ORIGINAL ARTICLE

The association of breastfeeding with insulin resistance at 17 years: Prospective observations from Hong Kong's "Children of 1997" birth cohort

Lai Ling Hui^{1,2} | Man Ki Kwok¹ | E. Anthony S. Nelson² | So Lun Lee³ | Gabriel M. Leung¹ | C. Mary Schooling^{1,4}

¹School of Public Health, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

²Department of Paediatrics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong

³Department of Paediatrics and Adolescent Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong

⁴CUNY School of Public Health, New York, New York, USA

Correspondence

C. Mary Schooling, School of Public Health, The University of Hong Kong, Patrick Manson Building, 7 Sassoon Road, Pokfulam, Hong Kong.
Email: cms1@hku.hk

Funding information

Health and Medical Research Fund, Grant/Award Number: 10111491; HHSRF, Grant/Award Number: 08090761; RFCID, Grant/Award Number: 04050172; Health and Health Services Research Fund, Grant/Award Number: 03040771; Health Care and Promotion Fund, Grant/Award Number: 216106

Abstract

Breastfeeding has many benefits for mother and infant. Whether breastfeeding also protects against type 2 diabetes is unclear. To clarify the role of breastfeeding in type 2 diabetes, we assessed the association of breastfeeding with insulin resistance in late adolescence in a birth cohort from a non-Western setting where breastfeeding was not associated with higher socio-economic position. We used multivariable linear regression, with multiple imputation and inverse probability weighting, to examine the adjusted associations of contemporaneously reported feeding in the first 3 months of life (exclusively breastfed, mixed feeding, or always formula-fed) with fasting glucose, fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) at 17 years in a subset ($n = 710$, 8.6% of entire cohort) of the Hong Kong Chinese birth cohort "Children of 1997." We found a graded association of breastfeeding exclusivity in the first 3 months of life with lower fasting insulin and HOMA-IR (p -for-trend $< .05$), but not fasting glucose, at 17 years. Exclusively breastfed adolescents (7%) had nonsignificantly lowest fasting insulin and HOMA-IR, adjusted for sex, birth weight, parity, length of gestation, pregnancy characteristics, parents' education, and mother's place of birth. Exclusively breastfeeding for 3 months may be causally associated with lower insulin resistance in late adolescence. Further follow-up studies into adulthood are required to clarify the long-term protection of breastfeeding from type 2 diabetes.

KEYWORDS

adolescents, birth cohort, breastfeeding, Chinese, infant feeding, insulin resistance, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes is particularly prevalent in Asia where the diabetes epidemic is a major public health concern, with the effects on quality of life, morbidity and mortality, and cost to the health care system. Breastfeeding is promoted as an intervention to improve the health of mother and infant. However, whether long-term protection against type 2 diabetes is an additional benefit of breastfeeding remains unclear, despite 3 decades of research.

A small randomized controlled trial (RCT) in the 1980s found that preterm infants fed breast milk or regular formula had lower insulin resistance in adolescence, assessed from the 32–33 split proinsulin, than those fed protein-enriched preterm formula (Singhal, Fewtrell, Cole, & Lucas, 2003). Although this suggested breastfeeding may

prevent type 2 diabetes in adulthood, the loss to follow-up in this trial was very high, and it was unclear whether this comparison generalizes to breastfeeding compared to formula feeding in term infants. An RCT of breastfeeding promotion "PROBIT" found no effect of breastfeeding on fasting glucose, fasting insulin, or the homeostasis model assessment of insulin resistance (homeostasis model assessment of insulin resistance [HOMA-IR]) at 11.5 years (Martin et al., 2014); however, whether a difference emerges later in adolescence is unknown.

Observationally, breastfeeding was associated with lower glucose intolerance in the Dutch famine cohort (Ravelli, van der Meulen, Osmond, Barker, & Bleker, 2000) and lower type 2 diabetes rate in the Pima Indian cohort (Pettitt, Forman, Hanson, Knowler, & Bennett, 1997). Systematic reviews concluded that breastfeeding

compared with formula feeding was associated with a lower risk of type 2 diabetes based on a limited number of observational studies (Horta, Loret de, & Victora, 2015; Owen, Martin, Whincup, Smith, & Cook, 2006). However, the most consistent associations of breastfeeding with lower fasting glucose and insulin were observed in infants not in adults (Owen et al., 2006). Moreover, these observational studies are open to publication bias, residual confounding, and information bias. Formula feeding and type 2 diabetes are often similarly socially patterned, with both being associated with disadvantage, particularly in Western populations (Brion, 2010). Recall bias of infant feeding by mother or relatives (Martin, Ben-Shlomo, et al., 2005a; Young et al., 2002) is likely differential when breastfeeding is desirable, which may overestimate the benefits of breastfeeding (Norris & Scott, 1996).

