

# Does (rapid) early weight gain cause adult disease and obesity?

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Annotated Reference List

Adair, L. S., et al. (2009). "Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter?" American Journal of Clinical Nutrition **89**(5): 1383-1392.

**BACKGROUND:** Promoting catch-up growth in malnourished children has health benefits, but recent evidence suggests that accelerated child weight gain increases adult chronic disease risk. **OBJECTIVE:** We aimed to determine how birth weight (BW) and weight gain to midchildhood relate to blood pressure (BP) in young adults. **DESIGN:** We pooled data from birth cohorts in Brazil, Guatemala, India, the Philippines, and South Africa. We used conditional weight (CW), a residual of current weight regressed on prior weights, to represent deviations from expected weight gain from 0 to 12, 12 to 24, 24 to 48 mo, and 48 mo to adulthood. Adult BP and risk of prehypertension or hypertension (P/HTN) were modeled before and after adjustment for adult body mass index (BMI) and height. Interactions of CWs with small size-for-gestational age (SGA) at birth were tested. **RESULTS:** Higher CWs were associated with increased BP and odds of P/HTN, with coefficients proportional to the contribution of each CW to adult BMI. Adjusted for adult height and BMI, no child CW was associated with adult BP, but 1 SD of BW was related to a 0.5-mm Hg lower systolic BP and a 9% lower odds of P/HTN. BW and CW associations with systolic BP and P/HTN were not different between adults born SGA and those with normal BW, but higher CW at 48 mo was associated with higher diastolic BP in those born SGA. **CONCLUSIONS:** Greater weight gain at any age relates to elevated adult BP, but faster weight gains in infancy and young childhood do not pose a higher risk than do gains at other ages.

IA Note - Data from 5 birth cohorts (Brazil, Guatemala, India, Phillipines, and South Africa) were analyzed to test whether CONDITIONAL WEIGHT (difference between actual weight and expected weight) and HTN were associated. Once adjusted for adult height, CW was not associated to BMI. Rapid early weight gain does not associate with HTN.

Baird, J., et al. (2005). "Being big or growing fast: systematic review of size and growth in infancy and later obesity." BMJ **331**(7522): 929.

**Objectives** To assess the association between infant size or growth and subsequent obesity and to determine if any association has been stable over time. **Design** Systematic review. **Data sources** Medline, Embase, bibliographies of included studies, contact with first authors of included studies and other experts. **Inclusion criteria** Studies that assessed the relation between infant size or growth during the first two years of life and subsequent obesity. **Main outcome measure** Obesity at any age after infancy. **Results** 24 studies met the inclusion criteria (22 cohort and two case-control studies). Of these, 18 assessed the relation between infant size and subsequent obesity, most showing that infants who were defined as "obese" or who were at the highest end of the distribution for weight or body mass index were at increased risk of obesity. Compared with non-obese infants, in those who had been obese odds ratios or relative risks for subsequent obesity ranged from 1.35 to 9.38. Ten studies assessed the relation of infant growth with subsequent obesity and most showed that infants who grew more rapidly were at increased risk of obesity. Compared with other infants, in infants with rapid growth odds ratios and relative risks of later obesity ranged from 1.17 to 5.70. Associations were consistent for obesity at different ages and for people born over a period from 1927 to 1994. **Conclusions** Infants who are at the highest end of the distribution for weight or body mass index or who grow rapidly during infancy are at increased risk of subsequent obesity.

IA Note - Infant size, growth, and obesity later on. 24 studies = 22 cohort and 2 case control studies. 18 studies evaluated the relationship between infant size and later obesity. Big infants are big children and big adults (who are labeled *obese*). Babies who grew the fastest are at risk for "obesity."

Barker, D. J., et al. (1993). "Fetal nutrition and cardiovascular disease in adult life." Lancet **341**(8850): 938-941.

Babies who are small at birth or during infancy have increased rates of cardiovascular disease and non-insulin-dependent diabetes as adults. Some of these babies have low birthweights, some are small in relation to the size of their placentas, some are thin at birth, and some are short at birth and fail to gain weight in infancy. This paper shows how fetal undernutrition at different stages of gestation can be linked to these patterns of early growth. The fetuses' adaptations to undernutrition are associated with changes in the concentrations of fetal and placental hormones. Persisting changes in the levels of hormone secretion, and in the sensitivity of tissues to them, may link fetal undernutrition with abnormal structure, function, and disease in adult life.

IA Note - These infants are born small and remain small. Hormonal changes, effects during fetal life (fetal undernutrition) may increase risk for smallness (LBW, SGA, etc.) at birth increasing risk for cardiovascular disease and T2DM

Bouhours-Nouet, N., et al. (2008). "High Birth Weight and Early Postnatal Weight Gain Protect Obese Children and Adolescents From Truncal Adiposity and Insulin Resistance." *Diabetes Care* **31**(5): 1031-1036.

**OBJECTIVE**—Low birth weight (LBW), no early catch-up weight, and subsequent fat accumulation have been associated with increased risks of insulin resistance from childhood onward and later cardiovascular disease. We sought to clarify the effects of high birth weight (HBW) and postnatal weight gain on insulin resistance.**RESEARCH DESIGN AND METHODS**—A total of 117 obese children aged  $10.4 \pm 2.4$  years were divided into three groups according to fetal growth after exclusion of maternal diabetes. They were comparable for age, sex, puberty, and percent body fat. Customized French birth weight standards, adjusted for maternal characteristics and gestation number, identified subjects with true altered fetal growth: 32 had increased fetal growth according to customized standards (HBW<sub>cust</sub>), 52 were eutrophic, and 33 had restricted fetal growth according to customized standards (LBW<sub>cust</sub>). Fat distribution by dual-energy X-ray absorptiometry, insulin sensitivity indexes from an oral glucose tolerance test (OGTT), and leptin, adiponectin, and visfatin levels were compared between groups.**RESULTS**—The HBW<sub>cust</sub> subjects had a higher adiponectin level, higher whole-body insulin sensitivity index (WBISI), and lower hepatic insulin resistance index, lower insulin and free fatty acid concentrations during OGTT, and lower trunk fat percent than eutrophic ( $P < 0.05$ ) and LBW<sub>cust</sub> subjects ( $P < 0.05$ ). Besides birth weight, weight gain between 0 and 2 years was a positive predictor ( $P < 0.05$ ) of WBISI, whereas weight gain after 4 years was a negative predictor ( $P < 0.05$ ).**CONCLUSIONS**—HBW and early weight gain may program insulin sensitivity and adipose tissue metabolism and contribute to so-called metabolically healthy obesity.

