TIMING OF INFANT FORMULA INTRODUCTION AND RISK OF ATOPIC DISEASES AND BEING OVERWEIGHT DURING EARLY CHILDHOOD

by

MINGYANG YUAN

A thesis submitted to the University of Birmingham for the degree of
DOCTOR OF PHILOSOPHY

Institute of Applied Health Research
College of Medical and Dental Sciences
University of Birmingham
September 2020

Abstract

Dietary exposure in early life, including formula feeding and early introduction of complementary foods, was considered as one of the main modifiable exposures associated with childhood allergy and obesity. During the past decades, the Chinese population has witnessed rapid economic development along with the unprecedented speed of industrialization and urbanization. Meanwhile, the consumption of infant formula has been increasing dramatically in recent decades worldwide, particularly in China. The observed remarkable growth in infant formula sales raises serious concern for child health. The research within this thesis focuses on the associations of feeding practice, especially the timing of infant formula introduction, with the development of atopic diseases and being overweight or obesity in young Chinese children.

Our systematic review and meta-analysis found that relatively little high-quality evidence was identified to allow for definitive conclusions on the association between early cow's milk or cow's milk formula introduction and risk of allergic diseases. Our meta-analysis on this topic highlights the specific gaps in information for public recommendations regarding cow's milk or cow's milk formula feeding practice in an early stage of life, particularly before 3 months of age. Then, we performed the studies based on the Born in Guangzhou Cohort Study (BIGCS), a population-based birth cohort in Guangzhou, China. The results suggested that early infant formula introduction, particularly within the first 3 months of life, may increase the risk of eczema during the first year of life. Also, food introduction patterns containing early infant formula introduction were related to a higher risk of eczema by the age of 3 years regardless of whether complementary foods were introduced relatively early or late. Furthermore, the later introduction of infant formula between 4 to 6 months seems to be associated with the lower BMI, weight-for-age and weight-for-length z-scores both at 1 year

and 3 years of age, compared with early introduction within the first 3 months. We also found that there may be a potential effect of early formula introduction on being persistently overweight from 1 year to 3 years old. The findings provide new evidence into the influence of formula feeding on early childhood health. The results need to be replicated in other cohorts to provide more robust evidence on the development of future health-related prevention guidelines for children.

Acknowledgements

I would like to give my great thanks to the people who contribute their time and assistance to my doctoral work.

First and foremost, I would like to thank my supervisors, Professor Kar Keung Cheng and Professor G. Neil Thomas. I am grateful for their endless patience, guidance, support, and encouragement they have provided throughout my PhD life. I particularly would like to thank Professor Kar Keung Cheng, who invested an amount of time in my PhD work. I would like to extend my thanks to Dr Hubert Lam, who is an associate professor in global health science and epidemiology at the University of Oxford, for finding the time to read and comment on my work. I also thank Professor Richard Lehman, who is the honorary Professor of the Shared Understanding of Medicine at the University of Birmingham, for his advice and comment on the literature review part within Chapter 1. I would also like to thank Mrs Miaoyu Tan and Dr David Moore for their contribution to my systematic review as the co-authors.

Furthermore, I would like to thank Professor Huimin Xia, who is the secretary of Guangzhou Women and Children's Medical Center, for allowing me to go to the University of Birmingham to complete my PhD. I also thank all of my colleagues working in the Born in Guangzhou Cohort Study, especially Professor Xiu Qiu, Mrs Jinhua Lu, Mrs Songying Shen and Mr Peiyuan Huang, for supporting me through this doctoral work. I would also like to thank Dr Jingya Wang, who is my fellow PhD student, for sharing her experience and putting up with my complaints and stress.

I would also like to say a special thanks to my family, particularly to my mother Mrs Qi Dong and my husband, Mr Heng Wang, for their constant and unwavering love and belief in me. Without their endless supports, encouragements, and understandings, I will not devote myself

to my work and finish this PhD. In addition, thanks to my sweet angel, Teeco, the apple of my eye who brings me so much happiness.

Table of Contents

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Chapter 6

List of Abbreviations

A	AAP	American Academy of Pediatrics
	ABCD	Amsterdam Born Children and their Development study
	AD	Atopic dermatitis
B	BiB	Born in Bradford
	BIGCS	Born in Guangzhou Cohort Study
	BMI	Body Mass Index
C	CDC	Centers for disease control and prevention
	CM	Cow's milk
	CMF	Cow's milk formula
	CMPA	Cow's milk protein allergy
	CNNHS	Chinese National Nutrition and Health Survey
	CNS	Chinese Nutrition Society
	CONER	Bologna Birth Cohort
	CPCSSN	Canadian Primary Care Sentinel Surveillance Network
D	DBPCFC	Positive double-blind, placebo-controlled challenge
	DHVCHD	Danish Health Visitors Child Health Database
	DNBC	Danish National Birth Cohort
E	EBF	Exclusive breastfeeding
F	FF	Formula feeding
	FLEHS I	Flemish Environment and Health Study I
	FSAI	Food Safety Authority of Ireland
G	GASPII	Genetica e Ambiente: Studio Prospettico dell'Infanzia in Italia
	GEJE	Great East Japan Earth-quake
	Generation R	the Generation R Study
	Generation XXI	the Generation XXI Birth Cohort
	GOC	Government of Canada
	GUI	Growing Up in Ireland
	GUSTO	Growing Up in Singapore towards Healthy Outcomes
	GWCMC	Guangzhou Women and Children’s Medical Center
H	HSE	Health Survey for England
	HSS	Department of Health and Human Services
	HUMIS	Norwegian Human Milk Study

I	IAP	India Academy of Pediatrics
	ICD	International Classification of Diseases
	IGF-1	insulin-like growth factor-1
	IL	Interleukin
	INMA	Infancia y Medio Ambiente-Environment and Childhood Project
	IOTF	International Obesity Task Force
	ISAAC	International Study of Asthma and Allergies in Childhood
K	KiGGS	Te German Health Interview and Examination Survey for Children and Adolescents
	KOALA	Kind Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg Birth Cohort Study
L	LC-PUFA	Long-chain polyunsaturated fatty acids
	Lifeways	Lifeways Cross Generation Cohort Study
	LucKi	Luchtwegklachten bij Kinderen
M	MaCHS	Maternal and Child Health Services
	MH	Ministry of Health
	MHLW	Ministry of Health, Labour and Welfare
	MI	Multiple Imputation
N	NHANES	National Health and Nutrition Examination Survey
	NHMRC	National Health and Medical Research Council
	NICE	National Institute for Health and Care Excellence
	NINFEA	Nascita e INFanzia: gli Effetti dell'Ambiente
	NSPGDC	National Survey on Physical Growth and Development of Children
O	OB	Obesity
	OFC	Oral food challenges
	OW	Overweight
P	PELAGIE	Endocrine disruptors: Longitudinal study on pregnancy abnormalities, infertility, and childhood
	PIAMA	Prevention and Incidence of Asthma and Mite Allergy
	PROBIT	Promotion of Breastfeeding Intervention Trial
	Project Viva	the Project Viva study
R	RCT	Randomized Controlled Trial
	RHEA	Mother Child Cohort in Crete
S	SCFAs	Shortchain fatty acids
	SD	Standard deviation

	SPT	Skin prick test
	SWS	Southampton Women's Survey
T	Th1	T-helper 1
	Th2	T-helper 2
U	UK	United Kingdom
	UNICEF	United Nations International Children's Emergency Fund
	US	United States
	USDA	United States Department of Agriculture
W	WHO	World Health Organisation

Chapter 1 General Introduction

Allergy and obesity are two of the most significant paediatric health problems worldwide, particularly in industrialised countries [1, 2]. Gene-environment interactions and various lifestyle factors have all been suggested as having a link to these two issues [3, 4]. Dietary exposures in early life, including formula feeding (FF), and early introduction of complementary foods have been considered as one of the main modifiable exposures associated with childhood allergy and obesity [5-10]. During the past decades, the Chinese population has witnessed rapid economic development along with the unprecedented speed of industrialisation and urbanisation. Such development has been associated with a dramatic increase in the prevalence of obesity and allergic disorders in children [11, 12]. The research within this thesis focuses on the associations of feeding practice, especially the introduction of infant formula, with the development of atopic diseases and being overweight or obesity in young Chinese children under 3 years of age. This chapter provides a general background and justification for the research.

1.1 Atopic diseases in children

Asthma, atopic dermatitis, allergic rhinitis and food allergy are common atopic diseases in children and potentially linked to each other [13, 14]. Definitions of these atopic diseases or symptoms are defined as follows:

Asthma: National Institute of Health (NIH) Guideline defines asthma as a chronic inflammatory disorder of the airways causing recurrent episodes of wheezing, coughing, breathlessness, and chest tightness particularly at night or in the early morning [15].

Eczema: Also known as atopic dermatitis, it is a chronic inflammatory skin disease characterised by intense itching and recurrent eczematous lesions [16].

Allergic rhinitis: It is an inflammatory disorder of nasal mucosa characterised by sneezing, pruritus, nasal congestion and rhinorrhoea. It is mediated by early-phase and late-phase

hypersensitivity responses to indoor and outdoor environmental allergens [17].

Food allergy: It is defined as a range of disorders, including acute, potentially fatal reactions, and a host of chronic diseases that mainly affect the skin and gastrointestinal tract, caused by an adverse immunological response (hypersensitivity) to food [18].

1.1.1 The prevalence of allergic diseases in children in China

Data from the Chinese centres participating in the International Study of Asthma and Allergies in Childhood (ISAAC) showed that there was a continuous rise in the prevalence of asthma, allergic rhinitis, and atopic eczema in children during the past decades in China [12]. The rate of childhood asthma has risen from 0.91% in 1999 to 6.8% in 2010 [19], and current wheezing rate has increased from 2.0% in 1994 to 7.9% in 2009 in the urban area [20]. Data from community-based random samples of schoolchildren aged 9 to 11 years in Beijing, Guangzhou, and Hong Kong, showed that the rate of atopy (symptoms of wheeze, asthma, rhinitis, and eczema) was 23.9%, 30.8% and 41.2%, respectively [21]. The first national survey in infants under 24 months of age from 33 Chinese cities in 2014 indicated that the prevalence of allergic symptoms was 40.9% (4,376 of 10,693 infants) [22]. In this survey, the parent-reported doctor diagnosis rate of food allergy, asthma, allergic rhinitis, and eczema was 2.5%, 0.2%, 0.9%, and 18.5%, respectively [22].

1.1.2 The prevalence of allergic diseases in preschool-aged children of other countries

The pooled data of 18 European and United States (US) birth cohort studies (all participating cohorts covered deliveries from 1996 to 2011) showed that 29.2%, 15.4%, and 13.1% of children had wheeze in infancy (0-2 years), at preschool age (3-4 years), and at school age (5-8 years), respectively; 9.2% and 10.5% of children had asthma at preschool age and school age, respectively; 5.4% of children had allergic rhinitis at school age [23]. A population-based

cohort in Australia showed that the prevalence of food allergy was 11% and 3.8% at age 1 year (year 2007-2011) and 4 years of age (year 2011-2015), respectively; the prevalence of doctor-diagnosed eczema and wheezing in the first year of life (year 2007-2011) was 27.6% and 16.2%, respectively; the prevalence of doctor-diagnosed allergic rhinitis was 3.6% at 4 years of age (year 2011-2015) [24]. Data from two Asian cohorts, in Japan and Singapore, showed that the prevalence of eczema in children under 3 years was 17.5% (year 2006-2007) and 27.3% (year 2012-2013), respectively, and the former was similar to the prevalence (18.5%) in China (year 2014) (**Table 1.1**) [25-28]. Compared with other countries, in China, the prevalence of asthma, allergic rhinitis and food allergy among children under 2 years of age seemed to be relatively lower, only 0.2%, 0.9%, and 2.5%, respectively (year 2014). However, several possible reasons for the differences observed between reported prevalence figures in different countries should be considered, such as ethnicities, socio-economic status, different diagnostic guidelines, substantial heterogeneity in definitions of outcomes in various studies, data collection methods (self-reported or clinical records), etc.

Table 1.1 The prevalence of allergic diseases in preschool-aged children in different countries

References	Countries	Population	Sample size	Year	Age	Atopic diseases	Prevalence	Measurement
Wang et al. **[22]**	China	33 cities of China	10,693	2014	0-24 months	Food allergy	2.5%	Parent report of doctor diagnosis
						Asthma	0.2%	
						Allergic rhinitis	0.9%	
						Eczema	18.5%	
Hill et al. **[29]**	USA	The Children's Hospital of Philadelphia care network	187,039	2001-2013	0-3 years	Asthma	12.3%	ICD-9
						Allergic rhinitis	5.6%	
						Eczema	7.3%	
Uphoff et al. **[30]**	UK	BiB	1,716	2007–2010	0-4 years	Asthma	13.5%	Parent report of doctor diagnosis
Stratakis et al. **[23]**		SWS	2,466	2001-2004	0-2 years	Wheeze	44.0%	ISAAC questionnaire
Grimshaw et al. **[31]**		EuroPrevall birth cohort (UK)	823	2008-2010		Food allergy	5.0%	DBPCFC
Schmidt et al. **[32]**	Finland	DIABIMMUNE	1,574	2011-2013	0-5 years	Wheeze	16.4%	ISAAC questionnaire
						Allergic rhinitis	29.5%	
					at 3 years	Eczema	22.9%	
Peters et al. **[24]**	Australia	HealthNuts	4,291	2007-2011	Before 1 year	Food allergy	13.0%	OFC
						Wheeze	16.2%	Parent report of doctor diagnosis
						Eczema	27.6%	
				2011-2015	At 4 years	Food allergy	3.8%	OFC
						Asthma	13.8%	Parent report of doctor diagnosis
						Allergic rhinitis	3.6%	
						Eczema	29.0%	
Ballardini et al. **[33]**	Belarus	PROBIT	11,668	2002-2005	Before 1 year	Eczema	5.0%	Skin examinations
Miyake et al. **[26]**	Japan	Fukuoka Child Health Study	2,004	2006-2007	2-3 years	Wheeze	22.1%	ISAAC questionnaire
						Asthma	9.0%	
						Eczema	17.5%	
Kaneko et al.		Kawasaki city	23,969	2016	1-5 years	Food allergy	5.3%	Primary care doctors

[34]								diagnosed
Loo et al. **[25, 35]**	Singapore	GUSTO	632	2012-2013	0-3 years	Wheeze	40.8%	Parent report of doctor diagnosis
			576			Eczema	27.3%	
			577			Allergic rhinitis	39.2%	
			769		18 months	Food allergy	2.7%	
Uphoff et al. **[30]**	18 European and US birth cohorts*		60,774	Born between 1996-2011	0-2 years	Wheeze	29.2%	ISAAC questionnaire
					3-4 years	Wheeze	15.4%	
						Asthma	9.2%	
					5-8 years	Wheeze	13.1%	
						Asthma	10.5%	
						Allergic rhinitis	5.4%	

18 European and US birth cohorts* Including: ABCD, Netherlands; CONER, Italy; DNBC, Denmark; FLEHS I, Belgium; GASPII, Italy; Generation R, Netherlands; Generation XXI, Portugal; HUMIS, Norway; INMA, Spain; KOALA, Netherlands; Lifeways Cross Generation, Ireland; LucKi, Netherlands; NINFEA, Italy; PELAGIE, France; PIAMA, Netherlands; Project Viva, United States; RHEA, Greece; SWS, United Kingdom

BiB: Born in Bradford; DBPCFC: Positive double-blind, placebo-controlled challenge; GUSTO: Growing Up in Singapore towards Healthy Outcomes; ICD: International Classification of Diseases; ISAAC: International Study of Asthma and Allergies in Childhood; OFC: Oral food challenges; PROBIT: Promotion of Breastfeeding Intervention Trial; SWS: Southampton Women's Survey

1.2 Overweight or obesity in children

World Health Organization (WHO) defines being overweight and obesity (OW/OB) as an excess in fat accumulation to impair health [36]. The prevalence of obesity worldwide has nearly tripled since 1975 [36]. Epidemiological data showed that there were approximately 40 million children under 5 years old with OW/OB in the world in 2018 [36]. OW/OB was a problem predominantly in high-income countries but is now increasing rapidly in some low- and middle-income countries, particularly in urban areas [36]. The WHO reported that in Asia, approximately 50% of the children under 5 years old were OW/OB in 2019 [36]. This prevalence has reached an alarming level that calls for urgent action.

International comparisons of the prevalence of OW/OB are complicated by the different reference standards used to define OW/OB. There are four most commonly used international reference standards for defining childhood OW/OB (**Table 1.2**) [37-40].

Table 1.2 Commonly used reference standards for being overweight and obesity

References	Criteria	Year of publication	Reference population	Sample size	Age range	Year of study	Applicable population
W. H. O. Multicentre Growth Reference Study Group [37]	WHO Growth Standards	2006	Brazil, Ghana, India, Norway, Oman and the US	882	0-24 months	1997-2003	0-5 years
				6,669	18-71 months		
Cole et al. [38]	IOTF	2000 (Revised 2012)	Brazil, UK, Hong Kong, the Netherlands, Singapore, US	192,727	0-25 years	1963-1993	2-18 years
Cole et al. [39]	2000 CDC Growth Charts for the US	2000	US	50,076	2 months-25 years	1963-1994	0-20 years
Kuczmarski et al. [40]	UK1990 growth charts	1990	England, Scotland, Wales	37,700	0-23 years	1972-1994	0-23 years

CDC: Centers for disease control and prevention; IOTF: International Obesity Task Force; WHO: World Health Organization

1.2.1 Prevalence of being overweight or obesity in children in China

The prevalence of OW/OB in Chinese children has increased continuously since 1985, particularly in urban areas [41]. A meta-analysis summarizing the research on the prevalence of OW/OB children and adolescents in China indicated that the prevalence of OW/OB rose from 5.0% and 1.7% in 1991–1995 to 11.7% and 6.8% in 2011–2015, respectively [42]. A study based on health care records of 55,925 Chinese children between 2009 and 2011 showed that the prevalence of OW/OB was 36.4% and 17.7% at 1 year, 26.6% and 11.0% at 2 years of age, 22.3% and 9.3% at 3 years of age, respectively [43]. Data from series from the National Survey on Physical Growth and Development of Children (NSPGDC), which includes the largest nationally representative sample of children under 7 years old in China, showed that the prevalence of being overweight increased from 0.70 to 3.48% and the prevalence of obesity increased from 0.17 to 0.86% between 1985 and 2015 [41].

1.2.2 Prevalence of being overweight or obesity in children in other countries

Table 3 illustrates the variability in the prevalence of OW/OB in children under 5 years in different countries. A review of studies reporting the prevalence of OW/OB in children under 5 years in the WHO European region member states showed that the rates ranged from 1% to 28.6% across member states from 1998 to 2015 [44]. The prevalence of OW/OB in 2- to 5-year-old children in the US and the UK, according to criteria of the International Obesity Task Force (IOTF), was 16.9% and 22.3%, respectively [45]. Children aged 2–5 years in Germany had a lower prevalence of OW/OB (9.5%) than those in the US and UK using the same criteria [46]. The prevalence of OW/OB among Danish infants was 1.2% to 7.3%, much lower than the rates in Ireland (19.4%) and Singapore (12.2%) using WHO growth standards. The rates of OW/OB at 3 years of age in Japanese children was 15.0% and 16.1% in

Australian children on the basis of body mass index (BMI) criteria of the IOTF [28, 47]. Though the lack of consistency in methods makes it difficult to compare the prevalence of OW/OB in children across countries, the rate of OW/OB among children aged under 5 years in China seems lower than that in the USA and Canada (**Table 1.3**).

Table 1.3 The prevalence of being overweight and obesity in preschool children in different countries

References	Countries	Age	Population	Sample size	Year	Overweight	Obesity	Standards
Yu et al.[48]	China	0-5 years	CNNHS	32,862	2010-2013	8.4%	3.1%	WHO Growth Standards
Lang et al. [45]	USA*	2-5 years	NHANES	14,540 (2-17 y)	1999-2016	24%#	11.9%	2000 CDC Growth Charts for the US
		2-5 years				21.2%#	11.3%	UK1990 growth charts
		2-5 years				16.9%#	5.6%	IOTF
Biro et al. [49]	Canada	0-2 years	CPCSSN database	1,127	2013	18%#	5.5%	WHO Growth Standards
		2-5 years		1,842		18.2%#	4.0%	
		0-5 years		2,969		18.1%#	4.5%	
Ramasubramanian et al. [50]	UK*	3 years	Millennium Cohort	10,465	2003	-	5.5%	IOTF
Lang et al. [45]		2-5 years	HSE	33,563 (2-17 y)	1999-2016	31.8%#	14.2%	2000 CDC Growth Charts for the US
		2-5 years				27.6%#	13.2%	UK1990 growth charts
		2-5 years				22.3%#	6.1%	IOTF
Jabakhanji et al. [51]	Ireland	9 months	GUI	10,733	2008	19.4%	19.5%	WHO Growth Standards
		3 years		9,349	2011	20.4%	22.7%	
Rajput et al. [52]	New Zealand	4-5 years	B4School Check	168,744	2009-2012	18.3%	16.3%	WHO Growth Standards
						17.2%	5.2%	IOTF
Hoffmann et al. [46]	Germany	2-5 years	KiGGS	3,288	2003-2006	9.5%#	-	IOTF
Schmidt Morgen et al. [53]	Denmark	3-15 months	DNBC	155,635	1998-2010	1.2-7.3%#	0-1.2%	WHO Growth Standards
			DHVCHD					
Nichols et al. [47]	Australia	2 years	MaCHS database	129,266	2007	12.9%	2.0%	IOTF
		3.5 years		96,164		16.1%	3.2%	
Kuniyoshi et al. [28]	Japan	3 years	GEJE Affected Areas	15,563	2012-2014	15%#	1.1%	IOTF
Cai et al. [27]	Singapore	12 months	GUSTO	727	2010-2012	12.2%	2.3%	WHO Growth Standards

Jones et al. [44]	35 WHO European region member states	0-5 years		317,763	1998-2015	1.2-28.6%[#]		WHO Growth Standards IOTF UK BMI German BMI reference Dutch reference growth curves

[#] Overweight, including obesity

[*] Sample size is the number of 2-17 years children and adolescents, the number of 2-5 years children was not provided.

BMI: Body Mass Index; CDC: Centers for disease control and prevention; CNNHS: Chinese National Nutrition and Health Survey; CPCSSN: Canadian Primary Care Sentinel Surveillance Network; DHVCHD: Danish Health Visitors Child Health Database; DNBC: Danish National Birth Cohort; GEJE: Great East Japan Earth-quake; GUI: Growing Up in Ireland; GUSTO: Growing Up in Singapore towards Healthy Outcomes; HSE: Health Survey for England; IOTF: International Obesity Task Force; KiGGS: German Health Interview and Examination Survey for Children and Adolescents; MaCHS: Maternal and Child Health Services; NHANES: National Health and Nutrition Examination Survey; WHO: World Health Organization

1.3 Infant formula consumption

1.3.1 The prevalence of infant formula consumption

Formula consumption under 6 months of age is very common worldwide despite international guidelines. In a multi-country study among 90 low- and middle-income countries, there were 26 countries where formula feed was introduced within 6 months in more than 20% of infants; in 5 of these countries over half of the infants started having formula feed within 6 months [54]. In recent decades, urbanization and rapid economic growth have led to dramatic changes in the lifestyle of the Chinese population, including the feeding practice of infants. The Chinese National Nutrition and Health Survey (CNNHS), a national representative survey conducted in China in 2013, reported that the exclusive breastfeeding (EBF) rate under 6 months was 20.7%, in urban-metropolis the rate was only 18.9%, which was much lower than that in 1985 (33.6%) [55, 56]. Meanwhile, infant formula consumption has been increasing dramatically in recent decades [57]. A study on changes in feeding patterns in Chinese city infants showed that from 1996 to 2007, the mixed feeding rate of 42-day-old infants in the urban area increased from 11.8 to 33.3% [58]. An increasing number of Chinese parents, influenced by formula advertisements which portray formula to be as good as or better than breast milk, introduce the products either as the only food or as supplementation to their infants at an early stage [59-63]. A population-based birth cohort study of China showed that in the first month of life, formula feeding (FF) rate was 27.1% and mix feeding rate was 31.7%; at the third month, FF rate was 32.5% and mix feeding rate was 34.1%; at the sixth month FF rate was 36.7% and mix feeding rate was 35.3% [316]. A study describing global trends and patterns of commercial milk-based formula sales reported that between 2008 and 2013, China has undergone the most rapid increase in formula sales in the world, growing by

106.0%, and widespread usage is a major public health problem [57, 64]. The observed increase in the infant formula consumption in the Chinese population raises serious concerns for child health and calls into question the effectiveness of current infant feeding policy and regulatory regimes on commercial products for breast milk substitutes.

1.3.2 The factors related to a mother's likelihood of formula feeding

Feeding practice can be influenced by many factors related to socioeconomic status, culture, and the environment [65-67]. The factors associated with mothers' decisions to formula-feed their infants have been reported, such as family support, feelings that formula feeding was more convenient and acceptable, previous feeding experience, and not receiving information about the benefits of breastfeeding [68, 69]. A study reporting the factors associated with Chinese mothers' decision to formula feed showed that the majority of women who chose formula feeding thought they had insufficient breast milk [70]. This study also found that some mothers had the belief that formula is more nutritious than breast milk [70]. This belief has also been described in studies from other countries [68, 71].

1.4 The potential mechanistic links between early infant formula introduction and the development of allergic diseases

Epidemiological studies have identified that early exposure to certain nutrients may influence the development of allergic diseases, although genetic and other environmental factors may also play a role [5, 7-9, 72]. The cellular and molecular mechanisms leading to the development of allergic diseases and how alterations in these mechanisms might promote the development of allergy are complex. Thus far, the nutritional impacts on allergy development have not been completely understood, although the influence on the immune system and gut microbiome has been hypothesised recently [73].

1.4.1 Early infant formula introduction and immune development and allergy

The function of the immune system is to protect the host against pathogenic organisms and also to ensure tolerance to the host “self”, food, commensal bacteria and other environmental components [74]. However, a breakdown of the complex pathways of the immune system can promote the development of inflammatory diseases, including atopic disorders [74]. Neonatal immunity is immature and still developing, which is different from that of adults [75]. During the first three months of life, the cellular immune system matures rapidly, but it is still vulnerable. The maturation process can be influenced by multiple factors, among which nutrition is considered as a significant element [73-75].

Early diet during infancy is the source of novel food antigens to which the immune system must become tolerant. Various dietary components, such as protein, fatty acids, nutritional antioxidants, prebiotics and probiotics may be involved in modulating the maturation and responses of the immune system, and manipulating T-helper 1 and T-helper 2 (Th1/Th2) balance [76, 77]. In 1986, Mosmann et al. proposed the Th1/Th2 balance hypothesis from observations in mouse T-helper cells expressing differing cytokine patterns [78]. Currently, much of the research indicated that the polarization of the Th1/Th2 balance is associated with many allergic and autoimmune disorders [79]. For avoiding the rejection of the immunologically compatible fetus, the immune system polarizes the Th cells towards a dominance of Th2 response in both mothers and fetuses. [75]. In addition, antigen-specific T cells are detectable in every newborn infant's cord blood, suggesting existing intrauterine sensitization [80]. The immune system down-regulate the pre-existing Th2 dominance promptly at and soon after birth in order to make the neonatal immune system competent and functional [75]. If the immune system cannot down-regulate the dominance of Th2 response effectively to maintain immune homeostasis, an allergic phenotype may develop [75]. Atopic

allergy, including asthma, eczema or atopic dermatitis, allergic rhinitis, and food allergy, is a Th2 cell-mediated disease. The timing of introducing infant formula and solid foods offer windows during which nutrition might affect the development of the immune system of the young infant [74].

Several potential mechanisms involved in the link between infant formula introduction and allergy have been investigated. During early infancy, particularly in the first 3 months when the immune system is immature and still developing, excessive protein provided by infant formula, in addition to the absence of bioactive substances and bifidobacteria, synergistically result in insufficient regulatory T-cells (Tregs) maturation. Consequently, Tregs insufficiency induces Th2 cells differentiation to promote the development of atopic diseases [77, 81]. Long-chain polyunsaturated fatty acids (LC-PUFA) derivatives can enhance or attenuate the inflammatory processes at various points in the cycle, which involves interfering with the Th1:Th2 cytokine ratio [82]. The lipid content is different between human milk and cow's milk formula. Compared with human milk, cow's milk has a smaller proportion of unsaturated fatty acids and a lower concentration of essential fatty acids [83]. Moreover, LC-PUFAs in human milk can be better absorbed than those in cow's milk [83]. Thus, during immune maturation, early introduction of infant formula might influence the intake of LC-PUFA and their derivatives in the body, which are capable of modulating Th1- or Th2-like cytokine patterns to induce allergic diseases.