In long-term developed Western countries, breastfeeding mothers tend to be better educated (Victora et al., 2016; Wright, Parkinson, & Scott, 2006). In contrast in Hong Kong in the 1990s, educated native-born mothers tended to start breastfeeding, whereas migrant mothers from the rest of China, who were on average less educated, tend to sustain breastfeeding (Lee, Wong, Lui, Chan, & Lau, 2007). Hence, currently developed Hong Kong may serve as an ideal non-Western developed setting with a different confounding structure in which to verify associations from Western societies that are potentially confounded by socio-economic position (Brion, 2010; Kwok, Schooling, Lam, & Leung, 2010). In the large and population representative birth cohort Hong Kong's "Children of 1997" (Schooling, Hui, Ho, Lam, & Leung, 2012), with contemporaneously reported infant feeding, we have previously reported several associations for breastfeeding consistent with the "PROBIT" RCT of breastfeeding promotion (Martin et al., 2014; Martin et al., 2013), such as exclusive breastfeeding in the first 3 months of life unrelated to body mass index (BMI) at 7 years (Kwok et al., 2010) and blood pressure at 13 years (Kwok, Leung, & Schooling, 2013b). Here to extend the evidence base concerning the role of breastfeeding in type 2 diabetes, we assessed the association of breastfeeding with insulin resistance at 17 years in the same setting.

2 | PARTICIPANTS AND METHODS

2.1 | Hong Kong "Children of 1997" birth cohort

The Hong Kong "Children of 1997" birth cohort is a population representative Chinese birth cohort ($n = 8327$) that covered 88% of all births from April 1, 1997, to May 31, 1997. The study was initially established to investigate the impact of second-hand smoke exposure on infant health (Schooling et al., 2012). Families were recruited at their first post-natal visit soon after birth to the 49 Maternal and Child Health Centres in Hong Kong, which parents of all newborns are encouraged to attend for free post-natal care, developmental checks, and vaccinations until the age of 5 years. Baseline characteristics were obtained at recruitment using a self-administered questionnaire in Chinese that included information on birth characteristics (birth weight, birth order, sex, and gestational age), parents' education, infant feeding, and second-hand smoke exposure.

Key messages

- Whether breastfeeding protects against type 2 diabetes is unclear with conflicting evidence from randomized controlled trials and observational studies.
- Our birth cohort in a setting where breastfeeding was unrelated to higher socio-economic position found that breastfeeding exclusivity in early infancy was associated with lower insulin resistance at 17 years old.
- Our finding suggested potential long-term benefits of exclusively breastfeeding on glucose metabolism and metabolic health.

Information on infant feeding was collected using standardized questionnaires administered shortly after birth and at 3, 9, and 18 months. At recruitment, shortly after birth, the respondent, mainly the mothers, was asked: "How is the infant currently fed?" specified as "exclusively breastfed" (i.e., only breast milk was given), "partially breastfed," and "only formula fed." At each of the follow-up visits at 3, 9, and 18 months, the respondent was asked: "How has the infant been fed from birth until now?" specified as one of the three original options or an additional option applying to the initially exclusively breastfed of "initially breastfed, but now formula fed" with the age in months when breastfeeding terminated. Information on in-hospital formula supplementation was not collected.

2.2 | Clinical follow-up at 17 years

This present investigation on infant feeding and insulin resistance in a subset of 710 (8.6%) selected by simple random sampling using computer-generated random numbers from 2,630 participants of "Children of 1997" who attended a clinic follow-up during January to August 2014. We set up follow-up clinics in different districts in Hong Kong, and thus, the participants were not only limited to certain geographic areas, and geographic distribution of participants had no role to play in the selection process. The follow-up was ongoing when we carried out the present investigation. To be cost-effective, we did not carry out the investigation among all the participants who attended the clinical follow-up, but on a sample designed to detect an effect size of 0.26 standard deviations, which is equivalent to 0.14 of HOMA-IR, based on the first RCT on breastfeeding and insulin resistance in adolescents (Singhal et al., 2003).

