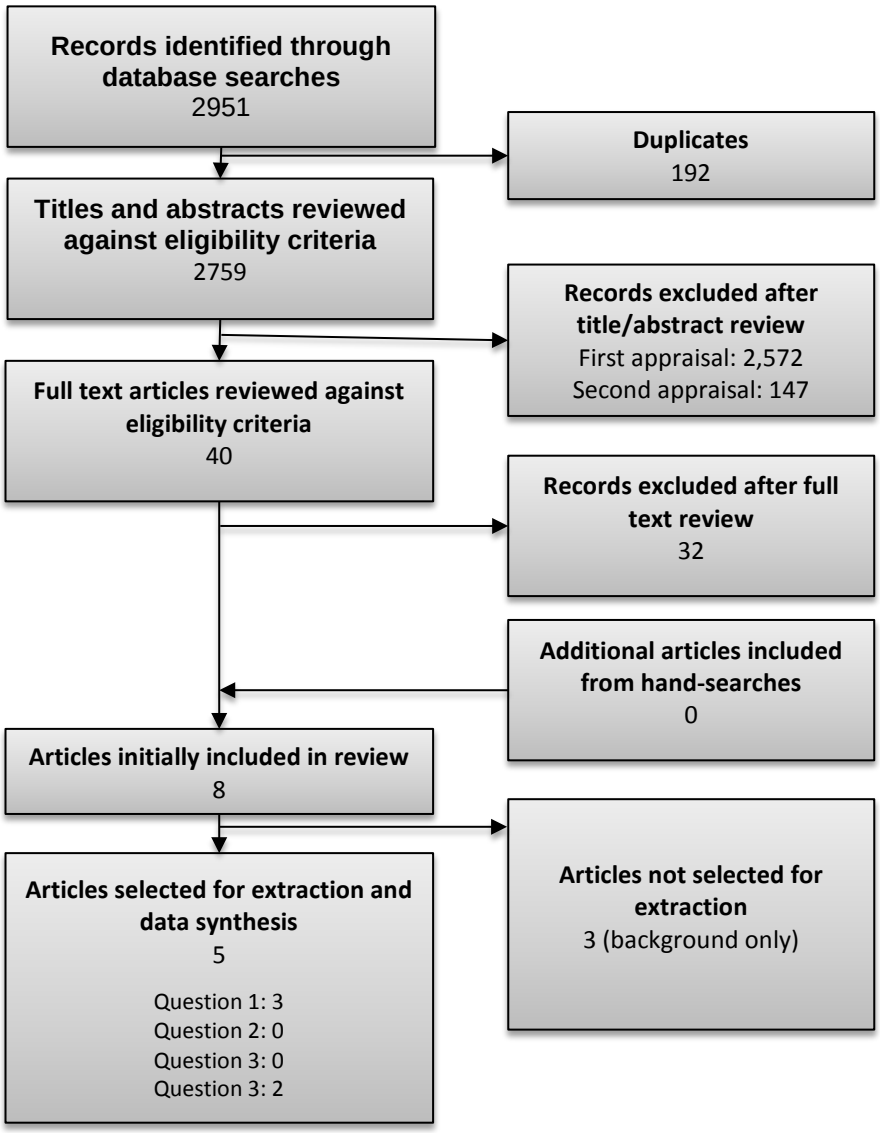
| Term Group | # | Search terms | Results |
|---|---|---|---|
| IDA in children | #1 | MeSH descriptor: [Infant] explode all trees | 14956 |
| IDA in children | #2 | MeSH descriptor: [Infant, Newborn] explode all trees | 14927 |
| IDA in children | #3 | MeSH descriptor: [Child] explode all trees | 213 |
| IDA in children | #4 | (neonat* or newborn*):ti,ab | 16186 |
| IDA in children | #5 | (child* or infant*):ti,ab | |
| IDA in children | #6 | #1 or #2 or #3 or #4 or #5 | 101624 |
| IDA in children | #7 | MeSH descriptor: [Anemia, Iron-Deficiency] this term only | 809 |
| IDA in children | #8 | (anemi* or anaemi*):ti,ab | 8284 |
| IDA in children | #9 | (iron next deficien*):ti,ab | 1577 |
| IDA in children | #10 | #7 or #8 or #9 | 8803 |
| IDA in children | #11 | #6 and #10 Publication Year from 2011 to 2017 | 934 (only CDSR, DARE and HTA exported) |
| Treatment – iron supplementation | #12 | MeSH descriptor: [Diet Therapy] this term only | 320 |
| Treatment – iron supplementation | #13 | MeSH descriptor: [Dietary Supplements] this term only | 8061 |
| Treatment – iron supplementation | #14 | (iron near/2 supplement*):ti,ab | 1284 |
| Treatment – iron supplementation | #15 | (iron near/2 diet*):ti,ab | 148 |
| Treatment – iron supplementation | #16 | #12 or #13 or #14 or #15 | 9379 |
| Treatment – iron supplementation | #17 | #11 and #16 Publication Year from 2011 to 2017 | 163 (RCTs exported) |

