

Predominantly nighttime feeding and weight outcomes in infants^{1,2}

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ABSTRACT

Background: The influence of circadian feeding patterns on weight outcomes has been shown in animal and human studies but not in very young children.

Objective: We aimed to examine the association of infant circadian feeding patterns at 12 mo of age with subsequent growth and weight status after 1 y.

Design: Mothers from a Singapore birth cohort ($n = 349$) reported the food given to their infants and the feeding time at 12 mo of age. Predominantly daytime (pDT) (0700–1859; $n = 282$) and predominantly nighttime (pNT) (1900–0659; $n = 67$) feeding infants were defined by whether daytime energy intake was $>50\%$ or $<50\%$ of total energy intake as assessed with the use of a 24-h recall. Body mass index-for-age z scores (BAZs) were computed with the use of the WHO Child Growth Standards 2006 to determine changes in BAZs from 12 to 24 mo of age and weight status at 24 mo of age. Multivariable linear and logistic regression analyses were performed.

Results: Compared with pDT feeding, pNT feeding was associated with a higher BAZ gain from 12 to 24 mo of age (adjusted $\beta = 0.38$; 95% CI: 0.11, 0.65; $P = 0.006$) and increased risk of becoming overweight at 24 mo of age (adjusted OR: 2.78; 95% CI: 1.11, 6.97; $P = 0.029$) with adjustments for maternal age, education, ethnicity, monthly household income, parity, infant BAZ at 12 mo of age, feeding mode in the first 6 mo of life, and total daily energy intake.

Conclusions: Our study suggests that the role of the daily distribution of energy consumption in weight regulation begins in infancy. The feeding of infants predominantly during nighttime hours was associated with adiposity gain and risk of overweight in early childhood. The inclusion of advice on the appropriate feeding time may be considered when implementing strategies to combat childhood obesity. This trial was registered at clinicaltrials.gov as NCT01174875. *Am J Clin Nutr* doi: 10.3945/ajcn.116.130765.

Keywords: adiposity, circadian, feeding, infant, nighttime, overweight

INTRODUCTION

Research on nutrition has traditionally focused on the type and amount of food ingested, thereby linking portion size (1), nutrient density (2), and macronutrient composition (3) with weight gain and obesity. However, comparatively less is known about the role of the circadian patterns of food intake. Because both food and light are important signals that entrain tightly regulated genes and proteins that control our body's biological rhythms (4), it is possible that the feeding rhythm over a 24-h day-night cycle influences weight-gain and body-weight outcomes.

Evidence has been accumulating that the time profile of feeding is metabolically relevant above and beyond the food portion and composition. Adults who consumed greater energy in the evening tended to be overweight or obese (5), whereas participants of weight-loss programs who were late-lunch and dinner feeders lost less weight than early feeders did although total energy intake, dietary composition, and energy expenditure

¹ Supported by the Singapore National Research Foundation under its Translational and Clinical Research Flagship Programme, which is administered by the Singapore Ministry of Health's National Medical Research Council (Singapore-NMRC/TCR/004-NUS/2008; NMRC/TCR/012-NUHS/2014). Additional funding was provided by the Singapore Institute for Clinical Sciences, Agency for Science Technology and Research, Singapore. KMG is supported by the National Institute for Health Research (NIHR) through the NIHR Southampton Biomedical Research Center and by the European Union's Seventh Framework Programme (FP7/2007-2013), project EarlyNutrition under grant agreement 289346. JKYC received salary support from the Ministry of Health's National Medical Research Council, Singapore (NMRC/CSA/043/2012).

² Supplemental Figure 1 and Supplemental Tables 1 and 2 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at <http://ajcn.nutrition.org>.

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Received January 15, 2016. Accepted for publication May 23, 2016.

doi: 10.3945/ajcn.116.130765.

were similar (6, 7). In children and adolescents, several studies of breakfast consumption and weight outcomes have shown that skipping breakfast was associated with increased BMI and overweight and obesity (8, 9), thus implying that meal timing may also be relevant during the earlier stages of life. However, these studies did not consider the pattern and periodicity of energy consumption, which leads to the question of whether the circadian distribution of feeding over 24 h plays an important role in weight regulation.

Infancy is the time when human growth is at its most rapid rate after birth, and height growth in the first 24 mo of childhood exceeds even the total pubertal height growth during adolescence (10). Consequently, poor growth is often of greater concern than is excessive growth during infancy. Because greater early postnatal weight gain is independently associated with higher risk of obesity and future metabolic disease, the early growth patterns are relevant to each child in the prediction of subsequent disease (11). In addition, infancy is the time of the first exposure to environmental influences including early-life nutrition and feeding rhythms that are unique to each child's circumstances. Feeding behaviors during infancy and early childhood may also establish eating patterns in adulthood because of habituation (12, 13). Therefore, early childhood is potentially a critical window for obesity prevention.

