

# Growth Pattern of Breastfed and Nonbreastfed Infants With Atopic Dermatitis in the First Year of Life

Carlo Agostoni, MD\*; Francesca Grandi, MD\*; Silvia Scaglioni, MD\*; Maria L. Gianni, MD\*;  
Marta Torcoletti, MD\*; Giovanni Radaelli, PhD‡; Alessandro Fiocchi, MD\*; and Enrica Riva, MD\*

**ABSTRACT.** *Objective.* The growth of infants with atopic dermatitis (AD) has been poorly investigated based on the early type of feeding. The aim of this study was to assess the growth pattern of AD infants during the first 12 months of life in comparison to healthy infants, according to the early type of feeding (breastfed or non-breastfed).

*Methods.* Fifty-five term AD infants (36 breastfed and 19 nonbreastfed) and 114 term healthy infants (58 breastfed and 56 nonbreastfed) were evaluated by standardized growth indices (z scores; National Center for Health Statistics-World Health Organization data) through the first 12 months of life.

*Results.* No difference was found between AD and healthy groups at birth. In AD infants, weight (WA) and length (LA) z scores decreased with age and were significantly lower, compared with healthy infants from the second month of age onward. The difference of mean z scores between AD and healthy infants at 12 months of age was  $-.69$  (95% confidence interval [CI]:  $-1.00$  to  $-.38$ ) for WA and  $-.67$  (95% CI:  $-.98$  to  $-.36$ ) for LA. The growth pattern of AD infants was not influenced by the early type of feeding, whereas in the 6- to 12-month period, the delay in growth was more pronounced in patients with more severe dermatitis.

*Conclusions.* In the first year of life, AD infants show a progressive impairment in growth irrespective of the early type of feeding. The severity of disease may be an independent factor negatively influencing growth. *Pediatrics* 2000;106(5). URL: <http://www.pediatrics.org/cgi/content/full/106/5/e73>; atopic dermatitis, breastfeeding, food allergy, formula-feeding, infant growth.

ABBREVIATIONS. AD, atopic dermatitis; BF, breastfed; SD, standard deviation; WA, weight for age; LA, length for age; SCORAD, severity scoring of atopic dermatitis; CI, confidence interval; ANOVA, analysis of variance.

Several studies have investigated the growth pattern of subjects affected by atopic dermatitis (AD) with childhood onset. Children with eczema have been found to be shorter than are healthy children,<sup>1</sup> but an impaired height achievement seems to be restricted to subjects with extensive disease affecting >50% of the skin surface area.<sup>2</sup> Different

factors, such as therapeutic elimination diets, use of corticosteroids, coexisting asthma, sleep disturbances, impaired growth hormone release, and a poor use or loss of nutrients caused by sustained allergic inflammation might negatively influence the growth pattern of AD children, although the primary cause has not been definitely identified yet.<sup>1-7</sup> The infant's growth pattern in the first months of life may be particularly relevant, because it may be associated with later health outcome.<sup>8</sup> Studies have found different growth patterns in breastfed (BF) and non-BF healthy infants through the first year of life.<sup>9-12</sup> Although a recent survey has shown a reduced growth in AD infants with allergy to cow's milk during the first year of life,<sup>7</sup> it is still unknown whether the type of early feeding can influence the growth pattern in AD.

The aim of the present study was to assess the effect of the early type of feeding on the growth pattern of AD infants during the first 12 months of life.

## METHODS

### Patient Populations and Measurements

Of 122 infants born in the maternity ward of our hospital during a 6-year period (1993-1998) and then consecutively admitted for symptomatic AD at our second level center for immune-allergic disorders, 55 (24 females and 31 males) entered the study according to the following eligibility criteria. Inclusion criteria were: gestational age, 37 to 42 weeks inclusive; Apgar score, >7 at 5 minutes; singleton birth; birth weight,  $\geq 2500$  g; no neonatal disease or congenital malformation; white parents; to be either exclusively or predominantly BF or non-BF (never BF) in the first 4 months of life; controls of growth performed in our hospital in the first 6 months of life; onset of AD within the first 6 months of life requiring a specialist care at a second level center; and to fulfill the Hanifin criteria for AD. Briefly, they are the presence of pruritus, family history of atopy, typical facial and extensor distribution, plus the presence of at least 3 minor features, such as, xerosis, early age of onset, tendency to skin infection, and food intolerance.<sup>13</sup> Exclusion criteria were: mother with any dysmetabolic and/or chronic disease and mother drug user.