# Appendix 2 — Included and excluded studies

## PRISMA flowchart

Figure 1 summarises the volume of publications included and excluded at each stage of the review. Five 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 summarised below.

**Figure 1. Summary of publications included and excluded at each stage of the review**




## Publications included after review of full text articles

The 5 publications included after review of full texts are summarised in Table 8 below.

Studies were prioritised for extraction and data synthesis. The following *a priori* approach was agreed to prioritise studies for extraction:

1. Systematic reviews and meta-analyses would be considered the highest quality of evidence if any were found. Following this, study designs would be prioritised for each question in the order listed in Table 2

2. Studies would be prioritised if they considered a UK population, followed by studies from Western populations analogous to the UK

Further criteria were applied after assessing the overall volume of evidence identified, as discussed in the description of evidence for each criterion above. Publications not selected for extraction and data synthesis are summarised in Table 9 below.

**Table 8. 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 | Comments |
|---|---|---|---|---|---|---|
| **Eussen et al 2015[5]** | Q1 | - | - | - | 1 | - |
| **McCarthy et al 2016[6]** | Q1 | - | - | - | 1 | - |
| **Vos et al 2016[4]** | Q1 | - | - | - | 1 | - |
| **Wang et al 2013[8]** | - | - | Q4 | - | 9 | - |
| **Abdullah et al 2013[9]** | - | - | Q4 | - | 9 | - |

## Publications excluded after review of full text articles

Of the 40 publications selected for full text appraisal after the [illegible] were ultimately judged not to be relevant to this review. These publications, a[illegible] are listed in Table 9. Note that some publications were marked as relevant for more than one key question.

**Table 9. Publications excluded after review of full text articles**

| Reference | Reason for exclusion |
|---|---|
| **Q1 – prevalence** | |
| Abdullah K, Maguire JL, Birken CS, et al. Prevalence, practice patterns and hematological outcomes of young canadian children identified with non-anemic iron deficiency (NAID): Implications of screening in primary care settings. Paediatrics and Child Health (Canada). 2014;19(6):e44-e5. | Abstract only available |
| Abdullah K, Thorpe KE, Maguire JL, et al. Risk factors, practice variation and hematological outcomes of children identified with non-anemic iron deficiency following screening in primary care setting. Paediatrics and Child Health (Canada). 2015;20(6):302-6. | Toronto study participants, uncertain applicability to UK; UK data reviewed in preference |
| Andersen ATN, Husby S, Sander SD, et al. Iron deficiency in healthy 18-month-old danish children: Prevalence and associated factors: A subproject in the odense child cohort. Journal of Pediatric Gastroenterology and Nutrition. 2016;63:S258-S9. | Abstract only available |
| Caballero J, Romero A, Aguilar M, et al. Profile of iron metabolism in pediatric age: Clinical and epidemiological impact on our environment. Hormone Research in Paediatrics. 2011;76:279. | Abstract only available |
| Ferrara M, Bertocco F, Ricciardi A, et al. Iron deficiency screening in the first three years of life: A three-decade-long retrospective case study. Hematology. 2014;19(4):239-43. | Small sample size and not representative (hospital) |
| Kristinsson G, Shtivelman S, Hom J, et al. Prevalence of occult anemia in an urban pediatric emergency department: What is our response? Pediatric Emergency Care. 2012;28(4):313-5. | Small sample size, no data specific to IDA and including those with history of anaemia |
| Levi M, Rosselli M, Simonetti M, et al. Epidemiology of iron deficiency anaemia in four European countries: a population-based study in primary care. European Journal of Haematology. 2016;97(6):583-93. | Only 5 Italian cases of IDA in <5s against which older age groups were compared for risk |