IA Note - LBW, catch up weight after 2 years of age, and fat accumulation is known to increase insulin resistance and risk of CVD. A group of 117 OBESE children were divided into LBW (n=33), Eutrophic (n=52), and HBW (n=32). The High Birth Weight had higher adiponectin, higher insulin sensitivity, and lower insulin resistance, and lower fat trunk accum confirming that high birth weight does not predispose to diabetes and also that there are some children that are healthy and obese.

Druet, C., et al. (2012). "Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis." Paediatric and Perinatal Epidemiology **26**(1): 19-26.

To assess the predictive ability of infant weight gain on subsequent obesity we performed a meta-analysis of individual-level data on 47,661 participants from 10 cohort studies from the UK, France, Finland, Sweden, the US and Seychelles. For each individual, weight SD scores at birth and age 1 year were calculated using the same external reference (British 1990). Childhood obesity was defined by International Obesity Task Force criteria. Each +1 unit increase in weight SD scores between 0 and 1 year conferred a twofold higher risk of childhood obesity (odds ratio = 1.97 [95% confidence interval (CI) 1.83, 2.12]), and a 23% higher risk of adult obesity (odds ratio = 1.23 [1.16, 1.30]), adjusted for sex, age and birthweight. There was little heterogeneity between studies. A risk score for childhood obesity comprising weight gain 0-1 year, mother's body mass index, birthweight and sex was generated in a random 50% selection of individuals from general population cohorts with available information (n = 8236); this score showed moderate predictive ability in the remaining 50% sample (area under receiving operating curve = 77% [95% CI 74, 80%]). A separate risk score for childhood overweight showed similar predictive ability (area under receiving operating curve = 76% [73, 79%]). In conclusion, infant weight gain showed a consistent positive association with subsequent obesity. A risk score combining birthweight and infant weight gain (or simply infant weight), together with mother's body mass index and sex may allow early stratification of infants at risk of childhood obesity.

IA Note - Strength in numbers, which means putting together results from several studies means increasing the sample size and this in turn means that with a big enough sample size almost anything can be proven. However, putting together several studies also means accepting the methodological flaws of each individual study and not knowing what study's results are contributing more or less to the \*new\* results. This means a more methodologically flawed study could be contributing more to the results and it is not always possible/straightforward to know this is happening, for each 1 z score increase in weight from 0 - 1 year there is a 2 fold increased risk in childhood obesity and a 23% increased risk in adult obesity. This study proves again a big baby is a big child and most likely a big adult. I think you need to repeat your big infant, big child big adult statemeng.

Eid, E. E. (1970). "Follow-up study of physical growth of children who had excessive weight gain in first six months of life." British Medical Journal **2**(5701): 74-76.

The aim of this study was to determine whether excessive weight gain in the first six weeks, three months, or six months of life was correlated. with overweight and

obesity at the age of 6 to 8 years. One hundred and thirty eight infants with excessive weight gain in the first six months of life, 53 children with slow weight gain, and 33 children with an average weight gain were re-examined at the age of 6, 7, or 8 years. The mean height and weight of children who had gained weight rapidly in infancy were significantly higher than those of children who had gained weight slowly; those of infants whose weight gain had been average fell in between. The number of obese children in the rapid-weight-gain group was significantly higher than that of the combined average and slow-weight-gain groups. The rapidity of weight gain in infancy was a better guide to the risk of overweight in later childhood than the weight of the parents.

IA Note - One of the first papers to define rapid early weight gain. Studied whether \*excessive\* weight gain in first 6 weeks, 3 mo, or 6 mo and obesity at 6 to 8 years of age were correlated. It was. Rapid early weight gain was a better predictor of obesity at 6-8 years of age than weight of parents. Another big baby, big child study. Neutralize this language, take out the words "excessive" and Obesity and what do you have?

Ekelund, U., et al. (2007). "Association of Weight Gain in Infancy and Early Childhood with Metabolic Risk in Young Adults." Journal of Clinical Endocrinology and Metabolism **92**(1): 98-103.

Context: Early postnatal life has been suggested as an important window during which risks for long-term health may be influenced. Objective: The aim of this study was to examine the independent associations between weight gain during infancy (0–6 months) and early childhood (3–6 yr) with components of the metabolic syndrome in young adults. Design: This was a prospective cohort study (The Stockholm Weight Development Study). Setting: The study was conducted in a general community. Participants: Subjects included 128 (54 males) singletons, followed from birth to 17 yr. Main Outcome Measure: None of these young adults met the full criteria for the metabolic syndrome. We therefore calculated a continuous clustered metabolic risk score by averaging the standardized values of the following components: waist circumference, blood pressure, fasting triglycerides, high-density lipoprotein cholesterol, glucose, and insulin level. Results: Clustered metabolic risk at age 17 yr was predicted by weight gain during infancy (standardized  $\beta = 0.16$ ;  $P < 0.0001$ ) but not during early childhood (standardized  $\beta = 0.10$ ;  $P = 0.23$ ), adjusted for birth weight, gestational age, current height, maternal fat mass, and socioeconomic status at age 17 yr. Further adjustment for current fat mass and weight gain during childhood did not alter the significant association between infancy weight gain with the metabolic risk score (standardized  $\beta = 0.20$ ;  $P = 0.007$ ). Conclusions: Rapid weight gain during

infancy (0–6 months) but not during early childhood (3–6 yr) predicted clustered metabolic risk at age 17 yr. Early interventions to moderate rapid weight gain even at very young ages may help to reduce adult cardiovascular disease risks.

IA Note - Studied association between 0-6 mo weight gain and 3-6 years old weight and risk factors for metabolic syndrome. Results: rapid early weight gain 0-6 mo predicted metabolic risk at 17 yr of age with  $\beta = .20$ . No one at 17 yr met criteria for met synd. therefore a met synd. risk score with waist circum, BP, fasting triglyc, HDL and glu was created.

Eriksson, J., et al. (2006). "Patterns of growth among children who later develop type 2 diabetes or its risk factors." *Diabetologia* **49**(12): 2853-2858.

