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Abstract

The wide variety of infant formula available on the market can be confusing for parents and physicians. We aimed to determine associations between predominant type of formula used from birth to 4 months and parental and child characteristics and type of physician consulted; then to describe relations between type of formula used and growth. Our analyses included 1,349 infants from the EDEN mother-child cohort. Infant's feeding mode and type of formula used were assessed at 4 months by maternal self-report. Infant's weight and height from birth to 4 months, measured in routine follow-up were documented by health professionals in the infant's personal health record. Anthropometric z-scores were calculated by using World Health Organization growth standards. Multinomial logistic regression was used to identify factors associated with type of formula predominantly used; relations with growth were analyzed by linear regressions. Partially hydrolyzed formulas were more likely to be used by primiparous women ($p<0.001$), those breastfeeding longer ($p<0.001$) and for infants with family history of allergies ($p=0.002$). Thickened formulas were more often used by mothers returning to employment in the first 4 months ($p=0.05$) and breastfeeding shortly ($p<0.001$). No significant relation was found between infant growth and type of formula ($p>0.20$). Infants breastfed shorter showed higher weight-for-age ($p<0.001$) and length-for-age ($p=0.001$) z-scores changes between birth and 4 months. The use of a specific type of infant formula seems to be mainly related to parental characteristics. Infant's growth in the first 4 months is related to other factors than to type of formula used.

Keywords: Infant – Breastfeeding – Formula Feeding – Growth – Sociodemographic Factors – Longitudinal Study

Introduction

The benefits of breastfeeding on child health are well described in the literature (Van Rossum *et al.* 2001; Ip *et al.* 2007). The World Health Organization (WHO) and most of the international pediatric societies promote breastfeeding as optimal infant nutrition and recommend exclusive breastfeeding until 6 months (Boland 2005; Gartner *et al.* 2005; Agostoni *et al.* 2009). Despite these recommendations, many parents use infant formula before 6 months. The wide range of formulas available can be confusing and overwhelming for parents and physicians. Formula companies target physicians with advertising campaigns, advocating functional and beneficial effects of their products for infant health. Thickening agents, prebiotic, probiotics are added in some infant formulas. Prebiotics might have the potential to increase the total number of bifidobacteria present in the gut, and to soften stools (Boehm & Moro 2008; Sherman *et al.* 2009); and probiotics might play a role in preventing childhood diseases, especially diarrhea (Moreau 2001). Their effects on infant growth are not well known.

Several studies have been conducted to describe determinants of infant feeding mode (Butler *et al.* 2004; Lanting *et al.* 2005; Bolling *et al.* 2007; Grjibovski *et al.* 2008; Kristiansen *et al.* 2010) and their effects on child growth (Kramer *et al.* 2007; Griffiths *et al.* 2009). However, determinants of use of a specific formula compared to others are poorly described in the literature and very few studies (Koletzko *et al.* 2009) conducted on samples of significant size assess and compare their specific impact on child growth.

The prevalence of overweight children is rising and there is a strong evidence for an association between rapid weight gain in infancy and later obesity (Stettler 2007). Early feeding, especially milk feeding has been identified as important factor. Studies relating milk feeding to growth pattern often compare breastfed to formula-fed infants without distinguishing the different types of formulas. Some formulas may be given specifically to fast or slow grower infants and the influence of a specific formula on infant growth may depend on the characteristics of this formula. Before considering formula-fed infants as a single group we aimed to determine the associations between type of formula used and parental, child and physicians characteristics; and to describe their relations with infant growth from birth to 4 months.

Materials and Methods

Study design

The EDEN mother-child cohort (study of pre- and early postnatal determinants of child health and development) recruited 2,002 pregnant women aged 18-45 years who presented before 24 weeks of gestation for prenatal care at the obstetrics and gynaecology department of Nancy and Poitiers University Hospitals. Enrolment started in February 2003 in Poitiers and September 2003 in Nancy; it lasted 27 months in each center. Exclusion criteria were multiple pregnancies, history of diabetes, illiteracy, moving outside the region planned in the next three years. The study received approval from the ethics committee (CCPPRB) of Kremlin-Bicêtre. Files have been declared to the 'National Committee for Processed Data and Freedom' (CNIL). Written consent was obtained from mothers at enrolment, for fathers between mother's enrolment and delivery and for infants after delivery.

