

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 90¹⁻³

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ABSTRACT

Background: It is unclear which exposures may cause or modify the adverse effect of rapid weight gain on fat mass development in term children whose birth weight is appropriate-for-gestational age (AGA).

Objective: To determine which intrauterine or postnatal exposures increase the risk of or modify the effect of rapid weight gain on body fat percentage (BF%) and body mass index (BMI) trajectories between 2 and 6 y of age.

Design: Term AGA singletons ($n = 370$) from the German Multicenter Allergy Study (MAS-90), a longitudinal birth cohort study, with repeated anthropometric measurements until 6 y, and data on breastfeeding status, exposure to smoking during pregnancy, and maternal anthropometric and socioeconomic characteristics were included in this analysis.

Results: A shorter gestation [multivariate-adjusted odds ratio (OR): 5.12; 95% CI: 2.22, 11.82; $P = 0.0001$], being firstborn (OR: 2.01; 95% CI: 1.10, 3.69; $P = 0.02$), and having been bottle-fed (OR: 3.02; 95% CI: 1.68, 5.43; $P = 0.0002$) all significantly increased a child's risk of gaining weight rapidly, whereas a larger BMI at birth was protective (OR: 0.54; 95% CI: 0.38, 0.77; $P = 0.0006$). Multilevel model analyses showed that rapid growers exposed to tobacco in utero subsequently gained more BF% between 2 and 6 y than did rapid growers who had not been exposed ($\beta \pm \text{SE}$: $0.78 \pm 0.28\%/y$; $P = 0.005$). Similarly, change in BF% was greater in rapid growers with an overweight mother than in those with a normal-weight mother ($1.01 \pm 0.30\%/y$; $P = 0.0007$).

Conclusions: The occurrence of rapid weight gain between birth and 2 y and the magnitude of its effect on BF% development in AGA children is influenced by both intrauterine and postnatal exposures. *Am J Clin Nutr* 2008;87:1356–64.

INTRODUCTION

Rapid weight gain in infancy has been identified as an important risk factor for later overweight and adiposity (1, 2) as well as for several other morbidities, including cardiovascular disease (3) and cancer (4). These outcomes have not only been observed in children who gained weight rapidly subsequent to being born small-for-gestational age (SGA), but also in some children whose birth weight was appropriate-for-gestational age (AGA) and who would therefore not be expected to gain weight rapidly to compensate for an obvious intrauterine growth deficit. In fact,

it has been suggested that rapid weight gain in AGA children has a selective effect on body fat mass, the component of body composition associated with the greatest risk of disease, resulting in a progressively increasing body fat percentage (BF%) throughout childhood (5).

Why a proportion of AGA children show this apparently detrimental growth pattern remains unclear, but it certainly deserves attention given that these children comprise the majority of births in developed countries. Furthermore, not all AGA children who gain weight rapidly subsequently develop a greater fat mass. Apart from genetic factors (6), the intrauterine environment as well as postnatal exposures are also likely to help explain these patterns of growth. Prenatal tobacco exposure, for example, has been shown to result in a poor pregnancy outcome (7, 8) and has been associated with subsequent obesity in the child (9, 10). On the other hand, parental obesity, socioeconomic status, as well as whether a child was breastfed or bottle-fed are all factors known to influence postnatal growth. The programming effect of infant feeding patterns in particular is currently being widely debated (11, 12). Thus, it is of interest whether these factors precede, modify, or amplify the effect of rapid weight gain on growth trajectories throughout childhood and whether fat mass and body mass index (BMI) are differentially affected.

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We therefore aimed to identify factors that increase a child's risk of gaining weight rapidly between birth and 24 mo and to determine whether these factors modify or amplify the association between rapid weight gain and body fat percentage (BF%) and BMI trajectories in AGA children throughout infancy and early childhood using data from the longitudinal German Multicenter Allergy Study (MAS-90).

SUBJECTS AND METHODS

Study population

The subjects in this analysis are participants of MAS-90, a longitudinal birth cohort study begun in 1990, to prospectively investigate the natural course of atopy-related traits (including asthma) and to identify early risk factors and predictors, with particular focus on the role of different environmental factors such as tobacco smoke, indoor allergens, and infections. This study was previously described in detail (13). Briefly, all infants born in the obstetric departments of 6 university hospitals in 5 German cities (Berlin, Munich, Mainz, Düsseldorf, and Freiburg) between January and December 1990 were eligible for inclusion in the study ($n = 7609$). Of these, 499 infants with a double positive family history and/or umbilical cord blood immunoglobulin (Ig) E values >0.9 kU/L were recruited as infants at risk, and 815 infants selected at random from the remaining newborns with neither of these risk factors participated as infants at random risk (14).

