UK National Screening Committee

Iron Deficiency Anaemia

An evidence map to outline the volume and type of evidence related to screening for iron deficiency anaemia in children under 5 years for the UK National Screening Committee

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The UK National Screening Committee secretariat is hosted by The Office for Health Improvement & Disparities.

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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The Office for Health Promotions & Disparities hosts the UK NSC

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Summary

This document discusses the findings of the evidence map on screening for iron deficiency anaemia (IDA) in children under 5 years of age.

Evidence maps are a way of scanning published literature to look at the volume and type of evidence in relation to a specific topic. Their purpose is to inform whether the evidence is sufficient to commission a more sustained analysis on the topic under consideration.

Based on the findings of this evidence map, there is insufficient published literature to justify further work on screening for IDA at the present time.

The UK National Screening Committee (UK NSC) will return to screening for IDA in 3-years' time.

Introduction and approach

Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or evidence reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Screening for IDA in children under 5 years of age is a topic currently due for an update external review.

Iron serves several purposes within the body, including, critically, being involved with many central nervous system functions. Iron is crucial for brain metabolism[1] and iron deficiency (ID) has been associated with long-lasting cognitive, motor and behavioural effects,[2] potentially through causing changes such as reduced myelin production and synaptogenesis.[1] However, some debate exists whether there is a causal link and whether iron supplementation can improve these outcomes.[3, 4] The requirements for iron are thought to be higher during late infancy and early childhood than during any other period of life, and therefore this age group is at particular risk of ID when dietary intake is inadequate.[5, 6]

Dietary iron is absorbed in the proximal duodenum of the small intestine. Absorption is regulated by body iron stores, decreasing with increasing iron stores, but can also be affected by other constituents in the diet. For example, supplementation with vitamin C enhances absorption by creating a more acidic environment in the stomach, enabling iron to be better dissolved .[7] Conversely, phytates (found in seeds or unprocessed whole grains) and calcium inhibit absorption; phytic acid, widely found in plant foods, forms complexes with iron, interfering with intestinal absorption.[8] Calcium, widely found in dairy products made from cow's milk and some green leafy vegetables, inhibits the absorption of haem and non-haem iron, interfering with iron transport during absorption.[8]

As iron is required for normal functioning of red blood cells, which carry oxygen around the body, if not reversed, ID can ultimately lead to IDA[6] and as anaemia is a late manifestation of ID, it may be preventable by early diagnosis and effective treatment of ID.[9] While inadequate dietary iron intake increases the risk of ID, other conditions or circumstances, such as coeliac disease, chronic kidney disease, eating avoidance or ethnicity can also affect the likelihood of ID.[10, 11] Furthermore, anaemia can also develop for reasons other than ID, for example due to haemoglobinopathies, such as thalassaemias or as a result of chronic disease, but this evidence map focuses on IDA only.[12]

The global prevalence of anaemia in 2010 was estimated at 32.9%, with the highest burden in children under 5 years old.[13] in 2011, The World Health Organisation (WHO) claimed that ~42% of childhood anaemia cases reported worldwide be a consequence of ID, however noting that the proportion varies among population groups and different areas of the world.[14] Nonetheless, these figures clearly demonstrate that ID and its consequence, IDA, are a substantial global health concern.

In Europe, the prevalence of ID in children in a recent systematic review was reported to range from 2 to 25% in infants aged 6 to 12 months, and 3 to 48% in children aged 12 to 36 months.[6] Prevalence of IDA in these age groups was generally lower than that of ID, between 9 and 16% in Eastern Europe (but as high as 50% in Albania) and mostly below 5% in Western and Northern Europe (but up to 8.5% in Dutch children),[6] which nevertheless represents a substantial proportion of this age group. Therefore, screening for ID and/or IDA in young children may be of interest from a public health perspective in European nations to prevent any adverse developmental outcomes potentially associated with these conditions.

Estimates of the prevalence of ID and IDA in children under 5 years for the UK are not readily available. As an individual may be iron deficient without suffering from anaemia, the incidence of ID may greatly surpass that of IDA; current evidence suggests that around 1 to 3 children in 100 in the UK may have IDA.[15] However, these figures are not certain because there is a lack of agreement around the cut-off blood levels of iron that confirm ID or IDA.[15]

Key diagnostic markers

Diagnosing IDA involves coupling the measurements for ID with determination of haemoglobin (Hb) levels in the blood, to confirm a concurrent diagnosis of both ID and anaemia. To establish a diagnosis of ID, the following are usually measured: 1) serum ferritin and C-reactive protein measurements, or 2) reticulocyte haemoglobin (CHr) measurements.[3] According to WHO guidelines, ID in children under 5 years is defined as serum ferritin levels <12 μg/L.[16] Anaemia in general, including IDA, is characterised by a reduction in Hb or haematocrit (Hct),[17] both of which can be measured after blood sample collection. Anaemia occurs if the Hb concentration falls 2 standard deviations (SD) below the mean for a normal population of the same age and gender.[3] For children aged 1 to 3 years, anaemia is defined as a Hb concentration of <11.0 g/dL.[3]

However, as anaemia can arise from sources other than iron deficiency, and Hb and Hct only decrease upon severe iron depletion, these markers cannot specify whether the diagnosed anaemia resulted from ID or another cause.[17, 18] Therefore, additional laboratory markers that specifically reflect the level of iron depletion must be measured to diagnose IDA, such as serum ferritin.[3, 16] Further markers that indicate iron levels include transferrin saturation and transferrin receptor (TfR).[9, 16]

Table 1 below describes the changes that would be expected for individuals with ID compared with IDA for the markers outlined above.

Table 1. Overview of expected changes in laboratory markers in ID and IDA compared with unaffected children[3]

Parameter	ID (without anaemia)	IDA
Serum ferritin*	Decreased	Severely Decreased
Transferrin saturation	Decreased	Decreased
TfR1	Severely Increased	Extremely Increased
CHr	Decreased	Decreased
Hb	Normal	Decreased

Footnotes: *Serum ferritin levels can be confounded by the presence of inflammation, and should therefore be analysed in parallel with inflammatory markers, such as C-reactive protein.[3] **Abbreviations:** CHr: reticulocyte haemoglobin; Hb: haemoglobin; ID: iron deficiency; IDA: iron deficiency anaemia; TfR1: transferrin receptor 1.