| Reference | Reason for exclusion |
|---|---|
| McCarthy EK, Hannon G, Ahearne C, et al. Low mean corpuscular volume and sub-optimal ferritin concentrations, without anaemia, are associated with decreased cognitive function at two years in a high-resource setting. European Journal of Pediatrics. 2016;175(11):1551. | Abstract only available |
| Petry N, Olofin I, Hurrell RF, et al. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: A systematic analysis of national surveys. Nutrients. 2016;8(11). | All surveyed countries not representative (non-OECD) |
| Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: A systematic review. European Journal of Haematology. 2016;96(6):618-28. | No relevant data |
| Vos T, Allen C, Arora M, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016;388(10053):1545-602. | No age specific relevant data. |
| **Q2 – adverse outcomes** | |
| Abdullah K, Maguire JL, Birken CS, et al. Prevalence, practice patterns and hematological outcomes of young canadian children identified with non-anemic iron deficiency (NAID): Implications of screening in primary care settings. Paediatrics and Child Health (Canada). 2014;19(6):e44-e5. | Abstract only available |
| Abdullah K, Thorpe KE, Maguire JL, et al. Risk factors, practice variation and hematological outcomes of children identified with non-anemic iron deficiency following screening in primary care setting. Paediatrics and Child Health (Canada). 2015;20(6):302-6. | No comparison group without ID |
| Algarin C, Reyes S, Peigneux P, et al. Sleep-dependent motor skill consolidation in adolescents with iron deficiency anaemia in infancy. Journal of Sleep Research. 2012;21:70. | Abstract only available |
| Beausang OA, Man RXG, Flavin B, et al. Iron deficiency and febrile seizures in children in the United Kingdom. Developmental Medicine and Child Neurology. 2012;54:63. | Abstract only available |
| Cortese S, Angriman M, Lecendreux M, et al. Iron and attention deficit/hyperactivity disorder: What is the empirical evidence so far? A systematic review of the literature. Expert Review of Neurotherapeutics. 2012;12(10):1227-40. | Cross sectional assessments, cannot imply causation |
| Costea RM, Leonida NM. Iron deficiency-potential risk factor for febrile seizures. Journal of Pediatric Gastroenterology and Nutrition. 2016;62:807. | Abstract only available |
| Habibian N, Alipour A, Rezaianzadeh A. Association between iron deficiency anemia and febrile convulsion in 3-to 60-month-old children: A systematic review and meta-analysis. Iranian Journal of | Cross sectional assessments, cannot imply causation |

