Formula-feeding and the risk of type-2 diabetes mellitus among Hong Kong adolescents

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KEY MESSAGES

1. Compared with exclusive breastfeeding, formula-feeding in the first 3 months of life is associated with poorer lipid profile and possibly greater insulin resistance but not greater adiposity at age 17.5 years.
2. Early infant nutrition may affect long-term health; therefore, breastfeeding should be encouraged.
3. Further studies are warranted, to investigate the effects of infant feeding on glucose metabolism and insulin resistance later in life.

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Introduction

The long-term effects of infant feeding mode on glucose metabolism and risk of type-2 diabetes mellitus (T2DM) remain unclear. In the 1980s, a randomised controlled trial demonstrated that formula-fed preterm infants, compared with breastfed preterm infants, had faster infant growth and greater insulin resistance during adolescence.[1] However, another randomised controlled trial found no effect of breastfeeding on cardiometabolic risk at age 11.5 years.[2] A systematic review of observational studies concluded that breastfeeding was associated with a lower risk of T2DM, compared with formula-feeding.[3] Nonetheless, publication bias and residual confounding by socio-economic status could not be ruled out. This study aimed to assess the association of infant feeding modes with risk factors for T2DM at age 17.5 years in the 'Children of 1997' birth cohort.[4]

Methods

This study was approved by the University of Hong Kong-Hospital Authority Hong Kong West Cluster Joint Institutional Review Board (UW 12-249) and the Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee (CRE-2013.507).

The 'Children of 1997' birth cohort (n=8327) covers 88% of all births from 1 April to 31 May 1997. Families were recruited at their first postnatal visit to the Maternal and Child Health Centres. Baseline characteristics including birth characteristics, parental education, and feeding mode were obtained using a self-administered questionnaire. Information on feeding mode was collected at age 3, 9, and 18 months. Since 2005, passive and active follow-ups have been carried out by means of data linkage and surveys to obtain health-related information.

Several sites were set up for clinical examination of the cohort at age 17.5 years. Fasting blood (30 mL) was drawn from participants in the morning to measure haemoglobin A1c, fasting glucose, insulin, cholesterol, triglyceride, and high-sensitivity C-reactive protein (hs-CRP). Body weight, % body fat, % muscle, standing height, waist circumference, and hip circumference were measured based on standard protocols. Handgrip strength (a proxy for muscle mass) of both hands was measured using a handgrip dynamometer. Pubertal stages were self-reported using line drawings of models at each Tanner stage.

Infant feeding mode at age 0-3 months was categorised as always formula-fed, mixed feeding, or exclusively breastfed. The duration of formula-feeding was categorised as 0-2 years, 3-5 years, or 6 years.

General adiposity was proxied by body mass index z-score relative to the 2007 World Health Organization growth reference and % body fat, whereas central adiposity was proxied by waist-to-height ratio z-score. Lean mass was proxied by total muscle mass and handgrip strength. Markers of glucose metabolism included fasting haemoglobin A1c, fasting glucose, fasting insulin, insulin resistance, and insulin sensitivity (estimated by the homeostasis model assessment). Other health markers included lipid profile (ie, total cholesterol), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, triglycerides, and systematic inflammation, proxied by hs-CRP. Log-transformed insulin and hs-CRP levels were used in the analyses.

Multivariable linear regression was used to assess the association of infant feeding mode with diabetes risk factors and other health markers at age 17.5 years. Model 1 adjusted for sex, pubertal stage, and age at follow-up and potential confounders,

including birth weight, gestational age, pregnancy characteristics (gestational diabetes, preeclampsia, and maternal smoking), mother's place of birth, and highest parental education. To test whether infant growth mediated any association, model 2 additionally adjusted for weight gain from birth to 3 months or birth to 12 months, defined in terms of the change in weight z-score. Whether the associations varied by sex and infant growth rate from the significance of interaction terms was tested. To minimise the bias from missing data, multiple imputation and inverse probability weighting were combined and the results summarised from 10 imputed datasets into single estimates.