In this study, we aimed to examine the association of infant circadian feeding patterns at 12 mo of age with subsequent growth over the next 1 y and weight status at 24 mo of age. Because sunlight is a strong environmental signal for the human circadian clock (14), we hypothesized that infants who consumed greater energy during nighttime hours (i.e., predominantly fed after sunset and before sunrise) would gain more weight and would be more likely to become overweight or obese.

METHODS

Study design and participants

Data were obtained from the ongoing prospective mother-offspring cohort study GUSTO (Growing Up in Singapore Towards Healthy Outcomes)¹⁹ (clinicaltrials.gov; NCT01174875) (15). A total of 1237 pregnant women were recruited during the first trimester of pregnancy (≤ 14 wk of gestation as determined with the use of ultrasound dating) at KK Women's and Children's Hospital and National University Hospital in Singapore between 2009 and 2010. These pregnant women were ≥ 18 y of age, were citizens or permanent residents, and had homogeneous parental ethnic groups (Chinese, Malay, or Indian). Written informed consent was obtained from each participant. This study was approved by the Centralized Institutional Review Board of SingHealth (reference 2009/280/D) and the Domain Specific Review Board of the Singapore National Healthcare Group (reference D/09/021).

¹⁹ Abbreviation used: BAZ, BMI-for-age z score; GUSTO, Growing Up in Singapore Towards Healthy Outcomes; pDT, predominantly daytime; pNT, predominantly nighttime.

Maternal and infant characteristics

Maternal demographics were ascertained with the use of interviewer-administered questionnaires at recruitment and at 26–28 wk of gestation. Mother's height was measured at 26–28 wk of gestation with the use of a stadiometer (seca 213; seca). Mother's weight in early pregnancy (≤ 14 wk of gestation), infant sex, and gestational age were abstracted from hospital case notes by trained health personnel. Mother's BMI (in kg/m^2) in early pregnancy (≤ 14 wk of gestation) was derived by dividing weight by the square of height and was classified as lean (BMI < 23) or overweight (BMI ≥ 23) on the basis of Asian cutoffs (16). Infant feeding modes in the first 6 mo of life and at 12 mo of age (exclusive breastfeeding, partial breastfeeding, and exclusive formula feeding) (17) were obtained from feeding questionnaires. The total sleep duration (in h and min) was calculated as the sum of sleep durations during the night and day, which were recorded by mothers at when their infants were 12 mo of age with the use of the validated Brief Infant Sleep Questionnaire (18). Also, the usual bedtime for infants was recorded in the 24-h clock format.

Dietary assessment

Infant dietary intakes were assessed at 12 mo of age, which is a time when sleep-wake cycles in infants have stabilized (19) and the weaning process is established. A 24-h dietary recall was administered to mothers by trained clinical staff with the use of the 5-stage, multiple-pass interviewing technique (20) to record food intakes and feeding times of the mothers' children on the previous day. Mothers were also asked whether the assessed infant food intakes were typical or atypical compared with those on other unrecorded days. Energy (kcal) and macronutrient composition (carbohydrate, fat, and protein) were estimated with the use of nutrient-analysis software (Dietplan7; Forestfield Software) on the basis of Singapore food-composition tables (21). For mixed dishes that were not present in the local database, nutrient analyses of recipes were conducted with the use of the nutrient software. For other food items that were not present in the database, nutrient information was obtained from either food labels or the USDA National Nutrient Database (22).

For bottle breast-milk feeding ($n = 6$), the quantity of milk intake was calculated on the basis of the reported volume. For direct breast-milk feeding ($n = 44$), the quantity of milk intake was estimated with the use of the methods as described by Ponza et al. (23). At 12 mo of age, children who were being fed with only breast milk were assumed to consume 600 mL breast milk/d; for those who consumed both breast milk and formula milk, the quantity of unmeasured breast-milk intake from direct breastfeeding was estimated by subtracting the volumes of formula milk and expressed breast milk from 600 mL (23). The breast-milk composition was estimated on the basis of the nutrient contents of breast-milk samples by Dewey et al. (24).

Infant circadian feeding patterns

We defined infants as 1) predominantly daytime (pDT) feeding if they consumed $> 50\%$ of total daily energy intake from 0700 to 1859 (i.e., sunrise to sunset) and 2) predominantly nighttime (pNT) feeding if they consumed $> 50\%$ of total daily energy intake from 1900 to 0659 (i.e., sunset to sunrise); we excluded infants who consumed exactly 50% in each period.

The classifications were determined on the basis of the premise that sunlight is a strong environmental signal for the human circadian clock (14). Singapore's equatorial location (1.3°N, 103.8°E) (25) also ensures that sunrise and sunset are relatively predictable at ~0700 and ~1900, respectively, throughout the year, and daylight hours are at a constant duration of 12 h (26).

