British Journal of Nutrition (2023), 129, 166–174
doi:10.1017/S000711452200071X

Timing of infant formula introduction in relation to BMI and overweight at ages 1 and 3 years: the Born in Guangzhou Cohort Study (BIGCS)

Mingyang Yuan[1,2,3], Minshan Lu[1,2,3], Yixin Guo[1,3], Kin Bong Hubert Lam[5], Jinhua Lu[1,2,3], Jianrong He[1,2,3], Songying Shen[1,3], Dongmei Wei[1,2,3], G. Neil Thomas[4], Kar Keung Cheng[4], Xiu Qiu[1,2,3]* and on behalf of the BIGCS Study Group

[1]*Division of Birth Cohort Study, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China*
[2]*Department of Women's Health, Provincial Key Clinical Specialty of Woman and Child Health, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, China*
[3]*Provincial Clinical Research Center for Child Health, Guangzhou, China*
[4]*Institute of Applied Health Research, University of Birmingham, Birmingham, UK*
[5]*Nuffield Department of Population Health, University of Oxford, Oxford, UK*

(Submitted 10 September 2021 – Final revision received 30 January 2022 – Accepted 28 February 2022 – First published online 10 March 2022)

Abstract
Mounting evidence suggests that the first few months of life are critical for the development of obesity. The relationships between the timing of solid food introduction and the risk of childhood obesity have been examined previously; however, evidence for the association of timing of infant formula introduction remains scarce. This study aimed to examine whether the timing of infant formula introduction is associated with growth *z*-scores and overweight at ages 1 and 3 years. This study included 5733 full-term (≥ 37 gestational weeks) and normal birth weight (≥ 2500 and < 4000 g) children in the Born in Guangzhou Cohort Study, a prospective cohort study with data collected at 6 weeks, 6, 12 and 36 months. Compared with infant formula introduction at 0–3 months, introduction at 4–6 months was associated with the lower BMI, weight-for-age and weight-for-length *z*-scores at 1 and 3 years old. Also, introduction at 4–6 months was associated with the lower odds of at-risk of overweight at age 1 (adjusted OR 0·72, 95 % CI 0·55, 0·94) and 3 years (adjusted OR 0·50, 95 % CI 0·30, 0·85). Introduction at 4–6 months also decreased the odds of overweight at age 1 year (adjusted OR 0·42, 95 % CI 0·21, 0·84) but not at age 3 years. Based on our findings, compared with introduction within the first 3 months, introduction at 4–6 months has a reduction on later high BMI risk and at-risk of overweight. However, these results need to be replicated in other well-designed studies before more firm recommendations can be made.

Key words: Early feeding: Infant formula: BMI: Overweight

The prevalence of being overweight in children under 5 years old has risen from 6·3 to 11·9 % between 1990 and 2016 in China[1]. By 2015, China had the largest number of children with obesity aged 5 years or under in the world[2]. Epidemiological studies have reported that early obesity was a significant predictor of obesity later in life and the development of cardiometabolic disorders during adulthood[3–6].

Mounting evidence suggests that the first few months of life are critical for the development of obesity [7]. The relationships between early solid food introduction (before aged 4 months) and risk of childhood obesity have been examined previously; however, findings were inconsistent [8]. Several cohort studies reported that the association between the timing of solid food introduction and adiposity varied by milk feeding status (formula fed or breastfed)[9–11]. They found the effects of early solid food introduction on later obesity were more significant in formula-fed infants. Infant formula was usually introduced earlier than solid food. A population-based birth cohort study of China, involving 98 097 maternal–infant pairs, showed that in the first month, infant formula exposure rate was 58·8 %; in the third month, the exposure rate was 66·6 % and in the sixth month, the exposure rate reached up to 72·0 % [12]. The association between formula feeding practice and excess weight gain in early childhood has been examined [13]. The explored mechanisms included overfeeding formula, putting a baby to bed with bottle, and compositions (higher protein) in formula [13]. However, to our knowledge, there were no studies primarily focusing on the association between the timing of infant formula

Abbreviation: MI, multiple imputation.