Measurement of the markers outlined above usually requires phlebotomy, which is an invasive procedure associated with challenges in young children.[19] The use of non-invasive or minimally invasive tests in screening to identify IDA would be preferable in infants and young children.

Current treatments

To reduce the burden of IDA in young children in populations where anaemia is a public health problem, WHO recommends administration of iron-based interventions, such as iron supplements or iron-containing multiple micronutrient powders.[20] Oral iron therapy is commonly used, however, insufficient responses have been reported in children due to inadequate iron uptake or undesirable side effects, such as gastrointestinal upset.[21] Due to these side effects, compliance to treatment can be poor and often treatment courses are altered (reduced frequency or dose), which can affect treatment response. Some studies recommend use of intravenous iron in children, especially in children with IDA that is refractory to oral iron therapy.[22, 23] However, as noted above, there is some uncertainty whether iron supplementation indeed improves developmental outcomes.[4] For example, a Cochrane systematic review has been conducted with the objective to determine the effect of iron therapy on psychomotor development and cognitive function among children under 3 years with IDA.[24] The review concluded that there was no convincing evidence that iron treatment in this age group has an effect on psychomotor or cognitive developmental outcomes in the short term (within 30 days after treatment initiation). Unfortunately, the long-term effects where one may have expected an effect, remain unclear, with an urgent need for research in this area.[24]

Screening policy

Currently, considerable variability in expert opinion exists regarding the best approach to early detection of children with ID and IDA. As briefly noted above, ID has been associated with adverse developmental outcomes, which may be worse if ID progresses to IDA, and some evidence exists that these outcomes improve when children are identified and treated early, indicating the potential benefit of screening.[18] However, the effect on developmental outcomes is debated.[18] There are also downsides to screening, such as false-positive results, anxiety and costs.[25]

The screening recommendations for Spain, the UK and the US are outlined in Table 2. The UK NSC's last review, published in 2017, concluded that a systematic population screening programme for IDA in children under 5 years old is not recommended (see below for further details).[15]

Table 2. Overview of screening recommendations for ID and IDA in children under 5 years old

Organisation	Geography	Year	Recommendation on screening for ID or IDA
CDC[26]	US	1998	Yes
WHO[18, 27]	International	2001	Yes
AAP[3]	US	2010	Yes
PrevInfad[28]	Spain	2011	No*
USPSTF[25]	US	2015	No†
UK NSC[15]	UK	2017	No

Footnotes: *Recommends testing in high-risk groups, such as preterm infants weighing less than 1,500 g, but does not recommend screening in children without risk factors; †Concluded that there was insufficient evidence on the benefits versus harms of screening for anaemia, with a focus on children aged 6 to 24 months. **Abbreviations:** AAP: American Academy of Pediatrics; CDC: Centre for Disease Control and Prevention; ID: iron deficiency; IDA: iron deficiency anaemia; NSC: National Screening Committee; USPSTF: United States Preventative Services Task Force; WHO: World Health Organisation.

Previous review on screening for iron deficiency anaemia in children under 5 years

The UK NSC currently recommends against screening for IDA in children under 5 years. This recommendation was based on the evidence provided by the 2017 UK NSC review, the key findings of which are outlined below:[15]

- prevalence estimates for ID/IDA in UK children under 5 years old are inconsistent
- no studies were identified assessing whether ID/IDA in children under 5 years old is associated with later adverse health and developmental outcomes

- no studies were identified assessing a screening 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 under 5 years old
- although 2 systematic reviews identified a number of small randomised controlled trials (RCTs) assessing treatment, they were in clinically detected children, inconsistent and inconclusive, and the trials included were published over 25 years ago, and so had limited applicability to a contemporary UK screening population

Aims of the evidence map

Evidence maps are rapid evidence products that aim to gauge the volume and type of evidence relating to a specific topic.

The aim of this evidence map was to address the following questions:

1. What are the adverse developmental outcomes of ID/IDA in children aged under 5 years?
2. Is there a non-invasive, simple, safe, precise and validated screening test for ID/IDA in children aged under 5 years?
3. What is the effect of iron supplementation on developmental complications of ID/IDA in asymptomatic children identified early through screening?

For each question, evidence was considered relevant if it provided data answering the questions with regards to (a) just ID, (b) just IDA or (c) both.

The objective is therefore to assess the volume and type of evidence relevant to screening for IDA in children under 5 years of age, with a focus on the impact of the condition on children, test accuracy of screening tests and the effect of intervention following screening.

The findings of this evidence map will provide the basis for discussion to support decision making on whether there is sufficient evidence to justify commissioning a more sustained review of the evidence on IDA in children under 5 years of age in 2022. The aim of this document is to present the information necessary for the UK NSC to decide this.

