

Infant feeding effects on early neurocognitive development in Asian children^{1–4}

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ABSTRACT

Background: Breastfeeding has been shown to enhance global measures of intelligence in children. However, few studies have examined associations between breastfeeding and specific cognitive task performance in the first 2 y of life, particularly in an Asian population.

Objective: We assessed associations between early infant feeding and detailed measures of cognitive development in the first 2 y of life in healthy Asian children born at term.

Design: In a prospective cohort study, neurocognitive testing was performed in 408 healthy children (aged 6, 18, and 24 mo) from uncomplicated pregnancies (i.e., birth weight >2500 and <4000 g, gestational age \geq 37 wk, and 5-min Apgar score \geq 9). Tests included memory (deferred imitation, relational binding, habituation) and attention tasks (visual expectation, auditory oddball) as well as the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Children were stratified into 3 groups (low, intermediate, and high) on the basis of breastfeeding duration and exclusivity.

Results: After potential confounding variables were controlled for, significant associations and dose-response relations were observed for 4 of the 15 tests. Higher breastfeeding exposure was associated with better memory at 6 mo, demonstrated by greater preferential looking toward correctly matched items during early portions of a relational memory task (i.e., relational binding task: P -trend = 0.015 and 0.050 for the first two 1000-ms time bins, respectively). No effects of breastfeeding were observed at 18 mo. At 24 mo, breastfed children were more likely to display sequential memory during a deferred imitation memory task (P -trend = 0.048), and toddlers with more exposure to breastfeeding scored higher in receptive language [+0.93 (0.23, 1.63) and +1.08 (0.10, 2.07) for intermediate- and high-breastfeeding groups, respectively, compared with the low-breastfeeding group], as well as expressive language [+0.58 (−0.06, 1.23) and +1.22 (0.32, 2.12) for intermediate- and high-breastfeeding groups, respectively] assessed via the BSID-III.

Conclusions: Our findings suggest small but significant benefits of breastfeeding for some aspects of memory and language development in the first 2 y of life, with significant improvements in only 4 of 15 indicators. Whether the implicated processes confer developmental advantages is unknown and represents an important area for future research. This trial was registered at www.clinicaltrials.gov as NCT01174875. *Am J Clin Nutr* 2015;101:326–36.

Keywords Asian, breastfeeding, cognition, infant, memory, toddler, attention, nutrition, electrophysiology, eyetracking

INTRODUCTION

Although breastfeeding is generally thought to positively influence cognitive development, research over 80 y (1) has yielded discrepant results. Some studies reported that breastfeeding enhances performance on global measures of intelligence (2–5), whereas others found small or no effects (6–8). Studies that combine exclusively and partially breastfed infants are likely to attenuate effects when assessing the influence of breastfeeding on cognition (9). Variation in formula composition (10) and dietary differences

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³Supplemental Methods are available from the “Supplemental data” 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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between lactating mothers (11) across study populations may also have contributed to mixed findings.

Inadequate adjustment for potential confounding variables, including maternal education and income, may also explain differences in published results (12, 13). Indeed, when confounding factors such as socioeconomic status and maternal intelligence quotient (IQ)⁵ are considered (5, 12, 14, 15), beneficial effects of breastfeeding are often attenuated. Maternal education has been reported to account for much of the difference observed between breastfed and formula-fed infants because highly educated mothers are more likely to breastfeed their infants (12, 16). However, breastfeeding was previously shown to influence cognitive development in a randomized controlled trial (2) and in settings in which longer breastfeeding duration is not associated with higher socioeconomic status (17, 18).

Despite the numerous investigations of breastfeeding and cognitive ability, few well-controlled studies have examined this association during infancy and early childhood (19). Examining this relation in early stages of development is important to limit the accumulating effects of sociodemographic variables. In addition, research with children often concentrates on global intelligence measures (e.g., the Wechsler IQ scales and McCarthy scales). Such measures may be insensitive to developmental differences in children compared with more specific electrophysiologic measures such as event-related potentials (ERPs) (20).

In summary, despite the long-standing history of research concerning breastfeeding and cognitive ability, few well-controlled studies have examined the potential benefits of breastfeeding on specific cognitive processes within the first 2 y of life. Moreover, very few studies focused on Asian populations, and those that did were conducted in low- and middle-income Asian countries and used global testing methods rather than detailed neurocognitive assessments (17, 21, 22). Understanding the role of infant feeding in Asians is especially important, because Asians make up >40% of the world's population (23). In this article, we report a study that assesses the relation between infant feeding and neurocognitive development among healthy children in Singapore of Chinese, Malay, and Indian ethnicity at 6, 18, and 24 mo of age.

PARTICIPANTS AND METHODS

Participants

Pregnant women aged ≥ 18 y ($n = 1247$) were recruited in their first trimester from the Kandang Kerbau Women's and Children's Hospital and National University Hospital in Singapore between June 2009 and September 2010 to participate in the Growing Up in Singapore toward Healthy Outcomes (GUSTO) birth cohort study (24). Infants in this study were born between November 2009 and May 2011. Priority in scheduling follow-up visits was given to infants who had participated in previous neurodevelopmental assessments administered within the first 2 wk of life. We also oversampled ethnic minorities (Malays and Indians) and infants who had high or low intakes of breast milk to improve statistical power. Nonparticipation at this stage ($n = 774$) was due

to busy schedules, lack of interest for their child to undergo neurocognitive assessments, or limitation of available test slots (Figure 1). Invitation to subsequent 18- and 24-mo cognitive testing was limited to toddlers who had participated in any of the previous neurodevelopmental assessments unless GUSTO parents specifically requested to be included in these visits. At 18 and 24 mo, nonparticipation ($n = 99$ and $n = 55$, respectively) was due to busy schedules, unable to contact the participants, or participant dropout from the cohort study. Within the current study, participating mothers and infants took part in neurocognitive assessments at 6 mo ($n = 473$), 18 mo ($n = 431$), and 24 mo ($n = 514$) of age, with 212 infants who underwent all 3 assessments. The neurocognitive data were collected from June 2010 until May 2013.