* **Corresponding author:** Xiu Qiu, email xiu.qiu@bigcs.org

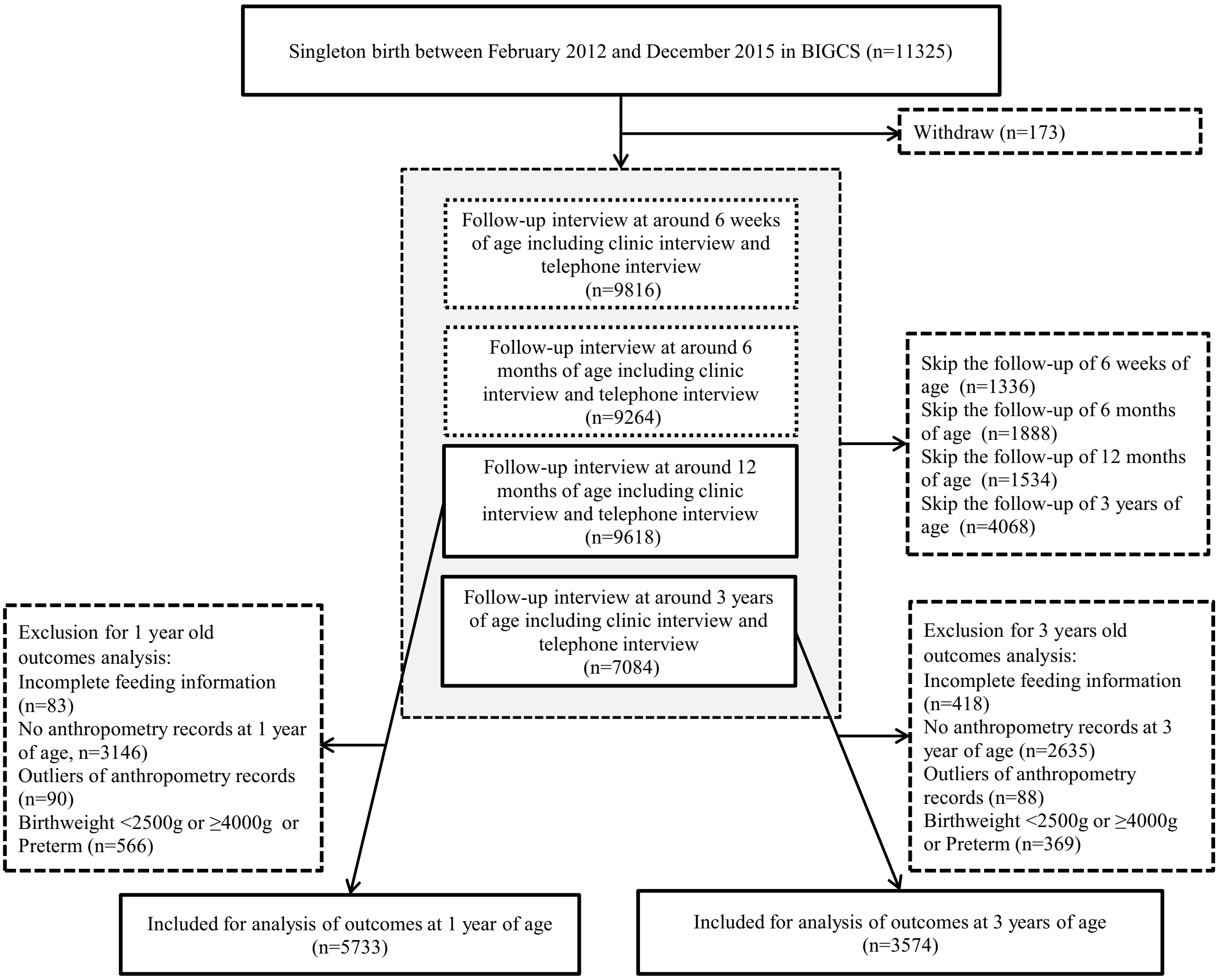

Fig. 1. Flow chart of the study population.

introduction and early growth. Though cessation of exclusive breast-feeding is essentially correlated with the introduction of infant formula, it is also related to the introduction of solid foods. Therefore, it is necessary to examine the effects of the timing of infant formula and solid food introduction on later growth separately.

This study has examined the hypothesis that the introduction of infant formula at early stage is associated with a higher risk of overweight in early childhood while considering the timing of solid food introduction and breast-feeding duration in a large-scale prospective birth cohort.

Methods

Study population

This is a longitudinal study on singleton births between February 2012 and December 2015 in the Born in Guangzhou Cohort Study (BIGCS), a large-scale prospective observational study in Guangzhou, China. Pregnant women were recruited before 20 gestational weeks from two campuses of Guangzhou Women and Children's Medical Center (GWCMC) from February 2012. Details of the BIGCS cohort with full inclusion and exclusion criteria can be found in the published protocol[14]. This study was approved by the Institutional Ethics Committee of the GWCMC. All participants signed a consent form at the time of recruitment. The baseline questionnaire was completed before week 20 of pregnancy. Follow-up of the children took place at paediatric clinics at the age of 6 weeks, 6, 12 and 36 months after birth and involved questionnaires (completed by the mother or guardian) and physical examinations. Although those who were unable to attend the appointments in person were interviewed on the telephone, they were excluded from the present analysis due to the lack of information on anthropometric measurements. Children with incomplete feeding data were also excluded (Fig. 1). In addition, all analyses were performed by restricting to full-term (≥ 37 weeks) infants with normal birth weight (≥ 2500 and < 4000 g).

Exposures

Feeding information. The age of first introduction of infant formula and other food and duration of breast-feeding were

British Journal of Nutrition
https://doi.org/10.1017/S000711452200071X Published online by Cambridge University Press

defined from several variables reported in the self-administered questionnaire at the age of 6 weeks as well as at 6, 12 and 36 months. At each time point, if the response to the question 'Has your child been fed infant formula?' was affirmative, the mother was asked to state the type of infant formula (standard cow's milk formula, hydrolysed formula, preterm formula, other types of formulas) and the age when the child first had the infant formula. If the child has been fed any food other than milk (cereal, rice porridge, vegetables, fruits, meat, offal, fish, other seafood, egg yolk, egg white), the age when he/she first ate the food was recorded and taken as the age of solid food introduction.

Infant outcomes

Anthropometric measurements were undertaken at each follow-up visit by trained fieldworkers. Abdomen circumference and upper arm circumference (cm) were measured in a supine position using a measuring tape to the nearest 0·1 cm. Length (cm) was measured in a supine position using a length board (Shekel Healthweigh™) to the nearest 0·1 cm. Body weight (kg) was measured without shoes and with light clothing (single layer) in a supine position using a stadiometer (Shekel Healthweigh™) to the nearest 0·01 kg. To account for additional weight due to clothes worn, 200 g was subtracted from the weight of each child. BMI was calculated using the formula kg/m^2. Children's sex- and age-specific *z*-scores of BMI were calculated using a SAS (WHO-source-code.sas) based on the 2006 WHO growth standards[15]. According to the WHO classifications for overweight and obesity in younger children (0–5 years), at-risk of overweight was defined as BMI-for-age *z*-score above +1 SD and less than +2 SD, overweight was defined as above +2 SD and less than +3SD and obesity was defined as above+3 SD [16]. Since the number of children with overweight and obesity was insufficient for reliable analyses, these high BMI statuses were analysed as a single category in this study (overweight). *Z*-scores for a child's sex and age for weight and height (length-for-age *z*-score, weight-for-age *z*-score, weight-for-length *z*-score) based on the WHO Growth Charts were also calculated. The cut-offs for extreme *z*-scores (biologically implausible values) were used as <–5 and >5 according to the WHO criteria [15]. The extreme values were excluded from data analysis.