Infant anthropometric measurements

Infant anthropometric measurements were taken by trained staff at birth (within 24 h) and 12 and 24 mo of age with the use of standardized techniques (27). Weight was recorded to the nearest 0.001 kg with the use of a seca 334 weighing scale (seca). Recumbent crown-heel length was measured to the nearest 0.1 cm with the use of a seca 210 Mobile Measuring Mat (seca). For children with missing recumbent length data at 24 mo of age, height was measured in a standing position with the use of a seca 213 Portable Stadiometer (seca) and was converted to length by adding 0.7 cm ($n = 71$; 7.9%) (27).

Anthropometric outcomes

On the basis of the WHO Child Growth Standards 2006, infant weight and length were used to derive BMI-for-age z scores (BAZs) with the use of WHO Anthro software (version 3.2.2; WHO). The change in BAZ from 12 to 24 mo of age was calculated as the difference in BAZs from 12 to 24 mo of age and was used as a proxy for adiposity change (28). Child weight status (BAZs at 12 and 24 mo) was defined according to WHO cutoffs as follows: 1) underweight (< -2 SDs), 2) normal weight (between -2 SDs and 1 SD), and 3) at risk of overweight or overweight (> 1 SD) (27). Underweight infants at 24 mo of age were excluded from the analysis because of the small sample size (13 pDT-feeding infants and 3 pNT-feeding infants), which was insufficient to draw a valid conclusion.

Statistical analyses

Differences between infant circadian feeding patterns (pDT feeding and pNT feeding) were compared with the use of Fisher's exact tests for categorical variables and independent sample t tests for continuous variables. The associations of infant circadian feeding patterns at 12 mo of age with the BAZ change from 12 to 24 mo of age and weight status at 24 mo of age were tested with the use of multivariable linear and logistic regressions, respectively. Potential confounders in the main analyses included ethnicity, mother's education, mother's age, household monthly income, parity, infant BAZ at 12 mo of age, feeding mode in the first 6 mo of life, and total daily energy intake at 12 mo of age. Separate models with additional adjustment for other covariates (infant sleep duration, mother's BMI in early pregnancy, or relative distribution of dietary macronutrients) were estimated. Substitution models were used to examine the relative distribution of one dietary macronutrient to another under isocaloric conditions (i.e., keeping total energy constant) (29). For example, a higher-carbohydrate, lower-protein diet was tested in a multivariate model in which percentages of energy from fat and carbohydrate and total daily energy intake were simultaneously included. This method was used because, when fat and total energy intakes are kept constant, the only macronutrient that can decrease as carbohydrate increases is protein (the sub-

stitution of carbohydrate for protein). Similarly, a higher-fat, lower-protein diet was tested when carbohydrate and total energy intakes were kept constant (the substitution of fat for protein). Similar interpretations were used for 2 additional models that included percentages of energy from carbohydrate and protein and total daily energy intake (higher-carbohydrate or -protein, lower-fat diets) as well as percentages of energy from fat and protein and total daily energy intake (higher-fat or -protein, lower-carbohydrate diets). Finally, we repeated the main analyses in a subsample of infants whose assessed feeding patterns were reported as typical to test the strength of our primary findings with the assumption that typical dietary assessments constitute more reliable data. Results are presented as n (%), means \pm SDs, and regression coefficients (β) or ORs with 95% CIs as appropriate. $P < 0.050$ was considered statistically significant. All statistical analyses were performed with the use of Statistical Package for the Social Sciences software (version 19.0; SPSS Inc.).

RESULTS

Study participants

Of 1237 participants who were recruited into the GUSTO study, a total of 349 singletons were included and comprised 67 pNT-feeding infants (19.2%) and 282 pDT-feeding infants (80.8%). The reasons for exclusion were as follows: 1) no 24-h dietary recall data at 12 mo of age ($n = 806$; 65.2%), 2) the consumption of exactly 50% of the total daily energy intake in each period ($n = 2$; 0.2%), and 3) no anthropometric measurements at 12 and 24 mo of age ($n = 80$; 6.5%) as shown in the flowchart in **Supplemental Figure 1**. Maternal household monthly income, marital status, age, infant sex, gestational age, and anthropometric measures (maternal weight and BMI status in early pregnancy, infant BAZ at birth, infant weight status, and infant BAZ at 12 mo of age) were similar in excluded and included participants, but subjects who were included were less likely to be nulliparous or of Chinese ethnicity, had a lower level of maternal education, and were more likely to be exclusively formula fed in the first 6 mo of life (**Supplemental Table 1**).

Table 1 shows a comparison of maternal and infant characteristics between pNT- and pDT-feeding groups. Participants with married mothers and those who were exclusively breastfed in the first 6 mo of life and at 12 mo of age were more likely to have pNT-feeding patterns than pDT-feeding patterns [100.0% compared with 94.2% ($P = 0.049$), 23.8% compared with 8.3% ($P = 0.003$), and 16.7% compared with 1.8% ($P < 0.001$), respectively], whereas other characteristics were comparable.

