Growth during Infancy and Childhood, and Adiposity at Age 16 Years: Ages 2 to 7 Years Are Pivotal

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Objective To assess the period during infancy and childhood in which growth is most associated with adolescent adiposity and the metabolic syndrome (MS) and whether this differs depending on maternal smoking during pregnancy.

Study design A longitudinal population-based cohort study among 772 girls and 708 boys.

Results Weight gains between ages 2-4 years and ages 4-7 years were most strongly associated with higher body mass index (BMI), sum of skinfold measurements, body fat percentage, and waist circumference at age 16. A one SD increase in weight between ages 2-4 and 4-7 years was associated with increases in outcome measures of +0.82 to +1.47 SDs (all $P < .001$), and with a less favorable MS score. In children whose mothers smoked during pregnancy, the association of relative weight gain during ages 2-4 years with adolescent BMI was stronger than in children whose mothers did not smoke. For adolescent BMI, the increase was 0.42 SD higher ($P = .01$). This was similar for the other adiposity measures.

Conclusions Large relative increases in weight from ages 2 to 7 years are associated with adolescent adiposity and MS. This is more pronounced in adolescents whose mothers smoked during pregnancy. *(J Pediatr 2013;162:287-92).*

O verweight is associated with an increased risk of cardiovascular morbidity, such as diabetes, hypertension, and dyslipidemia. These problems start in early life. It has been hypothesized that critical time periods exist in which accelerated growth constitutes a risk factor for subsequent adiposity and its associated metabolic complications.[1] Specifically, these critical time periods include gestation, early infancy, the period of adiposity rebound, and adolescence. Systematic reviews have shown consistently positive associations between rapid growth in early childhood (from birth to age 2 years and from age 2 to 7 years) and adolescent and adult overweight.[2] Moreover, an early adiposity rebound has been found to be associated with adult overweight, independent of the body mass index (BMI) at the start of the adiposity rebound.[3]

Strong evidence on the relative importance of these critical time period is lacking. This may be due to a scarcity of contemporary longitudinal population-based cohorts that include data on childhood weight gain.[4] Moreover, most longitudinal studies used only BMI as outcome measure. Although BMI is easy to obtain and very reliable, it does not differentiate between lean body mass and fat mass, whereas rapid weight gain in particular may lead to increased fat mass.[5] A third, statistical, problem concerns the collinearity of measurements during adjacent time periods, which creates challenges regarding the relative importance of these time periods.[6] Finally, the association between rapid weight gain in childhood and subsequent adiposity may be affected by other variables that have not been included in previous studies. This concerns both potential confounders, such as socioeconomic status (SES) and pubertal stage, and potential effect modifiers, such as smoking during pregnancy.[2,7] If not accounted for, these variables may affect study outcomes, which may have important implications for targeting preventive measures.

The primary aim of our study was to assess the period during infancy and childhood in which growth is most associated with adolescent adiposity and corresponding metabolic traits. Furthermore, we aimed to assess whether these associations differed depending on maternal smoking during pregnancy.

Methods

The current study used data from the Tracking Adolescents' Individual Lives Survey cohort (N = 2230).[8] Children were recruited through community

BF%	Body fat percentage
BMI	Body mass index
MS	Metabolic syndrome
SES	Socioeconomic status
WC	Waist circumference

registers and schools to obtain a representative sample of the 3 northern provinces of The Netherlands. Three assessment visits, which included weight and height measurements, have been performed between 2001 and 2007, at ages (mean ± SD) of 11.1 ± 0.6, 13.5 ± 0.6, and 16.2 ± 0.7 year. The response rate at the third assessment was 83.0% (n = 1838) of the initial cohort. We included children for whom growth data were available, leading to the exclusion of 245 children. We restricted our analyses to children born at term (37 weeks' gestational age or more), causing an additional 113 exclusions. This led to a final sample of 1480 children. All procedures were approved by the Dutch Central Committee on Research Involving Human Subjects, including written informed consent from parents or custodians.