For this analysis, we excluded subjects whose mothers had pregnancy complications (e.g., pre-eclampsia, gestational diabetes). Infant exclusion criteria included the following: having a last recorded Apgar score of < 9 (either at 5 or 10 min), birth weight < 2500 g or > 4000 g, gestational age of < 37 wk, or being tested outside of the neurocognitive assessment window periods (6-mo visit: 6 mo \pm 2 wk; 18-mo visit: 17–19 mo; and 24-mo visit: 23–25 mo). A total of 408 subjects who underwent one or more of the neurocognitive assessments met the eligibility criteria [6 mo ($n = 306$), 18 mo ($n = 285$), and 24 mo ($n = 344$)].

This study was approved by both the National Health Care Group Domain Specific Review Board (reference D/09/021) and the Sing Health Centralized Institutional Review Board (reference 2009/280/D). All participants who provided data gave informed written consent before their participation. This trial was registered at www.clinicaltrials.gov as NCT01174875.

Definition of breastfeeding groups

Interviewers administered feeding practice questionnaires to mothers at 3 wk, 3 mo, and 6 mo postpartum. At each interview, the mother was asked to classify the type of feeding [exclusive, predominant (only breast milk and water is given), partial (mixture of breast milk and formula is given), or no breastfeeding] for every week (until week 3) and every month thereafter. Mothers were also asked when they stopped breastfeeding and when they introduced solid food to their infants.

In our cohort, few subjects were exclusively/predominantly breastfeeding at 6 mo, probably because many women returned to full-time work after their maternity leave (up to 16 wk). Hence, in the current analysis, infants were defined as having high breastfeeding if they were exclusively or predominantly breastfed (25) until 4 mo and continued at least partial breastfeeding until the age of 6 mo or beyond. This is similar to the definitions used in previous research (26, 27). Because most infants in our study had some exposure to breastfeeding, infants were defined as having low breastfeeding if they were weaned from breast milk and exclusively formula-fed before the age of 3 mo. Infants who were breastfed beyond 3 mo but who did not meet the criteria for high breastfeeding were defined as having intermediate breastfeeding.

In a secondary analysis, we also categorized duration of any breastfeeding as < 1 mo, 1 to < 3 mo, 3 to < 6 mo, 6 to < 12 mo, and ≥ 12 mo. This categorization enabled us to evaluate the dose-response relation of breastfeeding duration and cognitive outcomes, which is less well studied, particularly at early ages (28).

⁵Abbreviations used: BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; EPDS, Edinburgh Postnatal Depression Scale; ERP, event-related potential; GUSTO, Growing Up in Singapore toward Healthy Outcomes; ISI, interstimulus interval; IQ, intelligence quotient; STAI, State-Trait Anxiety Inventory.

