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ORIGINAL CONTRIBUTION

Nutrient trajectories during infancy and their associations with childhood neurodevelopment

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Abstract

Purpose To examine the associations between infants' dietary nutrient trajectories and subsequent neurodevelopment during childhood in the Growing Up in Singapore Towards healthy Outcomes study.

Methods One-day food records were collected at ages 6, 9 and 12 months, whilst Bayley Scales of Infant and Toddler Development-III and Kaufman Brief Intelligence Test-2 were conducted at ages 24 and 54 months respectively. Nutrient trajectories were constructed using multi-level mixed modelling and associations with neurodevelopment (24 months: $n=484$; 54 months: $n=444$) were examined using adjusted multivariable linear regression.

Results At age 24 months, higher protein intake (at 6 months) and increasing rate of intake (from 6 to 12 months) were associated with higher fine motor score [$\beta=0.17$ SD (95% CI 0.03, 0.31) and 0.62 SD (0.10, 1.14) respectively]. Higher fat intake was associated with higher receptive language score [0.04 SD (0.003, 0.07)], but increasing rate of intake was associated with lower expressive language [− 0.20 SD (− 0.39, − 0.01)] and fine motor [− 0.29 SD (− 0.48, − 0.10)] scores. Higher carbohydrate intake was associated with lower gross motor score [− 0.07 SD (− 0.14, − 0.005)], but increasing rate of intake was associated with higher receptive language [0.44 SD (0.08, 0.81)] and fine motor [0.56 SD (0.18, 0.93)] scores. Increasing rate of dietary fibre intake was associated with higher fine motor scores [0.63 SD (0.16, 1.10)]. No significant associations were observed with neurodevelopment at 54 months.

Conclusion Our findings provide greater understanding of how nutrition over time could have varying effects on child neurodevelopment.

Keywords Infant nutrient trajectories · Cognition · Language · Motor development · Neurodevelopment

Introduction

The process of neurodevelopment is described as the interplay between the brain, environment and genes through which cognitive, motor, sensory, socioemotional, cultural and behavioural adaptive functions evolve over time [1]. One critical developmental period is the first 1000 days of life, from conception until age 2 years, when brain growth is rapid and plastic. This renders the brain vulnerable and highly sensitive to influences from environmental factors such as nutrition [2–4].

The importance of infant nutrition during the postnatal stage on neurodevelopment has been well documented in literature, with much focus placed on the quality of fats i.e. long-chain polyunsaturated fatty acids (LCPUFA), B vitamins, such as B12, folic acid and choline, and key minerals like zinc, iron and iodine [5, 6]. In fact, many benefits of breastfeeding on neurodevelopment have been attributed to these nutrients as well [7, 8]. Breastfeeding and its (longer) duration have been positively associated with improved cognitive, motor and language development and have potential protective effect against language impairment in infants [9–11]. However, as the infant grows and transits from breastmilk to solid foods, nutrients from complementary feeding do continue to build and maintain neurodevelopment [12, 13].

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The nutrient composition of complementary diets during infancy in relation to neurodevelopment has not been extensively studied [14, 15]. Our knowledge on the importance of dietary nutrients during infancy comes mostly from supplementation trials, which have generally been conducted in developing countries, where rates of malnourishment are relatively high [16–19]. Historically, studies have observed positive associations between protein intake and cognitive performance in toddlers from developing countries [20, 21], whilst intervention studies demonstrated that energy and protein supplementation of undernourished infants (age 6–24 months) were associated with improved cognitive and motor development at childhood [22–24]. More recently, amino acid supplementation in very low birth weight neonates showed positive correlations with better language and motor scores at age 2 years [25]. There is, however, limited literature examining the relationship between energy, energy yielding macronutrients including carbohydrate, fat and protein, dietary fibre and neurodevelopment in healthy infants living in developed countries [14].

Similarly, whilst most studies have evaluated diets at discrete time points, to our knowledge, there are no studies examining dietary nutrients trajectories in relation to neurodevelopment in young children. Examining individual nutrients longitudinally, via nutrient trajectories, could reveal the cumulative effect of nutrient intakes and expand our understanding of the association between long-term nutrient intakes and neurodevelopment. Additionally, trajectories allow researchers to estimate changes in an individual and how each individual compares to the population mean over time [26].

This paper aims to bridge existing gaps by examining infants' dietary nutrient trajectories from age 6 to 12 months and their associations with neurodevelopment at ages 24 and 54 months.

