**Weight gain in early infancy impacts appetite regulation in the first year of life. A prospective study of infants living in Cyprus**

Dona Hileti[1], Christiana A. Demetriou[2], Michalis C. Iasonides[2], Spyros Pipis[2], Amna Mahmood[3], Julie Lanigan[3] and Atul Singhal[3]

[1]Department of Life Sciences, University of Nicosia, Cyprus, [2]University of Nicosia Medical School, Cyprus, [3]Childhood Nutrition Research Centre, UCL GOS Institute of Child Health, London, UK

Address correspondence to: Dr Dona Hileti, Department of Life Sciences, School of Life and Health Sciences, University of Nicosia, 46 Makedonitissas Avenue, CY2417, Nicosia, Cyprus. E-mail: hileti.d@unic.ac.cy

Data described in the manuscript will be made publicly and freely available without restriction upon request

**ABBREVIATIONS:** β (Beta Regression Coefficient), BEBQ (Baby Eating Behaviour Questionnaire), BMI (Body Mass Index), CEBQ (Child Eating Behaviour Questionnaire), CI (Confidence Interval), cWFAZ (Conditional Weight for Age Z-score), cWFAZC (Conditional Weight for Age Z-score Change), EF (Enjoyment of Food), FR (Food Responsiveness), SE (Slowness in Eating), SR (Satiety Responsiveness), SD (Standard Deviation (SD), IQR (Interquartile Range), WFA (Weight for Age), WFAZ (Weight for Age Z-scores), WFAZC (Weight for Age Z-score change)

**ABSTRACT**

**Background:**

Eating behaviour is associated with weight gain in infancy and childhood. Few studies found a bi-directional association between weight gain and eating behaviour development in childhood but there is little data on the association in early infancy, a period critical for the programming of obesity risk.

**Objective:**

We investigated the bi-directional association between appetite traits and weight gain during the first year of life.

**Methods:**

Participants were part of a cohort of 432 infants born in Cyprus. Appetite traits were measured using the BEBQ or the CEBQ at age 2-4 weeks, 6 and 12 months. Weight and length were collected at birth, 4 weeks, 6 and 12 months. Multivariable linear regression was used to analyse associations between appetite traits at 2-4 weeks and 6 months and weight for age Z-score change (WFAZC) between 4 weeks-6 months and 6-12 months. Associations were also analysed in the opposite direction, between WFAZC from birth to 4 weeks, 4 weeks to 6 months, 6-12 months and appetite traits at 4 weeks, 6 months and 12 months.

**Results:**

Satiety responsive (SR) at 2-4 weeks was associated with lower WFAZC from 4 weeks to 6 months (β=-0.17; 95%CI: -0.30, -0.04) and SR at age 6 months was associated with lower WFAZC from 6 to 12 months (β=-0.09; 95%CI: -0.17, -0.02).

WFAZC from 4 weeks to 6 months was associated with higher EF at 12 months (β=0.11; 95%CI: 0.01, 0.20), higher FR at 12 months (β=0.17; 95%CI: 0.04, 0.30) and lower SR at both 6 (β=-0.11; 95%CI: -0.21, -0.01) and 12 months (β=-0.14; 95%CI: -0.24, -0.03).

**Conclusions:**

We found a bi-directional association between weight gain and appetite traits in infancy, suggesting that the effect of postnatal weight gain on obesity development is partly mediated by programming of appetite traits.

**Keywords:** Eating behaviour, BEBQ (Baby Eating Behaviour Questionnaire), CEBQ (Child Eating Behaviour Questionnaire), appetite, infant growth, childhood obesity, cohort studies

## INTRODUCTION

Obesity in children is a major public health issue. Although a result of a complex interplay between genetic, environment and socio-biological factors, eating behaviour in early life has been suggested to be key risk factor for weight gain in infancy and childhood (1).

Several studies have shown that appetite traits assessed using the Child Eating Behaviour Questionnaire (CEBQ) or the Baby Eating Behaviour Questionnaire (BEBQ), are associated prospectively with adiposity in infancy and childhood (2)(3)(4). This association is partly explained by genetics (5) and the Behavioral Susceptibility Theory proposes that those who inherit genes promoting an avid appetite are vulnerable to overeating, whereas those genetically predisposed to have a smaller appetite and low interest in food are protected from developing obesity (6)(7). However, the biological factors affecting the development of appetite are complex and a recent meta-analysis highlighted that there may be a bi-directional effect between weight and appetite behaviours in childhood even though findings are inconsistent (1).

Several prospective studies in children have demonstrated that, beside the effect of appetite traits on future body weight, body weight and adiposity can predict later appetite traits. Costa and colleagues, using data from the Portuguese Generation XXI cohort, demonstrated that BMI z-score at 7 years of age was associated with all appetite traits at 10 years, whilst only higher Slowness in Eating (SE) at 7 years was associated with lower BMI z-scores at 10 years (8). This group also demonstrated that higher fat mass and waist-to-height ratio at 7 years predicted increase in the food approach traits Enjoyment of Food (EF) and Food Responsiveness (FR) at age 10 years (9). Results from the Generation R study are consistent with these findings. Derks and colleagues found that a higher BMI and higher fat mass at 4 years of age predicted higher FR, higher EF and lower Satiety Responsiveness (SR) at 10 years of age, but there was no significant association in the opposite direction (3). Similarly, a study in Norwegian children found that greater BMI at age 6 was associated with higher FR and lower SR at 8 years of age. A reverse effect was also observed (10). The same group showed that between ages 6 to 8 and 8 to 10 years, higher fat mass predicted higher FR, whilst greater muscle mass predicted lower SR (11). A study using the Dutch Eating Behaviour Questionnaire, also found bi-directional associations between restrained eating behaviour and BMI in children aged 9 years of age (12).