Covariates

Socio-demographic characteristics and potential confounders, including maternal age, maternal educational level, maternal smoking and passive smoking status during pregnancy, maternal pre-pregnant BMI, paternal BMI and other health-related factors, were obtained by the baseline questionnaire before 20 weeks of gestation. Obstetrics-related variables, including delivery date, mode of delivery, gestational age, birth weight and infant sex, were extracted from the hospital clinical records.

Statistical analysis

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute). The timing of infant formula introduction was categorised into three groups, including ≤ 3, 4–6 and > 6 months or never received infant formula during the study period. The participants' characteristics were stratified by the timing of infant formula introduction (≤ 3, 4–6 and > 6 months). The information on characteristics was presented as mean values and standard deviations for continuous variables or as percentages for categorical variables. The overall associations of timing of infant formula introduction with abdomen circumference, upper arm circumference, BMI *z*-score, length-for-age *z*-score, weight-for-age *z*-score and weight-for-length *z*-score were analysed with linear regression models and presented as β and 95 % CI. The associations between timing of infant formula introduction and risk of overweight were analysed with logistic regression models and presented as OR and 95 % CI. Results were adjusted for potential confounders including maternal age at delivery (≤ 25, 26–30, 31–35, > 35 years of age), maternal education (high school or below, vocational/technical college, undergraduate, postgraduate), maternal pre-pregnancy BMI and paternal BMI (< 18·5, 18·5–23·9, 24–27·9, ≥ 28 kg/m^2)[17], maternal smoking during pregnancy (yes, no), passive smoking during pregnancy (yes, no), parity (primiparous, multiparous), mode of delivery (vaginal labour, caesarean delivery), birth weight (g, continuous value), infant sex, the duration of breast-feeding (0–6, > 6 months) and age at first introduction to solid foods (≤ 3, 4–6, > 6 months). For the analysis of children's length-for-age and weight-for-length *z*-scores, maternal and paternal heights were also adjusted. A two-tailed *P* value < 0·05 was considered statistically significant. Furthermore, a sensitivity analysis was performed by only including the children with longer breast-feeding duration (> 6 months), because the longer duration of breast-feeding was associated with a lower risk of excess weight gain during early life[18].

Given the proportion of missing data on confounder variables was from 0·1 to 10·3 %, analyses based on complete cases may be biased. Thus, we used multiple imputation (MI) analysis to cope with missing data [19]. We used the fully conditional method iterative method for imputation using SAS version 9·4. The following variables were imputed: pre-pregnancy BMI, paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, parity, mode of delivery, the duration of breast-feeding and the timing of introduction of any solid food. For the analysis of children's length-for-age and weight-for-length *z*-scores, maternal and paternal heights were also imputed. Exposure and outcome variables of each model were considered as observed covariates and used in the models to impute these variables. For each imputation model, ten imputations were run. We ran a procedure called proc mianalyze which combines all the estimates (coefficients and standard errors) across all the imputed data sets and outputs one set of parameter estimates for the model of interest [20]. The fraction of missing information analysis was performed to determine potential efficiency gains from MI (see online Supplementary Table S1 and Table S2). Values of fraction of missing information range between 0 and 1. A smaller fraction of missing information (close to 0) indicates low variability between imputed data sets, which means observed data in the imputation model provide much information about the missing values [21].

https://doi.org/10.1017/S000711452200071X Published online by Cambridge University Press

British Journal of Nutrition

Table 1. Baseline characteristics of participants in different timing of infant formula introduction groups in the Born in Guangzhou Cohort Study (BIGCS) study (numbers and percentages; mean values and standard deviations)

	Timing of any infant formulas introduction, months								
	≤ 3 months (*n* 4698)		4–6 months (*n* 522)		> 6 months* (*n* 513)			No. of cases missing out of 5733 (%)	
Characteristics	*n*	%	*n*	%	*n*	%	*P*		
Mother									
Age at delivery (years)									
Mean	29·4		29·1		29·0		0·030	0	0
SD	3·4		3·0		3·2				
Educational level							0·066	0	0
High school or below	367	7·8	37	7·1	34	6·6			
Vocational/technical college	1193	25·4	119	22·8	112	21·8			
Undergraduate	2611	55·6	289	55·4	296	57·7			
Postgraduate	527	11·2	77	14·8	71	13·8			
Pre-pregnancy BMI							0·373	137	2·4
< 18·5 kg/m^2	1139	24·9	121	23·6	109	21·6			
18·5–23·9 kg/m^2	3004	65·6	338	65·9	352	69·7			
24–27·9 kg/m^2	370	8·1	42	8·2	36	7·1			
≥ 28 kg/m^2	65	1·4	12	2·3	8	1·6			
Height (cm)									
Mean	160·0		159·7		160·0		0·550	41	0·7
SD	4·9		4·9		4·7				
Parity							0·012	3	0·1
Primiparous	4173	88·9	474	90·8	437	85·2			
Multiparous	522	11·1	48	9·2	76	14·8			
Delivery mode							0·561	1	0
Vaginal labour	3064	65·2	348	66·7	345	67·3			
Caesarean delivery	1633	34·8	174	33·3	168	32·7			
Smoking during pregnancy	25	0·5	4	0·8	3	0·6	0·792	40	0·7
Passive smoking during pregnancy	1458	31·3	169	32·6	149	29·2	0·475	38	0·7
Father									
BMI							0·668	592	10·3
< 18·5 kg/m^2	182	4·3	25	5·5	14	2·9			
18·5–23·9 kg/m^2	2361	56·1	253	55·9	276	57·9			
24–27·9 kg/m^2	1351	32·1	143	31·6	151	31·7			
≥ 28 kg/m^2	317	7·5	32	7·1	36	7·6			
Height (cm)									
Mean	172·7		172·7		172·8		0·874	102	1·8
SD	5·3		5·1		5·2				
Child									
Child's sex							0·006		
Male	2498	53·2	241	46·2	257	50·1		0	0
Female	2200	46·8	281	53·8	256	49·9			
Birth weight (g)									
Mean	3219·0		3197·4		3219·4		0·356	0	0
SD	328·5		321·0		327·6				
Duration of any breast-feeding							< 0·001	161	2·8
≤ 6 months	1304	28·7	98	18·8	2	0·4			
> 6 months	3234	71·3	424	81·2	510	99·6			
Timing of solid food introduction							< 0·001	8	0·1
≤ 3 months	501	10·7	33	6·3	34	6·6			
4–6 months	4094	87·3	476	91·2	460	89·8			
> 6 months	96	2·1	13	2·5	18	3·5			