We asked the participants to fast for 8 hr prior to the clinical follow-up. Blood was drawn at 08:00 a.m.–11:00 a.m., from which fasting plasma glucose (enzymatic reference method with hexokinase, Roche cobas C8000 System, Germany) and fasting serum insulin (chemiluminescent microparticle immunoassay, Abbott ARCHITECT assay) were determined. Body weight and standing height (Harpender stadiometer) were measured by trained staff using standard protocols. Pubertal stages of breast/genital were self-reported using line drawings of models at each Tanner stage. As a token of appreciation, we offered supermarket coupons worth HKD 200 (USD 24) per

participant. This study was reviewed by and received approval from the University of Hong Kong–Hospital Authority Hong Kong West Cluster Joint Institutional Review Board and the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee.

2.3 | Exposure—Feeding in the first 3 months of life

Infant feeding in the first 3 months was categorized, based on the most contemporaneous report, as always formula-fed, (i.e., never breastfed), mixed feeding (i.e., fed both breast milk and formula milk), or exclusively breastfed, consistent with our previous studies on breastfeeding in this birth cohort (Kwok et al., 2010; Kwok, Leung, Lam, & Schooling, 2012; Kwok, Leung, & Schooling, 2013a; Kwok, Leung, & Schooling, 2013b). As previously described, mixed feeding included those “partially breastfed for any length of time or exclusively breastfed for less than three months.”

2.4 | Outcome—Insulin resistance at 17 years

Insulin resistance was proxied by the HOMA-IR calculated from fasting plasma glucose and fasting serum insulin, using the HOMA calculator (Oxford Centre for Diabetes, Endocrinology, and Metabolism, Diabetes Trials Unit, <http://www.dtu.ox.ac.uk/>; Wallace, Levy, & Matthews, 2004). We also assessed the association of infant feeding with fasting plasma glucose and fasting serum insulin. Because the insulin concentration was not normally distributed, log-transformed insulin was used in the analyses. We excluded an impossible fasting insulin reading of 410 pmol/L.

2.5 | Statistical analysis

We used the chi-square test and analysis of variance to assess the difference in characteristics by mode of infant feeding. We used multivariable linear regression to assess the adjusted association of infant feeding with fasting glucose, fasting log insulin, and HOMA-IR, adjusted for age at follow-up and potential confounders. Confounders, selected as likely common factors influencing choices of infant feeding as well as adolescent glucose metabolism, included sex, birth weight, parity, gestational age, pregnancy characteristics (gestational diabetes, pre-eclampsia, and maternal smoking), mother's place of birth, parents' history of type 2 diabetes, and proxies of family socio-economic position (parents' education and household income per head). We tested whether the associations varied by sex from the significance of interaction terms. We obtained the *p*-for-trend for the association of breastfeeding exclusivity with markers of insulin resistance by treating the three infant feeding categories (always formula-fed, mixed feeding, or exclusively breastfed) as a continuous variable. Given boys at 17 years may be at varying stages of puberty, we adjusted for self-reported pubertal status at follow-up in a sensitivity analysis. We additionally used multivariable logistic regression to assess the consistency of the adjusted associations of mode of infant feeding with having higher fasting glucose, fasting log insulin, and HOMA-IR by assessing the adjusted association of being in the highest quartile for each outcome.

To weight back to the cohort, we combined multiple imputation and inverse probability weighting. We used multiple imputation to predict missing confounders based on a flexible additive regression model with predictive mean matching incorporating data on infant feeding, potential confounders, interactions of interest (i.e., infant feeding by sex), and the outcomes (i.e., HOMA-IR). Confounders were imputed for <5%, except for parents' history of type 2 diabetes (10%). We calculated the probability of an observation being present using logistic regression to identify predictors of being included in the study, from which we obtained subject inverse probability weights of response. We summarized the results from 10 imputed datasets using these weights into single estimates with confidence intervals adjusted for missing data uncertainty.

Statistical analyses were performed using Stata version 10 (Stata Corp, College station, TX, USA) and R version 2.3.1 (R Development Core Team, Vienna, Austria).

3 | RESULTS

3.1 | Study participants

Of the original 8,327 cohort participants, as of August 31, 2014, 8,283 were alive and had not withdrawn (*n* = 28 withdrawn), from which 710 (8.6%) were included. Their baseline characteristics were comparable to the entire birth cohort, with small differences in some distributions, including fewer boys, more gestational diabetes, and less maternal smoking during pregnancy (Table 1). However, the Cohen effect sizes were all small (<0.2), indicating the included participants were similar to the entire birth cohort. The percentage of exclusively breastfed for 3 months (7.3%) or with mixed feeding (43%) was also comparable with the rest of the cohort (respectively, 6.3% and 37%).

