Saga Nummela

Early Weight Gain in Infancy and Markers of Cardiometabolic Health in Young Adulthood

Syventävien opintojen kirjallinen työ

Kevätlukukausi 2022

Saga Nummela

Early Weight Gain in Infancy and Markers of Cardiometabolic Health in Young Adulthood

Turun yliopisto: Sydäntutkimuskeskus

Kevätlukukausi 2022

Vastuuhenkilö: Harri Niinikoski

Turun yliopisto

Lääketieteellinen tiedekunta

Nummela Saga : Early Weight Gain in Infancy and Markers of Cardiometabolic Health in Young Adulthood

Syventävien opintojen kirjallinen työ, 11 s., 3 liites.

HUHTIKUU 2022

It has been suggested that birth weight predicts risk for later non-communicable diseases. Further studies have shown that not only birth weight, but also early postnatal growth may predict later disease risk.

Using the data collected in the longitudinal Special Turku Coronary Risk Factor Intervention Project this study investigated in 454 healthy subjects how early weight gain in six age intervals (birth to 7 months, 7–13 months, 13–18 months, 18–24 months, and birth to 13 and 24 months) associates with measures of cardiometabolic health at age 20 years. Linear regression analyses were controlled for 1) child's sex, intervention/control group, gestational age, baseline weight and change in length for each interval, and 2) parents' education, mother's weight before pregnancy, height, and weight gain during pregnancy, and father's body mass index at the 7-month visit.

Weight gain after the first year of life associated directly, when adjusted for traits of the child and parents, with systolic blood pressure, waist circumference and body mass index at age 20 years. In the fully adjusted analyses weight gain from birth to 1 year and to 2 years of age associated inversely with insulin and insulin resistance. This study found no association between early growth and diastolic blood pressure or serum lipids.

Weight gain in early life is directly linked with body mass index, waist circumference and systolic blood pressure in young adulthood. Excess weight gain during transition from infant feeding to a diet similar to the family may be of utmost significance. Prevention of cardiovascular disease should begin in infancy.

Avainsanat: lapsuus, kasvu, terveys

Early Weight Gain in Infancy and Markers of Cardiometabolic Health in Young Adulthood

Authors: Saga Nummela, Pia Salo, Katja Pahkala, Olli Raitakari, Jorma Viikari, Tapani Rönnemaa, Antti Jula, Suvi P Rovio, Harri Niinikoski.

Acronyms and Abbreviations

Abbreviations: BW, birth weight. STRIP, Special Turku Coronary Risk Factor Intervention Project. BP, blood pressure. SES, socioeconomical status. BMI, body mass index. WC, waist circumference. CVD, cardiovascular disease. HDL-C, high-density lipoprotein cholesterol. LDL-C, low-density lipoprotein cholesterol. HOMA-IR, homeostatic model assessment of insulin resistance. SD, standard deviation. CI, confidence interval. SDS, standard deviation scores.

Abstract

Aim: We studied whether repeatedly measured weight gain from birth up to age 2 years associates with cardiometabolic health in young adulthood.

Methods: Using the data collected in the longitudinal Special Turku Coronary Risk Factor Intervention Project we investigated in 454 healthy subjects how early weight gain in six age intervals (birth to 7 months, 7–13 months, 13–18 months, 18–24 months, and birth to 13 and 24 months) associates with measures of cardiometabolic health at age 20 years. Linear regression analyses were controlled for 1) child's sex, intervention/control group, gestational age, baseline weight and change in length for each interval, and 2) parents' education, mother's weight before pregnancy, height, and weight gain during pregnancy, and father's body mass index at the 7-month visit.

Results: Weight gain after the first year of life associated directly, when adjusted for traits of the child and parents, with systolic blood pressure, waist circumference and body mass index at age 20 years. In the fully adjusted analyses weight gain from birth to 1 year and to 2 years of age associated inversely with insulin and insulin resistance. We found no association between early growth and diastolic blood pressure or serum lipids.

Conclusions: Early weight gain during first 2 years of life may predict later markers of cardiometabolic health.

Keywords: Infancy, weight gain, cardiometabolic health.

Keynotes: Weight gain in early life is directly linked with body mass index, waist circumference and systolic blood pressure in young adulthood. Excess weight gain during transition from infant feeding to a diet similar to the family may be of utmost significance. Prevention of cardiovascular disease should begin in infancy.