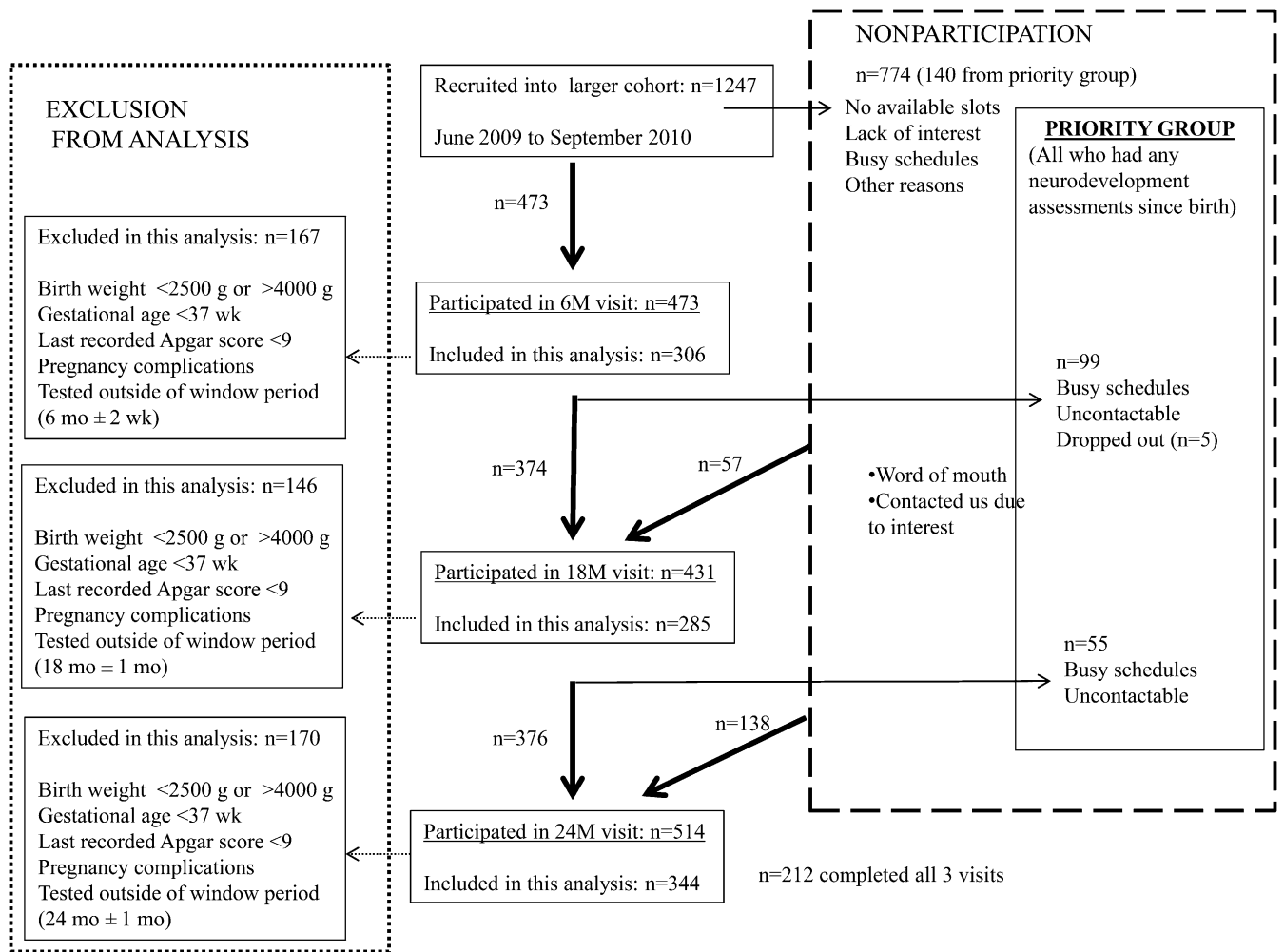


FIGURE 1 Flowchart describing the participation of children in neurocognitive assessments between 6 and 24 mo of age from the GUSTO (Growing Up in Singapore toward Healthy Outcomes) birth cohort study. The thick solid arrows indicate the distribution of participants who joined the study visit at each time point (both those who did and did not participate in the preceding visit), the thin solid arrows represent mother-child dyads who were unable to participate in the next visit, and dotted arrows refer to participants who attended the respective study visit but were excluded from the analysis reported in this article. 6M, 6-mo (180 d); 18M, 18-mo (545 d); 24M, 24-mo (730 d).

Outcome measurements

Neurocognitive assessments took place at the Singapore Institute of Clinical Sciences Neurocognitive Development Centre when infants were 6 and 18 mo old and in their homes at 24 mo (Table 1). Each visit lasted ~2–3 h. The number of subjects included in this analysis at each time point is indicated in Table 1. Not every child was able to complete all of the assessments due to fatigue, uncooperativeness, or fussiness, particularly at 6 and 18 mo. Neurocognitive measures at these visits included cognitive tasks, behavioral observation, eye tracking, and/or electrophysiology. Unless otherwise stated, computerized stimuli were presented via Eprime software (Psychology Software Tools), eye movements were recorded by a 60-Hz and/or 120-Hz TOBII eye tracker (TOBII Technology), and video recordings were taped on Canon Legria camcorders. Computerized data were generated for all tasks except for deferred imitation, mirror self-recognition, and the novelty preference aspect of habituation; in these tasks, videos were coded by trained and reliable (inter-rater reliability of $r \geq 0.79$) researchers blinded to infant feeding history. The methodology of the cognitive tests is de-

scribed in brief below, with a detailed description provided in the **Supplemental Methods**.

Memory tasks

Habituation: 6 mo

The Habit software version 2.2.5c (University of Texas, Austin) was used to generate a habituation test. Infants were repeatedly presented with either a picture of a bear or a wolf as the habituation stimulus. The infant was considered to have become habituated when the sum of the infant's look time in 3 consecutive trials became less than half the criterion, which was set as the sum of the 3 longest consecutive trial durations. After the infant was habituated, a novel stimulus was presented on one side of the monitor and the habituated stimulus was presented on the other. After 10 s, the images were presented on opposite sides for another 10 s. The infant's looking behavior was video-recorded, and duration and direction of looking were assessed by coders blinded to the feeding group and habituation stimulus used.

TABLE 1
Summary of neurocognitive assessments in 6- to 24-mo-old children

Type of task	Time point		
	6 mo (<i>n</i> = 306)	18 mo (<i>n</i> = 285)	24 mo (<i>n</i> = 344)
Memory	Habituation Deferred imitation Relational binding	Deferred imitation	Deferred imitation
Attention and preattention	Visual expectation Event-related potential	Visual expectation Event-related potential	—
Social development	—	Mirror self-recognition	—
Global measure	—	—	Bayley Scales of Infant and Toddler Development III • Cognition • Receptive language • Expressive language • Fine motor • Gross motor

Deferred imitation: 6, 18, and 24 mo

The deferred imitation tasks used at 6 mo (puppet paradigm) and 18 mo (rattle and tree paradigms) were adapted from Barr and Hayne (29). The task used at age 24 mo (slide task) was modified from Kolling et al. (30). Each deferred imitation task began with a baseline phase (90 s at 6 mo, 60 s at 18 and 24 mo), during which the child could interact with the props, to determine whether he or she could spontaneously produce any of the target actions. After the baseline phase, the experimenter demonstrated the target actions with the props. A test (90 s at 6 mo, 60 s at 18 and 24 mo) occurred 2–3 h after the training phase. The child was presented with the same items in the same context to determine whether he or she exhibited imitation of the demonstrated actions. The entire procedure was video-recorded and scored. Absolute (all time points) and sequential (at 18 and 24 mo) scores were assessed on the basis of number of target actions and correct sequences achieved.

Relational binding: 6 mo

This memory paradigm (31) was a modification of that used by Richmond and Nelson (32). Briefly, infants were shown blocks of trials involving scenes and pictures of toys. Each block consisted of 3 study trials and 1 test trial. Each study trial consisted of an audiovisual scene with a picture of a toy superimposed on the scene. During the test trial, the infants were shown 1 of the 3 audiovisual scenes, with all 3 pictures of toys viewed previously superimposed on the scene. The proportion of time the child spent looking at each picture and the background was captured by the eye tracker. Relational memory is inferred when the child preferentially looks at the correct match. We included lag 0 trials (matched pair of scene/toy appeared in the study trial immediately before the test trial) and lag 2 trials (matched pair of scene/toy appeared in 2 study trials before the test trial).