The control group ( $n = 138$ ; 66 females and 72 males) was a cohort of healthy infants born in our maternity ward in the period 1993-1994.<sup>14</sup> It included infants entering the same eligibility criteria of AD infants, except the presence of AD. Controls had no immune-allergic related disorders and/or chronic diseases during the study. Both patients (up to diagnosis) and controls were given similar advice on the introduction of solid foods from the fifth month of age onward according to present dietary recommendations.<sup>15</sup> The trial protocol was approved by the institutional ethics committee and all parents signed a written informed consent for the follow-up.

The growth parameters (body weight and length) of AD infants were retrospectively evaluated up to diagnosis and then prospectively through 12 months of life. The healthy infants were pro-

From the \*Department of Pediatrics, San Paolo Hospital, Milan, Italy; and the ‡Department of Informative Systems, University of Milan, Milan, Italy. Received for publication Feb 28, 2000; accepted Jul 3, 2000.

Address correspondence to Carlo Agostoni, MD, Department of Pediatrics, San Paolo Hospital, 8 Via A di Rudini, I-20142, Milan, Italy. E-mail: agostoc@tin.it

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spectively followed up from birth. The following data were further recorded: infant's birth date, mother's age, mother's height and prepregnancy body weight, education level of the mother, familial social status, gestational age, and parity. The severity of disease, elimination diets, and asthma were further assessed in AD infants.

Growth parameters were measured at birth and at age 1, 2, 3, 4, 6, 9, and 12 months with standardized techniques. The permissible time intervals around the actual chronological age for nominal age were within  $\pm 7$  days for the first 4 months of life and  $\pm 14$  days for the subsequent visits. The naked infant was weighed on an electronic Sartorius scale (Sartorius, AG, Göttingen, Germany) accurate to  $\pm 5$  g. Crown-heel length was measured on a portable measuring board to the nearest .1 cm. Experienced personnel at both the outpatient section and the second level center performed the measurements. In particular, the longitudinal growth measurements were performed according to a standardized procedure by the same 3 experienced pediatricians. At any time 3 measurements were taken for each growth parameter and the average value was then considered for the analysis. The coefficient of variation of the weight measurements ranged from .8% to 1.2% (observer 1), .8% to 1.1% (observer 2), and .9% to 1.2% (observer 3). The corresponding ranges of the coefficient of variation of the length measurements were .8% to 1.3% (observer 1), .9% to 1.4% (observer 2), and .9% to 1.2% (observer 3). The coefficient of variation in healthy infants ranged from .8% to 1.2% (weight) and from .9% to 1.2% (length), whereas in AD infants it ranged from .8% to 1.2% (weight) and from .9% to 1.4% (length). This makes the growth measurements and comparable interobservers' measurement variation accurate.

Actual chronological decimal age was used to calculate the standardized anthropometric indices (*z* scores). The *z* scores represent the distance in standard deviation (SD) units from the Center of Disease Control and Prevention-World Health Organization normative reference data adjusted for age and gender.<sup>16</sup> The weight and length *z* scores (on the following also called weight for age [WA] and length for age [LA] *z* scores) were calculated by means of the 1990 ANTHRO Pediatric Anthropometry Software Program, Version 1.01 (Centers for Disease Control and Prevention, Atlanta, GA).