Results

This study aimed to include 700 participants and finally included 710. Compared with the entire birth cohort, the 315 male and 395 female participants had parents with slightly higher education, a higher rate of gestational diabetes, and less maternal smoking during pregnancy. Clinical examinations were carried out at a mean age of 17.5 years. As expected, males on average were taller with lower % body fat, greater total muscle mass, and greater handgrip strength. Approximately 15% of male and 9% of female participants were overweight according to the International Obesity Task Force cut-offs. Few participants had LDL cholesterol (<1%) or triglycerides (<4%) above normal ranges (4.1 mmol/L and 1.7 mmol/L, respectively). Only five participants had elevated fasting glucose (range, 5.8-7.6 mmol/L), of whom four had normal haemoglobin A1c and one had clinically diagnosed T2DM. In both sexes, greater body mass index was associated with higher fasting glucose, insulin, insulin resistance, LDL cholesterol, triglycerides, and hs-CRP.

Approximately 7% of the participants were exclusively breastfed at 0-3 months; they were more likely to be female, with mainland-born mothers with a lower education level (Table 1). Compared with participants who were exclusively breastfed at 0-3 months, participants who were always formula-fed had less weight gain at 0-3 months, but not at 0-12 months (Fig). About 25% of parents reported their children had daily consumption of at least one glass of formula milk until 6 years. There was no difference in family and birth characteristics by duration of regular formula-feeding.

Compared with participants who were exclusively breastfed at 0-3 months, those who were always formula-fed tended to have marginally higher total cholesterol, LDL cholesterol, triglycerides, and insulin resistance (Table 2). Exclusive breastfeeding

TABLE 1. Characteristics of participants by infant feeding mode at age 0-3 months and duration of formula-feeding

Characteristics	Infant feeding mode at age 0-3 months			Duration of formula-feeding, y		
	Exclusively breastfed (n=51)	Mixed (n=302)	Always formula-fed (n=344)	0-2 (n=316)	3-5 (n=183)	6 (n=183)
Male sex, %	31	47	44	47	42	42
Gestational age, %						
≤36 weeks	5.9	4.6	2.9	4.4	4.9	1.6
37-38 weeks	24	26	29	29	26	26
39-40 weeks	55	55	52	50	57	58
≥41 weeks	16	15	16	17	11	15
Gestational diabetes, %	8.2	7.9	11	8.6	8.4	11
Preeclampsia, %	2.0	3.2	4.5	3.4	3.6	2.9
Maternal smoking during pregnancy, %	0	1.4	5.6	3.3	4.0	3.4
Infant feeding during 0-3 months, %						
Always formula-fed	-	-	-	50	50	47
Mixed	-	-	-	43	45	43
Always breastfed	-	-	-	6.7	5.0	10
Infant growth, weight z-score						
At birth	-0.31	-0.32	-0.17	-0.22	-0.29	-0.25
At 3 months	0.29	0.06	0.13	0.10	0.07	0.13
At 12 months	-0.01	0.01	0.10	0.03	0.05	0.10
Parents' highest education, %						
9th grade or below	40	20	29	26	26	25
10th to 11th grade	32	39	49	43	41	46
12th grade or above	28	41	22	32	33	29
Hong Kong born mother, %	30	64	64	63	62	61
Hong Kong born father, %	48	75	72	69	76	74

at age 0-3 months had a graded association with lower fasting insulin (P value for trend=0.02) and lower insulin resistance (P value for trend=0.03). When we repeated the analyses (except for insulin resistance and hs-CRP) with an additional 1920 participants with blood tested at a similar age in another study, these associations with total cholesterol (r=0.19, 95% confidence interval [CI]= −0.04 to 0.41) and higher LDL cholesterol (r=0.12, 95% CI= −0.08 to 0.32) became significant. Body mass index and % body fat at age 17.5 years did not differ by infant feeding modes.

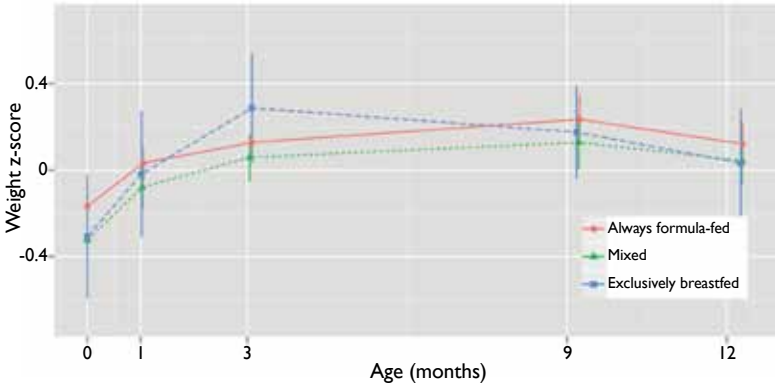

FIG. Weight z-score at age 0-12 months by infant feeding mode at age 0-3 months of life.