Data on infant and childhood growth, including birth weight and length, were extracted from records of well-child clinics. These clinics are attended by 95% of the Dutch population. Children attend at ages 1, 2, 3, 4, 6, 9, 11, 14, and 18 months and 2, 3, 4, 5, 10, and 13 years. During all visits, weight and length/height were measured by trained nurses. At the Tracking Adolescents' Individual Lives Survey study assessment visits, weight and height were measured with calibrated equipment (Models 770 and 214, respectively; Seca, Hamburg, Germany). In total, 18 (IQR 14-21) measurements of weight and height were available per participant. From weight and height, BMI (kg/m^2) was calculated. We defined "overweight" and "obesity" according to international age- and sex-adjusted BMI criteria.[9]

At a mean age of 16.2 (±0.68) years, skinfold thicknesses, waist circumference (WC), and systolic and diastolic blood pressures were measured. We performed hand-to-foot bioelectrical impedance analysis to calculate body fat percentage (BF%). For detailed information, we referred to a previous study within the same cohort.[10] Glucose, insulin, high-density lipoprotein cholesterol, and triglyceride levels were determined from a fasting blood sample. A composite score for the metabolic syndrome (MS) was calculated as the mean of z scores of glucose, insulin, high-density lipoprotein cholesterol, triglycerides, WC, and mean blood pressure, calculated within the study population.[11]

Infant feeding at age 3 months was reported by parents at the well-child clinics. Information on maternal weight and height and on smoking during pregnancy was obtained through parental questionnaires when children were aged 11.1 years. This information on smoking during pregnancy as obtained at child age 11.1 years showed good agreement with data from the well-child clinics (κ = .77).[12] In addition, questionnaires were filled out by child and parents regarding pubertal stage (Physical Development Scale questionnaire),[13] ethnicity, and SES. SES was calculated as the mean of SDS for family income and mother's and father's level of education and occupation based on the International Standard Classification of Occupations.[14] The 25% lowest, 50% intermediate, and 25% highest were considered to represent low, medium, and high SES, respectively.

Data Analyses

Weight, BMI, skinfold measurements, WC, systolic blood pressure, insulin, and triglycerides were log-transformed to obtain a better approximation of the normal distribution, before calculating age- and sex-specific SDSs. We also standardized all available weight and BMI data. These were used to construct growth curves from birth to age 15 years. Based on previous literature,[15-17] time periods were defined as birth to 6 months, 6 months to 1 year, and 1-2, 2-4, 4-7, 7-11, and 11-15 years of age. We assumed that growth is characterized by a straight line within each interval. These lines connect at the breakpoints in age mentioned and visually resemble a "broken stick."[18] The procedure resulted in 8 estimates per person (1 for each breakpoint in age). Changes in scores per period were calculated as the differences between the estimates at successive breakpoints in age.

In the analyses, we first assessed the association of changes in weight relative to same-age peers (ie, in SDS from birth until age 15 years), with the adiposity outcomes, using linear regression models. As outcomes we used BMI, skinfold measurements, BF%, WC, and the composite score of the MS at age 16 years. In these analyses, we started by entering weight SDS at the end of a certain age period. We then added change in weight SDS within this age period to estimate the additional effect of weight change during that period. We calculated the increase in explained variance after adding the change in weight to the model. Larger increases in explained variance indicate that the growth rate during this age period was more strongly associated with adiposity outcomes, compared with growth rates in other age periods. We performed stepwise adjustments for pubertal stage, SES, birth weight, breastfeeding until 3 months of age, smoking during pregnancy, and maternal BMI. Only the latter 2 factors changed the effect sizes significantly, and they were subsequently entered in an interaction analysis. Both variables seemed to modify the associations. In view of limiting the article, we chose to present only the analyses regarding smoking during pregnancy because this risk factor can be influenced during pregnancy; moreover, maternal BMI was hampered by many missing values.

We repeated all analyses using changes in BMI SDSs as predictors, instead of changes in weight, with adjustment for pubertal stage and SES, and with restriction to only white children.

Individual parameters of the broken stick model were fitted as randomly varying slopes in a linear multilevel model by use of the S Plus 8.0 (TIBCO, Palo Alto, California) function "lme."[19] All other statistical analyses were performed in SPSS version 16.0 (SPSS Inc, Chicago, Illinois). The level of statistical significance was set at $P < .05$. Our sample size yielded a 90% power to detect an R^2 of 0.007 attributed to one independent variable in an F test with $\alpha = .05$ (calculated using PASS 11; NCSS, Kaysville, Utah).

Results

Our population consisted of 772 girls and 708 boys, with a mean ± SD age at the last visit of 16.2 ± 0.7 year. Regarding

social class, 22.2% were in a low, 48.2% were in a middle, and 29.7% were in a high SES category. Of the population, 88.4% were white; 11.9% of our population was overweight, and 2.6% was obese (**Table I**). Changes in weight SDS over time showed that participants who were overweight or obese at age 16 years had a higher birth weight SDS (B = .14; 95% CI, 0.09-0.19; $P < .001$), then grew parallel to normal weight children until age 1 and later on gradually crossed weight percentiles (**Figure 1**).

