

ORIGINAL ARTICLE

## Association of breast-feeding and feeding on demand with child weight status up to 4 years

JESSICA S. GUBBELS<sup>1</sup>, CAREL THIJS<sup>2</sup>, ANNETTE STAFLEU<sup>3</sup>, STEF VAN BUUREN<sup>4,5</sup>  
& STEF P. J. KREMERS<sup>1</sup>

<sup>1</sup>NUTRIM School for Nutrition, Toxicology and Metabolism, Department of Health Promotion, Maastricht University Medical Centre, Maastricht, the Netherlands, <sup>2</sup>CAPHRI School for Public Health and Primary Care, Department of Epidemiology, Maastricht University Medical Centre, Maastricht, the Netherlands, <sup>3</sup>Department of Biosciences, TNO Quality of Life, Zeist, the Netherlands, <sup>4</sup>Department of Statistics, TNO Quality of Life, Leiden, the Netherlands, <sup>5</sup>Department of Methodology and Statistics, FSW, University of Utrecht, Utrecht, the Netherlands

### Abstract

**Objectives.** The mechanisms underlying the protective effect of breast-feeding on the development of childhood overweight are unclear. This study examines the association of breast-feeding with weight gain in the first year, and body mass index (BMI) and overweight up to 4 years. In addition, we examine possible mechanisms of this effect (i.e., feeding pattern, eating style, unhealthy snacking behavior). **Methods.** Data originated from the KOALA Birth Cohort Study (N = 2 834). Questionnaires assessed breast-feeding duration up to 12 months, feeding pattern (i.e., feeding on demand or feeding to schedule) at 3 months, BMI at 1, 2 and 4 years, eating style (e.g., slow eating) at age 1, and unhealthy snacking at age 2. Linear and logistic regression analyses were used to examine the association of breast-feeding and feeding pattern with eating style, unhealthy snacking, BMI z-scores and overweight. **Results.** Each additional month of breast-feeding was associated with less weight gain in the first year (regression coefficient B = −37.6 g, p < 0.001), a lower BMI z-score at age 1 (B = −0.02, p < 0.01), and a lower odds of being overweight at age 1 (odds ratio=0.96, p < 0.05). Breast-feeding was associated with fewer unhealthy snacking occasions per week at age 2 (B = −0.19 for each month of breast-feeding, p < 0.001), but was unrelated to eating style. Feeding pattern was unrelated to all outcome variables after adjustment for breast-feeding duration. **Conclusions.** The study showed a short-term protective effect of breast-feeding against overweight development. Possible mechanisms through which breast-feeding may protect against overweight include less unhealthy snacking behavior, but not feeding pattern or child's eating style.

**Key words:** Body mass index, bottle feeding, breast-feeding, cue feeding, eating behaviour, infant, infant formula, on demand feeding, overweight, schedule feeding

### Introduction

An unhealthy diet is among the most important determinants of childhood overweight (1). Dietary habits are often formed at a young age, and once established maintained throughout life (2,3). The first encounter with food in infancy is drinking milk, and many studies have examined the influence of breast-feeding compared with formula feeding on weight development (4–6). Most indicate that breast-feeding protects against overweight and obesity development (4–6), with a dose-response relationship (5). However, some studies reported no effect of breast-feeding on later overweight (8–10).

The mechanisms through which breast-feeding might protect against overweight development are unclear, although both behavioral and physiological mechanisms have been proposed to play a role (4,5,7). One of the behavioral mechanisms linked to the protective effect of breast-feeding regards the feeding pattern and practices used by mothers (11). The 'Start Healthy Feeding Guidelines for Infants and Toddlers' of the American Dietetic Association recommend responsive parenting, recognizing and appropriately responding to infant hunger and satiety cues, including feeding on demand (12). Dutch guidelines are in line with this (13). Some authors

Address for correspondence: Jessica Gubbels, Maastricht University Medical Centre, Department of Health Promotion, PO Box 616, 6200 MD Maastricht, the Netherlands. Fax: +31 43 367 1032. E-mail: Jessica.Gubbels@gvo.unimaas.nl

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suggest that breast-fed children may have more control over the amount they consume, as breast-feeding mothers can only rely on infants' signals for frequency and volume of feedings. Formula-fed children are more often fed to a fixed schedule, with a fixed volume to drink, possibly leading to overconsumption (11). However, although breast-fed children are more likely to be fed on demand and formula-fed children more often to schedule (11), these combinations are not fixed. Bartok and Ventura recently called for examination of interactive effects of infant feeding components (7).