Introduction

It has been suggested that birth weight (BW) predicts risk for later non-communicable diseases. (1,2,3) Further studies have shown that not only BW, but also early postnatal growth may predict later disease risk. (2) Low BW combined with rapid early weight gain is thought to increase the later risk factors for cardiovascular disease (CVD) more than low BW alone. (2,4,5) Similar results have been obtained in studies on infants with high BW, in whom rapid early weight gain also predicted a higher risk for later obesity. (3) Previous reviews have shown a link between rapid postnatal weight gain and increased risk for later obesity and CVD risk factors. (6,7,8) Rapid early weight gain has also been associated with higher blood pressure (BP) measured in children and adults. (9) Studies on the associations between of early growth with insulin resistance and risk for type 2 diabetes have found contradicting results (10). There also are indications that childhood socioeconomical status (SES) affects later risk for obesity and later CVD risk. (11)

Only few previous studies can combine early growth data measured repeatedly during the first years of life with several cardiometabolic risk factors measured in early adulthood. To fill this gap in knowledge, we applied longitudinal data from the Special Turku Coronary Risk Factor Intervention Project (STRIP) that is a prospective, randomized, controlled infancy-onset trial that offers unique data to provide evidence on the associations of early weight gain with multiple markers of cardiometabolic health in adulthood. Additional uniqueness of the data is that it is collected prospectively with well-established methods, and it also comprises of a relatively large number of participants who were measured repeatedly. Therefore, leveraging the repeatedly measured STRIP Study data, we investigated the association between early weight gain, from birth to age 2 years, and cardiometabolic health markers measured at the age of 20 years.

Patients and Methods

STRIP Study Design

The STRIP Study is a prospective, infancy-onset, randomized controlled trial to prevent atherosclerosis risk factors beginning from age seven months and continuing to the age of 20 years. The recruitment of 5-month-old infants and their families began in March 1990 at well-baby clinics in Turku, Finland, and continued until June 1992. 1062 infants participated in the study and were subsequently randomly allocated into the intervention group (n=540) or control

group (n=522).

The intervention group received individualized dietary counselling at least biannually, beginning from 8 months of age until 20 years of age. The control group was seen biannually until 7 years of age and annually between ages 7 to 20 years. The intervention in the STRIP study consisted of a dietary intervention to improve dietary fat quality and reduce cholesterol intake, as well as to increase consumption of vegetables, fruit, and whole grains. Previous results have shown that the STRIP intervention was successful in decreasing saturated fat intake (12) and improving many cardiometabolic health markers (13). Better adherence to the dietary targets, regardless of study group allocation, was associated with a decreased intake of saturated fatty acids and a 0.1-0.2 mmol/L decrease in low-density lipoprotein cholesterol (LDL-C). (14) The control group received basic health education given at Finnish baby-well clinics and school health care. Both study groups met the same study personnel and similar measurements were performed on both groups.

Informed consent was obtained from the parents at the beginning of the study and from the children at the ages 15 years and 18 years. The study protocol of the STRIP Study is approved by the local ethics committee and the guidelines of the Declaration of Helsinki are followed accordingly. (12,15)

The present study included all study participants who took part in the study visit at the age of 20 years. Eighteen subjects were excluded from the present analyses because of known conditions that could have influence on growth, blood cholesterol/triglyceride values, or insulin measurements (two twin pairs, Down syndrome, familial hypercholesterolemia, type 1 diabetes mellitus, cerebral palsy, and other developmental disorders). Finally, data of 454 participants were used. Out of these 235 (51.8%) were female and 219 (48.2%) were male. Of the study population 45.1% (n=205) belonged to the intervention group and 54.9% to the control group (n=249).

Measurements of Growth and Blood Pressure

Mother’s pre-pregnancy and pregnancy data, and the BW of the infant were obtained from databases maintained by well-baby clinics and maternity hospitals. Father’s body mass index (BMI) and parents’ SES were collected during 7-month or 13-month study visits. Weight and height of the infant was measured at the 7-month, 13-month, 18-month and 24-month study visits. Measurements collected at the 20-year study visit included BP, weight, height,

BMI and waist circumference (WC).

Before the age of 18 months, weight was measured with an infant scale (model 725; Seca, Murrhardt, Germany), and an infant board (Bekvil; Paljerakenne, Helsinki, Finland) was used for the measurement of length before the age 24 months.

Measurement of weight at the age of 24 months and thereafter was done with an electronic scale (S10; Soehnle, Murrhardt, Germany) to the nearest 0.1 kg. Height was measured to the nearest 0.1 cm with a Harpenden stadiometer (Holtain, Crymych, U.K.) from the age of 24 months forwards. Using these measures, BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

WC was measured at the age of 20 years with a flexible measuring tape to the nearest 0.5 cm midway between the iliac crest and the lowest rib at the midaxillary line.