Only three prospective studies have investigated the effect of postnatal weight gain in infancy on the development of appetite traits. Van Deutekom and colleagues demonstrated that conditional weight gain in the first year of life was associated with lower SR and higher energy intake at 5 years of age (13). More recently, results from the same cohort showed that children with higher growth trajectories from birth to 5 years of life had higher EF and FR at age 7, compared to those with normal weight gain trajectory (14). However, analysis of the bi-directional effect of appetite and body mass index in the first year of life in the Gemini twin cohort, showed that the path between appetite behaviour and subsequent weight gain was stronger than the path between weight gain and appetite development (4). Therefore, there is lack of consistent data for the possible effect of weight gain during the early postnatal period on the development of appetite traits.

The perinatal period is particularly important in the development of childhood obesity. Many studies in both animals and humans have shown that low birth weight followed by accelerated postnatal weight gain are associated with higher risk of obesity (15)(16)(17). Early growth and nutrition could therefore influence, or 'programme' the later risk of obesity (18), part of the 'Developmental Origins of Health and Disease' which proposes that environmental cues during critical periods of life such as the perinatal period, can lead to adaptive responses in developmental and metabolic pathways which can permanently affect later health and disease risk (19). Faster weight gain in infancy has also been shown to increase the risk of later obesity, the 'Growth acceleration hypothesis' (20) as suggested by several systematic reviews (21)(22)(23). A causal link between faster infant growth and higher risk of obesity was confirmed in randomised clinical trials where infants fed an energy-dense or higher protein formula had faster growth and higher risk of obesity in later life (16)(24).

The mechanism with which early postnatal growth can impact the risk of developing obesity and cardiovascular disease is still unknown but one possibility is  programming of appetite which influence energy intake and hence risk of obesity (25). Animal studies have shown that low birth weight followed by rapid postnatal weight gain results in adult hyperphagia (26)(27)(28). Humans may show similar effects of rapid postnatal growth on development of later appetite regulation thus affecting the risk of obesity development. However, very few human studies have examined the association of early postnatal growth and appetite development.

The aim of the present study was to investigate the association of postnatal weight gain and eating behavior in the first year of life and to investigate whether this association is bi-directional. We hypothesized that higher early postnatal growth is prospectively associated with higher food approach and lower food avoidant traits in the first year of life.

## SUBJECTS AND METHODS

### Participants

The participants were from the CYprus infant GROWth cohort (CYGROW), a birth cohort set up in 2017 in Cyprus with 432 term infants recruited from general paediatric clinics in the island. Eligibility criteria were: ≥ 36-week gestation, birth weight ≥ 2.5kg and no health issues which could influence feeding or growth. All eligible infants were invited to participate. The primary objective of the study was to investigate the effect of early life nutrition and life events on the risk of health outcomes later in life. Written, informed consent was obtained from the mothers and/or fathers of all participants. Ethical approval was granted by the Cyprus Bioethics Committee (EEBK/EP/2017/40).

**Infant and parental characteristics**

Infant sex, gestational age, weight and length at birth, 4 weeks, 6 and 12 months were obtained from clinic records. The initial interview with parents was conducted between age 2-4 weeks during routine monthly clinic appointments. At this initial interview, informed signed consent was obtained. Data on mode of delivery, parental ethnicity, age, BMI, weight increase during pregnancy, education, marital status, total household income, smoking, alcohol consumption and family medical background were also collected.

**Questionnaires**

Appetite traits were measured at age 2-4 weeks, 6 and 12 months. The Baby Eating Behaviour Questionnaire (BEBQ) (29) was used to measure appetite traits between 2-4 weeks and 6 months and the Child Eating Behaviour Questionnaire (CEBQ) (30) at 12 months. Both questionnaires are parent-reported and measure 'food approach' traits that indicate a more avid appetite and greater interest in food and 'food avoidant' traits which indicate a smaller appetite and less interest in food. The food approach traits measured were common in both questionnaires: Enjoyment of Food (EF; eg "my child loves food" or "my baby loved milk") and Food Responsiveness (FR; eg "given the choice my child would eat most of the time" or "my baby was always demanding a feed"). The food avoidant traits common to both questionnaires and measured were: Slowness in Eating (SE; eg "my child eats slowly" or "my baby fed slowly") and Satiety Responsiveness (SR; "my child gets full up easily" or "my baby got full up easily"). For both questionnaires, mothers were asked to score their infant's feeding style during a 'typical daytime feed' and responses were on 5-point Likert scales for each item: never, rarely, sometimes, often and always.

Information on infant feeding at 2-4 weeks and 6 months was assessed using the nutrition parts of the questionnaires given at 2-4 weeks and 6 months in the Avon Longitudinal Study of Pregnancy and Childhood (31). At 2-4 weeks mothers reported whether their infant had been (1) breastfed exclusively or fully, (2) formula fed or (3) mixed fed (combination of breast and formula feeding). Full breastfeeding included water and herbal tea but not formula. At 6 months, mothers reported whether their infant was (1) breastfed (with or without formula and with or without complementary feeding) or (2) Not breastfed (formula, with or without complementary feeding).

All questionnaires were completed either face-to-face (at age 2-4 weeks) or during telephone interviews (at 6 and 12 months of age), by trained research assistants who were able to clarify and explain any questions to parents.

**Statistical Analysis**

Descriptive characteristics for participants were calculated as proportions for categorical variables, and as mean and standard deviation (SD) or as median and interquartile range (IQR) for normal and non-normal numeric variables, respectively. These descriptive characteristics were compared between infant sex categories, using Wilcoxon rank sum test for non-normally distributed variables, Student's T-test for normally distributed variables, and the Pearson chi-square test for categorical variables.

Infant weight-for-age z-scores (WFAZ) were calculated using the WHO 2006 growth reference (32) using the software program WHO Anthro version 3.2.2 (33). Weight increase was assessed as WFAZ change (WFAZC) by taking the difference in WFAZs between two time points, while adjusting for the WFAZ at the start of the growth window. Weight gain was calculated as the WFAZC from birth to 4 weeks, from 4 weeks to 6 months and from 6 to 12 months.