| Reference | Reason for exclusion |
|---|---|
| Medical Sciences. 2014;39(6):496-505. | |
| Hermoso M, Vucic V, Vollhardt C, et al. The effect of iron on cognitive development and function in infants, children and adolescents: A systematic review. Annals of Nutrition and Metabolism. 2011;59(2-4):154-65. | Assessing effect of nutrient intake not iron status |
| McCarthy EK, Hannon G, Ahearne C, et al. Low mean corpuscular volume and sub-optimal ferritin concentrations, without anaemia, are associated with decreased cognitive function at two years in a high-resource setting. European Journal of Pediatrics. 2016;175(11):1551. | Abstract only available |
| Petry N, Olofin I, Boy E, et al. The effect of low dose Iron and zinc intake on child micronutrient status and development during the first 1000 days of life: A systematic review and meta-analysis. Nutrients. 2016;8(12). | No relevant data on effect of iron status on long-term outcomes |
| Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: A systematic review. European Journal of Haematology. 2016;96(6):618-28. | No relevant data |
| Venables PH, Raine A. Poor nutrition at age 3 and schizotypal personality at age 23: The mediating role of age 11 cognitive functioning. American Journal of Psychiatry. 2012;169(8):822-30. | Primarily looking at effect of malnutrition on non-representative Mauritian population; anaemia not defined as IDA |
| **Q3 – screen test** | |
| Akkermans MD, Uijterschout L, Vloemans J, et al. Red Blood Cell Distribution Width and the Platelet Count in Iron-deficient Children Aged 0.5-3 Years. Pediatric Hematology and Oncology. 2015;32(8):624-32. | Not fit to question. Selected sample of children having blood before surgery; comparison of parameters between those with and without IDA |
| Boghani S, Mei Z, Perry GS, et al. Accuracy of capillary hemoglobin measurements for the detection of anemia among U.S. Low-income toddlers and pregnant women. Nutrients. 2017;9(3). | Feasible diagnostic cohort but selected sample of US low income children |
| Crispin P, Sinclair F, Andriolo K. Low haemoglobin density for detecting iron deficiency across a large population, including pregnancy. International Journal of Laboratory Hematology. 2016;38(4):397-402 | Selected samples from hospital patients; assessing correlation between different |

| Reference | Reason for exclusion |
|---|---|
| | lab analysers |
| Hennek JW, Kumar AA, Wiltschko AB, et al. Diagnosis of iron deficiency anemia using density-based fractionation of red blood cells. Lab on a Chip - Miniaturisation for Chemistry and Biology. 2016;16(20):3929-39. | Discarded blood samples from children's hospital (all with apparent anaemia); new lab analysis to distinguish IDA |
| Hinchliffe RF, Bellamy GJ, Finn A, et al. Utility of red cell distribution width in screening for iron deficiency. Archives of Disease in Childhood. 2013;98(7):545-7. | Not fit to question. Small sample taking part in vaccine sample; bloods taken to assess response and analyse blood parameters |
| Yu C, Zhang J, Yuan Z, et al. A novel method for quantification of human hemoglobin from dried blood spots by use of tandem mass spectrometry. Analytical and bioanalytical chemistry. 2015;407(26):8121-7. | Anonymous samples from mixed child/adult population, assessing performance of different analysers; non-OECD |
| **Q4 – treatment** | |
| Abdullah K, Maguire JL, Birken CS, et al. Prevalence, practice patterns and hematological outcomes of young canadian children identified with non-anemic iron deficiency (NAID): Implications of screening in primary care settings. Paediatrics and Child Health (Canada). 2014;19(6):e44-e5. | Abstract only available |
| Abdullah K, Thorpe KE, Maguire JL, et al. Risk factors, practice variation and hematological outcomes of children identified with non-anemic iron deficiency following screening in primary care setting. Paediatrics and Child Health (Canada). 2015;20(6):302-6. | Study subsample clinically assigned to treatment; untreated comparison group may be influenced by confounding |
| De-Regil LM, Jefferds ME, Sylvetsky AC, et al. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. Cochrane database of systematic reviews (Online). 2011;12:CD009085. | Mixed/unknown ID/IDA status; mostly low/middle income countries; age range up to 12 years |
| Hermoso M, Vucic V, Vollhardt C, et al. The effect of iron on cognitive development and function in infants, children and adolescents: A systematic review. Annals of Nutrition and Metabolism. 2011;59(2-4):154-65. | Mixed/unknown ID/IDA status |

