



ASSOCIATION OF CARDIOVASCULAR RISK IN CHILDREN BORN WITH LOW BIRTH WEIGHT

Biochemistry

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ABSTRACT

INTRODUCTION: Most studies of early programming focus on very LBW or extremely LBW, even though the majority of all LBW children are born only with marginally LBW.² The pathogenesis behind CVD is multifactorial, and for health care providers to be able to assess the risk of each individual, we need to know more about this common subgroup.

AIM: Being born with LBW affects later cardiovascular risk.

RESULT: In Marginally LBW group, 4.7(0.6) patients had Fasting glucose(mmol/L), 2.7(2.3-3.8) patients had Fasting insulin(μ U/mL), 0.57(0.4-0.8) patients had HOMA-IR, 4.4(0.7) patients had Cholesterol(mmol/L), 0.50(0.2) patients had Triglyceride(mmol/L), 2.7(0.6) patients had LDL(mmol/L), 1.5(0.3) patients had HDL(mmol/L), 0.82(0.2) patients had ApoB(g/L), 1.4(0.2) patients had ApoA1 (g/L), 0.51(0.3) patients had ApoB/ApoA1 and 0.24(0.1-0.7) patients had hs-CRP(mg/L). In Controls group, 3.5(0.5) patients had Fasting glucose(mmol/L), 2.8(LD-3.5) patients had Fasting insulin(μ U/mL), 0.60(LD-0.7) patients had HOMA-IR, 5.5(0.8) patients had Cholesterol(mmol/L), 0.57(0.2) patients had Triglyceride(mmol/L), 2.9(0.7) patients had LDL(mmol/L), 1.4(0.3) patients had HDL(mmol/L), 0.71(0.2) patients had ApoB(g/L), 1.4(0.2) patients had ApoA1 (g/L), 0.57(0.1) patients had ApoB/ApoA1 and 0.18(0.1-0.5) patients had hs-CRP(mg/L).

CONCLUSION: Some risk factors originating from the fetal environment cannot be changed after birth, good cardiovascular health can be restored by influencing postnatal risk factors before adulthood. There were no significant differences in insulin, insulin resistance, hs-CRP or blood lipids between the marginally LBW children and controls.

KEYWORDS

Low Birth Weight, Cardiovascular Risk, Atherogenic Lipoproteins.

INTRODUCTION

The World Health Organization defines low birth weight (LBW) as birth weight less than 2500 g. Being born with a birth weight below this cut off is associated with a range of poor health outcomes, both early and later in life. Today, these children accounts for approximately 15 % of all births, ranging from 4 % in developed countries to 16 % in developing countries.^{1,2}

Most studies of early programming focus on very LBW or extremely LBW, even though the majority of all LBW children are born only with marginally LBW.² In Sweden, this accounts for over 2200 children every year. What these children potentially are at risk of is still unclear. Some studies have shown an inverse relationship between birth weight and cardiovascular risk, suggesting that also marginally LBW would be a risk factor, although lower. However, the pathogenesis behind CVD is multifactorial, and for health care providers to be able to assess the risk of each individual, we need to know more about this common subgroup.

Elevated levels of triglycerides and LDL (or Apolipoprotein B, [ApoB]) and lowered levels of HDL (or Apolipoprotein A1, [ApoA1]) are three markers included in the "lipid triad", a concept often used when discussing metabolic risk.³ These are all related to atherosclerosis and CVD, a risk that increases with prolonged exposure.^{4,5}

The atherogenic lipoproteins (LDL, very low-density lipoprotein [VLDL], intermediate-density lipoprotein [IDL]) are more prone to penetrate the vessel wall, where they bind to proteins in the extracellular matrix and triggers macrophages and inflammation. This process is the pathophysiological process that causes endothelial damage and atherosclerosis.³ Furthermore, HDL is an anti-atherogenic lipoprotein that can bind to the vessel wall and remove fat molecules from cells, thereby protecting them from excessive storage.⁵ On every atherogenic lipoprotein, there is a protein called ApoB, while every HDL particle contains ApoA1. Therefore, measuring these proteins correlates well to the lipid profile.⁵