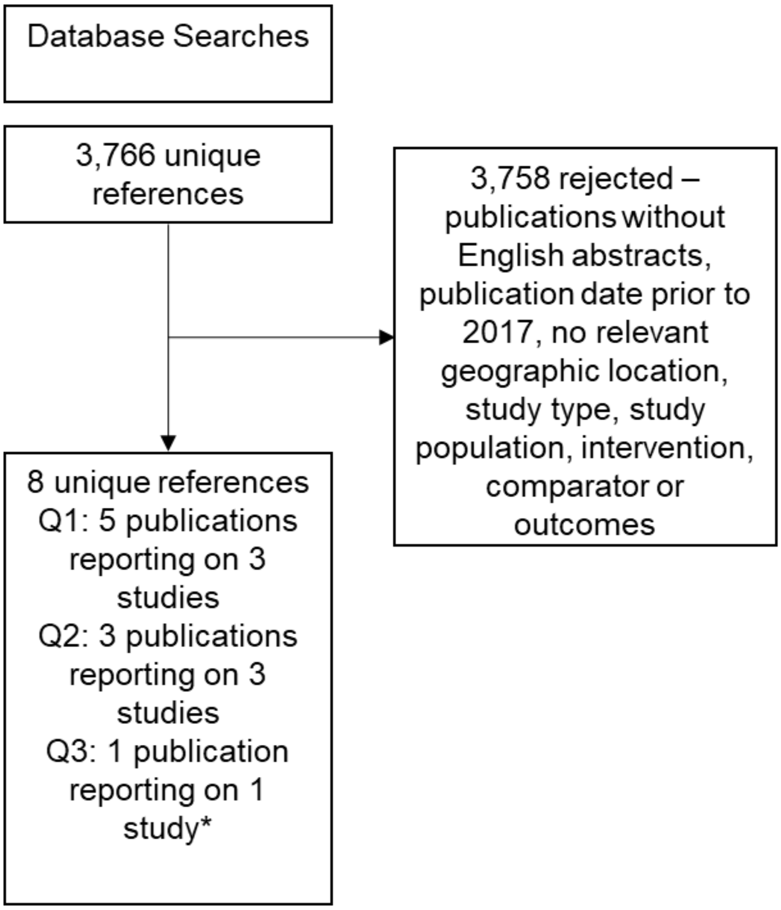
Search methods and results

The searches were conducted on 10 September 2021 on 4 databases: MEDLINE, Embase, Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL). The search period was restricted to 1 January 2017 to 9 September 2021 for MEDLINE and Embase. For CDSR searches were limited from March 2017 to September 2021 and for CENTRAL searches were limited from January 2017 to September 2021. MEDLINE (including MEDLINE In-Process, MEDLINE Daily and Epub Ahead of Print) and Embase were searched simultaneously via the Ovid SP platform. The Cochrane Library databases (CDSR and CENTRAL) were searched via the Wiley Online platform.

The detailed search strategies, including exclusion and inclusion criteria, are available in Appendix 1. One reviewer screened all titles and abstracts, with a second reviewer checking all included and 10% of excluded abstracts. In any case of discrepancies, a decision was made by consensus. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information. A formal quality appraisal of the evidence was not required, given the remit of the evidence map.

The search returned 3,919 results. After automatic and manual de-duplication, 3,766 unique references were reviewed for relevance to the questions and 8 unique references were included in the final evidence map. A flow diagram summarising the number of studies included and excluded is presented in Figure 1. Abstract reporting tables are available in Appendix 2.

Figure 1: Summary of included and excluded publications



Footnotes: *The relevant publication for question 3 was also of relevance to question 1, leading to the inclusion of 8 unique references in the evidence map overall. **Abbreviations:** Q: question.

Summary of findings

Question 1: What are the adverse developmental outcomes of ID/IDA in children aged under 5 years?

In total, 13 publications were identified as potentially relevant to question 1. The full texts were consulted for 9 of these to determine their relevance. Ultimately, 5 records reporting on 3 studies were included.

Larson 2019 conducted a systematic literature review (SLR) and meta-analysis with the objective to clarify the differences in outcomes in treated versus untreated low Hb concentration in children under 5 years old on development, growth and chronic disease.[29] As searching the studies included in this SLR is beyond the scope of this evidence map, it is unclear whether all included studies reported on patients with ID or IDA (some studies reporting on other types of anaemia are likely also included within the SLR). The SLR identified 56 interventional and 20 observational studies.[29] The authors observed heterogeneity among included studies, which precluded calculation of pooled associations between Hb and functional outcomes.[29] However, a metaregression indicated an association between effects on Hb and motor and mental development, suggesting that the SLR may contain studies where these outcomes are worse in children with low Hb (and ID or IDA).[29] The authors concluded that further research is needed to explore the associations of Hb with development and growth in diverse populations.[29]

Another SLR relevant to question 1 (McCann 2020) was identified in the searches.[30] This SLR aimed to understand whether untreated ID directly impacts developmental outcomes, and whether the impact differs by timing of exposure or developmental domain.[30] The SLR included studies that reported on neurodevelopmental outcomes for children aged 0 to 6 months, 6 to 24 months and 2 to 4 years.[30] While the number of included studies is not specified in the abstract, the authors commented on the low-quality of published studies in this field, considerable heterogeneity in study design, as well as a lack of studies that focused on early infancy.[30] The authors did not identify a clear relationship between iron status and developmental outcomes, and concluded that evidence for the impact of ID on early development is inconsistent, highlighting the need for high-quality research in this area.[30] The above is supported by Jullien 2021 (non-systematic review not included within the evidence map), who concluded that there is uncertainty between IDA in children and adverse developmental outcomes such as cognitive and psychomotor delays.[18]

Finally, 3 publications on the BASELINE cohort study in Ireland were identified, reporting on growth at age 2, as well as neurodevelopmental outcomes at age 2 and 5.[31-33] McCarty 2018 found that 5% of the overall cohort (n=704) had ID (ferritin <12 μg/L) and

1% had IDA (Hb <110 g/L + ferritin <12 µg/L) at age 2 years.[31] Weight gains from 6 to 12, 0 to 24, and 12 to 24 months were all inversely associated with ferritin concentrations at 2 years of age.[31] However, ferritin concentration was only significantly associated with weight gain from 12 to 24 months after adjustment for potential confounding factors, including cord ferritin (adjusted estimate: -4.40 µg/L; 95% CI: -8.43 to -0.37 µg/L; p=0.033).[31] Length gain from 0 to 24 months was positively associated with Hb at 2 years (adjusted estimate: 0.42 g/L; 95% CI: 0.07 to 0.76 g/L; p=0.019), but this association was not significant when adjusted for cord ferritin.[31] The authors concluded that iron stores at 2 years were inversely associated with weight gain in the second year, even after accounting for iron status at birth.[31]