Attention and social development tasks

Visual expectation at 6 and 18 mo

The visual expectation paradigm began with infants viewing 18 infant-appropriate movie clips presented in random locations on a screen (baseline). In the experimental phase, infants watched

similar clips presented in locations on the screen that varied according to a specified pattern (6 mo: left-left-right or right-right-left; 18 mo: center-left-center-right or center-right-center-left). A macro computed the following variables of interest used in this analysis, all except the first derived from data during the experimental phase of the task: 1) eye reaction time, the time taken during the random control portion of the experiment for the child to shift his or her gaze from a different location of the screen to the one where the stimulus eventually appeared; 2) reaction time, the average time taken for an individual to shift his or her gaze during the experimental portion of the task; 3) average proportion of time spent looking at stimuli presented; 4) proportion of trials in which infants correctly anticipated (i.e., looked where the stimuli were expected to appear next); 5) average duration of anticipation (when it occurred); and 6) average proportion of time spent looking at the correct location in advance of the stimulus appearing on the screen.

Auditory oddball (ERPs): 6 and 18 mo

Infants were presented with an auditory oddball experiment consisting of a stream of sound syllables common to all 4 of Singapore's languages (English, Bahasa Melayu, Mandarin, and Tamil): "ma" and "na." Whether the infants heard "ma" vs. "na" as the standard sound was counterbalanced. Stimuli were presented in 4 blocks with a total of 1600 trials (240 "oddball" sounds), with a 800-ms interstimulus interval (ISI), resulting in a 38-min oddball task that was immediately preceded by 3 min of resting state data collection (data not reported). Two distinct ERP components were observed in the infants at ages 6 and 18 mo that may reflect varying stages of processing. The components were named on the basis of similar components previously reported (33, 34). In our current sample, we observed a relatively early negative deflection (between 46 and 164 ms at 6 mo and between 38 and 164 ms at 18 mo), followed by a relatively early positive peak (between 223 and 444 ms at 6 mo and between 205 and 384 ms at 18 mo).

Mirror self-recognition: 18 mo

Similar to work done by Amsterdam (35), the child was placed in front of the mirror and his or her behaviors were videotaped.

The experimenter then placed a mark on either the child's nose or cheek when touching the face with a puppet. Trained observers assessed differential facial expressions (smiles, frowns, and squints), freezing behaviors (i.e., stays very still), and verbal indication of noticing a mark from their mirror reflection, in addition to mirror guidance actions (e.g., touches/points to the marking or points toward reflection). Verbal indication was defined as the child's having a vocalized reaction on seeing his or her reflection in the mirror. All behaviors were assessed both pre- and postmarking the infant's face so as to control for baseline rates of any target behaviors described above.

Bayley Scales of Infant and Toddler Development, Third Edition: 24 mo

The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III), is a standardized test that assesses development across a number of domains for children 1–42 mo of age. It provides 5 US age-norm-referenced subscale scores for cognition, expressive language, receptive language, fine motor, and gross motor (36). The BSID-III was administered by research coordinators trained by clinicians from the Kangar Kerbau Women's and Children's Hospital who were blinded to the feeding group.

Other data collected relevant to the current analyses

Questionnaires were administered to the mothers by the interviewer during the antenatal period to ascertain potentially relevant covariates, including demographic data, socioeconomic status, smoking and alcohol exposures, obstetric and medical histories, as well as the use of medicines and supplements. At 26–28 wk gestation and 3 mo postpartum, maternal well-being was assessed by using the Edinburgh Postnatal Depression Scale (EPDS), which has been validated in Singaporean women (37), and the State-Trait Anxiety Inventory (STAI). Birth outcomes (e.g., birth weight and gestational age) and Apgar scores were recorded by midwives at delivery. The child's language exposure was captured by questionnaire during the visit; monolingualism was defined as having $\geq 90\%$ exposure to a first language, whereas bilingualism was defined as having at least 25% exposure to a second language.

Statistical analysis

One-factor ANOVA and chi-square tests were used to compare continuous and categorical infant and maternal characteristics, respectively, across breastfeeding groups. Multivariable linear regression models were also constructed to assess the effect and linear trend of increasing breastfeeding category on each neurocognitive test. These multiple linear regression models were adjusted for maternal education, birth weight, ethnicity, and maternal antenatal anxiety scores (STAI). These covariates were chosen either because they were significantly different between groups and associated with cognitive outcomes or they were commonly adjusted for in related literature. For analysis of ERP data at 6 and 18 mo, we used repeated-measures ANOVA for component amplitudes and latencies according to breastfeeding group, brain region (frontal vs. central), hemisphere (left vs. right), and stimulus (oddball vs. standard) as independent variables. Interactions between these variables were also examined.

Data were missing on maternal age in 2.5% ($n = 10$), antenatal EPDS in 3.5% ($n = 14$), STAI scores in 7.6% ($n = 31$), household income in 8.3% ($n = 34$), and maternal education in 3.2% ($n = 13$) of participants. Multiple imputations of missing data (maternal education, maternal antenatal anxiety scores) using chained equations imputation (20 imputations) yielded findings very similar to those limited to subjects with complete data on all covariates (data available on request). All analyses were carried out by using SPSS version 21.0 (IBM).