BP was measured at the age of 20 years twice using an oscillometric noninvasive blood pressure monitor (Criticon Dinamap Compact T) after ≥15 minutes of rest. Accuracy of the device was regularly tested against a mercury manometer. An appropriate cuff size was chosen according to the subject's right arm. The average of the two measurements was used in statistical analyses. (15–17)

Laboratory Methods

Markers of cardiometabolic health obtained at the 20-year study visit included serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), calculated LDL-C, triglycerides, glucose, insulin, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR). All analyses were done from serum samples obtained after an overnight fast and performed at the laboratory of the National Public Health Institute in Turku, Finland. (13)

For serum lipid analyses the blood samples were low-speed centrifuged after clotting at room temperature and the separated serum was frozen until analysed. Serum total cholesterol and triglyceride concentrations were measured using a fully enzymatic cholesterol oxidase-p-aminophenazone method (Merck, Darmstadt, Germany) with an automatic Olympus AU400 analyser. (15) Serum HDL-C concentration was analysed after precipitation of non-HDL-lipoproteins with dextran sulfate 500 000. (13) LDL-C concentration was calculated using the Friedewald formula, none of the participants had

triglycerides >4.25 mmol/L (>400 mg/dL). (15)
Serum glucose was measured by a hexokinase method (Glucose Olympus System Reagent, Olympus, Ireland, interassay CV 1.8%). For insulin analyses, the blood samples were centrifuged immediately and 30 µL Trasylol was added to the 0.5-mL serum sample and the samples were frozen until analysed. Serum insulin was measured by radioimmunoassay (Pharmacia Diagnostics, Uppsala,Sweden). (15) Insulin sensitivity was estimated by calculating HOMA-IR (fasting insulin mU/L X [fasting glucose (mmol/L) / 22.5]). (18)

Statistics

Normally distributed measures are reported with the mean value and standard deviation (SD).
Distributions of the continuous variables were evaluated visually and using the Kolmogorof-Smirnov-test. The differences in the amount of weight gain within six age intervals (birth to 7 months, 7–13 months, 13–18 months, 18–24 months and birth to 13 months and 24 months) were analysed using pooled t-test when assumption of equal variances was met and with Satterthwaite-test when variances were assumed unequal. The equality of variances was tested with the Levene's test.
Association between early weight gain in different age intervals and cardiovascular health markers at the age of 20 years was studied using linear regression analyses. Non-normally distributed measures were logarithmically transformed prior to the analyses (triglycerides, insulin, and HOMA-IR). Weight gain in the different age intervals were converted to standard deviation scores (SDS). The results from the linear regression analyses were presented as beta-value, 95% confidence interval (CI) of the regression line and p-value and as the impact of +1SD excess weight gain in all intervals.
Statistical analyses were first adjusted for traits of the child (sex, STRIP study group, gestational age, baseline weight for each interval, and change in length for each interval; Model 1) and after that additionally for traits of the parents (parents' education, mother's weight before pregnancy, height, and weight gain during pregnancy, and father's BMI; Model 2).
Weight gain within all the different age intervals was normally distributed (**Table 1**).
To investigate whether the associations between early growth and the cardiometabolic markers at age 20 years differ in males and females, we

introduced a sex*interaction term to the analyses using mixed model analysis of variance.

Statistical analyses were conducted using SAS statistical software, release 9.4 (SAS Institute Inc., Cary, NC, USA). P-values <0.05 were considered statistically significant.

Results

The mean increase in weight from birth to age 24 months was 9280 (SD=1284) grams. There was no significant difference in weight gain in any of the age intervals between the STRIP Study groups (intervention/control). Boys gained more weight than girls from birth to age 7 months, birth to age 13 months, and birth to age 24 months, whilst girls gained more weight than boys from age 18 to 24 months (**Table 1).**

BMI and Waist Circumference

In all age intervals, direct association between early weight gain and BMI at age 20 years was observed in the analyses adjusted for the child's traits (Model 1). In the fully adjusted analyses (Model 2), the association was significant for BMI in the 13 to 18 months, the 18 to 24 months, and the birth to 24 months intervals. From birth to 24 months, a +1SD excess weight gain was associated with a 0.98 kg/m^2 (95% CI 0.48 – 1.49 kg/m^2, p<0.001) higher BMI at age 20 years. **(Table 2, Model 2)**.

In all age intervals, a direct association between early growth and WC at age 20 years was observed in the analyses adjusted for the child's traits (Model 1). In the fully adjusted analyses (Model 2), the association was significant in the 13 to 18 months, the 18 to 24 months, and the birth to 24 months intervals. (**Table 2**). Between birth and 24 months a +1SD excess weight gain was associated with a 1.62 cm (95% CI 0.40 – 2.84 cm, p=0.01) higher WC at age 20 years. (**Table 2, Model 2**).

Blood Pressure

There was a direct association between early weight gain and systolic BP at age 20 years, but no significant associations were observed between early growth and diastolic BP.

In the analyses adjusted for the child's traits (Model 1), the association of early weight gain with systolic BP was significant in the 13 to 18 months and the birth to 24 months intervals. In the fully adjusted analyses (Model 2), the association of early weight gain with systolic BP was significant in the age interval 18 to 24 months. For +1SD excess weight gain during this interval, systolic BP increased by 1.83 mmHg (95% CI 0.30 – 3.36 mmHg, p=0.02) at age 20 years (Model 2). (**Table 2**).