Methods

Study population

Data collected was part of the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, a prospective mother–offspring cohort that has been previously described in detail [27]. Briefly, 1247 pregnant women in their first trimester, aged 18–50 years old, were recruited from KK Women's and Children's Hospital (KKH) and National University Hospital (NUH) between June 2009 and September 2010. Participants were either Singapore citizens or permanent residents, of Chinese, Malay or Indian ethnicity with homogenous parental ethnic background, planned to reside in Singapore for the next 5 years and were willing to donate placenta, cord and cord blood at delivery. Excluded from the study were women on chemotherapy, psychotropic drugs or those with serious health conditions such as type 1 diabetes mellitus. The GUSTO study was approved by the Institutional Review Board of KKH and NUH, and written informed consent was obtained from all participants at each study visit.

Infant dietary assessment

Prior to the mother–infant postnatal visits at 6, 9 and 12 months, mothers were given a 3-day food diary to record their infant's dietary intakes at each time point. The food diaries were collected during the visits and mothers who were unable to complete the food diaries were interviewed by trained clinical staff, with the use of the 5-stage multiple-pass interviewing technique, to recall their infant's food intake in the past 24 h [28]. Mothers were also shown food pictures with standardised portion sizes and household measuring utensils to facilitate the 24-h food recall interview. For milk intakes, reported volumes of formula milk or expressed breastmilk consumed by infants were directly obtained from the food diaries or 24-h food recalls. For infants who were breastfed, volumes of breastmilk consumption were estimated using methods described by Ponza et al. [29]. Infants who were fed directly with breastmilk (latched-on) were estimated to have consumed 780 ml/day of breastmilk at age 6 months and 600 ml/day at ages 9 and 12 months. If infants took a mixture of breastmilk and infant formula (partial breastfeeding), the amount of infant formula consumption was deducted from these volumes and the remaining amounts estimated as breastmilk consumption. Nutrient compositions of breastmilk at the respective age groups were derived from existing literature that employed laboratory techniques to analyse the levels of macro- and micro-nutrients in breastmilk [30].

Data from either the 24-h food recalls or 1 randomly selected day from the food diaries were used for dietary nutrient analyses to maximise the sample size. Our previous study has established a moderate to strong correlation ($r = 0.43–0.82$) between the 1-day record and the two other days using a subset of infants with complete 3-day food diaries ($n = 163$) [31]. Nutrient analyses were performed using Dietplan 7 (Forestfield Software Ltd), a nutrient analysis software that includes a database of our local foods compositions. Energy and nutrient intakes values were tabulated and examined broadly without further classification of types and quality; protein, total fat and carbohydrate (available carbohydrates including sugars and starch [32]) were expressed as percentage contribution to total energy, whilst dietary fibre (non-digestible polysaccharides including lignin and resistant starch [32]) was expressed as grammes per 1000 kcal. Further details of dietary nutrient analysis were elaborated in Lim et al. [33]. Additionally from this study, it was observed

that the energy and nutrient intakes of GUSTO infants at age 6, 9 and 12 months met Institute of Medicine (IOM) guidelines [33] (Online Resource 1).

Infant nutrient trajectories

Infant energy and nutrient trajectories were constructed using multi-level mixed models with level-1 (age at 6, 9 and 12 months) and level-2 (individual infant) random effects. This accounts for repeated measures of infant dietary intakes, allowing variations in individual trajectories such that each infant has his/her own intercept and slope. Multilevel mixed modelling also allows for missing time points in data, with the assumption that the data is missing at random. The current estimates for intercept reflect the nutrient intake difference of each infant compared to the population mean at age 6 months, whilst estimates for slope represent the difference in the rate of change of each nutrient intake as compared to the population mean from age 6 to 12 months. These estimates were used as predictor variables in the subsequent analyses.

Child neurodevelopment assessments

At ages 24 (± 1 month) and 54 months (+ 2 months), a subset of the children underwent neurodevelopment assessments conducted by trained staff. The Bayley Scales of Infant and Toddler Development, 3rd Edition (BSID-III) and Kaufman Brief Intelligence Test, 2nd Edition (KBIT-2) were part of the questionnaires administered at ages 24 and 54 months respectively. BSID-III is a standardised test that evaluates children aged 1–42 months across 5 domains: cognition, expressive language, receptive language, fine motor and gross motor [34]. KBIT-2 can be used from 4 to 90 years old and consists of 2 domains: verbal and non-verbal IQ subtests. The verbal subtests measure verbal skills, concept formation and reasoning, whilst non-verbal subtests measure problem-solving abilities. Items are free of cultural and gender bias [35]. Further methodological details of the neurodevelopment assessments conducted in GUSTO have been described in Lai et al. [36].

