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1 **Infant feeding practices associated with adiposity peak and rebound in the EDEN**
2 **mother–child cohort**

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35 **Abstract (292/300 words)**

36 **Background/Objective**

37 High magnitude of adiposity peak and early adiposity rebound are early risk markers of later
38 obesity. Infant diet represents one of the main modifiable determinants of early growth. This
39 study aimed to investigate the association between infant feeding practices and age and
40 magnitude of adiposity peak and rebound.

41 **Subjects/Methods**

42 Analyses were based on data from the French EDEN mother–child cohort. Data on
43 breastfeeding and complementary feeding were collected at birth and 4, 8 and 12 months.
44 From clinical examinations and measurements collected in the child’s health booklet up to 12
45 years, individual growth curves were modeled, and ages and magnitudes of adiposity peak
46 and rebound were estimated. Associations between infant feeding practices and growth were
47 investigated by multivariable linear regression in children after testing a child-sex interaction.

48 **Results**

49 In the studied population (n=1 225), adiposity peak occurred at a mean of 9.9 ± 2 months and
50 adiposity rebound at 5.5 ± 1.4 years. Associations between infant feeding practices and
51 adiposity peak or rebound were moderated by child sex. For girls, each additional month of
52 breastfeeding was related to a 2-day increase in the age at adiposity peak ($p < 0.001$), and a 18-
53 day increase in the age at adiposity peak ($p = 0.004$). Whereas for boys, each additional month
54 for the age at complementary food introduction was associated with a 29-day increase in the
55 age at adiposity rebound ($p = 0.02$). For boys, long breastfeeding duration was only related to
56 reduced body mass index at adiposity peak.

57 **Conclusions**

58 Child sex has a moderating effect on the association between infant feeding practices and
59 adiposity peak or rebound. The well-known association between breastfeeding duration and
60 early growth seems stronger in girls than boys. The association found for complementary
61 feeding in boys may give new insights into preventing obesity.

62 **Keywords:**

63 breastfeeding, infant feeding, early growth, BMI, adiposity rebound, obesity.

64 **Introduction**

65 Several systematic reviews suggest that some patterns of body mass index (BMI) during early
66 life predict overweight and obesity later in life (1-3). During the first years of life, BMI varies
67 according to a particular pattern: a rapid increase leading to a peak between age 6 and 12
68 months, called adiposity peak (AP), then a decrease, most children reaching a nadir that
69 precedes the adiposity rebound (AR) around age 5 to 6 years. After this rebound, BMI
70 increases at a slower rate to reach adulthood BMI (4).

71 AP and AR are two milestones in the dynamics of early growth. The age at AR is considered
72 a predictor of further obesity and cardiometabolic risk (2, 5-8). As compared with AR, long-
73 term associations with AP are less known, but findings suggest that age and magnitude of AP
74 predict later childhood BMI and body composition (9-12) and adulthood BMI (13). Higher
75 magnitude and later age at AP are associated with less favorable anthropometric and
76 cardiometabolic factors in childhood (9-12).

77 Infant feeding practices are considered the main modifiable determinants of growth. Indeed, a
78 systematic review concluded that early introduction of complementary foods at or before age
79 4 months increases the risk of childhood overweight (14). Systematic reviews and meta-
80 analyses also highlighted long breastfeeding related to reduced risk of obesity later in life,
81 with a moderate effect size (15, 16). Concerning earlier growth, a recent systematic review
82 concluded that in high-income countries, long duration of exclusive breastfeeding was
83 associated with reduced weight and length gain during infancy and earlier AP (17).

84 Some studies examined the effect of early diet on AR, but the evidence remains sparse. In the
85 British ALSPAC cohort, dietary intake at age 18 months (energy, fat, protein and
86 carbohydrates) was not related to age at AR (18). In the German DONALD study, high
87 protein intake between 12 and 24 months was related to high BMI z-score at AR in girls but
88 not boys, with no associations found with age at AR (19). More recently, in the Australian

89 RAINE cohort, children who stopped breastfeeding before age 4 months showed earlier AR
90 and higher BMI at nadir than those who were breastfed longer (20).

91 In this context, this study aimed to investigate the association between the different
92 dimensions of infant feeding and the dynamic of BMI trajectories in early childhood,
93 examined by AP and AR.