Serum Lipids, Glucose, Insulin and HOMA-IR

No association was found between early weight gain and total cholesterol, HDL-C, LDL-C, or triglycerides measured at 20 years of age in models 1 or 2. (**table 3**) In the fully adjusted analyses (model 2) early weight gain associated inversely with glucose in the birth to 24 months interval, while insulin and HOMA-IR associated inversely with early weight gain in the birth to 13 months and the birth to 24 months intervals. (**table 4**).

Sex-interaction and Sex-specific Analyses

A significant sex-interaction was observed in seven analyses investigating the associations between early weight gain and the cardiometabolic markers at age 20 years: for BMI in the 7 to 13 months ($p<0.001$), 13 to 18 months ($p=0.01$), and birth to 13 months ($p=0.03$) age intervals; for WC in the 7 to 13 months ($p<0.001$), and 13 to 18 months ($p=0.02$) age intervals; for diastolic BP in the 18 to 24 months age interval ($p=0.002$); and finally for glucose in the birth to 13 months age interval ($p=0.03$). When subsequent sex-specific analyses were performed, the associations of early weight gain with diastolic BP and glucose remained non-significant in both males and females. (**data not shown**) For BMI and WC the association was stronger for females than for males in the sex-specific analyses. (**data not shown**).

Discussion

Studies have shown that metabolic measures obtained in childhood correlate with the same measures later in life (19) indicating that measures of BP, serum lipids and BMI in early adulthood can be considered to predict trends on measurements in middle age and later, when metabolic diseases and CVD become symptomatic.

The results in this study indicate that the weight gain during the first two years of life, especially in the 13 to 18 months and 18 to 24 months age intervals, is directly associated with BMI, WC and systolic BP measured at 20 years of age. Intriguingly, the transition from infant feeding to a diet similar to the older family members takes place during the second year of life. In addition to the changes in diet, this age interval coincides with increasing physical activity of the child. Excess weight gain in this age interval, where weight increase per month naturally decreases, seems to be of significance for future cardiometabolic health. Increased early weight gain could be connected to family food consumption and composition, suggesting that the dietary habits in the family start to shape later health early in life.

BMI and Waist Circumference

Our results indicate that increased weight gain during the first two years of life associates with a higher BMI and larger WC at 20 years of age. From birth to age 24 months the mean weight gain was 9.3 kg (SD 1.3 kg), and for a +1SD excess weight gain BMI measured at 20 years of age increased by 0.98 kg/m^2 and waist circumference increased by 1.62 cm, indicating an association that is clinically relevant.

Our results are in line with findings from studies focusing on the association between growth in infancy and risk for higher BMI later in life. (8,20) A systematic review found that rapid weight gain during the first year of life is associated with higher odds for later overweight than rapid weight gain from birth to two years. (20) In contrast to these findings, our study found the association between early weight gain and measures indicating higher adiposity at 20 years of age (higher BMI and bigger WC) to be stronger after the first year of life, in the 13–18 months, 18–24 months, and the birth to 24 months age intervals.

Blood pressure

We found a direct association between early weight gain and systolic BP in young adulthood. For a +1SD excess weight gain from 18 to 24 months, systolic BP measured at 20 years of age increased by 1.83 mmHg, indicating an association that is clinically relevant. BW as well as rapid postnatal growth have previously been associated with increased adult systolic BP. (21)

Total Cholesterol, HDL-C, LDL-C, Triglycerides

Some studies have found rapid early growth to predict higher levels of future triglycerides, total cholesterol and LDL-C, and lower levels of HDL-C (22) while other studies have found no association between early growth and serum lipids. (23) In this study, we found no association between early growth and any of the serum lipids measured at 20 years of age.

Fasting Glucose, serum Insulin and Insulin Resistance

Results from previous studies have been contradicting, finding both reduced (24) and increased (25) growth in infancy to predict later insulin resistance. Our results indicate there to be an inverse association between increased growth and later insulin resistance in the fully adjusted analyses, suggesting reduced growth in infancy to predict later insulin resistance. Taken together the findings from our and the previous studies, no firm conclusion can be made on the association between early weight gain and later serum glucose, insulin, and insulin resistance.

Sex-specific Analyses

Sex-specific analyses indicated that the associations of early weight gain with BMI and WC were stronger for females, but the directions of the associations were similar in both sexes. Diluted associations may be due to the decreased number of participants when males and females were analysed separately, combined with a relatively large inter-individual variation in weight gain.

Strengths and Limitations

The strengths of the STRIP Study are use of well-established methods, long follow-up period from infancy to young adulthood, and large number of repeatedly studied participants. Furthermore, the vast majority of the infants were adequate for gestational age. This study focused on the weight gain from birth to two years of age. The age intervals were chosen based on the available data from the STRIP Study, where the first study visit was at 7-months with the following study visits at 13, 18 and 24 months. This gave us an opportunity to study how early weight gain during approximately 6 month intervals associates with markers of cardiometabolic health at 20 years of age.