The cohort of 1314 singleton newborns were followed up at 1, 3, 6, 12, 18, and 24 mo and then annually until 10 y of age. In selecting the sample for this analysis, the following a priori defined inclusion and exclusion criteria were applied:

- 1) only term (37–42 wk gestation) singletons whose birth weight was >2500 g and whose birth weight and length were appropriate-for-gestational age, ie, all birth weights and lengths between the 10th and 90th percentiles of the German sex-specific birth weight- and height-for-gestational-age curves (15, 16) were included ($n = 772$);
- 2) children with systemic disease, growth disorders (eg, growth hormone deficiency), chromosomal or congenital abnormalities, or abnormalities of the heart, gastrointestinal tract, or urogenital tract were excluded ($n = 514$); and
- 3) only those children with complete information on breastfeeding status, maternal anthropometric measures, and in utero tobacco exposure were included ($n = 370$).

The subcohort analyzed herein included 370 AGA term singletons (46.8% female). Only those measurements up to and including age 6 y were included in this analysis because skinfold thicknesses were only measured until age 6 y. The MAS-90 Study was approved by the ethics committee of the Charité-Virchow-Klinikum, Humboldt University, Berlin, Germany. The parents of all the children gave written informed consent.

Anthropometric data

Participants were measured according to standardized procedures (17) at enrollment, on 6 further occasions during the first 2 y of life, and then once annually. Weight was measured to the nearest 10 g in infants and to the nearest 100 g in older children and adults with calibrated beam balances. Recumbent length was

measured in infants up to 2 y of age with a Harpenden measuring board. In children from age 2 onward and adults, standing height was measured with a Harpenden stadiometer. All length and height measurements were made to the nearest 0.2 cm. Triceps and subscapular skinfold thicknesses were determined to the nearest 1 mm with Harpenden calipers at each visit until the children were 6 y of age. Children were always completely undressed before being measured, whereas their parents (measured at 2–2.5 y postpartum) wore underwear. The observers' measurement techniques were calibrated by one of the authors (RLB), whose techniques had been calibrated by Whitehouse and Tanner.

Parental questionnaire

At each follow-up visit, study doctors conducted structured interviews with the participants' parents, focusing especially on any asthmatic or atopic symptoms in the child. Parents also completed standardized questionnaires regarding infant feeding (answers from the 1-, 3-, 6-, and 12-mo visits were used in this analysis), smoking during and after pregnancy, and socioeconomic status.

Variable definitions

Sex- and age-independent SD scores (SDS) were calculated by using the German reference curves for weight, height, and BMI (in kg/m^2) (18), and the Tanner and Whitehouse reference data for subscapular- and triceps-skinfold-thickness measurements (19). Because only 2 skinfold thicknesses were measured, BF% was calculated by using Slaughter et al's (20) equations for prepubertal children, which have been shown to predict fatness with negligible bias in children aged 5.8–11.3 y and have been recommended for group analyses (21). Overweight at age 6 y was defined according to the International Obesity Task Force (IOTF) BMI cutoffs for children, which correspond to an adult BMI of 25 (22).

Rapid weight gain was defined as an increase in weight SDS >0.67 between birth and 24 mo, as recommended by Monteiro and Victora (1). Children who had never been breastfed or were partially breastfed for up to 3 mo only were defined as bottle-fed. All other children (ie, those who had been exclusively or partially breastfed for >3 mo) were defined as not bottle-fed. Mothers who had stopped breastfeeding by 3 mo had usually started at least complementary bottle-feeding well before (23). A child was defined as having been prenatally exposed to tobacco if, at enrollment, their mother indicated that she had smoked during the pregnancy. Postnatal exposure was defined by using the mothers' answers from the 18 mo and the 3- and 5-y follow-up visits (mother reported having smoked at home on any of these visits). To allow for the effect of exposure to tobacco in childhood, initial analyses grouped maternal smoking status into 3 mutually exclusive categories: 1) never smoked, 2) smoked during and after pregnancy, and 3) smoked only after pregnancy. However, too few children fell into category 3 for meaningful analyses ($n = 7$ rapid growers). Moreover, multilevel analyses showed that those children who had only been exposed to tobacco after birth did not differ from those who had never been exposed, so categories 1 and 3 were combined. Allergy risk was defined according to whether or not a child had been initially recruited as an infant at risk, ie, with a double positive family history and/or an umbilical cord blood IgE value >0.9 kU/L.



Statistical analysis

Unadjusted associations between the independent variables and rapid weight gain were tested with the chi-square test, Student's *t* test, or Wilcoxon's rank-sum test as appropriate. There was no interaction between sex and rapid weight gain for either outcome (BF%, *P* for interaction = 0.3; BMI SDS, *P* for interaction = 1.0); therefore, boys and girls were pooled together for all statistical analyses. Multivariate logistic regression was used to calculate odds ratios for the risk of rapid weight gain between birth and 24 mo.