Multivariable linear regression was used to analyse associations between appetite traits (independent variables) and WFAZC (dependent variables). We analysed associations between appetite traits at 2-4 weeks and WFAZC from 4 weeks to 6 months and from 6 to 12 months. We also analysed associations between appetite traits at 6 months and WFAZC from 6 to 12 months. The appetite traits analysed were Enjoyment of food (EF), Food Responsiveness (FR), Satiety Responsiveness (SR) and Slowness in Eating (SE). Different combinations of confounding factors were adjusted for in different models according to models published elsewhere (2)(4)(13). Potential confounders included in the models were sex, gestational age, age at start [if not birth] and end of growth window, WFAZ at start of growth window, age at main independent variable appetite assessment, age and appetite trait score at previous appetite assessments, ethnicity, maternal and paternal BMI, mother's educational attainment, smoking during pregnancy, and infant feeding. For outcomes at the 4-week stage, adjustment for infant feeding included the variables (i) Current feeding at 4 weeks (Breastfeeding (BF), bottle, BF & bottle) and (ii) Scheduled feeding at 4 weeks ("yes always", "yes I try", "no; on demand"). For 6 month outcomes, adjustment for infant feeding included the variables describing infant feeding at 4 weeks ((i) and (ii) above) as well as for (iii) Breastfeeding at 6 months ("yes", "yes but stopped", "never"); (iv) Any solids introduced by 6 months (yes, no) and (v) On demand feeding at 6 months ("yes always", "yes sometimes", "no never").

Multivariable linear regression was also used to analyse associations between WFAZC (independent variables) and appetite traits (dependent variables). Associations were examined between (1) WFAZC from birth to 4 weeks and appetite traits at 4 weeks, 6 months and 12 months (2) WFAZC from 4 weeks to 6 months and appetite traits at 6 and 12 months and (3) WFAZC from 6-12 months and appetite traits at 12 months.

For the purpose of the analysis of the association between WFAZC from birth to 4 weeks, only participants who completed the BEBQ at 4 weeks of age or thereafter were included. Models were adjusted for factors known to influence growth and appetite (sex, gestational age, age and height at outcome appetite assessment, age at start [if not birth] and end of growth window, WFA z-score at start of growth window, age and appetitive trait score at previous appetite assessments, maternal and paternal BMI, mother's educational attainment, smoking during pregnancy, and infant feeding), as previously described. As above, different combinations of these factors were adjusted for in different models according to models published elsewhere (2)(4)(13).

Lastly, for sensitivity analyses, all multivariate models were run with growth assessed as conditional WFAZ change (cWFAZC) by saving the residuals from linear regression models of WFAZ at each successive time point versus WFAZ at the earlier time point. For the purpose of the analysis of the association between cWFAZC from birth to 4 weeks and appetite traits at 4 weeks, only participants who completed the BEBQ at 4 weeks of age or thereafter were included.

All statistical analyses were performed using STATA SE Version 15 (StataCorp. 2017. *Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC.)

## RESULTS

### Characteristics of Participants

Anthropometric, eating behaviour and infant feeding data were available for 428/432 infants at ages 2-4 weeks, 411 (96%) infants at 6 months and 392 (90%) infants at 12 months (**Supplementary Figure 1**). Main socio-demographics were not significantly different between participants who completed the study and those who did not.

Appetite scores at age 2-4 weeks, 4 weeks, 6 months and 12 months, and all descriptive characteristics of participants are shown in **Table 1**. The mothers of 75.9% of participants had an educational level up to a university level or above and 79.3% were of Cypriot ethnicity. The maternal median age was 33 years of age and the median maternal BMI 21.8. The median infant birth weight was 3.17kg. At 4 weeks 38% were exclusively breastfed and at 6 months 86.1% still had some breastfeeding. No differences in demographic or nutritional characteristics were found between boys and girls with the exception of Satiety Responsiveness (SR) at 2-4 weeks that was slightly lower in boys than girls.

**BEBQ and CEBQ**

The internal reliability coefficients (cronbach's alpha) were calculated for each subscale of the BEBQ at 2-4 weeks (EFα=0.56, FRα=0.80, SEα=0.60, SRα=0.24) and 6 months (EFα=0.60, FRα=0.77, SEα=0.40, SRα=0.38), as well as the CEBQ at 12 months (EFα=0.49, FRα=0.43, SEα=0.38, SRα=0.51)). Most appetite traits apart from the SR at 2-4 weeks ranged from 0.4-0.8, indicating a moderate to good internal reliability of the subscales. The coefficient for SR at 2-4 weeks was very low and possibly reflects the difficulties of mothers of new-borns to assess their appetite score.

**Associations between appetite traits and weight gain**

**Table 2** shows the associations of appetite traits measured by the BEBQ at 2-4 weeks of age with WFAZC between 4 weeks and 6 months as well as WFAZC between 6 to 12 months. SR at 2-4 weeks was significantly associated with lower WFAZC from 4 weeks to 6 months (β=-0.17; 95%CI: -0.30, -0.04), but not between 6 to 12 months (β=-0.03; 95%CI: -0.11, 0.05). FR at 2-4 weeks was significantly associated with higher WFAZC from 6 to 12 months only in the adjusted models (β=0.06; 95%CI: 0.01, 0.12).

The associations between appetite traits measured by the BEBQ at 6 months of age with WFAZC between 6 to 12 months are also shown in table 2. SR at 6 months was significantly associated with lower WFAZC between 6 to 12 months (β=-0.09; 95% CI: -0.17, -0.02).

Similar results were obtained when appetite traits at 2-4 weeks and 6 months were associated with conditional weight change for the same time points (**Supplementary Table 1**).

**Associations between weight gain and appetite traits**

**Table 3** shows the associations of WFAZC from birth to 4 weeks and appetite traits at 4 weeks, 6 months and 12 months. No significant associations were found between WFAZC from birth to 4 weeks and appetite traits (Table 3) and between the conditional WFAZ change from birth to 4 weeks and appetite traits (**Supplementary Table 2**).