Relative weight gains in the age periods between 1 and 15 years were significantly associated with higher BMI, sum of skinfold measurements, BF%, and WC at age 16 (**Table II**). Weight gains from birth to 0.5 and from 0.5 to 1 year of age were associated with lower anthropometric measurements at age 16, but not in all analyses with statistical significance (**Table II**). We found a consistent pattern of large increases in explained variances of all outcome measures by adding relative weight gains from 2 to 4 and 4 to 7 years (**Table II** and **Figure 2**). One SDS of weight gain during these periods was associated with increases of +0.82 to +1.47 SD in BMI, sum of skinfold measurements, BF%, and WC at age 16 (all $P < .001$). Weight gains between ages 2-4 and 4-7 years were also associated with a higher MS score (**Table II** and **Figure 3**; **Figure 3** available at www.jpeds.com). Weight gains between age 11-15 years were also associated with large increases in explained variance of the MS score. After adjustment for current BMI SDS, all estimates for the MS score were substantially reduced to statistically nonsignificant effects. Using gains in BMI SDS instead of weight SDS yielded weaker, but significant, results: +0.42 to +0.89 SD for the various adiposity measures (all $P < .001$)

Figure 1. Weight SDS in normal weight versus overweight/obese participants, by age. Differences between the 2 groups are statistically significant at all time points (ie, $P \leq .01$). ■, Overweight/obese (n = 214); ●, normal weight (n = 1245).

(data not shown). Adjustment for pubertal stage and SES had only minor effects on the results (<10% in the statistically significant associations; data not shown), which was similar for analyses restricted to white children (n = 1309, 88.4%).

We evaluated smoking during pregnancy as potential effect modifier in the 2 age periods in which we found the strongest associations between changes in weight (and BMI) SDS and anthropometric measurements at age 16 years. This yielded significant interaction terms ($P < .05$) for 7 of the 12 associations concerned (**Table III**; available at www.jpeds.com).

Next, we constructed separate models for adolescents who had been exposed to smoking during pregnancy and for adolescents who had not. Associations between gain in weight/BMI SDS and adiposity-related measures were consistently stronger in participants whose mothers smoked during pregnancy than in participants whose mothers did not smoke (B = .07-.42; $P = .70-.01$; **Table III**). For example, each unit increase in weight SDS between 2 and 4 years was associated with an increase of 1.72 (95% CI, 1.46-1.98) in BMI SDS at age 16 in adolescents whose mothers smoked during pregnancy, compared with 1.30 (95% CI, 1.11-1.49) in the other adolescents (B$_{interaction\ term}$, .42, 95% CI, 0.10-0.74). The growth curve for overweight/obese participants at age 16 years who were exposed to smoking during pregnancy showed that they started at a relatively lower birth weight and grew faster between ages 2-7 years (**Figure 4**; available at www.jpeds.com). However, adjustment for birth weight as a continuous variable did not alter the results substantially (<10% for all significant interactions; not shown). Also, adjustment for SES (both as a categorical and as a continuous variable), breastfeeding at 3 months of age, and pubertal stage did not affect our findings in the age period of 2-7 years (<10% for all significant interactions; not shown).

Table I. Sociodemographic, anthropometric, and metabolic characteristics; data refer to age 16 years unless otherwise indicated

	n	Value
Age, y	1480	16.2 ± 0.68
Smoking in pregnancy, % yes*	1478	30.2
Birth weight, g	1216	3470 (3165-3780)
Pubertal stage, % in 3 categories†	1381	15.8/28.3/55.9
Weight, kg	1480	62.9 (57.1-69.9)
Height, cm	1480	174.0 ± 9.0
BMI, kg/m²	1480	20.77 (19.18-22.62)
Overweight/obese, %	1473	11.9/2.6
Sum of skinfold measurements, mm	1464	47 (32-65)
Body fat, %	1433	28.3 ± 5.7
WC, cm	1458	73.8 (69.9-78.7)
Systolic blood pressure, mm Hg	1458	116 (110-127)
Diastolic blood pressure, mm Hg	1458	61 ± 7
Glucose, mM	870	4.54 ± 0.40
Insulin, mU/L	861	12.0 (9.2-16.0)
Triglycerides, mM	868	0.68 (0.51-0.92)
High density lipoprotein cholesterol, mM	868	1.46 ± 0.31
MS score‡	981	−0.01 ± 0.53