Table 2 compares the total daily energy and macronutrient intakes at 12 mo of age between pNT- and pDT-feeding infants. Total daily energy intake was not significantly different between pNT- and pDT-feeding infants (815 ± 229 compared with 764 ± 222 kcal; $P = 0.090$). Although total protein intake (26.0 ± 10.9 compared with 28.0 ± 8.9 g; $P = 0.127$) and carbohydrate intake (100.6 ± 33.4 compared with 100.1 ± 35.3 g; $P = 0.913$) were similar, lower percentages of energy from protein ($12.7\% \pm 2.8\%$ compared with $14.8\% \pm 3.2\%$; $P < 0.001$) and carbohydrate ($49.3\% \pm 7.7\%$ compared with $52.3\% \pm 7.9\%$; $P = 0.005$) were consumed by pNT-feeding infants than by pDT-feeding infants, respectively. Also, higher total fat (34.3 ± 11.3 compared with 28.1 ± 9.6 g; $P < 0.001$) and a higher percentage of

TABLE 1
Comparison of infant and maternal characteristics between pNT feeding and pDT feeding¹

	Feeding patterns		P
	pNT (n = 67)	pDT (n = 282)	
Mothers			
Ethnicity, n (%)			0.257
Chinese	32 (47.8)	158 (56.0)	
Malay	14 (20.9)	62 (22.0)	
Indian	21 (31.3)	62 (22.0)	
Household monthly income, Singapore dollars, ² n (%)			0.099
≤1999	7 (11.3)	53 (20.0)	
2000–5999	42 (67.7)	140 (52.8)	
≥6000	13 (21.0)	72 (27.2)	
Marital status, ² n (%)			0.049
Single/divorced	0 (0.0)	16 (5.8)	
Married	65 (100.0)	258 (94.2)	
Educational level, ² n (%)			0.690
None, primary, or secondary	21 (31.8)	102 (37.0)	
Postsecondary	26 (39.4)	94 (34.1)	
Tertiary	19 (28.8)	80 (29.0)	
Weight status in early pregnancy, ² n (%)			0.884
Lean	28 (49.1)	135 (50.8)	
Overweight	29 (50.9)	131 (49.2)	
BMI in early pregnancy, kg/m ²	23.84 ± 3.76 ³	23.77 ± 4.64	0.920
Age, y	30.27 ± 4.56	30.71 ± 5.44	0.543
Infants			
Sex, n (%)			0.892
M	35 (52.2)	152 (53.9)	
F	32 (47.8)	130 (46.1)	
Parity, n (%)			0.209
Nulliparous	21 (31.3)	114 (40.4)	
Multiparous	46 (68.7)	168 (59.6)	
Feeding mode in the first 6 mo of life, ² n (%)			0.003
Exclusively breastfeeding	15 (23.8)	22 (8.3)	
Partially breastfeeding	35 (55.6)	159 (60.2)	
Exclusively formula feeding	13 (20.6)	83 (31.4)	
Feeding mode at 12 mo of age, ² n (%)			<0.001
Exclusively breastfeeding	11 (16.7)	5 (1.8)	
Partially breastfeeding	13 (19.7)	25 (9.0)	
Exclusively formula feeding	42 (63.6)	248 (89.2)	
Weight status at 12 mo of age, ² n (%)			0.187
Underweight	5 (7.5)	12 (4.3)	
Normal weight	49 (73.1)	230 (82.1)	
Overweight/at risk of overweight	13 (19.4)	38 (13.6)	
Gestational age, wk	38.25 ± 1.17	38.33 ± 1.35	0.657
BAZ at birth	−0.29 ± 1.13	−0.30 ± 1.14	0.962
BAZ at 12 mo of age	−0.17 ± 1.27	−0.13 ± 1.00	0.782
Total sleep duration at 12 mo of age, ⁴ h	11.35 ± 1.55	11.87 ± 1.77	0.155
Bedtime, ⁴ h:min	21:57 ± 1:21	21:58 ± 1:01	0.975

¹Fisher's exact tests for categorical variables and independent-samples *t* tests for continuous variables were used to compare the 2 groups. BAZ, BMI-for-age *z* score; pDT, predominantly daytime; pNT, predominantly nighttime.

²Total sample size ranged from 323 to 347 because of missing values.

³Mean ± SD (all such values).

⁴On the basis of a subsample of 144 infants.

energy from fat (38.0% ± 7.8% compared with 33.1% ± 6.9%; $P < 0.001$) were observed in pNT-feeding infants than in pDT-feeding infants, respectively.

Figure 1 illustrates the 24-h energy consumption profile for pNT- and pDT-feeding infants. Lower energy was consistently consumed by pNT-feeding infants from 0700 to 1859 (sunrise to sunset), but this phenomenon was the opposite from 1900 to 0659 (sunset to sunrise). Two substantial rises in energy consumption

were noted from 1900 to 2159 and from 0600 to 0659 in pNT-feeding infants, whereas a single substantial rise in energy consumption was observed from 0700 to 0759 for pDT-feeding infants.