The type of feeding was defined according to World Health Organization definitions.<sup>9,10</sup> The BF group included exclusively (infant required to receive breast milk; drops, syrups allowed and anything else not allowed) or predominantly (infant required to receive breast milk as the predominant source of nourishment; liquids, ritual fluids, drops, syrups allowed and anything else not allowed) BF infants. Infants in the non-BF group were never BF during the first 4 months of life and were fed standard formulas, whose energy, protein, carbohydrate, fat, and micronutrient composition complied with that of the European Society of Pediatric Gastroenterology and Nutrition.<sup>15,17</sup> Infants who switched toward bottle feeding in the 0- to 4-month period did not enter the present study.

Maternal height and prepregnancy body weight were obtained from the obstetric clinical records. The maternal education level (number of school years) and familial social status were coded according to the Italian census. Gestational age was based on the last menstruation date and was confirmed by an ultrasound examination performed within the 20th week.

The severity of disease was evaluated by the severity scoring of atopic dermatitis (SCORAD) index.<sup>18,19</sup> An infant was categorized with severe (nonsevere) AD if he/she showed a SCORAD measurement  $>20$  ( $\leq 20$ ) within the first 6 months of life. Infants were assigned only to local therapy (local ointments and corticosteroids) if SCORAD measurements were  $\leq 20$ , while they were also administered oral antihistaminics if SCORAD measurements were  $>20$ .

The AD infants were tested at skin prick tests using the following foods: egg, milk, soy, wheat, peanut, and fish. Infants who tested positive ( $n = 38$ ) had food allergy confirmed by double-blind placebo-controlled challenge or open challenge, when appropriate. All these infants showed positive reactivity to milk proteins and had specific elimination diets. In particular, 22 of them were administered a soy formula and 16 a high-degree protein hydrolysate formula. The decision to pose infants on elimination diets was taken on the ground of AD itself and on the positiveness to skin tests. A pediatric dietician formulated the dietary schedules based on individual food intolerance to obtain a

balanced and adequate intake of nutrients, according to the recommendations of the National Institute of Nutrition.<sup>20</sup> Mothers of BF infants were advised to eliminate the sensitizing foods from their diet. No dietary monitoring was planned in this study.

Asthma was defined as 3 episodes of nocturnal cough with sleep disturbances or wheezing, separated by at least 7 days, in a clinical setting where asthma is likely.<sup>21</sup>

## Statistical Analysis

The sample size was determined to detect at any time a 1 SD unit of difference in the WA and LA *z* scores between BF and non-BF AD infants. Admitting a type I error level of 5% and a power of 80%, at least 17 patients in each group were required. Descriptive data are shown as mean (SD) or number of observation; 95% confidence intervals (CIs) were also calculated. Comparison of continuous and discrete variables between unpaired groups were performed by the Student's *t* test or by the Mann-Whitney *U* test, and by the  $\chi^2$  test or Fisher's exact test, as appropriate. Weight, length, and the relative *z* scores were normally distributed, so the growth patterns of AD and control groups, and those of BF and non-BF infants, were compared by analysis of variance (ANOVA) for repeated measures. Adjustment for possible confounders (infant's gender, infant's birth date, and maternal age) was also performed. Posthoc multiple comparisons were performed by Bonferroni's test. At 12 months of age, pairwise comparisons were based on estimated marginal means. ANOVA was further used in AD infants to assess the association of some variables (age at onset, severity of disease, elimination diets, and asthma) with the infants' growth pattern. *P* values  $<.05$  were considered to indicate statistical significance (2-tailed test). The SPSS 8.0 Package for Windows (SPSS Inc, Chicago, IL) was used for the statistical analysis.

## RESULTS

Follow-up data at the age of 12 months were available in all of the 55 AD infants (36 BF and 19 non-BF) and in 114 (82.6%) controls (58 BF and 56 non-BF). AD infants and controls were comparable for the baseline characteristics (Table 1). Mean (SD) age at AD onset was 3.0 (1.6) months in BF infants and 2.4 (1.2) months in non-BF infants ( $P = .12$ ). Asthma coexisted in 13 of the infants (23.6%) with AD (9 BF and 4 non-BF). Mean (SD; median) age at onset of asthma symptoms was 5.5 (3.8; 4.0) months in BF infants and 3.3 (1.5; 3.0) in non-BF infants ( $P = .41$ ).