94 **Subjects and methods**

95 Study population

96 The EDEN mother–child cohort (Étude des Déterminants pré et postnatals de la santé et du
97 développement de l’ENfant) enrolled 2 002 pregnant women attending their prenatal visit
98 before 24 weeks’ gestation at Nancy and Poitiers University Hospitals between 2003 and
99 2006 (21). Exclusion criteria were multiple pregnancies, diabetes history, French illiteracy,
100 and planning to move outside the region in the next 3 years.

101 Informed written consent was obtained from parents at enrollment, and consent for the child
102 to be in the study was obtained from both parents after the child's birth. The study received
103 approval from the ethics committee (CCPPRB) of Bicêtre hospital on December 12, 2002 and
104 from the Commission Nationale Informatique et Liberté (CNIL), the French data privacy
105 institution. Informed written consent and ethical approval concerned both data collection and
106 data analysis in line with the overarching objectives of the cohort described in the cohort
107 profile (21).

108 Infant feeding assessment

109 Data on infant feeding were collected at birth and age 4, 8 and 12 months. Any breastfeeding
110 duration (in months), age at infant formula introduction (in months) and age at
111 complementary food introduction (in months) were calculated as described (22, 23). In brief,
112 infant feeding mode was extracted at discharge from medical records and collected in the 4, 8

113 and 12-month questionnaires, wherein mothers reported, when relevant, the date of
114 breastfeeding cessation, the age at infant formula introduction and the age at introduction of
115 several food groups. Any breastfeeding duration correspond to the period where the infant
116 received breast milk, regardless of the other liquids or foods consumed. Age at
117 complementary feeding was defined as the age at introduction of the first food or liquid other
118 than breast or formula milk. At the time of the EDEN study, the French guidelines were to
119 begin complementary feeding ideally from 6 months onwards and in any case not before 4
120 months (24).

121 Because of the temporal superimposition of milk and CF, some studies found strong
122 associations between breastfeeding (BF) duration and age at CF introduction (23, 25, 26).
123 However, CF practices are characterized by the timing but also by the order of introduction of
124 the different food groups, and the type of food (home-made or commercial, specific baby
125 foods). We further considered the full infant diet, using infant feeding patterns previously
126 identified by principal component analysis (27) and labeled as follows: “Later dairy products
127 introduction and use of ready-prepared baby foods” (pattern 1), “Long breastfeeding, later
128 main meal food introduction and use of home-made foods” (pattern 2) and “Use of ready-
129 prepared adult foods” (pattern 3). The second pattern represents higher adherence to the
130 nutritional guidelines (24) and was associated with healthier dietary patterns in childhood
131 (28).

132 Growth and adiposity indicators

133 Anthropometric data were collected from medical record and by interviews, face-to-face or
134 self-administered questionnaires, and clinical examination. Child weight and height were
135 collected during clinical examination at birth and age 1, 3 and 5 years and from the child’s
136 health booklets at each follow-up (4, 8, 12 months, 2, 3, 4, 5, 8 and 9-12 years).

137 Individual growth curves for weight from birth to 12 years were obtained by using the adapted
138 Jenss-Bayley growth curve model (29). Data from the first 3 days (including birthweight)
139 were not included in the model because of a specific dynamic in this period (weight loss).
140 This growth modelling allows for predicting weight at any age included in the time period
141 modelled (from day 4 to 12 years). Predicted weight at 2 months (in grams) was considered
142 by using these individual growth curves.

143 The methods for growth modelling of age at AP and at AR were based on the publication of
144 Sovio et al. (30). BMI [calculated as weight (kilograms) divided by height (meters) squared]
145 curves were modelled separately for estimating AP and AR by using data from two different
146 time periods (infancy and childhood) (31). Therefore, AP and AR were derived separately for
147 two age groups but also separately for boys and girls. Data for day 3 and 24 months were used
148 to estimate AP, and data for 18 months and the maximum age were used to estimate AR. For
149 both estimations, the mixed-effects cubic model with random effects for intercept, slope,
150 quadratic and cubic terms best fit the data. The model was fitted for log-transformed BMI.
151 After individual BMI curves were obtained, age at AP and age at AR (and the corresponding
152 BMI) were estimated by first and second derivatives of curve functions: first derivative null
153 and second negative (or null) for AP and first null and second positive (or null) for AR.