Circadian feeding patterns and adiposity outcomes

Tables 3 and **4** show the associations of infant circadian feeding patterns with subsequent adiposity outcomes. Compared

TABLE 2

Comparison of total daily energy and macronutrient intakes of 12-mo-old infants between pNT feeding and pDT feeding¹

Intake and time	Feeding patterns		P
	pNT (<i>n</i> = 67)	pDT (<i>n</i> = 282)	
Energy, kcal			
0700–1859	301 ± 125	506 ± 153	<0.001
1900–0659	514 ± 176	258 ± 122	<0.001
Total	815 ± 229	764 ± 222	0.090
Protein, g			
0700–1859	11.2 ± 5.1	19.4 ± 6.8	<0.001
1900–0659	14.8 ± 8.5	8.6 ± 4.6	<0.001
Total	26.0 ± 10.9	28.0 ± 8.9	0.127
Fat, g			
0700–1859	10.2 ± 6.3	17.8 ± 6.9	<0.001
1900–0659	24.1 ± 9.4	10.3 ± 5.3	<0.001
Total	34.3 ± 11.3	28.1 ± 9.6	<0.001
Carbohydrate, g			
0700–1859	41.2 ± 17.4	67.4 ± 24.6	<0.001
1900–0659	59.4 ± 24.9	32.7 ± 17.1	<0.001
Total	100.6 ± 33.4	100.1 ± 35.3	0.913
Protein, %			
0700–1859	5.6 ± 2.3	10.4 ± 3.2	<0.001
1900–0659	7.1 ± 2.3	4.4 ± 1.9	<0.001
Total	12.7 ± 2.8	14.8 ± 3.2	<0.001
Fat, %			
0700–1859	11.1 ± 5.0	21.1 ± 6.5	<0.001
1900–0659	26.8 ± 9.1	12.0 ± 4.9	<0.001
Total	38.0 ± 7.8	33.1 ± 6.9	<0.001
Carbohydrate, %			
0700–1859	20.3 ± 7.0	35.5 ± 8.2	<0.001
1900–0659	29.0 ± 6.0	16.8 ± 6.0	<0.001
Total	49.3 ± 7.7	52.3 ± 7.9	0.005

¹All values are means ± SDs. Independent sample *t* tests were used to compare the 2 groups for continuous variables. pDT, predominantly daytime; pNT, predominantly nighttime.

with pDT feeding, pNT feeding was associated with a higher BAZ gain from 12 to 24 mo of age ($\beta = 0.31$; 95% CI: 0.06, 0.56; $P = 0.014$) and increased risk of becoming overweight at 24 mo of age (OR: 2.31; 95% CI: 1.21, 4.39; $P = 0.011$). These associations remained significant after adjustment for confounders [BAZ change from 12 to 24 mo of age: adjusted $\beta = 0.38$ (95% CI: 0.11, 0.65; $P = 0.006$); risk of becoming overweight at 24 mo of age: adjusted OR, 2.78 (95% CI: 1.11, 6.97; $P = 0.029$)].

When additional adjustment was made for maternal BMI in early pregnancy, pNT feeding remained associated with a higher BAZ change from 12 to 24 mo of age (adjusted $\beta = 0.38$; 95% CI: 0.09, 0.66; $P = 0.010$) and increased risk of becoming overweight at 24 mo of age, but the latter association was NS (adjusted OR: 2.49; 95% CI: 0.90, 6.85; $P = 0.078$) (data not shown). When additional adjustment was made instead for the total sleep duration of infants ($n = 144$), a nonsignificant association of pNT feeding with a higher BAZ change from 12 to 24 mo of age was observed (adjusted $\beta = 0.46$; 95% CI: -0.02 , 0.93; $P = 0.059$), whereas the association with becoming overweight at 24 mo of age was attenuated (adjusted OR: 2.04; 95% CI: 0.35, 11.79; $P = 0.424$) (data not shown).

In the isocaloric substitution models, in which protein (model 2), fat (model 3), or carbohydrate (model 4) was substituted by

other macronutrients, the association of pNT feeding with a higher BAZ gain from 12 to 24 mo of age remained strong [model 2: adjusted $\beta = 0.39$ (95% CI: 0.10, 0.67; $P = 0.007$); model 3: adjusted $\beta = 0.39$ (95% CI: 0.11, 0.67; $P = 0.007$); and model 4: adjusted $\beta = 0.39$ (95% CI: 0.11, 0.67; $P = 0.007$)] (Supplemental Table 2). Moreover, a tendency toward significance for the association of pNT feeding with being overweight at 24 mo of age was obtained [model 2: adjusted OR, 2.55 (95% CI: 0.97, 6.68; $P = 0.057$); model 3: adjusted OR, 2.61 (95% CI: 0.99, 6.86; $P = 0.052$); model 4: adjusted OR, 2.59 (95% CI: 0.98, 6.82; $P = 0.054$)] (Supplemental Table 2).