Data collection

At 24-28 weeks of gestation, mothers had a clinical examination performed by research midwives assistants, where their height was measured, using wall Seca 206 stadiometer (Hamburg, Germany) to the nearest 0.2 cm. Maternal education and pre-pregnancy weight, family income during pregnancy and family history of allergies were obtained by interviewing the mother. Paternal weight and height were measured with the same procedure at some point between mother's inclusion and delivery.

Data were collected from obstetrical and pediatric records on parity, gestational age at delivery, birthweight (measured with electronic Seca scales, Seca 737 in Nancy and Seca 335 in Poitiers; Hamburg, Germany), birth length (measured with a wooden somatometer; Testut, Béthune, France) and infant feeding at maternity discharge.

At 4 months, mothers completed questionnaires on which they reported infant's weight and length measured every month since birth in routine follow-up and documented by health professionals in the infant's personal health record (kept by the mother). Data on mothers' return to employment in the first 4 months, type of physician consulted for the infant, feeding practices and infant health (diarrhea, regurgitations, colics) were also collected. Mothers reported in the 4-month questionnaire, if any, the different formula consumed by their infant

and the duration of consumption of each: less than a week / between 1 week and 1 month / more than 1 month but less than 4 months / since birth.

Generated variables

In order to classify infants, because of frequent formula changes in the first 4 months in our sample, we estimated from the information collected the total duration of exposure to each type of formula. Infants were included into a specific predominant formula category if the total duration of exposure to that formula was higher than the total exposure to any other formula. Our study focused on regular, partially hydrolyzed, thickened (but not enriched in pre- or probiotics) and enriched in pre-or probiotics (thickened or not) formulas as these four types were the most consumed in our sample (Figure 1). We created a class *'others'* with infants who were equally exposed to different formulas, or who had predominantly consumed formulas such as extensively hydrolyzed protein formula but were too few to constitute a class of the variable of interest.

Duration of exclusive breastfeeding (only breast-milk as milk feeds) from hospital discharge to 4 months was calculated using the information recorded by midwives at discharge and self-reported maternal feeding practices in the 4-month questionnaire for infants who received both breast- and formula-milk during their first 4 months of life.

Since children's measurements were not collected at the same time point, we predicted individual infant weight and length at 4 months using non linear mixed effects models. Among the main parametric growth models (Hauspie 1989), Jenss Model ($y= a+b\times age–exp(c + d\times age)$) best fitted our weight and length growth data from birth to one year of age, according to AIC fit parameter and residuals distribution over time. The model with a random effect on every parameter allowed to have individual equations of the weight (height resp.) growth trajectories by computing each of the four equation's parameters as the fixed-effect coefficient plus the random-effect term (Pinheiro & Bates 2000). Using the individual equations, we calculated predicted weight and length at four months for all the subjects. All available infant weight and height from birth to the 1-year clinical examination were used in growth modeling. Median and interquartile range of the number of measurements (for weight as well as for height) were 10 [7-12]. There was a median of 4 measurements for the 0-4 month's period, 3 for the 4-8 month's period and 3 after 8 months. Among infants with at least one measurement during the first year, 100 % had at least one measurement of weight before 4 months, 81.9 % between 4 and 8 months and 87.2 % after 8 months (99.8 %, 81.6 %

and 87.4 % for height respectively). Finally, for the statistical analyses of associations, infants with fewer than 4 measurements in the first year were excluded since their growth trajectory could be shrunk toward the mean growth trajectory.

In order to facilitate comparisons of our data with other international studies, we used these predicted values to obtain weight-for-age (WFA), length-for-age (LFA) and weight-for-length (WFL) z-scores at birth and 4 months, according to WHO's growth reference data (WHO Multicentre Growth Reference Study Group 2006). The different z-scores were then used in the statistical analysis to study relationships between infant growth and breast and infant formula feeding.