WFAZC from 4 weeks to 6 months was significantly associated with higher EF at 12 months (β=0.11; 95% CI: 0.01, 0.20), higher FR at 12 months (β=0.17; 95% CI: 0.04, 0.30) and lower Satiety Responsiveness (SR) at both 6 (β=-0.11 (-0.21, -0.01) and 12 months (β=-0.14 (-0.24, -0.03) (Table 3). The associations for SR at 6 and 12 months were no longer significant when adjusting simultaneously for height at outcome assessment and age and appetite trait scores at previous time-points. Similar results were found when conditional weight change from 4 weeks to 6 months was associated with appetite traits at the same time points (Supplemental Table 2).

WFAZ change between 6 to 12 months was associated with higher EF at 12 months (β=0.18; 95% CI: 0.02, 0.34) and lower SR at 12 months (β=-0.23; 95% CI: -0.41, -0.06) only in adjusted models (Table 3). Conditional WFAZC between 6 and 12 months was significantly associated with SR at 12 months (β=-0.20; 95% CI: -0.35, -0.05) in all models (Supplemental Table 2).

## DISCUSSION

Human studies investigating the association between appetite traits and obesity risk have focused mainly on the genetic component of appetite traits and the behavioural susceptibility theory (6)(7)). Three studies have shown that appetite traits in infancy are prospectively associated with higher BMI and adiposity measures (2)(3)(4)). These studies provide evidence that, as the behavioural susceptibility theory suggests, genes promoting an avid appetite increase overeating and the risk of developing obesity, whereas genes promoting a smaller appetite and low interest in food are protective. However, this may present only part of the picture on the link between early weight gain, development of appetite traits and risk of developing obesity. Numerous animal studies have shown consistently that early accelerated postnatal growth alters eating behaviour and metabolic functions, causing hyperphagia and obesity in adulthood (27)(28)(34). Our study therefore suggests that in humans, like in animals, there may also be an association between early postnatal growth and later appetite behaviours. This finding is consistent with a recent systematic review which suggested a bi-directional effect between weight and appetite behaviours in childhood (1).

Weight gain and adiposity measures in childhood are prospectively associated with the development of appetite traits(3)(8) (9)(10)(11). However, few human studies have examined the effect of early postnatal growth on the programming of appetite traits. Van Deutekom and colleagues showed that conditional weight gain in the first year of life was associated with lower satiety responsiveness at 5 years of age, but other appetite traits were not examined (13). Data from the same cohort also showed that growth trajectories from birth to 5 years of age are associated with later appetite traits (14). In this study, children with normal weight gain were found to have higher EF and FR and lower SR and SE at 7 years of age compared to children who had either (1) catch up weight gain during infancy, (2) continuous weight gain since birth or (3) higher weight gain than average since birth. Van Jaarsveld and colleagues showed that there is bi-directional effect of appetite and body mass index in the first year of life but concluded that the path between appetite behaviour and subsequent weight gain was stronger than the path between weight gain and appetite development (4).

In agreement with previous studies (2)(3)(4)) we found that appetite traits in infancy are prospectively associated with later weight gain. This is the first study that assessed appetite traits as early as 2-4 weeks after birth, supporting the behavioural susceptibility theory that genetic factors expressed as early as age 2-4 weeks affects appetite and hence growth. Our study also provides evidence for the bidirectional association between weight gain in early life and the programming of appetite traits with the period between 4 weeks and 6 months seeming to be particularly critical for this effect. Weight gain during this period was associated with higher Enjoyment of Food (EF) and Food Responsiveness (FR) at 12 months of age and lower Satiety Responsiveness (SR) at both 6 and 12 months (Table 3). The association between postnatal weight gain and appetite traits shown in our study remained after adjusting for appetite traits at the start of the growth window which could indicate that the effect of postnatal weight gain on the programming of appetite traits is not completely dependent on the hereditability of appetite traits. The importance of the first 6 months in influencing later appetite traits associated with higher food intake is consistent with the evidence that weight gain in this period increases the later risk of obesity (16)(21)(22)(23)(35).

Our findings are in agreement with the studies of the Amsterdam Born Children and their Development cohort (13)(14). Warkentin and colleagues (14) found that weight trajectories deviating from normal weight gain in the first 5 years of life were associated with a more avid appetite at age 7. In particular, premature and low-birth weight infants with higher catch-up growth had significantly lower SE, lower SR, higher FR and higher EF compared to those of normal weight gain. Van Deutekom and colleagues reported an association between conditional weight gain between 0-1, 1-3, 3-6 and 6-12 months as well as between 1-5 years of age with lower SR and higher energy intake at 5 years of age (13) .

We also found associations between postnatal weight gain, particularly the period between 4 weeks and 6 months and the programming of higher food approach appetite traits, EF and FR. In agreement with the findings of van Deutekom and colleagues, we reported an association between postnatal growth between 4 weeks and 6 months as well as 6 to 12 months and the programming of lower SR. The associations between WFAZC from 4 weeks to 6 months and SR at both 6 months and 12 months were no longer significant in the final models, most likely due to a slightly smaller sample size and difficulties in measuring height in infancy. Van Deutekom and colleagues did not find any associations between conditional height increase between 0-1 months, 1-3 months and 1-5 years of age with SR at 5 years, although height increase during those time periods was negatively associated with energy intake at 5 years (13). Further studies are therefore needed to elucidate the effect of linear growth during the early postnatal period of life on the programming of appetite traits.