RESULTS

Participant characteristics

The participants who took part in the neurocognitive assessments were comparable to the rest of the nonparticipants in the cohort in terms of ethnic distribution, household income, and maternal age and education. The 2 groups also had comparable birth weights (3060 ± 485 vs. 3106 ± 435 g, $P = 0.085$), but nonparticipating children had a significantly lower gestational age (38.5 ± 1.7 vs. 38.7 ± 1.3 wk, $P = 0.031$). Mothers who consented to the neurocognitive assessments were more likely to score higher on measures of anxiety and depression during the antenatal period than those who did not consent (STAI-state: 30.1 ± 14.7 vs. 33.5 ± 11.8 ; STAI-trait: 31.8 ± 14.8 vs. 35.2 ± 11.7 ; EPDS: 6.1 ± 4.7 vs. 7.6 ± 4.6 ; all $P < 0.001$). Participants who took part in the neurocognitive assessments but were not successfully evaluated on one or more tasks were generally similar to those who completed those tasks, with the exception that Chinese children were more likely to complete habituation (59.4% vs. 44.4%, $P = 0.042$) and deferred imitation (62.0% vs. 49.7%, $P = 0.037$) at 6 mo, as well as mirror self-recognition (54.5% vs. 41.7%, $P = 0.030$) at 18 mo. Children who completed visual expectation at 18 mo were of higher gestational age (39.0 ± 1.0 vs. 38.7 ± 1.0 wk, $P = 0.040$) and had mothers with a higher educational level ($P = 0.041$) and age (30.6 ± 5.2 vs. 29.0 ± 5.1 y, $P = 0.026$). Those who successfully completed the ERP task at 18 mo were more likely to be from a household with higher income ($P = 0.037$), whereas those who completed deferred imitation at 24 mo had a lower birth weight (3120 ± 319 vs. 3226 ± 350 g, $P = 0.015$). In general, our completion rates were similar to those observed in past cognitive research in infants and young children (32, 38).

Among children who were included in this analysis, the feeding groups were similar with respect to birth weight, gestational age, and language exposure (Table 2). Infants in the intermediate-breastfeeding group had larger head circumference than those in the high-breastfeeding group. Mothers in the intermediate- and high-breastfeeding groups were older and had lower STAI and EPDS scores. They were also more likely to be of Chinese ethnicity and higher socioeconomic status (higher household income and education) than mothers in the low-breastfeeding group (Table 2).

Breastfeeding duration for the participants who took part in the neurocognitive assessments was distributed across the 5 groups as follows: < 1 mo ($n = 94$; 23%), 1 to < 3 mo ($n = 70$; 17%), 3 to < 6 mo ($n = 69$; 17%), 6 to < 12 mo ($n = 72$; 18%), and ≥ 12 mo ($n = 92$; 23%), with a small number ($n = 11$; 3%) who were unclassified because of missing data at one or more time points. The distribution of breastfeeding duration across the 5 groups was comparable to those who did not participate in the cognitive

TABLE 2
Comparison of participant characteristics in the 3 primary breastfeeding groups¹

	Low-BF (n = 170)	Intermediate-BF (n = 184)	High-BF (n = 54)	P-trend ²
Maternal age, y	28.4 ± 5.3 ³	31.4 ± 4.5	31.0 ± 4.6	<0.001
Maternal EPDS score ⁴	8.2 ± 4.5	7.6 ± 4.5	6.8 ± 4.3	0.026
Maternal STAI-state score ⁴	36.9 ± 9.8	34.3 ± 9.6	32.6 ± 9.9	0.002
Maternal STAI-trait score ⁴	38.6 ± 9.0	36.4 ± 8.8	34.9 ± 8.5	0.003
Gestational age, wk	39.0 ± 1.0	39.0 ± 1.0	38.9 ± 1.0	0.302
Sex of child, % male	52.4	59.8	53.7	0.483
Birth weight, g	3109 ± 324	3215 ± 328	3079 ± 338	0.751
Head circumference, cm	33.4 ± 1.2	33.7 ± 1.3	33.2 ± 1.3	0.008
Ethnicity, %				
Chinese	43.4	59.6	71.7	<0.001 ⁵
Malay	37.3	25.7	11.3	
Indian	19.3	14.8	17.0	
Maternal education, %				
Primary	4.7	4.3	0.0	<0.001
Secondary	35.9	17.4	16.7	
Diploma/technical education	42.4	35.9	20.4	
University	12.4	38.6	57.4	
Postgraduate	0.6	1.1	3.7	
Missing data	4.1	2.7	1.9	
Household income, %				
\$0–\$999	4.7	3.3	0.0	<0.001
\$1000–\$1999	16.5	9.2	1.9	
\$2000–\$3999	36.5	23.4	22.2	
\$4000–\$5999	19.4	24.5	18.5	
>\$6000	12.9	32.6	50.0	
Don't know/refused to answer/missing data	10.0	7.1	7.4	
Bilingual exposure (child), %	81.2	82.1	79.6	0.949

¹EPDS, Edinburgh Postnatal Depression Scale; High-BF, high exposure to breastfeeding; Intermediate-BF, intermediate exposure to breastfeeding; Low-BF, low exposure to breastfeeding; STAI, State-Trait Anxiety Inventory.

²Derived by 1-factor ANOVA with linear contrast.

³Mean ± SD (all such values).

⁴Administered at 26–28 wk of gestation.

⁵Comparing percentage of Chinese with non-Chinese ethnicity.

assessments: <1 mo (29%), 1 to <3 mo (19%), 3 to <6 mo (16%), 6 to <12 mo (17%), and ≥12 mo (19%).

Memory tasks

In terms of relational memory performance, there was no significant effect of breastfeeding on infants' performance on the lag 0 trials, which involved neither delay nor interference from other stimuli. However, in the lag 2 trials, which encompass both delay and interfering information, the proportion of time spent looking at the correctly matched picture in the first 2 1000-ms time bins (**Table 3**) was higher in the groups who received more breastfeeding. We then further examined the first 1000 ms because previous work (32, 39) observed memory effects with detailed analyses in this time bin for lag 2 trials. Post hoc analysis showed that high-breastfeeding infants demonstrated more preferential looking at the correct matched picture than did those in the low-breastfeeding group. This happened as early as 250 ms and was consistent for the remainder of the 1000-ms time bin, as well as for the second 1000-ms time bin.