Parental body mass indexes (BMI) were computed as the reported pre-pregnancy weight (kg) / measured height squared (m^2) for the mother and the measured weight (kg) / measured height squared (m^2) for the father. When measurements were unavailable from the father, reported weight by the father (14.9%) was used, and reported height by the father (13.9%) or by the mother (7.6%) was used. Underweight was defined as a BMI (kg/m^2) <18.5, normal weight as a BMI of 18.5-<25, overweight as a BMI of 25-<30 and obesity as a BMI ≥30. Because of small number of underweight fathers in the EDEN cohort (n=19; 1.0%), we grouped together fathers in the underweight and normal BMI categories. Parental heights were divided into quintiles.

To handle missing data, we proceeded as following: when percentage of missing value was lower than 5%, we imputed the modal class value (all except sex, EBF duration, gestational age, birthweight, paternal height and BMI) and when percentage of missing values was higher than 5%, they were grouped into a separate category (paternal height).

Study sample

Of the 2,002 recruited women, 96 were excluded because they left the study before or at the time of delivery for personal reasons, 4 because of intra-uterine death, and 3 because they delivered outside the study hospitals. Data on birthweight were available for 1,899 newborns. We excluded 232 infants because the 4-month questionnaire was unavailable. When compared to the included mothers, the excluded mothers were less educated (29.7% vs. 55.4% had a university degree, p<0.001) and less often born in France (80.6% vs. 90.4%, p<0.001). The excluded infants had a gestational age slightly higher than that of included infants (39.02 vs. 39.29, p=0.05). There were no statistical difference on infants' sex (p=0.08) and birthweight (p=0.15). For the analyses, we selected infants who received formula at least

one week during the first 4 months and who had information about type of formula used (missing(n=27)). Analyses on formula-fed infants were therefore based on 1,354 infants.

To perform the analyses on post-natal growth, we selected a sub-sample of 1,239 infants with growth data from birth to 4 months. The 115 pairs excluded at this stage differed from the others by maternal education (University degree: 41.7% vs. 54.1%, p=0.02), birthweight (2,710 g vs. 3,319 g, p<0.001) and gestational age (37 weeks of amenorrhea vs. 39, p<0.001).

Statistical analysis

Comparisons of means and proportions by formula group were performed by ANOVA or chi-square respectively (results not shown). Associations between type of formula (dependent variable) and covariates related to parental, child and health professional characteristics were measured by adjusted odds ratios estimated by multinomial logistic regression.

Relation between growth and type of formula were analyzed by multiple linear regressions. The dependent variable was the change in z-score between birth and 4 months (Δ z-score), which was the difference of z-scores between birth and 4 months. The models comprised type of formula, confounding variables that were significantly related to both growth and type of formula (center, education, family income, mother's return to employment, EBF duration and type of physician consulted), variables highly related to growth (parental heights and BMIs, infant' sex and gestational age), and variables related to type of formula used that might influence growth (occurrence of diarrhea and regurgitations). We also adjusted for the average z-score between 0 and 4 months to consider changes relative to the mean weight or height values.

Analyses were performed with SAS software (version 9.2; SAS Institute, NC, USA). A p-value ≤0.05 was considered to indicate statistical significance for all the analyses.

Results

Description of formula-fed infants

Mothers were on average 29.5 years old and approximately 48% of them were primipara (Table 1). More than half of mothers had a university degree and for 91.4% of the families, both parents were born in France. The mean birthweight was 3,267 g and 5.8% of the infants were born preterm. The mean exclusive breastfeeding duration was 0.9 month. The rate of any

breastfeeding was 68.1% at maternity and 21.7% at 4 months. One third of the infants were predominantly exposed to regular formula (Figure 1). For 39 % of the infants, type of formula used never changed in the first 4 months, while about 26 % had their formula-milk changed twice or more. In infants who received different formulas in the first 4 months, the predominant formula was used 83 % of the time on average for those whose formula changed once and 77 % of the time for those whose formulas changed twice or more.

In the sub-sample with available data on growth (n=1,239), 1.3% of infants had a WFA z-score > 2 standard deviation at birth and 0.3% at 4 months. The mean z-scores at different ages and by type of formula are presented in (Table 2).