Adipocytes in overweight and obese individuals become enlarged and saturated with lipids, which leads to impaired insulin sensitivity and release of FFA in the blood. The elevated levels of FFA further on result in an increased flux of FFA to hepatocytes in the liver, as well as increased storage in both the hepatocytes as well as in myocytes in muscle tissue. The FFAs in the liver are esterified to VLDL and IDL and released into the blood stream. The raised fat storage in the hepatocytes and myocytes damage the insulin sensitivity, further progressing the insulin resistance.³

Though less studied compared to insulin resistance, children and adults born with LBW have been suggested to have an adverse lipid profile, compared to those born with NBW, a correlation accentuated with increasing age.⁶ However, the evidence is scarce, especially from prospective studies, and systematic reviews have not yet established a consensus.⁷

OBJECTIVE

The objective of the present thesis was to answer the following research question:

- How does being born with LBW affect later cardiovascular risk?

MATERIALS AND METHODS

This study was hospital based comparative study.

STATISTICAL ANALYSIS:

For statistical analysis data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5. Data had been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Two-sample t-tests for a difference in mean involved independent samples or unpaired samples. Paired t-tests were a form of blocking and had greater power than unpaired tests. A chi-squared test (χ^2 test) was any statistical hypothesis test wherein the sampling distribution of the test statistic is a chi-squared distribution when the null hypothesis is true. Without other qualification, 'chi-squared test' often is used as short for

Pearson's chi-squared test. Unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate.

Explicit expressions that can be used to carry out various *t*-tests are given below. In each case, the formula for a test statistic that either exactly follows or closely approximates a *t*-distribution under the null hypothesis is given. Also, the appropriate degrees of freedom are given in each case. Each of these statistics can be used to carry out either a one-tailed test or a two-tailed test.

Once a *t* value is determined, a *p*-value can be found using a table of values from Student's *t*-distribution. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01 level), then the null hypothesis is rejected in favour of the alternative hypothesis.

p-value ≤ 0.05 was considered for statistically significant.

Table1. Baseline and parental data of the included marginally LBW children compared to the controls.

Marginally LBW	Controls
<i>Perinatal characteristics</i>	
Sex(girl)	110(50%) 39(53 %)
Birth weight(g)	2290(150) 3550(430)**
Birth length(cm)	45.3(1.4) 50.6(1.9)**
Head circumference at birth(cm)	32.2(1.2) 35.1(1.5)**
Gestational age at birth(weeks)	36.5(1.9) 40.0(1.2)**
Vaginal delivery	125(57%) 52(71 %)*
Multiple gestation	66(30 %) 1(1%)**
Parity	1.6(0.8) 1.6(0.7)
Mother's age at delivery(years)	35.3(5.8) 34.4(4.4)
Mother born outside Scandinavia	38(17 %) 6(8%)*
Mother's BMI(kg/m ²)	23.9(4.8) 13.7(1.8)
Father's BMI(kg/m ²)	25.4(3.1) 35.4(4.2)
Mother with university education	129(63%) 52(68 %)
Father with university education	119(62%) 38(56 %)

Table 2. Anthropometric characteristics and body composition at 7 years of age in marginally LBW children compared to controls.

	Marginally LBW	Controls
Weight(kg)	22.7(3.6)**	24.3(3.8)
Height(cm)	123.4(5.5)**	125.9(5.5)
BMI(kg/m ²)	15.1(1.6)*	16.5(1.6)
Waist circumference(cm)	54.3(4.9)	56.2(4.8)
FMI(kg/m ²)	3.5(2.3)	3.8(2.3)
FFMI(kg/m ²)	13.4(0.9)*	13.6(0.9)
Total bodyfat(%)	17.1(6.5)	17.6(5.9)
Trun caladipose tissue(%)	14.5(7.1)	15.7(6.6)

Table 3. Laboratory markers of cardiovascular risk in marginally LBW children and NBW controls