None of the above associations differed by sex or infant growth rate, and they were not attenuated after adjustment for infant growth (data not shown). The duration of formula-feeding was not associated with any risk factors of T2DM or other health markers at age 17.5 years (Table 2), with no interaction of sex (data not shown).

Discussion

Formula-feeding at 0-3 months was associated with higher LDL cholesterol but not associated with higher insulin resistance or adiposity markers at age 17.5 years. The lack of association between breastfeeding and adiposity in the present study and in the randomised controlled trial on breastfeeding promotion[2] is inconsistent with the protective effect of breastfeeding against obesity reported in some systematic reviews of observational studies.[3] Different social patterns on breastfeeding may result in various associations between infant feeding mode and subsequent adiposity in different stages of economic development. The null association of early infant feeding with adiposity at age 7 years and at young adulthood may be attributed to the lack of social patterns on breastfeeding in our population in the 1990s.

We also observed a null association of early infant feeding with fasting glucose levels. This is

TABLE 2. Adjusted associations of infant feeding mode at age 0-3 months and duration of formula-feeding with markers of health at age 17.5 years

	Value Mean±SD or median (range)		Infant feeding mode at age 0-3 months (β [95% CI])			Duration of formula-feeding, y (β [95% CI])		
	Male (n=315)	Female (n=395)	Exclusively breastfed	Mixed	Always formula-fed	0-1	3-5	6
Height, cm	172.1±6.0	159.6±5.4	Ref	−0.2 (−2.1 to 1.7)	0.1 (−1.7 to 1.9)	Ref	0.0 (−1.0 to 1.0)	0.2 (−0.8 to 1.3)
Body mass index, kg/m²	21.0±3.5	20.5±3.0	Ref	0.1 (−1.0 to 1.2)	0.1 (−1.0 to 1.1)	Ref	0.2 (−0.4 to 0.8)	−0.1 (−0.7 to 0.5)
Waist-to-height ratio z-score	0.43±0.05	0.43±0.04	Ref	0.0 (−0.3 to 0.3)	0.1 (−0.3 to 0.4)	Ref	0.0 (−0.1 to 0.2)	−0.1 (−0.3 to 0.1)
% body fat	15.1±5.8	27.7±5.5	Ref	0.2 (−1.7 to 2.1)	0.4 (−1.4 to 2.3)	Ref	−0.2 (−1.2 to 0.9)	−0.7 (−1.7 to 0.4)
Muscle mass, kg	49.7±6.2	35.2±3.2	Ref	−0.3 (−1.8 to 1.3)	−0.2 (−1.8 to 1.3)	Ref	0.8 (−0.1 to 1.6)	0.4 (−0.4 to 1.3)
Hand grip strength, kg	32.1±6.5	20.6±4.5	Ref	−0.4 (−2.2 to 1.5)	−0.7 (−2.5 to 1.1)	Ref	0.6 (−0.4 to 1.6)	0.7 (−0.3 to 1.7)
Haemoglobin A1c, %	5.4±0.2	5.4±0.2	Ref	−0.01 (−0.09 to 0.07)	−0.02 (−0.10 to 0.6)	Ref	0.01 (−0.03 to 0.05)	−0.04 (−0.08 to 0.01)
Fasting glucose, mmol/L	4.7±0.4	4.6±0.3	Ref	−0.08 (−0.19 to 0.04)	−0.07 (−0.18 to 0.05)	Ref	0.03 (−0.03 to 0.10)	0.01 (−0.06 to 0.08)
Fasting insulin, pmol/L*	63.7±28.1	60.0±36.1	Ref	0.02 (−0.04 to 0.08)	0.05 (−0.02 to 0.11)	Ref	−0.03 (−0.06 to 0.01)	−0.01 (−0.05 to 0.03)
Insulin resistance	1.09±0.65	1.16±0.51	Ref	0.03 (−0.17 to 0.22)	0.12 (−0.07 to 0.32)	Ref	−0.05 (−0.14 to 0.05)	−0.02 (−0.12 to 0.08)
Insulin sensitivity, % of homeostasis model assessment	115.1±53.9	101.9±44.8	Ref	−5.0 (−21.3 to 11.3)	−8.8 (−24.9 to 7.3)	Ref	6.9 (−2.1 to 15.8)	1.5 (−7.6 to 10.6)
Total cholesterol, mmol/L	3.9±0.7	4.1±0.7	Ref	0.19 (−0.03 to 0.42)	0.19 (−0.04 to 0.41)	Ref	−0.16 (−0.28 to −0.03)	−0.03 (−0.16 to 0.10)
Low-density lipoprotein cholesterol, mmol/L	2.0±0.6	2.2±0.6	Ref	0.15 (−0.05 to 0.35)	0.12 (−0.08 to 0.32)	Ref	−0.11 (−0.22 to 0.01)	0.01 (−0.11 to 0.12)
High-density lipoprotein cholesterol, mmol/L	1.4±0.3	1.6±0.3	Ref	0.06 (−0.05 to 0.17)	0.06 (−0.05 to 0.16)	Ref	−0.04 (−0.10 to 0.02)	−0.03 (−0.09 to 0.03)
Triglycerides, mmol/L	0.86±0.36	0.79±0.34	Ref	−0.00 (−0.12 to 0.11)	0.06 (−0.05 to 0.17)	Ref	−0.06 (−0.12 to 0.01)	−0.02 (−0.09 to 0.04)
High sensitive C-reactive protein, mg/dL*	0.03 (0.02-0.9)	0.03 (0.02-0.9)	Ref	−0.30 (−0.83 to 0.24)	−0.25 (−0.78 to 0.29)	Ref	0.23 (−0.07 to 0.53)	−0.10 (−0.40 to 0.21)