| Reference | Reason for exclusion |
|---|---|
| Kashif M, Rab ZZ, Ahmad J, et al. To compare the effect of iron therapy alone versus combined iron therapy and vitamin D supplementation on cardiovascular functions in children with iron deficiency anemia by echocardiography: A randomized controlled trial. Annals of Pediatric Cardiology. 2014;7:S93. | Abstract only available |
| Pasricha SR, Hayes E, Kalumba K, et al. Effect of daily iron supplementation on health in children aged 4-23 months: A systematic review and meta-analysis of randomised controlled trials. The Lancet Global Health. 2013;1(2):e77-e86. | Mixed/unknown ID/IDA status; mostly low/middle income countries |
| Petry N, Olofin I, Boy E, et al. The effect of low dose Iron and zinc intake on child micronutrient status and development during the first 1000 days of life: A systematic review and meta-analysis. Nutrients. 2016;8(12). | Mixed/unknown ID/IDA status |
| Powers JM, McCavit TL, Adix L, et al. Low dose once daily oral iron treatment of young children with nutritional iron deficiency anemia. Blood2015. p. 2147. | Abstract only available |
| Pratt JJ, Khan KS. Non-anaemic iron deficiency - a disease looking for recognition of diagnosis: A systematic review. European Journal of Haematology. 2016;96(6):618-28. | Brief report; no relevant data |
| Tang M, Frank DN, Sherlock L, et al. Effect of Vitamin E with therapeutic iron supplementation on iron repletion and gut microbiome in US iron deficient infants and toddlers. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(3):379-85. | Assessing vitamin E when added to iron; not assessing effect of iron and no development outcomes |
| Thompson J, Biggs BA, Pasricha SR. Effects of daily iron supplementation in 2- to 5-year-old children: Systematic review and meta-analysis. Pediatrics. 2013;131(4):739-53. | Mixed/unknown ID/IDA status; mostly low/middle income countries |
| Vucic V, Hermoso M, Arsic A, et al. Effect of iron intervention on growth in infants, children and adolescents: A systematic review. Annals of Nutrition and Metabolism. 2011;58:142-3. | Abstract only available |

# Appendix 3 — Summary and appraisal of individual studies

## Data Extraction

**Table 10. Studies relevant to criterion 1, Q1**

| Study reference | Study design | Population characteristics | Method of ID/IDA assessment | Prevalence and incidence outcomes | Appraisal points |
|---|---|---|---|---|---|
| Global Burden of Disease Pediatrics Collaboration, 2016 | Review of global registry data across 188 countries from between 1990 and 2013.<br><br>Aims to identify levels and trends fatal and non-fatal burden of diseases and injuries among young children (aged <5 years), older children (aged 5 to 9 years), and adolescents (10 to 19 years). | Reported data specific to UK children aged <5 years.<br><br>(Data for older children and other nationalities not reviewed here) | Disease prevalence estimated from epidemiological database compiling data from systematic reviews including nationally representative household surveys, antenatal clinic surveillance data, disease notifications, disease registries, hospital admissions data, outpatient visit data, and other administrative data.<br><br>Cause-specific mortality from maternal and child death surveillance and other registries. | <u>IDA in the UK children <5 years in 2013</u><br><br>771,753 cases (95% uncertainty interval (UI) 768,582 to 775,024),<br><br>20.2% prevalence (95% UI 20.1 to 20.2)<br><br>62nd cause of death<br><br><u>Developed countries overall</u><br><br>191,234,284 cases (95% UI 190,755,058 to 191,695,496)<br><br>32.6% prevalence (95% UI 32.5 to 32.7)<br><br>59th cause of death<br><br>Globally, in children aged <5 years IDA moved from rank as the 15th cause of disability adjusted life years | Unclear whether registries give full coverage of the UK.<br><br>Uncertain diagnostic criteria for IDA – high prevalence suggests some could be iron deficiency without anaemia. |