154 Other variables

155 The baseline questionnaire administered during pregnancy or at birth in the medical record
156 was used to collect data on maternal and family characteristics, including maternal education
157 level (in years), smoking status during pregnancy (yes/no), gestational weight gain (in kg),
158 monthly income (in euros), maternal and paternal BMI (in kg/m²). Child characteristics,
159 including sex, preterm birth (yes/no) and birth weight (g), were also extracted from the
160 medical record. Categories of birthweight-for-gestational-age z-scores (small for gestational

161 age/adequate for gestational age/large for gestational age) were defined according to the
162 French Audipog reference curves (32).

163 Sample selection

164 Among the 1907 newborns included in the EDEN cohort, 326 children were excluded as no
165 data on BMI were available after 18 months, 156 children as they had fewer than three BMI
166 measurements between age 18 months and 13 years and 26 children as adiposity rebound or
167 adiposity pic could not be estimated, leading to a sample of 1399 children.

168 For this analysis, we excluded infants with missing data on any breastfeeding duration or age
169 at complementary food introduction (n=3), or potential confounding factors (parental BMI,
170 gestational weight gain, maternal education level, family income or maternal smoking during
171 pregnancy; n=171), which led to a complete-case sample of 1225 individuals (585 girls and
172 640 boys) (**Figure 1**). Secondary analyses including patterns of infant feeding practices
173 involved 795 individuals (386 girls and 409 boys) because some data included in the infant
174 feeding patterns (type of food consumed in infancy: home-made food, ready-prepared baby
175 food, ready-prepared adult food) were collected for a subsample only.

176 Statistical methods

177 Comparisons between excluded and included participants involved chi-square test for
178 categorical variables (education level, family income, maternal smoking, parity) and Student *t*
179 test for continuous variables with normal distribution (age, birth weight).

180 The associations between infant feeding practices and both AP and AR were investigated by
181 multivariable linear regression. We studied four different outcomes separately: age at AP, age
182 at AR, BMI at AP and BMI at AR. The first model included breastfeeding duration and age at
183 complementary food introduction simultaneously. The second model included the three
184 previously identified infant feeding patterns (23). Both models accounted for potential

185 confounders identified from the literature and selected according to the directed acyclic graph
186 method (33): child sex, maternal education level, smoking status during pregnancy,
187 gestational weight gain, monthly income, maternal and paternal BMI, maternal age, preterm
188 birth, birth-weight z-score categories and predicted weight at 2 months.

189 The interactions between sex and both breastfeeding duration and age at complementary
190 feeding introduction were tested by introducing appropriate multiplicative interaction terms
191 into the adjusted models. For the four outcomes, the interaction between breastfeeding
192 duration and child sex was suggestive ($p=0.06$ for age and BMI at AP, $p=0.12$ for age at AR,
193 $p=0.13$ for BMI at AR). The interaction between age at complementary feeding introduction
194 and child sex was significant for only age at AP ($p=0.01$). Because of suggestions for such
195 interactions, we stratified by child sex for all analyses.

196 Sensitivity analyses were conducted excluding infants with major congenital abnormality
197 ($n=62$), or preterm infant ($n=60$) or small-for-gestational-age infants ($n=116$). Results of these
198 sensitivity analyses were not reported in the present paper but were similar to our main
199 results.

200 We conducted the main analyses in the complete-case sample and sensitivity analyses by
201 using the multiple imputation method to deal with missing data on infant feeding patterns and
202 adjustment variables. We assumed that data were missing at random and generated five
203 independent datasets with the fully conditional specification method, then calculated pooled
204 effect estimates. In imputation models, we included all variables of interest after their ranking
205 in ascending order of missing data. Categorical variables were imputed with a multinomial
206 model, ordinal or binary variables with logistic regression, and continuous variables with
207 linear regression. All participants with data for AR and age at AP were selected in this
208 analysis ($n=1\ 399$). To generate significance testing of categorical variables, we used the
209 median p rule as described by Eekhout et al. (34).

210 All analyses were conducted with SAS 9.4 (35). The significance level was set at 0.05.

211 **Results**

212 **Participants**

213 As compared with excluded mothers, included mothers were more educated, had higher
214 monthly income, and less often smoked during pregnancy. Excluded mothers were more
215 likely to be younger (<25 years) than included mothers (11% vs 24%, p-value<0.001).
216 Included infants were more often second-born than their excluded counterparts, with no
217 difference in birth weight categories (Table 1).