* The children who had never received infant formula during the study period were combined into > 6 months group.

Results

Characteristics of the study population

Characteristics of the participants included in the 1-year analysis based on the three infant formula introduction groups are shown in Table 1. Compared with infant formula introduction at 0–3 months group, the mothers in infant formula introduction after 6 months group were more likely to be younger and primiparous. The children in the later introduction group were more likely to be female, breastfed longer than 6 months and introduced to solid food later. For the population included in the 3-year analysis, compared with the mothers who introduced formula feeding at 0–3 months, those who introduced formula after 6 months group were more likely to be better educated and multiparous but experience higher levels of passive smoking during pregnancy. The children receiving formula later were, as expected, more likely to be breastfed longer than 6 months and be introduced to solid food later (see online

British Journal of Nutrition

Table 2. Anthropometric outcomes in different timing of infant formula introduction groups in the Born in Guangzhou Cohort Study (BIGCS) study (numbers and percentages; mean values and standard deviations)

	Timing of any infant formulas introduction, months						
	≤ 3 months		4–6 months		> 6 months*		
Anthropometric outcomes	Mean	SD	Mean	SD	Mean	SD	*P*
At 1 year of age	*n* 4698		*n* 522		*n* 513		
Abdomen circumference (cm)	42·9	4·0	42·7	3·5	42·9	3·9	0·749
Upper arm circumference (cm)	14·5	1·2	14·3	1·1	14·4	1·2	0·006
BMI (kg/m^2)	17·0	1·4	16·7	1·4	17·0	1·4	< 0·001
Overweight							
n	180		9		14		0·019
%	3·9		1·8		2·8		
At-risk of overweight							
n	992		82		104		0·021
%	21·6		16·3		20·8		
At 3 years of age	*n* 2955		*n* 327		*n* 292		
Abdomen circumference (cm)	46·3	4·5	46·1	4·3	46·2	4·2	0·896
Upper arm circumference (cm)	14·9	1·1	14·7	1·1	14·9	1·2	0·113
BMI (kg/m^2)	15·5	1·3	15·3	1·1	15·5	1·2	0·011
Overweight							0·193
n	62		3		5		
%	2·2		0·9		1·8		
At-risk of overweight							
n	349		20		30		0·007
%	12·2		6·3		10·7		

* The children who had never received infant formula during the study period were combined into >6 months group.

Supplementary Table S3). Characteristics of included and excluded participants of this study are also shown in online Supplementary Table S4. Compared with excluded population, included children were more likely to have higher educated and multiparous mothers, higher birth weight and earlier formula introduction.

Table 2 shows the anthropometric outcomes including abdomen circumference (cm), upper arm circumference (cm), BMI, the prevalence of at-risk of overweight and overweight, at 1 and 3 years old, respectively. The means of BMI at 1 year and 3 years old were different between the three infant formula introduction groups. The differences also existed in the prevalence of at-risk of overweight at 1 and 3 years old between these groups. Furthermore, we provided the proportions of children were introduced to infant formula at each month after birth, including who had never received formula by 3 years in online Supplementary Table S5.

Timing of introduction of infant formula and anthropometric outcomes

Table 3 presents the associations between the timing of infant formula introduction and anthropometric outcomes at 1 and 3 years of age. Compared with formula introduction within the first 3 months, introduction at 4–6 months was associated with lower upper arm circumference (adjusted β – 0·15, 95 % CI – 0·26, –0·05), BMI *z*-score (adjusted β – 0·18, 95 % CI –0·26, –0·09), length-for-age *z*-score (adjusted β – 0·09, 95 % CI – 0·17, –0·01), weight-for-age *z*-score (adjusted β – 0·21, 95 % CI – 0·29, –0·13) and weight-for-length *z*-score (adjusted β – 0·19, 95 % CI – 0·27, –0·10) at 1 year of age in MI models. Compared with formula introduction at 0–3 months, introduction after 6 months was associated with lower length-for-age *z*-score (adjusted β – 0·08, 95 % CI – 0·17, 0·00) and weight-for-age *z*-score (adjusted β – 0·10, 95 % CI – 0·18, –0·01).

For 3 years outcome, compared with infant formula introduction within the first 3 months, introduction at 4–6 months of age was associated with lower BMI *z*-score (adjusted β – 0·14, 95 % CI – 0·24, –0·03), weight-for-age *z*-score (adjusted β – 0·11, 95 % CI – 0·21, –0·01) and weight-for-length *z*-score (adjusted β – 0·14, 95 % CI – 0·25, –0·04) in MI models (Table 3).