The participants were assessed at the mean age of 17 years (ranging from 16.8 to 17.4 years). Only five participants had elevated fasting glucose (ranging from 5.8–7.6 mmol/L), of whom four had normal HbA1c and one had clinically diagnosed type 2 diabetes. Despite the normal fasting glucose (ranging from 3.7 to 7.6 mmol/L, mean 4.7 mmol/L) in the vast majority, insulin level ranged from 14.6 to 215 pmol/L with a mean of 61.9 pmol/L, whereas HOMA-IR ranged from 0.3 to 4.1 with a mean of 1.1 (standard deviation 0.5). Participants with parent's education of 9th grade or lower, compared to the rest, on average had higher HOMA-IR.

As in the entire cohort, participants in this study who were exclusively breastfed for at least 3 months were more likely to be girls, but less likely to be exposed to gestational diabetes, pre-eclampsia, and maternal smoking (Table 2). Their mothers were more likely to be born in mainland China and to have lower education. Exclusive breastfeeding for 3 months was not associated with higher parents' education.

3.2 | The associations of infant feeding with insulin resistance at 17 years

Table 3 shows a graded relation of breastfeeding exclusivity in the first 3 months of life with lower fasting insulin (*p* value for trend .02) and

TABLE 1 Baseline characteristics of the included participants compared to the entire birth cohort

	This study (n = 710)	The entire birth cohort (n = 8,299)	Cohen effect size ^b
Boys (%)	44%	53%	0.18
Birth weight z-score ^a (mean)	-0.24	-0.26	0.02
Parity (%)			
1st	51%	48%	0.06
2nd	39%	41%	
≥3rd	10%	11%	
Gestational age (%)			
≤36	3.8%	5.3%	0.10
37–38 weeks	27%	29%	
39–40 weeks	54%	52%	
≥41 weeks	15%	13%	
Gestational diabetes (%)	9.2%	6.2%	0.12
Pre-eclampsia (%)	3.8%	3.7%	0.01
Maternal smoking during pregnancy (%)	3.4%	5.1%	0.08
Infant feeding in the first 3 months of life (%)			
Always formula-fed	49%	57%	0.15
Mixed	43%	37%	
Exclusively breastfed	7.3%	6.3%	
Father's education (%)			
9th grade or below	38%	44%	0.13
10th–11th grade	36%	33%	
12th grade or above	27%	23%	
Mother's education (%)			
9th grade or below	38%	41%	0.06
10th–11th grade	45%	43%	
12th grade or above	17%	16%	
Household income per head in quintiles			
1st	18%	20%	0.11
2nd	17%	20%	
3rd	20%	20%	
4th	23%	20%	
5th	22%	20%	
Hong Kong born mother (%)	61%	60%	0.02

^aReferenced to the 2006 WHO growth standard.

^bCohen effect sizes are calculated as $\sqrt{\sum(p_{0i} - p_{1i})^2 / p_{0i}}$ where the sum is over the categories and p_{0i} is the proportion in the i th category in the entire birth cohort and p_{1i} is the proportion in the i th category in the subsample involved in this study.

lower insulin resistance (p value for trend .03), with adjustment for sex, birth weight, parity, gestational weeks, pregnancy characteristics including gestational diabetes, pre-eclampsia and maternal smoking, parents' education, mother's place of birth, and age at measurements. Compared to participants who were always formula-fed, those who were exclusively breastfed for 3 months had nonsignificantly lower HOMA-IR (-0.13 , 95% CI $[-0.31, 0.05]$) and fasting insulin (-0.05 , 95% CI $[-0.12, 0.01]$). They also had lower risk of having HOMA-IR (0.51 , 95% CI $[0.29, 0.89]$) and fasting insulin (0.59 , 95% CI $[0.29, 0.96]$) in the highest quartile. Breastfeeding in the first 3 months of life was not associated with fasting glucose.

None of the above associations was varied by sex (data not shown). Similar associations of infant feeding with insulin resistance were obtained when not adjusting for parents' education or additionally

adjusting for BMI or Tanner stage of puberty at follow-up (data not shown). We obtained similar results for log-transformed HOMA-IR.