All data are given as mean ± SD or median (IQR) unless otherwise indicated.
*Based on a parental questionnaire filled out at child age 11.1 years.
†Measured by the Physical Development Scale questionnaire, divided into pre/early pubertal, midpubertal, and late/postpubertal.
‡Defined according to international age- and sex-adjusted BMI criteria.[15]

Table II. Associations between weight SDS changes and anthropometric and metabolic traits at 16 years of age

Age period	Changes in weight SDS B_weight change (95% CI) P_weight change ∆ explained variance, P				
	BMI SDS* (n = 1480)	SF SDS* (n = 1464)	BF% SDS (n = 1433)	WC SDS* (n = 1458)	MS SDS (n = 981)
0-0.5 y	−0.07 (−0.12 to −0.01) .003, .02	−0.06 (−0.12 to −0.01) .003, .03	−0.02 (−0.08 to 0.04) <.001, .49	−0.07 (−0.12 to −0.01) .003, .02	−0.01 (−0.05 to 0.03) <.001, .68
0.5-1 y	−0.07 (−0.17 to 0.02) .001, .14	−0.13 (−0.22 to −0.03) .004, .01	−0.07 (−0.17 to 0.03) .001, .17	−0.10 (−0.20 to −0.01) .003, .03	−0.03 (−0.09 to 0.03) .001, .34
1-2 y	0.78 (0.62 to 0.94) .048, <.001	0.53 (0.36 to 0.71) .022, <.001	0.60 (0.42 to 0.77) .028, <.001	0.65 (0.49 to 0.82) .034, <.001	0.18 (0.07 to 0.29) .009, .002
2-4 y	1.47 (1.32 to 1.63) **.145, <.001**	1.24 (1.07 to 1.42) **.101, <.001**	1.30 (1.12 to 1.48) **.113, <.001**	1.29 (1.14 to 1.45) **.112, <.001**	0.49 (0.36 to 0.61) **.053, <.001**
4-7 y	1.11 (0.97 to 1.25) **.089, <.001**	1.08 (0.92 to 1.24) **.083, <.001**	1.18 (1.02 to 1.34) **.101, <.001**	0.82 (0.57 to 0.96) **.048, <.001**	0.37 (0.26 to 0.48) **.035, <.001**
7-11 y	0.47 (0.36 to 0.57) .023, <.001	0.56 (0.43 to 0.68) .033, <.001	0.61 (0.48 to 0.73) .04, <.001	0.19 (0.08 to 0.31) .004, <.001	0.16 (0.06 to 0.25) .009, .001
11-15 y	0.99 (0.88 to 1.10) .061, <.001	0.79 (0.64 to 0.94) .038, <.001	0.67 (0.51 to 0.83) .027, <.001	0.83 (0.70 to 0.96) **.044, <.001**	0.48 (0.36 to 0.60) **.048, <.001**

B, regression coefficient (effect size) from linear regression analyses; *SF*, sum of skinfold measurements.
Effect sizes (95% CI), explained variances, and *P* values are reported from multiple linear regression analyses adjusted for weight at the end of the period.
Large changes in explained variances are in bold.
*Data was log-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Discussion

Our study confirms findings from previous studies, but now in a large community-based cohort that covered a much wider age range. Earlier reports covered periods after birth that range from 21 months to 7 years, which were analyzed in relation to adult overweight.[20-22] Childhood growth had a stronger association than infant growth regarding adult BMI, fatness, and WC. A Finnish study on growth from birth to age 13 years yielded a similar finding, showing that growth started to deviate at age 2-3 for children who were overweight at age 13 years.[23] De Kroon et al[24] also identified the age period of 2-6 years as the most critical in the development of adult overweight, using a similar

methodology as the current study but with much lower response rates.

We found that a higher relative weight gain in the first year of life was associated with lower values on adolescent adiposity measures, whereas earlier studies found a higher gain to be associated with higher values but only assessed growth in the first year.[2] However, the association between infant growth and overweight in later life has been disputed by other studies that did not find any association between infancy weight gain and later fatness.[20,25]

Adolescents with overweight at age 16 years had a higher birth weight than normal-weight adolescents, at age 16 years. This is consistent with previous studies that showed an association between high birth weight and increased risk of subsequent overweight.[26]

We decided to present changes in weight SDS as the predictor in our **Tables** and **Figures**, because these models fit surprisingly better than the models with changes in BMI SDS as predictor (explained variances of 3.5%-14.5% for weight SDS vs 2.2%-7.1% for BMI SDS in the age periods between 2 and 7 years, for the various outcome measures). A possible explanation is the fact that we use BMI SDS. Height determines BMI in an important way and is highly correlated with age. BMI SDS is calculated to correct for age. This might lead to overcorrection for age, which could reduce the power of changes in BMI SDS to predict measures of overweight at age 16 years.