Timing of introduction of infant formula and weight statuses during the first 3 years

Compared with infant formula introduction within the first 3 months of life, introduction at 4–6 months was associated with the lower odds of at-risk of overweight at 1 year (adjusted OR 0·73, 95 % CI 0·55, 0·95) and 3 years old (adjusted OR 0·52, 95 % CI 0·31, 0·87) in MI models (Table 4). Infant formula introduction at 4–6 months was associated with a lower risk of overweight at 1 year old (adjusted OR 0·43, 95 % CI 0·22, 0·85), but the association was not significant for overweight at 3 years of age (adjusted OR 0·45, 95 % CI 0·14, 1·47). These findings were similar when we restricted the analysis to children with longer breast-feeding duration (> 6 months) (see online Supplementary Table S6).

Discussion

Results of this prospective longitudinal cohort indicated that compared with infant formula introduction within the first 3 months, introduction at 4–6 months was associated with the lower *z*-scores for BMI, weight-for-age and weight for length at ages 1 and 3 years. We also found that later formula introduction at 4–6 months of age was associated with the lower odds of

Table 3. Linear regression models to evaluate the associations between timing of formula introduction and anthropometric outcomes at 1 and 3 years of age (before and after multiple imputation) (β-coefficients and 95 % confidence intervals)

Anthropometric outcomes	Timing of formula introduction	Outcomes at 1 year of age: Crude β	Crude 95 % CI	Adjusted β before MI (95 % CI): β	95 % CI	Adjusted β after MI (95 % CI): β	95 % CI	P ‡	Outcomes at 3 years of age (n 3898): Crude β (95 % CI): β	95 % CI	Adjusted β before MI (95 % CI): β	95 % CI	Adjusted β after MI (95 % CI): β	95 % CI	P ‡
Abdomen circumference*		n 5590		n 4555		n 5590			n 3473		n 2768		n 3473		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·14	−0·52, 0·23	0·13	−0·27, 0·53	−0·03	−0·41, 0·34	0·857	−0·13	−0·66, 0·40	0·17	−0·42, 0·75	−0·04	−0·56, 0·48	0·874
	> 6 months§	−0·01	−0·38, 0·36	−0·05	−0·45, 0·34	−0·04	−0·42, 0·33	0·824	−0·01	−0·58, 0·55	−0·23	−0·85, 0·38	−0·05	−0·62, 0·52	0·869
Upper arm circumference*		n 5382		n 4543		n 4543			n 3338		n 2794		n 3338		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·17	−0·28, −0·06	−0·15	−0·27, −0·04	−0·15	−0·26, −0·05	0·004	−0·11	−0·24, 0·02	−0·07	−0·20, 0·07	−0·09	−0·22, 0·04	0·155
	> 6 months§	−0·05	−0·16, 0·06	−0·05	−0·17, 0·06	−0·04	−0·15, 0·06	0·424	0·08	−0·06, 0·21	−0·01	−0·15, 0·13	0·05	−0·09, 0·19	0·472
BMI *z*-score*		n 5590		n 4715		n 5590			n 3473		n 2905		n 3473		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·17	−0·26, −0·08	−0·17	−0·26, −0·07	−0·18	−0·26, −0·09	< 0·001	−0·16	−0·27, −0·05	−0·13	−0·25, −0·02	−0·14	−0·24, −0·03	0·014
	> 6 months§	−0·01	−0·10, 0·08	−0·06	−0·16, 0·03	−0·05	−0·14, 0·04	0·270	−0·02	−0·13, 0·10	−0·09	−0·21, 0·04	−0·03	−0·14, 0·09	0·647
Length-for-age *z*-score†		n 5652		n 4838		n 5652			n 3492		n 2979		n 3492		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·12	−0·21, −0·03	−0·09	−0·18, −0·01	−0·09	−0·17, −0·01	0·028	−0·05	−0·16, 0·06	−0·04	−0·15, 0·06	−0·05	−0·14, 0·05	0·358
	> 6 months§	−0·11	−0·20, −0·02	−0·06	−0·15, 0·02	−0·08	−0·17, 0·00	0·045	0·05	−0·06, 0·17	−0·01	−0·12, 0·11	0·03	−0·08, 0·13	0·600
Weight-for-age *z*-score*		n 5641		n 4758		n 5641			n 3518		n 2944		n 3518		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·21	−0·30, −0·13	−0·21	−0·30, −0·12	−0·21	−0·29, −0·13	< 0·001	−0·11	−0·24, 0·01	−0·10	−0·21, 0·00	−0·11	−0·21, −0·01	0·030
	> 6 months§	−0·08	−0·16, 0·01	−0·10	−0·19, −0·01	−0·10	−0·18, −0·01	0·021	0·04	−0·09, 0·17	−0·02	−0·13, 0·10	0·03	−0·08, 0·14	0·581
Weight-for-length *z*-score†		n 5590		n 4785		n 5590			n 3483		n 2970		n 3483		
	≤ 3 months	Ref.		Ref.		Ref.			Ref.		Ref.		Ref.		
	4–6 months	−0·19	−0·28, −0·10	−0·17	−0·27, −0·08	−0·19	−0·27, −0·10	< 0·001	−0·17	−0·28, −0·06	−0·14	−0·25, −0·02	−0·14	−0·25, −0·04	0·008
	> 6 months§	−0·03	−0·11, 0·06	−0·07	−0·16, 0·02	−0·06	−0·15, 0·02	0·153	−0·01	−0·13, 0·10	−0·09	−0·20, 0·03	−0·03	−0·14, 0·09	0·638

MI, multiple imputation.

* Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI and paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, parity, mode of delivery, infant sex, birth weight, the duration of breast-feeding and age at first introduction to solid foods.

† Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI, maternal height, paternal BMI, paternal height, maternal smoking during pregnancy, passive smoking during pregnancy, parity, mode of delivery, infant sex, birth weight, the duration of breast-feeding and age at first introduction to solid foods.

‡ Adjusted *P* values for multiple imputation models.