In the McCarty 2017 publication, the authors found no significant associations between ID or IDA and cognitive outcomes in the BASELINE cohort, as measured by Bayley Scales of Infant and Toddler Development-III (BSID-III) scores at 2 years of age.[32] In a more recent publication, McCarty 2021 confirmed that there was no association between neonatal ID and cognitive or behavioural outcomes at age 2 or 5 years, using fully adjusted models.[33] Additionally, the authors performed an *a priori* sensitivity analysis in 306 high-risk children, selected using known risk factors for neonatal ID (such as smoking, obesity, caesarean section delivery and small-for-gestational age birth).[33] Within the high-risk subgroup (cord ferritin concentrations <76 µg/L), similar cognitive outcomes were observed for children with ID at birth (12%), but the behavioural assessments showed higher internalising and total problem behaviour scores at 5 years of age compared with children born iron sufficient (cord ferritin concentrations ≥76 µg/L).[33] The median result for internal problems in the Child Behavioural Checklist was 9.0 (interquartile range [IQR]: 5.3 to 12.0) for the high-risk subgroup, compared with 5.0 (IQR: 3.0 to 10.0) in the iron-sufficient children (p=0.006).[33] The median result for total problem behaviour scores in the Child Behavioural Checklist was 24.5 (IQR: 15.3 to 40.8) for the high-risk subgroup, compared with 16.0 (IQR: 10.0 to 30.0) in the iron-sufficient children (p=0.009).[33] Even after adjustment for covariates, the associations with internalising (adjusted estimate 2.8; 95% CI: 0.5 to 5.1; p=0.015) and total problem scores (adjusted estimate 6.6; 95% CI: 0.1 to 13.1; p=0.047) remained significant.[33] The authors therefore concluded that neonatal ID causes lasting behavioural consequences, as demonstrated in the high-risk subgroup of the BASELINE cohort.[33]

There is some evidence linking ID or IDA to adverse developmental outcomes, including growth and neurological outcomes, however, 2 SLRs included for question 1 concluded that robust evidence for the impact of ID on developmental outcomes is at best inconclusive. The current evidence base is too limited to conclude whether an association between ID or IDA and adverse developmental outcomes exists. Therefore, at present, there is insufficient evidence in this area to justify commissioning an evidence summary.

Question 2: Is there a non-invasive, simple, safe, precise and validated screening test for ID/IDA in children aged under 5 years?

Out of the 12 publications that were identified as potentially relevant to question 2, full texts were consulted for 10 publications to determine their relevance. Ultimately, 3 publications reporting on 3 studies were included.

Boghani 2017, reported on the accuracy of measuring capillary Hb in blood samples from finger punctures, in comparison to venous Hb concentrations, in toddlers aged 12 to 35 months.[34] The study investigated a non-invasive test to detect anaemia generally, and was not designed to specifically investigate ID or IDA. Of note, the included toddler population was from a low-income background in the US,[34] therefore this population may have been more at risk of undernourishment and ID/IDA. The authors found that the sensitivity of capillary blood analyses to identify anaemia was 32.8% (95% CI: 21.3 to 46.0%) and 60.4% (95% CI: 44.1 to 71.4%) for toddlers living in Kansas City (n=413) and St Louis (n=213), respectively.[34] The corresponding specificities were 97.7% (95% CI: 95.6 to 99.0%) and 85.6% (95% CI: 79.2 to 90.7%).[34] Boghani 2017 concluded that Hb measurements of capillary blood with the HemoCue device were not optimal for determining the anaemia status of toddlers.[34]

Gerday 2021 explored the measurement of urinary ferritin as a non-invasive alternative to measuring serum ferritin in neonates in a prospective US study.[35] The study used paired serum/urine samples from neonates that were intensive care unit patients judged as at-risk for ID (n=49). The sensitivity of urine ferritin (corrected for urine creatinine and specific gravity) <12 ng/ml to detect iron-limited erythropoiesis was 82% (95% CI: 67 to 93%), the specificity was 100% (95% CI: 66 to 100%) and the positive predictive value (PPV) was 100% (95% CI: 89 to 100%).[35] The authors therefore concluded that measuring urinary ferritin in neonates is feasible and could provide a useful non-invasive screen for ID.[35]

Finally, Homan 2019, evaluated a non-invasive method to measure erythrocyte zinc protoporphyrin (ZnPP) by fluorescence measurements on the wet vermillion of the lower lip, in comparison to soluble transferrin receptor (sTfR), ferritin and ZnPP levels in blood samples.[36] The study population included hospitalised children aged 9 months to 5 years (n=99) in Germany.[36] The authors reported a sensitivity of 67% (95% CI: 39 to 88%) and specificity of 97% (95% CI: 91 to 99%) for non-invasive ZnPP measurements.[36] Additionally, a negative predictive value (NPV) and PPV of 94% (95% CI: 90 to 97%) and 80% (95% CI: 55 to 93%) were reported for detecting ID as defined by sTfR. The authors noted that higher ZnPP values were identified in groups with more severe ID, as confirmed by serum ferritin and sTfR measurements.[36] The highest ZnPP values were identified in the IDA group. Together, these results led the authors to conclude that the non-invasive ZnPP measurement is reliable and feasible in young children.[36]

The above findings stand in contrast with Jullien 2021 (non-systematic review not included within the evidence map), who also assessed the accuracy of available screening tests for detecting IDA in children under 5 years of age, and concluded that no non-invasive test with high accuracy for detecting IDA is available.[18] Of note, Jullien 2021 did not cite any of the 3 studies that were identified in this evidence map, although they briefly allude to the non-invasive ZnPP test reported in Homan 2019.

In summary, 3 studies were identified that reported on non-invasive screening tests for ID/IDA in children aged under 5. Overall, the amount of evidence available is limited, and insufficient for drawing conclusions on whether a non-invasive, simple, safe, precise and validated test for detecting ID or IDA is available. As such, a further evidence summary is not recommended, as it is unlikely to lead to a change in the UK NSC's current position on screening.

Question 3: What is the effect of iron supplementation on developmental complications of ID/IDA in asymptomatic children identified early through screening?

In total, 8 publications were identified as potentially relevant to question 3. The full texts were consulted for 7 of these publications to determine their relevance. Ultimately, 1 publication reporting on 1 study was included. Of note, this publication was also considered relevant to question 1.