	Marginally LBW	Controls
Fastingglucose(mmol/L)	4.7(0.6)	3.5(0.5)
Fastinginsulin(μ U/mL)	2.7(2.3-3.8)	2.8(LD-3.5)
HOMA-IR	0.57(0.4-0.8)	0.60(LD-0.7)
Cholesterol(mmol/L)	4.4(0.7)	5.5(0.8)
Triglyceride(mmol/L)	0.50(0.2)	0.57(0.2)
LDL(mmol/L)	2.7(0.6)	2.9(0.7)
HDL(mmol/L)	1.5(0.3)	1.4(0.3)
ApoB(g/L)	0.82(0.2)	0.71(0.2)
ApoA1 (g/L)	1.4(0.2)	1.4(0.2)
ApoB/ApoA1	0.51(0.3)	0.57(0.1)
hs-CRP(mg/L)	0.24(0.1-0.7)	0.18(0.1-0.5)

RESULT AND DISCUSSION

In consistency with the Danish study, several other studies have suggested an association between intra- and extrauterine growth, and later lean mass rather than fat mass.¹¹⁷ For instance, a longitudinal study of 9 year old boys born in a city in Brazil in 1993 showed that early weight gain (0-6 months) was positively associated with later height and lean mass, but not with fat mass.⁸ In their cohort, weight gain during childhood (1-4 years) was positively associated with obesity in the children.

We found that in Marginally LBW group, 110(50%) patients were female, 150 patients Birth weight(g) was 2290gm., 45.3(1.4) patients had Birth length(cm), 32.2(1.2) patients had Head circumference at birth(cm), 36.5(1.9) patients had Gestational age at birth(weeks), 125(57%) patients had Vaginal delivery, 66(30 %) patients had Multiple gestation and 107(43.9%) patients had Parity. In Controls group, 39(53 %) patients were female, 3550(430) patients had Birth weight(g), 50.6(1.9) patients had Birth length(cm), 35.1(1.5) patients had Head circumference at birth(cm), 40.0(1.2) patients had Gestational age at birth(weeks), 52(71 %) patients had Vaginal delivery, 1(1%) patient had Multiple gestation and 1.6(0.7) patients had Parity.

One Danish study of term born infants found that change in weight for age Z- scores was positively associated with BMI, FMI and FFMI at 3 years of age.⁹ However, the association between early growth and FMI was attenuated by breastfeeding, suggesting that breastfeeding was an effect mediator.

Our study showed that in Marginally LBW group, 35.3(5.8) patients were Mother's age at delivery (years), 38(17 %) patients had Mother born outside Scandinavia, 23.9(4.8) patients had Mother's BMI (kg/m²), 25.4(3.1) patients had Father's BMI (kg/m²), 129(63%) patients had Mother with university education and 119(62%) patients had Father with university education. In Controls group, 34.4(4.4) patients were Mother's age at delivery (years), 6(8%) patients had Mother born outside Scandinavia, 13.7(1.8) patients had Mother's BMI (kg/m²), 35.4(4.2) patients had Father's BMI (kg/m²), 52(68 %) patients had Mother with university education and 38(56 %) patients had Father with university education.

It was found that in Marginally LBW group, 22.7(3.6) patients had Weight(kg), 123.4(5.5) patients had Height(cm), 15.1(1.6) patients had BMI(kg/m²), 54.3(4.9) patients had Waist circumference(cm), 3.5(2.3) patients had FMI(kg/m²), 13.4(0.9) patients had FFMI(kg/m²), 17.1(6.5) patients had Total body fat(%) and 14.5(7.1) patients had Truncaladiposetissue(%). In Controls group, 24.3(3.8) patients had Weight(kg), 125.9(5.5) patients had Height(cm), 16.5(1.6) patients had BMI(kg/m²), 56.2(4.8) patients had Waist circumference(cm), 3.8(2.3) patients had FMI(kg/m²), 13.6(0.9) patients had FFMI(kg/m²), 17.6(5.9) patients had Total body fat(%) and 15.7(6.6) patients had Truncaladiposetissue(%).

Haas GM et al¹⁰(2015) found that though risk factors clustered between 3.0 kg and 4.0 kg of birth weight in both genders we found only one significant correlation of birth weight with TG for males and females and another one for HDL-C in males. The strongest clustering of significant regression coefficients occurred in the 2nd birth weight quintile for SBP (β 0.018), TC (β -0.050), LDL-C (β -0.039), non LDL-C (β -0.049) and log TG (β -0.001) in males and females.