The exact timing of postnatal weight gain in relation to later obesity risk is unclear. Identifying critical periods when weight gain is associated with appetite programming is valuable as it could inform when best to intervene and possibly help to prevent obesity development. In animal studies, the fastest growth in the first weeks after birth, was found to be a critical programming window (36). In early infancy, the development of hypothalamic centers responsible for energy balance are susceptible to environmental cues (37). In animal studies, perinatal malnutrition is associated with changes in hypothalamic circuity, with the induction of leptin resistance and long-term effects on food intake and metabolic regulation (27)(34)). Warkentin and colleagues found that higher weight gain and catch-up growth in infancy, was associated with a more avid appetite at 7 years (14). Our study indicates that the critical period for the effect of postnatal growth on the development of appetite traits is not in the first month of life but seems to be between 4 weeks and 12 months. The period between 4 weeks and 6 months seems to be particularly critical for the programming of the food approach appetite traits EF and FR in response to increased weight gain. The programming of the food avoidant appetite trait, SR was associated with lower weight gain from 4 weeks to 6 months as well as from 6 to 12 months. This is in agreement with the growth acceleration hypothesis which stipulates that the effect of postnatal growth on the development of cardiovascular risk and obesity is continuous throughout maturation and does not rely on a narrow window of sensitivity (20). Van Deutekom and colleagues interestingly found that conditional weight gain in childhood had an effect size almost three times that of conditional weight gain in infancy, both for its association with energy intake and satiety response (13). Weight gain in middle childhood was found to be prospectively associated with higher food approach and lower food avoidant appetite traits in four cohort studies (3)(8)(9)(10).

Programming of growth patterns in the first year of life, as shown by our study, offers significant possibilities for the improvement of later health._ Early intervention by health-care providers may help reduce long term adverse outcomes. For instance, breast- rather than formula-feeding, responsive feeding and avoiding too early introduction of complementary feeding may all help prevent over-feeding and too rapid weight gain in the first year of life. _Intervening between 4-12 months by offering patient-specific diet advice can be of particular importance as during this time period there is transition from milk feeding to complementary feeding. The complementary feeding period is critical for the setting of children's dietary behaviours which may influence appetite development and risk of obesity in later life. In our study, breast-fed and formula-fed infants were included in the same group. Our rational for combining the groups was that the association between weight gain in infancy and later risk of obesity was found to be similar in breast-fed and formula-fed infants (38). Furthermore, prospective cohort studies examining appetite traits and obesity risk also did not separate groups according to infant feeding (2)(3)(4)(13)(14). In our study, weight gain in the first month of life, a period of exclusive milk-feeding, did not affect the development of appetite traits, and therefore it is unlikely that the effect of weight gain on the development of appetite traits is mediated by breast or formula feeding alone. Furthermore, bidirectional associations between weight gain and appetite development remained after adjusting for infant feeding.

Early human studies on the effect of early perinatal growth and obesity risk development, used birth weight as a marker of prenatal growth and prenatal undernutrition was found to be associated with higher energy intake in adult life (39)(40). Postnatal weight gain on the development of appetite traits in our study is independent of birth weight, as all the infants in our cohort had a minimal birth weight of 2.5kg. van Deutekom and colleagues found no association between birth weight and SR at 5 years of age (13). Furthermore, associations between weight gain and development of appetite traits in our study persisted after adjusting for birth weight and also WFAZ at the start of the growth window. This indicates that the effect of weight gain on the programming of appetite traits depends on the change in body weight and is independent of the body weight status at the beginning of the growth window examined.

The present study has a number of strengths. It is a prospective study, with a very high follow-up rate (90%), whereby bi-directional associations between growth and appetite traits were examined at multiple time points. Secondly, anthropometric data were collected from clinical records and were performed by trained nurses. In contrast, parent-reported height and weight measures can introduce bias (41). Some limitations must also be addressed. The sample was a convenient sample, possibly not representative of all infants. Although tAlthough, the sample was representative of the Cyprus population in terms of maternal age at birth (42) BMI (43) and educational attainment (44), the generalizability of our results to other populations is uncertain. However, since biological relationships are being investigated results are expected to be generalizable to the reference population. Appetite traits are measured using questionnaires and therefore social desirability may influence parent ratings. Additionally, identifying and reporting appetite traits in the first weeks of life (2-4 weeks) is challenging, and the use of translated tools could introduce variation in parent responses, contributing to the low internal reliability coefficients observed at 2-4 weeks and suggesting that these results should be interpreted with caution. A similarly low internal reliability coefficient for Satiety Responsiveness measured at 10 weeks of age was also observed in a study of Filipino infants (45). However, the advantage of using questionnaires rather than laboratory tests is that they can reflect consistent eating behavior rather than behavior on one single occasion (46). Finally, we had limited data to investigate whether parental feeding style, and amount and frequency of feeding can influence appetite characteristics and infant weight gain.

In conclusion, our study confirms that, as in animal models, higher weight gain in early infancy alters eating behaviour, thus providing a possible mechanism for increasing obesity risk. infants who grow faster during the first 1-6 months of life are programmed to develop appetite traits that lead to overeating and that over-ride of their internal satiety cues, thus increasing their risk of obesity in later life. Accelerated weight gain in early infancy has a significant biological cost, with higher risk of developing obesity and cardiovascular disease in later life and our findings suggest that a possible mechanism for this is through the programming of appetite traits.

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**Table 1. Descriptive Characteristics of Participants (n=428 infants)**