Larson 2019 conducted an SLR and meta-analysis with the objective to clarify the consequences of low Hb concentration in children under 5 years old on development, growth and chronic disease.[29] As searching the studies included in this SLR is beyond the scope of this evidence map, it is unclear whether included studies reported on asymptomatic children with ID or IDA. The SLR identified 56 intervention and 20 observational studies.[29] The metaregression analysis among iron supplementation trials indicated associations between the effects of interventions on Hb and their effects on mental and motor development.[29] For each 1 SD increase in Hb, mental scores and motor scores increased by 0.24 SD and 0.28 SD, respectively.[29] Furthermore, the authors reported that in children with lower Hb concentrations at baseline, iron supplementation trials showed stronger associations between their effects on Hb and their effects on mental development (p=0.008).[29] As such, this study showed that iron supplementation has beneficial effects on resolution of anaemia, as indicated by Hb levels, as well as positive effects on mental and motor developmental outcomes. It is, however, unclear how many of the children in those studies would have been detected based on asymptomatic screening and how many had clinical symptoms at the time of treatment initiation. This uncertainty was further supported by Jullien 2021 (non-systematic review not included within the evidence map), who concluded that evidence on the effects of IDA screening in asymptomatic children aged under 5 years on developmental outcomes such as growth, cognitive and psychomotor development, is currently lacking.[18]

While not included in the evidence map due to the single-arm design of the study, Pachuta Wegier 2020 may be of interest, as it evaluated the efficacy, safety, and acceptability of a new ferrous sulphate oral solution (Tardyferon®, 2 mg/kg/day) in children with IDA.[37] The study population included children aged 6 to 17 months presenting with mild or moderate IDA as defined by Hb and serum ferritin levels, however, it is unclear whether these children were asymptomatic when treatment was started.[37] At month 3, mean Hb levels were 12.0 g/dL (SD: 0.7 g/dL) and mean ferritin levels were 31.5 ng/mL (SD: 19.4 ng/mL).[37] Hb levels were normalised in 18/19 (95%) and ferritin levels were normalised in 16/19 (84%) of the patients.[37] Only 1 patient did not achieve normalisation of Hb or ferritin levels at month 3, and therefore continued treatment with Tardyferon® for an additional 3 months.[37] The study authors concluded that treatment with Tardyferon® (2 mg/kg/day) provided therapeutic benefit in young children with mild or moderate IDA, by contributing to resolution of IDA as measured by Hb and serum ferritin levels.[37]

The identified study indicated positive effects of iron supplementation on resolution of IDA and developmental outcomes associated with this condition. Of note, it was not clear from the study whether the treated children were identified at an asymptomatic stage. The low volume of evidence currently available does not warrant conducting a further evidence summary at this point in time.

Conclusions

The findings of this evidence map are unlikely to impact on current recommendations on screening for IDA as no new evidence was identified that would change those conclusions.

Recommendations

On the basis of this evidence map, the volume and type of evidence related to screening for IDA is currently insufficient to justify an update review at this stage and so should be re-considered in 3-years' time.

Appendix 1–Search strategy for the evidence map

SOURCES SEARCHED:

- MEDLINE®, including MEDLINE® In-Process, MEDLINE® Daily and Epub Ahead of Print
- Embase®
- The Cochrane Library, including:
    - CDSR
    - CENTRAL

MEDLINE and Embase were searched simultaneously via the Ovid SP platform. The Cochrane Library databases was searched via the Wiley Online platform.

DATES OF SEARCH: 1 January 2017 to 9 September 2021 for MEDLINE and Embase (see Table 3 for the search terms). For CDSR searches were limited from March 2017 to September 2021 and for CENTRAL searches were limited from January 2017 to September 2021 (see Table 4 for the search terms). Searches were run on 10 September 2021 for all databases.

SEARCH STRATEGIES:

Table 3. Search terms for MEDLINE and Embase

MEDLINE and Embase (searched simultaneously via the Ovid SP platform)		
Term group	#	Search terms
Iron deficiency anaemia	1	exp Anemia, Iron-Deficiency/ or iron deficiency anemia/ or iron deficiency/
	2	(iron adj3 (deficien$ or deplet$)).ti,ab,kw,kf.
	3	Anemia/
	4	an?emi$.ti,ab,kw,kf.
	5	or/1-4
In children	6	exp child/
	7	(p?ediatric$ or child$).ti,ab,kw,kf.
	8	6 or 7
Screening	9	mass screening/ or screen$.ti,ab. or (detect$ or predict$ or identif$ or diagnos$ or test$).ti.
Developmental outcomes	10	exp developmental disorder/ or child development/
	11	exp motor development/
	12	exp behaviour disorder/
	13	(development adj3 (assessment or motor or psychomotor or delay$ or outcome or impair$ or general or mental or quotient$ or cognitive)).ti,ab,kw,kf.

	14	exp Neurodevelopmental Disorders/ or Developmental Disabilities/ or developmental delay/
	15	((neurodevelopmental or intellect$) adj3 (delay or disorder$)).ti,ab,kw,kf.
	16	Growth/ or body size/ or body height/ or body weight/ or body growth/
	17	"physical growth".ti,ab,kw,kf.
	18	or/10-17
Iron supplementation	19	diet supplementation/ or dietary supplements/
	20	(iron adj2 (supplement$ or diet$)).ti,ab,kw,kf.
	21	19 or 20
Exclusion terms	22	("Conference Abstract" or "Conference Review" or comment or editorial or note or case reports or news or news release).pt.
	23	(case stud$ or case report$).ti,ab.
	24	historical article/ or case study/
	25	exp animals/ not exp humans/
	26	or/22-25
Combinations	27	5 and 8 and 18
	28	27 and 21
	29	5 and 8 and 9
	30	27 or 28 or 29
	31	30 not 26
	32	limit 31 to yr=2017-current
	33	remove duplicates from 32

Table 4. Search terms for Cochrane Library

Cochrane Library (searched via the Wiley Online platform)		
Term group	#	Search terms
Iron deficiency anaemia	1	[mh "Anemia, Iron-Deficiency"]
	2	("iron" NEAR/3 (deficien* or deplet*)):ti,ab,kw
	3	[mh ^Anemia]
	4	(an?emi*):ti,ab,kw
	5	{OR #1-#4}
In children	6	[mh child]
	7	(p?ediatric* or child*):ti,ab,kw
	8	{OR #6-#7}
Screening	9	[mh ^"mass screening"] OR screen*:ti,ab OR (detect* or predict* or identif* or diagnos* or test*):ti
	10	[mh ^"child development"]

Developmental outcomes	11	(development NEAR/3 (assessment or motor or psychomotor or delay* or outcome or impair* or general or mental or quotient* or cognitive)):ti,ab,kw
	12	[mh "Neurodevelopmental Disorders"] OR [mh ^"Developmental Disabilities"]
	13	((neurodevelopmental or intellect*) NEAR/3 (delay or disorder*)):ti,ab,kw
	14	[mh ^Growth] OR [mh ^"body size"] OR [mh ^"body height"] OR [mh ^"body weight"]
	15	"physical growth":ti,ab,kw
	16	{OR #10-#15}
Iron supplementation	17	[mh ^"dietary supplements"]
	18	(iron NEAR/2 (supplement* or diet*)):ti,ab,kw
	19	{OR #17-#18}
Combinations	20	#5 AND #8 AND #16
	21	#20 AND #19
	22	#5 AND #8 AND #9
	23	#20 OR #21 OR #22
	24	#23 with Cochrane Library publication date Between March 2017 and September 2021, in Cochrane Reviews, Cochrane Protocols
	25	#23 with Publication Year from 2017 to 2021, in Trials

Unique results by database

MEDLINE and Embase	3,207
Cochrane Library	712
Total	**3,919**

Inclusions and exclusions

Studies were included based on the eligibility criteria listed in Table 5, Table 6 and Table 7 for question 1, question 2, and question 3, respectively.