Determinants of infant formulas' use

Partially hydrolyzed formulas were twice as likely to be used by the most educated mothers compared to regular formulas, but there was no statistical significant difference for the global comparison of the different formulas to regular formulas according to education level (Table 3). Partially hydrolyzed formulas were less likely to be used by multiparous mothers. Thickened formulas were more often used by mothers returning to employment in the first 4 months. Partially hydrolyzed and thickened formulas were more likely to be given to infants with family history of allergies than regular formula. Longer period exclusive breastfeeding was positively related to use of partially hydrolyzed formulas but negatively with thickened. Thickened formulas were more likely consumed by infants having regurgitations in the first 4 months. There was no significant association between family income or parent's country of birth and type of formula (all $p>0.19$).

The use of formulas, even the enriched pre- or probiotic formulas, was associated neither with infant characteristics nor with occurrence of diarrhea in the first 4 months. Infants consuming other formulas than regular tended to consult more specialists ($p=0.10$).

Relation with infant growth

No significant relation was found between weight and length growth and type of formula consumed predominantly during the first 4 months (Table 4) after adjustment on parental and child characteristics. Nonetheless, infants using partially hydrolyzed formula tended to have a lower WFL z-score change than those consuming regular. Infants that were shorter breastfed showed significant higher WFA and LFA z-scores changes but not WFL z-score.

WFA z-score change of infants of obese mothers was significantly lower than that of infants whom mothers had a normal BMI; there was no association between maternal BMI and WFL z-score change. While paternal BMI was associated with infant weight gain regardless of BMI category, only paternal obesity seemed to be related to infants' WFL z-score. There was no significant interaction between exclusive breastfeeding period or type of formula used on the one hand and gestational age, maternal education, parental heights or BMIs on the other hand on infant growth (all $p>0.10$).

In a sensitivity analysis, we ran the same models, excluding premature infants (n=35, 2.82%) and the results did not change (data not shown). To determine the effects of imputations on our results, we ran the same models, without infants with missing values (n=88, 5.5 %) and the results remained similar to those presented above (data not tabulated).

Discussion

Many studies have been conducted on determinants of feeding practices especially breastfeeding (Scott *et al.* 2006; Bonet *et al.* 2008; Grjibovski *et al.* 2008; Meedya *et al.* 2010), and impact of feeding on child growth (Agostoni *et al.* 1999; Harder *et al.* 2005) but as far as we are aware, ours is the first to examine relationships between type of formula used during the first months of life and characteristics related to parents, infants and type of physician consulted, including their associations with infant's growth. We found that types of formula most frequently used in our cohort were related to parity, mother's return to employment, family history of allergy, exclusive breastfeeding duration and infant's regurgitations, to infants' characteristics at birth to a lesser extent but not significantly to family income and parents' country of birth. We did not found any significant association between types of formula most frequently used in the first 4 months and infant growth during the same period.

The prospective nature of the EDEN study allowed us to collect precisely the types of formula used and the variety of information collected led us to examine factors determining their use among mothers who did not want or could not exclusively breastfeed. However, because information about infant formulas prescription by physicians was not collected, we could not determine whether their use was due to physician's advice or to mothers' personal decision. As changes in infant formula are quite frequent between birth and 4 months, we categorized children according to their predominant formula used. We acknowledge that this categorization does not take account of the reason for choice or for possible formula change

and may have weakened the relations, in particular with growth. Additional analyses were therefore performed to assess whether association between type of formula and growth was different in infants who received only the specific formula over the period or in those who changed formula and received it only as the predominant formula. Occurrence of formula changes in the first 4 months was not significantly related to growth (p-values: 0.30 for weight-for-age, 0.06 for length-for-age and 0.73 for weight-for-length z-score change). There were no significant interactions between change in formula and type of predominant formula in relation to growth (p-value for the interactions: 0.32 for weight-for-age, 0.10 for length-for-age and 0.62 for weight-for-length z-score change). Thus, we believe that our categorization do not mask any real associations with growth.