Linear mixed-effects regression models (using PROC MIXED) including both fixed and random effects were used to construct longitudinal models of BF% and BMI SDS trajectories subsequent to the period of rapid weight gain, ie, between 2 and 6 y of age, and to investigate the effect of rapid weight gain on baseline BF% or BMI SDS status at age 2 y and on their rate of

change over time. The random component of these models accounts for the nested nature of our data (children from 6 different cities) and the lack of independence between repeated observations on the same person. In addition, the intercepts and the slopes for time were also included as random effects. Basic models included either BF% or BMI SDS measurements between 2 and 6 y inclusive as the dependent continuous variable and rapid weight gain, time (chronological age and age²) and the interaction between rapid weight gain and time as the independent fixed effects. The effects of adding each of the following variables and their interaction with time (used to decide whether a variable had a significant effect on the change in BF% or BMI SDS over time) to the basic model were then investigated: sex, birth at early (weeks 37 or 38) or late (weeks 41 or 42) gestation, parity (nulliparous, parous), bottle-feeding status (yes, no), in utero tobacco exposure (yes, no), at risk of allergy (yes, no), season of birth,

TABLE 1

Birth and parental characteristics of those children in the German Multicenter Allergy Study (*n* = 370) who gained weight rapidly between the ages of 0 and 24 mo (*n* = 74) and those who did not (*n* = 296)

	Rate of weight gain ¹		<i>P</i> ²
	Normal	Rapid	
Female [% (<i>n</i>)]	45.7 (135/296)	51.4 (38/74)	0.4
Birth and feeding characteristics			
Birth weight (g)	3540 ± 289 ³	3273 ± 265	<0.0001
Birth length (cm)	52 (51, 53) ⁴	51 (50, 52)	0.0002
Birth BMI SDS	0.39 ± 0.70	-0.06 ± 0.65	<0.0001
Body fat at 3 mo (%)	16.1 ± 2.9	17.4 ± 2.0	<0.0001
Gestational age group [% (<i>n</i>)]			
37–38 wk	5.7 (17/296)	27.0 (20/74)	<0.0001
39–40 wk	51.0 (151/296)	46.0 (34/74)	
41–42 wk	43.2 (128/296)	27.0 (20/74)	
Head circumference (cm)	35 (34, 36)	35 (33, 35)	0.0006
Primiparous [% (<i>n</i>)]	52.0 (154/296)	70.3 (52/74)	0.005
Bottle-fed [% (<i>n</i>)] ⁵	31.4 (93/296)	55.4 (41/74)	0.0001
Exposed to tobacco in utero [% (<i>n</i>)]	19.3 (57/296)	28.4 (21/74)	0.09
At risk of allergy [% (<i>n</i>)] ⁶	47.6 (141/296)	47.3 (35/74)	1.0
Parental and socioeconomic characteristics			
Overweight mothers at 2 y [% (<i>n</i>)]	17.2 (51/296)	20.3 (15/74)	0.5
Overweight fathers at 2 y [% (<i>n</i>)]	41.5 (114/275)	37.7 (26/69)	0.6
Mothers aged >35 y [% (<i>n</i>)]	12.2 (36/296)	18.9 (14/74)	0.1
Mothers >12 y of schooling [% (<i>n</i>)]	37.6 (106/282)	46.5 (33/71)	0.2
Fathers >12 y of schooling [% (<i>n</i>)]	46.5 (131/282)	59.2 (42/71)	0.06
Reside in an urban location [% (<i>n</i>)]	68.6 (203/296)	78.4 (58/74)	0.1
Net family income at 1.5 y (DM/mo) ⁷	3500 (3000, 4750)	3500 (3000, 4500)	0.6
Anthropometric characteristics at age 6 y			
Weight SDS	-0.14 ± 0.88	0.85 ± 0.80	<0.0001
Height SDS	-0.13 ± 0.98	0.74 ± 0.94	<0.0001
BMI SDS	-0.10 ± 0.85	0.62 ± 0.84	<0.0001
Triceps skinfold SDS	0.12 ± 0.95	0.48 ± 1.07	0.02
Subscapular skinfold SDS	-0.82 ± 1.20	0.10 ± 1.20	<0.0001
Body fat (%)	13.2 (11.3, 16.2)	15.5 (13.0, 19.1)	0.0002
Overweight [% (<i>n</i>)] ⁸	9.3 (25/270)	28.2 (20/71)	<0.0001

¹ Defined as an increase in weight SD score (SDS) >0.67 between birth and 24 mo (1).

² Student's *t* test or Wilcoxon's test for continuous variables; chi-square test for categorical variables.

³ $\bar{x} \pm$ SD (all such values).

⁴ Median; quartiles 1 and 3 in parentheses (all such values).

⁵ Bottle-fed children had never been breastfed or had been partially breastfed for up to 3 mo only.

⁶ Defined as having a double positive family history and/or umbilical cord blood immunoglobulin E values > 0.9 kU/L.

⁷ 1 DM corresponds to €0.50.

⁸ Defined by using the International Obesity Taskforce definition (22).



maternal overweight status (BMI ≥ 25), high educational status (≥ 12 y of schooling), maternal age ≥ 35 y at birth, and either BF% at 3 mo of age or BMI SDS at birth (to adjust for baseline body composition). Those variables that had their own significant fixed effect or that modified the coefficient of rapid weight gain by $\geq 10\%$ (24) in the basic models were included in subsequent multivariate analyses. Akaike's Information Criterion (AIC) was also used to assess model fit (25). A 3-factor interaction between time, rapid weight gain, and each of the other fixed variables was also included to consider differential effects of rapid weight gain on the BF% or BMI SDS trajectories of children in various subgroups. When the 3-factor interaction was significant, it remained in the model along with all lower-order 2-factor interactions and main effects. A P value < 0.05 was considered statistically significant. All statistical analyses were carried out using SAS version 8.2 (SAS Inc, Cary, NC).