#### Abstract

**Aims/hypothesis** We studied fetal and childhood growth patterns that are associated with IGT and type 2 diabetes in adult life.

**Methods** We examined clinically 2,003 subjects born in Helsinki between 1934 and 1944. They had on average 11 measurements of height and weight between birth and 2 years of age, and seven measurements between 2 and 11 years of age. Glucose tolerance in adult life was assessed by a 75-g oral glucose tolerance test.

**Results** We identified 311 subjects with type 2 diabetes and 496 with IGT. Both IGT and type 2 diabetes were associated with low birthweight ( $p < 0.0001$  adjusting for current BMI). The risk of these conditions was increased by low weight gain between birth and 2 years. A 1 SD increase in weight at 2 years was associated with an odds ratio for either type 2 diabetes or IGT of 0.76 (95% CI 0.69–0.84). This effect was greatest in people who had low birthweight. Low growth in the first 6 months after birth was a critical period for the development of insulin resistance in later life; other critical periods were associated with slow fetal growth and rapid increase in BMI between age 2 and 11 years.

**Conclusions/interpretation** Low weight gain during infancy increases the risk of IGT and type 2 diabetes. The effect is greater in people who had low birthweight. The first 6 months after birth may be the most critical period for growth, in relation to development of glucose intolerance.

IA Note - Studied fetal and early growth risk factors for T2DM and IGT (impaired glucose tolerance) in 2003 individuals in Helsinki born in 1934-1944. All cases 311 with T2DM and 496 with IGT happened in LBW individuals. The risks of these conditions increased with low weight between birth and 2 years. LOW WEIGHT DURING INFANCY INCREASES THE RISK FOR T2DM AND IGT, AND THIS IS WORSE FOR INDIVIDUALS WITH LBW

Eriksson, J. G., et al. (2003). "Pathways of Infant and Childhood Growth That Lead to Type 2 Diabetes." *Diabetes Care* **26**(11): 3006-3010.

**OBJECTIVE**—Although a link between small body size at birth and later type 2 diabetes has been repeatedly documented, less is known about the associations between the disease and growth during infancy. The aim of this study was to explore the pathways of infant and early growth that lead to type 2 diabetes in adult life.**RESEARCH DESIGN AND METHODS**—We carried out a longitudinal study of 8,760 subjects born in Helsinki from 1934 to 1944. On average, they had 8 measurements of height and weight between birth and 1 year of age and another 10 measurements between 1 and 12 years of age. We identified people with type 2 diabetes using a national register.**RESULTS**—Among babies whose birth weights were  $\leq 3.5$  kg, the rate of infant growth was unrelated to later type 2 diabetes. Among babies with birth weights  $> 3.5$  kg, slow growth in length between birth and 3 months of age predicted later disease. Rapid gain in BMI after age 2 years increased the risk of later disease in both groups of babies, but this effect was greatest among children who had slow growth in length between birth and 3 months of age. In children whose Z-scores for length decreased, an SD increase in BMI at age 12 years was associated with an odds ratio (OR) for type 2 diabetes of 1.77 (95% CI 1.50–2.09). The corresponding OR in subjects whose Z-scores for length increased was 1.42 (95% CI 1.20–1.69). Rapid gain in childhood BMI was associated with high maternal BMI and socioeconomic factors (fewer people in the home and lower social class).**CONCLUSIONS**—Babies with above-average birth weights may develop type 2 diabetes later in life if poor living conditions lead to faltering growth in length in the first few months after birth. We speculate that growth faltering at this time is associated with lifelong impairment of insulin metabolism and inability to meet the challenge of rapid childhood increase in BMI.

IA Note - This study looked at factors that increase risk to T2DM in adults. Results showed for LBW people ( $< 3.5$  kg) the rate of infant growth was not related to T2DM. But among people with BW  $< 3.5$  kg SLOW GROWTH IN LENGTH BETWEEN BIRTH AND 3 MO PREDICTED T2DM. Now, this study also found that rapid weight gain after 2 years of age, especially in children with slow length gains in infancy associated with an almost two fold (1.77) OR increase of T2DM at 12 years of age (each 1 z score increase in BMI at 12 years of age). Two other factors included low SES and high maternal BMI.

Fabricius-Bjerre, S., et al. (2011). "Impact of Birth Weight and Early Infant Weight Gain on Insulin Resistance and Associated Cardiovascular Risk Factors in Adolescence." *PLoS One* **6**(6): e20595.



Background Low birth weight followed by accelerated weight gain during early childhood has been associated with adverse metabolic and cardiovascular outcomes later in life. The aim of this study was to examine the impact of early infant weight gain on glucose metabolism and cardiovascular risk factors in adolescence and to study if the effect differed between adolescents born small for gestational age (SGA) vs. appropriate for gestational age (AGA).  
Methodology/Principal Findings Data from 30 SGA and 57 AGA healthy young Danish adolescents were analysed. They had a mean age of 17.6 years and all were born at term. Data on early infant weight gain from birth to three months as well as from birth to one year were available in the majority of subjects. In adolescence, glucose metabolism was assessed by a simplified intravenous glucose tolerance test and body composition was assessed by dual-energy X-ray absorptiometry. Blood pressures as well as plasma concentrations of triglycerides and cholesterol were measured. Early infant weight gain from birth to three months was positively associated with the fasting insulin concentration, HOMA-IR, basal lipid levels and systolic blood pressure at 17 years. There was a differential effect of postnatal weight gain on HOMA-IR in AGA and SGA participants (P for interaction = 0.03). No significant associations were seen between postnatal weight gain and body composition or parameters of glucose metabolism assessed by the simplified intravenous glucose tolerance test. In subgroup analysis, all associations with early infant weight gain were absent in the AGA group, but the associations with basal insulin and HOMA-IR were still present in the SGA group. Conclusion This study suggests that accelerated growth during the first three months of life may confer an increased risk of later metabolic disturbances – particularly of glucose metabolism – in individuals born SGA.

IA Note - Studied early weight gain and glucose met and CVD risk factors in adolescence, 17.6 y. 30 SGA and 57 AGA adolescents were studied. Accelerated growth in 0-3 mom, particularly among SGA increases risk for later met disturbances (insulin and glucose metabolism).

Jarvelin, M. R. (1966). "Early life factors and blood pressure at age 31 years in the northern Finland birth cohort." *Hypertension* **44**: 838-846.