Table 5: Eligibility criteria for question 1

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	Children aged under 5 years with ID/IDA	• Children who are not under 5 years old • Adults
Intervention	No intervention	Iron supplementation or another intervention that might impact on child development or IDA resolution
Comparator (population)	Healthy children aged 5 years and under without ID/IDA	• Children who are not under 5 years old • Adults

PICOS domain	Inclusion criteria	Exclusion criteria
Outcomes	Adverse developmental outcomes, including: • Neurodevelopment • Motor development • Behaviour • Physical growth • Spontaneous resolution of ID/IDA	Non-developmental outcomes or outcomes not focused on ID/IDA resolution
Study design	• Observational studies • SLRs of observational studies	Any other study design, including: • Interventional studies • Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types that have not been peer-reviewed
Other considerations	• Articles published in the English language • Articles published since 2017 • Studies conducted in high-income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	• Studies with abstract not in the English language • Articles published before 2017 • Studies in ineligible countries, or international studies where outcomes for eligible countries are not presented separately to outcomes from ineligible countries

Abbreviations: EEA: European Economic Area; ID: iron deficiency; IDA: iron deficiency anaemia; OECD: Organisation for Economic Co-operation and Development; PICOS: Population, Intervention, Comparison, Outcomes and Study; SLR: systematic literature review; UK: United Kingdom.

Table 6: Eligibility criteria for question 2

PICOS domain	Inclusion criteria	Exclusion criteria
Patient population	All children aged under 5 years	• Children who are not under 5 years old • Adults
Intervention (index test)	Any non-invasive or minimally invasive test to identify ID/IDA	Any other test

PICOS domain	Inclusion criteria	Exclusion criteria
Comparator (reference standard)	Identification of ID/IDA by any of the following tests: • Hb concentration • Hct concentration • Serum ferritin • Transferrin saturation levels	Any other test
Outcomes	Test accuracy/validity outcomes: • Sensitivity and specificity • PPV and NPV • Likelihood ratios (+/-)	Any non-relevant outcomes
Study design	Prospective and retrospective studies with: • Consecutive or random samples of participants receiving both the index test(s) and the reference standard • Participants randomised to different index tests but all receiving the reference standard, and being assessed in a cross-sectional manner	Any other study design, including: • Case-control studies • Studies with longitudinal assessment of the reference standard • Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types that have not been peer-reviewed
Other considerations	• Articles published in the English language • Articles published since 2017 • Studies conducted in high-income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	• Studies with abstract not in the English language • Articles published before 2017 • Studies in ineligible countries, or international studies where outcomes for eligible countries are not presented separately to outcomes from ineligible countries

Abbreviations: EEA: European Economic Area; Hb: Haemoglobin; Hct: Haematocrit; ID: iron deficiency; IDA: iron deficiency anaemia; NPV: Negative predictive values; OECD: Organisation for Economic Co-operation and Development; PICOS: Population, Intervention, Comparison, Outcomes and Study; PPV: Positive predictive values; UK: United Kingdom.

Table 7: Eligibility criteria for question 3

PICOS domain	**Inclusion criteria**	**Exclusion criteria**
Patient population	Asymptomatic children with ID aged under 5 years Tier 1: • Screen detected Tier 2: • Clinically detected (through routine clinical diagnosis)	• Children who are not under 5 years old • Adults
Intervention	Iron supplementation	Any other intervention
Comparator	• No iron supplementation or placebo • Alternative intervention	No comparator
Outcomes	• Resolution of ID/IDA • Effect on long-term developmental outcomes	Any other outcomes
Study design	• RCTs • Cohort studies • SLR of these study designs	Any other study design, including: • Case reports • Narrative reviews • Editorials • Commentaries • Conference abstracts • Other publication types that have not been peer-reviewed
Other considerations	• Articles published in the English language • Articles published since 2017 • Studies conducted in high-income countries where the population, screening methods and technology are expected to be similar to that of the UK (OECD and EEA countries excluding South Korea and Mexico)	• Studies with abstract not in the English language • Articles published before 2017 • Studies in ineligible countries, or international studies where outcomes for eligible countries are not presented separately to outcomes from ineligible countries

Abbreviations: EEA: European Economic Area; ID: iron deficiency; IDA: iron deficiency anaemia; OECD: Organisation for Economic Co-operation and Development; PICOS: Population, Intervention, Comparison, Outcomes and Study; RCT: randomised controlled trial; SLR: systematic literature review; UK: United Kingdom.

Appendix 2–Abstract reporting tables

Question 1

TITLE	
Citation	*Larson et al. (2019). Effects of increased hemoglobin on child growth, development, and disease: a systematic review and meta-analysis. Annals of the New York Academy of Sciences. 1450(1):83-104.*[29]
BACKGROUND	
Study type	*SLR and meta-analysis*
Objectives	*To clarify the consequences of low Hb concentration in children under 5 years old on development, growth and chronic disease*
Components of the study	***Population:*** *Children under 5 years old* ***Intervention:*** *Some included studies are likely to include no intervention* ***Comparator:*** *Some included studies are likely to include healthy children under 5 years old as a comparator* ***Outcomes:*** *Effect of a range of Hb concentrations on development, growth and chronic disease*
RESULTS	
Results	*Outcomes relevant for question 1:* • *The SLR identified 56 interventional and 20 observational studies* • *Calculation of pooled associations between Hb and functional outcomes were precluded due to heterogeneity among studies* • *It was not possible to establish an inflection point at which decreasing Hb begins to be associated with negative functional outcomes using available evidence*
Conclusions	• *Further research is needed to elucidate the associations of Hb with development and growth in populations with different ages and settings, varying Hb concentrations and varying inflammation*

Abbreviations: Hb: haemoglobin; SLR: systematic literature review.