4 | DISCUSSION

In an understudied non-Western developed population, we found a graded association of breastfeeding exclusivity in the first 3 months of life with lower fasting insulin and lower HOMA-IR, at 17 years. The small effect size for fasting insulin and HOMA-IR in our study was consistent with that reported from a meta-analysis of observational studies (Owen et al., 2006), although these associations did not reach statistical significance, partly due to a small sample size. Nevertheless, our birth cohort, in a setting with little socio-economic confounding affecting the observed health benefits of breastfeeding,

TABLE 2 Baseline characteristics by infant feeding in the first 3 months of life

Characteristics	Always formula-fed (n = 354)	Mixed (n = 305)	Exclusively breastfed (n = 51)	p value ^a
Boys (%)	44%	47%	31%	.10
Birth weight z-score ^b (mean)	-0.16	-0.32	-0.31	.06
Parity (%)				
1st	46%	58%	49%	.03
2nd	41%	35%	45%	
≥3rd	13%	7.3%	6.6%	
Gestational age (%)				
≤36	3.0%	4.6%	5.9%	.86
37–38 weeks	28%	26%	23%	
39–40 weeks	53%	55%	55%	
41 weeks	15%	15%	16%	
Gestational diabetes (%)	11%	7.9%	8.2%	.64
Pre-eclampsia (%)	4.4%	3.3%	2.1%	.36
Maternal smoking during pregnancy (%)	5.7%	1.5%	0%	.01
Father's education (%)				
9th grade or below	43%	30%	48%	<.01
10th–11th grade	37%	36%	25%	
12th grade or above	20%	34%	25%	
Mother's education (%)				
9th grade or below	40%	33%	56%	<.01
10th–11th grade	50%	43%	25%	
12th grade or above	10%	24%	20%	
Household income per head in quintiles				
1st	17%	16%	27%	.08
2nd	18%	15%	20%	
3rd	23%	18%	22%	
4th	24%	24%	14%	
5th	19%	28%	18%	
Hong Kong born mother (%)	63%	63%	29%	<.01

^aBy chi-square tests for categorical parameters and analysis of variance for continuous parameters.

^bReferenced to the 2006 WHO growth standard.

TABLE 3 The adjusted mean difference [95% CI] in fasting glucose, log fasting insulin, and homeostasis model assessment of insulin resistance (HOMA-IR) by infant feeding in the first 3 months of life

		Always formula-fed (n = 344)	Mixed (n = 302)	Exclusively breastfed (n = 51)	p-for-trend
Model 1	Fasting glucose (mmol/L)	Ref	-0.01 [-0.06, 0.05]	0.05 [-0.07, 0.16]	.77
	Log fasting insulin (pmol/L)	Ref	-0.03 [-0.06, 0.00]	-0.04 [-0.10, 0.03]	.06
	HOMA-IR	Ref	-0.08 [-0.16, -0.00]	-0.10 [-0.27, 0.08]	.05
Model 2	Fasting glucose (mmol/L)	Ref	-0.01 [-0.07, 0.04]	0.07 [-0.05, 0.19]	.70
	Log fasting insulin (pmol/L)	Ref	-0.03 [-0.06, 0.00]	-0.05 [-0.12, 0.01]	.02
	HOMA-IR	Ref	-0.09 [0.17, -0.00]	-0.13 [-0.31, 0.05]	.03

Model 1 was unadjusted.

Model 2 was adjusted for sex, birth weight (kg), parity, gestational weeks, pregnancy characteristics including gestational diabetes, pre-eclampsia and maternal smoking, mother's place of birth, parents' history of type 2 diabetes, parents' education, household income per head, and age (years) at measurements.

which has previously replicated the null associations of breastfeeding with childhood adiposity and blood pressure (Kwok et al., 2010; Kwok, Leung, & Schooling, 2013b) found in the PROBIT RCT (Martin et al., 2014; Martin et al., 2013), now adds by showing a potential long-term benefit of breastfeeding on insulin resistance in late adolescence.

Few previous observational studies of breastfeeding and insulin resistance or type 2 diabetes are from a similar setting with little confounding by socio-economic position and use of contemporaneously reported infant feeding. Two observational studies from the U.K. on adults aged respectively 45–59 years (Martin, Ebrahim, et al., 2005b)

and 63–82 years (Martin, Ben-Shlomo, et al., 2005a) with similarly little social patterning of breastfeeding found a null association of breastfeeding with risk of type 2 diabetes. However long-term recall of infant feeding was used, which may have resulted in nondifferential misclassification of infant feeding and biased its potential health effects towards the null. In addition, these studies date from a time when the alternatives to breastfeeding may not be comparable with the formula in use in the recent 2 decades. On the other hand, evidence from RCTs is also limited. The PROBIT RCT reported a null association of breastfeeding with fasting insulin and HOMA-IR at 11.5 years. Despite the randomized design and high follow-up rate, the intervention arm included some fed formula infants, and so may be underpowered to assess effects of breastfeeding. An RCT from the 1980s reported higher insulin resistance in adolescence for preterms fed high protein infant formula compared to a group of preterms fed either regular infant formula or banked breast milk (Singhal et al., 2003). The preterms fed high protein formula in this RCT also did not differ in markers of insulin resistance from a group of term births. The effect of breastfeeding compared to the type of formula used today cannot be discerned from this RCT. Moreover, these RCTs did not examine any effects of breastfeeding that might arise in adulthood.

