

Does iron supplementation benefit development in children younger than two years?

Giving iron to young children: Implications for Public Health programs in developing countries

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Iron and child development

- Iron is an essential nutrient for brain development
 - animal models of iron deficiency anemia (IDA) show changes to brain metabolism, neurotransmission, myelination among others
- Infants with IDA show deficits in mental and motor performance and altered social-emotional behavior compared with non-IDA infants

Iron and child development

- Follow up studies generally show IDA/chronic severe iron deficiency in early life is associated with later deficits in various domains including IQ, behavior/mental health, educational achievement
- IDA associated with socio-economic and psychosocial disadvantages which also affect development

RCTs of iron supplementation in older children

- Several trials showing benefits to IQ, specific cognitive abilities and school achievement
- Within trials NS effects on some tests and some trials no benefits
- Pooled analysis showed significant benefit for IQ
(Sachdev et al, 2005)



Prior reviews of RCTs of iron supplementation and development

Several previous reviews – at least 2 in 2013

- Vary in studies included
- Include very short term supplementation with longer term trials
- Combine age groups
- Include treatment trials (non-RCT)

This presentation

- Only RCTs
- Duration of supplementation at least 1 month
- Included trials in high income countries
- Grouped by participant type:
 - IDA only
 - Non-selected, low/moderate initial prevalence of IDA
 - Non-selected high risk/prevalence of IDA

RCTs IDA subjects

UK (*Aukett et al, 1986*)

- 2 months supplementation (iron + Vit C/ Vit C) from age 17 months. Small sample (48/49)
- Initial status Hb 80-110g/L. Iron deficiency prevalence 47% (ferritin) to 91% (transferrin saturation)
- No benefit to items achieved on Denver Developmental screening test.

RCTs IDA subjects - 2

Indonesia (*Idjradinata & Pollitt, 1993*)

- IDA < Hb 105g/L, + ID by 2 measures
- Children aged 12-18 months, 4 month supplementation iron/placebo. Small sample 24/23 (also ID and IS groups randomised)
- Very large benefits to motor and mental development (Bayley scales) Effect sizes 1.38 & 1.44

Preventive trials in high income countries (UK, Canada)

- Three trials of iron fortified formula compared with unfortified formula (1 study only compared with cow's milk; 1 study iron content of high iron formula only 1.2 mg/L)
- Infants term NBW, current Hb > 90g/L, low SES (2 studies) enrolled at ages 2 months, 6-9 months, 9 months
- Duration 9-13 months

Preventive trials, high income countries - results

1. No difference in Bayley MDI or PDI at 18 months (low iron formula) (*Morley et al, 1994*)
2. No difference MDI, PDI higher at 9 & 12 months, NS at 15 months. (*Moffat et al, 1994*)
3. DQ (Griffiths test) 18 months NS, 24 months rate of decline less in iron fortified group (only cow's milk comparison group) (*Williams et al, 1999*)

One additional study iron supp vs placebo from age 1 to 6 months. Small sample. At 13 months MDI NS, PDI higher in iron group (*Friel et al, 2003*)

Preventive trials, middle income countries

Indonesia (*Lind et al, 2004*)

- Infants aged 6 months Hb > 90g/L, IDA prevalence 8%, stunting prevalence low
- 6 months supplementation iron vs placebo (also Zn and Zn+Fe groups) n 161-164/group. At end less IDA in iron group 9%, placebo 18%
- At 12 months Bayley MDI , NS, PDI iron > placebo. Behaviour (Bayley Infant behavior rating scale) NS
- Effect size for PDI 0.27

Preventive trials, middle income countries

Chile (*Lozoff et al, 2003*)

- Infants aged 6 months, term, BW \geq 3kg, non IDA , growth normal range
- First 3 years RCT high iron or low iron formula; Subsequent 2 years high iron (vitamins +iron for predominantly breast fed) vs no iron
- Combined iron groups (high & low) compared with no iron at 12 months; n 1082, 531. Iron group IDA 3%, no iron 23%

Chile - results

Test	Outcome
Fagan test: Looking time Novelty preference	Reduced time, effect size 0.10 NS
Age at crawling	Earlier age, effect size 0.09
Bayley: MDI, PDI Behavior	NS Benefits to 2 of 4 scales, effect size 0.20