1.4.2 Infant formula introduction and gut microbiome and allergy

Recently, an increasing number of studies have indicated that the gut microbiome plays a major role in the development of the host immune system during early life, and therefore can modify the risk of allergic diseases [84, 85]. Factors that have been suggested to influence the bacterial colonization process and diversification of infant's gut include maternal infection or

illness, gestational age, delivery mode, antibiotic use, type of feeding, and the surrounding environment [86]. Diet plays a critical role in the composition of the gut microbiome, especially in the early infancy, when the bacterial community colonization has not yet been established. Evidence has shown that the intestinal microbiome differed between breastfed and formula-fed infants [87]. Compared with formula-fed infants, breastfed infants' gut contains a larger number of bifidobacteria and smaller quantities of some facultative anaerobic bacteria such as staphylococci, streptococci, lactobacilli enterococci, and enterobacteria [86, 87]. It has been reported that bifidobacteria species have anti-inflammatory effects through upregulating Interleukin-10 (IL-10) production by dendritic cells (DC) and decreasing expression of the CD80 and CD40 [88]. The absence of bifidobacteria in cow's milk formula has also been reported to be related to insufficient Treg maturation which promotes the development of allergic diseases [77].

1.5 The potential mechanistic links between infant formula introduction and the development of obesity

A number of hypotheses have been raised on the potential mechanism in the relationship between the introduction of infant formula and the development of childhood excessive weight gain.

1.5.1 Formula introduction and intakes of energy and protein

Breast- and formula-fed infants have a different suckling pattern and suckling frequency, which might modulate later body size [89, 90]. Formula-fed infants seem to have a higher feeding volume than breastfed infants [89]. Furthermore, infant formula contains a higher average caloric density than the mean values of human milk [83]. In addition to calories, there is also an obvious difference in protein content between formula and human milk [91].

Cumulative evidence has shown that high protein intakes during early life were associated with early occurrence of adiposity rebound and high BMI during childhood [92]. The "early protein hypothesis" was proposed by Koletzko et al., in which they described that during early life, a high protein intake provided by infant formula in excess of metabolic requirements might give rise to the secretion of insulin and insulin-like growth factor-1 (IGF-1), which can enhance the infancy growth and adipogenic activity [93]. Excessive protein intake may also decrease lipolysis [93]. Furthermore, the introduction of infant formula is associated with the timing of complementary food introduction [94]. Previous evidence indicated that early introduction of infant formula was associated with early introduced complementary food [95], which caused increased daily energy intakes and predisposed the infants to increased obesity risk in later life [96-98].

1.5.2 Formula introduction and gut microbiome and metabolism

Early-life diet plays an important role in the composition of the intestinal ecosystem [86]. Evidence showed that the Bifidobacteria and Lactobacillus were predominant in breastfed infants, whereas the Ruminococcus was predominant in formula-fed infants [99]. In addition, the bifidobacterial population of breastfed infants was more stable and uniform than those of formula-fed infants [100]. The gastrointestinal microbiome composition also plays a critical role in host metabolism [101]. Both animal and human studies have indicated that the composition of the gut microbiome was associated with the risk of obesity [102-104]. The intestinal ecosystem is essential for maintaining host physiology, and its alteration can influence the immune system and metabolism, which links to the risk of development of metabolic diseases [84]. For example, the bacteria in the gut ferment dietary fibres into short-chain fatty acids (SCFAs), whose interaction with G-protein-coupled receptors (GPCRs) influences insulin sensitivity in several tissues, including liver, muscle, and adipose tissue,

thus regulating energy metabolism [101]. A case-control study has shown that compared with nonobese children, obese children have a higher amount of Escherichiacoli and a lower amount of Bifidobacteria [105]. In children, a high concentration of Bifidobacteria during the early stage of life has been reported to have protective effects on later obesity [106]. Therefore, the early introduction of infant formula might influence the composition and ecosystem of the gut microbiome, which links to the development of childhood overweight or obesity.

1.6 The potential relationships between adiposity and allergic disorders

The relationship between childhood obesity and the development of allergy has been reported previously [107-109]. The PROBIT study from Belarus found an association between weight gain velocity between 0 to 3 months and ever having wheezed by 6.5 years [110]. Another study from the United Kingdom showed that higher weight gain from birth to 6 months was associated with the increased risk of atopic wheeze by 3 years of age [111]. However, a birth cohort study in an Asian population reported a reverse association that higher weight gain in the first 15 months of life was associated with a reduced risk of allergen sensitization [112]. Existed evidence suggests that childhood obesity is related to extensive changes in the levels of inflammatory and anti-inflammatory proteins and cytokines, as well as immune cells and their behaviour, which might cause or exacerbate allergic diseases [107]. Furthermore, in 2009, Koletzko et al. proposed the "early protein hypothesis" that early formula feeding can lead to excessive protein intake inducing later obesity [113]. On the basis of this theory, a view of the cellular mechanisms to explain the links between infant formula feeding and the development of atopy and obesity has been proposed [77]. Infant formula feeding induces uncontrolled excessive protein intake, which overacts the infant's mammalian target of rapamycin complex 1 (mTORC1) signalling pathways. Overactivated mTORC1 enhances

S6K1-mediated adipocyte differentiation, but negatively regulates the growth and differentiation of FoxP3+ regulatory T-cells (Tregs), which are deficient in atopic individuals. Thus, formula feeding is considered to be associated with the development of mTORC1-driven diseases such as allergy and obesity [77].

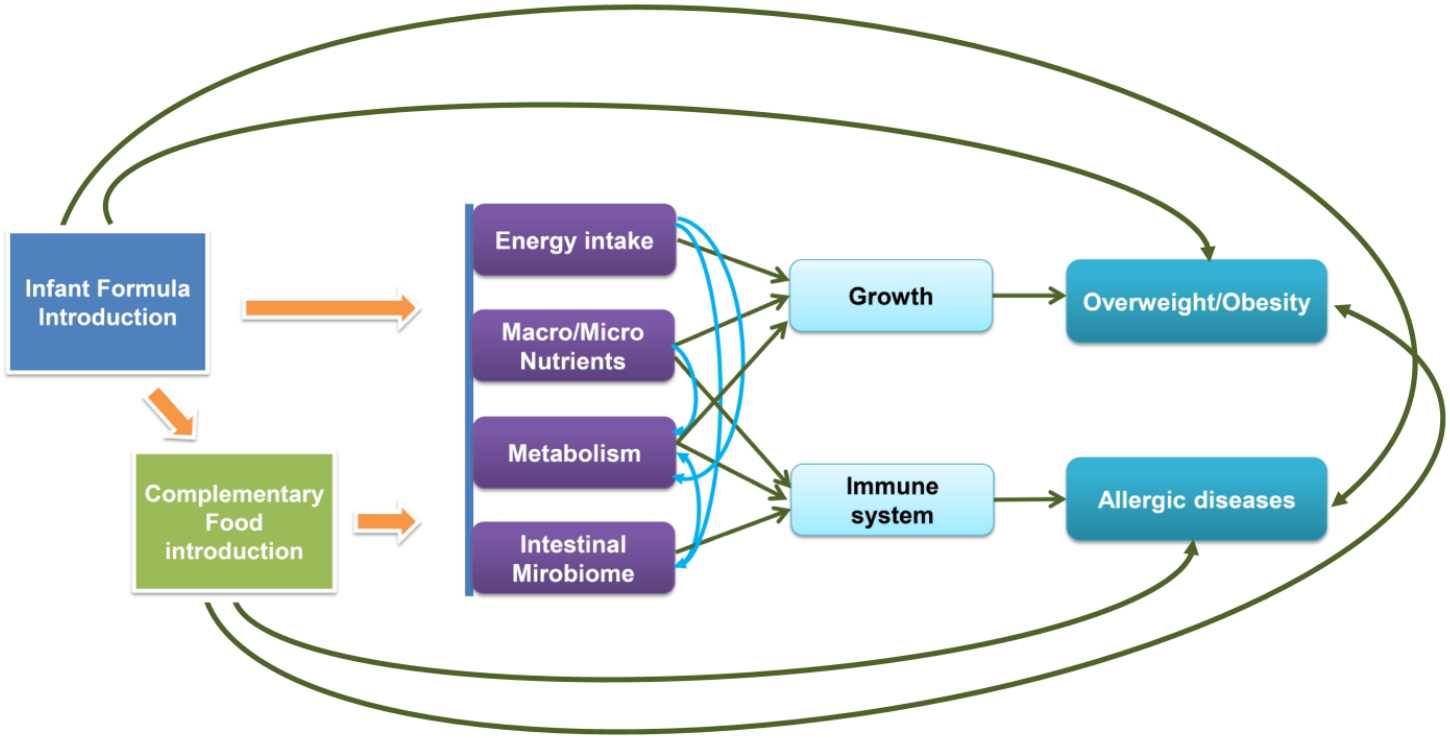


Figure 1.1 The potential mechanistic links between infant formula feeding and the risk of allergic diseases and OW/OB

1.7 Feeding guidelines on breastfeeding and formula feeding

Adequate nutrition during infancy is not only crucial for the growth and development of children but also has long-term effects on health during adulthood [91]. In 2003, the World Health Organization (WHO) and United Nations Children's Fund (UNICEF) jointly developed the Global Strategy for Infant and Young Child Feeding to raise global awareness of the impact of feeding practices on the health of infants and young children [114]. Many countries and authorities have published infant feeding guidelines for their health professionals and practitioners following the WHO feeding guidance [91, 115-123]. The WHO recommended that all infants should be fed exclusively on breast-milk until six months of age [114]. The term exclusive breastfeeding (EBF) means that an infant receives only breast milk and no other liquids or solids, not even water, with the exception of oral rehydration solution, drops or syrups consisting of vitamins, minerals supplements or medicines [83]. Then many countries followed this recommendation and recommended continuing breastfeeding beyond the first year of life [115, 120, 121, 124, 125]. However, this has raised concerns on whether six months' EBF reliably meets the requirements of growth for all infants [126, 127].

With the rapid economic development and urbanization, the consumption of commercial infant formula has dramatically increased worldwide, and many infants receive infant formula before six months of age [35, 64, 128-136]. Some national feeding guidelines recommended that the infants who are not breastfed should be fed infant formula, particularly iron-fortified infant formulas, for the first year of life [91, 115, 121, 137]. Although commercial infant formulas are the most appropriate alternatives for feeding the infants who cannot or should not be breastfed, the potential risks associated with FF should be considered.

This section focuses on reviewing feeding guidelines from different authorities, including the WHO, American Academy of Pediatrics (AAP) of USA, Government of Canada (GOC), National Institute for Health and Care Excellence (NICE) of UK, Food Safety Authority of Ireland (FSAI), National Health and Medical Research Council (NHMRC) of Australia, Ministry of Health (MH) of New Zealand, India Academy of Pediatrics (IAP), Ministry of Health, Labour and Welfare (MHLW) of Japan and Chinese Nutrition Society (CNS) of China. These infant feeding guidelines are regarded as authoritative in their respective countries and perhaps beyond.

1.7.1 Recommendations for breastfeeding duration

Most countries recommended EBF from birth until six months of life following the WHO guidance (**Table 1.4**). Only the FSAI of Ireland recommended that infants should be breastfed exclusively for the first four to six months of life and stated that some infants might benefit from a slightly earlier introduction of solid foods but no earlier than four months of age [117]. The WHO recommended that breastfeeding should continue throughout the second year and longer in the population with high rates of infection [91]. The GOC, FSAI, MH, IAP, and CNS recommended breastfeeding for up to two years or beyond as well [116-120]. The AAP and NHMRC recommended that breastfeeding should be continued until 12 months of age and beyond with appropriate complementary foods [115, 121]. The NICE suggested that breastfeeding should be continued for as long as the mother and the baby wish [122]. However, the data from many countries have shown that the current breastfeeding duration is far below the recommendations [115, 138-141].

1.7.2 Recommendations for the timing of formula feeding

Most of these feeding guidelines recommended that when infants were not breastfed, they should be fed infant formulas (**Table 1.4**). The WHO and AAP particularly recommended iron-fortified infant formulas [91, 115, 118, 120, 121]. The guidelines of FSAI and CNS recommended using infant formula as the supplement of breastfeeding after six months of age [116, 117]. The CNS also mentioned that feeding infant formula before six months of age was not beneficial for the baby's health [116]. The MH of New Zealand also pointed out that supplementing breastfeeding with formula should be strongly discouraged [120]. The WHO, AAP, FSAI, MH and NHMRC recommend that when the baby is not breastfed, milk-based infant formula should be fed through the first year of life [91, 115, 117, 120, 121].

Table 1.4 Summary of recommendations on the duration of breastfeeding and the timing of infant formula introduction in the infant feeding guidelines from different authorities

Country	Authorities	Guidelines	Year	Duration of breastfeeding		Infant formula	
				Exclusive breastfeeding	Any breastfeeding	Timing of introduction	Duration
	WHO	Feeding and nutrition of infants and young children *Guidelines for the WHO European region, with emphasis on the former Soviet countries*	2003	4-6 months from birth	At least 12 months Populations with high rates of infection: up to 2 years of age or beyond	If infants are not breastfed, they should be fed a commercial iron-fortified infant formula	In the absence of breastfeeding, it should be the main fluid in the diet for the first 9 months and possibly even beyond
		Infant and young child feeding *Model Chapter for textbooks for medical students and allied health professionals*	2009	The first 6 months	Up to 2 years of age or beyond		
USA	AAP	Pediatric Nutrition 7th Edition	2014	The first 6 months	At least 12 months.	In the absence of human milk	Iron-fortified infant formulas are the most appropriate substitutes for feeding healthy, full-term infants during the first year of life.
Canada	GOC	Principles and recommendations for infant nutrition from birth to six months	2015	The first 6 months	-	Recommend cow milk-based, commercial infant formula for an infant who is not exclusively fed breast milk.	-
		Nutrition for Healthy Term Infants: Recommendations from Six to 24 Months	2015	-	Up to 2 years of age or beyond	-	-

UK	NICE	Maternal and child nutrition	2008	The first 6 months	As long as the mother and baby wish	Mothers should have access to independent advice from a qualified health professional on the use of infant formula. This should include information on the potential risks associated with formula-feeding and how to obtain ongoing advice at home	-
Ireland	FSAI	Scientific Recommendations for a National Infant Feeding Policy,2nd Edition	2011	4-6 months from birth	Up to 2 years of age or beyond	For the infant who is not breastfed follow-on formula may be used from the age of six months	Suitable milk-based infant formula should be used during the first year of life.
Australia	NHMRC	Infant Feeding Guidelines	2012	The first 6 months	At least 12 months.	When infants are not breastfed	Cow's milk-based formula is suitable for the first 12 months of life
New Zealand	MH	Food and Nutrition Guidelines for Healthy Infants and Toddlers (Aged 0-2) A background paper	1995 revised in 2012	The first 6 months	Beyond six months	When infants are not breastfed	If the baby is not fed breast milk, then use an infant formula as the milk source until the baby is one year of age.
India	IAP	Infant and Young Child Feeding Guidelines (IYCF)	2004 revised in 2016	The first 6 months	Up to 2 years of age or beyond	-	-
China	CNS	Feeding Guidelines for Infant Under Six Months	2016	The first 6 months	-	Using as the supplement of breastfeeding after 6 months of age. Feeding infant formula before 6 months is not good for the baby's health.	-
		Feeding Guidelines for Infant From Seven to 24 Months	2016	-	Up to 2 years of age or beyond	-	-
Japan	MHLW	Breastfeeding and weaning assistance Guide	2007	The first 6 months	-	-	-

AAP: American Academy of Pediatrics; CNS: Chinese Nutrition Society; FSAI: Food Safety Authority of Ireland; GOC: Government of Canada; IAP: India Academy of Pediatrics; NHMRC: National Health and Medical Research Council; NICE: National Institute for Health and Care Excellence; MH: Ministry of Health; MHLW: Ministry of Health, Labour and Welfare; WHO: World Health Organization

1.7.3 Evidence supporting recommendations from national and international authorities

Exclusive breastfeeding

The advantages of breastfeeding on the infants' health described in these guidelines included decreased morbidity and mortality from infectious diseases, lower risk of allergy, better neurodevelopment, and long-term protective effects on OW/OB, diabetes, cancer/leukaemia, sudden infant death syndrome (SIDS), and cardiovascular diseases [91, 115-125, 137, 142-147]. Though most countries just follow the recommendations of the WHO, some of them developed their own feeding guidelines by synthesizing current evidence. Systematic reviews and cohort studies were the most common types of evidence used to develop recommendations on breastfeeding in these guidelines. The Guidelines of the USA, Canada, UK, Ireland, Australia, and New Zealand included results from cohort studies in their populations in formulating recommendations on breastfeeding. However, there was a limited number of domestic studies to underpin national recommendations on breastfeeding in the feeding guidelines of China, India, and Japan [116, 142, 145, 146, 148]. Feeding practice is likely to be influenced by complex interactions between socioeconomic status, culture, and the environment [65-67]. Thus, evidence from domestic studies, taking into account social conditions and culture should be considered as the reference standard for recommendations in all national feeding guidelines.

One systematic review commissioned by the WHO regarding the effects of EBF duration on the health outcomes of the child or mother was used as crucial evidence in many feeding guidelines [149]. Following this systematic review, the WHO revised the recommendation for EBF duration from 4-6 to 6 months for all infants. Then many countries changed their

recommendations to six months based on the WHO recommendations. However, potential biases within this systematic review are of concern. The systematic review indicated that the infants who were exclusively breastfed for six months had a lower risk of gastrointestinal and respiratory infection than those who were partially breastfed as of three or four months [149]. These conclusions were based on observational studies, and most of them came from low- and middle-income countries with poor sanitation [150-152]. Data from a nationally representative survey in the USA, the Third National Health and Nutrition Examination Survey (NHANES III), showed a decreased risk for respiratory tract infection in children who were exclusively breastfed for six vs. four months [153]. However, there might be reverse causality in this association. Infants with severe infection were likely to experience loss of appetite with reduced breast milk consumption that caused shorter breastfeeding duration [154]. By contrast, healthy infants with acceptable growth trajectory were likely to be exclusively breastfed continually [154].

A systematic review indicated that though little clear evidence was identified to allow for definitive conclusions on recommendations for the age of complementary foods introduction, exclusive breast milk feeding from birth until six months might not give sufficient nutrition for optimal growth and development of certain populations [155]. Another expert review for EFSA also concluded that introducing complementary food into the diet of healthy, term infants across the EU between four and six months of age was safe and did not induce a risk for adverse health effects [156]. In addition, there are some concerns about whether EBF for six months would appropriately meet the iron requirements of some infants. The systematic review underpinning the WHO recommendation indicated that compared with infants exclusively breastfed for four months, six months' EBF was associated with a lower mean haemoglobin and ferritin

concentrations [149]. But the authors explained that the evidence came from developing-country settings where iron stores of the newborn may be suboptimal [149]. Data from NHANES III also showed that compared with 4-6 months, infants exclusively breastfed for 6 months were more likely to have iron deficiency [157]. Based on the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial conducted in the Republic of Belarus, a series of studies examining the benefits of breastfeeding have been conducted [158-167]. However, data from the PROBIT cohort did not show significant long-term beneficial effects of 6 months' EBF compared with 3 months on child health [161, 162, 166, 167]. Fewtrell and colleagues stated that the proposed beneficial effects of 6 months' EBF on the risk of infection need to be weighed against the other areas of clinical concern including a higher risk of iron deficiency anaemia, food allergy, and coeliac diseases [126]. However, there were immediate objections [168, 169]. Wright suggested that the effects of 6 months' EBF on substantial reductions in infectious diseases were more important than the risk of anaemia or allergy [169].

An important issue is whether the WHO's revision on the recommendation for EBF duration from 4-6 to 6 months is generalisable to all populations. The main advantage of long EBF is preventing infection in infants. However, most of the evidence for this recommendation came from observational studies in low-income countries where the sanitary conditions are compromised. In addition, there are only a limited number of studies involving the delayed introduction of complementary foods after six months, which has an inextricable link with EBF. Therefore, more data are needed to justify currently recommended duration of EBF, particularly in high-income countries with good sanitary conditions and living environment.

Timing of introduction infant formula

As is well known, there is a reverse correlation between FF and EBF. Adding infant formula to the infant diet appears to be detrimental to breastfeeding duration [170-172]. Longer EBF means later introduction of other foods, including infant formula. However, for some infants, the infant formula is the sole source of early nutrition and is not referred to as a complementary food. Therefore, there is no specific recommendation on the appropriate timing of infant formula introduction to the infant diet in feeding guidelines. Most of these guidelines just recommend that when infants are not breastfed, the infant formula should be used. The NICE in the UK stated that the commissioners and managers responsible for maternity, children's and primary care services should ensure that a qualified health professional tells the potential risks of formula-feeding to the mothers who plan to feed formula to their babies [122]. Ministry of Health of New Zealand also emphasized that supplementing breastfeeding with infant formula should be strongly discouraged [120]. However, we did not find any evidence on the effects of FF on children's health in the chapter on FF in these feeding guidelines. In the chapter of breastfeeding, the evidence derived from studies of beneficial effects of breastfeeding found that FF or mix feeding was associated with a higher risk of infection in infants compared with EBF [173]. However, most of these studies were conducted in low- and middle-income countries where infant mortality was largely attributable to infection.

With increasing consumption of infant formula worldwide, the appropriate timing of infant formula introduction to the infant diet should be provided in feeding guidelines based on the scientific evidence. In addition, the evidence used in these guidelines (guidelines in Table 1.4) was over a decade old and may need to be updated.

1.8 Objectives

The aim of this thesis was to investigate the relationships between the timing of infant formula introduction and the risks of developing allergic diseases and OW/OB in children under 3 years old. Meanwhile, the timing of complementary foods introduction was additionally considered in our analyses.

Chapter 2 describes the general methods of the studies included in this thesis and the Born in Guangzhou Cohort Study (BIGCS). Data from primary research included in this thesis were all from this cohort study. **Chapter 3** is a systematic review and meta-analysis on the association between cow's milk (CM) or cow's milk formula (CMF) introduction and risk of allergic diseases in children. **In Chapter 4,** I report a prospective cohort study on the relationship between the timing of infant formula introduction and risk of wheezing and eczema before 1 year of age. **Chapter 5** investigates the association between patterns of foods introduction in the first year of life and risk of atopic conditions before 3 years of age. **Chapter 6** studies the influence of early infant formula introduction and body growth before 3 years of age. In addition, the associations of the timing of infant formula introduction with the risks of OW/OB at 1 year and 3 years of age were examined.

Chapter 2: General Methods

A detailed description of the methods of each study will be provided in individual chapters. Therefore, the general methods included in this thesis are described briefly in this chapter. In addition, as the study population included in this thesis was all from the Born in Guangzhou Cohort Study (BIGCS), a brief description of BIGCS is provided in this chapter.

2.1 Systematic review (Chapter 3)

We performed a study to systematically review the evidence describing the association of timing of CM or cow's milk formula (CMF) introduction with the development of atopic diseases during childhood. The protocol of this systematic review was registered in PROSPERO, registration ID CRD42018102108.

2.2 Born in Guangzhou Cohort Study (BIGCS)

2.2.1 Introduction

The Born in Guangzhou Cohort Study (BIGCS) is a population-based prospective study of the mother and child living in the urban setting of Guangzhou, China [174]. The BIGCS is a long-term research project from the prenatal period to adulthood to examine the environmental influences on maternal and child's health. It is the largest ongoing birth cohort in China. In this study, the environmental factors are defined broadly to include biological and chemical factors, physical surroundings, social, economic, cultural, educational, family, and behavioural influences. The BIGCS aims at exploring the potential causes of many childhood diseases and disorders by linking a variety of environmental factors to different health and developmental outcome measures.

2.2.2 Study population

The BIGCS was set at two campuses of the Guangzhou Women and Children's Medical Center (GWCMC), which is one of the best-equipped medical service providers of its kind in southern China. Between the two campuses, there are 12,000-15,000 deliveries annually. In the antenatal outpatient clinic setting of GWCMC, trained study personnel invited the participation of pregnant women attending for early pregnancy examination. The eligible criteria of BIGCS are including (1) gestational week less than 20 weeks; (2) residence in Guangzhou (3) intending to give birth at GWCMC. Women who were not ethnic Chinese or unable to complete questionnaires in Mandarin are excluded. Informed consent was obtained from all participants. Participation is entirely voluntary, and the participants can withdraw their consent at any time. The recruitment of BIGCS was commenced in February 2012, with an overall participation rate of 76.3% [174]. In addition, the population of BIGCS is not representative of the Guangzhou population. 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 generalizability of the findings [174]. However, in this study, a relatively widespread across all social-economic status indicators can be still observed within the participants of BIGCS, hence enabling us to explore the differences in health consequences across different social-economic status strata.

2.2.3 Follow up strategies

Pregnant women who agreed to participate were interviewed at recruitment (<20 weeks), 24-28 and 33-39 weeks of gestation at antenatal clinics to collect epidemiologic data and biological samples. Birth samples, including placental tissue, umbilical cord and cord blood, were collected at delivery. Neonatal birth information such as delivery mode, birth characteristics (e.g. birth

weight, birth length, Apgar score) and perinatal outcomes were obtained from routine medical records. Mother and child were interviewed and examined in GWCMC's child health care clinics at age 6 weeks, 6, 12 and 36 months, and the follow-up interview was planned to be continued until children's adulthood (**Figure 2.1**). Participants unable to attend the appointments in person at the clinic were interviewed on the telephone.

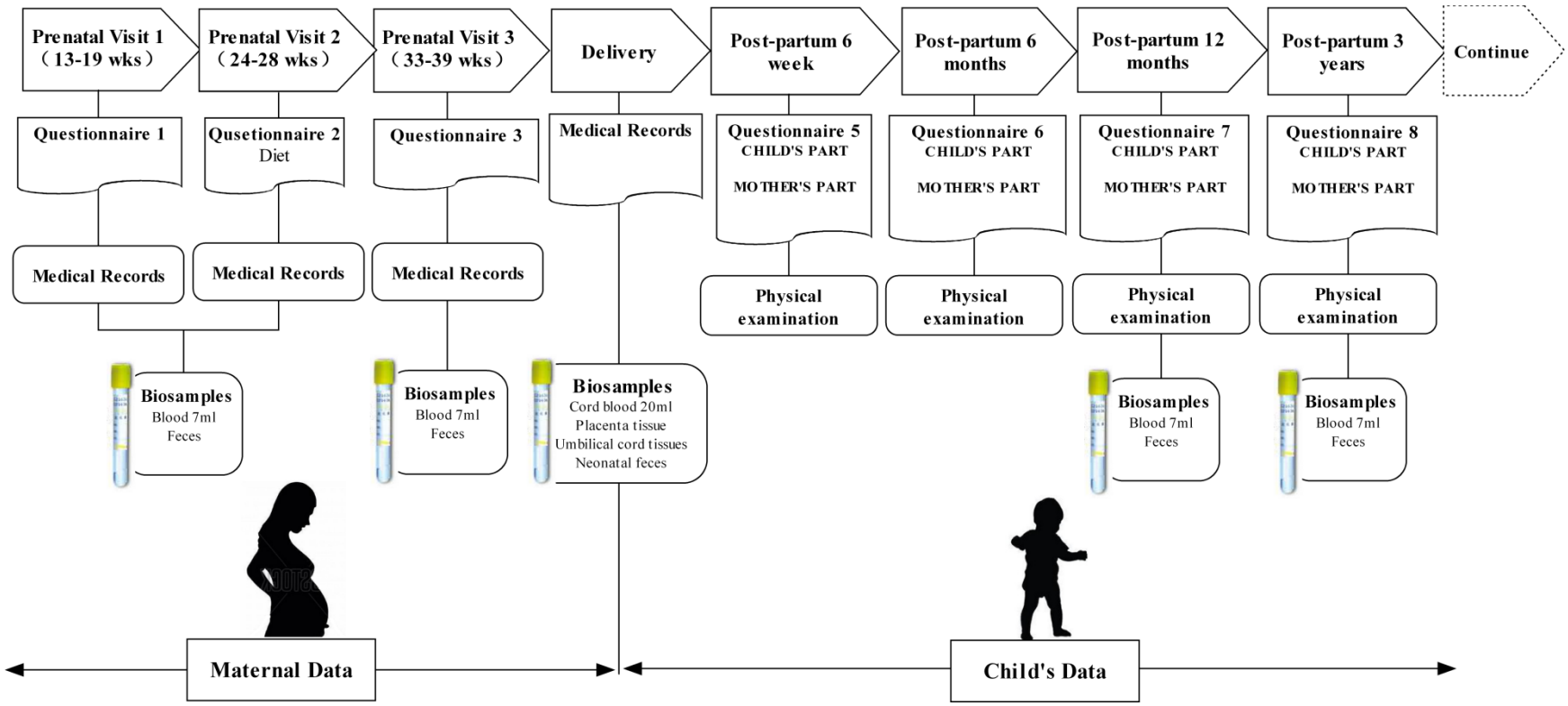


Figure 2.1 Flowchart of BIGCS study design

2.2.4 Data collection

Baseline characteristic information such as maternal age, educational level, income, lifestyle and other health-related factors were obtained by the first questionnaire. The information with the potential for change over time was queried at each visit. Details of question items in the questionnaires are presented in **Table 2.1**.