| Study reference | Study design | Population characteristics | Method of ID/IDA assessment | Prevalence and incidence outcomes | Appraisal points |
|---|---|---|---|---|---|
| | | | . | in 1990 to 13th in 2013 | |
| Eussen et al 2015 | Systematic review to assess the prevalence of inadequate iron intake and ID/IDA in European children.<br><br>PubMed, Medline, CAB Health and Embase searched from 2000 to Nov 2013, in addition to data collection from government organisations and expert interviews. | European children aged 6 to 36 months in 22 studies.<br><br>Exclusions: preterm, low birthweight and children with intestinal failure. RCT participants due to selection bias. | ID was preferably defined using WHO definitions: SF <12 µg/l; IDA in combination with Hb <110 g/l.<br><br>Unclear method of measurement in individual studies. | 5/22 studies covered UK populations:<br><br><u>Thane 2000</u><br><br>Nationally representative, 1992 to 2003, n=727 age 18 to 54 months: prevalence **ID 31%** (cut-off SF<12), **IDA 3.4%** (cut-off Hb <110, SF 10).<br><br><u>Hopkins 2007</u><br><br>Nationally representative, 1993 to 2004, age 8 months, prevalence **ID 5% breastfed** (of sample n=113), **2% formula** (n=687), **7% cow's milk** (n=126).<br><br>At 12 months **5% breastfed** (n=102), **3% formula** (n=574) and **11% cow's milk** (n=105).<br><br>(all SF <16)<br><br><u>Cowin 2001</u><br><br>Nationally representative, 1994, n=709 age 18 months, prevalence **ID 4%** (SF <12); prevalence **IDA 1.7%** (SF <12, Hb <110) | Published rather than collected data.<br><br>Uncertain recruitment to studies, measurement of iron status and sociodemographics, though most nationally representative.<br><br>Three studies (Thane, Hopkins and Cowin) with sample size >500 children; less confidence in results from smaller subgroups.<br><br>No uniform definition of ID/IDA and variable cut-offs used. Cowin only study compatible with WHO definitions.<br><br>Prevalence from older data collection may be outdated due to differences in exposures/risk factors. |

| Study reference | Study design | Population characteristics | Method of ID/IDA assessment | Prevalence and incidence outcomes | Appraisal points |
|---|---|---|---|---|---|
| | | | | Taylor 2004<br>Unclear if nationally representative, 1996 to 2008, prevalence **ID 0% age 4 months** (of sample n=85), **4.2% age 12 months** (n=92), **2.8% age 24 months** (n=101) (SF cut-off <10)<br>Wright 2004<br>Nationally representative, year of data collection not reported, n=414 age 13 months prevalence **ID 7.7%** (SF <10). | |
| McCarthy et al 2016 | Prospective birth cohort, Ireland.<br>The Cork BASELINE (Babies after SCOPE: Evaluating the Longitudinal Impact using Neurological and Nutritional Endopoints) Birth Cohort Study.<br>Recruitment 2008 | N=729 children providing blood samples at the 24 month assessment.<br>53% males, 0.2% taking iron supplements and 19% consuming iron-supplemented formula.<br>Representative of 47% attending assessment (n=1537) and 34% of those initially recruited (n=2137). | Measurement of Hb and mean corpuscular volume (MCV).<br>Exclusions: children with C-reactive protein (CRP) >5 mg/l. | ID prevalence<br>1.8% SF<10 µg/l<br>4.6% SF<12<br>20.8% SF<15<br>2.6% SF<12 and MCV <74 fl<br>IDA prevalence<br>0.2% Hb <110 g/l and SF <10 µg/l<br>1.0% Hb <110 and SF <12<br>1.3% Hb <110 and SF <15<br>0.2% Hb <105 and SF <10<br>0.4% Hb <105 and SF <12 and MCV <74 | Largest study in European toddlers to date and recent data.<br>Highlights variation in prevalence according to definition and need for standardisation of diagnostic criteria.<br>WHO and UK Science Advisory Committee on Nutrition have used SF <12; UK National Diet and Nutrition Survey (NDNS) use SF <10.<br>Iron fortification of foods may have had an influence.<br>May be differences in |

| Study reference | Study design | Population characteristics | Method of ID/IDA assessment | Prevalence and incidence outcomes | Appraisal points |
|---|---|---|---|---|---|
| | | | | | prevalence between those completing assessments and not.<br>Also prevalence may not be applicable to other regions of Ireland or the UK with different sociodemographic. |