Table 2 shows the growth indices of AD infants and controls during the first year of life. Subjects affected by AD showed a progressive impairment of growth both in WA and LA *z* scores ( $P < .001$ ).

The growth indices drastically impaired after the onset of disease, compared with the values from just before the onset of disease (mean difference:  $\Delta$ ,  $-.27$ ; 95% CI,  $-.41$  to  $-.14$ , for WA *z* score;  $\Delta$ ,  $-.17$ ; 95% CI,  $-.30$  to  $-.03$ , for LA *z* score), but before the onset of disease infants already showed a significantly negative mean LA *z* score ( $-.22$ ; 95% CI:  $-.19$  to  $-.60$ ).

Differences between AD infants and controls were significant from the second months of age onward, more markedly in the second 6 months of life. These differences remained significant after adjustment for confounders and early type of feeding (maximum  $P = .05$ ). In particular, at 12 months of age the adjusted mean difference was  $-.69$  (95% CI:  $-1.00$  to  $-.38$ ) for WA *z* score and  $-.67$  (95% CI:  $-.98$  to  $-.36$ ) for LA *z* score.

Figures 1 and 2 show the pattern of growth indices in AD and healthy infants for BF and non-BF groups during the first 12 months of life. In the AD group an impairment of growth occurred both in BF ( $P < .001$ )

**TABLE 1.** Demographic, Maternal, and Infants Characteristics According to the Early Type of Feeding

Characteristic*	BF	Non-BF	BF	Non-BF
	AD Infants (n = 36)	AD Infants (n = 19)	Controls (n = 58)	Controls (n = 56)
Mother's age (y)	30.8 (3.8)	32.9 (4.2)	30.0 (4.4)‡	32.8 (5.2)
Mother's body weight (kg)	55.2 (7.1)	56.1 (6.3)	54.7 (6.8)	56.8 (6.6)
Mother's height (cm)	162.5 (6.0)	163.6 (6.1)	163.3 (6.2)	163.8 (5.9)
Maternal education level				
Low/medium ( $\leq 13$ y)	28	16	47	49
High ( $> 13$ y)	8	3	11	7
Familial social status				
Low/medium	32	17	51	52
High	4	2	7	4
Gestational age (wk)	39.4 (1.0)	39.1 (1.5)	39.3 (1.2)	39.2 (1.4)
Parity				
1st	20	12	37	35
$> 1$ st	16	7	21	21
Infant's gender				
Female	16	8	28	25
Male	20	11	30	31
Infant's birth weight (g)	3342 (418)	3146 (445)	3399 (409)‡	3218 (441)
Infant's birth weight (cm)	50.6 (1.6)†	49.6 (1.4)	50.2 (1.5)	50.1 (2.2)

Values are mean (SD) or number of observations.

\* No significant difference between AD infants and controls.

†  $P < .05$  versus non-BF AD.

‡  $P < .05$  versus non-BF controls.

**TABLE 2.** Growth Indices of AD Infants and Controls in the First Year of Life

Age (Months)	WA z Score		LA z Score	
	AD Infants (n = 55)	Controls (n = 114)	AD Infants (n = 55)	Controls (n = 114)
0	.14 (-.15, .43)	.14 (-.04, .32)	.01 (-.19, .21)	-.01 (-.16, .14)
1	-.10 (-.31, .10)†	-.13 (-.31, .05)	-.30 (-.48, -.13)*‡	-.08 (-.25, .08)
2	-.13 (-.33, .07)*†	.12 (.02, .23)	-.35 (-.56, -.15)*‡	-.05 (-.21, .10)
3	-.21 (-.39, .03)**†	.18 (.04, .32)	-.33 (-.54, -.12)*‡	-.04 (-.21, .13)
4	-.29 (-.48, -.11)**†	.19 (.05, .33)	-.35 (-.57, -.13)**‡	.01 (-.14, .17)
6	-.47 (-.66, -.27)**†	.17 (.01, .32)	-.54 (-.73, -.35)**‡	.02 (-.14, .17)
9	-.52 (-.73, -.31)**†	.20 (.02, .39)	-.53 (-.75, -.30)**‡	.14 (-.04, .32)
12	-.51 (-.73, -.29)**†	.20 (.02, .38)	-.50 (-.73, -.26)**‡	.19 (.01, .37)

Values are mean (95% CI).

