Lower systolic blood pressure at age 7 in low birth weight children who received iron supplements in infancy – results from a randomized controlled trial

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Conflicts of interests: We have no conflicts of interest to declare.

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Council (ALF) and by a regional agreement on clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

**Short running head:** Iron supplements in infancy lowered blood pressure

**Abbreviations:** LBW - low birth weight; BP – blood pressure; SBP – systolic blood pressure; DBP – diastolic blood pressure; ID – iron deficiency; ANOVA – analyses of variance; ANCOVA – analyses of covariance; ACE – angiotensin converting enzyme; NO – nitric oxide; NOS – nitric oxide synthase.

**Clinical trial registry number and website:** NCT00558454, at [www.Clinicaltrial.gov](http://www.Clinicaltrial.gov).
Abstract

Background: Low birth weight (LBW; \( \leq 2500 \) g) is associated with iron deficiency in infancy and high blood pressure (BP) later in life.

Objective: The objective of this study was to investigate the effect of iron supplementation given to LBW infants on mid-childhood BP.

Design: This was a randomized double-blinded controlled trial, including 285 marginally LBW (2000-2500 g) infants at two Swedish centres between May 2004 and November 2007. The infants were randomized to placebo, 1, or 2 mg iron/kg/day, from six weeks to six months of age. In secondary analyses at the age of seven years, systolic BP (SBP), diastolic BP (DBP), and the prevalence of children having a BP within the hypertensive range (>90th percentile), were compared between the groups.

Results: BP was analysed by intention to treat in 189 children (66 %). Mean SBP was 103 (SD=8.1), 101 (7.5), and 101 (7.8) mmHg in children who had received placebo (n=70), 1 (n=54), or 2 (n=65) mg/kg/day of iron, respectively. When combining the iron supplemented groups in covariate adjusted analyses, SBP in LBW children who had received iron supplementation in infancy was on average 2.2 (95% CI: [0.3, 4.2]) mmHg lower than in those un-supplemented (p=0.026). Multivariate logistic regression showed that iron supplementation in infancy reduced the odds of having a SBP within the hypertensive range at seven years of age (odds ratio 0.32, [95 % CI 0.11, 0.96]). For DBP, there were no significant differences between the intervention groups.
Conclusions: LBW children who received iron supplementation (1 or 2 mg/kg/day) in infancy had lower SBP at 7 years. This novel observation suggests that the increased risk of hypertension observed in children and adults born small might be reduced with early micronutrient interventions. The trial was registered at Clinicaltrial.gov as NCT00558454.

Keywords: Low birth weight, iron supplementation, blood pressure, early programming, Barker hypothesis, hypertension, cardiovascular risk
Introduction

High blood pressure (BP) is an important risk factor for cardiovascular disease. Hypertension at the age of 30 increases the life-time risk for cardiovascular disease by 40% (1), and lowering the average BP by 5 mmHg in the population, has been estimated to reduce the risk of coronary heart disease by 21% and stroke by 34% (2).

Besides genetic traits and life-style, developmental factors in early life have been suggested to influence later BP. Low birth weight (LBW; ≤2500 g) due to fetal growth restriction and/or preterm birth, has been associated with increased BP in childhood (3-5), particularly if followed by accelerated growth in infancy (6, 7). This may have large relevance for later health outcomes, since high BP in childhood predicts increased risk of adult hypertension (8-10). The underlying mechanisms for a developmental contribution to hypertension are largely unknown but, supported by animal (11) and human data (12, 13) early nutritional factors are likely to play a key role.

Iron deficiency (ID) is a common nutritional problem in infancy and early childhood, and LBW infants are, due to their low iron stores at birth and rapid growth, at particular risk (14). While ID early in life can cause impaired cognitive development and increased risk of behavioral problems (15), little is known about possible effects on later BP. Low iron intake in adults has been associated with high systolic BP (SBP) in middle-aged humans (16-18) and animal studies in rats have demonstrated elevated BP in 40 days- (19), 3-months- (20), and 16 months-old (21) offspring of iron-restricted dams.

Herein, we report the results from a double-blinded randomized controlled trial of iron supplementation given from six weeks to six months of age to children born with marginally LBW (2000-2500 g). In secondary analyses from the follow-up data at seven years, our
Objective was to explore the hypothesis that iron supplementation given to infants at risk of ID could contribute to lower BP at school age.