§ The children who had never received infant formula during the study period were combined into > 6 months group.

https://doi.org/10.1017/S000711452200071X Published online by Cambridge University Press

Table 4. Logistic regression models to evaluate the associations of the timing of formula introduction with at-risk overweight and overweight at 1 and 3 years of age
(numbers and percentages; odds ratios and 95 % confidence intervals)

	Case		Crude		Adjusted before MI		Adjusted after MI		
Timing of introduction, months	*n*	%	OR	95 % CI	OR	95 % CI	OR	95 % CI	*P**
At-risk of overweight									
1 year of age			*n* 5373		*n* 4595		*n* 5373		
≤ 3 months	806	18·3	1		1		1		
4–6 months	69	14·1	0·73	0·56, 0·95	0·73	0·54, 0·98	0·73	0·55, 0·95	0·015
> 6 months†	86	17·8	0·97	0·76, 1·23	0·91	0·69, 1·18	0·89	0·69, 1·15	0·367
3 years of age			*n* 3403		*n* 2904		*n* 3403		
≤ 3 months	287	10·2	1		1		1		
4–6 months	17	5·4	0·50	0·30, 0·83	0·55	0·32, 0·95	0·52	0·31, 0·87	0·014
> 6 months†	25	9·1	0·88	0·57, 1·35	0·81	0·49, 1·32	0·93	0·60, 1·45	0·752
Overweight									
1 year of age			*n* 5590		*n* 4715		*n* 5373		
≤ 3 months	180	3·9	1		1		1		
4–6 months	9	1·8	0·45	0·23, 0·88	0·43	0·21, 0·89	0·43	0·22, 0·85	0·016
> 6 months†	14	2·8	0·70	0·41, 1·22	0·60	0·32, 1·09	0·60	0·33, 1·07	0·085
3 years of age			*n* 3473		*n* 2905		*n* 3473		
≤ 3 months	62	2·2	1		1		1		
4–6 months	3	0·9	0·43	0·13, 1·38	0·56	0·17, 1·81	0·45	0·14, 1·47	0·188
> 6 months†	5	1·8	0·82	0·33, 2·06	0·41	0·10, 1·74	0·89	0·34, 2·29	0·802

MI, multiple imputation.
Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI and paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, parity, mode of delivery, infant sex, birth weight, the duration of breast-feeding and age at first introduction to solid foods.
* *P* values for multiple imputation models.
† The children who had never received infant formula during the study period were combined into > 6 months group.

at-risk of overweight at 1 and 3 years of age and decreased odds of overweight at the age of 1 year but not at the age of 3 years. However, no significant association was observed between later introduction of formula after 6 months and the risk of overweight at ages 1 or 3 years.

Previous studies examining the associations between the timing of solid food introduction and risk of overweight or obesity found that the effects of the timing of solid food introduction on later development of obesity were different between breastfed and formula-fed infants [9,11]. These results suggested the effects of solid food introduction on later weight status may be affected by formula feeding. However, studies focusing on examining the effects of timing of infant formula introduction on later overweight or obesity are limited. A longitudinal cohort study indicated that the risk of overweight or obesity was significantly higher among infants who were introduced to infant formula or solids during the first 4 months of life compared with those introduced later [22]. Nevertheless, they did not distinguish the effects between solid and infant formula introduction. Infant formula usually was introduced to infants much earlier than other solid foods. In our study population, over 80 % infants were introduced to infant formula within the first 3 months of life, highlighting that infant formula is widespread used in this urban area of China. We found that infants who were introduced to infant formula at 4–6 months of age were more likely to have lower BMI, weight-for-age and weight-for-length *z*-scores at both 1 and 3 years old than those introduced earlier (≤ 3 months), independent of the timing of solid food introduction.

Potential mechanisms of infant formula introduction at early stage on later weight status might be associated with the immature intestinal ecosystem and immune system during the first few months of life. The establishment and interactive development of early gut microbiota are driven and modulated by specific compounds present in breast milk[23]. Evidence showed that the Bifidobacteria and Lactobacillus were predominant in breastfed infants, whereas the Ruminococcus was predominant in formula-fed infants[24]. In children, a high concentration of Bifidobacteria during the early stage of life has been reported to have protective effects on later obesity [25]. The bacteria in the gut ferment dietary fibres into SCFA, whose interaction with G-protein-coupled receptors influences insulin sensitivity in several tissues, including liver, muscle and adipose tissue, thus regulating energy metabolism[26]. Therefore, the introduction of infant formula at early stage of infancy might influence the composition and ecosystem of the gut microbiome, which links to the development of childhood overweight or obesity. Furthermore, infant formula feeding induces uncontrolled excessive protein intake, which overacts the infant's mammalian target of rapamycin complex 1 (mTORC1) signalling pathways[27]. Overactivated mTORC1 enhances S6K1-mediated adipocyte differentiation. Thus, early formula feeding is considered to be associated with the development of mTORC1-driven metabolic disease, including obesity [27].

In our study, no significant differences in outcomes between ≤ 3 and > 6 months formula introduction groups were observed. The recommended timing for solid foods introduction is not earlier than 4 months or later than 6 months of life [28]. Late solid food introduction (≥ 7 months of age) was found to be associated with an increased risk of later childhood overweight/obesity among exclusively breastfed children (exclusive breast-feeding over 6 months)[29]. After 6 months of age, it is difficult to distinguish the impacts of later introduction of infant formula or solid foods on weight status. Formula feeding and complementary feeding might be not independent decisions and may jointly explain variances in later obesity.

Although breast milk is recommended for all infants, preterm formulas are alternative sources of enteral nutrition for preterm or low birth weight infants when sufficient maternal breast milk and donor human milk are not available[30]. In addition, the association between feeding practice and excess weight during the early stage might be modified by birth weight[31]. Therefore, we performed the analysis by limiting it to full-term infants with normal birth weight.