The association between childhood weight gain and adolescent adiposity was stronger in the case of exposure to smoking during pregnancy. Exposed children also had a lower birth weight, but adjustment for birth weight did not affect this association, suggesting that birth weight per se does not explain the modifying effect of smoking during pregnancy. Others have found a similar influence of smoking during pregnancy, which also was independent of SES although in a relatively homogeneously financially secure cohort.[7] This
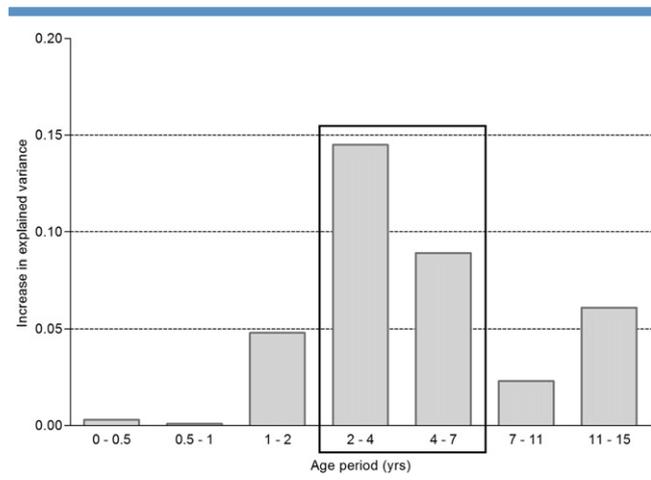
Figure 2. Increase in explained variance by adding change in weight SDS during the age period to predict BMI at age 16 years.

makes a socioeconomic explanation for these and our findings less likely. Another explanation for the moderating effect of intrauterine smoking exposure is a difference in lifestyle among children whose parents smoke. For example, nutrient intake and physical activity levels could vary between households in which parents smoke.[27]

Next to smoking during pregnancy, we evaluated maternal BMI as a potential effect modifier. We found significant interaction terms in all except 2 models (these exceptions were weight SDS change between 4 and 7 years in predicting skinfold measurements and BF%, P = .20 and .17, respectively) with effect sizes of 0.04-0.08 (P = .03 to <.001), suggesting that in children of mothers with a higher BMI, the association between weight gain from age 2-7 years and measures of adolescent overweight is stronger. As mentioned in the Methods section, we decided to focus on smoking during pregnancy because this risk factor is more amenable to change.

The main strengths of our study are the multiple measurements of weight and height from early infancy to adolescence available in a large contemporary cohort with high response rates. Furthermore, we included various measures of overall and abdominal adiposity at age 16 and various potential confounders and modifiers. A potential limitation may be that the measurements of weight and height had been performed by various professionals in the well-child clinics. This may have added measurement error, and thus have led to an underestimation of the strength of the associations. However, others have described robust findings using such routine examinations.[28] Another potential limitation is that we performed multiple statistical tests. Note that these concerned correlated outcome measures. A partial Bonferroni correction to adjust for this would lead to a significance level of .02. Use of this stricter significance level does not alter our conclusions. Moreover, the power achieved by our sample size of detecting an R^2 of 0.007 is still high, 82%, at an α of .02. Finally, compared with populations in the US and the United Kingdom, relatively few adolescents were obese at age 16 years. Caution is required in extrapolating our conclusions to other populations with a high prevalence of severe obesity.

We found that increases in weight and BMI SDS between ages 2 and 7 years are associated with overall and abdominal adiposity in adolescence. In adolescents whose mothers smoked during pregnancy, the influence of weight gain during these years is more pronounced. Our findings support an early start of preventive strategies, as early as 2 years of age. Moreover, interventions should especially target children whose mothers smoked during pregnancy. This offers important clues for interventions to contain the overweight epidemic. ∎