| | All participants (n=428) | Boys (n=234) | Girls (n=194) | p-value* |
|---|---|---|---|---|
| **Parental and Family Characteristics** | | | | |
| **Mother's age (yrs)** | 33 (5) | 33 (5) | 33 (5) | 0.654 |
| **Father's age (yrs)** | 35 (6) | 34 (6) | 35 (7) | 0.050 |
| **Mother's educational attainment** | | | | |
| No University degree n (%) | 103 (24.1) | 53 (22.6) | 50 (25.9) | 0.385 |
| University degree n (%) | 324 (75.9) | 181 (77.4) | 143 (74.1) | |
| **BMI of mother (kg/m$^2$)** | 21.8 (5.0) | 21.6 (6.6) | 22.2 (4.9) | 0.283 |
| **BMI of father (kg/m$^2$)** | 26.2 (3.9) | 26.2 (4.1) | 26.2 (3.9) | 0.539 |
| **Mother smoking during pregnancy, n (%)** | 29 (6.8) | 18 (7.7) | 11 (5.7) | 0.407 |
| **Infant Characteristics** | | | | |
| **Sex** | | | | |
| Male n (%) | 234 (54.7) | | | |
| Female n (%) | 194 (45.3) | | | |
| **Gestational age (weeks) n=422** | 38.8±1.1 (36-42) | 38.7±1.0 (36-41) | 38.9±1.1 36-42 | 0.062 |
| **Infant birth weight (kg)** | 3.17 (0.53) | 3.19 (0.51) | 3.13 (0.58) | 0.165 |
| **WFA z-score at birth n=428** | -0.25±0.82 (-2.02-2.84) | -0.30±0.78 (-1.95-2.31) | -0.19±0.87 (-1.73-2.84) | 0.145 |
| **WFA z-score at 4 weeks n=426** | -0.36±0.82 (-3.60-2.27) | -0.39±0.87 (-3.60-2.26) | -0.32±0.76 (-2.05-2.27) | 0.343 |
| **WFA z-score at 6 months n=423** | 0.12±0.95 (-2.24-3.09) | 0.12±0.98 (-2.00-3.09) | 0.12±0.91 (-2.20-2.44) | 0.980 |
| **WFA z-score at 12 months n=415** | 0.42±0.91 (-2.11-3.06) | 0.42±0.98 (-2.11-3.06) | 0.42±0.84 (-1.71-2.40) | 0.941 |
| **Infant ethnicity** | | | | |
| Cypriot n (%) | 338 (79.3) | 184 (79.0) | 154 (79.8) | 0.145 |
| Other n (%) | 88 (20.7) | 49 (21.0) | 39 (20.2) | |
| **Exclusive breastfeeding at 4 weeks,** n (%) | 162 (38.0) | 87 (37.2) | 75 (39.0) | 0.709 |
| **Mixed feeding at 4 weeks,** n (%) | 131 (30.8) | 70 (29.9) | 61 (31.8) | |
| **Formula feeding at 4 weeks,** n (%) | 133 (31.2) | 77 (32.9) | 56 (29.2) | |
| **Any breastfeeding at 6 months,** n (%) | 353 (86.1) | 193 (86.2) | 158 (85.9) | 0.933 |
| **Enjoyment of food at 2-4 weeks n=428** | 4.54±0.46 (1.50-5.00) | 4.56±0.47 (1.50-5.00) | 4.52±0.44 (2.50-5.00) | 0.426 |
| **Enjoyment of food at 4 weeks n=321** | 4.50±0.47 (1.50-5.00) | 4.52±0.48 (1.50-5.00) | 4.49±0.45 (2.50-5.00) | 0.552 |
| **Food responsiveness at 2-4 weeks n=428** | 2.26±0.93 (1.00-5.00) | 2.27±0.93 (1.00-5.00) | 2.25±0.94 (1.00-5.00) | 0.810 |

| | | | | |
|---|---|---|---|---|
| **Food responsiveness at 4 weeks n=321** | 2.30±0.93 (1.00-5.00) | 2.34±0.93 (1.00-5.00) | 2.25±0.93 (1.00-5.00) | 0.367 |
| **Satiety responsiveness at 2-4 weeks n=428** | 2.49±0.67 (1.00-5.00) | 2.43±0.63 (1.00-5.00) | 2.57±0.72 (1.00-5.00) | 0.042* |
| **Satiety responsiveness at 4 weeks n=321** | 2.54±0.71 (1.00-5.00) | 2.46±0.66 (1.00-5.00) | 2.63±0.75 (1.00-5.00) | 0.032* |
| **Slowness in eating at 2-4 weeks n=428** | 2.44±0.90 (1.00-5.00) | 2.44±0.90 (1.00-5.00) | 2.37±0.81 (1.00-5.00) | 0.062 |
| **Slowness in eating at 4 weeks n=321** | 2.46±0.90 (1.00-5.00) | 0.42±0.81 (1.00-5.00) | 2.50±1.00 (1.00-5.00) | 0.429 |
| **Enjoyment of food at 6 months n=411** | 4.63±0.49 (2.00-5.00) | 4.64±0.52 (2.00-5.00) | 4.64±0.44 (2.75-5.00) | 0.865 |
| **Food responsiveness at 6 months n=411** | 1.62±0.74 (1.00-5.00) | 1.65±0.77 (1.00-5.00) | 1.59±0.72 (1.00-5.00) | 0.376 |
| **Satiety responsiveness at 6 months n=411** | 2.62±0.72 (1.00-5.00) | 2.61±0.78 (1.00-5.00) | 2.62±0.64 (1.00-5.00) | 0.902 |
| **Slowness in eating at 6 months n=411** | 1.98±0.76 (1.00-5.00) | 1.94±0.75 (1.00-5.00) | 2.03±0.77 (1.00-5.00) | 0.275 |
| **Enjoyment of food at 12 months n=392** | 4.30±0.68 (1.00-5.00) | 4.35±0.63 (2.00-5.00) | 4.23±0.73 (1.00-5.00) | 0.076 |
| **Food responsiveness at 12 months n=392** | 2.10±0.98 (1.00-5.00) | 2.16±1.00 (1.00-5.00) | 2.04±0.96 (1.00-5.00) | 0.232 |
| **Satiety responsiveness at 12 months n=392** | 2.84±0.75 (1.00-5.00) | 2.79±0.72 (1.00-5.00) | 2.90±0.79 (1.00-5.00) | 0.125 |
| **Slowness in eating at 12 months n=392** | 2.41±0.81 (1.00-5.00) | 2.34±0.80 (1.00-5.00) | 2.48±0.81 (1.00-5.00) | 0.092 |

Mean±standard deviation (SD) are presented for normally distributed numeric variables with the range in parenthesis, median and interquartile range (IQR) for non-normally distributed numeric variables, and the category number and percentage for categorical variables.
*p-value from the independent samples t-test for normally distributed numeric variables, the Wilcoxon rank-sum test for non-normally distributed numeric variables, and the Pearson chi-square test for categorical variables. * Indicates statistical significance.