Covariates

Potential confounding variables were selected based on previous literature [10, 37–39]. Maternal age, ethnicity, and education were collected during recruitment whilst breastfeeding duration was determined from infant feeding questionnaires administered at 3 weeks, and at 3, 6, 9 and 12 months postpartum. Breastfeeding duration was subsequently categorised into 3 groups—any breastfeeding for less than 6 months, any breastfeeding for 6 to less than 12 months and any breastfeeding for 12 months or more. Infant gestational age, reported in completed weeks, was determined by ultrasonography during the first trimester by trained ultra-sonographers and information on sex and birth weight was obtained from delivery records. Gestational age and sex adjusted birth weight *z*-scores and subsequent percentile classification were derived based on methods from Mikolajczyk et al. [40].

Statistical analysis

Using the available dietary records at age 6 months ($n = 748$), 9 months ($n = 881$) and 12 months ($n = 899$), 1035 nutrient trajectories were generated. Of 1035 infants, 484 completed BSID-III and 444 completed KBIT-2 at ages 24 and 54 months, respectively. Due to the unavailability of age-specific norms for our population and to facilitate comparison between the neurodevelopment assessments, raw scores of BSID-III and KBIT-2 domains were converted to standard deviation (SD) scores. Independent sample t-test and One-way Analysis of Variance (ANOVA) with Bonferroni post hoc analyses were used to assess differences in BSID-III and KBIT-2 domains SD scores across various maternal sociodemographic characteristics and infant characteristics. Multivariable linear regression analyses were performed to study the associations between infant nutrient trajectories and neurodevelopment assessments. Models were adjusted for potential confounders—maternal age, ethnicity, maternal education, infant's exact age at neurodevelopment testing, gestational age, sex, birth weight *z*-scores and duration of breastfeeding. Models examining slopes were further adjusted for intercepts. Beta coefficients in intercept models are reflective of change in neurodevelopment outcome SD score per 1-unit higher nutrient intake than the population mean at age 6 months, whilst beta coefficients in slope models are reflective of change in neurodevelopment outcome SD score per 1-unit increase in rate of nutrient intake greater than the population mean from age 6 to 12 months. Missing covariate data [Education ($n = 2$); Breastfeeding Duration ($n = 9$)] were estimated by multiple imputation techniques with chained equations (20 times) and pooled analyses were presented. Further sensitivity analysis was done to examine associations amongst children who completed both BSID-III and KBIT-2 ($n = 373$). All statistical analyses were performed using Stata version 17 (StataCorp LLC, TX, USA). A 2-tailed *p*-value of < 0.05 was considered to be statistically significant.

Results

Study population characteristics

Maternal and infant characteristics in association with BSID-III and KBIT-2 domains SD scores are presented in Tables 1 and 2.

Mothers who had university or higher education had infants with significantly higher BSID-III scores across cognition, language and fine motor domains at age 24 months. Mothers who breastfed for 12 months or more also had infants with significantly higher cognition and language scores. Older mothers tended to have infants with higher receptive language score. Infants born to Chinese mothers had significantly higher receptive language score, whilst infants born to Malay mothers had higher gross motor score at age 24 months. With the exception of gross motor domain, female infants had higher scores across all other BSID-III domains than males at age 24 months.

Similar trends were observed for KBIT-2 domains, where mothers who had university or higher education and breastfed for 12 months or more had infants with significantly higher verbal and non-verbal scores at age 54 months. Infants born to Chinese mothers also had significantly higher verbal and non-verbal scores. No other significant characteristics differences were observed for KBIT-2 domains.

Associations of infant nutrient trajectories with BSID-III domains SD scores at age 24 months

The adjusted associations of infant energy and nutrient trajectories at age 6 to 12 months with BSID-III domains SD scores at age 24 months are shown in Table 3.

At age 6 months (intercept), higher total fat intake was associated with higher receptive language score [$\beta = 0.04$ SD (95% CI 0.003, 0.07)], whilst higher protein intake was associated with higher fine motor score [0.17 SD (0.03, 0.31)] and higher carbohydrate intake was associated with lower gross motor score [− 0.07 SD (− 0.14, − 0.005)]. No associations were observed for energy and fibre intakes at age 6 months with BSID-III domains at age 24 months.