Other researchers have suggested a negative influence of feeding on demand on weight development. Erlanson-Albertsson and Zetterström suggested that not adhering to a fixed feeding schedule when breast-feeding, but feeding on demand instead, would lead to overweight (14). The mechanism claimed to be responsible for this hypothetically increased risk is that children fed on demand consume smaller volumes several times throughout the day, leading to a habit of snacking in later life. This in turn would favor obesity development (14). They also argue that mothers feeding on demand might soothe children crying for reasons other than hunger, by providing them with milk, leading to overfeeding and overweight (15). Feeding in response to emotional cues is indeed considered undesirable (16). The hypothesis of Erlanson-Albertsson and Zetterström has received critique (17), as feeding on demand is considered to be important for establishing a balanced nutritional homeostasis (18).

We examined effects of both the type of infant feeding (breast-feeding versus formula feeding), and the feeding pattern (feeding to a fixed schedule versus feeding on the child's demand), on weight gain, body mass index (BMI) and overweight in early childhood. We explored the interactive effect of feeding pattern and type, to examine the possibility that their combination is responsible for the association with weight status. We also examined the relationship between infant feeding with children's eating style and unhealthy snacking behavior at later ages, to elucidate the possible overweight-related behavioral consequences of feeding types and patterns.

## Methods

### *Respondents and procedure*

The Dutch KOALA Birth Cohort Study is a prospective cohort study, which started in the year 2000. The KOALA cohort was initially focused on the etiology of atopic diseases (19). Pregnant women were recruited from a cohort of healthy women from the general population, recruited by midwives for a study of the etiology of pregnancy-related pelvic girdle

pain (conventional recruitment group (19,20)). A total of 38.6% of the approached mothers agreed to participate ( $N = 2\,343$ ). In addition, healthy pregnant women were recruited through 'alternative lifestyle' recruitment channels (e.g., anthroposophist midwives, organic food shops (19)). This alternative recruitment group ( $N = 491$ ) had an alternative lifestyle in terms of aspects like dietary habits (e.g., using organic foods). All 2 834 participating mothers signed informed consent, and ethical approval was obtained from the Maastricht University/University Hospital Maastricht medical ethics committee. Ten children were excluded because of congenital defects (e.g., Down's syndrome), leaving 2 824 children for analyses. Questionnaires at the child's ages of 3 ( $N = 2\,645$ ) and 7 months ( $N = 2\,606$ ), and at 1 ( $N = 2\,557$ ), 2 ( $N = 2\,569$ ) and 4 years ( $N = 2\,037$ ), were used to assess various characteristics of the children and their parents. Questionnaires at all five ages were returned for a total of 1 863 children (66.0%). Mothers who returned all five questionnaires had children with a slightly higher birth weight (3 529 vs. 3 460 g;  $p < 0.01$ ). There was no significant difference between these groups in maternal pre-pregnancy BMI (23.6 kg/m<sup>2</sup> in both groups;  $p > 0.05$ ).

### *Child feeding*

The 3-months questionnaire asked parents whether the child had received breast milk, formula feeding or a combination of both during the first three months of life. The questionnaires at 7 and 12 months asked parents to indicate the duration of breast-feeding in the period between the questionnaires (including non-exclusive breast-feeding). These questions were combined into one measure of breast-feeding duration in months. No breast-feeding in the first three months was coded 0; partly breast-feeding and partly formula feeding in the first three months was coded as the midpoint value of the category, i.e., 1.5 months. For children that were still being breast-fed at 3 months, the breast-feeding duration was derived from the questionnaire at 7 months. For children who were still being breast-fed at 7 months, the duration was derived from the questionnaire at 12 months.

The feeding pattern was assessed in the 3 months questionnaire, asking: 'How did you try to feed your baby during the last week?' Answering options were 'When the baby asked for it', which we called 'feeding on demand'; 'According to a fixed schedule', called 'feeding to schedule'; and 'Both', called 'mixed feeding'.

### *Child's eating style and unhealthy snacking behavior*

The child's eating style at 1 year was assessed by asking parents how they would describe their child's

eating behavior, using seven eating style characterizations: 'slow', 'eager', 'fast', 'with reluctance', 'with pleasure', 'doesn't like many things' and 'likes many things'. Each of these items was considered as a separate eating style characterization, and could either apply or not. Multiple eating style characterizations could therefore be applicable simultaneously (e.g., eating both slowly and with pleasure).