No significant difference was observed for deferred imitation in 6-mo-old infants; however, high-breastfeeding infants tended to recall more target behaviors than did low-breastfeeding infants (**Table 4**). For 18-mo-old toddlers, no observable differences

were observed across the breastfeeding groups for either of the deferred imitation tasks. At 24 mo of age, toddlers were able to reproduce comparable numbers of target behaviors across the breastfeeding groups. Although we observed that toddlers in both the intermediate- and high-breastfeeding groups tended toward better recall of the target behaviors in the correct sequence than those in the low-breastfeeding group, this difference was statistically significant only for the intermediate-breastfeeding group.

For the secondary analysis (based on duration of any breastfeeding; see Participants and Methods), similar results were obtained. For relational binding, the proportion of time spent looking at the correctly matched picture was greater with longer breastfeeding duration in the same time bins as observed with increased breastfeeding exposure [subdivisions within first 1000 ms (i.e., 1000-ms bin 1): 0–250 ms (*P*-trend across the 5 groups = 0.664), 251–500 ms (*P* = 0.046), 501–750 ms (*P* = 0.014), 751–1000 ms (*P* = 0.131); 1000-ms bin 2 (*P* = 0.035), 1000-ms bin 3 (*P* = 0.027), and 1000-ms bin 4 (*P* = 0.287)]. No significant trend was observed between breastfeeding duration and recall of target behaviors or their sequence at 6 or 18 mo. At 24 mo, toddlers with longer breastfeeding duration were able to recall more target behaviors in the correct sequence (*P*-trend = 0.009). No significant association was observed with breastfeeding (3 primary

TABLE 3Association between breastfeeding group and performance in relational binding at 6 mo (lag 2 trials)¹

Time bin ²	Breastfeeding group ³			Breastfeeding group ⁴		<i>P</i> -trend ⁵
	Low-BF (<i>n</i> = 74)	Intermediate-BF (<i>n</i> = 86)	High-BF (<i>n</i> = 25)	Intermediate-BF	High-BF	
1000-ms Bin 1	0.35 ± 0.22	0.40 ± 0.22	0.48 ± 0.26	+0.05 (−0.02, 0.13)	+0.14 (0.03, 0.26)	0.015
0–250 ms	0.37 ± 0.26	0.38 ± 0.27	0.41 ± 0.28	+0.00 (−0.09, 0.10)	+0.06 (−0.08, 0.19)	0.498
251–500 ms	0.35 ± 0.24	0.38 ± 0.25	0.50 ± 0.27	+0.04 (−0.04, 0.13)	+0.17 (0.04, 0.29)	0.017
501–750 ms	0.35 ± 0.25	0.43 ± 0.27	0.53 ± 0.28	+0.09 (−0.01, 0.18)	+0.17 (0.03, 0.30)	0.011
751–1000 ms	0.36 ± 0.26	0.44 ± 0.28	0.51 ± 0.29	+0.08 (−0.02, 0.17)	+0.14 (0.003, 0.28)	0.032
1000-ms Bin 2	0.35 ± 0.23	0.39 ± 0.30	0.46 ± 0.23	+0.06 (−0.04, 0.16)	+0.14 (−0.003, 0.28)	0.050
1000-ms Bin 3	0.45 ± 0.33	0.37 ± 0.32	0.38 ± 0.30	−0.07 (−0.20, 0.06)	−0.07 (−0.25, 0.12)	0.344

¹High-BF, high exposure to breastfeeding; Intermediate-BF, intermediate exposure to breastfeeding; Low-BF, low exposure to breastfeeding.²Time bins are defined in 1000-ms blocks after the pictures appear on the screen; 0–250, 251–500, 501–750, and 751–1000 ms are subdivisions of the first 1000-ms bin (i.e., 1000-ms bin 1).³Values are unadjusted means ± SDs.⁴Values are adjusted mean differences (95% CIs) from the reference group (low-BF) in proportion of looking at correctly matched picture, adjusted for maternal education, 26-wk State-Trait Anxiety Inventory scores, birth weight, and ethnicity.⁵*P*-trend values were obtained from linear regression.

groups or 5 secondary groups on the basis of duration only) and the habituation task (data not shown).

Attention and social development tasks

No significant associations were observed with breastfeeding (3 primary groups or 5 secondary groups on the basis of duration only) for visual expectation, novelty preference within the habituation task, and mirror self-recognition (data not shown). Similarly, no significant associations were observed with breastfeeding for overall amplitude or latency of ERP components. Nor were significant interactions seen between breastfeeding and variables such as ERP stimuli or brain hemisphere or region, suggesting no modification of effects on ERP amplitude and latency among feeding groups with specific stimuli or in particular brain regions or hemispheres (data not shown).

BSID-III

BSID-III scaled scores across the groups are shown in **Table 5**. Overall, a positive association was observed between breastfeeding group and language domain scores. Although both the intermediate- and high-breastfeeding groups performed significantly better than the low-breastfeeding group in the receptive language domain, only the high-breastfeeding group scored significantly better in the expressive language domain. The scores in cognition and motor (fine and gross) domains were comparable across the groups.

Similarly, our secondary analysis showed that higher scores in receptive (*P*-trend < 0.001) and expressive (*P*-trend = 0.002) language domains were associated with longer breastfeeding duration. However, we also noticed a similar trend for cognition domain scores (*P*-trend = 0.045), which was not observed in the primary analysis.