RESULTS

Overall, 20% (74/370) of the AGA children in this sample gained weight rapidly between birth and 24 mo (**Table 1**). The rapid growers were significantly lighter, were significantly

shorter, and had a significantly smaller head circumference at birth than did the normal growers. A larger proportion of the rapid growers than of the normal growers were born relatively early. Rapid growers were also significantly more likely to be firstborn and to have been bottle-fed and tended to have been exposed to tobacco in utero more often than normal growers ($P = 0.09$). However, the proportion of children at risk of allergy was the same in both growth groups. In terms of parental or socioeconomic characteristics, a larger proportion of the rapid growers' fathers tended to have > 12 y of schooling, but this information was not available for all children. Otherwise, no differences between the 2 growth groups were observed. By the age of 6 y, those children who had gained weight rapidly were significantly taller, heavier, and fatter than were the other children, and a larger proportion were classified as overweight (28% compared with 9%; $P < 0.0001$).

The odds ratios from the multivariable logistic regression analyses considering potential risk factors for gaining weight rapidly between birth and 24 mo are presented in **Table 2**. A relatively shorter gestation, being firstborn, and having been bottle-fed all independently increased a child's risk of gaining

TABLE 2

Multivariate analysis of the potential risk factors for rapid weight gain between birth and 24 mo of age in the German Multicenter Allergy Study population ($n = 370$)

Risk factor	Unadjusted (univariable)		Fully adjusted ¹ (multivariable)	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Sex				
Male	1	—	—	—
Female	1.26 (0.76, 2.10)	0.4	—	—
BMI SD score at birth	0.45 (0.32, 0.62)	< 0.0001	0.54 (0.38, 0.77)	0.0006
Gestational age group				
37–38 wk	5.23 (2.48, 11.02)	< 0.0001	5.12 (2.22, 11.82)	0.0001
39–40 wk	1	—	1	—
41–42 wk	0.69 (0.38, 1.27)	0.0001	0.72 (0.38, 1.37)	0.3
Firstborn child				
No	1	—	1	—
Yes	2.18 (1.26, 3.77)	0.005	2.01 (1.10, 3.69)	0.02
Intrauterine tobacco exposure				
No	1	—	1	—
Yes	1.66 (0.93, 2.97)	0.09	1.29 (0.66, 2.49)	0.5
Bottle-fed ²				
No	1	—	1	—
Yes	2.71 (1.61, 4.56)	0.0002	3.02 (1.68, 5.43)	0.0002
Tobacco exposure at 1.5 y				
No	1	—	—	—
Yes	1.31 (0.74, 2.33)	0.4	—	—
At risk of allergy ³				
No	1	—	—	—
Yes	0.99 (0.59, 1.64)	1.0	—	—
Mother				
Normal weight	1	—	—	—
Overweight	1.22 (0.64, 2.32)	0.5	—	—
Mother's education				
< 12 y of school	1	—	—	—
≥ 12 y of school	1.44 (0.85, 2.44)	0.2	—	—

¹ The fully adjusted model included all variables with a P value < 0.1 in the univariable analyses: BMI SD score at birth, gestational age group, firstborn status, and bottle-feeding.

² Bottle-fed children had never been breastfed or had been partially breastfed for ≤ 3 mo only.

³ Defined as having a double positive family history and/or umbilical cord blood immunoglobulin E values > 0.9 kU/L.

weight rapidly, whereas having a higher BMI at birth remained protective against rapid weight gain in the multivariable model.

The results of the linear mixed-models analyses for the association between rapid weight gain and BF% trajectories (**Table 3**) showed that, even after adjustment for birth, maternal, and other characteristics (final model), rapid growers had almost 2% more body fat than did normal growers by the age of 2 y ($\beta \pm \text{SE}$: $1.71 \pm 0.41\%$; $P = 0.009$). Furthermore, the relation between the rate of change in BF% between 2 and 6 y and rapid weight gain was significantly influenced by both intrauterine tobacco exposure and having an overweight mother. Those rapid growers whose mothers had smoked during pregnancy subsequently gained more BF% between 2 and 6 y of age than the rapid growers who were not exposed to tobacco in utero (adjusted difference between rapid-growth groups: $0.78 \pm 0.28\%/y$; $P = 0.005$; **Figure 1A**: solid circles compared with solid squares). Among normal growers, intrauterine exposure to tobacco appeared to have little impact on the trajectories of BF% (open squares and circles). Similarly, change in BF% was greater in those rapid growers with an overweight mother than in those with a normal-weight mother (adjusted difference between rapid-growth groups: $1.01 \pm 0.30\%/y$; $P = 0.0007$). In **Figure 1B**, the detrimental effect of having an overweight mother as a rapid grower is clearly visible when one compares this group (solid squares) to either those rapid growers with a normal-weight mother (solid circles) or normal growers with or without an overweight mother (open squares and circles).