Table 2.1 Summary of data collection items

Data	Antenatal (weeks)				Postnatal (months)				
Mother	**＜20**	**23-28**	**≥33**	**Delivery**	**1**	**6**	**12**	**36**	**Continue**
Demographics / Social									
Date of birth	√								
Ethnic group	√								
Education	√								
Marital status	√								
Family members	√								
Housing, income	√								
Occupation / employment									
Working status	√		√					√	
Working category, working hours, working posture	√		√						
Working environment	√		√						
Dwelling environment									
Decoration	√								
Pets	√		√						
Cleanness	√		√						
Lampblack, insecticide, incense	√		√						
Lifestyle									
Smoking status, passive smoking status	√		√		√				
Alcohol	√								
Drinking tea	√		√		√				
Beverage	√		√						
Drinking water	√		√						
Physical activity	√		√		√				
Hair Perming and Dying			√						
Health									
Height	√								

Weight	√	√	√	√	√	√	√	√
Blood Pressure		√	√		√	√	√	√
Blood glucose					√	√	√	√
Medical history	√							
General health	√		√			√		
Menstrual cycle	√							
Family medical history	√							
Obstetric history	√							
Medications	√		√		√	√	√	√
Vaginal bleeding during pregnancy	√		√					
Micronutrient supplements	√		√		√			
Mental health	√		√		√	√	√	√
Sleeping quality	√		√					
Diet/FFQ		√			√			
Biological samples								
Blood		√*	√					
Faeces		√	√					
Umbilical cord, placenta				√				
Medical Records								
Clinical test results				√				
Ultrasound data				√				
Pregnancy complications (such as GDM, PIH)				√				
Medication				√				
Delivery date, delivery mode				√				
Father								
Demographics / Social								
Date of birth	√							
Ethnic group	√							
Education	√							
Housing, income	√							
Health								
Height	√							
Weight	√							
Medical history	√							
General health	√							
Family medical history	√							
Biological samples								
Blood	√							

Child	＜20	23-28	≥33	Delivery	1	6	12	36	Continue
Gender				√	√				
Date of birth				√	√				
Birth weight / length, Apgar score				√	√				
Physical measurement									
Weight, body length/ height, head circumference, chest circumference, abdomen circumference, upper arm circumference, skinfold thickness					√	√	√	√	
Bregmatic fontanel					√	√	√		
Blood Pressure					√	√	√	√	
Hip joint examination					√				
Dental eruption						√	√		
Sexual development								√	
Diet									
Breastfeeding					√	√	√	√	
Formula feeding					√	√	√	√	
Food introduction/preference						√	√		
Eating behaviour/dietary restraint								√	
Chinese Herbs					√	√	√	√	
Drinking water					√	√	√		
Micronutrient supplements					√	√	√	√	
Family member, parenting practices					√	√	√	√	
Sleeping					√	√	√	√	
Dwelling environment									
Lampblack, insecticide, incense					√	√	√	√	
Cleanness						√	√	√	
Router use					√	√	√	√	
Passive smoking status						√	√	√	
Pets						√	√	√	
Negative events								√	
Illnesses (fever, skin rash, wheeze) & allergies					√	√	√	√	
Medications					√	√	√	√	
Immunization record					√	√	√		
Neurobehavioral development					√	√	√	√	
Language environment & learning languages								√	
ASQ-III					√	√	√	√	
Gesell							√		
Medical Records									
Clinical test results					√	√	√	√	
Medication					√	√	√	√	

Diagnosis			√	√	√	√
Biological samples						
Blood					√	√
Faeces	√			√		

2.2.5 Ethical approval

Ethical approval for the BIGCS study was obtained from the ethics committees of GWCMC. Individual research using BIGCS data do not require separate ethical approval if only anonymised BIGCS data is used.

2.2.6 Main variables included in the studies within the thesis

Exposures

Feeding practice

The age of first introduction infant formula and other food, and duration of breastfeeding was defined from several variables reported in the self-administered questionnaire at age 6 weeks as well as 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 formula feed (standard cow's milk formula, hydrolyzed formula, preterm formula, other types of formulas) and the age when the child first had the formula. If the child has been fed any food other than milk (cereal or rice porridge, vegetables, fruits, meat, offal, fish, other seafood, egg yolk, egg white), the age when he/she first ate the food was recorded.

Outcomes

Allergic disease

For measurement of allergic disease development in children, self-administered questionnaires were given to the mothers or caregivers when they took their children to the clinic for the follow-up interview at 6 weeks, 6, 12 and 36 months of age. The questions about the occurrence of the symptoms and physicians' diagnoses of allergic diseases, including itchy red rash, wheezing, eczema, asthma, atopic rhinitis, and food allergy, are included in the questionnaires. Although the parents or other guardians who were unable to take the child to attend the appointments at paediatric clinics in person were interviewed on the telephone,

these children were excluded in these studies due to the lack of information on the allergic disease.

Anthropometric Data

Anthropometric measurements were undertaken at each follow-up visit by trained fieldworkers at the clinic. Abdomen circumference and upper arm circumference, in centimetres (cm), was measured in a supine position, using a measuring tape to the nearest 0.1 cm. Length (cm) was measured in a supine position using an electronic scale (Shekel Healthweigh™) to the nearest 0.1 cm. Bodyweight, in kilograms (kg), was measured without shoes and with light clothing (single layer clothes) in a supine position, using a stadiometer (Shekel Healthweigh™) to the nearest 0.01 kg. Body mass index (BMI) measures were also calculated using the formula kg/m^2. Children's gender and age-specific z-scores of BMI were recalculated through the SAS program (WHO-source-code.sas) based on the 2006 WHO growth standards [175]. Given the number of obese children might be insufficient for reliable analyses, overweight and obese children will be combined as being overweight (BMI z-score > +1.00 SD). Z-scores for a child's sex and age for weight and height (length-for-age z-score, LAZ; weight-for-age z-score, WAZ; weight-for-length z-score, WLZ) based on the WHO Growth Charts were also calculated. The extreme or biologically implausible values will be removed.

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 recorded by the baseline questionnaire before 20 weeks of gestation. Obstetrics-related variables, including maternal parity, mode of delivery, gestational age, birth weight, and infant sex,

were extracted from the hospital clinical records. The duration of breastfeeding was also considered as a covariate. Given the proportion of missing data on confounder variables were from 0.1% to 17.3%, analyses based on complete cases may be biased. Thus, we used multiple imputation (MI) analysis to cope with missing data [176]. We used the fully conditional method (FCS) iterative method for imputation by using SAS 9.4. The confounder, exposure and outcome variables of each model were considered as observed covariates and used in the models to impute missing variables. For each imputation model, 10 imputations were run. We ran a procedure call proc mianalyze which combines all the estimates (coefficients and standard errors) across all the imputed datasets and outputs one set of parameter estimates for the model of interest [177].

Chapter 3 Timing of cow's milk or cow's milk formula introduction to the infant diet and atopic risk in children: a systematic review and meta-analysis (Published)

Yuan M, Tan M, Moore D, Shen S, Qiu X, Thomas GN, Cheng K. Timing of Cow's Milk or Cow's Milk Formula Introduction to the Infant Diet and Atopic Risk in Children: a Systematic Review and Meta-analysis. Clinical reviews in allergy & immunology, 2020 Aug;59(1):46-60. doi: 10.1007/s12016-019-08770-9. PMID: 31768874.

Link: https://pubmed.ncbi.nlm.nih.gov/31768874/

Abstract

Infant feeding is an important early-life exposure that may influence the development of atopic disease. The optimal timing of introduction of food allergens, including cow's milk (CM), is not known. This study aims to systematically review the evidence describing the effects of timing of CM or cow's milk formula (CMF) introduction to the infant diet on the development of atopic diseases during childhood. Pubmed, Embase, CINAHL, Cochrane CENTRAL, and CNKI were searched through May 30, 2019. Study screening and data extraction by two reviewers followed the PRISMA statement. Data were extracted independently in duplicate, and meta-analyses were performed by pooling unadjusted and adjusted odds ratio (OR) separately. Heterogeneity was explored using I^2 and publication bias by funnel plots and Begg's tests. In total, 45 studies from 20 countries were included. Meta-analyses using adjusted data showed that no associations were observed between early introduction of CM or CMF and the risk of asthma (<4 vs. ≥4 months: OR 1.16, 95% confidence interval (CI): 0.89, 1.51), wheeze (<6 vs. ≥6 months: OR, 1.15, 95% CI: 0.85, 1.56) and eczema or atopic dermatitis (<6 vs. ≥6 months: OR, 0.96, 95% CI: 0.65, 1.41). Overall, quite little high-quality evidence was identified to allow for definitive conclusions on the association between early CM or CMF introduction and risk of allergic diseases. Our meta-analysis on this topic highlights the specific gaps in information for public recommendations regarding CM or CMF feeding practice in an early stage of life, particularly before 3 months of age.

Keywords: timing of introduction, cow's milk, infant formula, allergy, systematic review, meta-analysis

Manuscript (Published)

Introduction

The prevalence of childhood atopic disease has been increasing considerably in worldwide during the past decades [178]. Infant feeding is a crucial early-life exposure that may influence the development of atopic disease [9]. It is universally acknowledged that breast milk is the preferred nutrition source for the growth of infants, containing essential nutrients (such as fat, carbohydrates, proteins, vitamins, and minerals) and multiple bioactive constituents (such as secretory IgA and IgG) [179, 180]. Early exposure to human milk is conducive to the development of host defence mechanisms and stimulates infant immune systems [181]. The World Health Organization (WHO) recommended that 'infants should be fed exclusively on breast milk from birth to 6 months of age' [182]. However, many infants receive cow's milk (CM) in the form of infant formula very early in life [35, 128-135, 183].

With the rapid development of economy and urbanization, the rate of commercial infant formula consumption has dramatically increased [64]. Most infant formulas are derived from cow's milk, which contains powerful food allergens. Although several studies assessing the role of infant formulas in the risk of atopic disease development have been performed to date, the findings were controversial [9, 35, 72, 128-132, 184, 185]. Previous systematic reviews describing the association between exposure to CM or cow's milk formula (CMF) and childhood allergy had been published but are limited in scope [9, 72, 184, 186]. Early introduction of food allergens, such as peanut, to the infant diet has been recommended in food allergy prevention guidelines [187, 188]. However, the optimal timing of other different allergens introduction, including cow's milk, is not known. Current evidence and theoretical rationales conclude that exposure to food proteins during a critical early window, likely to be 4-6 months of life, could benefit the development of immune tolerance [189], whereas too

early exposure to the allergen may give rise to a higher risk of allergic or autoimmune diseases due to immature gut colonization and local immune networks [190]. The effects of CM or CMF on childhood allergy may vary by the period of exposure.

Thus, the present review aims to systematically summarize the effects of timing of CM or CMF introduction to the infant diet on the risk of developing atopic diseases including wheeze, asthma, eczema or atopic dermatitis, rhinitis or conjunctivitis, food allergy, and cow milk allergy.

Methods

We reported this systematic review following the PRISMA statement [191] (**Supplementary material S1**). The protocol of this systematic review was registered within the International Prospective Register of Systematic Reviews (PROSPERO) (registration ID: CRD42018102108). The search results were updated in May 2019.

Search Strategy

We searched Pubmed, Embase (via OVID) (1974 to present), CINAHL (1937 to present), Cochrane CENTRAL (1992 to present) and CNKI (China National Knowledge Infrastructure) electronic databases through May 30, 2019. Reference lists from included studies were scanned to identify other relevant studies. Grey literature sources OpenGrey, Zetoc, Conference Proceeding Citation Index (CPCI) and Science Citation Index (SCI) were also searched. There was no language restriction. The MeSH (medical subject headings) terms and free-text keywords for relevant exposures or interventions (cow's milk, milk products, infant formula, breastfeeding, and breast milk) and outcomes (atopic diseases, wheeze, eczema, atopic dermatitis, asthma, rhinitis, conjunctivitis, food allergy, and cow milk allergy) were searched (**Supplementary material S2**).

Study Selection

Randomized controlled trials (RCT), prospective cohort or longitudinal studies, retrospective cohort studies, nested case-control studies or other case-control studies were included where the timing of the introduction of CM or CMF before one year of age is clearly described. If the authors did not specify the types of formula given to the infant, we considered the formula to be CMF. We excluded studies comparing CMF with hydrolyzed formula, soy formula, or milk from other animals. The studies focusing on infants experiencing specific diseases or conditions at baseline, such as preterm birth and low birth weight, were also excluded. The primary outcomes were allergic diseases, including asthma, wheeze, eczema/atopic dermatitis, allergic rhinitis /conjunctivitis, food allergy, and cow's milk allergy (CMA). We included studies published as full-text publications rather than only abstracts. Two researchers (M.Y. and M.T.) independently screened titles and abstracts of the relevant studies, selected the full-text articles for eligibility. Any disagreement during the screening process was discussed and re-examined. A third person (S.S.) was consulted when no consensus was reached.

Quality assessment

We used the Cochrane Collaboration's Risk of Bias Tool [182] to access the risk bias for RCT studies (**Supplementary material S3**) and the Newcastle-Ottawa quality assessment scale [192] for cohort studies (**Supplementary material S3**) and case-control studies (**Supplementary material S3**). The quality of all full-text reports was accessed independently by two reviewers (M.Y. and M.T.), and any disagreements were resolved by a third reviewer (S.S.)

We classified each RCT study into one of the following categories: low risk of bias (low risk of bias for all key domains); unclear (1 or more items assessed as unclear); high risk of

bias (1 or more items assessed as high risk) [193]. We classified each cohort study or case-control study into high quality with a Newcastle-Ottawa scale score ≥ 7 and low quality with a score <7, because standard validated criteria for cutting points of different quality level have not been established. According to the method used in a previous systematic review, we set the critical endpoints based on the mean values, 6.5 scores, for the cohort studies [194].

Data extraction

Data were extracted in duplicate and summarized in an excel spreadsheet. For RCT studies, the extracted information included study ID, location, interventions, controls, follow-up time, sample size, outcomes, age at outcomes, measurements, and response rate. For cohort studies, the extracted information included study ID, study design (prospective or retrospective cohort), location, cohorts' name, allergic disease risk, exposures (CM or CMF), the timing of CM or CMF introduction, sample size, outcomes, age at outcomes, measurements, and follow-up rate. For the case-control study, the extracted information included study ID, location, sample size, definitions of the case, feeding CM or CMF, the timing of introduction, age at outcomes, and methods of case ascertainment. Original data for each outcome at different timing of introduction extracted from the included studies were shown in tables in the supplementary file (**Supplementary material S3**).

Data analysis and synthesis

For the observational studies, the timing of CM or CMF introduction varied. Therefore we used the following categories for the timing of introduction to enable the combination of multiple studies: <1 vs. ≥1 or <3 vs. ≥3 or <4 vs. ≥4 or <6 vs. ≥6 months duration. The event data were extracted from the included studies. If we were unable to get event data from the study, unadjusted odds ratio (OR) was used for meta-analysis. We also extracted adjusted OR and included those in the meta-analysis. If a study reported zero events in a group, it was not

included in the meta-analysis. When studies had several time points for examining outcomes, the most complete dataset or the largest observational case number were selected. When studies used multiple methods to assess the same outcome, clinical assessments, or validated instruments were preferred. For example, we prioritized skin prick test or double-blind, placebo-controlled food challenge for diagnosis of CMA over the parental report.

The included studies were grouped by different outcomes being assessed within each time point comparison. The data are reported using OR with 95% confidence intervals (CI). The pooled OR with its 95% CI was calculated by a fix-effects model. Meta-analyses were undertaken using Review Manager (RevMan) (Version 5.3). Heterogeneity of the included studies was tested using a chi-squared test ($p<0.1$ to determine statistical significance) and I^2 statistic. Meta-analysis was performed when at least two studies were included in the analysis. When the number of studies in a meta-analysis was over 10, we used funnel plots and Begg's test to assess for the potential for the presence of publication bias.

We used sensitivity analyses to assess the findings restricted to high-quality studies. Additionally, we conducted subgroup analyses by including only children at high risk (family history of allergy in at least one first degree relative) of allergic diseases. Furthermore, some infants who cannot be breastfed for some specific reasons or conditions are fed infant formula as an alternative method. For example, breastfeeding remains a potential source of infection for the baby with a mother living with HIV and is being discouraged in high-income countries [195]. Thus, we further excluded children who were exclusively formula-fed to assess the associations in ever breastfed children.

Results

A considerable amount of literature (11648 unique records) was identified by this search strategy. However, when screening the title or abstract, we found that most of them just

compared different feeding patterns, such as breastfeeding, formula feeding or mix feeding, without providing further information on the timing of CM or CMF formula introduction; or some studies involved in infants experiencing specific diseases or conditions at baseline, such as preterm birth, low birth weight or congenital disorders. There were 463 articles deemed potentially relevant to the review and obtained for assessment against the selection criteria (**Figure 3.1**). Four RCT studies (**Table 3.1**), 37 cohort studies (**Table 3.2**), and four case-control studies (**Table 3.3**) from 20 countries met the inclusion criteria. **Table 3.1-3.3** shows a summary of the characteristics of the included studies.

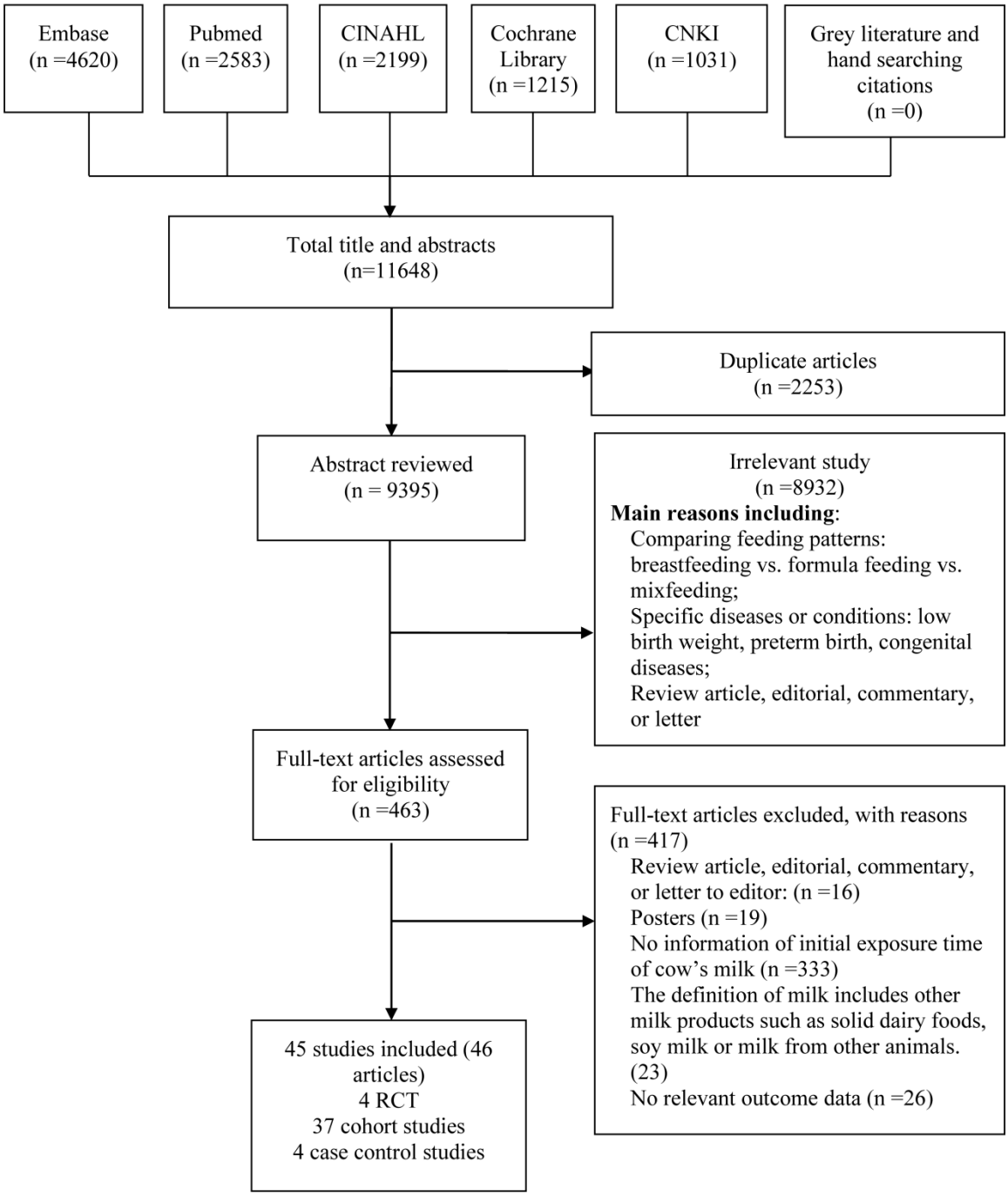


Figure 3.1 Flow diagram of Study selection

Table 3.1 Characteristics of included randomized control trials

Study ID	Location	Intervention	Exposure time	Sample size	Outcomes	Age at outcome	Measures of outcomes	Follow-up rate	Quality
Juvonen 1996	Sweden	Human milk (HM), cow's milk formula (CMF) during the first 3 days of life.	First 3 days	CMF: 39 HM: 53	Eczema	<3y	Unclear	CMF: 88.6% HM: 91.4%	High risk
Lindfors 1988	Sweden	Infants were randomized to receive either early feeding with formula before normal breastfeeding was started or "normal feeding" with breastmilk	Early feeding before normal breastfeeding was started	CMF:109 HM:98	Wheeze/ Eczema	18m	Examined by paediatricians	CMF: 97.3% HM: 94.2%	High risk
Lindfors 1992	Sweden	One group received cow milk formula during the first days of life before the mother's breastmilk production started and was then breastfed; the other was not given any formula before normal breastfeeding started.	Early feeding before normal breastfeeding was started	CMF: 95 HM:88	Asthma/Rhino-conj FA/CMA	4-6y	Examined by paediatricians SPT	CMF: 84.8% HM: 84.6%	High risk
Saarinen 1999 Saarinen 2000	Finland	The infants who required supplementary milk at the hospital because of insufficient secretion of breast milk were randomly assigned to one of 3 study groups according to the supplement given: liquid CM formula; pasteurized human milk	First few days at Maternity Hospital	CMF:1758 HM: 1844	CMA	2.8-12.7m	A challenge test with cow's milk at the hospital	CMF: 98.3% HM: 99.2%	High risk

CM: cow's milk; **CMA** cow's milk allergy; **CMF**: cow's milk formula; **DBPCFC** double-blind, placebo-controlled food challenge; **FA** food allergy; **RCT** randomized controlled trial; **Rhino-conj** rhinitis+conjunctivitis; **SPT** Skin prick test

Table 3.2 Characteristics of included 37 cohort studies

Study ID	Design	Location	Cohort Name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of the timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
Batool 2016	PC	Canada	FAMILY	Normal	CM or CMF	Yes	<6m, ≥6m	818	FA	1y	Parental report	99.2%	6
Cogswell 1987	PC	UK		High-risk	CM or CMF	Yes	<4w, 4-13w, ≥14w	73	Eczema	1y	Diagnosed by the paediatrician	73.0%	6
Azad 2017	PC	Canada	CHILD	Normal	CMF	No	<3m, ≥3m <6m, ≥6m	2773	Wheeze	1y	ISAACQ	84.0%	8
Elbert 2017	PC	Netherlands	Generation R	Normal	CM or CMF	Yes	<6m, ≥6m	5202	FA/Eczema	before 10y	Eczema: parental report of physician diagnosis of eczema Food allergy: parental report	71.0%	8
Filipiak-Pittroff 2018	Secondary analysis of RCT	Germany	GINI-plus Birth Cohort	High risk	CMF	No	<4m, ≥4m	2252	Asthma /Eczema /Allergic rhinitis	3-15 y 1-15 y 4-15 y	Parental report	90.5%	4
Fergusson 1990	PC	New Zealand		Normal	CM or CMF	Yes	<4m, ≥4m	1210	Eczema	10y	Mother's diary records or maternal recall or family doctor	95.7%	6
Gustafsson 1992	PC	Sweden		Normal	CMF	Yes	First 8 days	736	Asthma/ Rhino-conj/Eczema	7y	Hospital records Physician‘s findings	97.6%	7
Host 1991	PC	Denmark		Normal	CMF	Yes	0m, <1m, 1-3m, ≥4m	1749	CMA	1y	SPT and AL-RAST	100.0%	7
Ito 2014	PC	Japan		Normal	CMF	Yes	0m, <6m,	38757	AD	6 to	Parental report of	82.4%	7

Study ID	Design	Location	Cohort Name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of the timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
							≥6m			42m	physician diagnosis		
Katz 2010	PC	Israel		Normal	CMF	Yes	<1m, ≥1m	11633	CMA	3-5y	Blood test	98.4%	7
Kemeny 1991	PC	UK		Normal	CM	Yes	0m, <3m, ≥3m	189	Wheeze/ Eczema/ CMA	<1y	Wheeze/ Eczema: examined by a physician; CMA: SPT	94.2%	6
Kilingberg 2019	PC	Sweden	ABIS	Normal	CMF	No	< 2.5 weeks ≥ 2.5 to < 14 weeks Never	9727	Asthma	0-15 y	National Patient Register	60.7%	8
Klopp 2017	PC	Canada	CHILD	Normal	CMF	Yes	0m, <3m, ≥3m	2534	Asthma	3y	History report and physical examination	76.9%	8
Kumar 2010	RC	USA		Normal	CMF	Yes	<6m, ≥6m	789	FA Eczema	0-21y 0-21y	Blood test or SPT Parental report of physician diagnosis		7 6
Lossius 2018	PC	Norway	MoBa	Normal	CMF	Yes	<4m, 4-5.9m, ≥ 6	31930	Asthma	7y	Based on dispensed prescriptions	40.3%	7
Luccioli 2014	PC	USA	Y6FU	Normal High-risk	CM or CMF	Yes	4m, 4–5m, 6–12m	All: 1258 High-risk: 752	FA	6y	Parental report of physician diagnosis	81.6%	7
Marini 1996	PC	Italy		High-risk Normal	CMF CMF	Yes	0m, <4m, ≥4m 0m, <4m, ≥4m	221 62	Wheeze/AD/Rhino-conj	<3y	Physician-diagnosed	78.8%	5

Study ID	Design	Location	Cohort Name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of the timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
					CM		<6m, ≥6m	62					
Moore 1985	PC	UK		High risk	CMF	Yes	1-4w (0w), 5-8w, 9-12w, >12w	475	Eczema	3m	Medical history and clinical examination	90.5%	6
Nwaru 2010	PC	Finland	DIPP	High-risk	CM or CMF	Yes	<0.92m, 0.92-4m, >4m	994	FA	5y	Blood test	93.2%	6
Nwaru 2013a	PC	Finland	DIPP	Normal	CM or CMF	Yes	Cow's milk	3781	Asthma /Eczema/ Allergic rhinitis	5y	ISAACQ	82.0%	6
Nwaru 2013b	PC	UK	SEATON	Normal	CM CMF	Yes	<5.75m, ≥5.75m <0.5m, ≥0.5m	934	Wheeze/ Asthma/ Eczema	up to 10y	ISAACQ	49.0%	8
Perters 2019	PC	Australia	HealthNuts	Normal	CMF	Yes	<3m, ≥3m	2183	CMA	1y	Parent-reported reaction to milk & IgE-mediated & allergy and SPT.	41.4%	5
Poysa 1989	PC	Finland		High risk	CMF	Yes	<3m, 3-6m, >6m	70	Eczema	5y	Parental report	70.0%	5
Roduit 2012	PC	Austria, Finland, France, Germany, Switzerland	PASTURE	Normal	CM	Unkown	3-12m, >12m	912	AD	up to 4y	Parental report/ SCORAD scores	80.5%	8
Ruiz 1992	PC	UK		High-risk	CMF	Yes	<4m, ≥4m	39	AD	<1y	Hanifin and Rajka criteria	100.0%	5
Saarinen	PC	Finland		Normal	CMF	Yes	<2m,	All:236	FA	<1y	One of author	92.2%	5