**Subjects and Methods**

*Study sample*

This was a randomized double-blinded controlled trial of iron supplementation given to infants born with marginally LBW, at two university hospitals in Sweden (Stockholm and Umeå). Between May 1 2004 and November 30 2007, we included 285 marginally LBW infants at six weeks of age. Inclusion criteria were birth weight between 2000 and 2500 g, no diagnosed congenital diseases, and no prior treatment with iron supplements or blood transfusion at the time of inclusion. Using medical records, infants fulfilling the inclusion criteria were identified and their parents were invited to participate in the study. A written consent was collected from parents who accepted the invitation. This trial was approved by the Regional Ethical Review Boards in Umeå and Stockholm as well as registered at www.Clinicaltrials.gov as *Iron Supplementation of Marginally Low Birth Weight Infants*, number NCT00558454. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Details of the intervention have been presented elsewhere (22). Briefly, infants were stratified according to sex and study center and by computerized randomization they were allocated into three groups: placebo, 1 mg iron/kg/day and 2 mg iron/kg/day. The dose of iron supplementation (ferrous succinate drops of Ferromyn S [Astra Zeneca, Södertälje, Sweden]),
was divided in two daily doses and given from six weeks to six months of postnatal age. The
dose was adjusted according to weight at 12 and 19 weeks of age, and the placebo drops were
of similar taste and color, prepared by Apoteket Production & Laboratories (Stockholm,
Sweden). All parents received identical bottles and they were instructed to administer the dose
between meals using syringes. To identify those with low compliance, parents were instructed
to use a daily checklist. Low compliance was defined as having administered less than 70 %
of the total dose (n=63: 21 in the placebo group, 21 in the 1-mg group, and 22 in the 2-mg
group). To assess any side effects, the parents were asked to fill in daily checklists of possible
symptoms the infant experienced during the intervention, including hard stools, crying,
respiratory symptoms, fever (>38°C) as well as medical consultations. Growth during infancy
was also monitored (22).

Participants and all staff involved in data collection were blinded with regard to group
allocation. Diet was monitored during the intervention and we have previously shown that
there were no differences in proportions of infants who were breastfed, formula fed, or in
infants receiving complementary food between the intervention groups until 12 months of
age. Neither did the mean iron intake from diet differ between groups during the intervention
(22, 23).

Children diagnosed with any chronic disease that might affect their metabolic status were
excluded from all analyses (n=3: one child with muscular dystrophy, another with Williams
syndrome, and the third with 22q11 deletion syndrome). According to the primary study
design, infants with anemia (Hemoglobin concentration; Hb<90 g/L) at inclusion (n=16: two
in the placebo group, eight in the 1-mg group, and six in the 2-mg group), or diagnosed with
hemolytic disease in the neonatal period (n=2: one infant with Beta-thalassemia and one with
AB0-immunization at birth), were excluded from the trial. As a safety procedure, any
participating infant diagnosed clinically with anemia at 12 weeks (Hb <95 g/L) was assessed
by a pediatrician and occasionally prescribed non-blinded iron supplements. These cases were
still included in the primary analyses according to an intention to treat principle (n=9: five in
the placebo group, and two in each of the iron groups). However, in per protocol analyses,
these non-blinded cases as well as those with poor compliance from the 1- and 2-mg group
(n=43) were excluded.

Data collection

At inclusion, information about the parents’ age, the mother’s birth country as well as
perinatal data such as birth weight and gestational age, were collected from maternal and
infant delivery records and from the parents. The participants were longitudinally assessed at
seven visits at the following ages: six, 12 and 19 weeks, six and 12 months as well as at three
and seven years of age. The visits included phlebotomy for laboratory data and
anthropometric measures including length/height and weight. All children with blood samples
or anthropometric data outside reference values were referred to a pediatrician. The parents’
height and weight were measured or self-reported at any of the follow-up visits.