\*  $P < .05$  versus controls; \*\*  $P < .01$  versus controls; \*\*\*  $P < .0001$  versus controls.

†  $P < .001$  versus age 0; ‡  $P < .0001$  versus age 0.

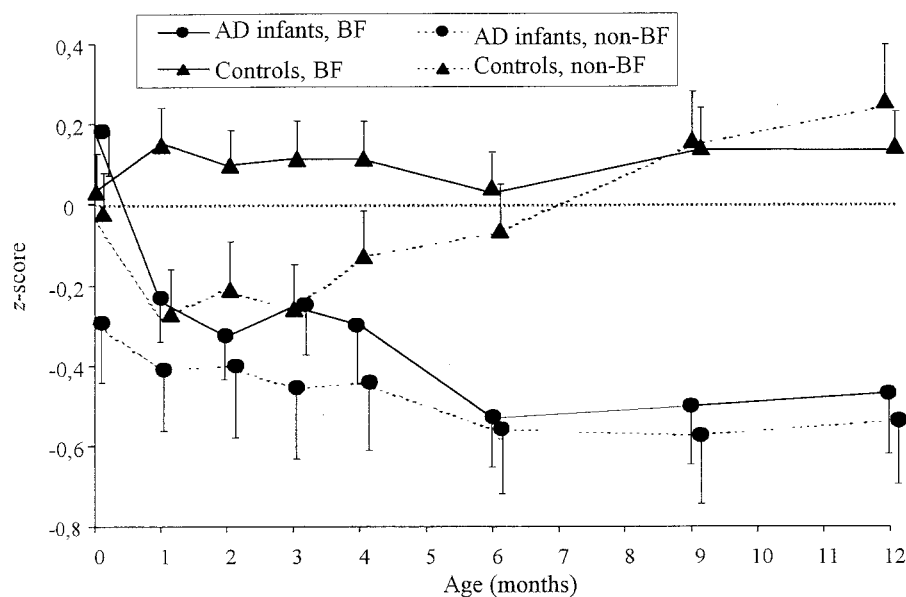
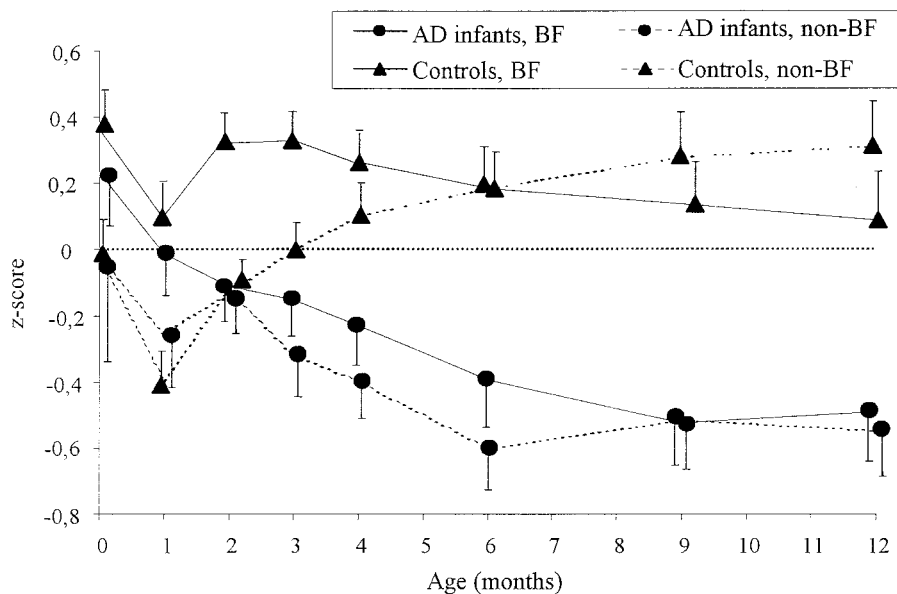
and non-BF ( $P < .001$ ) infants. At birth the mean LA z score was higher in BF than in non-BF infants (mean difference:  $\Delta$ , .47; 95% CI, .07–.88) but no other significant difference was found between the BF and non-BF infants both for WA z score (maximum  $\Delta$ : .26; 95% CI:  $-.34$ –.86, at birth) and LA z score (maximum  $\Delta$ : .20; 95% CI:  $-.23$ –.64 at 3 months of age). In contrast, in the control group the early type of feeding influenced both WA ( $P < .0001$ ) and LA ( $P < .01$ ) z score patterns. In particular in this group, BF infants had a WA z score significantly higher than the non-BF infants at birth and at 1, 2, and 3 months of age ( $\Delta$ : .39; 95% CI: .06–.72, at birth;  $\Delta$ : .57; 95% CI: .32–.83, at 1 month;  $\Delta$ : .51; 95% CI: .28–.75, at 2 months;  $\Delta$ : .38, 95% CI: .14–.64, at 3 months of age), and LA z score significantly higher than the non-BF infants at 1, 2, and 3 months of age ( $\Delta$ : .44; 95% CI: .55–.72, at 1 month;  $\Delta$ : .31; 95% CI: .02–.60, at 2 months;  $\Delta$ : .38; 95% CI: .07–.68, at 3 months of age).