Biological pathways exist by which breastfeeding could have long-term effects on glucose metabolism, including lower protein content (Koletzko et al., 2009; Lucas et al., 1980), lower glycaemic index (Pawlak, Kushner, & Ludwig, 2004), and higher polyunsaturated fatty acids (Das, 2007) in breast milk compared to infant formula. Specifically, based on the RCT of infant formula in preterm births (Singhal, Cole, Fewtrell, Deanfield, & Lucas, 2004; Singhal et al., 2003), it has been suggested that accelerated early infant growth, promoted by high protein infant formula, may generate later cardiovascular disease risk (Singhal & Lucas, 2004). Potential mechanisms include elevated insulin and/or IGF-1 in formula-fed infants (Dardevet, Manin, Balage, Sornet, & Grizard, 1991). Here, we observed a graded association between breastfeeding exclusivity in the first 3 months of life and lower insulin resistance in late adolescence, suggesting breastfeeding may protect from type 2 diabetes. Our small sample size may have precluded the association between exclusively breastfeeding and lower insulin resistance reaching statistical significance. Also, long-term health outcomes of early life exposures may only arise later in adulthood such that the impact, if any, observed in adolescence is small and difficult to detect. Nevertheless, in our setting, breastfeeding was not associated with higher socio-economic position, whereas insulin resistance was associated with lower socio-economic position; any protection of breastfeeding from insulin resistance observed here is likely to be conservative than confounded by socio-economic position. On the other hand, previous studies on the association between breastfeeding and insulin resistance, besides the Dutch Hunger study (Ravelli et al., 2000), mainly reported null associations in both adolescence (Lawlor et al., 2005; Martin et al., 2014) and adulthood (Martin, Ben-Shlomo, et al., 2005a; Williams et al., 2012). Given the mixed findings in the literature, further evidence is required to elucidate whether breastfeeding protects against type 2 diabetes. With changes in infant formula over time, longer-term follow-up studies in contemporary cohorts like ours are warranted to investigate the potential impact

of current infant formula on the risk of type 2 diabetes as well as to understand mediating pathways to clarify the causal relation between breastfeeding and glucose metabolism.

4.1 | Limitations

Our study used a population-representative birth cohort with contemporaneously reported information on infant feeding. Some caveats require consideration. First, only 8.6% of the cohort participants were included. Attending the clinical follow-up was voluntary; however, breastfeeding was not socially patterned in the cohort, suggesting that the association of infant feeding reported in infancy with insulin resistance were not biased by this selection. Furthermore, we used inverse probability weighting to address potential selection bias. Our sample size was designed to detect an effect size of 0.26 standard deviations, which is equivalent to 0.14 of HOMA-IR. Second, infant feeding was only assessed at 3, 9, and 18 months, and we cannot rule out recall bias even within 2 years after childbirth. However our recall bias should be comparatively less compared to the long-term recalls in some retrospective studies (Martin, Ben-Shlomo, et al., 2005a; Young et al., 2002). We did not have information on early hospital feeds or drinks consumed other than breast milk or infant formula. However, feeding of water and other drinks were not encouraged by health care professionals in the 1990s, and introduction of solid food before 3 months old was uncommon in our cohort (2%; Lin, Leung, Lam, & Schooling, 2013). Even if drinks other than breast milk and infant formula were given, the quantities were likely small in the first 3 months of life, and this will only make our observed benefits of breastfeeding exclusivity more conservative. Third, we did not use the oral glucose tolerance test or the hyperinsulinaemic-euglycaemic clamp to ascertain insulin secretion and insulin resistance. However, simple indices of insulin sensitivity are good surrogates (Hanson et al., 2000). Fourth, we do not have information on maternal alcohol consumption and or maternal weight during pregnancy, which may be unmeasured confounders. We may have potentially overestimated any protective effect of breastfeeding on diabetes, if these factors are associated with less breastfeeding and adverse health consequences in children. However, a very small proportion of pregnant women in Hong Kong use alcohol, and the observed association of exclusive breastfeeding with lower insulin resistance was independent of gestational diabetes, a factor positively linked with weight gain during pregnancy. Finally, we do not have sufficient power to assess reliably how much of this association is mediated by BMI; however, infant feeding was not associated with BMI at 17 years, and adjusting for BMI did not change the associations of infant feeding with insulin resistance.