Abstract—Data on the birth weight– blood pressure relationship are inconsistent. Although an inverse association has been suggested in several large studies, interpretation is complicated by publication and other biases. Few data are available on the relationship between other early growth measures and blood pressure. We examined the shape and size of association between determinants of fetal growth, size at birth, growth in infancy, and adult systolic and diastolic



blood pressure at 31 years in the prospective northern Finnish 1966 birth cohort of 5960 participants. Birth weight, birth length, gestational age, ponderal index, and birth weight relative to gestational age showed a significant inverse association with blood pressure at age 31. Rapid growth in infancy ("change-up") was positively associated with blood pressure. Adjusted regression coefficients for birth weight indicated systolic/diastolic blood pressure lower by 1.7 (95% confidence interval [CI], 2.5, 1.0)/0.7 (95% CI, 1.4, 0.02) mm Hg for 1 kg higher birth weight. The significant inverse association between birth weight and systolic blood pressure persisted without adjustment for adult body mass index for males. Among females, gestational age showed a stronger association with blood pressure than birth weight: gestational age higher by 7 weeks (equivalent to an average of 1 kg higher birth weight) among singletons associated with 2.9 (95% CI, 4.7, 1.1) mm Hg lower systolic blood pressure. Our results support the concept that birth weight, other birth measures, and infant growth are important determinants of blood pressure and hence cardiovascular disease risk in later life. (Hypertension. 2004;44:838-846.)

IA Note - Studied association between size at birth and adult BP. Showed that early fast weight gain also described by him as catch up in weight associated with blood pressure later in life. An increase of 0.67 z score weight for age from 0 to 1 year of age was associated with elevated systolic blood pressure at 31 years of age.

Kajantie, E., et al. (2008). "Growth before 2 years of age and serum lipids 60 years later: the Helsinki Birth Cohort study." International Journal of Epidemiology **37**(2): 280-289.

BACKGROUND: Small body size at birth and slow growth during the first 2 years after birth, leading to low body mass index (BMI) at 2 years, are associated with coronary heart disease and stroke in adult life. We tested the hypothesis that this path of growth is associated with an atherogenic lipid profile in later life.

METHODS: We measured serum lipid concentrations at age 57-70 years in 1999 members of the Helsinki Birth Cohort. They were randomly selected from an original cohort of 8760 people and had on average 11 measurements of height and weight between birth and 2 years of age.

RESULTS: The 18% of subjects who used lipid-lowering medication had a lower BMI at birth and at 2 years. These subjects were excluded from the analyses of lipid profiles. A 1 kg/m<sup>2</sup> lower BMI at birth was associated with 0.051 mmol/l (95% CI -0.001 to 0.103; P = 0.05) higher non-HDL cholesterol and 0.018 g/l higher (0.005-0.031; P = 0.006) apolipoprotein B concentrations. A slower increase in BMI during the first 6 months after birth was associated with lower HDL and higher non-HDL cholesterol concentrations. A 1 kg/m<sup>2</sup> lower BMI at 2 years was associated with 0.020 mmol/l lower (0.004-0.036; P = 0.02) HDL cholesterol and 0.059 mmol/l

(0.020-0.099; P = 0.003) higher non-HDL cholesterol and 0.018 mmol/l higher (0.008-0.028; P < 0.001) apolipoprotein B concentrations. The age at weaning off breast milk was not associated with lipid profile in later life. CONCLUSION: Small body size at birth and slow weight gain during infancy are associated with an atherogenic lipid profile in adult life.

IA Note- Studied whether small size at birth and slow growth in first 2 years associates with lipid profile (CVD) later in life in almost 2000 members of the Helsinki Birth Cohort (8,760 people with 11 measurements between birth and 2 years of age) The 18% of individuals taking lipid reducing meds had low BMI at birth and 2 years of age. A slow increase in BMI from birth to 6 mo associated with low HDL and high LDL and VLDL. Small body size and slow weight gain during infancy associate with worse lipid profile in adulthood.

Kerkhof, G. F., et al. (2012). "Does preterm birth influence cardiovascular risk in early adulthood?" Journal of Pediatrics **161**(3): 390-396 e391.

OBJECTIVE: To investigate the effect of preterm birth on risk factors for cardiovascular disease (CVD), independent of birth size. STUDY DESIGN: Observational study using data of 406 healthy participants aged 18-24 years, from the PROgramming factors for Growth And Metabolism and Prematurity and Small for Gestational Age studies. Associations between gestational age (GA), systolic blood pressure (SBP), diastolic blood pressure (DBP), pulse pressure (PP), blood pressure variability, heart rate (HR), pulse wave velocity, and carotid intima media thickness (cIMT) were studied. To study the differential effects of preterm birth and small birth size for gestational age, these parameters were also analyzed in subgroups born either preterm or term: young adults born small for gestational age with short or normal adult stature, and young adults born appropriate for gestational age with normal adult stature. RESULTS: Subjects born preterm (GA <36 weeks) had higher unadjusted SBP, PP, SBP and DBP variability, and HR, but a lower DBP than subjects born term. GA was inversely associated with SBP, PP, blood pressure variability, and HR, and positively associated with DBP, also after adjustment for confounders. There was no effect of GA on pulse wave velocity and cIMT, a marker of atherosclerosis. Of all the CVD risk factors measured, higher PP affected cIMT the most. CONCLUSIONS: Young adults born preterm might have a higher risk for CVD than those born term.

IA Note - Studied relationships between preterm and and BP, heart rate, pulse wave velocity, and carotid intima media thickness. Individuals born preterm had higher unadjusted BP and heart rate. GA was inversely assoc with BP, and heart rate, after adjusting for confounders. Individuals born preterm have a higher risk for CVD.

Larnkjær, A., et al. (2010). "Effect of growth in infancy on body composition, insulin resistance, and concentration of appetite hormones in adolescence." The American Journal of Clinical Nutrition **91**(6): 1675-1683.