In infants whose assessed dietary intakes were reported as typical, similar trends in findings to those observed in previous additional adjustment analyses were shown ($n = 235$) [BAZ change from 12 to 24 mo: adjusted $\beta = 0.37$ (95% CI: 0.05, 0.69; $P = 0.022$); risk of becoming overweight at 24 mo: adjusted OR, 2.19 (95% CI: 0.80, 5.95; $P = 0.126$)] (data not shown).

DISCUSSION

To our knowledge, this study provides new evidence that links circadian feeding patterns and weight regulation in very young children. Twelve-month-old infants who were predominantly fed during nighttime hours had a higher BAZ gain from 12 to 24 mo of age and greater risk of overweight at 24 mo of age than did those who were predominantly fed during daytime hours even after adjustment for confounders including ethnicity, mother's education, mother's age, household income, parity, and infant BAZ at 12 mo, feeding mode to age 6 mo, and total daily energy intake at 12 mo. Findings were similar after additional adjustment for infant sleep duration, mother's BMI in early pregnancy, or dietary macronutrient compositions. Together, our findings suggest that consuming larger quantities of energy predominantly during the nighttime may be metabolically disadvantageous, even at age 12 mo, and may be a modifiable risk factor against future health problems.

In other age groups, previous studies have linked the timing of feeding with weight outcomes. A cross-sectional study of adults that examined energy intake in the morning (0000–1100), midday (1100–1700), and evening (1700–0000) showed that adults who consumed >33% of daily energy intake in the evening were 2-fold more likely to be overweight or obese (5). Women who were participating in a 20-wk weight-loss program and were “dinner types” with increasing energy consumption from breakfast (0600–0900) to lunch (1200–1500h) and dinner (1800–2100) lost less weight than did “breakfast types” with decreasing energy consumption from breakfast to dinner (6). Similarly, Spanish women lost less weight over 12 wk if they were “late lunch feeders” (after 1500) than did their early lunch counterparts (before 1500) although total energy intake, dietary composition, and energy expenditure were similar (7). Unlike humans who are diurnally active, nocturnally active mice fed inappropriately during the light phase (when feeding is normally reduced) gained more weight than did those fed during the dark phase, independent of total daily calories, locomotor activity, light and dark cycles, and resting phase activity (30–32). These studies and our study suggest that, in addition to portions and proportions, feeding may need to be time appropriate.

Unlike the current study, most previous studies did not fully consider participants' distributions of energy intake over a 24-h