Our study population is not representative of the general population. Compared to the national perinatal survey carried out on 14,482 women who delivered in France in 2003 (Blondel *et al.* 2006), women included in the EDEN study were more educated and more often employed. However, infants' growth in the study fits well with the normal range of the WHO growth curves (WHO Multicentre Growth Reference Study Group 2006) (data not shown) and we believe that the relationships observed are applicable to a general population of infants born in France from middle class parents. However, we lacked power to detect associations related to low socioeconomic situations, which may explain that we do not find any association between income levels and type of formula.

Several studies have shown that primiparous mothers breastfed more than multiparous mothers at hospital discharge (Crost & Kaminski 1998; Bonet *et al.* 2008), and that breastfeeding duration was positively associated with being multiparous (Bolling *et al.* 2007). Our study goes further, analyzing associations between type of formula used and parity, and showing that multiparous (3 or more deliveries) use more often regular formula than others. Even if global family income was not related to type of formula, the previous associations may be related to family income available per child, as regular formulas are often considered as the cheapest on the French market. As already observed with breastfeeding (Butler *et al.* 2004), mothers' experience with their first child has probably an effect on their practices with the following children.

Most of the pediatric societies recommend, in case of family history of allergy and after breastfeeding cessation, a partially hydrolyzed formula (Høst *et al.* 1999; Committee on Nutrition of American Academy of Pediatrics 2000; Chouraqui *et al.* 2008a). In our study, consumption of partially hydrolyzed formulas was positively associated with family history of

allergies and exclusive breastfeeding duration, which is consistent with current recommendations.

It has been demonstrated that mothers giving formula to their infant returned to employment during the first 4 months after delivery (Stewart-Knox *et al.* 2003; Bolling *et al.* 2007; Hawkins *et al.* 2007). It has also been shown that adding cereals to babies' bottle to extend sleep bouts although not recommended, is part of maternal beliefs that can have an influence on feeding practices (Kannan *et al.* 1999; Kavanagh *et al.* 2010). We found a positive association between consumption of thickened formula and mother's return to employment, suggesting that mothers may use thickened formula to promote sleep or 'settle' their infant.

Research documenting the efficacy of pre- or probiotics is still emerging; the benefits of adding them in infant formulas remain unclear (Szajewska *et al.* 2006; Douglas & Sanders 2008; Thomas & Greer 2010; Braegger *et al.* 2011). Contrary to other studies (Guarino *et al.* 1997; Szajewska & Mrukowicz 2001), we found no significant association between using enriched pre- or probiotic formulas and digestive disorders, especially the occurrence of diarrhea in the first 4 months. However, because of our sample size, we had to group together all infants using pre- or probiotics (or both) regardless of the type of oligosaccharides or strains included in the formula. That could explain part of this lack of association as the effects of probiotics for instance are strains dependant (Szajewska & Mrukowicz 2005; Canani *et al.* 2007; Braegger *et al.* 2011). Our results showed an association between consuming enriched pre- or probiotic formulas and occurrence of regurgitations, probably because we grouped together enriched in pre- or probiotics formulas and those both thickened and enriched.

Growth parameters were not related to type of formula after adjustment for parental and child characteristics in our analysis. Formula-fed infants are known to grow more rapidly than breastfed infants from about the third month in the first year of life (Dewey *et al.* 1995; Kramer *et al.* 2004). We showed that infants who were breastfed longer had significant lower WFA and LFA z-scores changes between 0 and 4 months but not for WFL z-score suggesting a slower but, harmonious growth in weight and length. Evidences indicates long term effects of feeding practices and of rapid weight gain during early infancy on infant growth patterns (Ong *et al.* 2000) but mechanisms underlying the differences between the patterns are not well known. Regarding the use of infant formula, one might ask the question of the effect of the composition of infant formulas on early growth. A clinical trial showed that lower protein

content in infant formula was associated with a lower weight gain during the first 2 years of life (Koletzko *et al.* 2009). We could not explore the relation between consumption of lower protein formula and growth in our analyses because these formulas have been recently introduced in France and very few infants have used them in our sample (n=42, Figure 1). Furthermore, the basic composition of formulas consumed in the EDEN study was almost homogeneous in terms of protein and energy contents, according to European regulations.