At age seven, the assessment included a measure of BP and heart rate using an automated
oscillometric device (Welch Allyn spot vital signs 420, NY, USA). Three measurements,
approximately one minute apart, were performed with the cuff on the child’s right arm after
resting five minutes in a sitting position with back support, with the arm supported and resting
at heart level. The mean SBP and diastolic BP (DBP) as well as the mean heart rate were
calculated only in the cases with three completed measurements. In addition, we defined BP
within the hypertensive range as levels above the 90th percentile in a sex and age specific
Swedish population reference (above 110.9/69.3 and 112.2/68.3 mmHg for girls and boys
respectively) (24).
Statistical analyses

The power calculation for the present study was based on the neurocognitive outcomes. With a power of 80% and a significance level of 0.05, we aimed to detect an effect size between two groups of 0.5 SD (7.5 points in cognitive scores). This effect would require 64 analyzed children per group and after assuming a dropout rate of 20% and a poor compliance rate of 15%, the group size was set to 95 included infants (22, 25). This pre-defined effect size corresponds to a difference in SBP of 4.0 mmHg (24).

Statistical analyses were performed using SPSS 23.0 (SPSS Inc, Chicago, Illinois). Parental, infant and child characteristics were compared between the intervention groups using analyses of variance (ANOVA) for continuous variables and Chi Square test for categorical variables. To compare the mean SBP and DBP between the groups, we first used ANOVA for crude analyses followed by analyses of covariance (ANCOVA) for adjusted group comparisons. To standardize the outcome, we introduced the following known covariates in the ANCOVA models: sex, current age, height, and heart rate at the time of assessment since these covariates all independently correlated to BP in the present dataset.

To further explore the magnitude of the effect from iron supplements, we combined the 1- and 2 mg groups and used a multivariate linear regression model to explore the correlation between early iron supplements and later SBP. Similar to the ANCOVA model, all regression analyses were adjusted for sex, age, height and heart rate. Furthermore, a logistic regression model was used to explore whether early iron supplementation was a predictor of having a SBP within the hypertensive range at seven years of age.

Results
As presented in figure 1, a total of 205 marginally LBW children were assessed at seven years of age, following a drop out of 19 (20 %) in the placebo group, 23 (24 %) in the 1 mg group, and 17 (18 %) in the 2 mg group (p=0.550). Three children were diagnosed with congenital disorders, two with hemolytic disorders and 16 with anemia, and were therefore excluded in all analyses. There was a higher proportion of drop out in Stockholm compared to Umeå (23 % of Stockholm participants and 9 % of Umeå participants, p=0.043). No other significant differences were observed in the infant or maternal characteristics between dropouts and the participants. Of the children assessed at seven years of age, BP was measured in 189. For children who were not assessed for BP, 12 did not attend to the follow-up visit but only participated by questionnaires, one child declined BP assessments, and in three cases, BP measurements were unsuccessful. As shown in previous reports, there were no differences between the intervention groups in rates of drop out due to reported side effects (22).

Background characteristics of the parents and infants, as well as characteristics of the children at the follow-up visit are presented in table 1. Additional data on these children collected at three years of age are presented elsewhere (25). The mean maternal age at the time of the child’s birth was significantly higher in the 2 mg group than in the placebo group (33.3 vs 31.3 years).

Table 2 shows the BP at seven years of age in the three intervention groups. In crude analyses, children in the placebo group had approximately 1.8 mmHg higher SBP than those in the two iron groups. When adjusting the analyses for sex, current age, height and heart rate, the estimated mean (SD) difference in SBP compared to placebo was -1.9 (1.2) and -2.5 (1.1) mmHg for the 1 and 2 mg group respectively (p=0.108 and p=0.031 in post hoc analyses).
When combining both iron groups, the effect of any iron supplementation (1 or 2 mg/kg/d) compared to placebo was a significantly lower SBP in iron supplemented groups (p=0.026). As presented in table 3, a linear regression model suggested that any iron supplementation decreased the adjusted mean SBP by 2.2 mmHg (95 % CI: 0.3, 4.2). This model did not change when excluding cases with low compliance and those non-blinded from the intervention at 12 weeks of age due to anemia (per protocol analyses). Furthermore, the significant finding remained when adjusting for gestational age and current weight and the effect from the intervention did not interact with preterm birth or with being born small for gestational age.

The proportion of participants having a SBP within the hypertensive range was approximately doubled in the placebo group compared to the iron intervention groups (table 2). Using covariate adjusted logistic regression, as shown in table 4, the odds of having a SBP within the hypertensive range at seven years was markedly reduced in the group that received any iron supplementation compared to placebo (OR 0.32, 95 % CI: 0.11, 0.96, p=0.041).