Study ID	Design	Location	Cohort Name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of the timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
1979							2-6m, >6m	High risk:101	AD		recorded signs and symptoms of atopy		
Simon 2008	PC	USA		Normal	CMF	Yes	0m, <4m, ≥4m	303	Wheeze	<4y	Parental report	44.6%	5
Snijders 2008	PC	Netherlands	KOALA	Normal	CM or CMF	Yes	0–3m, 4–6m, 7–9m, >9m	1894	Wheeze/ Eczema	2y	Parental report	90.3%	7
									AD	2y	United Kingdom Working Party Criteria		8
									CMA		Blood test		
Soto-Ramirez 2017	PC	USA	IFPS II and Y6FU	Normal	CMF	Yes	0m, <1m, 1-3m, >3m	1379	Eczema	6y	Parental report of, physician diagnosis	89.9%	7
Strassburger 2010	PC	Brazil		Normal	CM	Yes	<4m, ≥4m	293	Wheeze/Asthma	3-4y	Parental report	73.8%	8
Tariq 1998	PC	UK		Normal	CMF	Yes	<3m, ≥3m	1086	Asthma	4y	The presence of typical diurnal variation and the response to bronchodilator medication.	74.6%	7
Tham 2018	PC	Singapore	GUSTO	Normal	CM or CMF	Yes	<10m, ≥10m	870	CMA	2y	SPT	75.5%	8
Tran 2017	PC	Canada	CHILD	Normal	CM or CMF	Yes	≤6m, 7-12m, <12	2124	CMA	1y	SPT	60.8%	7
Tromp 2011	PC	Netherlands	Generation R	Normal	CM or CMF	Yes	<6m, ≥6m	6905	Wheeze/Eczema	4y	ISAACQ	87.5%	8
Van Asperen	PC	Australia		High	CM	Yes	<4m, ≥4m	79	Wheeze//Rhinitis	20m	Parental report	85.9%	4

Study ID	Design	Location	Cohort Name	Allergic disease risk	Exposure	Including exclusive CMF feeding	Comparative groups of the timing of CM or CMF introduction	Sample size	Outcomes	Age of diagnosis	Measures	Follow-up rate	Quality scores
1984				risk									
									AD	20m	By examination		5
Wright 1994	PC	USA		Normal	CMF	Yes	<6m, ≥6m	747	Allergic rhinitis	<6y	Physician diagnosis	60.0%	5
Zutavern 2004	PC	UK		Normal	CM	Yes	<6m, ≥6m	620	Wheeze/Eczema	5.5y	Parental report	96.6%	7

Name of cohort studies: ABIS: All Babies In Southeast Sweden; **CHILD**: Canadian Healthy Infant Longitudinal Development ; **DIPP**: Finnish Type 1 Diabetes Prediction and Prevention ; **FAMILY**: Family Atherosclerosis Monitoring In earLY life; **GINI:** German Infant Nutritional Intervention; **GUSTO**: Growing Up in Singapore Towards healthy Outcomes; **IFPS II**: Infant Feeding Practices Study II ; **KOALA**: Child, Parent and health: lifestyle and genetic constitution (in Dutch); **MoBa**: The Norwegian Mother and Child Cohort Study; **PASTURE**: Protection Against Allergy–Study in Rural Environments ; **SEATON**: Study of Eczema and Asthma To Observe the influence of Nutrition; **Y6FU**: Year-6-Follow-Up Study

AD atopic dermatitis; **CM**: cow's milk; **CMA** cow's milk allergy; **CMF**: cow's milk formula; **FA** food allergy; **ISAACQ** international study of asthma and allergies in children questionnaire; **PC** prospective study; **RC** retrospective study; m months; y year; **Rhino-conj** rhinitis and/or conjunctivitis; **SPT** skin prick test;

Table 3.3 Characteristics of included 4 case-control studies

Study ID	Location	Sample size	Case	Feeding CM/CMF	Timing of introduction	Age of diagnosis	Methods of case ascertainment	Quality scores
Grimshaw 2013	UK	Case:41 Control:82	FA	CM	22w vs. 26w (mean age in each group)	2y	DBPCFC	7
Onizawa 2016	Japan	Case:51 Control:102	CMA	CMF	≤1m	2-8y	Blood test	6
Sariachvili 2010	Belgium	Case: 252 Control: 305	Eczema	CMF	<4m	<4y	ISAACQ	7
Turati 2016	Italy	Case: 329 Control: 329	AD	CM	at 1m vs. >5m at 2m vs. >5m at 3m vs. >5m at 4m vs. >5m at 5m vs. >5m	3-24m	Diagnosed by dermatologist	7

AD atopic dermatitis; **CM**: cow's milk; **CMA** cow's milk allergy; **CMF**: cow's milk formula; **DBPCFC**: double-blind, placebo-controlled food challenge; **FA** food allergy; **ISAACQ**: the international study of asthma and allergies in children questionnaire

All RCT studies were assessed as high risk of bias. Methodological quality was low in 16 (43.2%) of 37 cohort studies. In case-control studies, two of four studies were low quality (**Supplementary material S3**).

The key results of the meta-analyses are shown in **Figure 3.2-3.5**. The results of meta-analyses of cohort studies were grouped by different outcomes being assessed within each time point comparison (<1 vs. ≥1 or <3 vs. ≥3 or <4 vs. ≥4 or <6 vs. ≥6 months). There was a study only providing ORs in figures without numerical value [196]. For this study, we sent an email to the authors to request additional information about the data, but no response was received. No data of case-control studies were pooled into meta-analyses due to the different outcomes in these studies (**Supplementary material S3**). Forest plots of the effect sizes for individual studies included in the meta-analyses were shown in **Supplementary material S4.**

Asthma

Two RCT studies with a total of 275 participants and five cohort studies with a total of 48994 participants reported asthma. Both of the two RCT studies used CMF as the intervention. Results of pooled RCT studies showed that compared with breast milk feeding, there was no association between exposure to CMF in the first few days of life and risk of asthma (unadjusted OR, 0.78; 95% CI: 0.21, 2.86; I^2=17%) (**Figure 3.2**) [197, 198]. Likewise, one cohort study not included in the meta-analyses showed that giving CMF to healthy breastfed term infants on maternity wards does not increase the risk of developing asthma (unadjusted OR, 1.48; 95% CI: 0.5, 4.6) [199]. However, results of pooled cohort studies showed that earlier CM or CMF introduction to the infant diet before 3 (unadjusted OR, 1.56; 95% CI: 1.28, 1.90; I^2=0%) or 4 (unadjusted OR, 1.20; 95% CI: 1.08, 1.32; I^2=0%) months of age was

associated with higher risk of asthma (**Figure 3.3**) [128, 130, 131, 134, 200-202]. When pooling adjusted OR into the meta-analysis, the association between CM or CMF feeding before 4 months and risk of asthma was not significant (adjusted OR, 1.16; 95% CI: 0.89, 1.51; I^2=7%) [128, 131]. Introducing CM or CMF before 6 months of age had a marginal association with risk of asthma (unadjusted OR, 1.17; 95% CI: 1.00, 1.38; I^2=32%) (**Figure 3.3**) [130, 200]. When we restricted the meta-analysis to high-quality studies, the results did not change significantly (**Figure 3.4**).

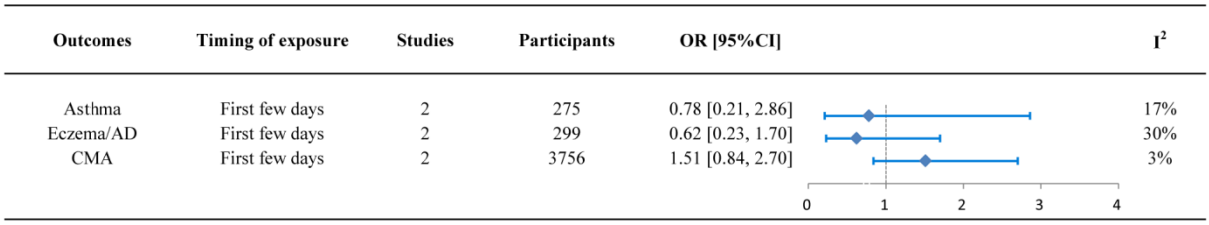


Figure 3.2 Key results of the meta-analysis of the timing of CMF introduction and risk of allergic diseases from randomized control trials.

AD, atopic dermatitis; CMA, cow's milk allergy; CMF, cow's milk formula.

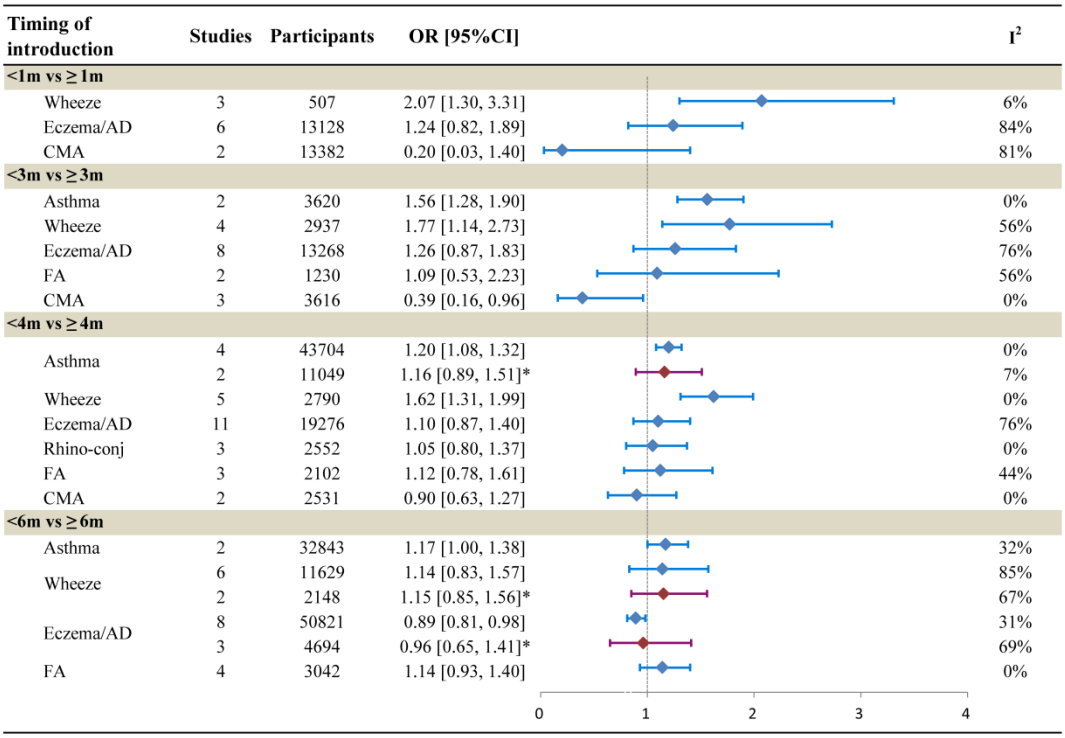


Figure 3.3 Key results of the meta-analysis of the timing of CM or CMF introduction and risk of atopic diseases from cohort studies.

*: Adjusted OR

AD, atopic dermatitis; CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula

Timing of introduction	Studies	Participants	OR [95%CI]	I^2
<1m vs ≥1m				
Eczema/AD	2	12275	0.88 [0.59, 1.32]	87%
CMA	2	13382	0.20 [0.03, 1.40]	81%
<3m vs ≥3m				
Asthma	2	3620	1.56 [1.28, 1.90]	0%
Eczema/AD	2	12153	0.86 [0.60, 1.23]	82%
<4m vs ≥4m				
Asthma	3	32223	1.20 [1.08, 1.34]	0%
Wheeze	2	2187	1.57 [1.24, 2.00]	0%
Eczema/AD	3	14785	0.87 [0.70, 1.08]	77%
CMA	2	2531	0.90 [0.63, 1.27]	0%
<6m vs ≥6m				
Asthma	2	32864	1.17 [1.00, 1.38]	32%
Wheeze	5	11567	1.24 [0.90, 1.70]	86%
	2	2148	1.15 [0.85, 1.56]*	67%
Eczema/AD	5	49726	0.87 [0.83, 0.91]	0%
	2	4626	0.84 [0.71, 1.00]*	0%
FA	2	2047	1.19 [0.92, 1.53]	0%

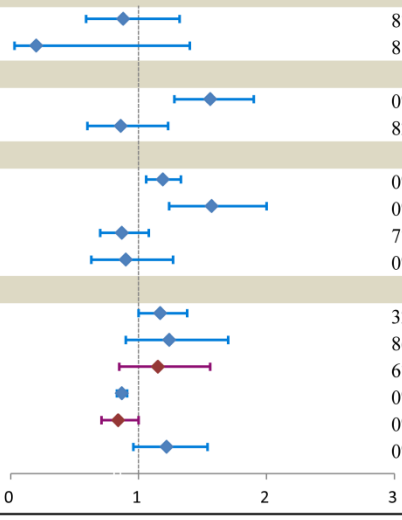


Figure 3.4 Key results of the sensitivity analysis of cohort studies with high quality (scores≥7)

*: Adjusted OR. AD, atopic dermatitis; CM, cow's milk; CMA, cow's milk allergy; CMF, cow's milk formula; FA, food allergy.

Wheeze

Ten cohort studies with 14024 participants reported CM or CMF introduction and risk of wheeze. The results of meta-analysis showed significant associations between CM or CMF introduction in earlier stages of infancy (<1, 3 or 4 months) and risk of wheeze (<1 vs. ≥1 month: unadjusted OR, 2.07; 95% CI: 1.30, 3.31; I^2=6%; <3 vs. ≥3 month: unadjusted OR, 1.77; 95% CI: 1.14, 2.73; I^2=56%; <4 vs. ≥4 month: unadjusted OR, 1.62; 95% CI: 1.31, 1.99; I^2=0%) (**Figure 3.3**) [135, 201, 203-207]. However, no association was observed in <6 vs. ≥6 months group (unadjusted OR, 1.14; 95% CI: 0.83, 1.57; I^2=85%; adjusted OR, 1.15; 95% CI: 0.85, 1.56; I^2=79%) (**Figure 3.3**) [135, 200, 204, 206, 208, 209].

When the analysis was restricted to high-quality studies, six cohort studies pooled in <4 vs. ≥4 months and <6 vs. ≥6 months groups for meta-analyses showed that introducing CM or CMF into the infant diet before 4 months of age was still significantly associated with a higher risk of wheeze (unadjusted OR, 1.57; 95% CI: 1.24, 2.00; I^2=0%), but no association was found in 6-month groups (unadjusted OR, 1.24; 95% CI: 0.91, 1.70; I^2=86%; adjusted OR, 1.15; 95% CI: 0.85, 1.56; I^2=79%) (**Figure 3.4**) [135, 200, 206, 208, 209]. Subgroup analysis with children at high risk of allergic diseases indicated that introducing CM or CMF before 4 months of life was not associated with the risk of wheeze (unadjusted OR, 1.07; 95% CI: 0.59, 1.94; I^2=43%) (**Figure 3.5**) [131, 204, 207]. When excluding exclusively formula-fed children, the pooled effects from included cohort studies showed that no significant association was observed between exposure to CMF before 4 or 6 months of age and risk of wheeze (<4 vs. ≥4 months: unadjusted OR, 1.65; 95% CI: 0.81, 3.37; I^2=43%; <6 vs. ≥6 months: unadjusted OR, 1.88; 95% CI: 0.83, 4.28) (**Figure 3.5**) [135, 203-205].

Timing of introduction	Studies	Participants	OR [95%CI]	I^2
High risk population				
<1m vs ≥1m				
Eczema/AD	3	728	2.00 [1.35, 2.96]	0%
<3m vs ≥3m				
Eczema/AD	5	830	1.69 [1.17, 2.44]	0%
<4m vs ≥4m				
Wheeze	3	2489	1.07 [0.59, 1.94]	43%
Eczema/AD	6	2710	1.09 [0.65, 1.81]	40%
Rhino-conj	3	2552	1.04 [0.79, 1.36]	0%
FA	2	800	1.40 [0.84, 2.35]	0%
<6m vs ≥6m				
Eczema/AD	2	171	1.55 [0.66, 3.62]	0%
FA	2	827	1.35 [0.78, 2.33]	0%
Excluding exclusive formula feeding				
<1m vs ≥1m				
Eczema/AD	2	1332	1.63 [1.21, 2.19]	8%
<3m vs ≥3m				
Wheeze	2	2495	1.65 [0.81, 3.37]	62%
Eczema/AD	3	1339	1.48 [1.13, 1.94]	0%
<4m vs ≥4m				
Asthma	2	11049	1.23 [0.98, 1.55]	0%
	2	11049	1.16 [0.89, 1.51]*	7%
Wheeze	2	368	1.88 [0.83, 4.28]	43%
Eczema/AD	4	3704	1.36 [1.13, 1.64]	0%
Rhino-conj	2	2420	1.06 [0.80, 1.41]	0%

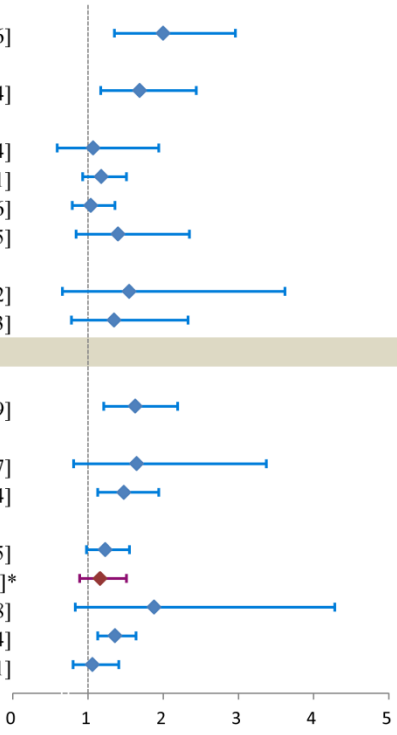


Figure 3.5 Key results of the subgroup analysis of cohort studies.

*: Adjusted OR. AD, atopic dermatitis; CMF, cow's milk formula; FA, food allergy; Rhino-conj, allergic rhinitis or conjunctivitis.

Eczema/Atopic dermatitis

We identified two RCT studies with a total of 299 participants, 21 cohort studies with a total of 60024 participants and two case-control studies with 1215 participants reporting the effects of initial exposure of CM or CMF on the risk of eczema or atopic dermatitis. A meta-analysis of two RCT studies found that there was no significant difference between feeding CMF in the first few days of life and human milk on the risk of eczema or atopic dermatitis (unadjusted OR 0.62; 95% CI: 0.23, 1.70; I^2=30%) (**Figure 3.2**) [197, 210]. Meta-analyses of cohort studies showed that no significant associations between CM or CMF introduction and risk of eczema or atopic dermatitis were observed in <1 vs. ≥1 month (unadjusted OR, 1.24; 95% CI: 0.82, 1.89; I^2=84%), <3 vs. ≥3 months (unadjusted OR, 1.26; 95% CI: 0.87, 1.83; I^2=76%) and <4 vs. ≥4 months groups (unadjusted OR, 1.10; 95% CI: 0.87, 1.40; I^2=76%) (**Figure 3.3**) [131, 135, 203, 204, 206, 207, 211-217]. A cohort study not included in the meta-analyses also found that giving CMF to healthy breastfed term infants on the maternity wards does not increase the risk of developing eczema or atopic dermatitis (unadjusted OR, 1.78; 95% CI: 0.80, 4.00) [199]. One case-control study reported that introducing CMF before 4 months of age was associated with a reduced risk for eczema up to 4 years (unadjusted OR 0.55; 95% CI: 0.38–0.81) [218]. The other case-control study also found that introducing CM at 1 month of age reduced the risk of atopic dermatitis (adjusted OR 0.62; 95% CI: 0.40–0.96) [219]. In <6 vs. ≥6 months groups, results of pooling eight cohort studies indicated that introducing CMF or CM before 6 months of age was associated with a lower risk of eczema or atopic dermatitis (unadjusted OR, 0.89; 95% CI: 0.81, 0.98; I^2=31%) (**Figure 3.3**) [200, 206, 208, 209, 212, 214, 220, 221]. However, the result of pooling adjusted ORs showed no significant association observed in <6 vs. ≥6 months group (adjusted OR, 0.96; 95% CI: 0.65, 1.41; I^2=69%) (**Figure 3.3**) [200, 204, 222]. Another cohort study not in this meta-analysis

showed that introducing CM within the first year of life showed an inverse association with the development of atopic dermatitis up to 4 years of age (adjusted OR, 0.46; 95% CI: 0.32, 0.65) [223].

In sensitivity analysis with only high quality studies, we found that introducing CM or CMF before 6 months of age had a protective effect on the development of eczema or atopic dermatitis (unadjusted OR 0.87 ; 95% CI: 0.83, 0.91; I^2=0%; adjusted OR, 0.84; 95% CI: 0.71, 1.00; I^2=0%) (**Figure 3.4**) [200, 206, 208, 209, 212, 222]. In subgroup analyses of high risk children, we found those given CM or CMF before 1 or 3 months of age had a higher risk of eczema or atopic dermatitis than those given later (<1 vs. ≥1 month: unadjusted OR, 2.00; 95% CI: 1.35, 2.96; I^2=0%; <3 vs. ≥3 month: unadjusted OR, 1.69; 95% CI: 1.17, 2.44; I^2=0%) (**Figure 3.5**) [204, 213, 214, 221, 224]. In other comparative groups, no associations were observed in the high risk children (<4 vs. ≥4 months: unadjusted OR, 1.09; 95% CI: 0.65, 1.81; I^2=40%, <6 vs. ≥6 months: unadjusted OR, 1.55; 95% CI: 0.66, 3.62; I^2=0%) (**Figure 3.5**) [131, 204, 207, 214, 215, 221]. When excluding exclusive formula fed children, introducing CM or CMF before 1, 3 or 4 months of age was associated with higher risk of eczema or atopic dermatitis (<1 vs. ≥1 month: OR, 1.63; 95% CI: 1.21, 2.19; I^2=8%; <3 vs. ≥3 month: OR, 1.48; 95% CI: 1.13, 1.94; I^2=0%; <4 vs. ≥4 month: OR, 1.36; 95% CI: 1.13, 1.64; I^2=0%) (**Figure 3.5**) [131, 203, 204, 213, 217].

Allergic rhinitis and/ or conjunctivitis

For allergic rhinitis and/ or conjunctivitis outcomes, six cohort studies with 4097 participants reported the risk of allergic rhinitis and/ or conjunctivitis with the timing of CM or CMF introduction. Data from three cohort studies showed that there was no association between CM or CMF introduction before 4 months of age and risk of allergic rhinitis and/ or conjunctivitis (unadjusted OR 1.05; 95% CI: 0.80, 1.37; I^2=0%) (**Figure 3.3**) [131, 204, 207]. The results did not substantially change in subgroup analyses. Likewise, one cohort study not in the meta-analysis found that giving CMF to healthy breastfed term children on the maternity wards does not increase the risk of developing rhinoconjunctivitis (unadjusted OR 0.6; 95% CI: 0.2, 1.7) [199].

Food allergy

We identified six cohort studies with 9297 participants and one case-control study with 123 participants reporting food allergy. Data from five cohort studies were pooled and showed that no associations between CM or CMF introduction and risk of food allergy were observed in different timing cut-off groups (<3 vs. ≥3 month: OR, 1.09; 95% CI: 0.53, 2.23; I^2=56%; <4 vs. ≥4 month: OR, 1.12; 95% CI: 0.78, 1.61 I^2=44%; <6 vs. ≥6 month: OR, 1.14; 95% CI: 0.93, 1.40; I^2=0%) (**Figure 3.3**) [220, 221, 225-227]. One cohort study not in the meta-analysis found that children introduced to cow's milk before 10 months of age were more likely to become allergic than those introduced later [35].

When pooling the data from studies with high-risk children into the meta-analysis, no association between timing of CM or CMF introduction before 4 or 6 months of life and risk of food allergy was observed (<4 vs. ≥4 month: OR, 1.40; 95% CI: 0.84, 2.35; I^2=0%; <6 vs. ≥6 month: OR, 1.35; 95% CI: 0.78, 2.33; I^2=0%) (**Figure 3.5**) [221, 226]. When we restricted

to high quality studies, there was no significant association observed in <6 vs. ≥6 month group (OR 1.19; 95% CI: 0.92, 1.53; I^2=0%) (**Figure 3.4**) [220, 226]. A case-control study indicated that the age at introduction of cow's milk was earlier in the food allergy group than that in the control group (*P*=0.049) [228].

Cow's milk allergy (CMA)

Two RCT studies with 3756 participants, seven cohort studies with 19530 participants, and one case-control study with 153 participants reported CMA. Data of two RCT studies showed that there was no difference between feeding human milk and CMF in the first few days of life on the risk of CMA (OR 1.51; 95% CI: 0.84, 2.70; I^2=3%) (**Figure 3.2**) [198, 216]. Data from cohort studies indicated that early exposure to CM or CMF before 1 or 4 months of age was not associated with risk of CMA (<1 vs. ≥1 months: unadjusted OR, 0.20 95% CI: 0.03, 1.40; I^2=81%; <4 vs. ≥4 months: unadjusted OR, 0.90; 95% CI: 0.63, 1.27; I^2=0%) (**Figure 3.3**) [203, 206, 229, 230]. Feeding CM or CMF before 3 months was associated with lower risk of CMA (unadjusted OR, 0.39; 95% CI: 0.16, 0.96; I^2=0%) (**Figure 3.3**) [185, 203, 229]. One cohort study not in the meta-analysis reported that compared with 7-12 months, introducing CM between 0-6 months of life had a protective effect on the development of CMA (adjusted OR, 0.29; 95% CI: 0.10, 0.70) [133]. Likewise, a case-control study found that compared with the children starting regular CMF within the first month of life, the delayed introduction was associated with a higher risk of CMA (adjusted OR, 23.74; 95% CI: 5.39, 104.52) [231].

When we restricted to high quality studies, no association was observed in 1 or 4 months groups (<1 vs. ≥1 months: unadjusted OR, 0.20; 95% CI: 0.03, 1.40; I^2=81%; unadjusted OR, 0.90; 95% CI: 0.63, 1.27; I^2=0%) (**Figure 3.4**) [206, 229, 230].

Evaluation of small-study effects

For the publication bias of the effects of introducing CM or CMF before 4 months of age on the risk of developing eczema or atopic dermatitis from 11 estimates, visual inspection of funnel plots and Begg's tests did not provide any evidence for meaningful small-study effects (**Supplementary material S4**).

Discussion

In this systematic review, we reviewed and comprehensively summarized the evidence about the associations between timing of CM or CMF introduction and development of atopic diseases. Overall, the pooled analyses of included cohort studies indicated unadjusted risks of asthma and wheeze in the children who were introduced CM or CMF in a very early stage of life. However, these associations were not significant when pooling adjusted data into the meta-analysis. The inconsistent results might be attributed to some important confounders. For example, the onset of wheeze and asthma is also associated with respiratory viral infections which are related to the duration of breastfeeding [232, 233]. The definitions of wheeze and asthma were not very clear in most included studies. It is challenging to identify which one was actually caused by an allergy. In addition, the absence of breastfeeding may increase risk of respiratory viruses that cause wheezing, which might be independent of allergy. However, we could not explore how these associations might be altered by restricting the analysis to long term breastfed children due to the limited number of studies conducted in breastfed children to examine the impact of CM or CMF as a supplement with breast milk on

the development of allergy. One cohort study found that exposure to infant formula before 14 weeks of age was associated with a higher risk of asthma after adjustment for the duration of breastfeeding and other covariates (adjusted OR 1.41; 95CI: 1.14,1.74) [128]. Another study conducted in children with breastfeeding at least 4 months found that feeding CMF as a supplement to breast milk during the first 4 months of age was not associated with the cumulative incidence of asthma from 3 to 15 years of age (adjusted RR 1.05; 95CI: 0.67,1.66) [131]. In this review, the meta-analysis of RCT studies with high-risk of bias found no association between CMF introduction in the first few days of life and risk of asthma, eczema or atopic dermatitis, or CMA. In summary, these findings do not provide strong evidence for the association between early introduction of CM or CMF to the infant diets and risk of atopic diseases.