## Table 11. Studies relevant to criterion 9, Q4

| Study | Study design | Population characteristics | Intervention | Comparator | Outcomes/Results | Appraisal points |
|---|---|---|---|---|---|---|
| Wang et al 2013[8] | Cochrane systematic review update.<br>Aim: to determine the effects of iron therapy on psychomotor development and cognitive function in children with IDA <3 years of age.<br>Search: April 2013<br>Inclusion: | Children ≤3 years with IDA based on Hb, Hb+SF, or other author-defined.<br>8 RCTs (n=385; range 24 to110 per study).<br>All included studies <26 months.<br>Recruitment: community (4 studies), clinics (3 studies) and 1 study in an orphanage | Iron (+/- vitamin C)<br>Delivery: oral (4 studies), intramuscular (3 studies) and both methods in 1 study. | Placebo (or vitamin C alone)<br>7 studies compared with placebo, 1 study compared with vitamin C alone. | <u>Bayley Psychomotor Development Index (PDI) by 30 days:</u><br>-1.25 (95% CI -4.56 to 2.06)<br>Low quality evidence based on 5 studies (n=162), $I^2$ 33%<br><u>Bayley Mental Development Index (MDI) by 30 days:</u><br>+1.04 (95% CI -1.30 to 3.39)<br>Low quality evidence, 5 studies (n=164) $I^2$ 31%<br><u>Bayley PDI above 30 days:</u><br>*+18.4 (95% CI 10.16 to 26.64)*<br>Moderate quality evidence, 1 study (n=47)<br><u>Bayley MDI above 30 days:</u><br>*+18.8 (95% CI 10.17 to 27.43)* | Small body of evidence and short-term assessment<br>Studies published 1978 to 1993.<br>Countries: 2 UK, US, Greece, Chile, Costa Rica, Indonesia, Guatemala.<br>May be limited applicability.<br>Trials at unclear risk of randomisation bias and some uncertain |

| Study | Study design | Population characteristics | Intervention | Comparator | Outcomes/Results | Appraisal points |
|---|---|---|---|---|---|---|
| | RCTs | | | | Moderate quality evidence, 1 study (n=47)<br><u>Denver Developmental Screening Test above 30 days</u><br>+0.8 (95% CI -0.18 to 1.78)<br>Moderate quality evidence, 1 study (n=97) | allocation and blinding bias. Otherwise low risk. Evidence graded as low to moderate quality due to potential publication bias and imprecision.<br>No assessment of harms. |
| Abdullah et al 2012[9] | Systematic review.<br>Aim: to determine the effects of iron therapy on development outcomes in pre-school children with non-anaemic ID (NAID).<br>Search: January 2011<br>Inclusion: RCTs and prospective controlled comparison | Healthy children aged 1 to 5 years with non-anaemic ID (SF <12µg/l and Hb >110g/l).<br>Exclusions: development disorders, chronic or congenital disease.<br>2 RCTs identified: both included children with IDA but analysed subgroups with ID only:<br>Akman (2004, Turkey) n=40 with NAID aged 6 to 30 months.<br>Idjradinata (1993, | Oral iron at dose ≥2mg/kg for ≥3 months<br>(+/- vitamin C, folic acid or dietary counselling)<br>Akman: 3mg/kg twice daily for 3 months.<br>Idjradinata: 3mg/kg once daily for 4 months. | Placebo or no treatment.<br>Placebo in Idjradinata trial, no placebo in Akman trial. | <u>Bayley PDI post-treatment:</u><br>Akman: -0.23 (95% CI -7.07 to 6.61)<br>Idjradinata: +1.20 (95% CI -5.99 to 8.39)<br><u>Bayley MDI post-treatment:</u><br>*Akman: +6.26 (95% CI 1.54 to 10.98)*<br>Idjradinata: -1.60 (95% CI -9.38 to 6.18)<br><u>Hb change</u><br>Akman: +2.70 (95% CI -1.74 to 7.14)<br>*Idjradinata: +11.50 (95% CI 5.08 to 17.92)*<br><u>SF change</u><br>Akman: +17.06 (95% CI 7.51 to *26.61)*<br>*Idjradinata: +51.10 (95% CI 33.62* | Only 2 small studies with limited applicability.<br>Trials of moderate quality, both with unclear allocation and Akman study single blind due to lack of placebo.<br>High heterogeneity prevented pooling.<br>Lack of statistical power to assess effects in children with |

| Study | Study design | Population characteristics | Intervention | Comparator | Outcomes/Results | Appraisal points |
|---|---|---|---|---|---|---|
| | studies. | Indonesia) n=29 with NAID aged 12 to 18 months. Study used higher Hb cut-off of >120g/l | | | *to 68.58)* | NAID specifically<br>No assessment of harms. |