Mothers participating in BIGCS are likely to be more affluent, older and have higher education than the contemporary pregnant women in Guangzhou, hence limiting the generalisability of the findings[14]. However, in this study, a relatively widespread across all socio-economic status indicators can be still observed within the participants of BIGCS, hence enabling us to explore the differences in health consequences across different socio-economic status strata. Our data showed that a large proportion of infants were given infant formula as a supplement to breast milk (mix feeding) during the early months of life. And the main findings of this study remained significant in children with longer breast-feeding duration (over 6 months), though the longer breast-feeding was suggested to protect against subsequent obesity [18]. The aggressive marketing for infant formula and other breast milk substitutes has influenced the parents' preferences in China[32]. A study reporting the factors associated with Chinese mothers' decision to formula feeding showed that the majority of women choosing formula feeding thought they had insufficient breast milk[33]. The authors also found that some mothers had the belief that formula is more nutritious than breast milk[33]. This belief has also been described in some studies from other countries[34,35]. In addition, child-related factors, such as weight and appetite in early life, can influence the parental feeding practices. A cohort study from the UK reported that mothers of lower birth weight or lower appetite infants, or those perceiving their children are at-risk of underweight tend to overfeed the infant in order to achieve greater weight gain[36]. The government and health professionals should provide more information on the differences in health benefits between breast milk and infant formula to let the parents understand that there is no better early food than breast milk for their young infants during the early stage.

One strength of our study is the longitudinal study design with a large number of participants, which enabled us to measure the associations with adequate statistical power. A further strength is the repeated assessment of feeding practice, at 6 weeks, 6 and 12 months, allowing specific descriptions of feeding patterns during infancy. A wide range of confounders was adjusted or controlled for in our MI models while assessing our exposure–outcome relationship. However, the associations might be confounded by some potential factors for which we did not adjust, such as the amount and the duration of infant formula consumption. Limitations of this study should be considered. First, the population size in 3 years age group was smaller than 1 year age group. Thus, there was a relatively lower power to detect differences at 3 years of age as opposed to 1 year of age. Second, the assessment of feeding practices was based on parental self-report, but recall of infant feeding practices is regarded as sufficiently accurate[37]. Third, a proportion of the cohort did not have anthropometry measured at 1 (37 %) and 3 (51 %) years, which limits the generalisability of our findings. In addition, a lower proportion (71·8 %) of children without anthropometry data at 1 year were introduced to formula within the first 3 months, compared with that of those with anthropometry data (82·2 %) (see online Supplementary Table S3). Based on our findings, it is possible that the included population is at a higher risk of overweight than those in the full cohort due to the higher proportion of children who have infant formula exposure at early stage. However, it is difficult to specify whether this difference would affect the associations that we found due to the absence of outcomes in the excluded population. Therefore, these results need to be replicated in other cohort studies before more firm recommendations can be made. Fourth, the information on the specific quantity of infant formula and solid food introduced was absent in this analysis. We also have no information on whether the consumption of infant formula was sustained after the introduction. Further evidence is needed to explore the short-term and long-term effects of the timing and quantity of infant formula introduction on the risk of overweight or obesity in later life.

Conclusion

Overall, compared with infant formula introduction within the first 3 months, introduction at 4–6 months was associated with the lower z-scores for BMI, weight-for-age and weight for length at both 1 and 3 years old. Also, introduction after 3 months was associated with decreased odds of at-risk overweight at the ages of 1 and 3 years. Although the results need to be replicated in other well-designed studies before more firm recommendations can be made, avoiding unnecessary infant formula introduction, particularly in the first 3 months, should be promoted to reduce the possibility of excess or rapid weight gain during early childhood.

Acknowledgements

We are grateful to all the families who took part in this study and the whole Born in Guangzhou Cohort Study team, which includes interviewers, research scientists, nurses, computer and laboratory technicians, clerical workers and volunteers.

This study was supported by the Guangzhou Municipal Science and Technology Bureau, Guangzhou, China (grant number: 201807010086) and National Natural Science Foundation of China (grant numbers 81673181, 81703244 and 81903311).

M. Y., G. N. T., X. Q. and K. K. C. conceived the study design; M. Y., M. L., Y. G., J. L., J. H., S. S. and D. W. collected the data; M. Y. conducted the data analysis and wrote the initial manuscript. Y. G., J. L., K. B. H. L. and J. H. assisted with the statistical analysis. All authors contributed to data interpretation and the writing of the manuscript and critically reviewed and approved the final manuscript.