References

1. Dietz WH. Critical periods in childhood for the development of obesity. Am J Clin Nutr 1994;59:955-9.
2. 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;331:929.
3. Whitaker RC, Pepe MS, Wright JA, Seidel KD, Dietz WH. Early adiposity rebound and the risk of adult obesity. Pediatrics 1998;101:E5.
4. Gardner DS, Hosking J, Metcalf BS, Jeffery AN, Voss LD, Wilkin TJ. Contribution of early weight gain to childhood overweight and metabolic health: a longitudinal study (EarlyBird 36). Pediatrics 2009;123:e67-73.
5. Karaolis-Danckert N, Buyken AE, Bolzenius K, Perim de Faria C, Lentze MJ, Kroke A. Rapid growth among term children whose birth weight was appropriate for gestational age has a longer lasting effect on body fat percentage than on body mass index. Am J Clin Nutr 2006;84:1449-55.
6. Stettler N. Nature and strength of epidemiological evidence for origins of childhood and adulthood obesity in the first year of life. Int J Obes (Lond) 2007;31:1035-43.
7. Karaolis-Danckert N, Buyken AE, Kulig M, Kroke A, Forster J, Kamin W, et al. How pre- and postnatal risk factors modify the effect of rapid weight gain in infancy and early childhood on subsequent fat mass development: results from the Multicenter Allergy Study 90. Am J Clin Nutr 2008;87:1356-64.
8. Huisman M, Oldehinkel AJ, de Winter A, Minderaa RB, de Bildt A, Huizink AC, et al. Cohort profile: the Dutch 'TRacking Adolescents' Individual Lives' Survey'; TRAILS. Int J Epidemiol 2008;37:1227-35.
9. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-3.
10. Liem ET, Vonk JM, Sauer PJ, van der Steege G, Oosterom E, Stolk RP, et al. Influence of common variants near INSIG2, in FTO, and near MC4R genes on overweight and the metabolic profile in adolescence: the TRAILS (TRacking Adolescents' Individual Lives Survey). Study. Am J Clin Nutr 2010;91(2):321-8.
11. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB, et al. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). Diabetes Care 2004;27:2141-8.
12. Jaspers M, de Meer G, Verhulst FC, Ormel J, Reijneveld SA. Limited validity of parental recall on pregnancy, birth, and early childhood at child age 10 years. J Clin Epidemiol 2010;63:185-91.
13. Carskadon MA, Acebo C. A self-administered rating scale for pubertal development. J Adolesc Health 1993;14:190-5.
14. Amone-P'Olak K, Burger H, Ormel J, Huisman M, Verhulst FC, Oldehinkel AJ. Socioeconomic position and mental health problems in pre- and early-adolescents: the TRAILS study. Soc Psychiatry Psychiatr Epidemiol 2009;44:231-8.
15. Dennison BA, Edmunds LS, Stratton HH, Pruzek RM. Rapid infant weight gain predicts childhood overweight. Obesity (Silver Spring) 2006;14:491-9.
16. Vogels N, Posthumus DL, Mariman EC, Bouwman F, Kester AD, Rump P, et al. Determinants of overweight in a cohort of Dutch children. Am J Clin Nutr 2006;84:717-24.
17. Eriksson JG, Osmond C, Kajantie E, Forsen TJ, Barker DJ. Patterns of growth among children who later develop type 2 diabetes or its risk factors. Diabetologia 2006;49:2853-8.
18. Ruppert D, Wand MP, Carroll RJ. Semiparametric regression. New York: Cambridge University Press; 2003.
19. Pinheiro JC, Bates DM. Mixed effects models in S and S-Plus. New York: Springer; 2002.
20. McCarthy A, Hughes R, Tilling K, Davies D, Smith GD, Ben-Shlomo Y. Birth weight; postnatal, infant, and childhood growth; and obesity in

young adulthood: evidence from the Barry Caerphilly Growth Study. Am J Clin Nutr 2007;86:907-13.

21. Corvalan C, Gregory CO, Ramirez-Zea M, Martorell R, Stein AD. Size at birth, infant, early and later childhood growth and adult body composition: a prospective study in a stunted population. Int J Epidemiol 2007; 36:550-7.

22. Ekelund U, Ong K, Linne Y, Neovius M, Brage S, Dunger DB, et al. Upward weight percentile crossing in infancy and early childhood independently predicts fat mass in young adults: the Stockholm Weight Development Study (SWEDES). Am J Clin Nutr 2006;83: 324-30.

23. Lagstrom H, Hakanen M, Niinikoski H, Viikari J, Rönnemaa T, Saarinen M, et al. Growth patterns and obesity development in over-weight or normal-weight 13-year-old adolescents: the STRIP study. Pediatrics 2008;122:e876-83.

24. De Kroon ML, Renders CM, Van Wouwe JP, Van Buuren S, Hirasing RA. The Terneuzen birth cohort: BMI changes between 2 and 6 years correlate strongest with adult overweight. PLoS One 2010;5:e9155.