Table 3 shows the adjusted mean of the WA and LA z scores at 12 months of age in AD and controls for BF and non-BF infants, respectively. Growth indices were remarkably lower among atopics than

among controls (maximum  $P = .007$ ). In BF infants the mean difference between AD and controls was  $-.57$  (95% CI:  $-.97$  to  $-.18$ ) for WA z score and  $-.59$  (95% CI:  $-.98$  to  $-.21$ ) for LA z score. In non-BF infants the mean difference between AD and controls was  $-.80$  (95% CI:  $-1.29$  to  $-.30$ ) for WA z score and  $-.72$  (95% CI:  $-1.24$  to  $-.20$ ) for LA z score.

Finally, an analysis was performed in AD infants only to assess any possible association of the growth with the age at onset, severity of disease, elimination diet, and asthma. At univariate ANOVA only the severity of disease was associated with a more pronounced WA growth impairment in the second 6 months of life ( $P < .05$ ). Infants with severe dermatitis ( $n = 18$ ) had a lower WA z score in the 6- to 12-month period than did those with nonsevere disease ( $n = 37$ ; mean difference:  $\Delta$ ,  $-.51$ ; 95% CI,  $-.91$  to  $-.12$ , at 6 months;  $\Delta$ ,  $-.42$ ; 95% CI,  $-.85$ –.00, at 9 months;  $\Delta$ ,  $-.46$ ; 95% CI,  $-.92$ –.00, at 12 months of age). The difference remained significant at 6 months of age also after adjustment for confounders and the early type of feeding ( $\Delta$ :  $-.47$ ; 95% CI:  $-.87$  to  $-.08$ ),

**Fig 1.** Mean (standard error of the mean) WA z score. AD versus controls: significant difference (maximum  $P < .05$ ) among BF infants at 2, 3, 4, 6, 9, and 12 months of age and among non-BF infants at 3, 4, 6, 9, and 12 months. BF versus non-BF: significant difference (maximum  $P < .05$ ) among controls at 0, 1, 2, and 3 months of age.



**Fig 2.** Mean (standard error of the mean) LA z score. AD versus controls: significant difference (maximum  $P < .05$ ) among BF at 1, 2, 3, 4, 6, 9, and 12 months of age and among non-BF at 6, 9, and 12 months. BF versus non-BF: significant difference (maximum  $P < .05$ ) among controls at 1, 2, and 3 months of age and among AD infants at birth.