Of the other variables considered, having been bottle-fed or being a firstborn child also influenced the rate of change in BF%

over time among rapid growers in the initial models (3-factor interaction for bottle-feeding: $0.47 \pm 0.26\%/y$, $P = 0.07$; 3-factor interaction for firstborn status: $-0.56 \pm 0.28\%/y$, $P = 0.04$), but these associations were greatly attenuated once maternal and socioeconomic characteristics were adjusted for (3-factor interaction for bottle-feeding: $0.24 \pm 0.55\%/y$, $P = 0.3$; 3-factor interaction for firstborn status: $-0.33 \pm 0.26\%/y$, $P = 0.2$) and did not improve the fit of the final model and were therefore excluded. None of the other variables, allergy risk included, interacted with rapid weight gain to influence its effect on BF% at 2 y or on the rate of BF% change between 2 and 6 y of age.

The parameter estimates from the multilevel models with BMI SDS as the outcome are presented in **Table 4**. Rapid weight gain between birth and 24 mo resulted in a significantly larger BMI SDS at age 2 y, even after adjustment for birth, maternal, and socioeconomic (final model) characteristics (a difference of 1.07 ± 0.13 SDS in comparison with normal growth; $P = 0.0004$). Of the potential 3-factor interactions considered, only having an overweight mother significantly influenced the relation between change in BMI SDS between 2 and 6 y of age and rapid weight gain. Rapid growers whose mother was overweight experienced a larger increase in BMI SDS than did those rapid growers with a normal-weight mother (0.13 ± 0.06 SDS/y; $P = 0.03$). In initial models, the 3-factor interaction between the rate of BMI SDS change, rapid weight gain, and exposure to tobacco in utero suggested an increased BMI SDS change in those rapid growers whose mother had smoked during pregnancy (0.11 ± 0.06 SDS/y; $P = 0.05$). However, adjustment for birth and maternal

TABLE 3

Linear mixed models of the association between rapid weight gain and baseline percentage body fat (BF%) at age 2 y and BF% slope between 2 and 6 y of age in the German Multicenter Allergy Study population ($n = 370$)¹

Risk factor	Basic model	P	Final model ²	P
Initial status at 2 y				
Intercept ³	14.27 ± 0.42^d	<0.0001	9.47 ± 0.89	0.0001
Rapid weight gain	1.83 ± 0.35	0.004	1.71 ± 0.41	0.009
Sex (female)	0.55 ± 0.28	0.1	0.82 ± 0.25	0.02
IU tobacco exposure	—	—	-0.23 ± 0.37	0.6
Overweight mother	—	—	0.32 ± 0.38	0.4
IU tobacco exposure $\times$ overweight mother	—	—	0.24 ± 0.86	0.8
Rapid weight gain $\times$ IU tobacco exposure	—	—	0.12 ± 0.72	0.9
Rapid weight gain $\times$ overweight mother	—	—	-0.34 ± 0.81	0.7
Rate of change, 2–6 y				
Intercept ³	0.51 ± 0.14	0.0003	0.05 ± 0.16	0.8
Time $\times$ time ³	-0.05 ± 0.03	0.07	-0.05 ± 0.03	0.1
Time $\times$ rapid weight gain ⁵	0.10 ± 0.13	0.4	-0.42 ± 0.15	0.01
Time $\times$ sex	0.37 ± 0.11	0.0004	0.30 ± 0.10	0.002
Time $\times$ IU tobacco exposure	—	—	0.14 ± 0.14	0.3
Time $\times$ overweight mother	—	—	0.17 ± 0.14	0.2
Time $\times$ rapid weight gain $\times$ IU tobacco exposure	—	—	0.78 ± 0.28	0.005
Time $\times$ rapid weight gain $\times$ overweight mother	—	—	1.01 ± 0.30	0.0007

¹ IU, intrauterine.

² Final model: as basic model and adjusted for BF% at 3 mo, gestational age group, firstborn, time $\times$ firstborn, time $\times$ bottle-feeding, season of birth, and time $\times$ season of birth.

³ The multilevel models have 3 intercepts, 1 for baseline BF% at age 2 y and 1 each for subsequent linear and quadratic change in BF% between 2 and 6 y. Each represents the mean value of the dependent variable at baseline when all other predictors are 0.

⁴ Estimate $\pm$ SE (all such values).

⁵ Including 3-factor interactions in this model means that, by definition, the estimate of the effect of rapid weight gain on BF% change between 2 and 6 y ($-0.42 \pm 0.15\%/y$; $P = 0.01$) refers to the subgroup of rapid growers for whom the predictors intrauterine tobacco exposure and having an overweight mother are both 0, ie, they were not exposed to tobacco in utero and their mothers were not overweight.