There are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S000711452200071X

References

1. Yang B, Huang X, Liu Q, *et al.* (2020) child nutrition trends over the past two decades and challenges for achieving nutrition SDGs and national targets in China. *Int J Environ Res Public Health* **17**, 1129–1140.
2. Di Cesare M, Sorić M, Bovet P, *et al.* (2019) The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. *BMC Med* **17**, 212–231.
3. Umer A, Kelley GA, Cottrell LE, *et al.* (2017) Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. *BMC Public Health* **17**, 683–706.
4. Simmonds M, Burch J, Llewellyn A, *et al.* (2015) The use of measures of obesity in childhood for predicting obesity and the development of obesity-related diseases in adulthood: a systematic review and meta-analysis. *Health Technol Assess* **19**, 1–336.
5. Llewellyn A, Simmonds M, Owen CG, *et al.* (2016) Childhood obesity as a predictor of morbidity in adulthood: a systematic review and meta-analysis. *Obes Rev* **17**, 56–67.
6. Simmonds M, Llewellyn A, Owen CG, *et al.* (2016) Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. *Obes Rev* **17**, 95–107.
7. Gillman MW (2008) The first months of life: a critical period for development of obesity. *Am J Clin Nutr* **87**, 1587–1589.
8. Woo Baidal JA, Locks LM, Cheng ER, *et al.* (2016) Risk factors for childhood obesity in the first 1000 days: a systematic review. *Am J Prev Med* **50**, 761–779.
9. Huh SY, Rifas-Shiman SL, Taveras EM, *et al.* (2011) Timing of solid food introduction and risk of obesity in preschool-aged children. *Pediatrics* **127**, e544–e551.
10. Baker JL, Michaelsen KF, Rasmussen KM, *et al.* (2004) Maternal prepregnant body mass index, duration of breastfeeding, and timing of complementary food introduction are associated with infant weight gain. *Am J Clin Nutr* **80**, 1579–1588.
11. Moss BG & Yeaton WH (2014) Early childhood healthy and obese weight status: potentially protective benefits of breastfeeding and delaying solid foods. *Matern Child Health J* **18**, 1224–1232.
12. Yang S, Mei H, Mei H, *et al.* (2019) Risks of maternal prepregnancy overweight/obesity, excessive gestational weight gain, and bottle-feeding in infancy rapid weight gain: evidence from a cohort study in China. *Sci China Life Sci* **62**, 1580–1589.
13. Appleton J, Russell CG, Laws R, *et al.* (2018) Infant formula feeding practices associated with rapid weight gain: a systematic review. *Matern Child Nutr* **14**, e12602.
14. Qiu X, Lu JH, He JR, *et al.* (2017) The born in Guangzhou Cohort Study (BIGCS). *Eur J Epidemiol* **32**, 337–346.
15. World Health Organization (2006) WHO Child Growth Standards. Methods and Development. Length/Height-for-Age, Weight-for-Age, Weight-for-Length, Weight-for-Height and Body Mass Index-for-Age. https://www.who.int/publications/i/item/924154693X (accessed May 2021).
16. de Onis M & Lobstein T (2010) Defining obesity risk status in the general childhood population: which cut-offs should we use? *Int J Pediatr Obes* **5**, 458–460.
17. Chen C & Lu FC (2004) The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed Environ Sci* **17**, 1–36.
18. Zheng M, Cameron AJ, Birken CS, *et al.* (2020) Early infant feeding and BMI trajectories in the first 5 years of life. *Obesity* **28**, 339–346.
19. Sterne JA, White IR, Carlin JB, *et al.* (2009) Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* **338**, b2393.
20. UCLA (2021) Multiple Imputation in SAS Part 1. Statistical Consulting. Institute for Digital Research & Education. https://stats.idre.ucla.edu/sas/seminars/multiple-imputation-in-sas/mi_new_1/ (accessed January 2021).
21. Madley-Dowd P, Hughes R, Tilling K, *et al.* (2019) The proportion of missing data should not be used to guide decisions on multiple imputation. *J Clin Epidemiol* **110**, 63–73.
22. Mannan H (2018) Early infant feeding of formula or solid foods and risk of childhood overweight or obesity in a socioeconomically disadvantaged region of Australia: a longitudinal cohort analysis. *Int J Environ Res Public Health* **15**, 1685–1696.
23. Milani C, Duranti S, Bottacini F, *et al.* (2017) The first microbial colonizers of the human gut: composition, activities, and health implications of the infant gut microbiota. *Microbiol Mol Biol Rev* **81**, e00036–00017.
24. O'Sullivan A, He X, McNiven EM, *et al.* (2013) Early diet impacts infant rhesus gut microbiome, immunity, and metabolism. *J Proteome Res* **12**, 2833–2845.
25. Kalliomäki M, Collado MC, Salminen S, *et al.* (2008) Early differences in fecal microbiota composition in children may predict overweight. *Am J Clin Nutr* **87**, 534–538.
26. Pihl AF, Fonvig CE, Stjernholm T, *et al.* (2016) The role of the gut microbiota in childhood obesity. *Child Obes* **12**, 292–299.
27. Melnik BC (2014) The potential mechanistic link between allergy and obesity development and infant formula feeding. *Allergy Asthma Clin Immunol* **10**, 37.
28. Jones SW, Lee M & Brown A (2020) Spoonfeeding is associated with increased infant weight but only amongst formula-fed infants. *Matern Child Nutr* **16**, e12941.
29. Papoutsou S, Savva SC, Hunsberger M, *et al.* (2018) Timing of solid food introduction and association with later childhood overweight and obesity: the IDEFICS study. *Matern Child Nutr* **14**, e12471–e12478.
30. Hay WW & Hendrickson KC (2017) Preterm formula use in the preterm very low birth weight infant. *Semin Fetal Neonatal Med* **22**, 15–22.
31. Goetz AR, Mara CA & Stark LJ (2018) Greater breastfeeding in early infancy is associated with slower weight gain among high birth weight infants. *J Pediatr* **201**, 27–33.
32. Tang L, Lee AH, Binns CW, *et al.* (2014) Widespread usage of infant formula in China: a major public health problem. *Birth* **41**, 339–343.
33. Zhang K, Tang L, Wang H, *et al.* (2015) Why do mothers of young infants choose to formula feed in China? Perceptions of mothers and hospital staff. *Int J Environ Res Public Health* **12**, 4520–4532.
34. Sheehan A, Schmied V & Cooke M (2003) Australian women's stories of their baby-feeding decisions in pregnancy. *Midwifery* **19**, 259–266.
35. Bonia K, Twells L, Halfyard B, *et al.* (2013) A qualitative study exploring factors associated with mothers' decisions to formula-feed their infants in Newfoundland and Labrador, Canada. *BMC Public Health* **13**, 645–654.
36. Fildes A, van Jaarsveld CH, Llewellyn C, *et al.* (2015) Parental control over feeding in infancy. Influence of infant weight, appetite and feeding method. *Appetite* **91**, 101–106.
37. Launer LJ, Forman MR, Hundt GL, *et al.* (1992) Maternal recall of infant feeding events is accurate. *J Epidemiol Community Health* **46**, 203–206.