From age 6 to 12 months (slope), increasing rate of carbohydrate intake was associated with higher receptive language [0.44 SD (0.08, 0.81)] and fine motor [0.56 SD (0.18, 0.93)] scores. Increasing protein and fibre intakes were also associated with higher fine motor score [0.62 SD (0.10, 1.14) and 0.63 SD (0.16, 1.10) respectively]. Conversely, increasing total fat intake was associated with lower expressive language [− 0.20 SD (− 0.39, − 0.01)] and fine motor scores [− 0.29 SD (− 0.48, − 0.10)]. No associations were observed for nutrient intakes from age 6 to 12 months with cognition and gross motor scores at age 24 months.

Similar trends were observed from the sensitivity analysis. However, the association between increasing rate of carbohydrate intake from age 6 to 12 months with higher receptive language score at age 24 months was lost. (Online Resource 2).

Associations of infant nutrient trajectories with KBIT-2 domains SD scores at age 54 months

The adjusted associations of infant energy and nutrient trajectories at age 6 to 12 months with KBIT-2 domains SD scores at age 54 months are shown in Table 4. For both intercepts (age 6 months) and slopes (age 6 to 12 months), no significant associations between nutrient trajectories and KBIT-2 scores at age 54 months were observed.

However, from the sensitivity analysis, there were associations observed between total energy intake and verbal score. At age 6 months, higher energy intake was associated with higher verbal score [$\beta = -0.003$ SD (95% CI − 0.01, − 0.0005)] at age 54 months. In contrast, increasing rate of energy intake from age 6 to 12 months was associated with lower verbal score [− 0.01 SD (− 0.02, − 0.002)] at age 54 months. (Online Resource 3).

Discussion

In the present study, we found that protein, total fat and carbohydrate intake trajectories from 6 to 12 months of infancy had significant but opposing associations with childhood language and motor development, whilst dietary fibre intake trajectory was positively associated with fine motor development at age 24 months. However, total energy trajectory showed no significant associations with neurodevelopment outcomes. Additionally, no associations were found between nutrient trajectories and neurodevelopment outcomes at 54 months of age.

Positive associations were observed between higher protein intake at age 6 months and across 6 to 12 months with higher fine motor score at age 24 months. Protein is essential for brain development and regions associated with fine motor development—cortex and cerebellum [41], are vulnerable to protein inadequacy [42]. Much of the literature focussed on protein supplementation in preterm, low birthweight or malnourished infants and results on fine motor scores were mixed [43–45]. Even though findings from literature may not be directly comparable to our study sample of healthy infants, protein remains to be an important nutrient for brain development and findings from our study suggest possible influence on motor development.

Higher fat intake at age 6 months was positively associated with receptive language development at age 24 months. This is in line with literature, where dietary fats, in particular fatty acids, have been reported to play a crucial role in neurodevelopment [5]. It is also possible that our findings were in part contributed by breastmilk consumption, as a substantial proportion of our study population (43%) were breastfed for 6 months or more. However, when considering the rate of change in fat intake from age 6 to 12 months, increased rate of fat intake greater than the population mean was negatively

Table 1 Characteristics of study population and BSID-III domains SD scores at 24 months ($n=484$)