**Table 2. Association between appetite traits at 2-4 weeks and 6 months and WFAZ change between different time windows**

| | | **Model 1** | | **Model 2** | | **Model 3** | | **Model 4** | |
|---|---|---|---|---|---|---|---|---|---|
| **Appetite Scores (Independent Variable)** | **WFA Z-score change (Dependent Variable)** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Enjoyment of food at 2-4 weeks | 4wk – 6 months | 0.09 (-0.1, 0.29) | 0.343 | 0.10 (-0.08, 0.28) | 0.272 | 0.13 (-0.06, 0.31) | 0.184 | 0.13 (-0.06, 0.32) | 0.167 |
| | 6-12 months | -0.01 (-0.12, 0.11) | 0.919 | 0.01 (-0.11, 0.11) | 0.970 | -0.01 (-0.12, 0.11) | 0.904 | -0.01 (-0.12, 0.11) | 0.874 |
| Food responsiveness at 2-4 weeks | 4wk – 6 months | 0.03 (-0.06, 0.12) | 0.522 | 0.05 (-0.03, 0.14) | 0.232 | 0.07 (-0.02, 0.16) | 0.130 | 0.07 (-0.03, 0.16) | 0.158 |
| | 6-12 months | 0.04 (-0.01, 0.10) | 0.115 | 0.06 (0.01, 0.11) | 0.024* | 0.06 (0.01, 0.12) | 0.022* | 0.06 (0.01, 0.12) | 0.029* |
| Satiety responsiveness at 2-4 weeks | 4wk – 6 months | -0.17 (-0.30, -0.04) | 0.012* | -0.16 (-0.28, -0.03) | 0.013* | -0.16 (-0.29, -0.04) | 0.011* | -0.17 (-0.30, -0.04) | 0.008* |
| | 6-12 months | -0.03 (-0.11, 0.05) | 0.459 | -0.04 (-0.11, 0.04) | 0.306 | -0.02 (-0.10, 0.05) | 0.591 | -0.02 (-0.09, 0.06) | 0.622 |
| Slowness in eating at 2-4 weeks | 4wk – 6months | 0.01 (-0.09, 0.11) | 0.824 | -0.03 (-0.13, 0.06) | 0.482 | -0.01 (-0.10, 0.09) | 0.917 | -0.01 (-0.11, 0.09) | 0.880 |
| | 6-12 months | 0.03 (-0.03, 0.08) | 0.363 | 0.01 (-0.05, 0.06) | 0.884 | 0.01 (-0.04, 0.07) | 0.659 | 0.01 (-0.05, 0.07) | 0.745 |
| Enjoyment of food at 6 months | 6-12 months | -0.02 (-0.13, 0.09) | 0.700 | 0.06 (-0.05, 0.16) | 0.296 | 0.04 (-0.06, 0.14) | 0.451 | 0.06 (-0.05, 0.16) | 0.310 |
| Food responsiveness at 6 months | 6-12 months | 0.02 (-0.05, 0.09) | 0.653 | 0.01 (-0.06, 0.08) | 0.714 | 0.06 (-0.01, 0.12) | 0.093 | 0.03 (-0.04, 0.11) | 0.394 |
| Satiety responsiveness at 6 months | 6-12 months | -0.08 (-0.15, -0.01) | 0.036* | -0.11 (-0.18, -0.04) | 0.002* | -0.09 (-0.16, -0.02) | 0.014* | -0.09 (-0.17, -0.02) | 0.013* |
| Slowness in eating at 6 months | 6-12 months | 0.06 (-0.01, 0.13) | 0.086 | 0.04 (-0.02, 0.11) | 0.169 | 0.06 (-0.01, 0.12) | 0.089 | 0.06 (-0.1, 0.12) | 0.113 |

[Model 1] Unadjusted model (n=413-421), [Model 2] Adjusted for sex, gestational age, WFA z-score at start of growth window, age at start [if not birth] and at end of growth window, age at main independent variable appetite assessment, age and appetitive trait score at previous appetite assessments (n=393-415), [Model 3] Adjusted for sex, gestational age, WFA z-score at start of growth window, age at end of growth window, ethnicity, maternal BMI, paternal BMI, mother's educational attainment, smoking during pregnancy and infant feeding (n=375-383), and [Model 4] Adjusted for sex, gestational age, WFA z-score at start of growth window, age at start [if not birth] and at end of growth window, age at main independent variable appetite assessment, age and appetitive trait score at previous appetite assessments, ethnicity, maternal BMI, paternal BMI, mother's educational attainment, smoking during pregnancy and infant feeding (n=369-377). * Indicates statistical significance

**Table 3. Association between WFAZ change during different time windows and appetite at 4 weeks, 6 months and 12 months**

| | | Model 1 | | Model 2 | | Model 3 | | Model 4 | |
|---|---|---|---|---|---|---|---|---|---|
| **WFA Z-score change (Independent** | **Appetite Scores (Dependent Variable)** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** | **β (95% CI)** | **p-value** |