# Appendix 4 – UK NSC reportin vidence 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 12.

**Table 2. 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. | 7 |
| **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 | 10 |
| | | Objectives – What are the questions the current evidence summary intends to answer? – statement of the key questions for the current evidence summary, | 11 |

| | Section | Item | Page no. |
|---|---|---|---|
| | | criteria they address, and number of studies included per question, description of the overall results of the literature search.<br><br>Method – briefly outline the rapid review methods used. | 13 |
| **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*. | 13 |
| **2.3** | Appraisal for quality/risk of bias tool | Details of tool/checklist used to assess quality, e.g. QUADAS 2, CASP, SIGN, AMSTAR. | 17 |
| **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. | 16 and 32 |
| **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.<br><br>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. | 32 |
| **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. | 13 |
| **4.** | STUDY LEVEL REPORTING OF RESULTS (FOR EACH KEY QUESTION) | | |
| **4.1** | Study level reporting, results and | 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 | 49 |

| | Section | Item | Page no. |
|---|---|---|---|
| | risk of bias assessment | period, outcomes reported, statistical analyses etc.).<br>Provide a simple summary of key measures, effect estimates and confidence intervals for each study where available.<br>For each study, present the results of any assessment of quality/risk of bias. | |
| **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. | 17, 21, 24, 26 |
| **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. | 18, 28 |
| **5.3** | Summary of findings | Provide a description of the evidence reviewed and included for each question, with reference to their eligibility for inclusion.<br>Summarise the main findings including the quality/risk of bias issues for each question.<br>Have the criteria addressed been 'met', 'not met' or 'uncertain'? | 22, 25, 30 |
| **6.** | REVIEW SUMMARY | | |
| **6.1** | Conclusions and implications for policy | Do findings indicate whether screening should be recommended?<br>Is further work warranted?<br>Are there gaps in the evidence highlighted by the review? | 31 |

| | Section | Item | Page no. |
|---|---|---|---|
| **6.2** | Limitations | Discuss limitations of the available evidence and of the review methodology if relevant. | 31 |

# References


1. Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: A systematic review. American Journal of Clinical Nutrition. 2015; 02(6):1585-94.
2. McDonagh MS, Blazina I, Dana T, et al. Screening and routine supplementation for iron deficiency anemia: A systematic review. Pediatrics. 2015;135(4):723-33.
3. Bazian. Screening for iron deficiency anaemia in children under 5 years of age: External review against programme appraisal criteria for the UK National Screening Committee. London: UK NSC, 2012. Available from: http://legacy.screening.nhs.uk/irondeficiency/.
4. Vos T, Kyu HH, Pinho C, et al. Global and national burden of diseases and injuries among children and adolescents between 1990 and 2013 findings from the global burden of disease 2013 study. JAMA Pediatrics. 2016;170(3):267-87.
5. Eussen S, Alles M, Uijterschout L, et al. Iron intake and status of children aged 6-36 months in Europe: A systematic review. Annals of Nutrition and Metabolism. 2015;66(2-3):80-92.
6. McCarthy EK, ní Chaoimh C, O'B Hourihane J, et al. Iron intakes and status of 2-year-old children in the Cork BASELINE Birth Cohort Study. Maternal and Child Nutrition. 2016.
7. Siu AL. Screening for iron deficiency anemia in young children: USPSTF recommendation statement. Pediatrics. 2015;136(4):746-52.
8. Wang B, Zhan S, Gong T, et al. Iron therapy for improving psychomotor development and cognitive function in children under the age of three with iron deficiency anaemia. The Cochrane database of systematic reviews. 2013;6:CD001444.
9. Abdullah K, Kendzerska T, Shah P, et al. Efficacy of oral iron therapy in improving the developmental outcome of pre-school children with non-anaemic iron deficiency: a systematic review. Public health nutrition. 2013;16(8):1497-506.
10. Tang M, Frank DN, Sherlock L, et al. Effect of Vitamin E with therapeutic iron supplementation on iron repletion and gut microbiome in US iron deficient infants and toddlers. Journal of Pediatric Gastroenterology and Nutrition. 2016;63(3):379-85.