	n	Cognition		Receptive language		Expressive language		Fine motor		Gross motor	
		Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P	Mean ± SD	P
Maternal											
Age (years)			0.10		< 0.01		0.10		0.27		0.99
18–24	64	− 0.25 ± 0.94		− 0.38 ± 1.14[a]		− 0.28 ± 0.87		− 0.197 ± 1.02		− 0.03 ± 0.94	
25–29	146	− 0.05 ± 1.07		− 0.03 ± 0.9[a,b]		0.06 ± 0.94		− 0.004 ± 1.00		0.01 ± 0.10	
30–34	165	0.09 ± 0.93		0.09 ± 1.02[b]		0.01 ± 1.07		0.09 ± 1.00		0.01 ± 0.91	
≥ 35	109	0.07 ± 1.03		0.13 ± 0.97[b]		0.08 ± 1.01		− 0.02 ± 0.98		0.004 ± 1.17	
Ethnicity			0.48		< 0.01		0.90		0.19		< 0.01
Chinese	280	− 0.02 ± 1.06		0.11 ± 1.10[a]		− 0.01 ± 1.07		− 0.06 ± 1.06		− 0.08 ± 1.04[a]	
Malay	122	0.09 ± 0.99		− 0.24 ± 0.81[b]		0.04 ± 0.83		0.13 ± 0.96		0.25 ± 0.94[b]	
Indian	82	− 0.07 ± 0.80		− 0.01 ± 0.86[a,b]		− 0.01 ± 0.98		0.02 ± 0.83		− 0.09 ± 0.88[a]	
Highest education			< 0.01		< 0.01		< 0.01		< 0.01		0.24
Secondary and below	129	− 0.33 ± 1.01[a]		− 0.38 ± 0.86[a]		− 0.32 ± 0.97[a]		− 0.23 ± 0.91[a]		− 0.11 ± 1.11	
Post-Secondary	178	− 0.06 ± 0.93[a]		− 0.13 ± 0.94[a]		− 0.05 ± 0.94[b]		− 0.05 ± 1.01[a]		− 0.002 ± 0.97	
University and above	175	0.29 ± 0.98[b]		0.40 ± 1.02[b]		0.27 ± 1.01[c]		0.21 ± 1.02[b]		0.08 ± 0.94	
Infant											
Sex			0.04		< 0.01		< 0.01		0.03		0.62
Female	227	0.097 ± 0.95		0.13 ± 0.86		0.16 ± 0.93		0.16 ± 0.93		− 0.02 ± 0.90	
Male	257	− 0.09 ± 1.04		− 0.11 ± 1.10		− 0.14 ± 1.04		− 0.14 ± 1.04		0.02 ± 1.08	
Gestational age (weeks)			0.63		0.33		0.41		0.38		0.92
< 37	28	0.07 ± 0.72		0.18 ± 0.89		− 0.15 ± 0.93		0.16 ± 0.94		− 0.02 ± 0.74	
≥ 37	456	− 0.004 ± 1.02		− 0.01 ± 1.01		0.01 ± 1.00		− 0.01 ± 1.00		0.001 ± 1.01	
Birth weight			0.45		0.20		0.54		0.82		0.22
AGA (10–90%)	356	0.01 ± 1.02		0.01 ± 1.02		0.01 ± 1.002		0.001 ± 1.02		0.01 ± 1.02	
LGA (> 90%)	70	− 0.13 ± 0.93		− 0.16 ± 0.97		− 0.11 ± 0.94		− 0.05 ± 0.90		− 0.17 ± 0.93	
SGA (< 10%)	58	0.08 ± 0.93		0.15 ± 0.92		0.08 ± 1.07		0.06 ± 0.99		0.13 ± 0.94	
Breastfeeding duration			< 0.01		< 0.01		< 0.01		0.07		0.27
< 6 months	271	− 0.14 ± 1.01[a]		− 0.21 ± 0.95[a]		− 0.15 ± 0.96[a]		− 0.06 ± 0.98		− 0.05 ± 1.02	
6 to < 12 months	85	0.07 ± 0.95[a,b]		0.19 ± 0.95[b]		0.10 ± 0.98[a,b]		− 0.06 ± 0.92		− 0.02 ± 0.91	
≥ 12 months	119	0.28 ± 0.98[b]		0.41 ± 0.99[b]		0.33 ± 1.02[b]		0.18 ± 1.09		0.13 ± 1.02	

Missing data: education ($n=2$); breastfeeding duration ($n=9$)

AGA: appropriate for gestational age; LGA: large for gestational age; SGA: small for gestational age

[a,b]Values in the same row not sharing the same superscript are significantly different at $P<0.05$ in the Bonferroni post hoc test; $P<0.05$ is considered significant

Table 2 Characteristics of study population and KBIT-2 domains SD scores at 54 months ($n = 444$)