25. Wells JC, Hallal PC, Wright A, Singhal A, Victora CG. Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. Int J Obes (Lond) 2005;29:1192-8.

26. Monteiro PO, Victora CG, Barros FC, Monteiro LM. Birth size, early childhood growth, and adolescent obesity in a Brazilian birth cohort. Int J Obes Relat Metab Disord 2003;27:1274-82.

27. Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JC, Ness AR. Smoking during pregnancy and offspring fat and lean mass in childhood. Obesity (Silver Spring) 2006;14:2284-93.

28. Bundred P, Kitchiner D, Buchan I. Prevalence of overweight and obese children between 1989 and 1998: population based series of cross sectional studies. BMJ 2001;322:326-8.

50 Years Ago in THE JOURNAL OF PEDIATRICS

A Chromosome Anomaly in an Infant with a Degenerative Disease of the Central Nervous System

Bray P, Mukherjee B. J Pediatr 1963;62:230-4

Fifty years ago, Bray and Mukherjee described an infant with microcephaly, severe spastic quadriparesis, impaired gag, slow neurologic deterioration, and episodes of infection and dehydration. Pneumoencephalography revealed ex vacuo ventriculomegaly and electroencephalography demonstrated decreased background amplitude. The karyotype showed a balanced reciprocal translocation of chromosomes 16 and 17, the first time a translocation of chromosomes 16-18 had been reported. The finding was also novel because balanced translocations were previously presumed to be asymptomatic. Presciently, the authors postulated that this case may not actually represent a balanced translocation, as the "naked-eye method of karyotype analysis may fail to detect the loss of small amounts of genetic material."

G-banded karyotyping was the first-line genetic test for approximately 40 years, advantageous for its pictorial and intuitive representation of the entire genome. Its disadvantages include the relative subjectivity of analysis, and the failure to detect deletions/duplications of genetic material less than 5 million base pairs. With ongoing advancements in DNA analysis, the chromosome microarray has now emerged as the first-step genetic test when no specific condition is suspected. This represents a sea change from a structural image (the karyotype) to a quantitative assessment (copy number variant). In addition, the microarray can simultaneously detect copy number changes at multiple loci in a genome, as compared with FISH analysis.

There are various types of arrays, but all compare DNA from the patient and the control. This DNA, which can either be "whole genome" or "targeted," is labeled with either oligonucleotides, single nucleotide polymorphisms, complementary DNAs, or bacterial artificial chromosomes. It thus follows that the smaller the size of the nucleic acid targets and the greater the density of their coverage over the genome, the greater the resolution power of the microarray. Also, as microarrays become more powerful the finding of results of "uncertain significance" will increase. Previously unreported deletions/duplications will need to be archived and, once sufficient cases are collected, categorized as pathogenic or benign. This is a task that the International Standard Cytogenomic Array Consortium is investigating. Compared with 50 years ago, the chromosome microarray is a powerful genetic tool in our armamentarium.

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Appendix

Table III. Smoking during pregnancy as potential effect modifier in the associations between weight changes and anthropometric traits at 16 years of age

	BMI SDS* (n = 1593)	SF SDS* (n = 1573)	BF% SDS (n = 1543)	WC SDS* (n = 1589)
Weight change 2-4 y (SDS)				
$B_{interaction}$ (95% CI), $P_{interaction}$	.42 (.10 to .74), .01	.28 (−.07 to .64), .12	.33 (−.03 to .69), .08	.39 (.07 to .72), .02
$B_{weight\ change}$ (95% CI), $P_{weight\ change}$ in model for nonsmoking exposure	1.30 (1.11 to 1.49), <.001	1.12 (.91 to 1.33), <.001	1.16 (.94 to 1.38), <.001	1.13 (.94 to 1.32), <.001
$B_{weight\ change}$ (95% CI), $P_{weight\ change}$ in model for smoking exposure	1.72 (1.46 to 1.98), <.001	1.40 (1.11 to 1.69), <.001	1.49 (1.19 to 1.78), <.001	1.53 (1.26 to 1.79), <.001
Weight change 4-7 y (SDS)				
$B_{interaction}$ (95% CI), $P_{interaction}$	.22 (−.07 to .50), .14	.18 (−.14 to .51), .27	.07 (−.27 to .40), .70	.38 (.08 to .68), .01
$B_{weight\ change}$ (95% CI), $P_{weight\ change}$ in model for nonsmoking exposure	1.01 (.84 to 1.18), <.001	1.00 (.80 to 1.19), <.001	1.13 (.94 to 1.33), <.001	.66 (.49 to .84), <.001
$B_{weight\ change}$ (95% CI), $P_{weight\ change}$ in model for smoking exposure	1.22 (.99 to 07), <.001	1.18 (.91 to 1.45), <.001	1.20 (.93 to 1.47), <.001	1.04 (.80 to 1.29), <.001
BMI change 4-7 y (SDS)				
$B_{interaction}$ (95% CI), $P_{interaction}$	.38 (.15 to .61), .001	.46 (.16 to .76), .002	.37 (.08 to .67), .01	.56 (.27 to .85), <.001
$B_{BMI\ change}$ (95% CI), $P_{BMI\ change}$ in model for nonsmoking exposure	.67 (.55 to .79), <.001	.73 (.57 to .89), <.001	.77 (.61 to .93), <.001	.52 (.36 to .68), <.001
$B_{BMI\ change}$ (95% CI), $P_{BMI\ change}$ in model for smoking exposure	1.05 (.85 to 1.25), <.001	1.19 (.94 to 1.45), <.001	1.14 (.89 to 1.40), <.001	1.08 (.83 to 1.33), <.001