TABLE 4Association between breastfeeding group and deferred imitation task at 6, 18 and 24 mo of age¹

Age	Breastfeeding group ²			Breastfeeding group ³		<i>P</i> -trend ⁴
	Low-BF	Intermediate-BF	High-BF	Intermediate-BF	High-BF	
6 mo (<i>n</i> = 121)						
3 points recall	0.79 ± 0.71	0.84 ± 0.66	1.04 ± 0.69	−0.04 (−0.34, 0.26)	+0.39 (−0.02, 0.73)	0.098
18 mo						
Rattle task (<i>n</i> = 180)						
Absolute score	1.63 ± 1.09	1.97 ± 0.87	1.56 ± 1.01	+0.45 (−0.09, 1.00)	−0.02 (−0.80, 0.77)	0.581
Sequential score	0.88 ± 0.74	0.95 ± 0.71	0.93 ± 0.75	+0.09 (−0.18, 0.36)	+0.07 (−0.30, 0.49)	0.642
Tree task (<i>n</i> = 165)						
Absolute score	0.83 ± 0.68	0.68 ± 0.63	0.82 ± 0.81	−0.11 (−0.43, 0.20)	+0.06 (−0.36, 0.49)	0.922
Sequential score	0.09 ± 0.34	0.11 ± 0.31	0.09 ± 0.29	+0.06 (−0.07, 0.18)	+0.01 (−0.16, 0.18)	0.753
24 mo (<i>n</i> = 274)						
Absolute score	1.10 ± 1.03	1.17 ± 1.04	1.08 ± 1.00	+0.09 (−0.21, 0.40)	−0.05 (−0.46, 0.37)	0.977
Sequential score	0.18 ± 0.47	0.41 ± 0.73	0.26 ± 0.59	+0.28 (0.11, 0.46)	+0.17 (−0.08, 0.41)	0.046

¹High-BF, high exposure to breastfeeding; Intermediate-BF, intermediate exposure to breastfeeding; Low-BF, low exposure to breastfeeding.²Values are unadjusted means ± SDs.³Values are adjusted mean differences (95% CIs) from the reference group (low-BF) in number of correct targeted behaviors demonstrated, adjusted for maternal education, 26-wk State-Trait Anxiety Inventory scores, birth weight, and ethnicity. Delay duration and equipment arrangement are also adjusted for 6 mo and 24 mo absolute score respectively.⁴*P*-trend values were obtained from linear regression.

TABLE 5

Association between breastfeeding group and BSID-III score¹

Domain	Breastfeeding group ²			Breastfeeding group ³		<i>P</i> -trend ⁴
	Low-BF	Intermediate-BF	High-BF	Intermediate-BF	High-BF	
Cognition (<i>n</i> = 339)	9.71 ± 2.46	10.74 ± 2.62	10.65 ± 2.56	+0.63 (−0.16, 1.27)	+0.31 (−0.60, 1.20)	0.262
Receptive language (<i>n</i> = 337)	8.25 ± 2.66	9.65 ± 3.02	10.10 ± 2.36	+0.93 (0.23, 1.63)	+1.08 (0.10, 2.07)	0.010
Expressive language (<i>n</i> = 336)	8.43 ± 2.31	9.36 ± 2.66	10.10 ± 2.86	+0.58 (−0.06, 1.23)	+1.22 (0.32, 2.12)	0.007
Fine motor (<i>n</i> = 334)	10.43 ± 2.32	11.05 ± 2.43	10.54 ± 2.21	+0.38 (−0.23, 0.99)	−0.33 (−1.18, 0.51)	0.776
Gross motor (<i>n</i> = 332)	10.63 ± 2.76	11.68 ± 3.07	11.19 ± 2.92	+0.84 (0.08, 1.61)	+0.27 (−0.78, 1.32)	0.301

¹BSID-III, Bayley Scales of Infant and Toddler Development, Third Edition; High-BF, high exposure to breastfeeding; Intermediate-BF, intermediate exposure to breastfeeding; Low-BF, low exposure to breastfeeding.

²Values are unadjusted means ± SDs.

³Values are adjusted mean differences (95% CIs) from the reference group (low-BF) in scaled scores for each domain, adjusted for maternal education, 26-wk State-Trait Anxiety Inventory-state score, birth weight, and ethnicity.

⁴*P*-trend values were obtained from linear regression.

DISCUSSION

Consistent with past research, our large (*n* = 408) study of breastfeeding in healthy term Asian infants suggests beneficial effects of breastfeeding on neurocognitive development. However, the observed effect sizes were small compared with those previously reported for maternal education, maternal depression, and socioeconomic status (12, 40, 41). Thus, our results may have greater implications at a population, rather than individual, level. Moreover, we cannot rule out the potential for chance findings; breastfeeding was associated with better performance in only 4 of 15 cognitive measures, and we observed no significant associations between breastfeeding and the highly sensitive electrophysiologic measurement. However, past research that used similar auditory oddball tasks also yielded discrepant findings. Pivik et al. (19) observed greater syllable discrimination in 6-mo-old breastfed infants. In addition, he identified significant a difference only between breastfed and soy formula-fed infants but not infants fed milk formula (42). Jing et al. (10), on the other hand, did not see any effect of diet on ERPs. Thus, our results suggest that it is not simply task sensitivity but also specificity that is important in the study of breastfeeding effects on cognitive development.