Background: High infancy weight gain is associated with increased body mass index (BMI) and insulin resistance (IR) in later life, but the association with later body composition has not been well explored. Appetite regulatory hormones may be programmed in early life, but data to support this are lacking. Objective: We investigated the effect of weight gain in infancy on body composition, IR, leptin, ghrelin, and adiponectin at 17 y of age. Design: This was an observational study of 95 term and appropriate-for-gestational-age infants. We measured weight at birth and 9 mo of age and, for a subgroup (n = 60), at 3 and 6 mo of age. Changes in weight SD scores from 0 to 9, 0 to 3, 3 to 6, and 6 to 9 mo of age were calculated. Follow-up examinations at 10 and 17 y of age included body fat (BF) assessment by dual-energy X-ray absorptiometry scanning. We measured serum leptin, ghrelin, adiponectin, and IR at 17 y of age. Results: Weight gain from 0 to 9 mo of age was positively associated with BMI (P < 0.003), percentage BF (P < 0.05), and percentage trunk fat (TF) (P < 0.03) but not with percentage TF relative to total BF, in childhood and adolescence, and most of these effects were explained by growth from 0 to 3 mo of age. Weight gains from 0 to 9 and 0 to 3 mo of age were not related to IR or leptin but were negatively associated with ghrelin and adiponectin corrected for BF at 17 y of age. Conclusion: Our findings suggest that high weight gain in infancy, especially from 0 to 3 mo of age, has a role in programming both BF and concentrations of ghrelin and adiponectin in adolescence, whereas there was no effect on IR or leptin in this study.

IA Note - Studied effect in 95 infants (AGA and term) of weight gain in infancy on body composition, IR, leptin (peptide hormone neurotransmitter produced by fat cells and involved in the regulation of appetite), ghrelin, and adiponectin at 17 y of age. Weight gain from 0-3 mo relate to body fat, but not related to IR or leptin. However, early weight gain was related to ghrelin (hunger stimulating peptide, involved in growth hormone secretion) and adiponectin (hunger stimulating peptide and a hormone that regulates glucose levels and fatty acid breakdown).

Law, C. M., et al. (2002). "Fetal, Infant, and Childhood Growth and Adult Blood Pressure." Circulation **105**(9): 1088-1092.

Background— People who are small at birth tend to have higher blood pressure in later life. However, it is not clear whether it is fetal growth restriction or the accelerated postnatal growth that often follows it that leads to higher blood pressure. Methods and Results— We studied blood pressure in 346 British men and women aged 22 years whose size had been measured at birth and for the

first 10 years of life. Their childhood growth was characterized using a conditional method that, free from the effect of regression to the mean, estimated catch-up growth. People who had been small at birth but who gained weight rapidly during early childhood (1 to 5 years) had the highest adult blood pressures. Systolic pressure increased by 1.3 mm Hg (95% CI, 0.3 to 2.3) for every standard deviation score decrease in birth weight and, independently, increased by 1.6 mm Hg (95% CI, 0.6 to 2.7) for every standard deviation score increase in early childhood weight gain. Adjustment for adult body mass index attenuated the effect of early childhood weight gain but not of birth weight. Relationships were smaller for diastolic pressure. Weight gain in the first year of life did not influence adult blood pressure. **Conclusions**— Part of the risk of adult hypertension is set in fetal life. Accelerated weight gain in early childhood adds to this risk, which is partly mediated through the prediction of adult fatness. The primary prevention of hypertension may depend on strategies that promote fetal growth and reduce childhood obesity.

IA Note - Studied what affects more risk of HTN, small at birth or accelerated postnatal growth. Small at birth individuals had the highest BP in adulthood systolic pressure increased 1.3 mm Hg for every 1 z score decrease in BW and 1.6 mmHg increase for every 1 z score increase in childhood weight (although this was not true anymore once it was adjusted for adult BMI index) **WEIGHT GAIN IN FIRST YEAR OF LIFE DID NOT INFLUENCE ADULT BLOOD PRESSURE.**

Leunissen, R. W., et al. (2009). "Timing and tempo of first-year rapid growth in relation to cardiovascular and metabolic risk profile in early adulthood." *JAMA* **301**(21): 2234-2242.

**CONTEXT:** Growth during infancy appears to be an important determinant of cardiovascular disease and type 2 diabetes later in life. **OBJECTIVES:** To specify which period in the first year of life is related to determinants of cardiovascular disease and type 2 diabetes in early adulthood and to investigate the association between tempo of first-year weight gain (>0.67 SDs) and these determinants. **DESIGN, SETTING, AND PARTICIPANTS:** Observational study using longitudinal data collected in the Programming Factors for Growth and Metabolism (PROGRAM) study of 217 healthy participants, aged 18 to 24 years, including a relatively large sample of participants born small for gestational age and participants with short stature, performed at a medical center in The Netherlands between August 2004 and September 2007. The association of cardiovascular disease and type 2 diabetes with tempo of weight gain was assessed in a subgroup of 87 participants. **MAIN OUTCOME MEASURES:** Associations between periods of first-year growth and tempo of weight gain and determinants of cardiovascular disease and type 2 diabetes in early adulthood. **RESULTS:** Weight

gain in the first 3 months of life was inversely associated with insulin sensitivity (beta, -0.223; 95% confidence interval [CI], -0.386 to -0.060) and serum high-density lipoprotein cholesterol level (beta, -0.053; 95% CI, -0.090 to -0.016) and positively associated with waist circumference (beta, 1.437; 95% CI, 0.066 to 2.808), acute insulin response (beta, 0.210; 95% CI, 0.024 to 0.395), ratio of total cholesterol to high-density lipoprotein cholesterol (beta, 0.052; 95% CI, 0.010 to 0.094), and level of triglycerides (beta, 0.066; 95% CI, 0.003 to 0.129) in early adulthood. Rapid weight gain during the first 3 months of life resulted in a higher percentage of body fat, more central adiposity, and reduced insulin sensitivity in early adulthood than when slower weight gain occurred during the entire first year. CONCLUSION: Rapid weight gain in the first 3 months of life is associated with several determinants of cardiovascular disease and type 2 diabetes in early adulthood.

IA Note - Determine when between birth and 2 years old is weight gain more important for CVD and T2DM risk and what is the tempo of weight gain and increased risk for CVD and T2DM in the first year. Weight gain 0-3 was inversely associated with insulin sensitivity and HDL and positively assoc with waist circum, acute ins response, ratio of chol to HDL, and triglyc in early adulthood. Rapid early weight gain 0-3 mo meant higher BF, central adiposity, and lower insulin sensitivity in early adulthood.

Nazmi, A., et al. (2009). "Life course weight gain and C-reactive protein levels in young adults: findings from a Brazilian birth cohort." *Am J Hum Biol* **21**(2): 192-199.