Previous evidence indicated that genetics, microbial colonization, and nutrition had essential impacts on the allergy development by regulating the permeability of the gut barrier and passage of antigens in the early stage of life [234]. Proteins as one of the biologically active substances presenting in cow's milk have a positive effect on human health [235]. However, some proteins, such as casein fractions and β-lacto globulin, which are naturally not present in human milk, may cause positive reactions in human [236]. A previous systematic review concerning early feeding practice in infants and the risk of atopic diseases indicated that exposure to CM during the first days of life was associated with a higher risk of CMA [6]. In a guinea pig model, researchers evaluating the allergenicity of different infant formulas found that feeding pasteurized cow milk and CMF had more anaphylactic sensitivity to

antigens than feeding whey hydrolyzed formula [237]. In this review, pooling unadjusted data from included cohort studies showed that exposure to CM or CMF before 3 months was associated with a lower risk of CMA. However, the results of included RCTs showed that there was no significant association between exposure to CMF during the first days of life and risk of CMA. The inconsistent results might be attributed to the heterogeneity of the risk bias of included studies, measurement of exposures and outcomes, populations (high risk or normal) or complex interactions of nutrition with the immune system. Furthermore, all included RCTs examined whether feeding newborn infants CMF during the first few days of life increases the risk of CMA, with breastfeeding infants as the control group. However, in cohort studies, the exposure periods (in months) were much more extended than those of RCTs studies, and some cohorts included not only CMF but also CM [35, 133, 230].

Sensitivity analysis of high-quality studies found that exposure to CM or CMF before 6 months of age had a protective effect on the risk of eczema or atopic dermatitis in the general population. However, in the subgroup analyses, we found the earlier introduction of (before 1 or 3 months of age) CM or CMF to the infant was associated with a higher risk of eczema or atopic dermatitis in high-risk children or non-exclusive formula-fed children.

The inconsistent results may be due to the confounding bias or reverse causality by a family history of atopic diseases. In addition, the included studies differed in the diagnostic measurement of outcomes. Some studies used physical examination and some based on parental reporting. Besides, feeding practice was measured by the self-report approach in most of the included studies. This approach can be affected by recall bias and can alter the

validity of the findings. Many mothers may fail to recall the formula given while in the maternity hospital. In addition, the evaluation of the effects of early and late introduction of CM or CMF could not disregard the impact of other solid food introduction. The heterogeneity identified in our meta-analysis indicates a need for more standardized approaches to evaluate the effects of early feeding practice on children's health.

The current evidence and theoretical rationales concluded that early exposure to food proteins during a critical time window, likely to be 4-6 months of life, could benefit the development of immune tolerance [189]. However, too early exposure to the allergen may give rise to a higher risk of allergic or autoimmune diseases due to immature gut colonization and local immune networks [190]. One cohort study found that compared with children initiating formula feeding after 6 months of age, introducing between 4 to 6 months associated with a higher risk of asthma at age 7 years (adjusted RR 1.21; 95CI: 1.03, 1.44), but no significant association was observed between introducing before 4 months and the risk of asthma (adjusted RR 1.10; 95CI: 0.98, 1.25) [130]. In this review, the timing of CM or CMF introduction between comparison groups in included studies was varied. Initially, we wanted to identify a critical window of CM or CMF exposure during infancy, which was associated with the risk of atopic diseases. However, according to the data distribution and the limited number of eligible studies for each outcome, we instead set several timing cut-off points for meta-analyses. Therefore, we could not identify the critical periods related to the outcomes, for example, between 4 to 6 months or 7 to 9 months of age.

There are several strengths of our systematic review. We included multiple databases,

searches of grey literature, and hand searching of citations to reduce the likelihood of missing the primary research corresponding to our inclusion criteria. In this review, we excluded the studies comparing CM or CMF with hydrolyzed formula, soy formula, or milk from other animals to minimize the heterogeneity of comparative groups. Different types of foreign proteins may have different effects on the health of children. [184, 238-241]. In addition, the potential for the presence of heterogeneity and small-study effects were quantitatively evaluated. Studies were identified across a range of countries (20 countries), increasing generalizability.

This review has some limitations. First, for some outcomes, the statistical power was limited due to the sizes of the included studies. Second, most of the data extracted from included studies for meta-analysis was unadjusted data. The results might be affected by some significant confounders such as duration of breastfeeding, respiratory viral infections, the gender of children, maternal age at delivery, parental social status, and smoking status. Third, most included studies were observational studies. As a result, the observed associations may be attributable to confounding by factors other than the exposure being investigated. However, it is probably unethical to conduct a controlled trial in which some participants are randomised to "early feeding of infant formula" group.

Based on the findings of this review, we think that future studies should employ a large sample size, a prospective design (which could establish the temporal direction of the associations), use validated exposure and outcome measurement methods (e.g., diet records for the infants, medical records for the diseases and long-term follow-up), and adjust for a

wide range of potential confounders (e.g., duration of breastfeeding, respiratory viral infections, the gender of children, maternal smoking status, and timing of other allergic food introduction).

Conclusion

Pooled analysis of the cohort studies indicated an unadjusted risk of asthma and wheeze in the children who were introduced CM or CMF in a very early stage of life. However, these results should be interpreted with caution due to the limitations of included studies and the limited number of studies included for each outcome. Overall, quite little high-quality evidence was identified to allow for definitive conclusions. Our meta-analysis on this topic highlights the specific gaps in information for public recommendations regarding infant feeding practice, particularly in an early stage; therefore, more future high-quality research is needed.

Chapter 4 Timing of infant formulas introduction and eczema and wheezing in the first year of life: the Born in Guangzhou Cohort Study (BIGCS)

Abstract

Background

Incidence of atopic conditions in children is rising rapidly in China, where widespread usage of infant formula is also a major public health problem. The timing of infant formula introduction may have a critical effect on the risk of atopic disorders in infancy, but there is limited evidence on the question.

Methods

This is a longitudinal study on singleton births between February 2012 and December 2015 in the BIGCS, a population-based birth cohort in Guangzhou, China. We examined the relationship between the timing of introduction of infant formula and the development of eczema and wheezing before 1 year of age using information collected by questionnaires at 6 weeks, 6 and 12 months of age. Multiple imputation analysis was performed for dealing with missing covariate data.

Results

Among 6334 infants, 17.4% had physician-diagnosed eczema, and 7.2% had at least one episode of wheezing between 6 and 12 months of age. In multiple imputation models, compared with introducing infant formula after 6 months, introducing it within the first 3 months (adjusted odds ratio [OR], 1.43; 95% confidence interval [CI], 1.10-1.87) and between 4 to 6 months of life (adjusted OR, 1.30; 95% CI, 0.93-1.83) was likely to be associated with the higher risk of eczema in the first year, although the latter did not reach statistical significance. For wheezing, after multiple imputation for missing confounders, the associations of introducing infant formula within the first 3 months (adjusted OR, 1.16; 95% CI, 0.80-1.69) or between 4 to 6 months of age (adjusted OR, 0.77; 95% CI, 0.46-1.31) with the risk of wheezing were not significant. However, when looking at the feeding pattern by

combining timing of formula introduction and breastfeeding duration, introducing infant formula within the first 3 months combined with shorter breastfeeding duration was associated with the higher risk of wheezing, compared with introducing formula after 6 months of age (aOR, 1.52; 95% CI, 1.02-2.27).

Conclusions

Compared with introducing infant formula after 6 months, introducing it within the first 3 months was significantly associated with the higher risks of eczema during the first year. In addition, introducing infant formula within the first 3 months combined with having shorter breastfeeding duration was associated with a higher risk of wheezing, compared with introducing formula after 6 months of age. However, the results need to be replicated in other well-designed studies before more firm recommendations can be made.

Introduction

Incidence of childhood atopic disease has been increasing rapidly worldwide, particularly in the Asia-Pacific region [178]. In China, the prevalence of childhood asthma rose from 0.91% in 1999 to 6.8% in 2010 [19], and current wheezing increased from 2.0% in 1994 to 7.9% in 2009 in urban areas [20]. The first national survey on allergic diseases in infants under 24 months of age in 2014 showed that nearly one-fifth of infants had physician-diagnosed eczema in China [22]. Eczema may cause distressing itch, mood changes and sleep deprivation and affect neurodevelopment and behaviours [242].

Early diet has been implicated as an important modifiable factor associated with the development of atopic disorders [243]. The protective effects of breastfeeding on atopic diseases have been examined by comparing exclusive with non-exclusive breastfeeding or short with long duration of breastfeeding [8, 244]. However, these findings have been inconsistent, particularly for the effects on eczema/atopic dermatitis [245, 246]. A cluster-randomized controlled trial [159] and two cohort studies [247, 248] showed protective effects of breastfeeding, whereas three other population-based cohort studies suggested that breastfeeding was associated with a higher risk of eczema [212, 249, 250]. Several reasons may explain the heterogeneous findings. One important factor is that among the breastfed children early or late introduction of different allergenic foods, including infant formula, might have different effects on the development of allergy. The timing of complementary food introduction and risk of allergy has been studied extensively [7, 9, 155, 251], yet there is limited evidence on the effects of the timing of infant formula introduction [252], despite the

fact that in many populations infant formula is usually the first food introduced for infants who are not exclusively breastfed. Two Australian cohort studies focusing on the effects of introduction of milk other than breast milk found that it was the age that milk other than breast milk was introduced rather than the duration of breastfeeding that was more closely associated with childhood asthma [132, 253]. However, the definition of milk other than breast milk was very broad, including cow's milk, soy milk, goat's milk and other dairy products. Another cohort study in the Netherlands found that introducing cow's milk before 6 months of age was not significantly associated with eczema or wheezing at 2, 3, or 4 years [209]. These inconsistent results might be due to the heterogeneous effects of different type of milk on the risk of allergic diseases [240, 241].

In the United States, the Department of Agriculture (USDA) and Department of Health and Human Services (HSS) commissioned a series of systematic reviews on diet and health [254]. One of these systematic review questions was to examine the associations of shorter versus longer duration of exclusive breast milk feeding prior to infant formula introduction with asthma, atopic dermatitis, food allergies, and allergic rhinitis [252]. However, only one case-control study, which was also included in our systematic review (**Chapter 3**), met their inclusion criteria [219]. Our own systematic review on the evidence describing the effects of the timing of cow's milk (CM) or cow's milk formula (CMF) introduction on the development of atopic diseases during childhood (**Chapter 3**) [5] also revealed that there was not enough high-quality evidence that would allow definitive conclusions on the associations of early CM or CMF introduction and risk of allergic diseases in children. Most of the studies

related to CMF introduction just focused on comparing different feeding patterns (such as exclusive breastfeeding vs. mixed feeding or exclusive breastfeeding vs. formula feeding) [134, 135, 204, 205, 212, 213, 217], or comparing exposure with non-exposure groups over a period of time [185, 200, 202, 215, 247, 255] but did not address the question of whether there is a critical window of infant formula exposure during infancy related to the development of atopic diseases. The review shows that there are only two cohort studies (both in European populations) that have examined the associations of different time of initiating formula feeding with the risk of childhood asthma [128, 130]. The first study was based on a Swedish cohort of 9,727 children, which showed that compared with children never introduced to infant formula, initiating formula feeding before 14 weeks of age was associated with increased risk of non-atopic asthma until age 15 to 17 years, but introduction after 14 weeks was not [128]. They also found that compared with children never introduced to infant formula, introducing infant formula before 4 weeks of age was associated with a higher risk of non-atopic asthma regardless of shorter (<4 weeks) or longer (≥ 16 weeks) breastfeeding duration. The Norwegian Mother and Child Cohort Study (MoBa) on 31,930 children showed that compared with the introduction at 6 months of age or later, the risk of asthma at age 7 years was increased when formula was introduced between 4 to 5.9 months of age, but not for introduction before 4 months of age [130].

Use of formula milk under 6 months is widespread despite international guidelines [54]. In a study among 90 low- and middle-income countries, there were 26 countries where formula feed was introduced within 6 months in more than 20% of infants; in 5 of these countries over

half of the infants started having formula feed within 6 months [54]. In China, exclusive breastfeeding is in decline, and at least 60% of infants were introduced to formula before 6 months [57, 256]. In this study, we examined the associations of different exposure window periods of initiating formula feeding with the risk of eczema and wheezing in the first year of life within a large birth cohort in China.

Methods

Setting & Study Population

The Born in Guangzhou Cohort Study (BIGCS), starting in February 2012, was set at two campuses of Guangzhou Women and Children's Medical Center (GWCMC), which is one of the best-equipped medical service providers of its kind in southern China and handles 12 000–15 000 deliveries annually. Details of the recruitment have been described elsewhere [174]. Children of the BIGCS who were singleton births between February 2012 and December 2015 were included in this analysis. Information about the mother and pregnancy was collected at recruitment (<20 gestational weeks) (Questionnaire 1, Q1), 24-28 (Q2) and 33-39 (Q3) weeks of gestation at antenatal clinics. Follow-up of the children took place at paediatric clinics at the age of 6 weeks, 6, and 12 months after birth and involved questionnaires (completed by the mother or guardian, Q5-7) and physical examinations. Although the parents or other guardians who were unable to take the child to attend the appointments at paediatric clinics in person were interviewed on the telephone, these children were excluded in this analysis due to the lack of information on the allergic disease (**Figure 4.1**). All the participants of BIGCS were unaware of the specific questions to be studied. Ethical approval

for the study was obtained from the ethics committees of GWCMC.

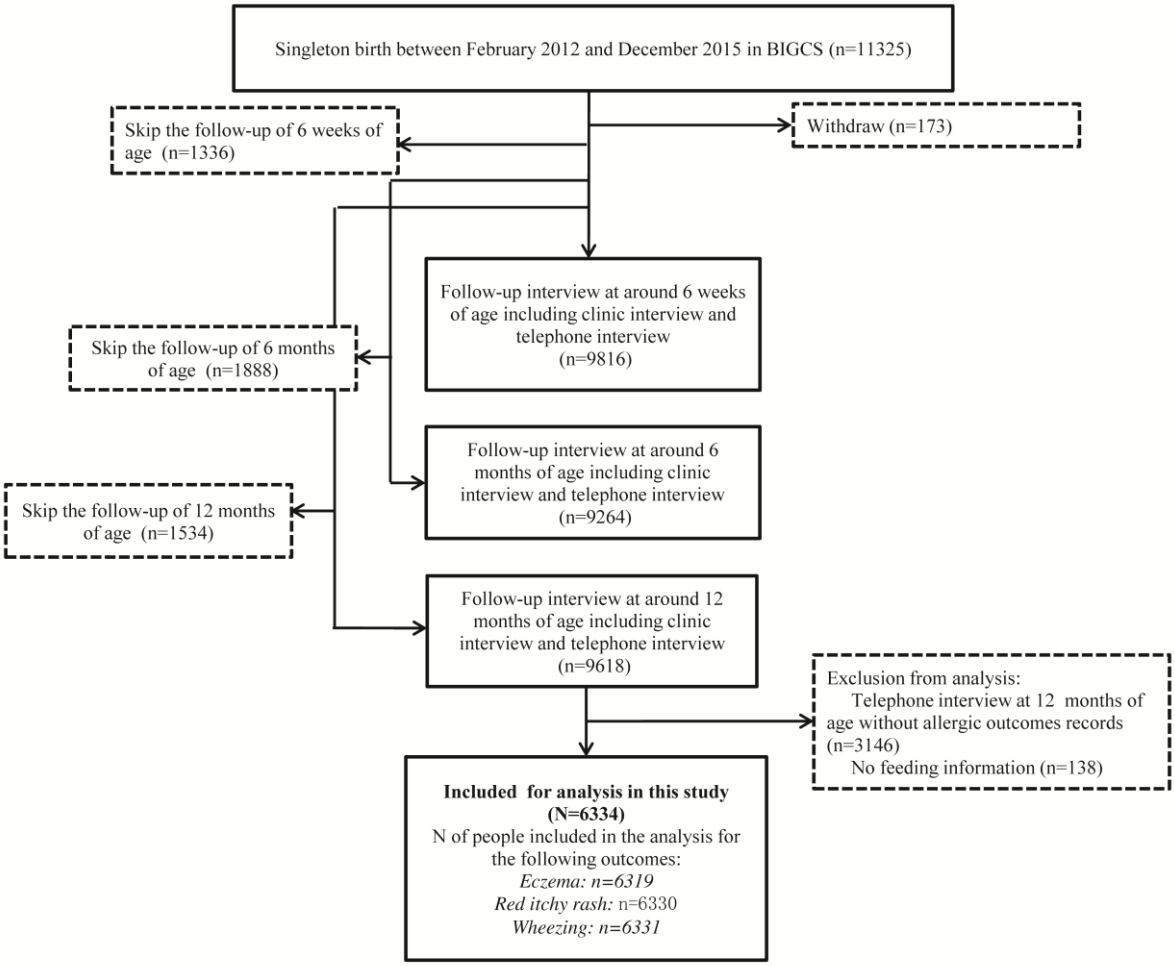


Figure 4.1 Flow chart of the study population

BIGCS, Born in Guangzhou Cohort Study

Measurements and assessments

Timing of infant formula and complementary food introduction

Information on formula feeding, complementary food introduction, and breastfeeding was collected via the self-administered questionnaires at 6 weeks (Q5), 6 months (Q6), and 12 months (Q7). 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 formula feed (standard cow's milk formula (CMF), Hydrolyzed formula, Preterm formula, and other types of formulas) and the age when the child first had the 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 the earliest time as the timing of the complementary food introduction.

Infant Outcomes

Eczema was defined as the parental report in the 12-month questionnaire that the infants had eczema diagnosed by a physician at least once between 6 months and 1 year of age. We also collected the information on the occurrence of itchy red rash, which is a typical symptom of eczema, before 1 year of age. Wheezing was defined as having at least one episode of wheezing or whistling breathing sounds between 6 months and 1 year of age based on the modified International Study of Asthma and Allergies in Children (ISAAC) questionnaire [257].

Covariates

Socio-demographic characteristics and potential confounders including maternal age,

maternal educational level, maternal smoking and passive smoking status during pregnancy, parental history of allergic diseases, and other health-related factors were recorded by the baseline questionnaire before 20 weeks of gestation. Obstetrics-related variables, including gestational age, birth weight, and infant sex, were extracted from the hospital clinical records. Information on antibiotics use was gathered at 6 and 12 months.

Statistical analysis

Logistic regression models were built to assess the relationships between the timing of infant formula introduction (categorized into three groups: 0-3, 4-6 and >6 months) and the development of eczema, itchy red rash and wheezing. The potential confounders, including maternal age at conception (≤25, 26-30, 31-35, >35 years), maternal education (high school or below, vocational/technical college, undergraduate, postgraduate), pre-pregnancy body mass index (BMI) (<18.5, 18.5-23.9, 24-27.9, ≥28 kg/m^2) [258], maternal smoking during pregnancy (yes, no), passive smoking during pregnancy (yes, no), preterm birth (yes, no), parity (primiparous, multiparaous), mode of delivery (vaginal labour, cesarean delivery), infant sex, parental history of atopic diseases (yes, no), antibiotic usage before 12 months of age (yes, no), the duration of breastfeeding (0-6, >6 months), and the timing of introduction any complementary food (0-3, 4-6 and >6 months) were entered into the model simultaneously. In addition, according to the timing of infant formula introduction and breastfeeding duration, five combined feeding patterns were defined: early formula introduction within 3 months of age and short breastfeeding (6 months or less) (≤3 m Formula + ≤6 m BF); early formula introduction within 3 months of age and long breastfeeding (over 6

months) (≤3 m Formula + >6 m BF); formula introduction between 4 to 6 months and short breastfeeding (4-6 m Formula + ≤6 m BF); formula introduction between 4 to 6 months and long breastfeeding (4-6 m Formula + >6 m BF); and formula introduction after 6 months (>6 m Formula). The modification effects of breastfeeding duration and complementary food introduction were also examined by adding an interaction term of these variables and the timing of infant formula introduction, respectively, in the models.

Given the proportion of missing data on confounder variables were from 0.1% to 17.3%, analyses based on complete cases may be biased. Thus, we used multiple imputation (MI) analysis to cope with missing data [176]. We used the fully conditional method (FCS) iterative method for imputation by using SAS 9.4. The following variables were imputed: pre-pregnancy BMI, maternal smoking during pregnancy, passive smoking during pregnancy, parity, mode of delivery, parental history of atopic diseases, antibiotic usage before 12 months of age, the duration of breastfeeding, and the timing of introduction of any complementary food. 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, 10 imputations were run. We ran a procedure call proc mianalyze which combines all the estimates (coefficients and standard errors) across all the imputed datasets and outputs one set of parameter estimates for the model of interest [177].

To reduce the potential overlaps in the timing between exposure and the occurrence of disease outcomes, we also performed sensitivity analyses. For eczema, we limited the analysis on the children with further information on the age at diagnosis of eczema, which was

collected by questionnaires at 3 years of age. Among the 6334 infants, 3018 children had completed questionnaires at 3 years old, 422 of them were diagnosed with eczema during the first year of life, and 32 were diagnosed with eczema before infant formula introduction. Therefore, 2986 infants were included in this sensitivity analysis. For itchy red rash and wheezing, we did not collect the information on the age of having these two symptoms by 3-year-old questionnaire. Thus, we only excluded the infants who had pre-existing wheezing and itchy red rash within the first 6 months of life, which were collected by questionnaire at 6 months old. Among the 6334 children, 4051 children had completed questionnaires at 6 months of age. For itchy red rash, 2484 infants were included for this sensitivity analysis. For wheezing, 3833 infants were included for this sensitivity.

Furthermore, the onset of wheezing is also associated with respiratory viral infections, which are related to the duration of breastfeeding [232, 233]. Thus, it is difficult to identify which one was actually caused by allergy. Therefore, sensitivity analyses were performed by excluding infants who had a history of respiratory infection before 12 months of age for wheezing.

The results are presented as crude odds ratios (OR) and adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI). The value of $P \leq 0.05$ was used to indicate statistical significance. The absolute risk difference for each outcome between different introduction groups was also assessed to estimate the population impact of early introduction of infant formulas on eczema. Predicted incidence and absolute risk differences were calculated by use of odds ratio and 95% confidence intervals based on the methods conducted

by Easton et al. [259].

All analyses were two-tailed and performed using SAS version 9.4 software (SAS Institute, Cary, NC).

Results

Study Population

There were 11,325 singleton births between February 2012 and December 2015, 6,334 of whom attended the BIGCS pediatric clinic at 12 months with information on their feeding practice and allergic disease status recorded (**Figure 4.1**). Of the 6,334 infants, the prevalence of eczema, itchy red rash and wheezing between 6 to 12 months of age was 17.4%, 28.5% and 7.2%, respectively. **Table 4.1** shows the characteristics of maternal and obstetric information relating to their infants between different infant formula introduction groups. In the early introduction group, mothers were more likely to be older and tended to have a lower education level, lower maternal pre-pregnancy BMI, and more likely to have a cesarean delivery. The infants were more likely to be male, have birth weight less than 2,500g, and be breastfed shorter than 6 months. Their parents were more likely to have a history of allergy. Also, the infants were more likely to have early-onset of eczema and wheezing (**Table 4.1**). The characteristics of maternal and obstetric information relating to the infant between the analytic sample and those who were excluded (interviewed on the phone only) were shown in **Supplementary material S5**. In the telephone call interview group, mothers were more likely to be younger and tended to have a lower education level, lower maternal pre-pregnancy BMI, and more likely to be multipara. The children in the telephone call interview group were more

likely to have a shorter duration of breastfeeding and an earlier infant formula introduction.

Table 4.1 Baseline characteristics of maternal and obstetric information relating to their infants between different infant formula introduction groups

Characteristics	Timing of any infant formulas introduction, months			No. of cases missing out of 6334 (%)
	≤3 m (n=5196)	4-6 m (n=575)	> 6 m (n=563)	
Mother				
Age at delivery (y), mean (SD)	29.5 (3.4)	29.1 (3.1)	29.0 (3.1)	0 (0%)
Educational level,n (%)				0 (0%)
High school or below	417 (8.0)	42 (7.3)	39 (6.9)	
Vocational/technical college	1315 (25.3)	129 (22.4)	127 (22.6)	
Undergraduate	2890 (55.6)	320 (55.7)	318 (56.5)	
Postgraduate	574 (11.1)	84 (14.6)	79 (14.0)	
Pre-pregnancy BMI, n (%)				153 (2.4%)
<18.5 kg/m^2	1229 (24.3)	128 (22.7)	117 (21.1)	
18.5-23.9 kg/m^2	3335 (65.9)	376 (66.7)	386 (70.0)	
24-27.9 kg/m^2	420 (8.3)	47 (8.3)	42 (7.6)	
≥28kg/m^2	79 (1.6)	13 (2.3)	9 (1.6)	
Parity, n (%)				3 (0%)
Primiparous	4615 (88.9)	520 (90.4)	481(85.4)	
Multiparous	578 (11.1)	55 (9.6)	82 (14.6)	
Delivery mode, n (%)				7 (0.1%)
Vaginal labor	3343 (64.4)	389 (67.7)	370 (65.8)	
Cesarean delivery	1847 (35.6)	186 (32.3)	192 (34.2)	
Smoking during pregnancy, n (%)	27 (0.5)	4 (0.7)	4 (0.7)	46 (0.7%)
Passive smoking during pregnancy, n (%)	1607 (31.4)	182 (32.0)	160 (28.5)	44 (0.7%)
Child				
Child's gender, n (%)				0 (0%)
Male	2787 (53.6)	269 (46.8)	283 (50.3)	

Female	2409 (46.4)	306 (53.2)	280 (49.7)	
Birth weight <2500g, n (%)	205 (4.0)	21 (3.7)	19 (3.4)	6 (0.1%)
Preterm birth, n (%)	250 (4.8)	28 (4.9)	21 (3.7)	0 (0%)
Duration of any breastfeeding, n (%)				189 (3.0%)
≤6 months	1453 (29.0)	107 (18.6)	2 (0.4)	
> 6 months	3555 (71.0)	468 (81.4)	560 (99.6)	
Parental history of allergy, n (%)	1484 (31.9)	143 (27.6)	149 (28.1)	637 (10.1%)
Antibiotic use before 12 months, n (%)	1247 (28.9)	120 (26.1)	142 (31.1)	1098 (17.3%)
Eczema, n (%)	939 (18.1)	92 (16.0)	71 (12.6)	15 (0.2%)
Eczema symptom (Red itchy rash), n (%)	1532 (29.5)	156 (27.1)	115 (20.4)	4 (0.1%)
Wheezing, n (%)	394 (7.6)	27 (4.7)	35 (6.2)	3 (0%)
Complementary food introduction, n (%)				10 (0.2%)
≤3 m	560 (10.8)	39 (6.8)	35 (6.2)	
4-6 m	4512 (87.0)	523 (91.0)	506 (90.0)	
>6 m	115 (2.2)	13 (2.2)	21 (3.8)	

Timing of infant formula and complementary food introduction

The distribution of the timing of infant formula and complementary food introduction is shown in **Figure 4.2**. A large proportion of infants (78.4%) were introduced to infant formula before 4 weeks of age. Among the 6334 children, 5600 children provided information on the type of formula. There were 5142 (91.8%) children fed CMF, 279 (5.0%) fed hydrolyzed formula, 61 (1.1%) fed preterm formula, and 118 (2.1%) fed other types of formula. Cereal, fruit, and egg yolk were the most common complementary foods firstly introduced to the infant diet. Allergenic foods such as fish, other seafood, and egg white were on average introduced beyond 30 weeks of age in most of the infants. The distribution of formula introduction and breastfeeding patterns are shown in **Figure 4.3**. More than half of the infants had additionally received infant formula as a supplement within 3 months and continued to be breastfed for more than 6 months.