**TABLE 3.** Growth indices of AD Infants and Controls at 12 Months of Age in BF and non-BF Groups

	BF			Non-BF		
	<i>n</i>	WA z Score	LA z Score	<i>n</i>	WA z Score	LA z Score
AD infants	36	-.49 (-.80, -.17)*	-.47 (-.78, -.17)*	19	-.50 (-.92, -.10)*	-.49 (-.93, -.09)*
Controls	58	.08 (-.15, .32)	.12 (-.10, .36)	56	.30 (.05, .54)	.23 (-.03, .48)

Values are mean (95% CI) adjusted for infant's gender, birth date, weight and length at birth, and mother's age.

\*  $P < .01$  versus controls.

and then decreased ( $\Delta$ :  $-.38$ ; 95% CI:  $-.85$ – $-.09$ , at 12 months of age).

### DISCUSSION

An impairment of growth pattern has been recognized as complication of AD in childhood,<sup>2–6</sup> but it is unknown when it begins. Moreover, it has been shown that the early type of feeding can influence the growth of healthy infants during the first year of life,<sup>7</sup> but in AD infants, this factor has been investi-

gated only within a BF group in relation to the effects of discontinuing breastfeeding.<sup>22</sup>

The aims of this study were to compare the growth pattern of AD and healthy infants during the first year of life and to evaluate whether any difference exists between BF and non-BF infants.

We have found an impairment in growth of AD infants in the first year of life beginning in the first months of life. The impairment was notably marked after the onset of disease, but in length it was evident



before the onset of disease. Indeed, in the healthy group the mean values of WA and LA z score ranged during the first year of life between approximately the corresponding 50th and 57th percentiles of reference age- and gender-adjusted growth curves.<sup>16</sup> These results are consistent with values found in other studies.<sup>12</sup> In contrast, AD infants showed a value of growth indices averaging the 50th percentile only at birth, whereas at 3, 6, and 12 months of age the WA and LA z scores regressed approximately to the 41st, 31st, and 30th percentiles and to the 38th, 30th, and 31st percentiles, respectively. The difference between AD and healthy infants remained both in BF and non-BF infants.

These findings, while confirming that young AD children have an impaired growth compared with healthy controls,<sup>7,23</sup> further point out that an impairment in growth of AD infants is already evident during the early months of life. However, unlike healthy infants, the early type of feeding seems to have only a marginal influence on growth in AD infants during the first year of life. In contrast, severity of disease may be associated with a more pronounced impairment of growth. This finding is supported by Miyoshi and colleagues,<sup>23</sup> who found that the WA and LA z scores of AD infants were significantly lower in subjects with more severe dermatitis. The negative effect of severity of disease on growth may suggest some speculations about the causes of growth impairment in AD. In particular, a reduced growth might be related to a decreased energy and protein intake for the less acceptable dietary schedules and/or the disturbing symptoms. A negative effect of AD on absorption from local mucosal reactions in the intestinal tract may be also hypothesized, as well as an increased energy and protein expenditure for a modified skin turnover and a major infant's reactivity. Finally, a neurohormonal action negatively affecting growth progression could be mediated by the drug treatment. More studies are desirable to investigate the previous hypotheses to clarify the underlying mechanism of the poor growth of the AD infants during the first year of age. Whichever the cause, dietary interventions may be required to reduce the negative effect of AD on growth. Recently, Isolauri et al<sup>22</sup> found that atopic infants with onset of allergic disease during exclusive breastfeeding reduced significantly the severity of AD after stopping breastfeeding, while the relative length of infants increased. In this context the immediate advantage deriving from allergen avoidance should be weighed with the long-term benefits of breastfeeding on the prevention of allergic disorders.<sup>24</sup>

### CONCLUSION

The atopic status itself seems to represent a major risk condition for the impairment of growth of infants with AD during the first year of life, while the early type of feeding may have just a marginal role. Although we still need to identify the metabolic pro-

cess adversely affecting growth in AD infants, "individually tailored elimination diets"<sup>7</sup> may be required to sustain an adequate growth in this population.

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