| Variable) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **0-4 weeks** | EF at 4 weeks | -0.03 (-0.10, 0.05) | 0.488 | -0.02 (-0.10, 0.06) | 0.631 | -0.07 (-0.16, -0.02) | 0.127 | -0.07 (-0.16, 0.02) | 0.148 |
| | EF at 6 months | 0.04 (-0.04, 0.11) | 0.323 | 0.04 (-0.04, 0.11) | 0.330 | 0.01 (-0.08, 0.09) | 0.987 | -0.01 (-0.09, 0.08) | 0.951 |
| | EF at 12 months | -0.03 (-0.14, 0.11) | 0.535 | -0.07 (-0.18, 0.04) | 0.209 | -0.06 (-0.18, 0.06) | 0.343 | -0.08 (-0.2, 0.04) | 0.193 |
| | FR at 4 weeks | -0.09 (-0.24, 0.05) | 0.219 | -0.07 (-0.23, 0.09) | 0.415 | -0.11 (-0.28, 0.07) | 0.223 | -0.10 (-0.28, 0.08) | 0.276 |
| | FR at 6 months | -0.05 (-0.16, 0.06) | 0.360 | 0.03 (-0.09, 0.14) | 0.648 | -0.06 (-0.19, 0.07) | 0.356 | -0.01 (-0.14, 0.11) | 0.821 |
| | FR at 12 months | -0.09 (-0.25, 0.06) | 0.220 | -0.01 (-0.16, 0.14) | 0.885 | -0.11 (-0.28, 0.07) | 0.232 | -0.04 (-0.21, 0.12) | 0.608 |
| | SR at 4 weeks | 0.03 (-0.08, 0.14) | 0.543 | 0.06 (-0.06, 0.18) | 0.296 | 0.10 (-0.03, 0.23) | 0.129 | 0.09 (-0.05, 0.22) | 0.196 |
| | SR at 6 months | 0.04 (-0.07, 0.15) | 0.448 | -0.01 (-0.13, 0.10) | 0.848 | 0.06 (-0.06, 0.19) | 0.311 | 0.02 (-0.11, 0.14) | 0.791 |
| | SR at 12 months | -0.03 (-0.14, 0.09) | 0.619 | -0.01 (-0.13, 0.11) | 0.841 | 0.01 (-0.14, 0.14) | 0.980 | -0.02 (-0.16, 0.11) | 0.727 |
| | SE at 4 weeks | -0.09 (-0.23, 0.05) | 0.200 | -0.12 (-0.27, 0.04) | 0.145 | -0.15 (-0.32, 0.02) | 0.082 | -0.14 (-0.32, 0.03) | 0.103 |
| | SE at 6 months | -0.09 (-0.20, 0.03) | 0.141 | -0.08 (-0.20, 0.04) | 0.209 | -0.11 (-0.24, 0.02) | 0.108 | -0.08 (-0.21, 0.05) | 0.236 |
| | SE at 12 months | -0.10 (-0.22, 0.02) | 0.113 | -0.06 (-0.19, 0.07) | 0.385 | -0.10 (-0.24, 0.05) | 0.208 | -0.04 (-0.19, 0.11) | 0.584 |
| **4 weeks – 6 months** | EF at 6 months | 0.05 (-0.01, 0.01) | 0.079 | 0.06 (0.01, 0.12) | 0.025* | 0.01 (-0.05, 0.08) | 0.691 | 0.01 (-0.06, 0.07) | 0.862 |
| | EF at 12 months | 0.10 (0.03, 0.18) | 0.006* | 0.09 (0.01, 0.17) | 0.035* | 0.10 (0.01, 0.19) | 0.033* | 0.11 (0.01, 0.20) | 0.027* |
| | FR at 6 months | 0.04 (-0.04, 0.12) | 0.355 | 0.04 (-0.04, 0.13) | 0.275 | 0.10 (-0.01, 0.21) | 0.052 | 0.07 (-0.03, 0.17) | 0.167 |
| | FR at 12 months | 0.11 (0.01, 0.22) | 0.037* | 0.12 (0.01, 0.23) | 0.027* | 0.24 (0.10, 0.37) | 0.001* | 0.17 (0.04, 0.30) | 0.008* |
| | SR at 6 months | -0.12 (-0.20, -0.05) | 0.001* | -0.12 (-0.20, -0.04) | 0.004* | -0.11 (-0.21, -0.01) | 0.033* | -0.07 (-0.17, 0.03) | 0.165 |
| | SR at 12 months | -0.12 (-0.20, -0.04) | 0.003* | -0.10 (-0.19, -0.01) | 0.023* | -0.14 (-0.24, -0.03) | 0.010* | -0.10 (-0.20, 0.01) | 0.067 |
| | SE at 6 months | -0.01 (-0.10, 0.07) | 0.717 | -0.04 (-0.13, 0.05) | 0.367 | -0.08 (-0.19, 0.03) | 0.135 | -0.08 (-0.19, 0.03) | 0.139 |
| | SE at 12 months | -0.04 (-0.13, 0.05) | 0.379 | -0.04 (-0.14, 0.05) | 0.356 | -0.07 (-0.18, 0.05) | 0.256 | -0.06 (-0.17, 0.05) | 0.278 |
| **6 – 12 months** | EF at 12 months | 0.12 (-0.01, 0.25) | 0.071 | 0.14 (-0.01, 0.28) | 0.053 | 0.17 (0.02, 0.33) | 0.030* | 0.18 (0.02, 0.34) | 0.025* |
| | FR at 12 months | 0.04 (-0.14, 0.23) | 0.640 | 0.12 (-0.07, 0.31) | 0.233 | 0.19 (-0.03, 0.42) | 0.094 | 0.15 (-0.06, 0.37) | 0.159 |
| | SR at 12 months | -0.11 (-0.26, 0.03) | 0.128 | -0.15 (-0.30, 0.01) | 0.053 | -0.24 (-0.41, 0.06) | 0.007* | -0.23 (-0.41, -0.06) | 0.009* |
| | SE at 12 months | 0.04 (-0.12, 0.19) | 0.633 | -0.02 (-0.19, 0.14) | 0.783 | 0.05 (-0.14, 0.24) | 0.618 | -0.04 (-0.22, 0.15) | 0.716 |

[Model 1] Unadjusted model (n=388-424), [Model 2] Adjusted for sex, gestational age, WFA z-score at start of growth window, age at start [if not birth] and at end of growth window, age at outcome appetite assessment, age and appetite trait score at previous appetite assessments (n=377-399), [Model 3] Adjusted for sex, gestational age, WFA z-score at start of growth window, age and height at outcome appetite assessment, ethnicity, maternal BMI, paternal BMI, mother's educational attainment, smoking during pregnancy and infant feeding (n=352-406), and [Model 4] Adjusted for sex, gestational age, WFA z-score at start of growth window, age at start [if not birth] and at end of growth window, age and height at outcome appetite assessment, age and appetite trait score at previous appetite assessments, ethnicity, maternal BMI, paternal BMI, mother's educational attainment, smoking during pregnancy and infant feeding (n=344-400). * Indicates statistical significance