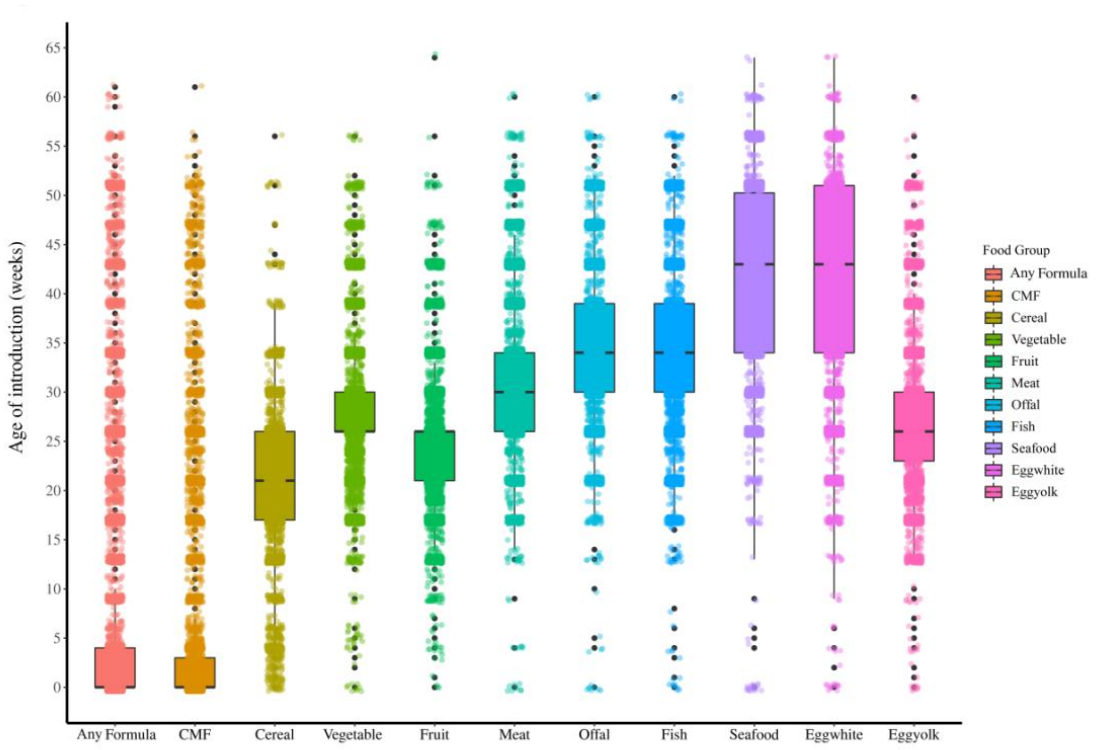


Figure 4.2 The distribution of the timing of infant formula and complementary food introduction (n=6334)

CMF:cow's milk formula

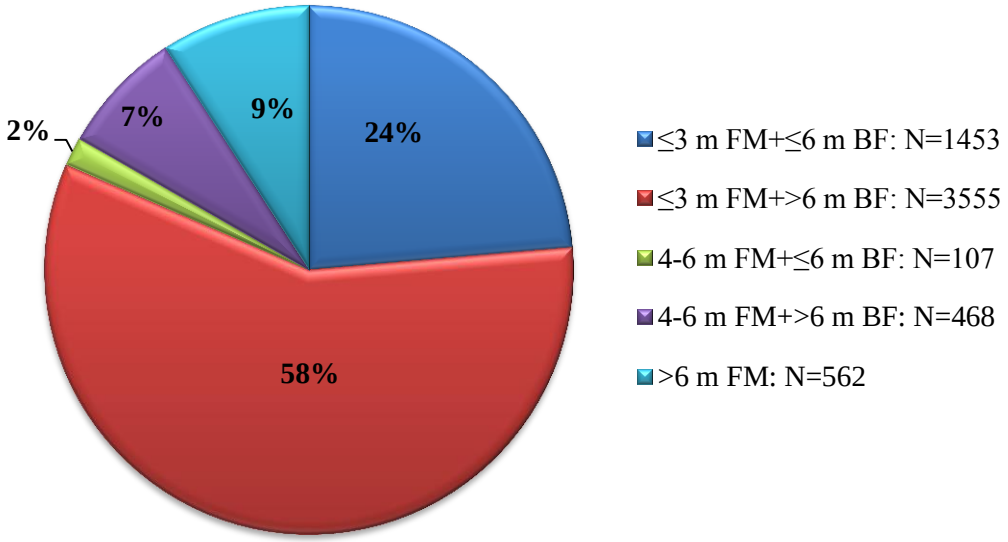


Figure 4.3 The distribution of combined feeding patterns of infant formula introduction and breastfeeding duration in BIGCS population.

≤3 m FM+≤6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was 6 months or less
≤3 m FM+>6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was over 6 months
4-6 m FM+≤6 m BF: Formula was introduced between 4-6 months of age and breastfeeding was 6 months or less
4-6 m FM+>6 m BF: Formula was introduced between 4-6 months of age and duration of breastfeeding was over 6 months
>6 m FM: Formula was introduced after 6 months of age
FM: formula feeding, BF: breastfeeding

Associations between the timing of infant formula and risk of eczema or itchy red rash before 1 year of age

Among infants who started to be fed infant formula within the first 3 months of life, the risk of eczema before 1 year of age was 44% greater (aOR, 1.44; 95% CI, 1.06 to 1.95) and the risk of itchy red rash was 59% greater (aOR, 1.59; 95% CI, 1.23 to 2.05) than the risks among infants who were introduced to formula after 6 months of age (**Figure 4.4**). After multiple imputation, the effect size for introducing formula within the first 3 months and risk of eczema (aOR, 1.43; 95% CI, 1.1.10 to 1.87) and itchy red rash (aOR, 1.55; 95% CI, 1.25 to 1.93) were changed slightly (**Figure 4.4**). The modification effects of breastfeeding duration and the complementary food introduction on these associations were non-significant (**Supplementary material S6**).

Timing of introduction, months	Case （n%）	Unadjusted	Adjusted before multiple imputation	Adjusted after multiple imputation
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Eczema		**n=6319**	**n=4445**	**n=6319**
Any formula				
⩽3 m	939 (18.1)	1.53 (1.18-1.99)	1.44 (1.06-1.95)	1.43 (1.10-1.87)
4-6 m	92 (16.0)	1.32 (0.95-1.84)	1.36 (0.92-2.01)	1.30 (0.93-1.83)
> 6 m	71 (12.6)	1	1	1
CMF				
⩽3 m	747 (18.0)	1.48 (1.13-1.94)	1.35 (0.98-1.85)	1.39 (1.07-1.80)
4-6 m	75 (15.9)	1.27 (0.89-1.82)	1.26 (0.83-1.92)	1.27 (0.87-1.85)
> 6 m	65 (12.9)	1	1	1
Itchy rash		**n=6330**	**n=4451**	**n=6330**
Any formula				
⩽3 m	1532 (29.5)	1.63 (1.32-2.02)	1.59 (1.23-2.05)	1.55 (1.25-1.93)
4-6 m	156 (27.1)	1.45 (1.10-1.91)	1.50 (1.08-2.08)	1.42 (1.08-1.88)
> 6 m	115 (20.4)	1	1	1
CMF				
⩽3 m	1227 (29.5)	1.57 (1.25-1.96)	1.50 (1.15-1.96)	1.56 (1.24-1.96)
4-6 m	128 (27.1)	1.39 (1.04-1.87)	1.44 (1.02-2.05)	1.40 (1.06-1.87)
> 6 m	106 (21.0)			1
Wheezing		**n=6331**	**n=4453**	**n=6331**
Any formula				
⩽3 m	394 (7.6)	1.24 (0.87-1.77)	1.24 (0.80-1.90)	1.16 (0.80-1.69)
4-6 m	27 (4.7)	0.75 (0.44-1.25)	0.78 (0.42-1.45)	0.76 (0.45-1.29)
> 6 m	35 (6.2)	1	1	1
CMF				
⩽3 m	324 (7.8)	1.29 (0.88-1.88)	1.17 (0.75-1.83)	1.25 (0.85-1.85)
4-6 m	22 (4.7)	0.75 (0.43-1.31)	0.74 (0.38-1.43)	0.78 (0.44-1.38)
> 6 m	31 (6.2)	1	1	1

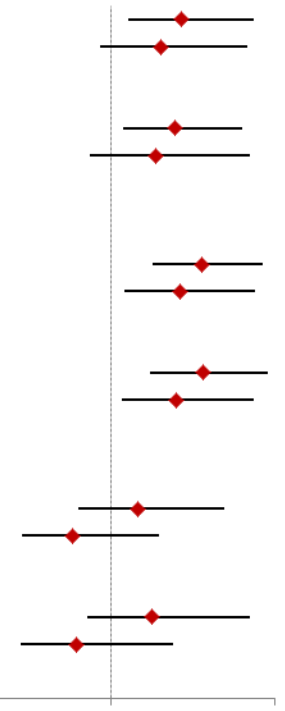


Figure 4.4 The associations between timing of introducing infant formulas and the risk of eczema and wheezing up to the age of 1 year old (Before and after multiple imputation) (n=6334)

Adjusted for maternal age at baseline, maternal education, pre-pregnancy BMI, smoking status during pregnancy, passive smoking status during pregnancy, parity, delivery mode, preterm birth, the gender of infant, parental history of atopy, antibiotic usage before 12 months, breastfeeding duration, and the timing of introduction of any complementary food. CMF: cow's milk formula.

When looking at the feeding pattern by combining timing of formula introduction and breastfeeding duration, compared with late infant formula introduction (after 6 months), introducing formula within 3 months of age was associated with an increased risk of eczema and itchy red rash regardless of whether the children were breastfed less than 6 months (Eczema: aOR, 1.57; 95% CI, 1.18 to 2.09; aOR, 1.69; Itchy red rash: 95% CI, 1.33 to 2.14, respectively) or over 6 months (Eczema: aOR, 1.45; 95% CI, 1.12 to 1.90; Itchy red rash: aOR, 1.55; 95% CI, 1.25 to 1.94) in multiple imputation models (**Table 4.2**).

We also performed an analysis by stratifying the infants according to the parental history of atopy, and found that the associations between feeding patterns and the risk of eczema were kept significant in the children without a parental history of atopy. However, in the high-risk children, who had one or more parent with a history of atopy, the associations between feeding pattern and the risk of eczema became non-significant (**Table 4.3**).

Table 4.2 Combined feeding patterns of infant formula introduction and breastfeeding duration in association with risk of eczema and wheezing (Before and after multiple imputation)

Feeding pattern	Case （n%）	Unadjusted	Adjusted before multiple imputation	Adjusted after multiple imputation
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Eczema		**n=6319**	**n=4445**	**n=6319**
≤3 m FM + ≤6 m BF	280 (19.4)	1.69 (1.27-2.24)	1.60 (1.15-2.23)	1.57 (1.18-2.09)
≤3 m FM + >6 m BF	627 (17.7)	1.51 (1.16-1.97)	1.43 (1.05-1.94)	1.45 (1.12-1.90)
4-6 m FM + ≤6 m BF	15 (14.0)	1.15 (0.63-2.09)	0.88 (0.40-1.93)	1.15 (0.63-2.09)
4-6 m FM+ >6 m BF	77 (16.5)	1.38 (0.98-1.96)	1.48 (0.99-2.22)	1.38 (0.98-1.96)
>6 m FM	70 (12.5)	1	1	
Itchy rash		**n=6330**	**n=4451**	**n=6330**
≤3 m FM + ≤6 m BF	448 (30.8)	1.73 (1.37-2.19)	1.81 (1.37-2.39)	1.69 (1.33-2.14)
≤3 m FM + >6 m BF	1032 (29.1)	1.59 (1.28-1.98)	1.59 (1.23-2.05)	1.55 (1.25-1.94)
4-6 m FM + ≤6 m BF	30 (28.0)	1.51 (0.95-2.42)	1.57 (0.89-2.79)	1.49 (0.93-2.40)
4-6 m FM+ >6 m BF	126 (26.9)	1.43 (1.07-1.91)	1.52 (1.08-2.15)	1.43 (1.06-1.92)
>6 m FM	115 (20.5)	1	1	
Wheezing		**n=6331**	**n=4453**	**n=6331**
≤3 m FM + ≤6 m BF	128 (8.8)	1.46 (0.99-2.14)	1.89 (1.20-2.99)	1.52 (1.02-2.27)
≤3 m FM + >6 m BF	248 (7.0)	1.13 (0.78-1.63)	1.26 (0.82-1.93)	1.16 (0.79-1.70)
4-6 m FM + ≤6 m BF	7 (6.5)	1.05 (0.46-2.44)	1.61 (0.63-4.12)	1.13 (0.46-2.77)
4-6 m FM+ >6 m BF	20 (4.3)	0.67 (0.38-1.18)	0.69 (0.35-1.38)	0.74 (0.42-1.33)
>6 m FM	35 (8.0)	1	1	1

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age and the timing of introduction any complimentary food.

≤3 m FM+≤6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was 6 months or less

≤3 m FM+>6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was over 6 months

4-6 m FM+≤6 m BF: Formula was introduced between 4-6 months of age and breastfeeding was 6 months or less

4-6 m FM+>6 m BF: Formula was introduced between 4-6 months of age and duration of breastfeeding was over 6 months

>6 m FM: Formula was introduced after 6 months of age

FM: formula feeding, BF: breastfeeding

Table 4.3 Combined feeding patterns of infant formula introduction and breastfeeding duration in association with risk of eczema and wheezing according to the parental history of allergy

	High risk (n=1722)		Children with no parents with allergies (n=3809)		Likelihood-ratio test
	Unadjusted	Adjusted after MI	Unadjusted	Adjusted after MI	*P-value*
	OR (95% CI)		OR (95% CI)		
Eczema					
≤3 m FM + ≤6 m BF	1.48 (0.87-2.50)	1.43 (0.84-2.41)	1.79 (1.25-2.56)	1.63 (1.15-2.31)	0.820
≤3 m FM + >6 m BF	1.54 (0.95-2.50)	1.49 (0.93-2.40)	1.55 (1.11-2.17)	1.45 (1.05-2.00)	0.503
4-6 m FM + ≤6 m BF	0.81 (0.26-2.54)	0.79 (0.25-2.50)	1.21 (0.56-2.61)	1.30 (0.62-2.73)	0.510
4-6 m FM+ >6 m BF	1.54 (0.80-2.97)	1.52 (0.79-2.90)	1.34 (0.86-2.08)	1.33 (0.87-2.03)	0.439
>6 m FM	1	1	1	1	
Itchy rash					
≤3 m FM + ≤6 m BF	2.14 (1.36-3.38)	2.17 (1.36-3.45)	1.48 (1.11-1.97)	1.47 (1.11-1.95)	0.372
≤3 m FM + >6 m BF	1.93 (1.26-2.95)	1.95 (1.28-2.98)	1.40 (1.08-1.82)	1.41 (1.09-1.82)	0.484
4-6 m FM + ≤6 m BF	1.27 (0.52-3.10)	1.34 (0.56-3.20)	1.50 (0.83-2.69)	1.57 (0.88-2.81)	0.254
4-6 m FM+ >6 m BF	2.22 (1.26-3.90)	2.18 (1.25-3.81)	1.16 (0.81-1.66)	1.20 (0.85-1.69)	0.071
>6 m FM	1	1	1	1	
Wheezing					
≤3 m FM + ≤6 m BF	0.96 (0.52-1.77)	0.97 (0.51-1.84)	2.01 (1.17-3.45)	1.97 (1.14-3.41)	0.894
≤3 m FM + >6 m BF	0.77 (0.44-1.35)	0.78 (0.43-1.41)	1.50 (0.90-2.52)	1.54 (0.92-2.58)	0.905
4-6 m FM + ≤6 m BF	0.52 (0.11-2.38)	0.46 (0.10-2.17)	1.76 (0.62-4.93)	1.84 (0.64-5.29)	0.729
4-6 m FM+ >6 m BF	0.32 (0.10-0.98)	0.37 (0.12-1.13)	0.94 (0.45-1.97)	1.08 (0.52-2.25)	0.407
>6 m FM	1	1	1	1	

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive

smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age and the timing of introduction any complimentary food.

≤3 m FM+≤6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was 6 months or less

≤3 m FM+>6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was over 6 months

4-6 m FM+≤6 m BF: Formula was introduced between 4-6 months of age and breastfeeding was 6 months or less

4-6 m FM+>6 m BF: Formula was introduced between 4-6 months of age and duration of breastfeeding was over 6 months

>6 m FM: Formula was introduced after 6 months of age

BF: breastfeeding; FM: formula feeding; MI: multiple imputation

In the sensitivity analyses, we considered potential overlap between timing of formula introduction and diagnosis of eczema by limiting to the infants with further information on the age at diagnosis. Among the 6334 infants, 3018 infants had completed questionnaires at 3 years old, 422 of them were diagnosed with eczema during the first year of life, 32 were diagnosed eczema before infant formula introduction. Therefore, 2986 infants were included in this sensitivity analysis. We found that introducing formula within 3 months of age remained associated with a higher risk of eczema (aOR, 2.28; 95% CI, 1.35 to 3.87) (**Table 4.4**). Furthermore, early signs of atopic sensitivity may influence breastfeeding and/or decision on when to introduce infant formula. The consequence could also bias the estimates of the association. Therefore, we performed further analysis by excluding infants with itchy red rash before 6 months. There were 1995 infants' parents reported having no itchy red rash before 6 months and between 6 to 12 months of age, and 489 reported having itchy red rash only between 6 to 12 months. Finally, 2484 infants were included for this sensitivity analysis. The associations between early formula introduction and risk of itchy red rash remained significant (**Table 4.5**).

Table 4.4 Sensitivity analyses on associations between timing of infant formula introduction and the risk of eczema by excluding infants who have diagnosed eczema earlier than the initiation of formula feeding (n=2986)

Timing of introduction, months	Case (%)	OR (95% CI)		
		Unadjusted	Adjusted before MI	Adjusted after MI
Any formula				
≤3 m	341 (14.1)	2.18 (1.30-3.67)	2.71 (1.35-5.43)	2.28 (1.35-3.87)
4-6 m	25 (9.8)	1.43 (0.74-2.75)	1.74 (0.74-4.08)	1.49 (0.77-2.88)
> 6 m	16 (7.0)	1	1	
CMF				
≤3 m	257 (13.5)	1.49 (0.82-2.72)	2.13 (0.96-4.73)	1.50 (0.81-2.79)
4-6 m	14 (8.0)	1.00 (0.47-2.12)	1.15 (0.41-3.22)	1.00 (0.46-2.17)
> 6 m	10 (6.9)	1	1	1

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age, the duration of breastfeeding, and the timing of introduction any complimentary food.

CMF: cow's milk formula; MI: multiple imputation

Table 4.5 Sensitivity analyses on associations between timing of infant formula introduction and the risk of the itchy red rash by excluding children with the symptom before 6 months of age (n=2484)

Timing of introduction, months	Case (%)	OR (95% CI)		
		Unadjusted	Adjusted before MI	Adjusted after MI
Any formula				
≤3 m	418 (20.5)	1.91 (1.27-2.88)	1.68 (1.08-2.62)	1.77 (1.17-2.69)
4-6 m	43 (20.9)	1.96 (1.17-3.29)	1.76 (0.99-3.12)	1.88 (1.12-3.17)
> 6 m	28 (11.9)	1	1	1
CMF				
≤3 m	356 (20.8)	1.62 (1.09-2.40)	1.39 (1.00-1.92)	1.52 (1.01-2.26)
4-6 m	39 (20.3)	1.61 (0.96-2.70)	1.53 (1.00-2.34)	1.57 (0.94-2.61)
> 6 m	26 (12.4)	1	1	1

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age, the duration of breastfeeding, and the timing of introduction any complimentary food.

CMF: cow's milk formula; MI: multiple imputation

Associations between the timing of infant formula introduction and wheezing before 1 year of age

In the fully adjusted model including the timing of any complementary food introduction, no significant associations between the timing of infant formula (≤3 vs. >6 months: aOR, 1.24; 95% CI: 0.80 to 1.90; 4-6 vs. >6 months: aOR, 0.78; 95% CI: 0.42 to 1.45) or CMF (≤3 vs. >6 months: aOR, 1.17; 95% CI: 0.75 to 1.83; 4-6 vs. >6 months: aOR, 0.74; 95% CI: 0.38 to 1.43) introduction and risk of wheezing before 1 year of age was found (**Figure 4.4**). After multiple imputation, the association between introducing formula within the first 3 months and the risk of wheezing was still not significant (aOR, 1.16; 95% CI, 0.80 to 1.69) (**Figure 4.4**). When we limited the analysis to children without wheezing before 6 months, no significant associations between the timing of infant formula introduction and the risk of wheezing were found (**Table 4.6**).

When looking at the feeding pattern by combining timing of formula introduction and breastfeeding duration, both before and after multiple imputation, introducing infant formula within the first 3 months and shorter breastfeeding duration was associated with the higher risk of wheezing compared with introducing formula after 6 months of age (Before multiple imputation: aOR, 1.89; 95% CI, 1.20-2.99; After multiple imputation: aOR, 1.52; 95% CI, 1.02-2.27) (**Table 4.3**). When we excluded the infants with respiratory infections before 1 year of age, there were no significant associations between these feeding patterns and the risk of wheezing observed in multiple imputation models (**Table 4.7**).

Table 4.6 Sensitive analyses on associations between timing of introducing infant formula and the risk of the wheezing by excluding pre-existing wheezing before 6 months of age (n=3833)

Timing of introduction, months	Case (%)	OR (95% CI)		
		Unadjusted	Adjusted before MI	Adjusted after MI
Any formula				
≤3 m	186 (5.8)	1.30 (0.76-2.23)	1.14 (0.62-2.08)	1.13 (0.65-1.98)
4-6 m	18 (5.7)	1.27 (0.63-2.57)	1.08 (0.48-2.43)	1.17 (0.57-2.41)
> 6 m	15 (4.6)	1	1	1
CMF				
≤3 m	159 (6.0)	1.26 (0.72-2.19)	1.02 (0.55-1.90)	1.10 (0.61-1.95)
4-6 m	18 (6.1)	1.25 (0.60-2.58)	1.01 (0.45-2.27)	1.16 (0.55-2.44)
> 6 m	14 (4.7)	1	1	1

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age, the duration of breastfeeding, and the timing of introduction any complimentary food.

CMF: cow's milk formula; MI: multiple imputation

Table 4.7 Sensitivity analyses on associations of combined feeding patterns of infant formula introduction and breastfeeding duration with the risk of wheezing by excluding respiratory infection before 1 year of age (n=3545)

Timing of introduction, months	Case (%)	Adjusted OR (95% CI)		
		Unadjusted	Adjusted before MI	Adjusted after MI
≤3 m FM + ≤6 m BF	39 (5.0)	2.01 (0.93-4.35)	4.27 (1.28-14.21)	1.95 (0.89-4.26)
≤3 m FM + >6 m BF	79 (3.9)	1.58 (0.76-3.28)	3.05 (0.94-9.85)	1.61 (0.77-3.38)
4-6 m FM + ≤6 m BF	3 (4.7)	1.99 (0.50-7.86)	5.60 (1.08-29.11)	1.87 (0.47-7.49)
4-6 m FM+ >6 m BF	4 (1.5)	0.61 (0.18-2.03)	1.21 (0.24-6.10)	0.65 (0.19-2.16)
>6 m FM	8 (6.0)	1	1	1

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12 months of age and the timing of introduction any complimentary food.

≤3 m FM+≤6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was 6 months or less

≤3 m FM+>6 m BF: Formula was introduced within 3 months of age and duration of breastfeeding was over 6 months

4-6 m FM+≤6 m BF: Formula was introduced between 4-6 months of age and breastfeeding was 6 months or less

4-6 m FM+>6 m BF: Formula was introduced between 4-6 months of age and duration of

breastfeeding was over 6 months
>6 m FM: Formula was introduced after 6 months of age
BF: breastfeeding; FM: formula feeding; MI: multiple imputation

Discussion

In this population-based prospective cohort study, we found that compared with introducing infant formula after 6 months, introducing it within the first 3 months and between 4 to 6 months of life was likely to be associated with the higher risk of eczema in the first year, though the latter did not reach statistical significance. In addition, introducing infant formula within the first 3 months combined with having shorter breastfeeding duration seems to be associated with the higher risk of wheezing, compared with introducing formula after 6 months of age.

The protective effects of breastfeeding on atopic diseases have been studied extensively [8, 245]. A multicentre, cluster-randomized controlled trial conducted in the Republic of Belarus, the Promotion of Breastfeeding Intervention Trial (PROBIT), indicated that the breastfeeding promotion intervention, increasing the duration and exclusivity of breastfeeding, was associated with a lower risk of atopic eczema in the first year of life (3.3% vs. 6.3%, adjusted OR 0.54, 95% CI: 0.31 to 0.95) [159]. However, even continuing breastfeeding, early introduction of milk other than breast milk may also contribute to the development of allergic diseases. Two Australian cohort studies demonstrated that the age of non-breast milk introduction was more closely related to asthma rather than the breastfeeding duration [253, 260]. In this study, we only looked at the timing of introduction of one type of non-breast milk, infant formula. Although most infant formula is based on processed cow's milk, we chose not to examine infant formula and cow's milk together, because there is a clear recommendation for optimal timing of cow's milk

introduction, not before 9 months of age [83].

During early infancy, particularly the first 3 months, the immune system matures rapidly but is still vulnerable [75]. The maturation process can be influenced by multiple factors, among which nutrition is considered to be a significant element [74]. A dietary trial in Germany among high-risk infants indicated that when compared to supplement feeding of CMF, exclusive breastfeeding during the first 4 months showed a protective effect on eczema before 3 years old (adjusted OR, 0.64; 95% CI, 0.45 to 0.90) [247]. A cohort study from the UK showed that during the first 3 months of life, compared with no formula feeding, children introduced to formula had significantly more asthma at age 4 years [202]. In addition to early exposure, before 3 or 4 months of age, the effects of formula exposure during 4-6 months of age on the risk of asthma have been examined by the MoBa study. They showed that compared with after 6 months of age, the risk of asthma was increased when infant formula was introduced between 4 to 5.9 months of age (adjusted RR: 1.21, 95%CI: 1.03 to 1.44), but the association was not significant for introduction before 4 months (adjusted RR 1.10, 95%CI: 0.98 to 1.25) [130]. In our study, the risk of eczema before 1 year of age was increased when infant formula was introduced within 3 months of life compared with after 6 months.

Longer duration of breastfeeding has been considered as a preventive factor for the development of allergy [8, 159]. However, when we stratified the children by combining the timing of infant formula introduction and duration of breastfeeding, the results showed that introducing infant formula within 3 months of life increased the risk of eczema regardless of

short (≤6 months) or long (>6 months) duration of breastfeeding. The Sweden cohort study also found that in children with longer breastfeeding duration (over 16 weeks), early introduction of formula before 4 weeks of age was associated with increased risk of asthma, compared with those never introduced [128]. These findings indicated that, even in children with longer duration of breastfeeding, early infant formula introduction might be associated with a higher risk of allergy.

Most evidence on the effects of early feeding emanated from observational studies, the possible influence of reverse causation, whereby parental history of allergy or early skin symptoms might influence breastfeeding behaviour and/or decision on when to feed infant formula, should be taken into careful consideration [261]. In our study, we found that the parents who reported a history of allergy did not delay the formula introduction to their infants. Furthermore, we performed the sensitivity analyses respectively by only including the infants who were diagnosed eczema after the infant formula introduction, and who started to have itchy red rash after 6 months. The associations were still significant, suggesting that reverse causation is unlikely in our study.

For wheezing, before and after multiple imputation for missing confounders, no significant associations between the timing of infant formula introduction and risk of wheezing were found. However, the prevalence of wheezing (7.2%) was much lower than eczema (17.4%) in our population. Thus, we had a more modest power to detect a relationship with wheezing. When looking at the feeding pattern by combining timing of formula introduction and breastfeeding duration, we found that introducing infant formula within the first 3 months

combined with shorter breastfeeding duration was associated with the higher risk of wheezing, compared with introducing formula after 6 months of age. However, when limited the analyses to the infants without the respiratory infection before 1 year of age, the associations of combined feeding patterns with risks of wheezing turned to non-significant after multiple imputation. These results could be explained by the findings from previous studies that the onset of wheezing and asthma is also associated with respiratory viral infections which are related to the duration of breastfeeding [232, 233]. Further studies need to be considered to classify the type of wheezing in order to distinguish whether it is caused by allergy or infection.

In this cohort, over 80% of infants initiated infant formula supplementation within the first 3 months of life. Sales of infant formula are flourishing in China, which has undergone the greatest increase in formula sales in the world, growing by 106.0% in 2008-2013 [64]. The infant formula "sales boom" is not only underway in China, but also in other middle-income countries [64]. However, the influence of these changes of feeding practice on the short or long term health problems has not been assessed well outside Western countries. Our findings contribute new evidence regarding the association between timing of infant formulas introduction and risk of early-onset eczema and wheezing during infancy in an Asian population. Eczema/atopic dermatitis is one of the most common atopic disorders in infants and young children and over 60% of cases manifest during the first year of life [262]. Eczema may cause distressing itch, mood changes and sleep deprivation and affect neurodevelopment and behaviours [242]. Also, caring for an infant with eczema/atopic dermatitis influences

parenting, spousal relationships and family life [263]. Several studies have provided evidence that early eczema was associated with the subsequent development of allergic airway diseases [264-266]. Therefore, early eczema should also be taken seriously. The management of breast milk substitute's sales should be strengthened to eliminate the sales promotion of these products for young infants. In addition, the adverse health effects of formula feeding, including exclusive formula or partial formula feeding, at a young age on children's health should be mentioned in guideline chapters on formula feeding, rather than simply emphasizing the benefits of breastfeeding.