218 In the selected population (n=1 225), mean age at complementary food introduction was $4.5 \pm$
219 1.6 months and mean duration of any breastfeeding was 3.4 ± 3.7 months. The AP occurred at
220 a mean of 9.9 ± 2.0 months of age and the mean BMI at AP was 17.5 ± 1.3 kg/m². The AR
221 occurred at a mean of 65.7 ± 16.4 months of age, corresponding to 5.5 ± 1.4 years, and did not
222 differ by sex; and the mean BMI at AR was 15.3 ± 1.1 kg/m².

223 **BMI at AP**

224 For boys, long breastfeeding duration was associated with reduced BMI at AP, but neither age
225 at complementary food introduction nor infant feeding patterns was related to BMI at AP
226 (Table 2). Girls showed no association with any feeding practice and BMI at AP.

227 **Age at AR**

228 Breastfeeding duration was positively associated with age at AR for girls but not boys (Table
229 3). Age at complementary food introduction was associated with age at AR for boys (β , 29;
230 95% CI, 5 to 54) but not girls.

231 For girls, the only pattern associated with age at AR was long breastfeeding duration, late
232 food introduction and home-made food, with greater adherence to this pattern associated with

233 later age at AR (Table 3). For boys, the only pattern associated with age at AR was late dairy
234 introduction and use of ready-prepared baby foods, with greater adherence to this pattern
235 associated with later age at AR (Table 3).

236 Age at AP and BMI at AR

237 For girls, breastfeeding duration was associated with later age at AP: a 1-month increase in
238 breastfeeding duration was associated with 2-day later AP occurrence. Boys showed no
239 association between breastfeeding duration and age at AP. Age at complementary food
240 introduction was not associated with age at AP for either sex (Table 3). Similarly, for girls,
241 age at AP was associated with the pattern long breastfeeding duration, late food introduction
242 and home-made food, with greater adherence to this pattern associated with later age at AP;
243 no pattern was associated with age at AP for boys.

244 Infant feeding practices were not related to BMI at AR in girls or boys (Table 2).

245 For the four outcomes, analyses based on multiple imputation of missing data gave similar
246 results (Table 2 and Table 3).

247 **Discussion**

248 The associations between infant feeding practices and BMI at AP or age at AR were
249 moderated by child sex. Longer breastfeeding duration for girls but older age at
250 complementary food introduction for boys were related to later age at AR. For boys, long
251 breastfeeding duration was related to reduced BMI at AP. The type of foods used during
252 complementary feeding did not appear to be related to strongly related to adiposity peak or
253 rebound.

254 To our knowledge, no previous study had investigated the association between age at
255 complementary food introduction and age at AR. However, some studies explored
256 associations between diet (especially protein intake) in toddlerhood and age at AR. In the

257 French ELANCE study, children experiencing early AR (≤ 4 years) had higher protein intake
258 at age 2 years than children experiencing late AR (16.6% vs 14.9% of energy intake) (36). In
259 the German DONALD cohort, protein intake between the age 12 and 24 months was not
260 related to age at AR but was positively associated with BMI at AR for only girls (19). None of
261 these studies investigated infancy, which limits comparisons with the association between
262 later complementary food introduction and later AR we found.

263 Previous literature on the association between breastfeeding and AP highlighted inconsistent
264 results. In our analysis, breastfeeding duration, considered directly or within a pattern
265 including other related practices, was associated with later age at AP. A previous work
266 showed that high score on the feeding pattern characterized by long breastfeeding duration
267 was associated with less increase in weight and height between birth and age 1 year (27). In
268 other settings, long breastfeeding duration was related to younger age at AP in the Danish
269 SKOT and the Singaporean GUSTO cohort studies (11, 12). However, the US Project Viva
270 cohort study did not find any association (37). In these studies, analyses were not stratified by
271 child sex, which limits the comparison with our findings. In the British ALSPAC cohort, long
272 exclusive breastfeeding duration was associated with older age at AP for boys and girls but
273 only for children with high genetic susceptibility to obesity (38). Most of these studies did not
274 find any association between breastfeeding duration and BMI at AP (11, 12, 37). In our
275 analysis of French data, breastfeeding duration was associated with low BMI at AP for boys.
276 This negative association agrees with previous results showing slow growth (low weight and
277 length gain) in the first months of life among breastfed infants (17, 39-43).

