Neurodevelopment and cardiovascular risk in 7-year old children born with marginally low birth weight

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie/medicine doktorsexamen framläggs till offentligt försvar i Sal D, unodT9, by 1D, plan 9, Norrlands Universitetssjukhus, fredagen den 23 februari, kl. 09:00. Avhandlingen kommer att förvaras på engelska.

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**Abstract**

**Background:** Being born preterm (<37+0 gestational weeks) or with low birth weight (LBW, <2500 g) has been associated with a number of adverse health outcomes later in life. Most studied are cardiovascular and neurodevelopmental consequences in those born preterm and with very LBW (<1500 g). However, a majority of LBW children are born with a birth weight between 2000 and 2500 g, herein referred to as marginally LBW. The long-term risk profile for this substantially large group of children, is not known.

**Aim:** The aim of this study was to explore cardiovascular risk and neurocognitive development in marginally LBW children born in Sweden.

**Method:** This was originally a randomized controlled double-blinded trial aiming to explore the effects of iron supplementation in 285 children born with marginally LBW. The children were randomized to receive 0 mg/kg/day (placebo), 1 mg/kg/day or 2 mg/kg/day of iron supplements between 6 weeks and 6 months of age. As part of this observational follow-up study, 95 matched control children born with normal birth weight (NBW, 2501-4500 g) were recruited former to the first follow-up at 3.5-years. This thesis presents data from a follow-up at 7 years, including anthropometric data, blood pressure (BP), body composition (from a dual-energy X-ray absorptiometry) and laboratory markers of cardiovascular risk such as fasting glucose, insulin and lipid profile. Also, the children were tested using the validated neurocognitive tests WISC-IV (Wechsler Intelligence Scale for Children), Beery VMI (Beery-Buktenica developmental test of visual-motor integration) and TEA-Ch (Test of Everyday Attention for Children).

**Results:** The marginally LBW children were thinner (15.1 vs 15.5 kg/m², p=0.046), shorter (122.4 vs 124.9 cm, p=0.001) and had a higher prevalence of underweight (10.7 % vs 2.9 %, p=0.050) compared to their NBW peers. In addition, the LBW children had a significantly larger prevalence of high fasting insulin levels (>90th percentile of the control group). The subgroup of children born small for gestational age (SGA) also had a higher mean fasting glucose level, compared to NBW controls. There were no differences in prevalence of overweight or having an adverse lipid profile between the groups. The marginally LBW children who had received iron supplements, as part of the original intervention trial, had approximately 2 mmHg lower systolic BP, compared to the placebo group (p=0.026). The odds of having a high BP was lowered by 68 % (OR 0.32; CI 0.11-0.96) in the supplemented groups.

The marginally LBW children had 3.1 points lower verbal comprehension IQ (p=0.004), 3.5 points lower Beery VMI (p=0.028) and poorer selective attention compared to those born with NBW.

**Conclusions:** The marginally LBW children were thinner and shorter and they had an imbalanced glucose and insulin homeostasis, particularly those born SGA. Early iron supplements lowered systolic BP to a level similar to controls, suggesting a novel hypothesis regarding a long term protective effect against adverse programming. Finally, the children born with marginally LBW had poorer neurocognitive outcomes, prompting particular attention at school age.

**Keywords:** Low birth weight, early programming, accelerated catch-up growth, neurodevelopment, cardiovascular risk