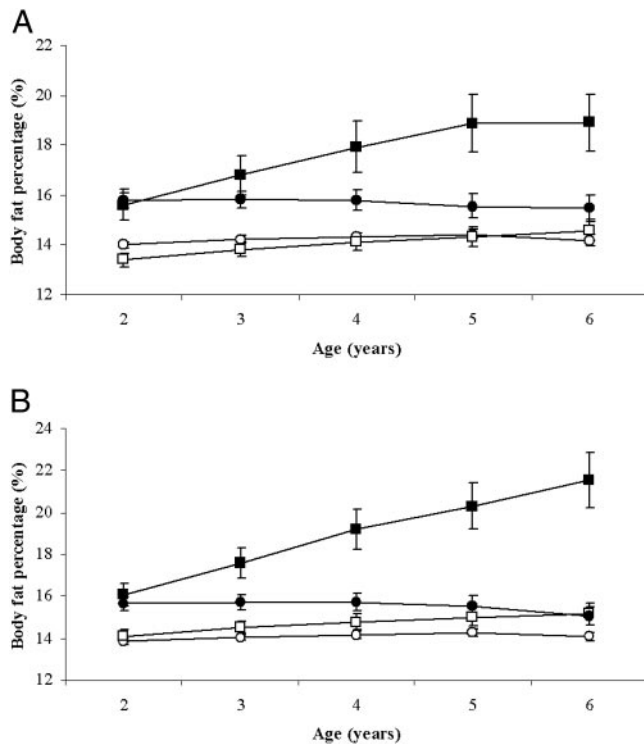


FIGURE 1. Predicted mean ($\pm$ SEM) percentage body fat (BF%) trajectories by subgroups of rapid weight gain and intrauterine tobacco exposure and maternal overweight status in 370 children in the German Multicenter Allergy Study. See Table 3 for the multivariable-adjusted linear mixed model used for prediction. A: Rapid growers who were exposed to tobacco in utero ($\blacksquare$, $n = 21$) compared with rapid growers who were not exposed to tobacco in utero ($\bullet$, $n = 53$), normal growers who were exposed to tobacco in utero ($\square$, $n = 57$), and normal growers who were not exposed to tobacco in utero ($\circ$, $n = 239$). The plot shows the 3-factor interaction between rapid weight gain and intrauterine tobacco exposure ($P = 0.005$ for interaction). B: Rapid growers whose mothers were overweight ($\blacksquare$, $n = 15$) compared with rapid growers whose mothers were not overweight ($\bullet$, $n = 59$), normal growers whose mothers were overweight ($\square$, $n = 51$), and normal growers whose mothers were not overweight ($\circ$, $n = 245$). The plot shows the 3-factor interaction between rapid weight gain and maternal overweight status ($P = 0.0007$ for interaction).

characteristics (final model) considerably attenuated this association (0.09 ± 0.06 SDS/y; $P = 0.1$). The 3-factor interactions from the final BMI SDS model are presented in Figure 2, A and B.

DISCUSSION

In this study we were able to identify factors that increase the risk of gaining weight rapidly between birth and 24 mo in term AGA children, namely a relatively shorter gestation (37–38 wk), being a firstborn child, and having been bottle-fed. More importantly though, we also identified factors that influence the extent to which rapid weight gain influences BF% development between 2 and 6 y of age in these children. Having an overweight mother or exposure to tobacco in utero both adversely affected subsequent BF% trajectories in those children who had gained weight rapidly.

It is known that the offspring of overweight mothers have a higher risk of themselves being overweight (26, 27). This association, as well as the effect modification seen in this study, may be a consequence of either shared genes, shared pre- and postnatal

environments or, most likely, a combination of both. A genetic predisposition to being overweight runs in families (28). Moreover, overweight or obese women have significantly more pregnancy complications, eg, gestational diabetes and pre-eclampsia (29). This metabolic environment may also adversely program in utero development. On the other hand, there are important behavioral and lifestyle differences between overweight or obese mothers and their normal-weight counterparts, eg, maternal prepregnancy overweight or obesity significantly predicts the success of breastfeeding initiation and duration (29–31). In accordance with other studies, overweight MAS-90 mothers were less likely to exclusively breastfeed their infants for ≥ 3 mo (9% compared with 20%; $P = 0.05$) and were more likely to bottle-feed their infants (50% compared with 33%; $P = 0.01$). Exposure to a combination of these factors in children susceptible to rapid weight gain could explain their apparently unfavorable BF% development.

Numerous studies have now shown an independent, increased risk of subsequent overweight (odds ratios from 1.1 to 2.5) in children exposed to tobacco in utero (7, 9, 10, 32–35). However, how this exposure interacts with growth patterns in childhood is unclear. Ong et al (36) showed that, whereas infants of smokers were lighter and shorter at birth than were infants of nonsmokers, they experienced catch-up growth in the first year of life and by 12 mo of age did not differ in weight, length, or head circumference from the other children. In this study we were able to contribute to this discussion by showing that, although exposure to tobacco in utero only slightly increased a child's risk of gaining weight rapidly between birth and 24 mo, those rapid growers whose mothers had smoked during pregnancy were particularly prone to developing an increased BF% between 2 and 6 y. This effect was independent of known socioeconomic confounders, and the growth patterns of those children who were only exposed to smoking after birth did not differ from those children who had never been exposed (data not shown), which suggests that a socioeconomic explanation is less likely. Support for a metabolic explanation comes from animal studies that have shown accelerated postnatal growth and weight gain and increased (visceral) adiposity after in utero exposure to tobacco (37, 38). Interestingly, differences in body weight between exposed and unexposed offspring only became apparent much later. Although BMI is a convenient proxy measure of adiposity, it cannot differentiate between lean and fat mass (39); therefore, it is perhaps not surprising that the detrimental effect of exposure to tobacco or having an overweight mother in rapid growers was more strongly discernible in the models of BF% than in those of BMI SDS.