For DBP, there were no significant differences between the intervention groups, either in mean levels or in proportions having high DBP.

Discussion

In this randomized controlled trial we found lower SBP in seven year old children that had been randomized to receive iron supplements during their first half year of life, with an effect size of 2.2 mmHg. Moreover, the iron supplementation reduced the odds of having a SBP within the hypertensive range (>90th percentile) by 68 %. This novel observation is likely to be clinically relevant, considering that previous studies show that high BP in school age is
associated with increased risk of hypertension in adulthood, and consequently with the long
term risk of cardiovascular disease (1, 8-10).

In accordance with the hypothesis of early metabolic programming, first suggested by David
Barker and colleagues (3), there are numerous studies confirming that LBW is associated with
an increased risk of developing an adverse metabolic profile, including high BP (4, 5, 7, 10).
To date, the exact mechanisms and different risk panoramas are still unclear. Studies have
suggested that these negative outcomes are programmed in utero and/or postnatally, as an
effect of different metabolic and nutritional alterations (7, 12, 13). The key question in
preventing such developmental programming, is to identify any possible modifiable factor
mediating this process.

It has previously been shown that nutritional interventions in infancy may influence the long-
term programming effect on BP (11). Singhal et al. randomized infants born small for
gestational age at term to either standard formula or nutrient-enriched formula. At 6-8 years of
age, they found that children fed standard formula had significantly lower BP and suggested
that the effect was mediated by the more rapid weight gain observed in the enriched formula
group (13). The correlation between growth rate and later BP has been explored repeatedly
and it has been confirmed that accelerated postnatal growth is positively associated with later
BP, though the mechanisms are not fully known (6, 7). Both formulas from the study by
Singhal et al. contained equal amount of iron. However interestingly, accelerated growth is
correlated to increased iron requirements and the children with nutrient-enriched formula and
faster growth rate might have been at a higher risk of depleted iron stores compared to the
slower growing group, possibly contributing to the observed differences on later BP.

With regard to micronutrients in general and iron in particular, very little is known about its
correlation to BP. However, our findings are partly supported by experimental studies in rats
conducted by two independent research groups. Crowe et al demonstrated in 1995 that the 80 rat offspring from iron restricted dams showed higher BP at 40 days of age compared to 64 controls, from unrestricted dams (19). More recently, this observation was confirmed in similar studies performed by Lewis et al, in which pups from iron restricted dams presented a higher SBP until three and 16 months of age, compared to controls (20, 21).

Apart from the animal studies described above, we identified two large epidemiological studies exploring the correlation between iron intake and BP. Tzoulaki et al conducted a cross-sectional dietary study in >4000 adults, and found that non-heme iron and total iron intake correlated to lower SBP, even after adjusting for several different confounders, such as urinary sodium and potassium (16). Similarly, Mc Carty et al explored >9000 subjects from a population based cohort and found that intake of iron supplements in adults was associated with lower DBP (18). This and other epidemiological research regarding iron intake and cardiovascular health was recently reviewed by Lapice et al, who found inconsistent data but concluded that ID is associated with higher risk of cardiovascular disease (17). This gives further support to our observation, even though the observational studies above are only able to identify cross sectional associations.

Very little is known regarding any possible mechanism behind a programming effect of iron status on BP. The study by Crowe above found that the pups born to iron restricted dams had lower birth weight, followed by a more rapid postnatal weight gain (19). They speculated that the increased BP may have been caused by accelerated growth rather than by the anemic insult or ID. In the present study, there was no effect of the intervention on growth during infancy (22). Furthermore, Lewis and colleagues detected higher levels of serum angiotensin converting enzyme (ACE) in the iron restricted rats at three months of age, although they could not detect an association between ACE and BP (20). In an additional follow up, they
performed post mortem examination at 18 months and found a lower glomerular number and
an inverse relationship between glomerular number and SBP in the iron restricted rats, both at
three and 16 months of age (26). Lapice and colleagues discussed whether a possible cellular
ischemia, following ID and ID anemia, may damage myocardial cells and kidney tissue,
causing an sub-optimal activation of the renin-angiotensin system, later followed by elevated
BP (17).