Unhealthy snacking behavior at age 2 was assessed by asking parents how often their child consumed the following types of snacks: chocolate, cookies and pastry, chips and other savory snacks, and sweets. Response categories for each type were 'never', 'less than once a week', '1–3 times a week', '4–6 times a week', 'once a day', 'twice a day', '3 times a day' and 'more than 3 times a day'. The intake was recoded into weekly intake frequency (e.g., once a day was recoded as 7 times a week). For response categories that comprised a certain range of frequencies, the midpoint value of this range was used (e.g., 1–3 times was translated into 2 times a week). Intake of the various snacks (i.e., chocolate, cookies and pastry, chips and other savory snacks, sweets) was then summed, resulting in one measure of total unhealthy snack intake frequency. Portion size of the snacks was not assessed.

#### *Child's weight gain, BMI and overweight*

Parents were asked to report their child's birth weight, as well as height and weight at 1, 2 and 4 years. Weight gain in the first 12 months of life was calculated by subtracting birth weight from weight at age 12 months (standardized for age; both in grams). BMI (i.e., weight [kg]/(height [m])<sup>2</sup>) was calculated at ages 1, 2 and 4 and converted to z-scores, using data from the national reference population (21). BMI z-scores indicate by how many standard deviations a child differs from the median BMI of the reference population for his/her age. We classified children with a BMI z-score above the 85<sup>th</sup> percentile as overweight (22), including those who were obese.

#### *Other parental and child characteristics*

Mothers were asked to indicate their own height and weight before they got pregnant, and their pre-pregnancy BMI was calculated. Maternal age at delivery and smoking during pregnancy were also assessed, as well as the child's gender.

#### *Data analyses*

The distribution of demographic background variables, breast-feeding duration and feeding pattern were explored, after which regression analyses were performed. Children fed according to a mixed feeding

pattern (on demand as well as to schedule) were excluded from all regression analyses (N = 216). Missing values were excluded pair-wise. The influence of breast-feeding duration (in months) and feeding pattern on eating style at 1 year was explored using binary logistic regression analyses with each of the seven eating style characterizations (applicable/non-applicable) as dependent variables. The influence on unhealthy snack intake at age 2 was explored using linear regression analyses. The analyses were adjusted for the influence of several potential confounders: child gender and birth weight, maternal age and pre-pregnancy BMI, maternal smoking during pregnancy (yes/no) and recruitment group (alternative vs. conventional). To test for potential effect-modification (i.e., moderation) of feeding pattern in the relationship between breast-feeding duration and eating style, an interaction term was included in the second step of the analyses. Stratified regression analyses were performed in case of significant interaction terms.

The influence of breast-feeding and feeding pattern on weight gain in the first year and on BMI z-score and overweight (yes/no) at ages 1, 2, and 4 years was examined in a similar manner, using linear and logistic regression. The feeding variables and covariates were included in the first step, the interaction between feeding pattern and breast-feeding duration in a separate step. Stratified regression analyses were performed for significant interaction terms. P-values <0.05 were considered statistically significant.

## **Results**

A little over half (51.2%) of the children were male, and mean birth weight was 3 506 g (Standard deviation [SD] = 511). Mean maternal pre-pregnancy BMI was 23.6 kg/m<sup>2</sup> (SD = 4.0) and 7.3% of the mothers smoked during pregnancy. Mean maternal age at delivery was 32 years (SD = 4).

Children gained an average of 6 288 g (SD = 958) during their first year. Mean BMI z-score at 1 year was -0.01 (SD = 1.03), and 365 children (15.1%) were overweight (including those who were obese). Mean BMI z-score at age 2 was -0.04 (SD = 1.05), and 340 children (14.5%) were overweight. A total of 170 children (8.9%) were overweight at age 4, with a mean BMI z-score of -0.26 (SD = 0.99).

#### *Breast-feeding duration and feeding patterns*

The vast majority (80.2%) of the mothers had initiated breast-feeding. Table I shows the feeding patterns used by mothers in different categories of breast-feeding duration. There was a strong association between feeding pattern and duration of breast-feeding (Pearson Chi<sup>2</sup> = 334.6, p < 0.001). Of the

Table I. Feeding pattern according to breast-feeding duration (N = 2 634).