* Measured in 710 participants only; log-transformed value was used in regression analyses

consistent with findings from a meta-analysis of observational studies, which concluded that infant feeding has little effect on fasting glucose levels in adulthood.[3] Breastfed infants have a marginally lower insulin level and a significantly lower risk of T2DM in adulthood.[3] We observed associations between the always formula-fed participants and higher insulin resistance, and between exclusive breastfeeding at age 0-3 months and lower insulin resistance. However, these associations were not statistically significant, perhaps owing to the small sample size. Furthermore, we cannot rule out a delayed effect of early-life exposure on glucose metabolism that may only become obvious later in adulthood. Longer-term follow-up in a larger sample within the birth cohort are warranted to confirm the long-term effects of infant feeding on insulin resistance and glucose metabolism.

We found higher total and LDL cholesterol and marginally higher triglycerides among formula-fed participants. Systematic reviews have concluded that breastfeeding is associated with a modest reduction in total cholesterol in adulthood.[5] The literature on the association between breastfeeding and triglycerides is rather mixed. The association of formula-feeding with higher LDL cholesterol and triglycerides but not with adiposity indicates that different mechanisms may be involved. Breast milk contains higher cholesterol, and breastfed infants synthesised less cholesterol. It has been speculated that such change in homeostasis of cholesterol in early life may programme lipid profile in adulthood.

In the early 2000s, prolonged infant formula-feeding was common in Hong Kong, with 30% of our participants having daily consumption of infant formula at age 6 years. We did not observe any effects of duration of formula-feeding on any risk factor for T2DM or health markers at age 17.5 years. Prolonged formula-feeding may be a result of perceived poor growth or ill health. Therefore, 6-year-olds who did not receive infant formula may have been healthier or even overweight, suggesting a reverse causality in the association between prolonged formula-feeding and subsequent health.

There are some limitations to this study. We included only a subset of the birth cohort and participation in the follow-up was voluntary. However, breastfeeding was not socially patterned in the cohort, suggesting little residual confounding by unmeasured socio-economic status. Inverse probability weighting was used to mitigate any selection bias. Information on formula milk use provided by mothers was prone to recall bias. The societal value on prolonged formula-feeding was unclear, so there was unlikely any differential recall bias. Breastfeeding duration was commonly short in the 1990s in Hong Kong, which did not allow assessment on dose-response effect.

Conclusions

Compared with exclusive breastfeeding, formula-feeding at age 0-3 months was associated with poorer lipid profile and maybe greater insulin resistance but not associated with adiposity at age 17.5 years. Prolonged formula-feeding was unrelated to any markers of cardiovascular and metabolic health. Early infant nutrition may affect long-term health; exclusive breastfeeding, even for a short period, was associated with a healthier lipid profile. Our findings support the promotion of breastfeeding in Hong Kong. Further studies are warranted to assess the biological mechanisms by which breastfeeding duration affects health later in life.

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