Effects of pre- or probiotics and of thickened formulas on infant growth are poorly documented. As most of the studies on the topic (Chouraqui *et al.* 2008b; Braegger *et al* 2011), we found that adding pre- or probiotics in infant formulas was not related to infant's weight and length gain. We found a negative relation between type of physician consulted and WFL z-score change. Infants consulting pediatricians are more likely to be the sickest which probably explains their significantly lower WFL z-score change during the study period. However, we acknowledge that our analyses cannot attribute cause and effect.

In our study, maternal obesity was related to a significantly slower weight growth while paternal BMI was related to a faster infant weight and length growth and parental heights to a faster infant length growth. As we discussed previously (Mok *et al.* 2008; Regnault *et al.* 2010), both genetic and pre- and postnatal environmental factors are known to contribute to parental influence on infant growth. Our analysis showed that these parent-infant relationships, and especially those with parental BMI, are observed whatever the infant feeding mode, including the type of formula used.

Conclusion

The range of infant formulas is quite varied and factors related to the infant, such as prematurity, digestive disorders and allergy, may influence the use. Besides these factors, our results pointed out relationships with other factors related to family, such as parity, maternal education level and employment status, that should be taken into account when describing relationships between the use of infant formulas and growth. In our study, after adjusting for these factors, the type of formula used was not related to infant growth nor to other health aspects such as diarrhea. In contrast, exclusive breastfeeding duration seems to affect significantly infant growth between birth and 4 months after taking into account family and child characteristics.

Key messages

- The use of infant formulas (partially hydrolyzed, thickened, enriched in pre- or probiotic and others) in the first four months of life seems to be essentially related to maternal return to employment, parity and parental history of allergies.
- Infant growth was not related to type of formula predominantly used in our study.
- Infants who were breastfed shorter showed higher growth between birth and 4 months.

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Figure 1: Types of formula used predominantly or not in the EDEN study. Includes 1354 infants exclusively formula-fed or not in the first 4 months of life. In infants who were in the regular category, regular formulas were used 95 % of the time on average. Similarly, in the other groups, pre- or probiotics, thickened and partially hydrolyzed formulas were used respectively 89, 85 and 95 % of the time on average. *Regular, pre- or probiotic, thickened and partially hydrolyzed formulas: successive or concomitant use.

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TABLE 1: Characteristics of parents and offspring (n=1354).

Variable	n	Mean ± SD or % yes
Parental characteristics		
Education (% university degree)	1332	53.0 %
Monthly family income ≤3,000 €	1346	72.1 %
Primiparous	1351	48.0 %
Mother lives with a partner	1335	95.3 %
Mother returned to employment in the first 4 months	1341	45.7 %
Family history of allergy	1346	50.5 %
Both parents born in France	1354	91.4 %
Maternal age at delivery (yrs)	1354	29.5 ± 4.8
Maternal height (cm)	1334	163.4 ± 6.1
Paternal height (cm)	1344	176.8 ± 6.4
Maternal prepregnancy BMI < 25 kg/m²	1324	71.2 %
Paternal BMI < 25 kg/m²	1252	50.1 %
Child characteristics		
Female sex	1354	47.3 %
Duration of exclusive breastfeeding (mo)	1352	0.9 ± 1.1
Gestational age (weeks of amenorrhea)	1354	39.2 ±1.7
Birthweight (g)	1354	3267 ± 509
Occurrence of diarrhea between 0-4 mo	1337	21.3 %
Occurrence of regurgitations between 0-4 mo	1328	62.2 %
Other variables		
Recruitment center (% Poitiers)	1354	50.8 %
Type of physician consulted between 0-4 mo, General practitioner	1350	28.4 %

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TABLE 2: Z-scores at birth and 4 months by type of formula predominantly used in the EDEN cohort study (n=1,239).