In our study, bottle-feeding was identified as a stimulus for rapid weight gain between birth and 24 mo. This may be because formula-fed infants have a higher energy and protein intake per kilogram body weight than do breastfed infants (40, 41). Higher protein intakes may stimulate the secretion of insulin and insulin-like growth factor I (IGF-I), both of which may accelerate growth (42, 43). Differences in appetite control, feeding frequency, and meal size between bottle-fed and breastfed babies could also explain the increased risk of rapid weight gain (44). In the initial partially adjusted multilevel models of BF% development between 2 and 6 y, the combination of bottle-feeding and rapid weight gain was also associated with an increased BF%. However, this disappeared once maternal overweight and maternal



TABLE 4

Linear mixed models of the association between rapid weight gain and baseline BMI SD score at age 2 y and BMI SD score change between 2 and 6 y in the German Multicenter Allergy Study population ($n = 370$)¹

Risk factor	Basic model	<i>P</i>	Final model ²	<i>P</i>
Initial status at 2 y				
Intercept ³	-0.22 ± 0.07^4	0.02	-0.30 ± 0.09	0.02
Rapid weight gain	0.91 ± 0.10	0.0003	1.07 ± 0.13	0.0004
IU tobacco exposure	—	—	0.08 ± 0.12	0.5
Overweight mother	—	—	0.22 ± 0.12	0.1
IU tobacco exposure $\times$ overweight mother	—	—	-0.50 ± 0.25	0.1
Rapid weight gain $\times$ IU tobacco exposure	—	—	0.06 ± 0.23	0.8
Rapid weight gain $\times$ overweight mother	—	—	-0.07 ± 0.26	0.8
Rate of change, 2–6 y				
Intercept ³	0.03 ± 0.02	0.2	0.003 ± 0.02	0.9
Time $\times$ rapid weight gain ⁵	-0.06 ± 0.02	0.02	-0.12 ± 0.03	0.0001
Time $\times$ IU tobacco exposure	—	—	0.06 ± 0.03	0.03
Time $\times$ overweight mother	—	—	0.04 ± 0.03	0.2
Time $\times$ rapid weight gain $\times$ IU tobacco exposure	—	—	0.09 ± 0.06	0.1
Time $\times$ rapid weight gain $\times$ overweight mother	—	—	0.13 ± 0.06	0.03

¹ IU, intrauterine.

² Final model: as basic model and adjusted for BMI SD score at birth, gestational age group, time $\times$ bottle-feeding.

³ The multilevel models have 2 intercepts, 1 for baseline BMI SD score at age 2 y and 1 for subsequent linear change in BMI SD score between 2 and 6 y. Each represents the mean value of the dependent variable at baseline, when all other predictors are 0.

⁴ Estimate $\pm$ SE (all such values).

⁵ Including 3-factor interactions in this model means that, by definition, the estimate of the effect of rapid weight gain on BMI SD score change between 2 and 6 y ($-0.12 \pm 0.03\%/y$; $P = 0.0001$) refers to the subgroup of rapid growers for whom the predictors intrauterine tobacco exposure and having an overweight mother are both 0, ie, they were not exposed to tobacco in utero and their mothers were not overweight.

smoking during pregnancy had been adjusted for. Hence, although bottle-feeding increases a child's risk of gaining weight rapidly, it does not appear to modify the effect of rapid weight gain. Recent analyses of ours using data from another cohort came to the same conclusion (45).

A shorter gestation and being a firstborn child were the 2 other risk factors for rapid weight gain between birth and 24 mo. Because only term, AGA children were included in these analyses they would not have visibly displayed obvious growth restriction at birth. However, a relatively shorter gestation and primiparity may well be indicators of an inadequate intrauterine environment, as shown by the higher risk of neonatal morbidity and mortality among infants born to primigravid women, who themselves have a higher risk of complications during pregnancy and delivery (46, 47). Rapid postnatal weight gain could perhaps be seen as the organism's postnatal attempt to compensate for these restrictions.

The life course approach to modeling disease causation encourages consideration of the temporal ordering of exposure variables and possible pathways with potential intermediaries and confounding factors (48). This approach requires prospectively collected longitudinal growth data and precise classification of social and environmental circumstances. The most important strength of this analysis, therefore, is that the data used were prospectively collected, with precise information on confounding variables. This made it possible to identify combinations of exposures and their effect on longitudinal growth development. A number of limitations must nevertheless be considered. The participants of MAS-90 were recruited in academic teaching hospitals and, therefore, may not be representative of the general population. On the other hand, nonrepresentativeness is less relevant for longitudinal analyses and internal validity. As with most other observational studies, the mothers'

smoking status in MAS-90 was self-reported and therefore prone to underreporting. This being an allergy study may have further discouraged women who smoked to report their true status. Nevertheless, other studies have shown moderate to high agreement between self-reported number of cigarettes smoked and cotinine concentrations in maternal blood or meconium (49, 50), and misclassification of smokers as nonsmokers would have lead to an underestimation of the true effect of smoking during pregnancy on postnatal growth. Furthermore, when possible interactions between maternal cigarette smoking or maternal overweight and weight gain in children are examined, it is important to consider postnatal feeding practices. It was not, however, possible to adjust for dietary factors other than breast or bottle-feeding. However, these factors are usually related to socioeconomic status, which was adjusted for in all models.