RCTs in populations with high risk/prevalence of IDA

Bangladesh (*Black et al 2004*)

- Age 6 months, Hb >90 g/L , 68% Hb < 110 g/L, 18% stunted (severely malnourished excluded)
- Weekly iron + riboflavin vs riboflavin n 49/45 (also Zn, Zn+Fe, MM groups)
- At 12 months MDI, PDI NS; Behavior benefits to 1 of 3 scales (orientation-engagement) effect size 0.30

Zanzibar studies

Stoltzfus et al 2001

- Age 12-48 months, 97% Hb < 110g/L. Children with Hb < 70g/L treated for 1 month then randomized
- Iron/placebo n 179/170 (Also RCT of mebendazole) for 1 year
- Parent report of language and motor milestones

Zanzibar studies

Olney et al 2006

- Age 5-11 months
- Iron + folate/placebo n 89/103 (Also Zn and Zn+Fe groups) for 1 year (children with Hb < 70g/L treated for 3 months then continued in trial)
- 14 Motor milestones by 2 weekly observation

Zanzibar results

	Main results	Interaction with iron status
Stoltzfus et al, 2001	Increase in language milestones effect size 0.14 Motor NS	Children with initial Hb < 80g/L benefits to motor milestones
Olney et al, 2006	Earlier age at walking – approx 15 days (other milestones not reported)	Infants IDA at enrolment approx 30 days earlier

Nepal study

Iron + folate/placebo (Also Zn and Zn+ Fe groups)

44% IDA; 22% stunted (*Siegel et al*)

- Aged 1-35 months - analysis of those not yet walking on enrolment. N 195/216 Parent report of motor milestones (*Katz et al 2010*)
- Age 1-12 months - Cognitive tests at 39 and 52 weeks (n 200-325) (*Siegel et al 2011*)
- Age 4-17 months - N 117/142 Parent report of language and motor milestones (5 motor observed) (*Surkan et al 2013*)

Nepal results

	Main results
Katz et al, 2010	Trend towards later walking unassisted ($p=0.09$) Analysis of those at least 60 days supplementation NS Children < 12 months on enrolment later age at walking (28 days) Other milestones NS
Seigel et al, 2011	NS information processing and object permanence
Surkan et al, 2013	NS rate of acquisition of language and motor milestones

Summary

Infants with IDA: One small study suggesting large benefits to mental and motor development

Preventive: 6 trials

- Mental: 1 suggestive of benefits to global DQ, 5 NS for Bayley MDI
- Motor: 2 NS, 3 benefits (1 transient)
- Behavior: 1 benefits, 1 NS

Summary

Populations with high initial prevalence of IDA

- MDI: 1 study NS
- Cognitive tests: 1 study NS
- Language milestones: 1 benefits, 1 NS
- Motor milestones: 1 benefits, 1 benefit if initial Hb < 80g/L, 1 NS
- Behavior: 1 study benefits

Do benefits emerge later?

- Evidence suggestive of benefits to motor development and behavior
- Facilitate greater engagement/exploration
- Studies of other interventions show benefits detected may increase with age as more complex skills are measured



Follow-up studies

- *Thailand, (Pongcharoen et al 2011)* Infants 4-6 months iron/placebo for 6 months. 29% Hb < 100g/L but ID low; 3% stunted. 92% follow-up at 9y, n=147/139
 - IQ, Raven's matrices NS
- *Chile, (Lozoff et al, 2012)* High iron vs low iron formula. 57% follow-up at 10 y, n=244/229
 - High iron worse in 2 of 6 measures. Others NS
 - Interaction with initial iron status, high (Hb >128g/L) worse on 5 tests; low Hb < 105 g/L benefits on 2 tests

- 1999 Commentary “Iron deficiency and developmental deficit—the jury is still out”
“Large trials of both iron supplementation in infants... are urgently needed”
- 2013 Systematic review of RCTs children 4-23 months
“..benefits on cognitive development and growth remain uncertain. Our data can inform the design of well-conducted, adequately powered trials that are still needed..” (Pasricha et al, 2013)

Going forward

- Need studies with sufficient power in populations at high risk of IDA
- Range of measurements
- Studies in infancy and 12-24 months
- Analyse by initial iron status