Effect sizes (95% CI), and *P* values are reported from multiple linear regression analyses adjusted for BMI at the end of the period.
Similar results were obtained after adjustment for pubertal stage and SES.
*Log-transformed before calculation of SD scores to obtain a better approximation of the normal distribution.

Growth during Infancy and Childhood, and Adiposity at Age 16 Years: Ages 2 to 7 Years Are Pivotal
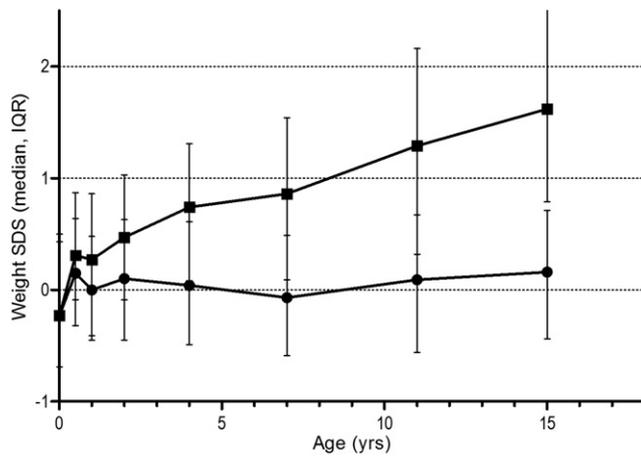
Figure 3. Weight SDS for 2 groups of participants, with an MS score >+1 SD and ≤+1 SD, by age. Differences between the 2 groups are statistically significant at all time points from age 2 (ie, $P \le .01$). ■, Participants with an MS score >+1 SD; ●, participants with an MS score of ≤+1 SD.
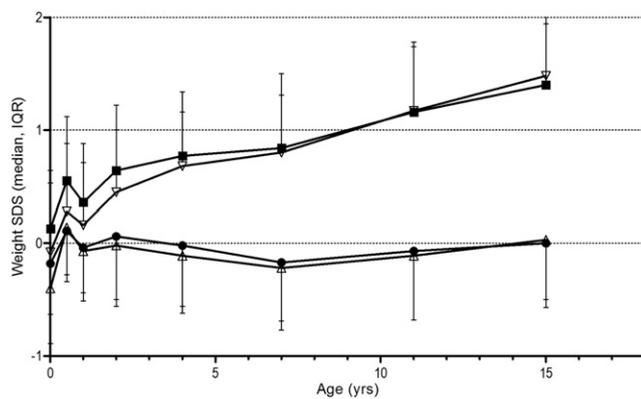
Figure 4. Weight SDS in overweight/obese versus normal weight participants whose mothers did or did not smoke during pregnancy, by age. In the group whose mothers did not smoke, differences between the overweight/obese and normal weight participants are statistically significant at all time points (ie, $P \le .005$). In the group whose mothers did smoke, differences between the overweight/obese and normal weight participants are statistically significant at all time points except age 0.5 year (ie, $P \le .017$). ∇, Overweight/obese and smoking mother during pregnancy (n = 87); ■, overweight/obese and nonsmoking mother during pregnancy (n = 127); ●, normal weight and nonsmoking mother during pregnancy (n = 888); Δ, normal weight and smoking mother during pregnancy (n = 355).