Strengths and limitations of the study

In this large prospective cohort study, we adjusted for a wide range of potential confounders, including the timing of complementary foods introduction and evaluated the modification effects of parental history of atopy, breastfeeding duration, and infant's gender. To examine impact of missing confounders we performed imputation analyses addressing this. Results from imputation analysis strengthened our main findings that the early introduction of infant formula was associated with a higher risk of eczema. Also, for imputed models, we found a reasonable low fraction of missing information (FMI) < 0.20 (The Supplementary material S7) which indicates low variability between imputed data sets; that means the observed data in the imputation models provide much information about the missing values [267]. However, several limitations need to be considered when interpreting our results. The high prevalence of formula feeding within the first 3 months of life in the study limits the power to study the subgroup who was introduced between 4 to 6 months. In addition, the information on the

timing of infant formulas and complementary foods introduction was collected retrospectively when the child was 6 weeks, 6 and 12 months old. Thus, misclassification due to differential recall was possible but unlikely as the parents and interviewers were not informed of the specific research questions. However, for some parents, the information on formula feeding at the maternity ward might be forgotten to report, which may cause misclassification. In addition, some risk factors related to the development of allergy such as indoor and outdoor air pollution [268], microbiota [269], and pet ownership [270], were not collected in this study, which may have impact on our results. Another limitation of this study is the lack of information on the amount and duration of formula feeding which also might be associated with the development of allergy. For the outcomes, though the clinical diagnosis of eczema and wheezing would be more accurate, misclassification due to parental reports was unlikely to have influenced the effect of timing of food allergen introduction on the outcomes. In addition, the rate of parental reports of physician-diagnosed eczema in our population was 17.4% very closed to the national survey in infants under 24 months of age that reported an 18.5% prevalence of physician-diagnosed eczema [22]. In this study, we have only analysed that early-onset eczema and wheezing before 1 year of age, because previous evidence has indicated eczema or wheezing during this critical period could predict allergic diseases and autoimmune disorders later in life. It has also been shown previously that infant diet had a stronger effect on short-term atopic diseases than on long-term outcomes [271]. Nevertheless, follow-up of the BIGCS cohort is still ongoing, allowing extended evaluation of the association between infant diet and atopic diseases beyond the first year.

Conclusions

Compared with introducing infant formula after 6 months, introducing it within the first 3 months was significantly associated with the higher risks of eczema during the first year. In addition, introducing infant formula within the first 3 months combined with having shorter breastfeeding duration was associated with a higher risk of wheezing, compared with introducing formula after 6 months of age. However, the results need to be replicated in other well-designed studies before more firm recommendations can be made.

Chapter 5 Patterns of food introduction in the first year of life and atopic risk in children under 3 years of age: the Born in Guangzhou Cohort Study (BIGCS)

Abstract

Importance: Cumulative evidence indicates that early dietary factors play an important role in the development of atopic diseases. However, prospective data on the effects of a gradual transition process of early infant diet on allergy development is scarce.

Objective: To assess the association between food introduction patterns in the first year of life and development of atopic diseases by age 3 years.

Design, Setting, And Participants: This prospective birth cohort study used information from the BIGCS cohort. There were 4346 children born between 2012 and 2015 included in this study.

Exposures: Timing of introduction of infant formula and complementary food, and breastfeeding duration was collected by self-administered questionnaires at 6 weeks, 6 and 12 months of age. Multiple imputation analysis was performed for dealing with missing covariate data.

Main Outcomes: Information on the outcomes was collected by questionnaire on parentally reported physician diagnoses for eczema, asthma, atopic rhinitis, and food allergy at age 3 years.

Results: The four introduction patterns identified were labelled as the ‘early formula & late seafood & late egg white’, ‘early formula & late complementary food’, ‘early formula & early complementary food’ and ‘late formula’. These patterns, which reflect variations in weaning practice, are associated with allergy development. After multiple imputation, compared with ‘late formula’ pattern, ‘early formula & late seafood & late egg white’, ‘early formula & late

complementary food', and 'early formula & early complementary food' were all associated with the increased risk of eczema (adjusted OR: 1.72; 95%CI, 1.06-2.80; adjusted OR: 1.85; 95%CI, 1.08-3.19; adjusted OR:1.69; 95%CI, 1.04-2.77). There were no significant associations between introduction patterns and risks of other allergic outcomes.

Conclusions: Compared with 'late formula' pattern, 'early formula & late seafood & late egg white', 'early formula & late complementary food', and 'early formula & early complementary food' patterns were all associated with the increased risk of eczema before 3 years of age. Though the associations of food introduction patterns with asthma, allergic rhinitis, and food allergy were not significant in this study, the possible association should be considered in further studies. The results need to be replicated in other larger cohorts to provide more robust evidence on the development of future allergy prevention guidelines.

Introduction

Atopic diseases have reached epidemic proportions worldwide, and become the most common chronic conditions in childhood [257]. Atopic dermatitis or eczema, asthma, allergic rhinitis, and food allergy, are common atopic diseases in childhood and pose a great burden to the family and society [17, 242, 272, 273]. Early-life exposure has been considered as an important role in modifying the likelihood of developing atopic diseases [274]. There is sustained interest in the role of diet during infancy in the risk of developing allergic manifestations, with research looking at the timing of important feeding events, such as the first time of allergic food introduction, during early life [5, 9, 275]. A systematic review on the timing of allergic food introduction to the infant diet and risk of allergic or autoimmune diseases found that the first introduction of peanut between 4 to 11 months of age was related to decreased peanut allergy and the first introduction of egg between 4 to 6 months of age was related to reduced egg allergy compared with later introduction of these foods [9].

Although the diet of infants is much simpler than that of adults, the gradual transition process from milk-based to solid-food are complex and may be the source of new antigens to the infants whose immune system is not mature and still vulnerable [74]. This process containing a number of dietary variables might be contributing to the development of allergic diseases in infants. Most previous studies mainly focused on the impacts of a particular nutrient or a single food on the development of atopic diseases [9, 276, 277], which oversimplifies the synergistic effects and the complex interrelationships between many foods. Therefore, looking at the pattern of food introduction to the infant diet instead of focusing on

single food introduction can better inform about interactions of known or unknown effects between many foods and nutrients. The dietary pattern analysis has been broadly used in nutritional epidemiology [278]. While accumulated data showed that the timing of solid food introduction is associated with the development of atopic diseases, quite limited studies looking at the effects of food introduction patterns during early infancy have been reported. As far as we know, only one nested, case-control, within-cohort study investigated whether infant feeding patterns were associated with the development of food allergy [279].

This study focused on the timing patterns of introducing different food to the infant diet, i.e. introduction patterns, and allergy outcomes including eczema, asthma, allergic rhinitis, and food allergy, before 3 years of age by using data from a large prospective cohort study, Born in Guangzhou Cohort Study (BIGCS).

Methods

Study Design and Population

The BIGCS is a prospective birth cohort study conducted in Guangzhou, China. The detail of BIGCS study has been described previously [174]. Pregnant women were recruited before 20 gestational weeks from two campuses of Guangzhou Women and Children's Medical Center (GWCMC) from February 2012. 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 pediatric 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 some parents or caregivers who were unable to take their children to attend the appointments in person were interviewed on the telephone, they were excluded in this analysis due to the lack of information on allergic disease. Children with incomplete feeding data were also excluded.

Feeding Information

Information on age of first introduction of infant formula and complementary foods, and duration of breastfeeding was collected via the self-administered questionnaire at age 6 weeks as well as 6 and 12 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 formula feed (standard cow's milk formula, hydrolyzed formula, preterm formula, other types of formulas) and the age when the child first had the formula. For complementary food, at each time point, the question "Has your child been introduced to the cereal/ rice/ porridge/ vegetables/ fruits/ meat/ offal/ fish/ other seafood/ egg yolk/ egg white?" was asked. If the response was affirmative, the age when the child first introduced to this food should be answered.

Infant Outcomes

In the 3 years' postpartum questionnaires, eczema/ asthma/ allergic rhinitis/ food allergy was defined from the answers of the following questions: "Has your child ever been diagnosed as having eczema/ asthma/ allergic rhinitis/ food allergy by a physician/paediatrician?" When this question was answered affirmatively, the age when he/she first diagnosed was recorded. For food allergy, the question was about all food allergies, and no further information about

the food type was collected. In this study, to avoid potential overlaps in the timing between exposure and the occurrence of disease outcomes, we excluded children who were diagnosed with allergic diseases before infant formula and complementary food introduction (**Figure 5.1**).

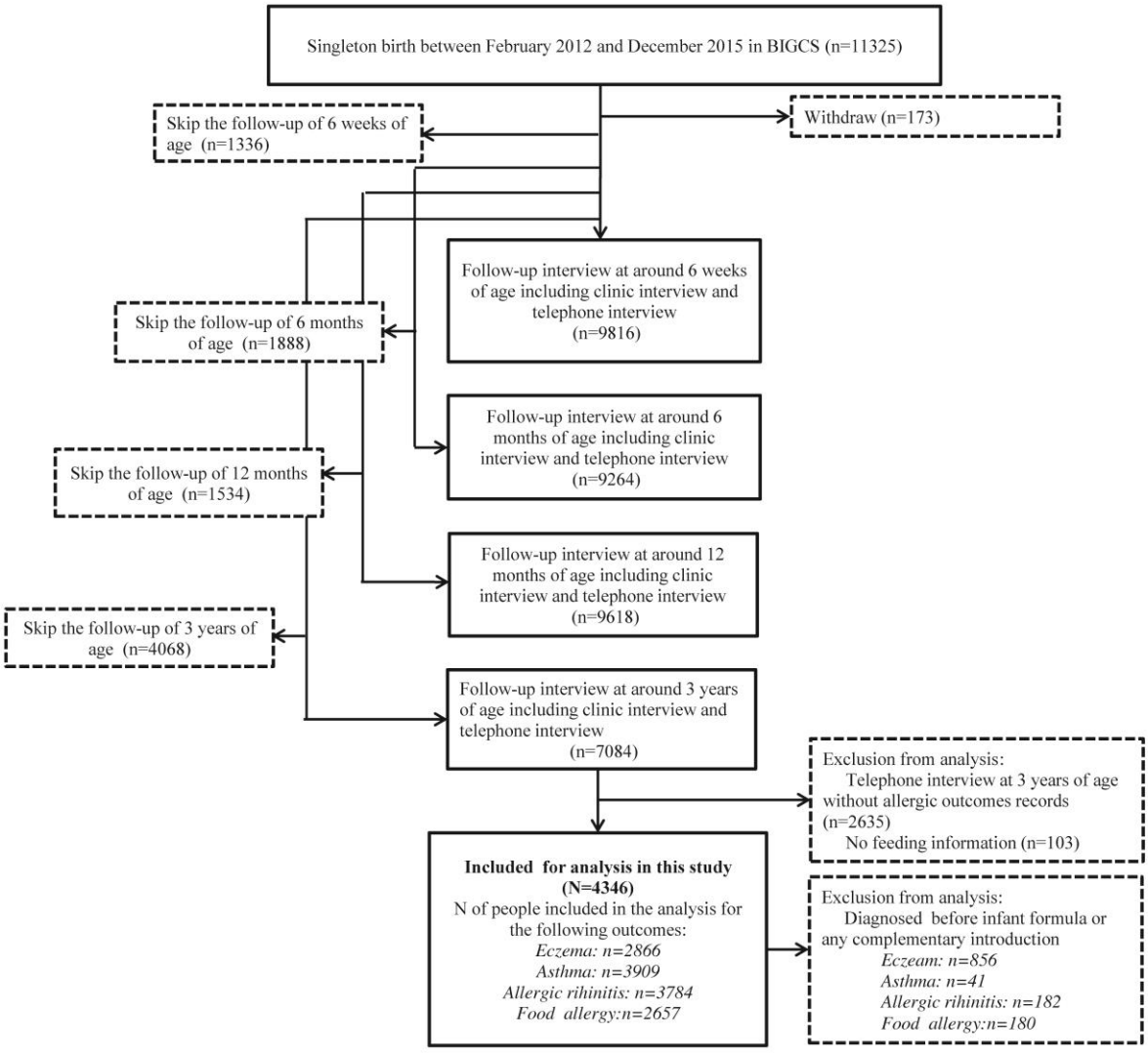


Figure 5.1 Flow chart of participants in this study

Covariates

Duration of any breastfeeding was defined as the age in months at the cessation of breastfeeding and classified as ≤6 months and >6 months. The obstetrics-related information such as delivery mode, infant sex, birth order and gestational age were documented from hospital records. Maternal age, educational level, smoking status during pregnancy, passive smoking status during pregnancy, and other health-related factors were self-reported during pregnancy. Information on antibiotic use by the infant was gathered at 6 and 12 months.

Statistical Analyses

Cluster analysis was performed by R version 3.6.1, and the remaining analyses were performed using SAS 9.4.

The patterns of food introduction were defined by using cluster analysis, which has been used in our previous studies [280, 281]. Cluster analysis can provide a clear description of the timing that the food was first introduced to the infant diet in each subgroup. The subgroups were created based on maximally separate introduction patterns, with descriptions of mean age of months at which the food was first introduced to the infant. Cluster analysis was performed using the k-means procedure, as described previously [280, 281]. The procedure was applied to separate individuals into a predetermined number of mutually exclusive groups by comparing Euclidean distances between any single individual and each cluster centre in an interactive process until no further changes occur. Several runs were conducted by varying the number of clusters from two to five, to identify the optimal number of clusters. After several runs, we found that clusters identified from the four-cluster solution could better reflect the

diversity of the introduction pattern of infant formula and complementary foods.

The baseline characteristics were summarised by clusters of food introduction patterns. Logistic regression models were built to estimate the relationships between clusters of food introduction pattern and each outcome of interest. Then, according to the previous studies included in our systematic review (Chapter 3) [128, 130], some potential confounders, including maternal age (continuous), maternal education (high school or below), vocational/technical college, undergraduate, postgraduate), pre-pregnancy body mass index (BMI; <18.5, 18.5-23.9, 24-27.9, ≥28 kg/m^2) [258], maternal smoking during pregnancy (yes, no), passive smoking during pregnancy (yes, no), preterm birth (yes, no), parity (primiparous, multiparous), mode of delivery (vaginal labour, cesarean delivery), infant sex, parental history of atopic diseases (yes, no), antibiotic usage before 12 months of age (yes, no) and the duration of breastfeeding (0-6, >6 months), were entered into the model simultaneously. The results are presented as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI).

Given the proportion of missing data on confounder variables were from 0.1% to 14.7%, analyses based on complete cases may be biased. Thus, we used multiple imputation (MI) analysis to cope with missing data [176]. We used the fully conditional method (FCS) iterative method for imputation by using SAS 9.4. The following variables were imputed: pre-pregnancy BMI, maternal smoking during pregnancy, passive smoking during pregnancy, parity, delivery mode, parental history of atopic diseases, the duration of breastfeeding, and antibiotic usage before 12 months of age. 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, 10 imputations were run. We ran a procedure call proc mianalyze which combines all the estimates (coefficients and standard errors) across all the imputed datasets and outputs one set of parameter estimates for the model of interest [177]. The fraction of missing information (FMI) analysis was performed to determine potential efficiency gains from MI (Supplementary material S8). Values of FMI range between 0 and 1. A smaller FMI (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 [267].

Furthermore, early skin symptoms might influence breastfeeding behaviour and/or decision on when to feed infant formula or complementary food. Therefore, the sensitivity analyses were performed by excluding infants with early symptoms of itchy red rash before 12 months of age. For asthma, when we excluding children with wheezing symptoms before 1 year of age, only 19 cases were left. Thus, it is not available to perform the regression analysis. We performed subgroup analyses by stratifying the children according to the combined categories of food introduction patterns and breastfeeding duration. Children were also stratified by parental history of allergic diseases.

Results

Clusters of Foods Introduction Pattern

Four clusters of food introduction pattern were identified and named based on the mean age of months at which the food was first introduced to the infant as follows (**Table 5.1 and Figure**

5.2):

Early formula & late seafood & late egg white: The average age when infant formula was first introduced was less than 1 month old, the average age when seafood or egg white was first introduced was older than 12 months old, and the average ages when other complementary foods were first introduced were less than 12 months old (n=1652, 38.0%).

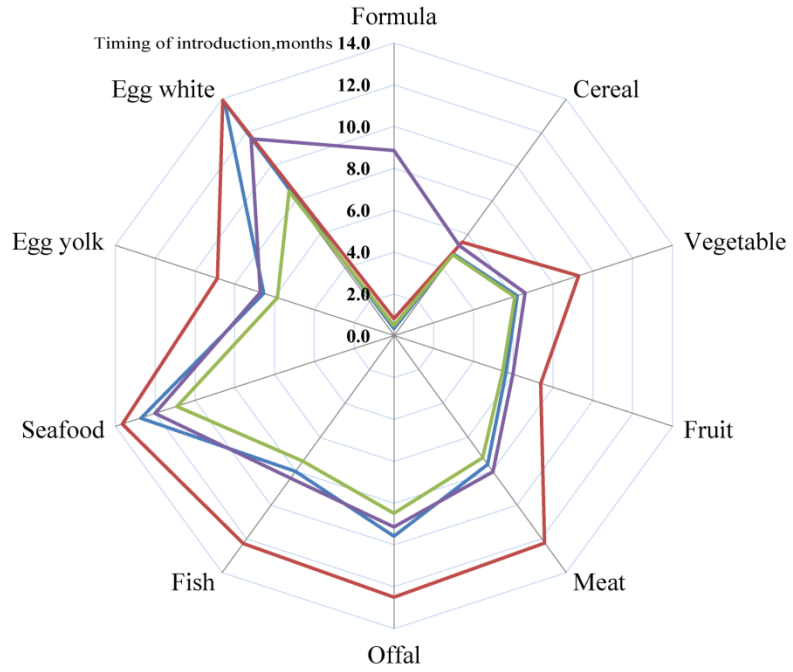
Early formula & late complementary food: The average age when infant formula was first introduced was less than 1 month old, the average ages when complementary foods were first introduced were relatively late compared with other pattern groups (n=655, 15.1%).

Early formula & early complementary food: The average age when infant formula was first introduced was less than 1 month old, and the average ages when complementary foods were first introduced were less than 12 months of age (n=1430, 32.9%).

Late formula: The average age when infant formula was first introduced was over 6 months of age (n=609, 14.0%).

Table 5.1 Mean age of months at which the food was first introduced to the infant within each cluster in the BIGCS study (n=4346)

Food groups	Clusters/ Patterns							
	Early formula & late seafood & late egg white n=1652		Early formula & late complementary food n=655		Early formula & early complementary food n=1430		Late formula n=609	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Formula	0.3	1.0	0.8	1.7	0.5	1.3	8.9	2.4
Cereal	4.9	1.1	5.5	1.3	4.8	1.1	5.3	1.1
Vegetable	6.2	1.3	9.3	2.1	6.1	1.2	6.6	1.4
Fruit	5.6	1.1	7.4	1.8	5.5	1.1	6.0	1.2
Meat	7.6	1.4	12.2	1.5	7.2	1.4	8.1	1.5
Offal	9.6	1.6	12.5	1.4	8.5	1.6	9.1	1.6
Fish	8.0	1.6	12.3	1.6	7.4	1.5	8.4	1.6
Seafood	12.7	1.9	13.7	1.9	10.9	2.1	12.0	1.9
Egg yolk	6.6	1.7	8.9	2.0	5.9	1.3	6.7	1.4
Egg white	13.8	0.9	13.9	1.8	8.5	2.0	11.6	2.0



Clusters/ Patterns	N (%)	Food groups (timing of first introdcution, month)									
		Formula	Cereal	Vegetable	Fruit	Meat	Offal	Fish	Seafood	Egg yolk	Egg white
Early formula & late seafood & late egg white	1652 (38.0)	0.3	4.9	6.2	5.6	7.6	9.6	8.0	12.7	6.6	13.8
Early formula & late complementary food	655 (15.1)	0.8	5.5	9.3	7.4	12.2	12.5	12.3	13.7	8.9	13.9
Early formula & early complementary food	1430 (32.9)	0.5	4.8	6.1	5.5	7.2	8.5	7.4	10.9	5.9	8.5
Late formula	609 (14.0)	8.9	5.3	6.6	6.0	8.1	9.1	8.4	12.0	6.7	11.6

Figure 5.2 Four introduction patterns in the population by the mean age of months at which the food was first introduced to the infant within each cluster

Characteristics of the participants

There were 4346 participants included in this study (**Figure 5.1**), of whom 1652 (38.0%) were classified into the ‘early formula & late seafood & late white egg’ pattern, 655 (15.1%) into ‘early formula & late complementary food’ pattern, 1430 (32.9%) into ‘early formula & early complementary food’ pattern, and 609 (14.0%) into ‘late formula’ pattern. According to the parental report, among the 4346 children, 1126 (30.3%) children have been diagnosed with eczema before 3 years, 89 (2.3%) have been diagnosed with asthma, 402 (10.1%) have been diagnosed with allergic rhinitis, and 292 (10.3%) have been diagnosed with food allergy. Among the children diagnosed with allergic diseases before the introduction of infant formula and complementary foods, 856 children had been diagnosed with eczema, 41 children had been diagnosed with asthma, 182 had been diagnosed with allergic rhinitis, and 180 had been diagnosed with food allergy. These children were excluded from the regression analyses for the associations of food introduction patterns with allergic outcomes, respectively.

The characteristics of the study participants for each cluster at baseline are presented in **Table 5.2**. Overall, in the cluster of ‘late formula’ pattern, mothers were more likely to be higher educated and chose vaginal labour. Infants with ‘late formula’ pattern were more likely to be a girl and have a longer duration of breastfeeding. The characteristics of mothers and infants between the analytic sample and those who were excluded (interviewed on the phone only) are shown in **Supplementary material S9**. In the telephone call interview group, mothers were more likely to be younger and tended to have a lower education level, and more likely to be multipara. The children in the telephone call interview group were more likely to

have a shorter duration of breastfeeding, less likely to have a parental history of allergic diseases, and tended to use antibiotics during the first year of life (**Supplementary material S9**).

Table 5.2 Baseline characteristics of participants in different clusters in the BIGCS study (n=4346)

Characteristics	Early formula & late seafood & late egg white (n=1652)	Early formula & late complementary food (n=655)	Early formula & early complementary food (n=1430)	Late formula (n=609)	No. of cases missing out of 6334 (%)
Mother					
Age at delivery (y), mean (SD)	29.4 (3.3)	29.8 (3.5)	29.6 (3.4)	29.2 (2.9)	0 (0)
Educational level,n (%)					0 (0)
High school or below	119 (7.3)	31 (4.8)	100 (7.0)	36 (5.9)	
Vocational/technical college	379 (22.9)	148 (22.6)	353 (24.7)	126 (20.7)	
Undergraduate	965 (58.4)	407 (62.1)	792 (55.4)	344 (56.5)	
Postgraduate	189 (11.4)	69 (10.5)	185 (12.9)	103 (16.9)	
Pre-pregnancy BMI, n (%)					92 (1.5)
<18.5 kg/m^2	395 (24.5)	148 (22.9)	327 (23.4)	132 (22.2)	
18.5-23.9 kg/m^2	1071 (66.4)	432 (67.1)	917 (65.5)	405 (67.8)	
24-27.9 kg/m^2	122 (7.6)	52 (8.1)	135 (9.6)	48 (8.0)	
≥28kg/m^2	25 (1.5)	12 (1.9)	21 (1.5)	12 (2.0)	
Parity, n (%)					1 (0)
Primiparous	1472 (89.1)	558 (85.3)	1276 (89.2)	528 (86.7)	
Multiparous	180 (10.9)	96 (14.7)	154 (10.8)	81 (13.3)	
Delivery mode, n (%)					4 (0.1)
Vaginal labor	1064 (64.5)	433 (66.1)	949 (66.4)	425 (69.9)	
Cesarean delivery	586 (35.5)	222 (33.9)	480 (33.6)	183 (30.1)	
Smoking during pregnancy, n (%)					21 (0.3)
Yes	12 (0.7)	1 (0.1)	1 (0.1)	5 (0.8)	

No	1632 (99.3)	650 (99.9)	1421 (99.9)	603 (99.2)	
Passive smoking during pregnancy, n (%)					18 (0.3)
Yes	481 (29.2)	178 (27.3)	413 (29.0)	181 (29.8)	
No	1165 (70.8)	473 (72.7)	1010 (71.0)	427 (70.2)	
Child					
Child‘s gender, n (%)					0 (0)
Male	888 (53.8)	342 (52.2)	755 (52.8)	295 (48.4)	
Female	764 (46.3)	313 (47.8)	675 (47.2)	314 (51.6)	
Birth weight <2500g, n (%)					2 (0)
Yes	78 (4.7)	43 (6.6)	43 (3.0)	25 (4.1)	
No	1573 (95.3)	612 (93.4)	1386 (97.0)	584 (95.9)	
Preterm birth, n (%)					0 (0)
Yes	98 (5.9)	42 (6.4)	45 (3.2)	28 (4.6)	
No	1554 (94.1)	613 (93.6)	1385 (96.9)	581 (95.4)	
Duration of any breastfeeding, n (%)					252 (4.0)
≤6 months	481 (31.1)	202 (32.9)	427 (31.9)	53 (8.9)	
> 6 months	1064 (68.9)	412 (67.1)	910 (68.1)	545 (91.1)	
Parental history of allergy, n (%)					387 (6.1)
Yes	527 (35.1)	177 (29.6)	418 (32.4)	193 (33.8)	
No	973 (64.9)	421 (70.4)	872 (67.6)	378 (66.2)	
Antibiotic use before 1 year of age, n (%)					929 (14.7)
Yes	354 (25.7)	121 (30.6)	345 (28.9)	127 (28.2)	
No	1022 (74.3)	275 (69.4)	849 (71.1)	324 (71.8)	

Association of Food Introduction Patterns with Atopic Diseases

Figure 5.3 shows associations between the 4 food introduction patterns and risks of atopic diseases. Among these food introduction patterns, the 'late formula' pattern was closest to the infant feeding guidelines that all infants should be exclusively breastfed about 6 months after birth, and at least for the first 4 months [83]. Therefore, the 'late formula' pattern was selected as the reference pattern. Compared with 'late formula' pattern, 'early formula & late seafood & late egg white', 'early formula & late complementary food', and 'early formula & early complementary food' patterns were all associated with the increased risk of eczema before 3 years of age (aOR: 2.15; 95%CI, 1.10-4.18; aOR: 2.28; 95%CI, 1.06-4.90; aOR:2.20; 95%CI, 1.13-4.32). After multiple imputation, slightly reduced effect size but narrower confidence intervals for the three patterns and eczema (aOR: 1.72; 95%CI, 1.06-2.80; aOR: 1.85; 95%CI, 1.08-3.19; aOR: 1.69; 95%CI, 1.04-2.77) were found. There were no significant associations between food introduction patterns and the risk of other allergic outcomes observed in our population (**Figure 5.3**)

Outcomes / Clusters of Food Introduction Patterns	Cases (%)	Crude	Adjusted before multiple imputation	Adjusted after multiple imputation
		OR (95% CI)	OR (95% CI)	OR (95% CI)
Eczema		n=2826	n=2054	n=2826
Early formula & late seafood & late egg white	101 (9.3)	1.60 (0.99-2.58)	2.15 (1.10-4.18)	1.72 (1.06-2.80)
Early formula & late complementary food	43 (9.9)	1.72 (1.01-2.93)	2.28 (1.06-4.90)	1.85 (1.08-3.19)
Early formula & early complementary food	86 (9.2)	1.59 (0.98-2.59)	2.20 (1.13-4.32)	1.69 (1.04-2.77)
Late formula	22 (6.0)	Reference	Reference	Reference
Asthma		n=3857	n=2513	n=3857
Early formula & late seafood & late egg white	14 (0.9)	1.18 (0.39-3.59)	1.04 (0.28-3.90)	1.09 (0.35-3.38)
Early formula & late complementary food	6 (1.0)	1.23 (0.35-4.38)	0.63 (0.10-3.87)	1.14 (0.31-4.14)
Early formula & early complementary food	22 (1.8)	2.21 (0.76-6.45)	1.50 (0.41-5.46)	2.01 (0.68-5.98)
Late formula	4 (0.8)	Reference	Reference	Reference
Allergic rhinitis		n=3730	n=2431	n=3730
Early formula & late seafood & late egg white	89 (6.1)	1.14 (0.73-1.78)	1.31 (0.73-2.36)	1.11 (0.70-1.75)
Early formula & late complementary food	29 (5.0)	0.91 (0.53-1.57)	1.05 (0.51-2.19)	0.89 (0.51-1.55)
Early formula & early complementary food	70 (5.7)	1.06 (0.67-1.68)	1.18 (0.65-2.16)	1.04 (0.65-1.67)
Late formula	26 (5.4)	Reference	Reference	Reference
Food allergy		n=2617	n=1762	n=2617
Early formula & late seafood & late egg white	46 (4.4)	1.13 (0.61-2.13)	1.49 (0.64-3.46)	1.12 (0.59-2.12)
Early formula & late complementary food	14 (3.3)	0.83 (0.39-1.79)	1.03 (0.36-2.94)	0.79 (0.36-1.72)
Early formula & early complementary food	34 (4.2)	1.07 (0.56-2.05)	1.25 (0.52-2.99)	1.03 (0.53-2.00)
Late formula	13 (3.9)	Reference	Reference	Reference

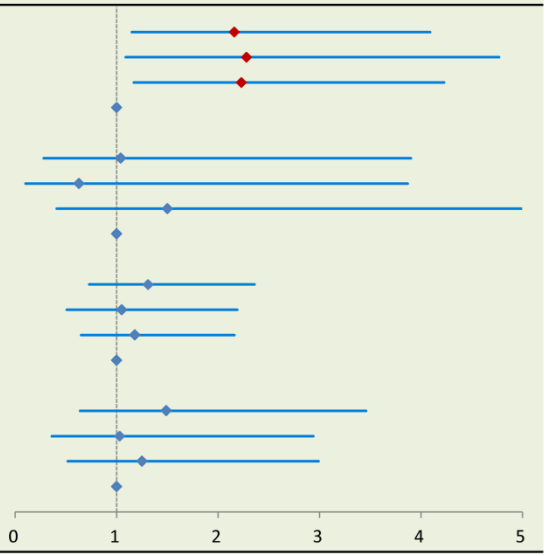


Figure 5.3 Risks of atopic diseases (eczema, asthma, allergic rhinitis, food allergy) and different clusters of food introduction pattern (Before and after multiple imputation)

Adjusted for maternal age at baseline, maternal education, pre-pregnancy BMI, smoking status during pregnancy, passive smoking status during pregnancy, parity, delivery mode, preterm birth, the gender of infant, parental history of atopy, antibiotics use before 1 year of age and breastfeeding duration.