Indeed, our findings may indicate potential specificity of effects within the memory domain. First, 6-mo-old infants in the high-breastfeeding group looked significantly more at a correctly matched picture in early portions of the relational binding task than did those in the low-breastfeeding group. In keeping with past research demonstrating that preferential looking toward the matched stimuli tends to occur very early in the task (32), the effects of breastfeeding were observed as early as 250 ms after the stimulus appeared. Longer looking by high-breastfeeding infants at the correct matched picture suggests stronger relational memory. Second, during the deferred imitation test, the number of target behaviors reproduced by 2-y-old toddlers was comparable across breastfeeding groups. However, both intermediate- and high-breastfeeding groups exhibited more target behaviors in the correct sequence compared with the low-breastfeeding group, albeit this was only statistically significant in the intermediate-breastfeeding group. Given the relatively small effect sizes, the lack of statistical significance for high breastfeeding may be attributable to statistical power. Deferred imitation is a way of assessing declarative memory, a deliberate

recollection of information and events (43). Similar to the relational binding task, in which infants display memory for items paired in space, sequential behavior during deferred imitation requires that infants display memory for items paired in time. Both deferred imitation (44) and relational binding (45, 46) may relate to memory processes that primarily involve the hippocampus, a region susceptible to nutritional influence (47). In contrast, and consistent with a previous study that reported no effect of breastfeeding initiation or duration on recognition memory and novelty preference (48), we did not observe any effect of breastfeeding on habituation. Habituation is a visual recognition memory task that involves novelty preference and also likely involves the hippocampus and medial temporal lobe memory system (49), but not relational memory. Thus, our findings suggest that breastfeeding may have greater effects on memory tasks involving relational memory and retrieval as opposed to recognition and may help to resolve past discrepancies in studies that used general memory tests (50–52).

Consistent with findings concerning prolonged breastfeeding and higher IQ (2, 52), we also observed associations between breastfeeding duration and higher cognitive scores on the BSID-III. Breastfeeding has been associated with improved motor skills in 3- and 6-mo-old infants (53). However, we did not observe an association with motor scores at 24 mo, which is consistent with work conducted in toddlers (53–55). We did, however, observe associations with expressive and receptive language development, which can also be characterized as requiring relational memory between conceptual meanings and particular sounds or signs during vocabulary acquisition (56, 57). Our results are thus consistent with reports of higher language scores in breastfed children of similar age (28, 53, 55). However, because of differences in type of measurements used [e.g., Deoni et al. (55) used the Mullen Scales of Early Learning, Bernard et al. (28) used the Communicative Development Inventory, and Andres et al. (53) used the BSID-II and Preschool Language Scale-3], we were unable to explicitly compare the magnitude size.

In their study in 18-mo-old children, Leventakou et al. (58) reported that breastfeeding duration was positively associated with BSID-III cognitive, receptive, and expressive language. We did not observe relations between breastfeeding and ERPs during the auditory oddball paradigm, despite past research linking this task to language (59) and literacy (60). However, many of the

conclusions from such past research are reflective of an overall pattern observed from a large number of reported results. For example, Leppanen et al. (61) conducted 132 statistical tests and found only 18 significant ($P < 0.05$) findings related to various aspects of language skills, with only one directly relevant to expressive vocabulary. Differences in testing paradigm, identified components, and study participants may also have led to discrepant results among reported studies. For example, neuro-linguistic paradigms often use very short ISIs (e.g., 70 ms vs. the 800 ms used in our paradigm) with nonspeech sounds and language abilities may only be predicted when ISIs of ≤ 70 ms are used (62). Much of the work linking ERPs and language included high-risk children (59–61) and, in some cases, alternate aspects of the electroencephalogram wave (e.g., mismatch response) were evaluated. In summary, methodologic and study population differences may help to explain why we observed an association between breastfeeding and Bayley language scores but not ERPs.

Age at testing may also influence whether effects of breastfeeding are observed within certain domains; indeed, breastfeeding was found to influence the development of late-developing regions that subserves a variety of functions, including language (55). Thus, it is possible that the effects of breastfeeding are more readily observable later in development, when it becomes easier to detect differences in processes associated with brain regions that mature at later stages.

Task difficulty may also modify associations. Interestingly, children from intermediate- and high-breastfeeding groups or those who were breastfed for a longer duration performed better in more difficult tasks. For example, although no differences were observed in the immediate memory condition of our relational memory task (i.e., lag 0 trials), breastfeeding positively related to performance in the more difficult delay-plus-interference condition (i.e., lag 2 trials). Likewise, although they did not exhibit differences in the number of remembered items in our deferred imitation paradigm, the children who were breastfed more demonstrated better sequential memory. Furthermore, breastfeeding also positively affected language development, which may be slower for children exposed to multiple languages (63–65), as are $\sim 80\%$ of GUSTO children.

Our study adds to the existing literature in a variety of ways. A common criticism of studies not observing significant effects is the lack of specificity in testing. Here, we used a variety of specific cognitive measures. Unfortunately, the validity of most of these highly specific research tools for predicting future standardized developmental outcomes and IQ has been relatively unexplored, with a few exceptions, such as the auditory oddball ERPs (10) and habituation tasks (66, 67). Thus, the degree to which the observed associations may affect children's subsequent development is unknown. Nevertheless, to balance concerns with regard to specificity and predictive validity, we included a general developmental battery. Another strength of the current research is its focus on Asian children in the first 2 y of life, whereas other studies focused on school-aged children and adolescents of other ethnicities.

We extensively controlled for a large number of potential confounders, including maternal anxiety. As in all observational studies, however, residual confounding cannot be excluded. Although our cohort may not be representative of the Singapore population, the participants were recruited from the 2 largest

maternity hospitals in the country and included both private and subsidized patients.

Studies reporting the effects of breastfeeding on cognition often attribute observed differences to nutrition, but bonding during breastfeeding has also been associated with enhanced neurodevelopment (9, 68). As such, breastfeeding method (direct or expressed) is another important area for future investigation. Future work should measure and adjust for parental cognitive ability.

Although we analyzed a large number of outcomes and cannot exclude the possibility of chance findings, the fact that the outcomes with significant associations were limited to the memory and language domains is highly consistent with previous studies (44–48). In conclusion, our comprehensive, intensive neuro-cognitive testing of Asian children in the first 2 y of life suggests a significant, albeit modest, beneficial effect of breastfeeding on young children's memory and language development.

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