A potential limitation of the STRIP study is the possible selection bias in the recruitment of the subjects, as the participating families might have been more

health oriented than the non-participants, possibly affecting the association of early growth with later cardiometabolic health because of health awareness. Also, the extensive 20-year study period inevitably caused loss to follow-up among the participants. During the first study years, the most common reasons for discontinuation were moving away from the Turku area, recurrent infections, and reluctance to have blood sampled. (26) Loss to follow-up has been stable, with no apparent peaks. The characteristics of study participants and who were lost to follow-up have been compared (26), and no significant differences in body weight, BMI, serum total cholesterol, or saturated fat intake have been found. Thus, a systematic selection bias should not have influenced the present findings. While the intervention conducted in the STRIP study did not affect early weight gain, we chose additionally to control our analyses with belonging to the control or intervention group.

A limitation of this study also is that we did not account for breastfeeding or its duration. Information on the duration of breastfeeding was partly retrospective and not always available. Solid foods were introduced at 3–5 months and the mean duration of breastfeeding was 5 (SD 4, range 0–12) months in both the intervention and control groups. All infants were weaned and had changed from infant formulas to cows' milk by 1 year of age. (27) Breastfeeding has been suggested to decrease the risk for obesity and for type 2 diabetes and it seems to protect more from risk of obesity in childhood and adolescence than from obesity in adulthood. (28)
All subjects in the STRIP study are Caucasian, thus the results may not be generalizable to other ethnicities.

Conclusions

Early weight gain, especially during the second year of life, is linked with markers of cardiometabolic health - BMI, WC, systolic BP, insulin and insulin resistance - in young adulthood. Prevention of CVD should begin in infancy. Investing in nutrition and lifestyle counselling during early childhood, especially during and after weaning, is of importance for later cardiometabolic health.

References

(1) Barker DJ, Osmond C, Golding J, Kuh D, Wadsworth ME. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. BMJ. 1989 Mar 4;298(6673):564-7.

(2) Kelishadi R, Haghdoost AA, Jamshidi F, Aliramezany M, Moosazadeh M. Low birthweight or rapid catch-up growth: which is more associated with cardiovascular disease and its risk factors in later life? A systematic review and cryptanalysis. Paediatr Int Child Health 2015 May;35(2):110-123.

(3) Woo Baidal JA, Locks LM, Cheng ER, Blake-Lamb TL, Perkins ME, Taveras EM. Risk factors for childhood obesity in the first 1,000 days: a systematic review. Am J Prev Med. 2016 Jun;50:761-779.

(4) Singhal A, Cole TJ, Fewtrell M, Deanfield J, Lucas A. Is slower early growth beneficial for long-term cardiovascular health? Circulation. 2004 Mar;109(9):1108-13.

(5) Eriksson JG, Forsén T, Tuomilehto J, Osmond C, Barker DJ. Early growth and coronary heart disease in later life: longitudinal study. BMJ. 2001 Apr 21;322(7292):949-53. doi: 10.1136/bmj.322.7292.949. PMID: 11312225; PMCID: PMC31033.

(6) Ong KK, Loos RJ. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. Acta Paediatr 2006;95(8):904-908.

(7) Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ. 2005 Oct;331(7522):929.

(8) Monteiro PO, Victora CG. Rapid growth in infancy and childhood and obesity in later life – a systematic review. Obes Rev 2005 May;6(2):143-154.

(9) Law CM, Shiell AW, Newsome CA, Syddall HE, Shinebourne EA, Fayers PM, et al. Fetal, infant, and childhood growth and adult blood pressure: a longitudinal study from birth to 22 years of age. Circulation. 2002 Mar;105(9):1088-92.

(10) Yeung MY, Smyth JP. Early postnatal undernutrition in preterm infants and reduced risk of insulin resistance {author reply]. Lancet. 2003 Jun;361(9376):2248-9

(11) Tamayo T, Herder C, Rathmann W. Impact of early psychosocial factors (childhood socioeconomic factors and adversities) on future risk of type 2 diabetes, metabolic disturbances and obesity: a systematic review. BMC Public Health. 2010 Sep 1;10:525.

(12) Lehtovirta M, Pahkala K, Niinikoski H, Kangas AJ, Soininen P, Lagström H, et al. Effect of Dietary Counseling on a Comprehensive Metabolic Profile from Childhood to Adulthood. J Pediatr. 2018 Apr;195:190-198.e3.

(13) Niinikoski H, Pahkala K, Ala-Korpela M, Viikari J, Rönnemaa T, Lagström H, et al. Effect of repeated dietary counseling on serum lipoproteins from infancy to adulthood. Pediatrics. 2012 Mar;129(3):e704-13.

(14) Lehtovirta M, Matthews L, Laitinen T, Nuotio J, Niinikoski H, Rovio S, et al. Achievement of the Targets of the 20-Year Infancy-Onset Dietary Intervention—Association with Metabolic Profile from Childhood to Adulthood. Nutrients 2021, 13, 533.