278 Even if few studies have examined the association between breastfeeding duration and age at
279 AR, their results are more consistent. In the Australian RAINE cohort study, AR was 10.6
280 months later for children breastfed for > 4 months as compared with those who were breastfed
281 for a shorter duration (20). Similarly, in the Project Viva cohort, AR was 3.4 months earlier

282 for never-breastfed than ever-breastfed children (37). We found a similarly delayed age at AR
283 among breastfed infants but only for girls. This finding may add a milestone in the pathway
284 between breastfeeding in infancy and obesity in adulthood in that a protective effect of
285 breastfeeding on obesity has been suggested in numerous studies summarized in a large meta-
286 analysis (15), and early AR is considered an important marker for the risk of obesity (44).

287 In this analysis, we found a moderating effect by sex: later age at AR was associated with
288 breastfeeding for girls but with delayed complementary food introduction for boys. Similar
289 differential effects were highlighted in the ALSPAC cohort, finding breastfeeding duration
290 positively associated with age at AR for only girls (38). Findings from animal studies suggest
291 that these differences may be explained by differences in breast milk composition, such as
292 higher protein content among males than females (45, 46)(47)(48). This hypothesis has to be
293 confirmed in humans, as evidence remains sparse and other factors could be involved (e.g.,
294 socioeconomic position and maternal BMI) (45). In the present study, it was not possible to
295 test such hypothesis as data on breastmilk composition were not available. Furthermore, we
296 tried to account the different confounding factors as best as possible but cannot exclude
297 residual confounding.

298 This is the first study we know of that considered simultaneously the different dimensions of
299 infant feeding practices in relation to these indicators or early growth. From analyses based on
300 infant feeding patterns, the type of foods used during the CF period (home-made, commercial
301 complementary foods or adult ready-prepared foods) did not appear to be strongly associated
302 to adiposity peak or rebound compared to breastfeeding duration and age at CF introduction.
303 Data on breastfeeding duration and timing of complementary feeding were collected
304 prospectively throughout the first year, which limits the recall bias. The EDEN mother-child
305 cohort is a regional cohort and is not representative of the French general population, with an
306 underrepresentation of disadvantaged families (21). This selection bias was increased with the

307 attrition bias as disadvantaged families were also less likely to be included in the present
308 analyses. To generalize our results, replication studies in more disadvantaged families are
309 needed. Moreover, we cannot exclude residual confounding even if several socioeconomic
310 indicators were collected and used as potential confounding factors. Further analyses are also
311 needed by weight for gestational age, especially among infants born small for gestational age,
312 to investigate the “developmental mismatch” hypothesis. Under this hypothesis, low prenatal
313 growth associated with a normal postnatal nutritional environment may increase later
314 cardiometabolic risk because this postnatal environment is richer in nutrients than the infant’s
315 metabolism has been accustomed to and becomes maladaptive (49-52). Our sample size didn’t
316 allow us to investigate those associations among small for gestational age, but analyses
317 conducted on the subsample of adequate for gestational age babies were similar to our main
318 results (data not shown). Finally, reverse causation in this subject cannot be excluded. Indeed,
319 breastfeeding and complementary food introduction are suspected to affect growth, but
320 growing evidence also suggests the opposite: early growth as a potential determinant of early
321 breastfeeding cessation or early introduction to complementary foods (53-56). In our analyses,
322 we tried to integrate this hypothesis by adjusting for weight at 2 months, although analyses
323 without this adjustment gave similar results (data not shown).

324 In the EDEN mother–child cohort, our findings highlight the moderating effect of child sex on
325 the potential influence of infant feeding practices on AP and AR. Although associations
326 between breastfeeding duration and early growth are well demonstrated, the associations
327 appeared stronger in girls than boys. Moreover, among boys, we highlighted the potential
328 effect of age at complementary food introduction on AR. These findings need to be confirmed
329 in other studies but bring new evidence that infant feeding practices are relevant modifiable
330 factors in obesity prevention.

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337 **Competing interests**

338 The authors declare no competing financial interest.

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494 **Figure 1.** Flow chart. AP, adiposity peak; AR, adiposity rebound