It is important to point out that not all rapid growers experienced faster %BF gain. Our findings suggest that the effect of rapid weight gain in the first 2 y of life on subsequent fat mass development is dependent on the presence of additional exposures, ie, maternal overweight or in utero exposure to tobacco. This has important public health implications, especially in view of current levels of adult overweight and obesity on the one hand and pregnancy-related smoking rates on the other. The role of parental overweight in influencing offspring weight has received considerable attention. This is not the case for smoking however. On average, 20.3% of pregnant German women admit to smoking during pregnancy (51), a value that is comparable with values in other European countries (52) and with that in the United States (53). Because women are especially motivated to give up smoking when they become pregnant, public health campaigns should stress the negative effects of smoking during pregnancy, particularly the fact that these effects are still detectable in the child's growth many years later. Regularly monitoring growth

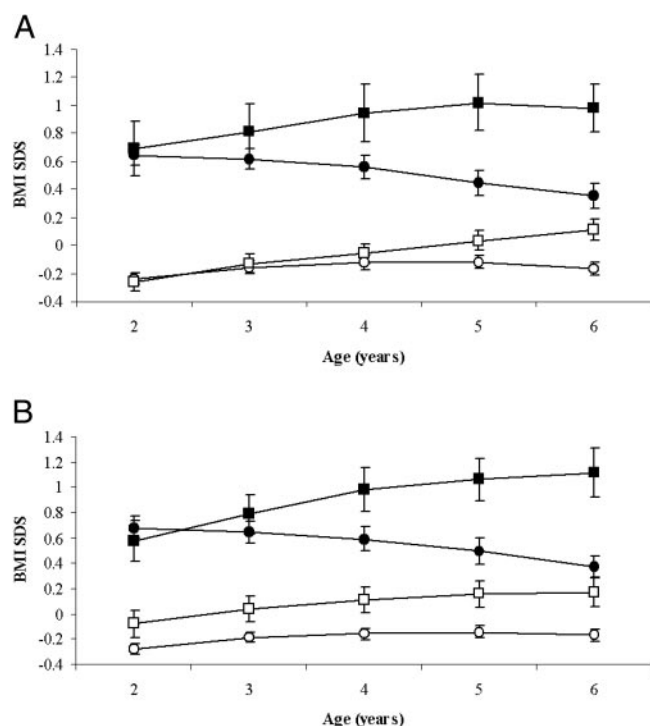


FIGURE 2. Predicted mean ($\pm$ SEM) BMI SD score (SDS) trajectories by subgroups of rapid weight gain and intrauterine tobacco exposure and maternal overweight status in 370 children in the German Multicenter Allergy Study. See Table 4 for the multivariable-adjusted linear mixed model used for prediction. A: Rapid growers who were exposed to tobacco in utero ($\blacksquare$, $n = 21$) compared with rapid growers who were not exposed to tobacco in utero ($\bullet$, $n = 53$), normal growers who were exposed to tobacco in utero ($\square$, $n = 57$), and normal growers who were not exposed to tobacco in utero ($\circ$, $n = 239$). The plot shows the 3-factor interaction between rapid weight gain and intrauterine tobacco exposure ($P = 0.1$ for interaction). B: Rapid growers whose mothers were overweight ($\blacksquare$, $n = 15$) compared with rapid growers whose mothers were not overweight ($\bullet$, $n = 59$), normal growers whose mothers were overweight ($\square$, $n = 51$), and normal growers whose mothers were not overweight ($\circ$, $n = 245$). The plot shows the 3-factor interaction between rapid weight gain and maternal overweight status ($P = 0.03$ for interaction).

velocity in infancy and early childhood generally, and in those children whose mothers are overweight or who smoked during pregnancy in particular, could be an important tool for identifying children at risk as early as possible.

In conclusion, we identified pre- and postnatal factors that increase a child's risk of gaining weight rapidly between birth and 24 mo. Furthermore, we showed that the magnitude of the effect of rapid weight gain on BF% development in term AGA children is influenced by both intrauterine exposure to tobacco and postnatal exposure to maternal obesity.

The authors' responsibilities were as follows—NK-D, AEB, MK, and AK: conceived this project; NK-D performed the data analyses and drafted the manuscript; NK-D, AEB, MK, AK, and CH: contributed to the initial interpretation of the data; AEB, AK, and CH: supervised the project; MK, JF, WK, AS, TK, RLB, UW, and SL: responsible for data acquisition for the MAS-90; and RLB and UW: obtained funding for the MAS-90. All of the authors contributed to the revision of the manuscript. None of the authors had any personal or financial conflicts of interest.

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