Beside systemic hypertension, ID has been linked to increased risk of pulmonary
hypertension (27). In fact, iron supplements have recently been suggested as possible
treatment for pulmonary hypertension in adults (28). The mechanism for this effect is unclear
but it gives further support to the hypothesis that iron availability may influence
hemodynamic regulation. A possible mechanism by which iron may affect BP, systemic or in
the pulmonary circulation, might be through nitric oxide (NO), a regulatory molecule that
signals relaxation of vascular smooth muscle cells. NO is synthesized by NO synthase (NOS),
for which iron is an essential component. Consequently, iron availability may modulate NO
synthesis. Indeed, ID has been reported to reduce NOS activity in rats (29), and we speculate
that low iron availability may lead to higher BP mediated by lack of NO production.
Mechanistic studies should be launched to explore this hypothesis.

Based on previous studies of ID prevalence in LBW infants and the negative correlation
between ID and neurodevelopment, iron supplementation is already recommended to LBW
infants (15, 22). We have shown that present intervention did not only reduce the risk of ID
but also the risk of behavioral problems at preschool age (22, 25). Furthermore, we have
previously reported that there were no adverse effects of the iron supplementation on the
prevalence of infections, gastrointestinal symptoms, or in short and long term growth and
neurological development (22, 23). The clinical interpretation of the findings presented here is
that the recommended iron supplementation, in addition, may reduce the risk of high BP later in life. The major strength of the present study is its blinded and randomized design, supporting that the observed effect represents a causal correlation. Furthermore, our main outcome is a clinically relevant outcome with regard to programming of metabolic risk, the dropout rate is reasonably low for a long-term follow-up study and the study followed a comprehensive and well-controlled design. The study was limited by the fact that it was not originally powered to detect differences of this effect size, and only when combining two different randomization arms did our observed difference reach significance. Another limitation was the fact that no mechanistic hypothesis was assessed.

In summary, this randomized double-blinded controlled trial showed lower systolic BP and reduced risk for systolic BP in the hypertensive range at seven years of age, in LBW children who received iron supplements between six weeks and six months of age. Our findings generates a hypothesis suggesting that the previously described association between LBW and increased risk for adult hypertension may be modifiable using a safe and well-tolerated micronutrient intervention in infancy. Further short and long-term studies exploring the magnitude and relevance of these findings in other settings, as well as the possible mechanisms behind this novel and clinically relevant observation, are warranted.

Acknowledgements

We want to thank all participating families and our dedicated research nurses Kerstin Andersson and Åsa Sundström.
The authors’ responsibilities were as follows – NM, BW, MD, and SKB designed the study; BW, MD, and SKB supervised the data collection; JL and SKB analyzed the data and performed the statistical analysis; JL and SKB wrote the paper; SKB had primary responsibility for final content. All authors contributed to interpret the results, read and approved the final version of the manuscript and agreed with its content. The authors declared no conflicts of interests.
References


Table 1. Parental and participant characteristics in low birth weight children analyzed for blood pressure at 7 years of age following an intervention of different doses of iron supplements given from 6 weeks to 6 months of age.

<table>
<thead>
<tr>
<th>Characteristics of the parents</th>
<th>Placebo</th>
<th>1 mg Fe/kg/day</th>
<th>2 mg Fe/kg/day</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother from Scandinavia</td>
<td>59 (84 %)</td>
<td>44 (81 %)</td>
<td>54 (83 %)</td>
<td>0.918</td>
</tr>
<tr>
<td>Mother smoking during pregnancy*</td>
<td>2 (2.9 %)</td>
<td>0 (0.0 %)</td>
<td>4 (6.3 %)</td>
<td>0.088</td>
</tr>
<tr>
<td>Mothers age at child birth (years)</td>
<td>31.3 (5.0)</td>
<td>32.9 (4.4)</td>
<td>33.3 (4.6)</td>
<td>0.036</td>
</tr>
<tr>
<td>Mother's BMI (kg/m²)</td>
<td>23.9 (4.8)</td>
<td>24.6 (5.0)</td>
<td>23.5 (3.4)</td>
<td>0.434</td>
</tr>
<tr>
<td>Father's BMI (kg/m²)</td>
<td>25.4 (3.3)</td>
<td>25.4 (3.1)</td>
<td>25.6 (3.0)</td>
<td>0.918</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of the infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Birth weight (kg)</td>
</tr>
<tr>
<td>Birth length (cm)</td>
</tr>
<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Gestational age at birth (weeks)</td>
</tr>
<tr>
<td>Preterm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristics of the child at the follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>Age (months)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
</tr>
</tbody>
</table>

Data are number (%) or mean (standard deviation). P-value for group differences using Chi Square test for proportions, and ANOVA for means.
* Fisher exact
Table 2. Blood pressure at 7 years of age in low birth weight children supplemented with different doses of iron between 6 wk and 6 mo of age.