TITLE	
Citation	*McCann et al. (2020). The role of iron in brain development: A systematic review. Nutrients. 12(7):2001.*[30]
BACKGROUND	
Study type	*SLR*
Objectives	*To understand whether ID directly impacts developmental outcomes, and whether impact differs by timing of exposure or developmental domain*
Components of the study	***Population:** Individuals with ID aged 0 to 6 months, 6 to 24 months, or 2 to 4 years* ***Intervention:** Some included studies are likely to include no intervention* ***Comparator:** Some included studies are likely to include healthy children under 5 years old as a comparator* ***Outcomes:** Neurodevelopmental assessments*
RESULTS	
Results	*Outcomes relevant for question 1:* • *No clear relationship between iron status and developmental outcomes was identified across any of the time windows or domains included* • *A large quantity of identified studies were of low-quality, and there was significant heterogeneity in study design, as well as a lack of research that focused on early infancy*
Conclusions	• *Evidence for the impact of ID on early development is inconsistent. Further high-quality research is needed, particularly within early infancy*

Abbreviations: ID: iron deficiency; SLR: systematic literature review.

TITLE	
Citation	*McCarthy et al. (2017). Microcytosis is associated with low cognitive outcomes in healthy 2-year-olds in a high-resource setting. British Journal of Nutrition. 118(5):360-367.*[32]
BACKGROUND	
Study type	*Cohort Study*
Objectives	*To investigate associations between iron status and neurodevelopmental outcomes in low risk, healthy 2-year-olds*
Components of the study	***Population:** Healthy 2-year-olds* ***Intervention:** No intervention* ***Comparator:** Healthy children* ***Outcomes:** Cognitive or behavioural outcomes*
RESULTS	

Results	*Outcomes relevant for question 1:* • *No significant associations between ID or IDA and cognitive outcomes, as measured by BSID-III scores, at 2 years of age* *[Full text consulted]*
Conclusions	• *There is a need for re-evaluation of the diagnostic criteria for ID in young children, with further research in adequately powered studies warranted* *[Full text consulted]*

Abbreviations: BSID-III: Bayley Scales of Infant and Toddler Development-III; ID: iron deficiency; IDA: iron deficiency anaemia.

TITLE	
Citation	*McCarthy et al. (2018). Iron status, body size, and growth in the first 2 years of life. Maternal and Child Nutrition. 14(1):e12458.*[31]
BACKGROUND	
Study type	*Cohort Study*
Objectives	*To explore the effect of growth and body size on iron status at age 2 years*
Components of the study	***Population:*** *Maternal-infant pairs in the prospective Cork BASELINE Birth Cohort* ***Intervention:*** *No intervention* ***Comparator:*** *Healthy children* ***Outcomes:*** *Infant weight and length*
RESULTS	
Results	*Outcomes relevant for question 1:* • *5% of the cohort had ID (ferritin <12 µg/L) and 1% had IDA (Hb <110 g/L + ferritin <12 µg/L) at age 2 years* • *Weight gain from 6 to 12, 0 to 24, and 12 to 24 months were all inversely associated with ferritin concentrations at 2 years of age* • *Ferritin concentration was only significantly associated with weight gain from 12 to 24 months after adjustment for potential confounding factors, including cord ferritin (adjusted estimate: -4.40 µg/L; 95% CI: -8.43 to -0.37 µg/L; p=0.033)* • *Length gain from 0 to 24 months was positively associated with Hb at 2 years (adjusted estimate: 0.42 g/L; 95% CI: 0.07 to 0.76 g/L; p=0.019), but this association was not significant when adjusted for cord ferritin*

Conclusions	• *Iron stores at 2 years were inversely associated with weight gain in the second year, even after accounting for iron status at birth*

Abbreviations: CI: confidence interval; Hb: haemoglobin; ID: iron deficiency; IDA: iron deficiency anaemia.

TITLE	
Citation	*McCarthy et al. (2021). Behavioral consequences at 5 y of neonatal iron deficiency in a low-risk maternal-infant cohort. American Journal of Clinical Nutrition. 113(4):1032-1041.*[33]
BACKGROUND	
Study type	*Cohort Study*
Objectives	*To investigate the association between neonatal ID and neurologic development at age 2 and 5 years*
Components of the study	***Population:*** *Maternal-infant pairs in the prospective Cork BASELINE Birth Cohort (n=697 pairs)* ***Intervention:*** *No intervention* ***Comparator:*** *Healthy children* ***Outcomes:*** *Cognitive or behavioural outcomes*
RESULTS	
Results	*Outcomes relevant for question 1:* • *There was no association between neonatal ID and cognitive or behavioural outcomes at age 2 or 5 years, using fully adjusted models* • *An a priori sensitivity analysis was performed in 306 high-risk children, selected using known risk factors for neonatal ID (such as smoking, obesity, caesarean section delivery, small-for-gestational age birth)* • *Within the high-risk subgroup (cord ferritin concentrations <76 μg/L), similar cognitive outcomes were observed for children with ID at birth (12%), but the behavioural assessments showed higher internalising and total problem behaviour scores at 5 years of age compared with children born iron sufficient (cord ferritin concentrations ≥76 μg/L)* • *The median result for internal problems in the Child Behavioural Checklist was 9.0 (IQR: 5.3 to 12.0) for the high-risk subgroup, compared with 5.0 (IQR: 3.0 to 10.0) in the iron-sufficient children (p=0.006). The median result for total problem behaviour scores in the Child Behavioural Checklist was 24.5 (IQR: 15.3 to 40.8) for the high-risk subgroup, compared with 16.0 (IQR: 10.0 to 30.0) in the iron-sufficient children*

	(p=0.009). Even after adjustment for covariates, the associations with internalising (adjusted estimate 2.8; 95% CI: 0.5 to 5.1; p=0.015) and total problem scores (adjusted estimate 6.6; 95% CI: 0.1 to 13.1; p=0.047) remained significant *[Full text consulted]*
Conclusions	• *Neonatal ID causes lasting behavioural consequences, as demonstrated in the high-risk subgroup of the BASELINE cohort*

Abbreviations: CI: confidence interval; ID: iron deficiency; IQR: interquartile range.