5 | CONCLUSIONS

In this study within a subsample of Hong Kong's "Children of 1997" birth cohort, where breastfeeding was not associated with higher socio-economic position, we found an association between breastfeeding and lower insulin resistance in late adolescence. Further

studies in adulthood in this birth cohort will clarify whether breastfeeding provides long-term protection against type 2 diabetes.

ACKNOWLEDGMENTS

The authors thank colleagues at the Student Health Service and Family Health Service of the Department of Health for their assistance and collaboration. They also thank the late Dr. Connie O for coordinating the project and all the fieldwork for the initial study in 1997–1998.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

LLH and CMS developed the study conception, directed the study's analytic strategy, wrote the manuscript, and approved the final manuscript as submitted. MKK, EASN, SLL, and GML contributed to the interpretation of the data, critically revising the paper, and approved the final manuscript as submitted.

REFERENCES

- Brion, M. J. (2010). Commentary: Assessing the impact of breastfeeding on child health: Where conventional methods alone fall short for reliably establishing causal inference. *International Journal of Epidemiology*, 39, 306–307.
- Darvevet, D., Manin, M., Balage, M., Sornet, C., & Grizard, J. (1991). Influence of low- and high-protein diets on insulin and insulin-like growth factor-1 binding to skeletal muscle and liver in the growing rat. *The British Journal of Nutrition*, 65, 47–60.
- Das, U. N. (2007). Breastfeeding prevents type 2 diabetes mellitus: But, how and why? *The American Journal of Clinical Nutrition*, 85, 1436–1437.
- Hanson, R. L., Pratley, R. E., Bogardus, C., Narayan, K. M., Roumain, J. M., Imperatore, G., ... Knowler, W. C. (2000). Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. *American Journal of Epidemiology*, 151, 190–198.
- Horta, B. L., Loret de, M. C., & Victora, C. G. (2015). Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: A systematic review and meta-analysis. *Acta Paediatrica. Supplement*, 104, 30–37.
- Koletzko, B., von Kries, R., Closa, R., Escribano, J., Scaglioni, S., Giovannini, M., ... Grote, V. (2009). Lower protein in infant formula is associated with lower weight up to age 2 y: A randomized clinical trial. *The American Journal of Clinical Nutrition*, 89, 1836–1845.
- Kwok, M. K., Leung, G. M., Lam, T. H., & Schooling, C. M. (2012). Breastfeeding, childhood milk consumption, and onset of puberty. *Pediatrics*, 130, e631–e639.
- Kwok, M. K., Leung, G. M., & Schooling, C. M. (2013a). Breast feeding and early adolescent behaviour, self-esteem and depression: Hong Kong's 'Children of 1997' birth cohort. *Archives of Disease in Childhood*, 98, 887–894.
- Kwok, M. K., Leung, G. M., & Schooling, C. M. (2013b). Breastfeeding and adolescent blood pressure: Evidence from Hong Kong's "Children of 1997" birth cohort. *American Journal of Epidemiology*, 178, 928–936.
- Kwok, M. K., Schooling, C. M., Lam, T. H., & Leung, G. M. (2010). Does breastfeeding protect against childhood overweight? Hong Kong's 'Children of 1997' birth cohort. *International Journal of Epidemiology*, 39, 297–305.
- Lawlor, D. A., Riddoch, C. J., Page, A. S., Andersen, L. B., Wedderkopp, N., Harro, M., ... Smith, G. D. (2005). Infant feeding and components of the metabolic syndrome: Findings from the European Youth Heart Study. *Archives of Disease in Childhood*, 90, 582–588.
- Lee, W. T., Wong, E., Lui, S. S., Chan, V., & Lau, J. (2007). Decision to breastfeed and early cessation of breastfeeding in infants below 6 months old—A population-based study of 3,204 infants in Hong Kong. *Asia Pacific Journal of Clinical Nutrition*, 16, 163–171.
- Lin, S. L., Leung, G. M., Lam, T. H., & Schooling, C. M. (2013). Timing of solid food introduction and obesity: Hong Kong's "Children of 1997" birth cohort. *Pediatrics*, 131, e1459–e1467.
- Lucas, A., Sarson, D. L., Blackburn, A. M., Adrian, T. E., ynsley-Green, A., & Bloom, S. R. (1980). Breast vs bottle: Endocrine responses are different with formula feeding. *Lancet*, 1, 1267–1269.