	n	Verbal		Non-verbal	
		Mean ± SD	*P*	Mean ± SD	*P*
Maternal					
Age (years)			0.10		0.05
18–24	61	− 0.25 ± 1.00		− 0.28 ± 1.13	
25–29	133	− 0.06 ± 1.01		− 0.06 ± 1.00	
30–34	146	0.09 ± 1.02		0.07 ± 0.96	
≥ 35	104	0.09 ± 0.94		0.13 ± 0.95	
Ethnicity			< 0.01		0.01
Chinese	254	0.19 ± 1.06[a]		0.12 ± 0.97[a]	
Malay	117	− 0.39 ± 0.85[b]		− 0.18 ± 1.10[b]	
Indian	73	− 0.04 ± 0.83[a]		− 0.15 ± 0.86[a,b]	
Highest education			< 0.01		< 0.01
Secondary and below	136	− 0.33 ± 0.93[a]		− 0.20 ± 1.06[a]	
Post-secondary	154	− 0.10 ± 0.94[a]		0.002 ± 1.07[a,b]	
University and above	149	0.41 ± 1.00[b]		0.21 ± 0.81[b]	
Infant					
Sex			0.17		0.87
Female	213	0.07 ± 1.04		− 0.01 ± 0.92	
Male	231	− 0.06 ± 0.96		0.01 ± 1.07	
Gestational age (weeks)			0.49		0.96
< 37	27	0.13 ± 1.00		0.01 ± 1.03	
≥ 37	417	− 0.01 ± 1.00		− 0.001 ± 1.00	
Birth weight			0.74		0.21
AGA (10–90%)	323	0.003 ± 1.00		0.03 ± 0.98	
LGA (> 90%)	68	− 0.07 ± 1.00		0.05 ± 1.07	
SGA (< 10%)	53	0.07 ± 1.01		− 0.23 ± 1.01	
Breastfeeding duration			< 0.01		< 0.01
< 6 months	253	− 0.25 ± 0.87[a]		− 0.13 ± 1.03[a]	
6 to < 12 months	81	0.25 ± 1.01[b]		0.16 ± 0.87[b]	
≥ 12 months	101	0.43 ± 1.10[b]		0.27 ± 0.87[b]	

Missing data: education (n = 5); breastfeeding duration (n = 9)

AGA: appropriate for gestational age; LGA: large for gestational age; SGA: small for gestational age

[a,b]Values in the same row not sharing the same superscript are significantly different at $P < 0.05$ in the Bonferroni post hoc test; $P < 0.05$ is considered significant

associated with expressive language and fine motor development at age 24 months. This suggests that whilst fat intake may be important for language and motor development during infancy, a greater increase in fat intakes over time (from age 6 to 12 months) could attenuate its beneficial effects at age 24 months. It is recommended that dietary fats contribute 40–60% of total energy in the first 6 months of life and gradually reduce to 30–35% up to 3 years of age [46]. Consistent higher intakes of fat during the first year of life could be a reflection of poor diet, which in turn is associated with poor childhood cognitive development [47].

To the best of our knowledge, no previous study has examined the influence of carbohydrate intake during infancy on neurodevelopment in childhood. We observed that higher carbohydrate intake at age 6 months was associated with lower gross motor scores at age 24 months. This inverse association may be due to the higher percentage of carbohydrate contribution to energy at the expense of lower fat contribution. Interestingly, our study also observed that an increased rate of carbohydrate intake from 6 to 12 months was positively associated with better receptive language and fine motor development at age 24 months. Whilst the current evidence in this area remain equivocal [48], findings from our study suggests that sustained carbohydrate intake could benefit neurodevelopment. As carbohydrate, in the form of glucose, is the main energy source that the brain uses for neurodevelopment [49], it is essential for developing infants to consume sufficient carbohydrates, to maintain the brain's development and processes [50]. We were not able to examine the type and quality of carbohydrates consumed in our current study and future research should consider

Table 3 Associations of 6–12 months infant nutrient trajectories with BSID-III domains SD scores at 24 months ($n=484$)

Nutrients	Cognition β (95% CI)	Receptive language β (95% CI)	Expressive language β (95% CI)	Fine motor β (95% CI)	Gross motor β (95% CI)
Intercept					
Energy (kcal)	− 0.001 (− 0.003, 0.002)	− 0.0002 (− 0.003, 0.002)	− 0.001 (− 0.003, 0.002)	− 0.001 (− 0.003, 0.002)	0.001 (− 0.001, 0.004)
Protein (% energy)	0.10 (− 0.04, 0.24)	0.08 (− 0.06, 0.21)	0.01 (− 0.13, 0.15)	0.17 (0.03, 0.31)*	0.10 (− 0.04, 0.25)
Total fat (% energy)	0.03 (− 0.01, 0.07)	0.04 (0.003, 0.07)*	0.03 (− 0.01, 0.06)	0.02 (− 0.01, 0.06)	0.03 (− 0.01, 0.07)
Carbohydrate (% energy)	− 0.06 (− 0.13, 0.001)	− 0.06 (− 0.12, 0.01)	− 0.01 (− 0.08, 0.05)	− 0.04 (− 0.1, 0.03)	− 0.07 (− 0.14, − 0.005)*
Dietary fibre (g/1000 kcal)[b]	− 0.02 (− 0.10, 0.06)	− 0.04 (− 0.12, 0.04)	0.06 (− 0.02, 0.14)	− 0.01 (− 0.09, 0.08)	− 0.003 (− 0.09, 0.08)
Slope[a]					
Energy (kcal)	− 0.002 (− 0.01, 0.01)	− 0.001 (− 0.01, 0.01)	− 0.003 (− 0.01, 0.01)	− 0.003 (− 0.01, 0.01)	0.004 (− 0.01, 0.01)
Protein (% energy)	0.36 (− 0.15, 0.88)	0.28 (− 0.22, 0.79)	0.03 (− 0.49, 0.55)	0.62 (0.10, 1.14)*	0.38 (− 0.16, 0.91)
Total fat (% energy)	− 0.05 (− 0.24, 0.14)	− 0.16 (− 0.34, 0.03)	− 0.20 (− 0.39, − 0.01)*	− 0.29 (− 0.48, − 0.10)**	0.03 (− 0.17, 0.23)
Carbohydrate (% energy)	0.23 (− 0.14, 0.60)	0.44 (0.08, 0.81)*	0.37 (− 0.0005, 0.74)	0.56 (0.18, 0.93)**	0.10 (− 0.29, 0.48)
Dietary fibre (g/1000 kcal)[b]	0.28 (− 0.18, 0.75)	0.28 (− 0.18, 0.74)	0.22 (− 0.24, 0.69)	0.63 (0.16, 1.10)**	0.33 (− 0.16, 0.81)