	Type of formula-milk				
WHO Z-scores	**Regular (n=432)**	**Partially hydrolyzed (n=165)**	**Thickened (n=166)**	**Pre-/ Probiotics (n=278)**	**Others (n=198)**
Birth					
Weight-for-age	0 .04 ± 0 .88[a]	0 .12 ± 0 .91	0 .002 ± 0 .94	-0 .01 ± 0 .89	-0 .07 ± 1 .01
Length-for-age	0 .18 ± 0 .98	0 .22 ± 1 .08	0 .07 ± 1 .11	0 .12 ± 1 .00	0 .05 ± 1 .20
Weight-for-length	-0 .07 ± 1 .11	-0 .01 ± 1 .11	-0 .005 ± 1 .15	-0 .07 ± 1 .13	-0 .10 ± 1 .20
4 months					
Weight-for-age	-0 .25 ± 0 .82	-0 .31 ± 0 .86	-0 .21 ± 0 .78	-0 .26 ± 0 .86	-0 .42 ± 0 .87
Length-for-age	-0 .10 ± 0 .90	-0 .03 ± 0 .96	-0 .12 ± 0 .91	-0 .09 ± 0 .92	-0 .18 ± 0 .97
Weight-for-length	-0 .20 ± 0 .88	-0 .34 ± 0 .95	-0 .11 ± 0 .78	-0 .21 ± 0 .85	-0 .34 ± 0 .85

[a] : mean ± SD

TABLE 3: Adjusted Odds-Ratios (OR) of the relations between predominant type of formula used and parental and child characteristics, and type of physician consulted (n=1,354).

	Type of formula-milk (Regular as reference, n=463))								
	Partially hydrolyzed (n=176)		Thickened (n=187)		Pre-/probiotics (n=293)		Others (n=235)		Global p-value[a]
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	
Parental characteristics									
Maternal Education (Ref: No degree)									0.10
High school degree	1.26	0.68-2.36	1.33	0.80-2.19	1.38	0.88-2.17	1.07	0.65-1.77	
2-year university degree	1.38	0.75-2.54	0.86	0.49-1.49	1.20	0.75-1.92	1.36	0.82-2.34	
≥ 3-year university degree	2.37	1.31-4.27	0.94	0.53-1.64	1.31	0.81-2.10	1.69	1.02-2.78	
Monthly family income (Ref: 1501-2300 €)									0.54
<1501	1.06	0.56-2.00	0.93	0.53-1.61	0.81	0.49-1.36	0.78	0.46-1.33	
2301-3000	1.05	0.63-1.75	0.97	0.60-1.58	1.50	0.83-1.87	1.12	0.73-1.73	
>3000	1.57	0.91-2.71	1.57	0.91-2.70	1.51	0.95-2.39	1.06	0.64-1.75	
Parity (Ref: 1)									<0.001
2	0.64	0.40-0.98	1.65	1.11-2.46	1.28	0.91-1.80	1.13	0.78-1.65	
≥ 3	0.27	0.14-0.50	0.71	0.40-1.29	0.63	0.38-1.02	0.62	0.37-1.03	
Mother returned to employment in the first 4 months (Ref: No)	0.85	0.57-1.28	1.49	1.01-2.22	1.17	0.84-1.64	0.83	0.57-1.19	0.05
Family history of allergy (Ref: No)	2.11	1.44-3.08	1.49	1.04-2.14	1.19	0.87-1.61	1.32	0.95-1.83	0.002
Country of birth (Ref: Both born in France)									0.19
One of them born outside France	0.87	0.46-1.66	1.25	0.64-2.45	1.70	0.91-3.17	0.77	0.45-1.31	

Child characteristics									
Female sex (Ref: Male)	0.96	0.66-1.40	0.82	0.57-1.18	1.00	0.73-1.36	1.12	0.80-1.55	0.68
Duration of exclusive breastfeeding (mo)	1.48	1.25-1.75	0.73	0.60-0.89	1.02	0.88-1.90	1.01	0.86-1.18	<0.001
Gestational age (weeks of amenorrhea)	0.94	0.82-1.09	0.93	0.82-1.06	1.03	0.91-1.15	0.91	0.81-1.02	0.32
Birthweight (g)	1.27	0.79-2.03	0.87	0.55-1.37	0.84	0.57-1.25	0.69	0.45-1.05	0.20
Occurrence of diarrhea between birth and 4 mo (Ref: No)	0.74	0.46-1.20	0.66	0.43-1.02	0.73	0.50-1.08	0.94	0.63-1.39	0.25
Occurrence of regurgitations between birth and 4 mo (Ref: No)	0.99	0.68-1.45	2.68	1.80-3.98	1.74	1.27-2.39	1.48	1.06-2.08	<0.001
Other variables									
Recruitment center: Nancy (Ref: Poitiers)	0.58	0.39-0.86	0.89	0.61-1.30	0.86	0.62-1.18	0.92	0.65-1.30	0.10
Type of physician consulted between birth and 4 mo (Ref: GP[b])									0.10
Pediatrician	1.46	0.84-2.53	1.14	0.65-1.97	1.57	1.01-2.46	1.82	1.11-2.99	
GP and pediatrician	1.22	0.74-1.99	1.41	0.89-2.23	1.16	0.77-1.73	1.73	1.11-2.67	
Specialist with/no GP or pediatrician	1.95	1.13-3.36	1.71	1.01-2.89	1.71	1.09-2.69	1.98	1.20-3.27	