		Feeding pattern N (%) <sup>a</sup>			N (%) <sup>b</sup>
		On demand	To schedule	Mixed	Total
<b>Breast-feeding duration</b>	No breast-feeding	67 (16.4%)	319 (78.0%)	23 (5.6%)	409 (15.5%)
	1–3 months	236 (26.9%)	577 (65.7%)	65 (7.4%)	878 (33.3%)
	4–6 months	230 (52.1%)	171 (38.8%)	40 (9.1%)	441 (16.7%)
	>6 months	508 (56.1%)	310 (34.2%)	88 (9.7%)	906 (34.4%)

<sup>a</sup>% for each feeding pattern category are calculated horizontally (as proportion of the breast-feeding duration category; for N's see final column).

<sup>b</sup>% for each breast-feeding duration category are calculated vertically (as proportion of the total sample; N = 2 634).

mothers who never breast-fed their child (i.e., exclusively formula feeding), about three quarters (78.0%) fed to schedule. By contrast, slightly over half of those who breast-fed for 4 months or more did so on demand.

#### *Association of feeding with eating style and unhealthy snacking behavior*

Table II shows the association of feeding pattern and breast-feeding duration with children's eating style at age 1 and unhealthy snacking behavior at age 2. Feeding pattern was unrelated to eating style and unhealthy snacking, and breast-feeding duration was not associated with eating style either. However, each additional month of breast-feeding duration was associated with 0.19 fewer unhealthy snacking occasions a week at age 2 ( $p < 0.001$ ). Feeding pattern and breast-feeding duration did not interact in determining unhealthy snacking behavior or eating style (tests for statistical interaction  $p < 0.05$ ).

#### *Association of feeding with weight gain, BMI and overweight*

Table III shows the association of feeding pattern and breast-feeding duration with weight development. The influence of feeding pattern was adjusted for breast-feeding (and vice versa). Feeding pattern was unrelated to weight gain, BMI or overweight. Breast-feeding duration was negatively associated with weight gain: children gained, on average, 37.6 g less in their first year for each additional month of breast-feeding ( $p < 0.001$ ). Breast-feeding duration was also slightly negatively associated with BMI z-score at age 1, decreasing by 0.02 for each additional month of breast-feeding ( $p < 0.01$ ). Consistent with this finding, each additional month of breast-feeding significantly decreased the odds of being overweight at age 1 (OR = 0.96, 95% CI = 0.93–1.00). No associations between breast-feeding and BMI or overweight were found at ages above 1 year, and breast-feeding and feeding pattern did not interact in determining weight gain, BMI, or overweight.

## Discussion

The current study examined the association of infant feeding type and pattern with weight development in early childhood. Breast-feeding duration was found to be inversely associated with weight gain in the first year of life, BMI, and overweight at age 1. This confirms conclusions of previous reviews regarding the (dose-dependent) protective effect of breast-feeding against overweight (4–6). We failed to find effects on BMI or overweight beyond the age of 1 year.

One of the mechanisms through which breast-feeding has been proposed to protect against overweight is the feeding pattern, suggesting that breast-fed children are more often fed on demand, which is postulated to be preferable to feeding to schedule because a fixed feeding schedule could disturb a child's internal regulation of satiety and hunger (11). In line with this, breast-feeding has previously been found to be associated with less maternal controlling behavior at the age of 1 year (23), which partly explained the association between breast-feeding and overweight (24). The current study shows that children breast-fed for more than 3 months were indeed mostly fed on demand, whereas formula-fed children were more often fed to schedule. However, children breast-fed for less than 3 months were also most often fed to schedule. This probably results from the way feeding pattern was assessed, by asking parents at infant age 3 months. Mothers who breast-fed up to 3 months switched to formula feeding somewhere in those first three months. They were therefore formula feeding, and thus probably feeding to schedule, at the time of the questionnaire. An alternative explanation could be that mothers who breast-fed to schedule were less successful than those breast-feeding on demand, and therefore stopped breast-feeding at an earlier age. In addition, mothers who explicitly choose to breast-feed for a longer time, might also explicitly choose to feed on demand, as both are recommended by professionals (12,13), while mothers who breast-feed for a shorter duration might be less conscious in their choice, or less successful in following the recommendations.



Table II. Association of feeding pattern and breast-feeding duration with children's eating style at 1 year (N = 2 225), and unhealthy snacking behavior at 2 years (N = 2 185).