(15) Laitinen TT, Nuotio J, Juonala M, Niinikoski H, Rovio S, Viikari JSA, et al. Success in Achieving the Targets of the 20-Year Infancy-Onset Dietary Intervention: Association With Insulin Sensitivity and Serum Lipids. Diabetes Care. 2018 Oct;41(10):2236-2244.

(16) Oranta O, Pahkala K, Ruottinen S, Niinikoski H, Lagström H, Viikari JS, et al. Infancy-onset dietary counseling of low-saturated-fat diet improves insulin sensitivity in healthy adolescents 15-20 years of age: the Special Turku Coronary Risk Factor Intervention Project (STRIP) study. Diabetes Care. 2013 Oct;36(10):2952-9.

(17) Laitinen TT, Nuotio J, Niinikoski H, Juonala M, Rovio SP, Viikari JSA, et al. Attainment of Targets of the 20-Year Infancy-Onset Dietary Intervention and Blood Pressure Across Childhood and Young Adulthood: The Special Turku Coronary Risk Factor Intervention Project (STRIP). Hypertension. 2020 Nov;76(5):1572-1579.

(18) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985 Jul;28(7):412-9.

(19) Juhola J, Magnussen CG, Viikari JS, Kähönen M, Hutri-Kähönen N, Jula A, et al. Tracking of serum lipid levels, blood pressure, and body mass index from childhood to adulthood: the Cardiovascular Risk in Young Finns Study. J Pediatr 2011;159(4):584-590.

(20) Zheng M, Lamb KE, Grimes C, Laws R, Bolton K, Ong KK, et al. Rapid weight gain during infancy and subsequent adiposity: a systematic review and meta-analysis of evidence. Obes Rev. 2018 Mar;19(3):321-332.

(21) Huxley RR, Shiell AW, Law CM. The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. J Hypertens. 2000;18(7):815-31.

(22) Buffarini R, Restrepo-Méndez MC, Silveira VM, Gonçalves HD, Oliveira IO, Menezes AM, et al. Growth across life course and cardiovascular risk markers in 18-year-old adolescents: the 1993 Pelotas birth cohort. BMJ Open. 2018 Jan 23;8(1):e019164.

(23) Marinkovic T, Toemen L, Kruithof CJ, Reiss I, van Osch-Gevers L, Hofman A, et al. Early Infant Growth Velocity Patterns and Cardiovascular and Metabolic Outcomes in Childhood. J Pediatr. 2017 Jul;186:57-63.e4.

(24) Eriksson JG, Osmond C, Kajantie E, Forsén TJ, Barker DJ. Patterns of growth among children who later develop type 2 diabetes or its risk factors. Diabetologia. 2006 Dec;49(12):2853-8.

(25) Fabricius-Bjerre S, Jensen RB, Faerch K, Larsen T, Molgaard C, Michaelsen KF, et al. Impact of birth weight and early infant weight gain on insulin resistance and associated cardiovascular risk factors in adolescence. PLoS One. 2011;6:e20595

(26) Simell O, Niinikoski H, Rönnemaa T, Raitakari OT, Lagström H, Laurinen M, et al. Cohort Profile: the STRIP Study (Special Turku Coronary Risk Factor Intervention Project), an Infancy-onset Dietary and Life-style Intervention Trial. Int J Epidemiol. 2009 Jun;38(3):650-5.

(27) Lapinleimu H, Viikari J, Jokinen E, Salo P, Routi T, Leino A, et al. Prospective randomised trial in 1062 infants of diet low in saturated fat and cholesterol. Lancet. 1995 Feb 25;345(8948):471-6.

(28) Horta BL, Loret de Mola C, Victora CG. Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis. Acta Paediatr. 2015 Dec;104(467):30-7.

Table 1. Mean (SD) weight gain (g) in different age intervals from birth to 2 years of age.

Age interval (n)	All	Boys	Girls	P-value between boys and girls	Intervention group	Control group	P-value between groups
Birth to 7 months (450)	4896 (799)	**5141 (744)**	**4667 (783)**	**<0.0001**	4953 (815)	4848 (785)	0.16
7 to 13 months (449)	1774 (542)	1795 (511)	1754 (569)	0.43	1793 (514)	1758 (564)	0.50
13 to 18 months (425)	1314 (501)	1282 (494)	1344 (506)	0.20	1342 (466)	1290 (528)	0.28
18 to 24 months (415)	1304 (562)	**1219 (519)**	**1385 (588)**	**0.002**	1287 (542)	1318 (577)	0.57
Birth to 13 months (453)	6675 (922)	**6943 (886)**	**6424 (887)**	**<0.0001**	6745 (939)	6617 (907)	0.14
Birth to 24 months (440)	9276 (1288)	**9436 (1157)**	**9127 (1387)**	**0.01**	9357 (1321)	9209 (1259)	0.23

n referenced to subjects with measurements at 20-years
Bold indicates $P < 0.05$

Table 2. Associations of early weight gain with BMI, waist circumference and blood pressure (BP) at age 20 years.

