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Abstract (292/300 words)

Background/Objective

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

Subjects/Methods

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

Results

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

Conclusions

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

Keywords:

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

Introduction

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

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

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

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

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

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

Subjects and methods

Study population

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

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

Infant feeding assessment

Data on infant feeding were collected at birth and age 4, 8 and 12 months. Any breastfeeding duration (in months), age at infant formula introduction (in months) and age at complementary food introduction (in months) were calculated as described (22, 23). In brief, infant feeding mode was extracted at discharge from medical records and collected in the 4, 8 and 12-month questionnaires, wherein mothers reported, when relevant, the date of breastfeeding cessation, the age at infant formula introduction and the age at introduction of several food groups. Any breastfeeding duration correspond to the period where the infant received breast milk, regardless of the other liquids or foods consumed. Age at complementary feeding was defined as the age at introduction of the first food or liquid other than breast or formula milk. At the time of the EDEN study, the French guidelines were to begin complementary feeding ideally from 6 months onwards and in any case not before 4 months (24).

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

Growth and adiposity indicators

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

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

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

Other variables

The baseline questionnaire administered during pregnancy or at birth in the medical record was used to collect data on maternal and family characteristics, including maternal education level (in years), smoking status during pregnancy (yes/no), gestational weight gain (in kg), monthly income (in euros), maternal and paternal BMI (in kg/m^2). Child characteristics, including sex, preterm birth (yes/no) and birth weight (g), were also extracted from the medical record. Categories of birthweight-for-gestational-age z-scores (small for gestational age/adequate for gestational age/large for gestational age) were defined according to the French Audipog reference curves (32).

Sample selection

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

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

Statistical methods

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

The associations between infant feeding practices and both AP and AR were investigated by multivariable linear regression. We studied four different outcomes separately: age at AP, age at AR, BMI at AP and BMI at AR. The first model included breastfeeding duration and age at complementary food introduction simultaneously. The second model included the three previously identified infant feeding patterns (23). Both models accounted for potential confounders identified from the literature and selected according to the directed acyclic graph method (33): child sex, maternal education level, smoking status during pregnancy, gestational weight gain, monthly income, maternal and paternal BMI, maternal age, preterm birth, birth-weight z-score categories and predicted weight at 2 months.

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

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

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

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

Results

Participants

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

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

BMI at AP

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

Age at AR

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

For girls, the only pattern associated with age at AR was long breastfeeding duration, late food introduction and home-made food, with greater adherence to this pattern associated with later age at AR (Table 3). For boys, the only pattern associated with age at AR was late dairy introduction and use of ready-prepared baby foods, with greater adherence to this pattern associated with later age at AR (Table 3).

Age at AP and BMI at AR

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

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

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

Discussion

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

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

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

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

Even if few studies have examined the association between breastfeeding duration and age at AR, their results are more consistent. In the Australian RAINE cohort study, AR was 10.6 months later for children breastfed for > 4 months as compared with those who were breastfed for a shorter duration (20). Similarly, in the Project Viva cohort, AR was 3.4 months earlier for never-breastfed than ever-breastfed children (37). We found a similarly delayed age at AR among breastfed infants but only for girls. This finding may add a milestone in the pathway between breastfeeding in infancy and obesity in adulthood in that a protective effect of breastfeeding on obesity has been suggested in numerous studies summarized in a large meta-analysis (15), and early AR is considered an important marker for the risk of obesity (44).

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

This is the first study we know of that considered simultaneously the different dimensions of infant feeding practices in relation to these indicators or early growth. From analyses based on infant feeding patterns, the type of foods used during the CF period (home-made, commercial complementary foods or adult ready-prepared foods) did not appear to be strongly associated to adiposity peak or rebound compared to breastfeeding duration and age at CF introduction. Data on breastfeeding duration and timing of complementary feeding were collected prospectively throughout the first year, which limits the recall bias. The EDEN mother–child cohort is a regional cohort and is not representative of the French general population, with an underrepresentation of disadvantaged families (21). This selection bias was increased with the attrition bias as disadvantaged families were also less likely to be included in the present analyses. To generalize our results, replication studies in more disadvantaged families are needed. Moreover, we cannot exclude residual confounding even if several socioeconomic indicators were collected and used as potential confounding factors. Further analyses are also needed by weight for gestational age, especially among infants born small for gestational age, to investigate the “developmental mismatch” hypothesis. Under this hypothesis, low prenatal growth associated with a normal postnatal nutritional environment may increase later cardiometabolic risk because this postnatal environment is richer in nutrients than the infant’s metabolism has been accustomed to and becomes maladaptive (49-52). Our sample size didn’t allow us to investigate those associations among small for gestational age, but analyses conducted on the subsample of adequate for gestational age babies were similar to our main results (data not shown). Finally, reverse causation in this subject cannot be excluded. Indeed, breastfeeding and complementary food introduction are suspected to affect growth, but growing evidence also suggests the opposite: early growth as a potential determinant of early breastfeeding cessation or early introduction to complementary foods (53-56). In our analyses, we tried to integrate this hypothesis by adjusting for weight at 2 months, although analyses without this adjustment gave similar results (data not shown).

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

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Competing interests

The authors declare no competing financial interest.

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