	Eating style 1 year OR (95% CI)				Unhealthy snacking 2 years B (95% CI) (no. of snacks/week)	
	Slow	Eager	Fast	With reluctance	Doesn't like many things	Likes many things
<b>Feeding pattern<sup>a</sup></b>						
To schedule (0)/On demand (1)	1.10 (0.74;1.63)	0.93 (0.77;1.13)	0.80 (0.62;1.03)	1.16 (0.74;1.83)	0.86 (0.55;1.35)	1.01 (0.84;1.21)
<b>Breast-feeding duration (months)</b>	1.04 (0.99;1.09)	0.99 (0.97;1.02)	1.00 (0.97;1.04)	1.02 (0.96;1.08)	1.04 (0.98;1.10)	0.99 (0.97;1.01)
						0.37 (-0.24;0.98) -0.19*** (-0.27;-0.11)

\*p < 0.05; \*\*p < 0.01; \*\*\*p < 0.001.

OR = Odds Ratio (from logistic regression analysis), CI = Confidence Interval, B = unstandardized regression coefficient (from linear regression analysis). ORs and Bs are adjusted for covariates and for the other feeding variable (i.e., breast-feeding was adjusted for feeding pattern and vice versa). Each eating style could apply (1) or not (0), multiple eating styles could apply simultaneously.

<sup>a</sup>Mixed feeding pattern (N = 216) was excluded.

Although breast-feeding mothers more often fed on demand, feeding on demand was unrelated to BMI or overweight. This contradicts the suggestion by Gillman et al. that feeding pattern and its influence on the child's self-regulation of energy intake is the mechanism through which breast-feeding protects against overweight development (11). On the other hand, the hypothesis of Erlanson-Albertsson and Zetterström that feeding on demand causes overweight (14) was not confirmed either: feeding on demand was not associated with a higher BMI or increased odds of becoming overweight.

Bartok and Ventura (7) suggested that the interactive effects of the many components of infant feeding are responsible for the association with weight status and that these components are inseparable. We found no interaction between breast-feeding and feeding pattern, which means that there was no moderation (i.e., effect-modification) of feeding pattern in the relationship between breast-feeding and weight status. Thus, the effect of breast-feeding was not dependent on whether the feeding pattern was on demand or to schedule. However, as our analyses were based on a single measurement of feeding pattern, our results do not rule out a dynamic interaction over time.

We further examined possible mechanisms explaining the protective effect of breast-feeding by assessing the association of breast-feeding and feeding pattern with subsequent eating styles and unhealthy snacking. Although breast-feeding was unrelated to eating style, breast-fed children consumed significantly fewer unhealthy snacks at age 2, especially with longer breast-feeding duration. Previous research also found that breast-fed children consumed fewer snacks at age 7, although this did not explain the difference in overweight between breast-fed and formula-fed children (25). Breast-feeding has further been shown to influence children's food preferences (26,27), which might explain the inverse association found between breast-feeding and unhealthy snacking. Breast-feeding has also been found to be associated with later parental feeding style and practices (23,28,29), which could indicate that breast-feeding merely reflects parents' global parenting philosophy. Other suggested behavioral mechanisms include children's fruit and vegetable intake (25,30,31), sweetened beverage intake and added sugar intake (32), and sedentary behavior (25,31), although most studies did not find significant mediation of these factors in the relationship between breast-feeding and weight development (25,31). Some suggested that mothers who breast-feed might be more nutrition-conscious in general (33). This does not; however, exclude the possibility that maternal nutrition-consciousness

Table III. Association of feeding pattern and breast-feeding duration with child's weight gain in the first year (N = 2 034), and body mass index (BMI) z-scores and overweight at ages 1 (N = 2 111), 2 (N = 1 592) and 4 years (N = 1 733).

	Weight gain (grams) <i>B (CI)</i>	BMI z-score <i>B (95% CI)</i>				Overweight (BMI z-score ≥ 85 <sup>th</sup> percentile) <i>OR (95% CI)</i>		
	0–12 months	1 year	2 years	4 years	1 year	2 years	4 years	
<b>Feeding pattern<sup>a</sup></b>	2.4	0.03	−0.06	0.02	1.21	1.01	0.97	
<i>To schedule (0)/On demand (1)</i>	(−79.2;84.1)	(−0.07;0.12)	(−0.15;0.04)	(−0.08;0.12)	(0.92;1.58)	(0.76;1.33)	(0.67;1.41)	
<b>Breast-feeding duration</b>	−37.6***	−0.02**	0.00	0.01	0.96*	1.01	1.00	
<i>(months)</i>	(−48.2;−27.1)	(−0.03;−0.01)	(−0.01;0.01)	(−0.01;0.02)	(0.93;1.00)	(0.97;1.05)	(0.96;1.05)	

\*p&lt;0.05; \*\*p&lt;0.01; \*\*\*p&lt;0.001.

