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1 **Determinants of infant formula use and relation with growth in the first 4 months**

2 Aisha Betoko MPH^{1,2}, Marie-Aline Charles MD MPH^{1,2}, Régis Hankard MD³, Anne Forhan
3 MPH^{1,2}, Mercedes Bonet PhD^{4,5}, Nolwenn Regnault PhD^{1,2}, Jérémie Botton PharmD PhD^{1,2},
4 Marie-Joséphine Saurel-Cubizolles PhD^{4,5}, Blandine de Lauzon-Guillain PhD^{1,2} and the EDEN
5 mother-child cohort study group.

6 ¹ INSERM, CESP, Centre for research in Epidemiology and Population Health, U1018,
7 Epidemiology of diabetes, obesity and chronic kidney disease over the life course, F-94807,
8 Villejuif, France.

9 ² Paris Sud 11 University, UMRS 1018, F-94807, Villejuif, France.

10 ³ INSERM, CIC 0802, Clinical Investigation Centre, University hospital, F-86021, Poitiers,
11 France.

12 ⁴ INSERM, UMRS 953, Epidemiological Research Unit on Perinatal Health and Women's and
13 Children's Health, F-94807, Villejuif, France.

14 ⁵ UPMC, Paris 06 University, Paris, France.

15

16 **Corresponding author:**

17 Betoko Aisha,

18 INSERM UMRS 1018

19 15-16 av. Paul Vaillant Couturier, 94807 Villejuif, FRANCE

20 Tel: +33145595194; Fax: +3314726945; aisha.betoko@inserm.fr

21

22

23 **Abstract**

24 The wide variety of infant formula available on the market can be confusing for parents and
25 physicians. We aimed to determine associations between predominant type of formula used
26 from birth to 4 months and parental and child characteristics and type of physician consulted;
27 then to describe relations between type of formula used and growth. Our analyses included
28 1,349 infants from the EDEN mother-child cohort. Infant's feeding mode and type of formula
29 used were assessed at 4 months by maternal self-report. Infant's weight and height from birth
30 to 4 months, measured in routine follow-up were documented by health professionals in the
31 infant's personal health record. Anthropometric z-scores were calculated by using World
32 Health Organization growth standards. Multinomial logistic regression was used to identify
33 factors associated with type of formula predominantly used; relations with growth were
34 analyzed by linear regressions. Partially hydrolyzed formulas were more likely to be used by
35 primiparous women ($p<0.001$), those breastfeeding longer ($p<0.001$) and for infants with
36 family history of allergies ($p=0.002$). Thickened formulas were more often used by mothers
37 returning to employment in the first 4 months ($p=0.05$) and breastfeeding shortly ($p<0.001$).
38 No significant relation was found between infant growth and type of formula ($p>0.20$).
39 Infants breastfed shorter showed higher weight-for-age ($p<0.001$) and length-for-age
40 ($p=0.001$) z-scores changes between birth and 4 months. The use of a specific type of infant
41 formula seems to be mainly related to parental characteristics. Infant's growth in the first 4
42 months is related to other factors than to type of formula used.

43

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

46

47 **Introduction**

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

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

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

77

78 **Materials and Methods**

79 *Study design*

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

90 *Data collection*

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

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

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

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

109 *Generated variables*

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

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

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

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

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

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

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

161 *Study sample*

162 Of the 2,002 recruited women, 96 were excluded because they left the study before or at
163 the time of delivery for personal reasons, 4 because of intra-uterine death, and 3 because they
164 delivered outside the study hospitals. Data on birthweight were available for 1,899 newborns.
165 We excluded 232 infants because the 4-month questionnaire was unavailable. When
166 compared to the included mothers, the excluded mothers were less educated (29.7% vs.
167 55.4% had a university degree, $p<0.001$) and less often born in France (80.6% vs. 90.4%,
168 $p<0.001$). The excluded infants had a gestational age slightly higher than that of included
169 infants (39.02 vs. 39.29, $p=0.05$). There were no statistical difference on infants' sex ($p=0.08$)
170 and birthweight ($p=0.15$). For the analyses, we selected infants who received formula at least

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

173 To perform the analyses on post-natal growth, we selected a sub-sample of 1,239 infants
174 with growth data from birth to 4 months. The 115 pairs excluded at this stage differed from
175 the others by maternal education (University degree: 41.7% vs. 54.1%, $p=0.02$), birthweight
176 (2,710 g vs. 3,319 g, $p<0.001$) and gestational age (37 weeks of amenorrhea vs. 39, $p<0.001$).

177 *Statistical analysis*

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

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

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

194 **Results**

195 *Description of formula-fed infants*

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

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

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

209 *Determinants of infant formulas' use*

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

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

224 *Relation with infant growth*

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

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

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

241 **Discussion**

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

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

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

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

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

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

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

297 It has been demonstrated that mothers giving formula to their infant returned to
298 employment during the first 4 months after delivery (Stewart-Knox *et al.* 2003; Bolling *et al.*
299 2007; Hawkins *et al.* 2007). It has also been shown that adding cereals to babies' bottle to
300 extend sleep bouts although not recommended, is part of maternal beliefs that can have an
301 influence on feeding practices (Kannan *et al.* 1999; Kavanagh *et al.* 2010). We found a
302 positive association between consumption of thickened formula and mother's return to
303 employment, suggesting that mothers may use thickened formula to promote sleep or 'settle'
304 their infant.

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

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

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

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

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

349 **Conclusion**

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

359 **Key messages**

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

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380

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

522

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/m ²	1324	71.2 %
Paternal BMI < 25 kg/m ²	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 %

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				
	Regular (n=432)	Partially hydrolyzed (n=165)	Thickened (n=166)	Pre-/ Probiotics (n=278)	Others (n=198)
WHO Z-scores					
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)								Global p-value ^a
	Partially hydrolyzed (n=176)		Thickened (n=187)		Pre-/probiotics (n=293)		Others (n=235)		
	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.

529

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/m ² (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/m ² (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

531 ^a Change in z-score between birth and 4 months.

532 ^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-
533 age z-score) average z-score between 0 and 4 months.

534 ^c Confidence interval

535 ^d General practitioner

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