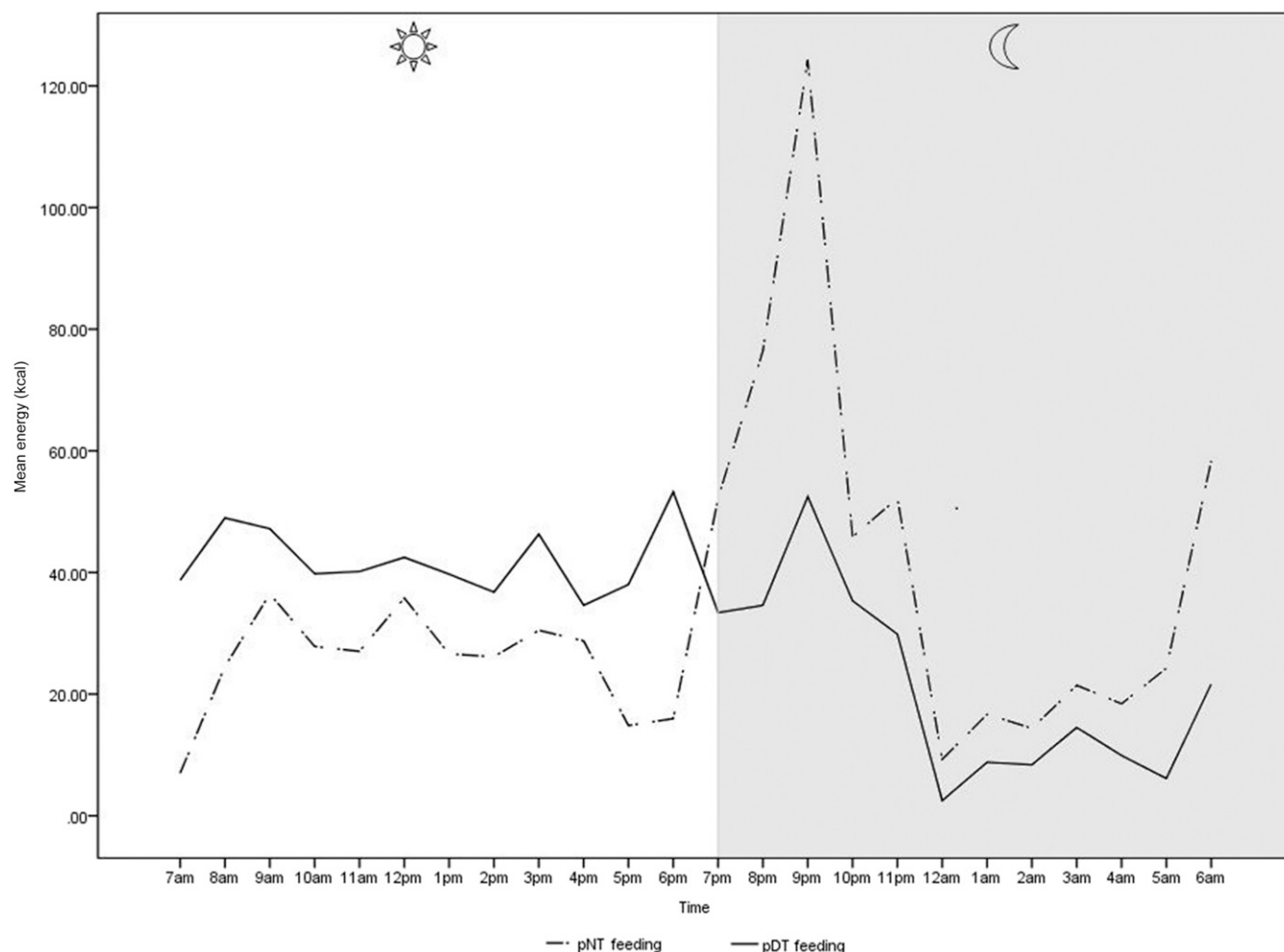


FIGURE 1 Mean 24-h energy-consumption patterns at age 12 mo for pNT-feeding infants ($n = 67$) and pDT-feeding infants ($n = 282$). Descriptive statistics were performed to calculate the mean energy at each time interval. pNT, predominantly nighttime; pDT, predominantly daytime.

time frame but instead investigated specific feeding behaviors (8, 9, 33). For example, studies on breakfast skipping did not consider if breakfast typically happened during daylight or nondaylight hours or the calorie intake profile for the rest of the day; which may explain the inconsistent associations between breakfast skipping and growth in previous studies (8, 9, 34–36). Our study classified infants by considering their individual distribution of energy intake over 24 h and capitalized on the geographical setting of the GUSTO cohort, where Singapore's equatorial location allowed a predictable ~ 0700 daily sunrises

and ~ 1900 sunsets with ~ 12 h of daylight each day. These variables provided novel insights of the circadian food-intake practices of 12-mo old infants. First, although 24-h total calorie intake was similar, pNT-feeding infants consumed consistently less energy from sunrise to sunset and higher energy from sunset to sunrise than did pDT-feeding infants. Second, pNT-feeding infants had 2 energy-consumption surges during nighttime hours, whereas pDT-feeding infants had one energy-consumption surge during daytime hours. Third, we observed a large energy-intake surge from 2100 to 2159, just before

TABLE 3
Association of feeding patterns with BAZ change at 12–24 mo of age¹

	Change in BAZ at 12–24 mo of age				
	Mean \pm SD ²	β (95% CI) ³	<i>P</i>	Adjusted β (95% CI) ⁴	<i>P</i>
pDT feeding	-0.08 ± 0.88	Reference	—	Reference	—
pNT feeding	0.23 ± 1.09	0.31 (0.06, 0.56)	0.014	0.38 (0.11, 0.65)	0.006

¹BAZ, BMI-for-age z score; pDT, predominantly daytime; pNT, predominantly nighttime.

²Descriptive statistics were performed to calculate the mean BAZ change for each group.

³Analysis was performed with the use of linear regression without adjustment.

⁴Analysis was performed with the use of linear regression and was adjusted for ethnicity, mother's educational level, mother's age, household monthly income, parity, BAZ at 12 mo of age, feeding mode, and total daily energy intake.

TABLE 4Association of circadian feeding patterns with being overweight at 24 mo¹

	<i>n</i> (%) ²		Overweight			
	Normal (<i>n</i> = 276)	Overweight (<i>n</i> = 57)	OR (95% CI) ³	<i>P</i>	Adjusted OR (95% CI) ⁴	<i>P</i>
pDT feeding	230 (81.6)	39 (13.8)	Reference	—	Reference	—
pNT feeding	46 (68.7)	18 (26.9)	2.31 (1.21, 4.39)	0.011	2.78 (1.11, 6.97)	0.029

¹BAZ, BMI-for-age *z* score; pDT, predominantly daytime; pNT, predominantly nighttime.²Descriptive statistics were performed to calculate frequencies of weight status for each group.³Values are odds of being overweight at 24 mo of age. Analyses were performed with the use of binary logistic regression without adjustment.⁴Values are odds of being overweight at 24 mo of age. Analyses were performed with the use of binary logistic regression and were adjusted for ethnicity, mother's educational level, mother's age, household monthly income, parity, BAZ at 12 mo of age, feeding mode, and total daily energy intake.

bedtime at ~2200, in pNT-feeding infants but not in pDT-feeding infants, which may have reflected the body's need to synchronize fasting schedules and sleep-wake cycles for optimal metabolic regulation (37). We propose that research involving nutrition and health should not be limited to single behaviors or practices but should include circadian phases, the daily distribution of energy consumption, and sleep patterns.