OR=Odds Ratio (from logistic regression analysis), CI=Confidence Interval, B=unstandardized regression coefficient (from linear regression analysis). ORs and Bs are adjusted for covariates and for the other feeding variable (i.e., breast-feeding was adjusted for feeding pattern and vice versa).

<sup>a</sup>Mixed feeding pattern (N=216) was excluded.

can develop or change during early motherhood (with its dietary changes related to the psychophysiology of pregnancy and lactation), as mothers gain more experience with child feeding. The possibility that breast-feeding reflects a general nutrition or lifestyle orientation seems specifically probable in the respondents from the alternative recruitment group in the current study (19), but all analyses were corrected for recruitment group. Feeding pattern was unrelated to eating style or unhealthy snack intake in the current study. These findings further refute the hypothesis of Erlanson-Albertsson and Zetterström (14).

Note that non-exclusive breast-feeding was included in our measure of breast-feeding duration. Performing the same analyses with exclusive breast-feeding duration could possibly have yielded different results, as exclusivity of breast-feeding has been reported to strengthen the protective effects against overweight (7). In line with this, introduction to solid foods might confound current findings, as breast-feeding duration and age of introduction to solids have been found to be negatively correlated (see e.g., 34). A recent study showed that the effects of breast-feeding on long term BMI decreased when age of introduction to solid foods was added to the analyses (35). The relationships of solid food introduction and exclusive breast-feeding with infant feeding patterns are unclear, and should be further examined in future research. In addition, we did not assess whether children drank expressed breast-milk from a bottle instead of directly from their mother's breast. Examining the effect of bottle-fed breast-milk could be an important step in sorting out the mechanisms behind the effects of breast-feeding on weight status.

Some limitations should be taken into account when interpreting our results. Overweight percentages in this study were relatively low, compared with the reference population (e.g., 8.9% vs. 15% at age

4 (21)), which perhaps limits the generalizability of the current findings. In addition, all data, including weight, height and feeding variables, were reported by parents and could therefore be biased. Previous research in the Netherlands has shown that parental reports of weight and height showed only small differences from measured weight and height. However, parents especially tended to underestimate overweight children's weight (36). Possibly this also resulted in underestimation of children's BMI and overweight prevalence in the current study. However, the questionnaires at ages 1 and 2 years were completed shortly after visits to infant welfare centers (typically scheduled around 11 and 24 months, respectively), and parents were asked to report the results of anthropometric measurements taken there. Furthermore, data were gathered longitudinally, which decreases the probability of recall bias. The assessment of the feeding variables also poses some limitations. Breast-feeding in the first three months was not assessed for each month specifically, but rather as a categorical variable (no breast-feeding, partly breast-feeding or completely breast-feeding). Feeding pattern was assessed only once, at 3 months. Finally, several concepts (e.g., feeding pattern, eating style, snacking behavior) were assessed with questions that were developed for the current study, and have not been previously validated.

This study showed that breast-feeding had a short-term protective effect against overweight at the age of 1 year. In the longer run; however, no association was found between breast-feeding and BMI or overweight. The present study was, to our knowledge, the first to examine the influence of feeding pattern, and found no significant association between feeding pattern and BMI, overweight, unhealthy snacking, or eating style. The results do support the notion that feeding on demand is an element in mother-child adaptations contributing to successful

breast-feeding continuation. Breast-feeding duration was associated with less unhealthy snacking at age 2, which might be one of the behavioral mechanisms through which breast-feeding favorably influences weight development. By contrast, an influence of breast-feeding on eating style does not seem to be a major protective mechanism. We conclude, first, that feeding on demand is not deleterious in terms of eating habit formation and the development of overweight; and second, that breast-feeding is associated with less unhealthy snacking, protecting against overweight development in childhood, and therefore possibly also against later obesity.

## Abbreviations

BMI: Body mass index; CI: Confidence interval; KOALA: Dutch abbreviation for: Child: Parents and health: Lifestyle and Genetic constitution; OR: Odds ratio.

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The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. Financial support for the KOALA Birth Cohort Study was provided by the Triodos Foundation, Royal FrieslandCampina, Suikerstichting Netherlands, the Dutch Ministry of Economic Affairs, University Hospital Maastricht, and funds unrelated to commercial organizations (Iona Foundation, Phoenix Foundation, Foundation for the Advancement of Heilpädagogiek), all in the Netherlands. All research by J. S. Gubbels is financed by NUTRIM School for Nutrition, Toxicology and Metabolism. None of the funding sources had any influence on the data analyses, interpretation and presentation.

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