		Model 1 Beta* (CI), p-value	Model 2 Beta* (CI), p-value
BMI, kg/m^2	Birth to 7 months	**0.68 (0.21 – 1.16), 0.005**	0.33 (-0.19 – 0.85), 0.22
	7 to 13 months	**0.52 (0.10 – 0.93), 0.01**	0.32 (-0.12 – 0.77), 0.15
	13 to 18 months	**1.03 (0.63 – 1.44), <0.0001**	**0.78 (0.33 – 1.24), <0.001**
	18 to 24 months	**0.67 (0.27 – 1.06), <0.001**	**0.72 (0.27 – 1.17), 0.002**
	Birth to 13 months	**0.91 (0.44 – 1.38), <0.001**	0.49 (-0.03 – 1.00), 0.07
	Birth to 24 months	**1.41 (0.97 – 1.86), <0.0001**	**0.98 (0.48 – 1.49), <0.001**
Waist circumference, cm	Birth to 7 months	**1.14 (0.03 – 2.26), 0.04**	0.34 (-0.90 – 1.59), 0.59
	7 to 13 months	**1.02 (0.03 – 2.01), 0.04**	0.53 (-0.54 – 1.60), 0.33
	13 to 18 months	**2.57 (1.60 – 3.53), <0.0001**	**2.06 (0.97 – 3.15), <0.001**
	18 to 24 months	**1.24 (0.29 – 2.19), 0.01**	**1.25 (0.14 – 2.35), 0.03**
	Birth to 13 months	**1.55 (0.43 – 2.67), 0.007**	0.54 (-0.70 – 1.78), 0.39
	Birth to 24 months	**2.58 (1.51 – 3.65), <0.0001**	**1.62 (0.40 – 2.84), 0.01**
Systolic BP, mmHg	Birth to 7 months	0.67 (-0.74 – 2.09), 0.35	0.18 (-1.56 – 1.91), 0.84
	7 to 13 months	0.71 (-0.56 – 1.98), 0.27	0.49 (-1.00 – 1.98), 0.52
	13 to 18 months	**1.35 (0.09 – 2.61), 0.04**	1.05 (-0.48 – 2.59), 0.18
	18 to 24 months	1.18 (-0.04 – 2.40), 0.06	**1.83 (0.30 – 3.36), 0.02**
	Birth to 13 months	1.09 (-0.36 – 2.54), 0.14	0.45 (-1.30 – 2.19), 0.61
	Birth to 24 months	**1.55 (0.16 – 2.95), 0.03**	1.19 (-0.54 – 2.93), 0.18
Diastolic BP, mmHg	Birth to 7 months	0.22 (-0.74 – 1.17), 0.65	0.25 (-0.90 – 1.41), 0.67
	7 to 13 months	0.52 (-0.33 – 1.37), 0.23	0.39 (-0.60 – 1.38), 0.44
	13 to 18 months	0.05 (-0.79 – 0.88), 0.91	0.03 (-0.97 – 1.03), 0.96
	18 to 24 months	0.17 (-0.64 – 0.98), 0.68	0.37 (-0.63 – 1.37), 0.47
	Birth to 13 months	0.64 (-0.32 – 1.61), 0.19	0.47 (-0.68 – 1.62), 0.42
	Birth to 24 months	0.44 (-0.51 – 1.38), 0.36	0.52 (-0.63 – 1.67), 0.37

*the beta estimate represents association of 1 SD increase in early growth with the outcome variable
Bold indicates $P < 0.05$

Table 3. Associations of early weight gain with total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides at age 20 years.