The larger adiposity gain from 12 to 24 mo of age and the >2-fold greater risk of overweight at 24 mo of age in pNT-feeding infants than in pDT-feeding infants in this study suggest that predominantly feeding between sunset and sunrise may be physiologically inappropriate even in young children. These findings were partially explained by sleep duration but were less likely explained by other maternal factors (i.e., sociodemographic characteristics and BMI in early pregnancy) and infant factors (i.e., infant BAZ at 12 mo, feeding mode to age 6 mo, and food compositions at 12 mo). The infant total sleep duration attenuated risk of becoming overweight at 24 mo of age but not of BAZ gain from 12 to 24 mo of age in pNT-feeding infants, which suggested a stronger effect of sleep duration on weight status than of weight change (38). A weak association between a shorter sleep duration and higher BMI in infants was also shown in a recent GUSTO study (39). Additional studies with a larger sample size are needed to confirm the relations between sleep, feeding patterns, and weight outcomes. The underlying mechanisms that fully explain our findings remain unclear. One hypothesis was that time-inappropriate feeding patterns alter physiologic function, which exhibit 24-h circadian rhythms. For example, gastric emptying, which is typically slower in the evening than in the morning, may be deregulated by high-energy evening meals that impair alimentary digestive and absorptive processes and lead to unbalanced energy intake and expenditure (40). Inappropriate circadian feeding patterns may also modify the circadian rhythmicity of metabolic and satiety hormones including insulin, glucagon, leptin, and ghrelin (40) and cause excess deposition and an altered distribution of body fat through inappropriate expression patterns of lipid metabolic enzymes including lipoprotein lipase (41). Desynchronization between circadian feeding patterns and physiological rhythms during a critical period of development may lead to long-term unhealthy weight outcomes in keeping with the concept of developmental programming (42).

Strengths of our study include a good sample size, a longitudinal approach, and standardized measurements of infants by

trained research staff, which increased the power of analyses and the precision of our findings. Our findings were not likely to have been affected by imprecise estimations of sunrise and sunset that were experienced by participants or by seasonal changes in light-dark cycles because of Singapore's small land size and equatorial location. Limitations of the study include differences in maternal and infant characteristics in excluded and included subjects; however, these characteristics were adjusted for in the multivariable analyses. Infant epigenetics and daily energy expenditure, maternal feeding preferences, as well as seasonal factors including maternal employment, activity, diet, and environmental exposures were not recorded in this study and could not be accounted for in the analyses. The mother's early pregnancy BMI was used as an indicator of maternal obesity because her postpartum weight was not measured. Infant BAZ was used as a proxy for adiposity because the fat composition was not measured; however, BMI has been correlated with the percentage of body fat mass measured with the use of the isotope-dilution method in children aged 3–4 y (28). We acknowledge that the analyses with the use of sleep data were limited because the sample with these data was small. Although the quantity of infant breast-milk intake from direct breastfeeding was estimated, the proportion of breastfeeding was substantially lower in infants at 12 mo of age. Finally, the reliability of our findings may have been weakened by recall bias of the food given to infants because of the administration of a single maternal 24-h dietary recall, which we minimized through sensitivity analyses.

In conclusion, this study shows that the circadian distribution of energy consumption in infants is associated with adiposity gain and weight status in early childhood. Infants who are predominantly fed during nighttime hours have a larger adiposity gain and higher risk of becoming overweight than do infants who are predominantly fed during daytime hours. Importantly, our study raises the possibility of including advice on the appropriate feeding time when implementing strategies to combat childhood obesity. We propose that similar studies should be replicated with more-comprehensive dietary data throughout the study period especially in populations who experience variable light-dark cycles throughout the year because of seasonal changes. In addition, studies on whether circadian feeding patterns are driven by maternal or infant factors are warranted for future policy implementation. Finally, additional studies should explore

interrelations between the time of feeding, adiposity, hormones, and light-dark cycles to gain more insights into the metabolic realm of circadian rhythms.

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The authors' responsibilities were as follows—TSC, SLL, and JYT: performed the data management and analysis; TSC, SLL, YBC, JKYC, NL, MF-FC, and FY: interpreted the findings; TSC, SLL, and FY: drafted the manuscript; YBC: advised on the statistical analysis; KMG, PDG, SMS, and Y-SC: designed the GUSTO cohort study; FY: designed the current study; and all authors: participated in the critical review, revision, and approval of the final manuscript. KMG, PDG, Y-SC, and YSL have received reimbursements for speaking at conferences sponsored by companies involved in the sale of nutritional products. KMG, PDG, and Y-SC are part of an academic consortium that has received research funding from Abbott Nutrition, Nestlé, and Danone. The remaining authors reported no conflicts of interest related to the study.

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