Adjusted for maternal age, ethnicity, education, infant's age at neurodevelopment testing, gestational age, sex, birth weight and duration of breastfeeding

Intercept: Difference in intake of each subject at age 6 months compared to the population mean

Slope: Difference in the rate of change of each nutrient intake from age 6 to 12 months as compared to the population mean

*$P<0.05$, **$P<0.01$

[a]Additionally adjusted for intercept

[b]Missing data $n=1$

Table 4 Associations of 6–12 months infant nutrient trajectories with KBIT-2 domains SD scores at 54 months ($n=444$)

Nutrients	Verbal β (95% CI)	Non-verbal β (95% CI)
Intercept		
Energy (kcal)	− 0.002 (− 0.004, 0.001)	− 0.001 (− 0.003, 0.002)
Protein (% energy)	0.03 (− 0.11, 0.17)	0.09 (− 0.06, 0.24)
Total fat (% energy)	0.03 (− 0.01, 0.07)	0.03 (− 0.01, 0.07)
Carbohydrate (% energy)	− 0.06 (− 0.13, 0.01)	− 0.06 (− 0.13, 0.01)
Dietary fibre (g/1000 kcal)[b]	− 0.01 (− 0.10, 0.07)	− 0.01 (− 0.10, 0.07)
Slope[a]		
Energy (kcal)	− 0.01 (− 0.02, 0.002)	− 0.003 (− 0.01, 0.01)
Protein (% energy)	0.11 (− 0.42, 0.64)	0.35 (− 0.21, 0.91)
Total fat (% energy)	− 0.02 (− 0.22, 0.17)	− 0.07 (− 0.28, 0.13)
Carbohydrate (% energy)	0.22 (− 0.17, 0.60)	0.16 (− 0.25, 0.56)
Dietary fibre (g/1000 kcal)[b]	− 0.16 (− 0.62, 0.31)	− 0.22 (− 0.72, 0.27)

Adjusted for maternal age, ethnicity, education, infant's age at neurodevelopment testing, gestational age, sex, birth weight and duration of breastfeeding

Intercept: Difference in intake of each subject at age 6 months compared to the population mean

Slope: Difference in the rate of change of each nutrient intake from age 6 to 12 months as compared to the population mean

*$P<0.05$, **$P<0.01$

[a]Additionally adjusted for intercept

[b]Missing data $n=1$

exploring this to ascertain the influence of carbohydrates on neurodevelopment. Additionally, long-term intake of carbohydrate has been linked to gut microbiota composition [51], and several studies have observed associations between gut microbiota composition and neurodevelopment in infants [5, 52, 53]. Further research is needed to elucidate the mechanism underpinning carbohydrate intake–gut microbiota interactions and neurodevelopment.

Dietary fibre intake from age 6 to 12 months also exhibited positive associations with fine motor skills at age 24 months. A cross-sectional study in pre-pubertal children aged 7 to 9 years old showed that children with greater dietary fibre intake performed better at tasks needing different levels of cognitive control [54]. Although this study was conducted in older children, it is possible that the association of dietary fibre with child neurodevelopment could have occurred earlier in life. A study examining maternal diet high in dietary fibre and protein was shown to be associated with lower risk of non-competency in cognitive and gross motor development in 1-year old infants [55]. Khan et al. suggested that dietary fibre could affect neurocognitive development via immunomodulation or gut microbiota–brain interactions, where bacterial fermentation of dietary fibre produces short-chain fatty acids that could reduce pro-inflammatory cytokines and support neuronal survival and growth [54].