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>1 mg Fe/kg/d</th>
<th>2 mg Fe/kg/d</th>
<th>Model 1</th>
<th>Model 2</th>
<th>1 or 2 mg Fe/kg/day</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=70</td>
<td>n=54</td>
<td>n=65</td>
<td>p\text{unadj}</td>
<td>p\text{adj}</td>
<td>n=119</td>
<td>p\text{unadj}</td>
</tr>
<tr>
<td>Systolic Blood Pressure (mmHg)</td>
<td>103.0 (8.06)</td>
<td>101.2 (7.45)</td>
<td>101.3 (7.82)</td>
<td>0.322</td>
<td>0.076</td>
<td>101.2 (7.63)</td>
<td>0.133</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (mmHg)</td>
<td>62.98 (5.40)</td>
<td>62.99 (4.99)</td>
<td>62.81 (5.54)</td>
<td>0.979</td>
<td>0.704</td>
<td>62.89 (5.28)</td>
<td>0.913</td>
</tr>
<tr>
<td>SBP in hypertensive range</td>
<td>12 (17.4 %)</td>
<td>4 (7.4 %)</td>
<td>7 (10.8 %)</td>
<td>0.222</td>
<td></td>
<td>11 (8.3 %)</td>
<td></td>
</tr>
<tr>
<td>DPB in hypertensive range</td>
<td>4 (5.8 %)</td>
<td>3 (5.6 %)</td>
<td>4 (6.2 %)</td>
<td>0.990</td>
<td></td>
<td>7 (5.3 %)</td>
<td></td>
</tr>
</tbody>
</table>

Data are mean (standard deviation) or number (%). \( p_{\text{unadj}} \) for the crude group differences using ANOVA for continuous values and Chi Square test for proportions. \( p_{\text{adj}} \) for the group differences adjusted for sex, age, height, and heart rate using ANCOVA. Model 1: Overall group differences. Model 2: Any iron supplements (1 or 2 mg Fe/kg/day) vs. placebo. Blood pressure in the hypertensive range was defined using a Swedish population based reference (24).
Table 3. Multivariate linear regression model assessing the effect of receiving iron supplementation between 6 weeks and 6 months of age on blood pressure at 7 years of age in low birth weight children.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>B (95% CI)</th>
<th>$r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female)</td>
<td>-1.076 (-2.97, 0.82)</td>
<td>0.005</td>
</tr>
<tr>
<td>Age (months)</td>
<td>0.340 (-0.33, 0.98)</td>
<td>0.004</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>0.486 (0.30, 0.67)</td>
<td>0.110</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>0.359 (0.27, 0.45)</td>
<td>0.250</td>
</tr>
<tr>
<td>1 or 2 mg Fe/kg/day</td>
<td>-2.238 (-4.21, -0.27)</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Model summary R square: 0.304

Multivariate linear regression model where B is unstandardized regression coefficient with 95% CI for each predictor and $r$ is standardized coefficient.
Table 4. Logistic regression model assessing the risk contribution of iron supplementation given between 6 weeks and 6 months of age on systolic blood pressure in the hypertensive range at 7 years of age in children born with low birth weight.

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Odds ratio</th>
<th>CI (95 %)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (months)</td>
<td>1.12</td>
<td>0.79, 1.59</td>
<td>0.541</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>1.21</td>
<td>1.09, 1.36</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>1.16</td>
<td>1.09, 1.24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1 or 2 mg Fe/kg/day</td>
<td>0.32</td>
<td>0.11, 0.96</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Multivariate logistic regression model for predictors of a BP in the hypertensive range, defined as based on the >90th percentile in a Swedish population based reference (24).
Figure legends

**Figure 1.** Trial profile of 285 low birth weight children included at six weeks of age and randomized into three iron intervention groups. Sixteen children were excluded from the intervention study at 6 weeks due to diagnosed anemia (Hb<90g/L) and two due to haematolytic disorder. * Of the 205 children assessed at seven years of age, 189 were included in the present analyses.