		Model 1 Beta* (CI), p-value	Model 2 Beta* (CI), p-value
Total cholesterol, mmol/L	Birth to 7 months	-0.05 (-0.14 – 0.04), 0.31	-0.04 (-0.15 – 0.07), 0.43
	7 to 13 months	-0.002 (-0.08 – 0.08), 0.96	-0.03 (-0.12 – 0.07), 0.58
	13 to 18 months	0.03 (-0.05 – 0.11), 0.53	0.03 (-0.07 – 0.12), 0.55
	18 to 24 months	0.02 (-0.06 – 0.09), 0.69	-0.03 (-0.12 – 0.06), 0.53
	Birth to 13 months	-0.05 (-0.15 – 0.04), 0.27	-0.07 (-0.18 – 0.04), 0.21
	Birth to 24 months	-0.02 (-0.11 – 0.07), 0.73	-0.05 (-0.15 – 0.06), 0.40
HDL-C, mmol/L	Birth to 7 months	-0.01 (-0.05 – 0.03), 0.55	-0.01 (-0.05 – 0.04), 0.76
	7 to 13 months	0.02 (-0.01 – 0.05), 0.19	0.04 (-0.0003 – 0.07), 0.052
	13 to 18 months	-0.01 (-0.04 – 0.02), 0.45	-0.02 (-0.05 – 0.02), 0.44
	18 to 24 months	0.01 (-0.02 – 0.04), 0.62	0.01 (-0.03 – 0.05), 0.61
	Birth to 13 months	0.01 (-0.03 – 0.04), 0.72	0.02 (-0.02 – 0.07), 0.35
	Birth to 24 months	0.0004 (-0.04 – 0.04), 0.98	0.01 (-0.04 – 0.05), 0.76
LDL-C, mmol/L	Birth to 7 months	-0.02 (-0.10 – 0.06), 0.64	-0.01 (-0.11 – 0.08), 0.77
	7 to 13 months	-0.02 (-0.09 – 0.05), 0.51	-0.05 (-0.13 – 0.03), 0.22
	13 to 18 months	0.02 (-0.05 – 0.09), 0.55	0.03 (-0.06 – 0.11), 0.53
	18 to 24 months	0.01 (-0.06 – 0.08), 0.75	-0.04 (-0.12 – 0.04), 0.33
	Birth to 13 months	-0.04 (-0.12 – 0.04), 0.30	-0.06 (-0.15 – 0.04), 0.22
	Birth to 24 months	-0.003 (-0.08 – 0.08), 0.95	-0.03 (-0.12 – 0.06), 0.53
Triglycerides**, mmol/L	Birth to 7 months	-0.04 (-0.09 – 0.02), 0.19	-0.05 (-0.11 – 0.02), 0.14
	7 to 13 months	0.01 (-0.04 – 0.05), 0.79	-0.02 (-0.07 – 0.04), 0.52
	13 to 18 months	0.02 (-0.02 – 0.07), 0.34	0.02 (-0.04 – 0.08), 0.49
	18 to 24 months	-0.01 (-0.05 – 0.04), 0.76	-0.01 (-0.06 – 0.05), 0.83
	Birth to 13 months	-0.03 (-0.08 – 0.02), 0.29	-0.06 (-0.12 – 0.01), 0.08
	Birth to 24 months	-0.03 (-0.08 – 0.02), 0.26	-0.06 (-0.12 – 0.01), 0.09

*the beta estimate represents association of 1 SD increase in early growth with the outcome variable (mmol/L)

** Logarithmically transformed values used in the analyses

Table 4. Associations of early weight gain with serum glucose, serum insulin and HOMA-IR at age 20 years.

		Model 1	Model 2

		Beta* (CI), p-value	Beta* (CI), p-value
Glucose, mmol/L	Birth to 7 months	-0.03 (-0.08 – 0.02), 0.17	-0.03 (-0.10 – 0.03), 0.27
	7 to 13 months	0.02 (-0.02 – 0.06), 0.39	0.02 (-0.03 – 0.07), 0.41
	13 to 18 months	-0.01 (-0.05 – 0.04), 0.81	-0.03 (-0.08 – 0.03), 0.31
	18 to 24 months	-0.02 (-0.06 – 0.02), 0.35	-0.05 (-0.10 – 0.005), 0.07
	Birth to 13 months	-0.02 (-0.07 – 0.03), 0.46	-0.02 (-0.08 – 0.04), 0.58
	Birth to 24 months	-0.04 (-0.09 – 0.01), 0.12	**-0.07 (-0.13 – -0.004), 0.04**
Insulin**, mU/L	Birth to 7 months	-0.03 (-0.08 – 0.03), 0.37	-0.05 (-0.12 – 0.02), 0.15
	7 to 13 months	0.002 (-0.05 – 0.05), 0.94	-0.03 (-0.09 – 0.02), 0.25
	13 to 18 months	0.03 (-0.02 – 0.08), 0.19	0.03 (-0.03 – 0.09), 0.36
	18 to 24 months	-0.01 (-0.06 – 0.04), 0.59	-0.01 (-0.07 – 0.05), 0.68
	Birth to 13 months	-0.02 (-0.08 – 0.04), 0.50	**-0.07 (-0.14 – -0.003), 0.04**
	Birth to 24 months	-0.03 (-0.08 – 0.03), 0.34	**-0.08 (-0.14 – -0.01), 0.02**
HOMA-IR**	Birth to 7 months	-0.04 (-0.11 – 0.02), 0.15	-0.07 (-0.14 – 0.001), 0.054
	7 to 13 months	0.01 (-0.04 – 0.06), 0.69	-0.02 (-0.08 – 0.04), 0.44
	13 to 18 months	0.03 (-0.03 – 0.08), 0.34	0.01 (-0.05 – 0.08), 0.67
	18 to 24 months	-0.02 (-0.07 – 0.03), 0.45	-0.02 (-0.09 – 0.04), 0.44
	Birth to 13 months	-0.03 (-0.09 – 0.03), 0.37	**-0.08 (-0.15 – -0.01), 0.03**
	Birth to 24 months	-0.04 (-0.10 – 0.02), 0.16	**-0.10 (0.17 – -0.03), 0.005**

*the beta estimate represents association of 1 SD increase in early growth with the outcome variable (mmol/L)

** Logarithmically transformed values used in the analyses

Bold indicates $P < 0.05$