It is well recognised that brain growth occurs rapidly during the first two years of life and is especially sensitive around age one year, due to developments associated with frontal lobe maturation [56, 57]. From our study, the observed associations of dietary nutrient trajectories in the first year of life with neurodevelopment suggest that it may be possible to improve neurodevelopment outcomes of young children through changing infant diet, with a focus on balancing protein, total fats and carbohydrate intakes. The construction of dietary nutrient trajectories enabled us to maximise the potential of repeated measures in a longitudinal cohort study, taking into account changes in intake over time as the infant grows progressively from consuming baby foods to table foods. In addition, presence of intercepts and slopes allowed us to observe how dietary intakes could potentially affect neurodevelopment cross-sectionally (intercept) and over time (slope). Though it is not possible to determine specific causality of the associations due to influence from factors, such as genetics and the environment, we have adjusted for several common and important confounders. However, as with all observational studies, there could be residual confounding that was not be accounted for. The large sampling frame of 484 infants also provided greater power to the regression models, reducing the probability of chance findings. The study sample of healthy infants also allows for greater generalisability of findings to populations in developed countries. Although dietary intakes obtained from single day food records may not accurately represent the infant's usual diet, in our previous study, we have established strong correlation between single day intake and 2 day intakes from a 3 day food diary, indicating reproducibility of the single day food records [31]. Lastly, whilst breastmilk intakes of infants who were directly breastfed were estimated using established methods, there could still be deviations from the actual amounts and nutrients consumed. However, this should have minimal impact on our findings as majority of the GUSTO infants were predominantly formula fed (63–80%) [33].

Conclusion

In this study on Asian infants, intakes of dietary protein, total fat, carbohydrate and fibre between ages 6 and 12 months showed differing associations with language and motor outcomes at age 24 months. Cross-sectionally at age 6 months, higher protein and total fat intake, but not carbohydrate intake, was beneficial for language and motor development. However, the opposite was observed when dietary fat and carbohydrate were examined across time from 6 to 12 months, where an increase rate of carbohydrate intake was favourable for language and motor outcomes, whilst fat was not. Separately, increasing rate of dietary fibre intake from 6 to 12 months was beneficial for fine motor development. Trajectory of total energy intake during infancy had no significant associations with childhood neurodevelopment outcomes. The ability to examine longitudinal dietary intakes of infants and identifying differences in association with neurodevelopment potentially provides a more in-depth understanding of how nutrition over time could have varying effects on child neurodevelopment. Further studies could also consider looking into the quality of macronutrients and how these change over time, which could shed some light on the mechanism underlying the associations between macronutrients and neurodevelopment.

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Author contributions The authors' responsibilities were as follows: YSL, LP-CS, KHT, FY, KMG, Y-SC, JGE, BFPB and AR-G were responsible for conceiving designing and leading the GUSTO cohort study. JYT and MF-FC designed the present work. JYT, SC, SXL and WWP contributed to the data collection. JYT, SC, SXL and WWP contributed to data processing and cleaning. MF-FC supervised and guided the data collection and cleaning process. JYT and MF-FC analysed and interpreted the data. JYT and MF-FC were responsible for drafting and finalising the manuscript. All authors have read and agreed to the published version of the manuscript.

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Data availability The datasets generated and/or analysed during the current study are not publicly available due to an ethical restriction (patient confidentiality) which was imposed by the Centralised Institutional Review Board of SingHealth. Interested researchers may request for the data by contacting the corresponding author.

Declarations

Conflict of interest K.M.G. and Y.-S.C. report being part of an academic consortium that has received research funding from Abbott Nutrition, Nestle and Danone. K.M.G. and Y.-S.C. report receiving reimbursement for speaking at conferences sponsored by companies selling nutritional products. The other authors declared no conflict of interests. The funders had no role in the choice of research project, design of this study, data collection and statistical analyses, preparation of manuscript and decision to publish.

Ethical standards The GUSTO study was approved by the National Healthcare Group Domain Specific Review Board (D/2009/00021 and D/2014/00414) and Singhealth Centralized Institutional Review Board (2018/2767/D). All procedures were performed in line with the principles of the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed written consent at each study visit. The GUSTO study was registered at http://www.clinicaltrials.gov as NCT01174875.

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