- Martin, R. M., Ben-Shlomo, Y., Gunnell, D., Elwood, P., Yarnell, J. W., & Davey, S. G. (2005a). Breast feeding and cardiovascular disease risk factors, incidence, and mortality: The Caerphilly study. *Journal of Epidemiology and Community Health*, 59, 121–129.
- Martin, R. M., Ebrahim, S., Griffin, M., Davey, S. G., Nicolaidis, A. N., Georgiou, N., ... Gunnell, D. (2005b). Breastfeeding and atherosclerosis: Intima-media thickness and plaques at 65-year follow-up of the Boyd Orr cohort. *Arteriosclerosis, Thrombosis, and Vascular Biology*, 25, 1482–1488.
- Martin, R. M., Patel, R., Kramer, M. S., Guthrie, L., Vilchuck, K., Bogdanovich, N., ... Oken, E. (2013). Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: A randomized trial. *JAMA*, 309, 1005–1013.
- Martin, R. M., Patel, R., Kramer, M. S., Vilchuck, K., Bogdanovich, N., Sergeichick, N., ... Oken, E. (2014). Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: A cluster-randomized, controlled trial. *Circulation*, 129, 321–329.
- Norris, J. M., & Scott, F. W. (1996). A meta-analysis of infant diet and insulin-dependent diabetes mellitus: Do biases play a role? *Epidemiology*, 7, 87–92.
- Owen, C. G., Martin, R. M., Whincup, P. H., Smith, G. D., & Cook, D. G. (2006). Does breastfeeding influence risk of type 2 diabetes in later life? A quantitative analysis of published evidence. *The American Journal of Clinical Nutrition*, 84, 1043–1054.
- Pawlak, D. B., Kushner, J. A., & Ludwig, D. S. (2004). Effects of dietary glycaemic index on adiposity, glucose homeostasis, and plasma lipids in animals. *Lancet*, 364, 778–785.
- Pettitt, D. J., Forman, M. R., Hanson, R. L., Knowler, W. C., & Bennett, P. H. (1997). Breastfeeding and incidence of non-insulin-dependent diabetes mellitus in Pima Indians. *Lancet*, 350, 166–168.
- Ravelli, A. C., van der Meulen, J. H., Osmond, C., Barker, D. J., & Bleker, O. P. (2000). Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. *Archives of Disease in Childhood*, 82, 248–252.
- Schooling, C. M., Hui, L. L., Ho, L. M., Lam, T. H., & Leung, G. M. (2012). Cohort profile: "Children of 1997": A Hong Kong Chinese birth cohort. *International Journal of Epidemiology*, 41, 611–620.
- Singhal, A., Cole, T. J., Fewtrell, M., Deanfield, J., & Lucas, A. (2004). Is slower early growth beneficial for long-term cardiovascular health? *Circulation*, 109, 1108–1113.
- Singhal, A., Fewtrell, M., Cole, T. J., & Lucas, A. (2003). Low nutrient intake and early growth for later insulin resistance in adolescents born preterm. *Lancet*, 361, 1089–1097.
- Singhal, A., & Lucas, A. (2004). Early origins of cardiovascular disease: Is there a unifying hypothesis? *Lancet*, 363, 1642–1645.
- Victora, C. G., Bahl, R., Barros, A. J., Franca, G. V., Horton, S., Krasevec, J., ... Rollins, N. C. (2016). Breastfeeding in the 21st century: Epidemiology, mechanisms, and lifelong effect. *Lancet*, 387, 475–490.
- Wallace, T. M., Levy, J. C., & Matthews, D. R. (2004). Use and abuse of HOMA modeling. *Diabetes Care*, 27, 1487–1495.
- Williams, D. M., Martin, R. M., Davey, S. G., Alberti, K. G., Ben-Shlomo, Y., & McCarthy, A. (2012). Associations of infant nutrition with

insulin resistance measures in early adulthood: Evidence from the Barry-Caerphilly Growth (BCG) study. *PloS One*, 7, e34161.

Wright, C. M., Parkinson, K., & Scott, J. (2006). Breast-feeding in a UK urban context: Who breast-feeds, for how long and does it matter? *Public Health Nutrition*, 9, 686–691.

Young, T. K., Martens, P. J., Taback, S. P., Sellers, E. A., Dean, H. J., Cheang, M., & Flett, B. (2002). Type 2 diabetes mellitus in children: Prenatal and early infancy risk factors among native Canadians. *Archives of Pediatrics & Adolescent Medicine*, 156, 651–655.

How to cite this article: Hui LL, Kwok MK, Nelson EAS, Lee SL, Leung GM, Schooling CM. The association of breastfeeding with insulin resistance at 17 years: Prospective observations from Hong Kong's "Children of 1997" birth cohort. *Matern Child Nutr*. 2018;14:e12490. <https://doi.org/10.1111/mcn.12490>