Jornayvaz FR et al¹¹(2016) found that women with low birth weight (≤ 2.5 kg) had higher levels of fasting plasma glucose, insulin, HOMA, diabetes and metabolic syndrome; a non significant similar trend was seen in men. In both genders, height increased with birth weight, whereas a U-shaped association was found between birth weight and body mass index, waist circumference and body fat percentage. After adjusting for age, smoking status, physical activity and fat mass, an inverse association was found between leptin and birth weight categories: adjusted mean $\pm$ standard error 17.3 $\pm$ 0.7, 16.2 $\pm$ 0.3, 15.6 $\pm$ 0.5 and 14.0 $\pm$ 0.8 ng/dL for birth weight categories ≤ 2.5 , 2.6-3.5, 3.6-4.0 and >4.0 kg, respectively, in women ($p < 0.05$) and 9.8 $\pm$ 0.8, 9.1 $\pm$ 0.3, 7.8 $\pm$ 0.4 and 7.7 $\pm$ 0.5 ng/dL in men ($p < 0.05$). An inverse association was also found between reported birth weight and leptin to fat mass ratio: mean $\pm$ standard error 0.77 $\pm$ 0.04, 0.73 $\pm$ 0.02, 0.69 $\pm$ 0.03 and 0.62 $\pm$ 0.04 in women ($p < 0.05$); 0.46 $\pm$ 0.05, 0.45 $\pm$ 0.02, 0.39 $\pm$ 0.02 and 0.38 $\pm$ 0.03 in men ($p < 0.05$). No differences in adiponectin levels were found between birth weight groups.

Starnberg J et al¹² (2019) found no significant differences in levels of insulin, HOMA-IR, hs-CRP or blood lipids were observed between marginally LBW and NBW children. At 7 years there was a higher proportion of marginally LBW children with elevated levels of insulin, defined as above the 90th percentile of the control group (21% vs 8.6%, $p = 0.038$). This association was, however, confounded by maternal ethnicity. In marginally LBW children born small for gestational age (SGA), mean fasting glucose was significantly higher compared to controls (4.7 vs 4.5 mmol/L, $p = 0.020$).

We also found that in Marginally LBW group, 4.7(0.6) patients had Fasting glucose(mmol/L), 2.7(2.3-3.8) patients had Fasting

insulin(μ U/mL), 0.57(0.4-0.8) patients had HOMA-IR, 4.4(0.7) patients had Cholesterol(mmol/L), 0.50(0.2) patients had Triglyceride(mmol/L), 2.7(0.6) patients had LDL(mmol/L), 1.5(0.3) patients had HDL(mmol/L), 0.82(0.2) patients had ApoB(g/L), 1.4(0.2) patients had ApoA1 (g/L), 0.51(0.3) patients had ApoB/ApoA1 and 0.24(0.1-0.7) patients had hs-CRP(mg/L). In Controls group, 3.5(0.5) patients had Fasting glucose(mmol/L), 2.8(LD-3.5) patients had Fasting insulin(μ U/mL), 0.60(LD-0.7) patients had HOMA-IR, 5.5(0.8) patients had Cholesterol(mmol/L), 0.57(0.2) patients had Triglyceride(mmol/L), 2.9(0.7) patients had LDL(mmol/L), 1.4(0.3) patients had HDL(mmol/L), 0.71(0.2) patients had ApoB(g/L), 1.4(0.2) patients had ApoA1 (g/L), 0.57(0.1) patients had ApoB/ApoA1 and 0.18(0.1-0.5) patients had hs-CRP(mg/L).

CONCLUSION

In our study birth weight, Birth length, Head circumference at birth and Gestational age at birth were high in control group patients. We found that Mother's BMI was higher in Marginally LBW patients compared to control group patients. Both low and high birth weights have an impact on later cardiometabolic health, and cardiovascular risk factors can be detected already in childhood. Even though some risk factors originating from the fetal environment cannot be changed after birth, good cardiovascular health can be restored by influencing postnatal risk factors before adulthood. There were no significant differences in insulin, insulin resistance, hs-CRP or blood lipids between the marginally LBW children and controls.

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