Question 2

TITLE	
Citation	*Boghani et al. (2017). Accuracy of capillary hemoglobin measurements for the detection of anemia among U.S. Low-income toddlers and pregnant women. Nutrients. 9(3): 253.*[34]
BACKGROUND	
Study type	*Observational study*
Objectives	*To evaluate the accuracy of capillary Hb measurements in detecting anaemia among low-income toddlers (aged 12 to 35 months)*
Components of the study	***Population:*** *Low-income toddlers (aged 12 to 35 months)* ***Intervention (index test):*** *Capillary Hb measurements in finger puncture samples* ***Comparator (reference standard):*** *Venous Hb concentrations* ***Outcomes:*** *Test accuracy*
RESULTS	
Results	*Outcomes relevant for question 2:* • *Sensitivity of capillary blood analyses to identify anaemia was 32.8% (95% CI: 21.3 to 46.0%) and 60.4% (95% CI: 44.1 to 71.4%) for toddlers living in Kansas City (n=413) and St Louis (n=213), respectively* • *Corresponding specificities were 97.7% (95% CI: 95.6 to 99.0%) and 85.6% (95% CI: 79.2 to 90.7%) for toddlers living in Kansas City and St Louis, respectively* *[Full text consulted]*
Conclusions	• *Hb measurements of capillary blood with the HemoCue device were not optimal for determining the anaemia status of toddlers* *[Full text consulted]*

Abbreviations: CI: confidence interval; Hb: haemoglobin.

TITLE	
Citation	*Gerday et al. (2021). Urinary ferritin; a potential noninvasive way to screen NICU patients for iron deficiency. Journal of Perinatology. 41(6):1419-1425.[35]*
BACKGROUND	
Study type	*Prospective analysis*
Objectives	*To conduct a feasibility evaluation of urinary ferritin as a potential non-invasive screening test for ID*
Components of the study	***Population:*** *Newborn intensive care unit (NICU) patients* ***Intervention (index test):*** *Urine ferritin levels* ***Comparator (reference standard):*** *Serum ferritin levels* ***Outcomes:*** *Correlation of urine ferritin with serum ferritin, including sensitivity, specificity and PPV of urine ferritin*
RESULTS	
Results	*Outcomes relevant for question 2:* • *A total of 49 paired serum/urine samples were collected from neonates judged as at-risk for ID* • *Urine ferritin was corrected for urine creatinine and specific gravity* • *Corrected urine ferritin <12 ng/mL had a sensitivity of 82% (95% CI: 67 to 93%) and a specificity of 100% (95% CI: 66 to 100%) for detecting iron-limited erythropoiesis, with a PPV of 100% (95% CI: 89 to 100%)*
Conclusions	• *Urinary ferritin is a feasible, non-invasive test for ID in NICU patients*

Abbreviations: CI: confidence interval; ID: iron deficiency; NICU: Newborn intensive care unit; PPV: positive predictive value.

TITLE	
Citation	*Homann et al. (2019). Non-invasive measurement of erythrocyte zinc protoporphyrin in children. Pediatric Research. 85(3):349-354.[36]*
BACKGROUND	
Study type	*Observational study*
Objectives	*To evaluate a new, non-invasive method to measure erythrocyte ZnPP in children*
Components of the study	***Population:*** *Hospitalised children aged 9 months to 5 years* ***Intervention (index test):*** *ZnPP measurements on the wet vermillion of the lower lip*

	Comparator (reference standard): *Conventional ID parameters (sTfR and serum ferritin) and ZnPP determined from blood samples* ***Outcomes:*** *Sensitivity, specificity, PPV and NPV of the non-invasive ZnPP measurement*
RESULTS	
Results	*Outcomes relevant for question 2:* • *Non-invasive ZnPP measurements had sensitivity and specificity of 67% (95% CI: 39 to 88%) and 97% (95% CI: 91 to 99%) and NPV and PPV of 94% (95% CI: 90 to 97%) and 80% (95% CI: 55 to 93%), for detecting ID as defined by the sTfR* • *In groups with more severe ID, as defined by serum ferritin and sTfR, higher ZnPP values were found, with the highest ZnPP values for the group with IDA* *[Full text consulted]*
Conclusions	• *ZnPP measurements are a non-invasive, reliable and feasible screening test for ID*

Abbreviations: CI: confidence interval; ID: iron deficiency; IDA: iron deficiency anaemia; NPV: negative predictive value; PPV: positive predictive value; sTfR: soluble transferrin receptor; ZnPP: erythrocyte zinc protoporphyrin.

Question 3

TITLE	
Citation	*Larson et al. (2019). Effects of increased hemoglobin on child growth, development, and disease: a systematic review and meta-analysis. Annals of the New York Academy of Sciences. 1450(1):83-104.*[29]
BACKGROUND	
Study type	*SLR and meta-analysis*
Objectives	*To clarify the consequences of low Hb concentration in children under 5 years old on development, growth and chronic disease*
Components of the study	***Population:*** *Children under 5 years old* ***Intervention:*** *Some included studies are likely to include iron supplementation* ***Comparator:*** *Some included studies are likely to report on results with no iron supplementation, placebo or an alternative intervention* ***Outcomes:*** *Effect of a range of Hb concentrations on development, growth and chronic disease*
RESULTS	
Results	*Outcomes relevant for question 3:*

	• *The SLR identified 56 intervention and 20 observational studies* • *A metaregression analysis among iron supplementation trials indicated significant associations between the effects of interventions on Hb and their effects on mental and motor development. For each 1 SD increase in Hb, mental scores and motor scores increased by 0.24 SD and 0.28 SD, respectively* • *In children with lower Hb concentrations at baseline, iron supplementation trials showed stronger associations between their effects on Hb and their effects on mental development (p=0.008)*
Conclusions	• *Further research is needed to elucidate the associations of Hb with development and growth in populations with different ages and settings, varying Hb concentrations and varying inflammation*

Abbreviations: Hb: haemoglobin; SD: standard deviation; SLR: systematic literature review.

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