Rapid weight gain in childhood is associated with increased risk of chronic diseases in adults. C-reactive protein (CRP) is a mediator of atherosclerosis and chronically elevated levels predict cardiovascular outcomes. The effects of life course weight gain on CRP levels are not clear. The 1982 Pelotas (Brazil) birth cohort study (n = 5,914) has prospectively collected weight and health data at several follow-ups since birth. The most recent was in 2004-05, when 77.4% of the cohort was traced and CRP levels were measured in 89% of those interviewed (n = 3827). Geometric mean (SE) C-reactive protein levels were 0.89 mg/l (0.03) and 1.66 mg/l (0.04) in men and women, respectively. In analyses adjusted for confounding variables, weight gain in infancy showed a weak negative association among males, but from the second year onwards, weight gain was positively associated with CRP levels. In females, weight gain was associated with higher CRP at every period tested. The strongest associations were observed in the most recent (18-23 years) period; CRP ratios (95% CI) per z score increase in weight gain were 1.78 (1.57-2.00) and 1.52 (1.30-1.78) for men and women, respectively. Males who were stunted at 2 years and centrally obese at 23 years

had the highest CRP levels ( $P = 0.002$  for interaction). In summary, rapid weight gain throughout life predicted higher CRP levels. Public health efforts need to tackle chronic under-nutrition in infancy, together with rapid weight gain in later childhood and adolescence, especially in countries undergoing the nutritional transition.

IA Note - CRP levels are known to predict CVD outcomes. In males from 2 years of age weight gain predicted CRP levels, in females weight gain predicted CRP levels at all ages.

Norris, S. A., et al. (2012). "Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts." *Diabetes Care* **35**(1): 72-79.

OBJECTIVE: We examined associations of birth weight and weight gain in infancy and early childhood with type 2 diabetes (DM) risk in five cohorts from low- and middle-income countries. RESEARCH DESIGN AND METHODS: Participants were 6,511 young adults from Brazil, Guatemala, India, the Philippines, and South Africa. Exposures were weight at birth, at 24 and 48 months, and adult weight, and conditional weight gain (CWG, deviation from expected weight gain) between these ages. Outcomes were adult fasting glucose, impaired fasting glucose or DM (IFG/DM), and insulin resistance homeostasis model assessment (IR-HOMA, three cohorts). RESULTS: Birth weight was inversely associated with adult glucose and risk of IFG/DM (odds ratio 0.91[95% CI 0.84-0.99] per SD). Weight at 24 and 48 months and CWG 0-24 and 24-48 months were unrelated to glucose and IFG/DM; however, CWG 48 months-adulthood was positively related to IFG/DM (1.32 [1.22-1.43] per SD). After adjusting for adult waist circumference, birth weight, weight at 24 and 48 months and CWG 0-24 months were inversely associated with glucose and IFG/DM. Birth weight was unrelated to IR-HOMA, whereas greater CWG at 0-24 and 24-48 months and 48 months-adulthood predicted higher IR-HOMA (all  $P < 0.001$ ). After adjusting for adult waist circumference, birth weight was inversely related to IR-HOMA. CONCLUSIONS: Lower birth weight and accelerated weight gain after 48 months are risk factors for adult glucose intolerance. Accelerated weight gain between 0 and 24 months did not predict glucose intolerance but did predict higher insulin resistance.

IA Note - Studied the association between DM risk factors and BW and weight 24 to 48 mo of age. Lower BW and ACCELERATED weight gain after 48 mo assoc to insulin resistance (but NOT glucose intolerance), a known risk factor for DM.

Ong, K., et al. (2000). "Size at birth and cord blood levels of insulin, insulin-like growth factor I (IGF-I), IGF-II, IGF-binding protein-1 (IGFBP-1), IGFBP-3, and the soluble IGF-



II/mannose-6-phosphate receptor in term human infants. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood." *Journal of Clinical Endocrinology and Metabolism* 85(11): 4266-4269.

Experimental rodent studies demonstrate that insulin-like growth factor II (IGF-II) promotes fetal growth, whereas the nonsignaling IGF-II receptor (IGF2R) is inhibitory; in humans their influence is as yet unclear. A soluble, circulating form of IGF2R inhibits IGF-II mediated DNA synthesis and may therefore restrain fetal growth. We measured cord blood levels of IGF-II, soluble IGF2R, insulin, IGF-I, IGF-binding protein-1 (IGFBP-1), and IGFBP-3 and examined their relationships to weight, length, head circumference, ponderal index, and placental weight at birth in 199 normal term singletons. IGF-II levels correlated with levels of IGF-I ( $r = 0.29$ ;  $P < 0.0005$ ), IGFBP-3 ( $r = 0.45$ ;  $P < 0.0005$ ), and soluble IGF2R ( $r = 0.20$ ;  $P < 0.005$ ). Insulin and IGF-I were positively related to all parameters of size at birth. IGF-II was weakly related to ponderal index ( $r = 0.18$ ;  $P < 0.05$ ) and placental weight ( $r = 0.18$ ;  $P < 0.05$ ), and the molar ratio of IGF-II to IGF2R was also related to birth weight ( $r = 0.15$ ;  $P < 0.05$ ). Correlations between the IGFs and size at birth were stronger in nonprimiparous pregnancies; in these, IGF-I ( $r = 0.52$ ;  $P < 0.0005$ ), IGFBP-3 ( $r = 0.41$ ;  $P < 0.0005$ ), and the IGF-II to IGF2R ratio ( $r = 0.40$ ;  $P < 0.0005$ ) were most closely related to placental weight, together accounting for 39% of its variance. We demonstrate for the first time relationships between circulating IGF-II and soluble IGF2R levels and size at birth, supporting their putative opposing roles in human fetal growth.

IA Note - Using 0.67 w/a z score is arbitrary and may not apply to US pop. In this study confounders such as maternal weight and paternal height, maternal smoking, and parity were considered clearly other mediating variables needs to be included (e.g. feeding dynamics, method of feeding, etc.) to explain better the relationship between weight and catch-up growth.

Ong, K. K. and R. J. Loos (2006). "Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions." *Acta Paediatrica* **95**(8): 904-908.