527 [a] Multinomial logistic regression with regular formula as a reference group.

528 [b] General practitioner.

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TABLE 4 : Linear regression models with weight-for-age, weight-for-length and length-for-age z-score change between birth and 4 months as dependent variables and covariates related to parents, child and type of physician consulted (n=1,239).

	Δ WHO Z-scores[a]					
	Weight-for-age		Weight-for-length		Length-for-age	
	Estimate[b]	95% CI[c]	Estimate	95% CI	Estimate	95% CI
Child characteristics						
Type of formula-milk (Ref: Regular)						
Partially hydrolyzed	-0.07	-0.22, 0.07	-0.19	-0.41, 0.04	0.08	-0.07, 0.24
Thickened	0.05	-0.09, 0.19	0.03	-0.19, 0.25	0.07	-0.09, 0.22
Enriched in pre- or probiotics	0.08	-0.04, 0.20	0.06	-0.12, 0.25	0.05	-0.08, 0.18
Others	-0.04	-0.18, 0.09	-0.09	-0.30, 0.12	0.01	-0.14, 0.15
Duration of exclusive breastfeeding (mo)	-0.08	-0.12, 0.04	-0.04	-0.11, 0.03	-0.08	-0.12, -0.03
Gestational age (weeks of amenorrhea)	-0.21	-0.25, -0.17	-0.12	-0.17, -0.07	-0.11	-0.15, -0.07
Occurrence of diarrhea between birth and 4 mo (Ref: No)	-0.01	-0.12, 0.10	0.04	-0.13, 0.21	-0.05	-0.17, 0.07
Occurrence of regurgitations between birth and 4 mo (Ref: No)	0.01	-0.08, 0.10	0.08	-0.06, 0.22	-0.04	-0.14, 0.06
Parental characteristics						
Maternal BMI, kg/m² (Ref: Normal)						
Thin	-0.08	-0.25, 0.09	-0.18	-0.45, 0.08	–	–
Overweight	-0.08	-0.20, 0.04	0.02	-0.16, 0.21	–	–
Obese	-0.25	-0.42,-0.09	-0.10	-0.35, 0.16	–	–
Paternal BMI, kg/m² (Ref: Normal)					–	–
Missing	0.21	0.03, 0.39	0.12	-0.16, 0.39	–	–
Overweight	0.11	0.01, 0.20	0.12	-0.03, 0.27	–	–
Obese	0.25	0.08, 0.42	0.47	0.21, 0.74	–	–
Other variables						

Type of physician consulted between birth and 4 mo (Ref: GP[d])						
Pediatrician	-0.12	-0.25, 0.01	-0.31	-0.51, -0.11	0.01	-0.04, 0.24
GP and pediatrician	-0.03	-0.15, 0.09	-0.12	-0.30, 0.06	0.01	-0.12, 0.13
Specialist with/no GP or pediatrician	-0.01	-0.15, 0.12	-0.06	-0.27, 0.14	-0.01	-0.16, 0.13

[a] Change in z-score between birth and 4 months.

[b] Adjusted for recruitment center, maternal education, monthly family income, mother's return to employment, infant's sex, parental heights (for the analyses on length-for-age z-score) average z-score between 0 and 4 months.

[c] Confidence interval

[d] General practitioner