In a systematic review, we identified 21 separate studies with data on the association between rapid infancy weight gain, up to age 2 y, and subsequent obesity risk. Uniformly all studies reported significant positive associations. We transformed the reported effect sizes to a standard infancy weight gain exposure, and found that further differences in study design accounted for much of the variation in risk. An accompanying paper by Melinda Yeung reminds us that there are benefits of postnatal catch-up growth in certain populations, and suggests that genetic and nutritional factors could moderate the unhealthy translation of rapid infancy weight gain to visceral fat and insulin resistance. Further evidence is



needed, and we will need to rigorously test the benefits and risks of any interventions. However, the concept of "healthy" rapid catch-up infancy growth is an attractive prospect. CONCLUSION: Rapid infancy weight gain is consistently associated with increased subsequent obesity risk, but the predictive ability of different weight gain cut-offs needs to be tested.

IA Note - Systematic review - 21 separate studies about rapid early infancy weight (up to 2 yr of life) and risk of obesity. Methodologic differences makes it difficult to assess risk of obesity. 'Nutritional Factors' could moderate the different outcomes: insulin resistance and CVD.

Plagemann, A. (2005). "Perinatal programming and functional teratogenesis: impact on body weight regulation and obesity." *Physiology and Behavior* **86**(5): 661-668.

It is increasingly accepted that alterations of the intrauterine and early postnatal nutritional, metabolic, and hormonal environment may cause predispositions for the development of diseases in later life. Studies in the offspring of diabetic mothers have decisively contributed to this perception. Alterations of the fetal and neonatal environment which offspring of diabetic mothers 'experience' seem to program a disposition to develop obesity, diabetes mellitus and Syndrome X-like alterations throughout later life. Underweight at birth is also suggested to lead to an increased risk of Syndrome X in later life ('Barker hypothesis'). Pathophysiological mechanisms are unclear. Hormones are important environment-dependent organizers of the developing neuro-endocrine-immune network, which finally regulates all fundamental processes of life. When present in non-physiological concentrations during 'critical periods' of perinatal life, induced by alterations in the intrauterine or neonatal environment, hormones can act as 'endogenous functional teratogens'. Perinatal hyperinsulinism is pathognomonic in the offspring of diabetic mothers. Early hyperinsulinism also occurs as a result of early postnatal overfeeding. In rats, endogenous hyperinsulinism, as well as peripheral or only intrahypothalamic insulin treatment during perinatal development, may lead to 'malprogramming' of neuroendocrine systems regulating body weight, food intake and metabolism. This results in an increased disposition to become obese and to develop diabetes throughout life. In conclusion, a complex malprogramming of the central regulation of body weight and metabolism may provide a general etiopathogenetic concept, explaining perinatally acquired dispositions, thereby opening a wide field of primary prevention.

IA Note - Perinatal effects on adult diseases are being recognized. Underweight at birth may increase the risk for Syndrome X later in life (Barker's hypothesis). Early high insulin levels occur due to overfeeding or having a mother with DM this

'program' people to have neuro-endocrine-immune anomalies that increase the risk of disease in adulthood.

Singhal, A., et al. (2003). "Low nutrient intake and early growth for later insulin resistance in adolescents born preterm." The Lancet **361** 1089-1097.

**Summary** Background In animals, acceleration of neonatal growth is thought to increase the later propensity to insulin resistance and non-insulin-dependent diabetes, whereas slow growth as a consequence of undernutrition is thought to have a beneficial effect. To test this hypothesis in people, we measured fasting concentrations of 32–33 split proinsulin, a marker of insulin resistance, in adolescents born preterm who had participated in randomised intervention trials of neonatal nutrition, and in adolescents born at term. **Methods** We determined fasting 32–33 split proinsulin concentration in participants aged 13–16 years born preterm and randomised to receive a nutrient-enriched or lower-nutrient diet (n=216) or in a reference group born at term (n=61). **Findings** Fasting 32–33 split proinsulin concentration was greater in children given a nutrient-enriched diet (geometric mean 7.2 pmol/L, 95% CI 6.4–8.1) than in those given the lower-nutrient diet (5.9 pmol/L [5.2–6.4]; mean difference 20.6% [5.0–36.3]; p=0.01). Healthy babies born at term had similar fasting 32–33 split proinsulin concentrations (6.9 pmol/L; 6.0–8.2) to the nutrient-enriched group. In non-randomised analyses, fasting 32–33 split proinsulin concentration was associated with greater weight gain in the first 2 weeks of life (13.2% [5.4–20.9] change per 100 g weight increase; p=0.001) independent of birthweight, gestation, neonatal morbidity, and demographic, anthropometric, and socioeconomic factors. **Interpretation** Our results suggest that relative undernutrition early in life in children born preterm may have beneficial effects on insulin resistance.

IA Note - Studied pre-term babies who received enriched formula or standard formula and a control term normal group (n=61) whose diet is unclear. Premies fed enriched formula AND control group had high ~21% higher 32-32 split proinsulin concentration compared to premies fed standar formula. Randomized control trial, but breastfed babies were NOT randomized (per author). This introduces bias because one it is allowed for parents to choose behaviors that may influence the endpoint, how is it possible toknow that the results are due to the intervention or other variables?

Singhal, A., et al. (2007). "Promotion of faster weight gain in infants born small for gestational age: is there an adverse effect on later blood pressure?" Circulation **115**(2): 213-220.

**BACKGROUND:** Being born small for gestational age is associated with later risk factors for cardiovascular disease, such as high blood pressure. Promotion of postnatal growth has been proposed to ameliorate these effects. There is evidence in animals and infants born prematurely, however, that promotion of growth by increased postnatal nutrition increases rather than decreases later cardiovascular risk. We report the long-term impact of growth promotion in term infants born small for gestational age (birth weight <10th percentile). **METHODS AND RESULTS:** Blood pressure was measured at 6 to 8 years in 153 of 299 (51%) of a cohort of children born small for gestational age and randomly assigned at birth to receive either a standard or a nutrient-enriched formula. The enriched formula contained 28% more protein than standard formula and promoted weight gain. Diastolic and mean (but not systolic) blood pressure was significantly lower in children assigned to standard compared with nutrient-enriched formula (unadjusted mean difference for diastolic blood pressure, -3.2 mm Hg; 95% CI, -5.8 to -0.5;  $P=0.02$ ) independent of potential confounding factors (adjusted difference, -3.5 mm Hg;  $P=0.01$ ). In observational analyses, faster weight gain in infancy was associated with higher later blood pressure. **CONCLUSIONS:** In the present randomized study targeted to investigate the effect of early nutrition on long-term cardiovascular health, we found that a nutrient-enriched diet increased later blood pressure. These findings support an adverse effect of relative "overnutrition" in infancy on long-term cardiovascular disease risk, have implications for the early origins of cardiovascular disease hypothesis, and do not support the promotion of faster weight gain in infants born small for gestational age.

Stettler, N., et al. (2003). "Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans." *American Journal of Clinical Nutrition* **77**(6): 1374-1378.

**BACKGROUND:** Obesity is increasing in the United States. Evidence-based prevention is a public health priority and should target well-defined risk factors and critical periods. **OBJECTIVE:** We tested the hypothesis that rapid weight gain during early infancy is associated with obesity in African American young adults, a group at increased risk of obesity. **DESIGN:** A cohort of 300 African Americans born at full term was followed from birth to 20 y of age. A pattern of rapid weight gain was defined as an increase in weight-for-age  $\geq 1$  SD between birth and 4 mo. **RESULTS:** About 29% of subjects had a pattern of rapid weight gain during infancy; 8% were obese [body mass index (in  $\text{kg}/\text{m}^2$ )  $\geq 30$ ] at age 20 y. One-third of the obesity at age 20 y could be attributed to rapid weight gain in the first 4 mo of life. After adjustment for confounding factors, subjects with rapid

weight gain during early infancy were more likely to become obese at age 20 y (odds ratio = 5.22; 95% CI: 1.55, 17.6; P = 0.008). The results were confirmed by using a combination of body mass index and skinfold thickness (odds ratio = 6.72; 95% CI: 1.93, 23.4; P = 0.003). CONCLUSIONS: The results of the present study provide evidence that a pattern of rapid weight gain during early infancy is associated with obesity not only in childhood but also in young adulthood. We propose that early infancy constitutes a critical period for the development of obesity. Mechanisms of action and prevention strategies require further investigation.

IA Note - Rapid early weight gain is assoc with obesity young African American adults. 29% had rapid early weight gain, 8% were obese as young adults. One third of obese as young adults was related to early rapid weight gain.

Stettler, N., et al. (2005). "Weight gain in the first week of life and overweight in adulthood: a cohort study of European American subjects fed infant formula." Circulation **111**(15): 1897-1903.

BACKGROUND: Successful prevention of obesity and related cardiovascular risk factors requires a clear understanding of its determinants over the life course. Rapid infancy weight gain is associated with childhood obesity, whereas low infancy weight is associated with coronary heart disease. Our aim was to identify during which periods in infancy weight gain is associated with adult obesity. METHODS AND RESULTS: A cohort of European American formula-fed subjects, measured on 7 occasions during infancy as part of several infant formula studies, were contacted at age 20 to 32 years, when they reported usual adult weight and height. A life-course plot was used to identify critical periods of weight gain associated with adulthood overweight (body mass index  $>$  or  $=25$  kg/m<sup>2</sup>). These associations were tested with logistic regressions. Data were available for 653 subjects (72% of eligible subjects). Approximately 32% of them were overweight adults. The period between birth and age 8 days was identified as potentially critical. After adjustment for important confounding factors, weight gain during the first week of life was associated with adulthood overweight status (OR for each 100-g increase 1.28, 95% CI 1.08 to 1.52), as was weight gain during the first 112 days of life (OR 1.04, 95% CI 1.01 to 1.08). Similar results were obtained after standardization with z scores from a reference population. CONCLUSIONS: In formula-fed infants, weight gain during the first week of life may be a critical determinant for the development of obesity several decades later. These results contribute to the understanding of chronic disease programming and suggest new approaches to obesity prevention.

IA Note - Studied European American individuals. Identify which period in infancy (in formula fed infants) is most assoc with adult obesity. Weight gain in first week of life and first 112 days of life were most assoc with adult overweight.

Woods, K.A., et al.(2002). "The somatotrophic axis in short children born small for gestational age: relation to insulin resistance." Pediatric Research **51**(1):76-80

To determine whether hyperinsulinemia and reduced insulin sensitivity in individuals born small for gestational age (SGA) could be related to persisting abnormalities of the GH/IGF-I axis, we assessed overnight GH secretory profiles and measured fasting glucose, insulin, intact and 32,33 split proinsulin, and IGF-I levels in 16 short SGA children (age range 2.3-8.0 y) and in controls. Insulin sensitivity was calculated using the homeostasis model. Compared with short normal-birthweight controls (n = 7, age range 2.3-5.0 y), short SGA children had higher fasting insulin levels (means: 26.8 vs 20.6 pmol/L, p = 0.02), lower insulin sensitivity [means: 204 vs 284 %homeostasis model assessment (HOMA), p = 0.01], and higher beta cell function (112 vs 89 %HOMA, p = 0.04). SGA children also had lower levels of IGFBP-1 (87.0 vs 133.8, p = 0.04), but similar IGF-I levels (IGF-I SDS: -1.1 vs -1.7, p = 0.4). Compared with normal-height controls (n = 15, age range 5.6-12.1 y), SGA children had higher overnight GH secretion (GH maximum: 55.9 vs 39.6 mU/L, p = 0.01; mean: 13.1 vs 8.9, p = 0.004; minimum: 1.2 vs 0.6, p = 0.02). Interestingly, among SGA children, fasting insulin levels and insulin sensitivity were significantly related to overnight GH secretion (insulin sensitivity vs maximum GH: r = -0.68, p = 0.01; vs GH pulse amplitude r = -0.71, p = 0.007). The only hormone level significantly related to current height velocity was C-peptide (r = 0.75, p = 0.008). In conclusion, elevated fasting insulin levels and reduced insulin sensitivity in short SGA children was related to elevated levels of overnight GH secretion. We hypothesize that resistance to the somatotrophic actions of GH and IGF-I in short SGA children may contribute directly to reduced insulin sensitivity.

IA Note - Small study of 16 short SGA (SGA who did not achieve catch up growth) and 7 short normal BW controls with detailed investigation of glucose and growth hormone metabolism (hyperinsulinemia and insulin sensitivity). Results showed short SGA children had lower insulin sensitivity, but higher beta cell function suggesting compensatory hyperinsulinemia (higher fasting insulin levels). Both short SGA and short normal BW had similar high levels of IGF-1, which reflects insulin resistance.