Sensitivity and Subgroup Analyses

In sensitivity analyses, we excluded children with early skin symptoms, itchy red rash, before 12 months of age. For eczema, the ORs for ‘early formula & late seafood & late egg white’ introduction pattern became marginally significant after multiple imputation (aOR: 1.75; 95% CI, 0.94-3.26). The ORs for ‘early formula & late complementary food’ (aOR: 2.38; 95% CI, 1.22-4.64) and for ‘early formula & early complementary food’ (aOR: 2.38; 95% CI, 1.28-4.42) introduction patterns were significant after multiple imputation. For asthma, allergic rhinitis and food allergy, the associations were all non-significant (**Table 5.3**).

Table 5.3 Sensitivity analysis by excluding children with itchy red rash before 12 months of age

Outcomes and clusters	cOR (95% CI)	aOR (95% CI) before MI	aOR (95% CI) after MI
Eczema			
Early formula & late seafood & late egg white	1.75 (0.95-3.23)	2.32 (0.96-5.62)	1.75 (0.94-3.26)
Early formula & late complementary food	2.37 (1.23-4.57)	3.24 (1.22-8.62)	2.38 (1.22-4.64)
Early formula & early complementary food	2.34 (1.27-4.31)	3.27 (1.35-7.88)	2.38 (1.28-4.42)
Late formula	Reference	Reference	Reference
Asthma			
Early formula & late seafood & late egg white	1.53 (0.32-7.23)	1.81 (0.21-15.67)	1.30 (0.27-6.28)
Early formula & late complementary food	2.11 (0.41-10.94)	0.80 (0.05-13.20)	1.67 (0.31-8.92)
Early formula & early complementary food	3.66 (0.84-16.00)	2.80 (0.34-23.28)	3.13 (0.70-13.98)
Late formula	Reference	Reference	Reference
Allergic rhinitis			
Early formula & late seafood & late egg white	1.03 (0.63-1.68)	1.19 (0.62-2.27)	0.99 (0.60-1.64)
Early formula & late complementary food	0.98 (0.56-1.74)	1.31 (0.61-2.81)	0.93 (0.52-1.68)
Early formula & early complementary food	1.09 (0.66-1.79)	1.24 (0.64-2.38)	1.06 (0.64-1.77)
Late formula	Reference	Reference	Reference
Food allergy			
Early formula & late seafood & late egg white	1.07 (0.53-2.15)	1.13 (0.47-2.75)	1.10 (0.54-2.25)
Early formula & late complementary food	0.88 (0.38-2.02)	0.93 (0.30-2.90)	0.87 (0.37-2.04)
Early formula & early complementary food	0.98 (0.47-2.05)	0.97 (0.38-2.47)	1.00 (0.47-2.12)
Late formula	Reference	Reference	Reference

Adjusted for maternal age at baseline, maternal education, pre-pregnancy BMI, smoking status during pregnancy, passive smoking status during pregnancy, parity, delivery mode, preterm birth, the gender of infant, parental history of atopy, antibiotics use before 1 year of age and breastfeeding duration.

MI: multiple imputation

In subgroup analyses, as the number of children in the category of ‘late formula’ pattern and short breastfeeding duration (≤6 months) was too small (n=53) to provide a stable model for analysis, we therefore just used the ‘late formula’ as the reference group regardless of the breastfeeding duration. **Table 5.4** showed that, the associations of ‘early formula & late seafood & late egg white’ (aOR: 1.87; 95%CI, 1.22-4.69) and ‘early formula & early complementary food’ (aOR: 2.15; 95%CI, 1.08-4.29) patterns with the risk of eczema were significant in children with longer breastfeeding duration (>6 months). No significant associations of combined categories of food introduction patterns and breastfeeding duration with risks of other allergic outcomes were observed.

Table 5.4 Combined categories of food introduction patterns and breastfeeding duration in associations with risk of allergic outcomes

Outcomes/ Patterns groups	Case (%)	cOR (95% CI)	aOR (95% CI) before MI	aOR (95% CI) after MI
Eczema				
Breastfeeding<6m				
Early formula & late seafood & late egg white	22 (6.5)	1.08 (0.59-1.99)	1.56 (0.70-3.47)	1.11 (0.60-2.05)
Early formula & late complementary food	13 (9.8)	1.70 (0.83-3.48)	2.97 (1.13-7.80)	1.76 (0.85-3.62)
Early formula & early complementary food	24 (8.8)	1.51 (0.83-2.75)	2.27 (1.03-4.97)	1.57 (0.85-2.88)
Breastfeeding≥6m				
Early formula & late seafood & late egg white	73 (10.6)	1.86 (1.14-3.05)	2.39 (1.22-4.69)	1.87 (1.13-3.07)
Early formula & late complementary food	26 (9.4)	1.63 (0.90-2.94)	1.96 (0.85-4.53)	1.64 (0.90-2.97)
Early formula & early complementary food	61 (10.2)	1.79 (1.08-2.97)	2.15 (1.08-4.29)	1.77 (1.06-2.95)
Late formula	22 (6.0)	Reference	Reference	Reference
Asthma				
Breastfeeding<6m				
Early formula & late seafood & late egg white	6 (1.4)	1.73 (0.49-6.17)	1.91 (0.44-8.28)	1.85 (0.51-6.70)
Early formula & late complementary food	3 (1.6)	2.00 (0.44-9.02)	1.18 (0.12-11.74)	2.02 (0.44-9.24)
Early formula & early complementary food	8 (2.2)	2.74 (0.82-9.17)	1.16 (0.23-5.97)	2.88 (0.85-9.78)
Breastfeeding≥6m				
Early formula & late seafood & late egg white	8 (0.8)	1.04 (0.31-3.48)	0.79 (0.19-3.36)	1.05 (0.31-3.53)
Early formula & late complementary food	2 (0.5)	0.65 (0.12-3.56)	0.47 (0.05-4.62)	0.68 (0.12-3.73)
Early formula & early complementary food	13 (1.6)	2.04 (0.66-6.29)	1.83 (0.50-6.78)	2.07 (0.67-6.41)
Late formula	4 (0.8)	Reference	Reference	Reference
Allergic rhinitis				
Breastfeeding<6m				

Early formula & late seafood & late egg white	31 (7.3)	1.36 (0.79-2.33)	1.55 (0.78-3.08)	1.30 (0.76-2.25)
Early formula & late complementary food	7 (3.9)	0.71 (0.30-1.66)	0.91 (0.29-2.82)	0.69 (0.29-1.63)
Early formula & early complementary food	19 (5.3)	0.96 (0.52-1.77)	1.19 (0.57-2.51)	0.94 (0.51-1.74)
Breastfeeding≥6m	55 (5.9)			
Early formula & late seafood & late egg white	20 (5.5)	1.09 (0.67-1.76)	1.26 (0.69-2.32)	1.06 (0.65-1.72)
Early formula & late complementary food	47 (6.0)	1.00 (0.55-1.83)	1.16 (0.53-2.55)	0.98 (0.54-1.79)
Early formula & early complementary food	26 (5.4)	1.12 (0.68-1.83)	1.23 (0.66-2.30)	1.11 (0.68-1.83)
Late formula		Reference	Reference	Reference
Food allergy				
Breastfeeding<6m				
Early formula & late seafood & late egg white	17 (5.8)	1.51 (0.72-3.17)	2.23 (0.91-5.48)	1.55 (0.73-3.28)
Early formula & late complementary food	3 (2.2)	0.56 (0.16-1.99)	0.82 (0.17-4.04)	0.56 (0.16-2.04)
Early formula & early complementary food	8 (3.6)	0.91 (0.37-2.23)	0.68 (0.20-2.34)	0.86 (0.35-2.14)
Breastfeeding≥6m				
Early formula & late seafood & late egg white	28 (4.1)	1.04 (0.53-2.04)	1.05 (0.45-2.45)	1.03 (0.52-2.04)
Early formula & late complementary food	11 (4.1)	1.05 (0.47-2.39)	0.99 (0.33-2.95)	0.99 (0.43-2.26)
Early formula & early complementary food	24 (4.4)	1.14 (0.57-2.27)	1.32 (0.56-3.07)	1.11 (0.55-2.23)
Late formula	13 (3.9)	Reference	Reference	Reference

Adjusted for maternal age at baseline, maternal education, pre-pregnancy BMI, smoking status during pregnancy, passive smoking status during pregnancy, parity, delivery mode, preterm birth, gender of infant, parental history of atopy, and antibiotics use before 1 year of age.
MI: multiple imputation

In addition, we stratified the children according to the parental history of allergic diseases and found that in high risk children, the association between ‘early formula & early complementary food’ and risk of eczema was significant (aOR, 2.75; 95% CI, 1.02-7.42). In children with no parental history of allergic diseases, the association between ‘early formula & late complementary food’ and the risk of eczema was significant (aOR, 1.88; 95% CI, 1.00-3.51). The associations of food introduction patterns with risk of asthma, allergic rhinitis and food allergy were non-significant in subgroup analyses (**Table 5.5**).

Table 5.5 Subgroup analyses on the associations between introduction patterns and allergic outcomes

Outcomes	Case (%)	High risk (n=1315)			Case (%)	No parental history of atopic diseases (n=2644)			Likelihood-ratio test
		cOR (95% CI)	aOR (95% CI) before MI	aOR (95% CI) after MI		cOR (95% CI)	aOR (95% CI) before MI	aOR (95% CI) after MI	*P-value*
Eczema									
Early formula & late seafood & late egg white	33 (9.6)	2.16 (0.82-5.67)	1.76 (0.57-5.39)	2.41 (0.91-6.39)	60 (9.3)	1.39 (0.78-2.46)	2.43 (1.05-5.61)	1.50 (0.84-2.65)	0.696
Early formula & late complementary food	7 (6.3)	1.37 (0.42-4.47)	1.28 (0.30-5.57)	1.53 (0.47-4.96)	34 (11.6)	1.77 (0.95-3.30)	2.85 (1.12-7.23)	1.88 (1.00-3.51)	0.403
Early formula & early complementary food	31 (11.2)	2.58 (0.98-6.83)	2.00 (0.64-6.21)	2.75 (1.02-7.42)	48 (8.6)	1.27 (0.71-2.29)	2.31 (0.99-5.38)	1.34 (0.74-2.42)	0.886
Late formula	5 (4.7)	Reference	Reference	Reference	16 (6.9)	Reference	Reference	Reference	
Asthma									
Early formula & late seafood & late egg white	7 (1.5)	2.38 (0.29-19.51)	1.63 (0.18-15.17)	2.43 (0.29-20.59)	5 (0.6)	1.11 (0.61-2.02)	0.75 (0.14-4.16)	0.66 (0.16-2.71)	0.668
Early formula & late complementary food	1 (0.6)	0.98 (0.06-15.82)	1.22 (0.07-21.85)	1.32 (0.08-22.52)	3 (0.8)	0.92 (0.46-1.86)	0.48 (0.04-5.62)	1.01 (0.21-4.97)	0.681
Early formula & early complementary food	7 (1.9)	3.09 (0.38-25.32)	2.10 (0.23-19.34)	3.14 (0.37-26.6)	11 (1.5)	1.22 (0.67-2.23)	1.31 (0.26-6.71)	1.68 (0.46-6.14)	0.737
Late formula	1 (0.6)	Reference	Reference	Reference	3 (1.0)	Reference	Reference	Reference	
Allergic rhinitis									
Early formula & late seafood & late egg white	35 (7.5)	1.67 (0.72-3.83)	1.45 (0.57-3.73)	1.56 (0.68-3.57)	48 (5.7)	1.11 (0.61-2.02)	1.16 (0.54-2.49)	0.89 (0.50-1.58)	0.958
Early formula & late complementary food	9 (5.8)	1.28 (0.46-3.52)	0.75 (0.20-2.81)	1.13 (0.41-3.11)	18 (4.8)	0.92 (0.46-1.86)	1.11 (0.45-2.73)	0.76 (0.38-1.52)	0.554
Early formula & early complementary food	19 (5.4)	1.18 (0.48-2.86)	1.06 (0.39-2.89)	1.11 (0.46-2.68)	46 (6.3)	1.22 (0.67-2.23)	1.18 (0.55-2.55)	0.97 (0.54-1.74)	0.622

Late formula	7 (4.6)	Reference	Reference	Reference	15(5.2)	Reference	Reference	Reference	
Food allergy									
Early formula & late seafood & late egg white	18 (5.4)	0.77 (0.33-1.82)	2.16 (0.82-5.67)	0.74 (0.30-1.83)	24 (3.8)	1.88 (0.64-5.47)	6.07 (0.80-46.22)	1.79 (0.62-5.12)	0.059
Early formula & late complementary food	4 (3.4)	0.48 (0.14-1.63)	1.37 (0.42-4.47)	0.42 (0.12-1.49)	10 (3.5)	1.73 (0.53-5.59)	4.62 (0.54-39.62)	1.41 (0.44-4.55)	0.062
Early formula & early complementary food	9 (3.6)	0.51 (0.19-1.35)	2.58 (0.98-6.83)	0.46 (0.17-1.25)	21 (4.2)	2.09 (0.71-6.17)	6.48 (0.85-49.54)	2.03 (0.70-5.89)	0.016
Late formula	8 (6.9)	Reference	Reference	Reference	4 (2.1)	Reference	Reference	Reference	

High risk: children with the parental history of atopic diseases

Adjusted for maternal age at baseline, maternal education, pre-pregnancy BMI, smoking status during pregnancy, passive smoking status during pregnancy, parity, delivery mode, preterm birth, gender of infant, parental history of atopy, antibiotics use before 1 year of age and breastfeeding duration.

MI: multiple imputation

Discussion

The present study examines the associations between different food introduction patterns during infancy and the risks of atopic diseases before 3 years of age. There were four clusters of food introduction patterns identified in this population based on the average age of months at which infant formula and complementary foods were first introduced to the infant diet. The results showed that infants who were introduced formula at a relatively early age, average age was less than 1 month old, had a higher risk of eczema during the first 3 years of life regardless of whether complementary foods were introduced relatively early or late. However, the associations between food introduction patterns with the risks of asthma, allergic rhinitis or food allergy were not significant as those with eczema.

The cluster analysis of food introduction during early infancy identified 4 patterns among our participants. We named these 4 patterns according to the average age of each food group first introduced to the infant. Children with 'early formula & late seafood & late egg white' pattern had a relatively early introduction of infant formula (average age was less than 1 month old), late introduction of some allergic foods such as seafood and egg white (average age was over 12 months of age) and early introduction of other foods (average age was less than 12 months old); children with 'early formula & late complementary food' had an early introduction of infant formula (average age was less than 1 month of age) and relatively late complementary feeding with most of the allergic foods, such as meat, fish, seafood, and egg white, introduced after 12 months of age on average; children with 'early formula & early complementary food' had the earliest average timing of food introduction; children with 'late

formula' pattern had a late infant formula introduction with an average age of introduction of 8.9 months. Most of the children (38.0%) were classified into 'early formula & late seafood & late egg white' pattern, and the fewest were classified into 'late formula' introduction (14.0%). In our participants, most of the infants started complementary feeding between 4 to 12 months of age (89.2%), which meets infant feeding recommendations that complementary feeding should not be initiated before 4 months of age [83]. However, most infants were introduced to infant formula quite early, which led to a quite low exclusive breastfeeding rate before 4 months of age, only 26.0%. The high proportion of early formula introduction was also found in another Asian cohort, Growing Up in Singapore Towards healthy Outcomes (GUSTO) study [35]. Most of the GUSTO infants (66.7%) were introduced to cow's milk in the form of infant formula before age 4 months.

Although the effects of first food eaten and the age of introduction of a specific food on the risk of atopic diseases have been reported [9, 282], the effects of the gradual transition process of early infant diet (from milk-based to solid-food based) were not well assessed. In this study, we used cluster analysis on feeding practice data to investigate whether food introduction patterns in infant diet are associated with the development of atopic diseases. Our results showed that compared with 'late formula' introduction pattern, other patterns containing early infant formula introduction were all associated with increased risk of eczema. These findings were consistent with the findings in **Chapter 4** that early introduction of infant formula (within 3 months of age) was associated with eczema during the first year of life. In this chapter, the effects of early introduction of infant formula in combination with

complementary food introduction were examined, and our results further suggested that early formula introduction plays an essential role in the development of eczema. One systematic review focusing on the timing of complementary food introduction, (not including infant formula), found that there is no association between the age at which complementary food first begins and the risk of atopic dermatitis/eczema, childhood asthma, allergic rhinitis and food allergy [7]. To our best knowledge, only one case-control study assessed the relationship between infant dietary patterns and the development of food allergy [279]. In this study, principal component analysis (PCA) was used to analyse the diet diary data from 41 infants with food allergy before 2 years of age and their 82 age-matched control subjects. The authors found that there was no difference between the case and control groups for the early infant diet pattern [279]. We also did not found significant associations between food introduction patterns and food allergy before 3 years of age. Nevertheless, the methods used to define dietary patterns were different between the two studies. The PCA method, a form of factor analysis, creates factor scores to measure the extent to which an individual conforms to the intake of specific food groups. However, the scores do not provide clear descriptions of what food is exactly being consumed, and the same score can be achieved with different combinations of foods [283]. Cluster analysis allows a clear description of subgroups based on maximally separate eating patterns by providing mean values for food groups within each cluster [283]. The aim of our study is to identify different food introduction patterns and examine the associations of clearly defined introduction patterns with allergic outcomes. Thus, cluster analysis is the preferred method.

Breastfeeding has been suggested as a protective factor for the development of allergic diseases [8]. A cluster RCT study showed a reduced risk of eczema during the first year in a group of children with longer duration and exclusivity of breastfeeding compared with those with less breastfeeding [159]. In subgroup analyses, we found that the 'early formula & late seafood & late egg white' and 'early formula & early complementary food' patterns were significant associated with the increased risk of eczema in children with longer breastfeeding duration. In addition, the family history of allergies has been suggested as the as the most vital determinant of eczema [284]. Therefore, we stratified the children according to the parental history of allergic diseases. We found that in high risk children, the association between 'early formula & early complementary food' and risk of eczema was significant, whereas, in children with no parental history of allergic diseases, the association between 'early formula & late complementary food' and the risk of eczema was significant. However, the stratification by breastfeeding duration or the family history of allergies might cause the analysis underpowered due to the small number of cases in each group. Therefore, we cannot conclude the potential effects of these factors on the association between food introduction patterns and risk of eczema.

In this study, due to the limited number of cases in asthma, allergic rhinitis and food allergy, the power to detect any associations with these allergic outcomes might be quite low. Therefore, the results need to be replicated in other large cohorts to provide more robust evidence on these associations. In this population, the prevalence of asthma is low, only 2.4%, but closed to the result of a previous report on childhood asthma in mainland China (2.1%)

[285]. These results were below the global average level [285]. Some potential reasons need to be considered, including that an erroneous diagnosis and a missed diagnosis happen frequently in cough-variant asthma in China [285]. In addition, there are no specific detection methods and indicators for the diagnosis of asthma in preschool children with wheezing [286]. In addition, for young children under 3 years old, it is challenging to complete the pulmonary function testing successfully, which is a key method contributing to setting the diagnosis of asthma [286]. Extended evaluation of the associations between infant diet and these atopic diseases beyond 3 years old is needed.

The possible mechanisms for the observed results are the effects of early nutrition on the intestinal microbiome and immune responses, which have been reported in previous studies [73, 287]. The microbiome, particularly the gastrointestinal microbiota, plays an important role in modulating the development of early host immune system and therefore potentially contributing to the development of the atopic disease [288]. Previous evidence showed that infant formula and breast milk had different effects on the interplay of the microbiota with the developing mucosal immune function [289-293]. During early infancy, breast milk may provide greater plasticity for the infant gut microbiome that eases the transition into solid foods [294]. The gradual transition process of infant diet (from milk-based to solid-food based) has significant impacts on microbial composition [294, 295]. Early exposure to infant formula may influence the composition and the ecological balance of gut microbiota which related to the risk of allergic manifestations [296]. Furthermore, various dietary components, such as fatty acids, antioxidant vitamins, prebiotics and probiotics, could influence allergic outcomes

due to their effects on the process of inflammatory [73]. The differences in composition and concentrations of fatty acid between infant formula and human milk might also contribute to the higher risk for the development of atopic disease in formula feeding children [297, 298].

The present study aimed to examine the effects of the food introduction patterns during infancy on the development of allergic diseases. Introduction patterns can better inform about the transition process of early infant diet than the introduction of individual food. In this study, we found the patterns containing early infant formula introduction were associated with a higher risk of eczema. The cluster analysis developed the subgroups based on maximally distinct eating patterns by providing the mean age when food groups first introduced in each cluster. These four clusters reflect the different feeding patterns in our population. In our analysis, all three patterns containing early formula introduction with different timing of complementary food introductions were all associated with the risk of eczema. In addition, infant formula was usually introduced much earlier than other foods to the infant diet. It seems the early formula introduction contribute more to the associations with the risk of eczema. However, a number of nutritional or dietary variables might be acting on the development of allergy in infants. The complex interactions between these nutritional variables cannot be explained clearly. Therefore, our results just reflect the effects of different patterns of food introduction, but cannot adequately distinguish between the effects of infant formula and complementary food on the allergy. In addition, to avoid potential overlaps in the timing between exposure and the occurrence of disease outcomes, we excluded children who were diagnosed with allergic diseases before infant formula and complementary food

introduction. We found food introduction patterns containing early formula introduction were the risk factors for eczema before 3 years of age. The findings from this study provided new insight into how the early diet of infants might modify allergy development. However, several limitations of our study warrant mention. First, the information about infant feeding was based on parental report, but frequent questionnaires during the first year of life shortened the time interval between data collection and exposures. The use of parental report to identify the outcomes is another limitation, although we required the diseases should have been diagnosed by physicians or paediatricians. However, self- and caregiver-reported diagnosis of allergic disease has been suggested as a sufficient validated method for the epidemiological study of atopic disease [299]. Moreover, we did not collect information on the types of food allergy. The presence of each type of food allergy in infants was significantly influenced by the timing of the introduction of different allergenic foods [251]. In addition, due to fear of allergy, some parents might avoid allergic foods, such as shrimp, shellfish, and egg white during early infancy. Thus, the failure to classify food allergies may influence the results. As with all observational studies, the possibility of residual confounding cannot be excluded, although a wide range of confounders have been adjusted for in our analysis.

Conclusions

In conclusion, the present study has shown compared with ‘late formula’ pattern, ‘early formula & late seafood & late egg white’, ‘early formula & late complementary food’, and ‘early formula & early complementary food’ patterns were all associated with the increased risk of eczema before 3 years of age. Early exposure to infant formula might modify the

development of eczema in infants. Though the associations of food introduction patterns with asthma, allergic rhinitis, and food allergy were not significant in this study, the possible association should be considered in further studies. The findings provide new insight into how food introduction patterns, particularly early formula introduction, might modify allergy development. The results need to be replicated in other larger cohorts to provide more robust evidence on the development of future allergy prevention guidelines.

Chapter 6 Effects of the timing of infant formula introduction on growth and overweight in early childhood: a prospective birth cohort study

Abstract

Background

Accelerated growth during infancy has been reported to be associated with obesity and cardiometabolic disorders later in life. Formula feeding has been suggested as being associated with excess or rapid weight gain during infancy. However, evidence for the role of timing of formula introduction in childhood excess weight remains scarce and fragmented.

Objective

To examine associations of the timing of infant formula introduction with growth and overweight before 3 years of age.

Methods

This prospective study was included 6279 Chinese children from the BIGCS study, who provided feeding information at 6 weeks, 6 and 12 months, and anthropometric measurements at 1 and 3 years of age. Z-scores of growth were calculated based on the WHO Growth Standard. age. Obesity and overweight were defined as BMI-for-age z-score $\geq$2 and between 1 and 2, respectively. As the numbers of obesity cases were too small to provide a stable model for analysis, we combined the obese and overweight individuals in the overweight group. According to the BMI-for-age z-score at 1 year and 3 years of age, four weight status groups were defined: never overweight (reference group), early overweight, later overweight, and persistent overweight. Multiple imputation analysis was performed for dealing with missing covariate data in models of z-scores.

Results

In multiple imputation model, compared with early formula introduction (≤3 months), later introduction was associated with the lower BMI, weight-for-age and weight-for-length z-scores at 1 and 3 years old. In addition, later introduction of infant formula was negatively associated with the risk of overweight at 1 year (4-6 months vs. ≤3 months: adjusted odds ratio [OR] 0.71, 95% confidence interval [CI] 0.56, 0.90; >6 months vs. ≤3 months: adjusted OR 0.87, 95% CI 0.69, 1.09) and 3 years old (4-6 months: adjusted OR 0.62, 95% CI 0.41, 0.95; >6 months: adjusted OR 0.90, 95%CI 0.61, 1.33). Furthermore, later introduction of infant formula was negatively associated with the risk of persistent overweight (4-6 months: adjusted OR 0.49, 95% CI 0.24, 1.00; over 6 months: adjusted OR 0.63, 95% CI 0.31, 1.28).

Conclusion

Overall, compared with the introduction within the first 3 months of life, infant formula introduction between 4-6 months was associated with the lower z-scores for BMI, weight-for-age and weight for length at both 1 year and 3 years of age. We also found that the infants introduced to infant formula between 4 to 6 months of age were appeared less likely to be persistently overweight before 3 years of age than those introduced within the first 3 months.

Introduction

In China, in children aged 1 to 4 years, the prevalence of being overweight has risen from 6.3% to 11.9%, and the prevalence of obesity has risen from 2.2% to 6.9% between 1990 and 2016, respectively [300]. By 2015, China had the largest number of obese children aged 5 years or under in the world [301]. Epidemiological studies have reported that early obesity was a significant predictor of obesity later in life and the development of cardiometabolic disorders during adulthood [302-305]. Existing evidence has suggested that some modifiable dietary factors during early life, including formula feeding (FF) (as opposed to breastfeeding) [306] and early introduction (at or before 4 months) of complementary foods [307], were associated with the risk of obesity in later life.

Despite being advocated by health authorities, the exclusive breastfeeding (EBF) rate remains at a low level worldwide, including in China [308, 309]. In 1985, the EBF rate under 6 months of age was 39.6% in urban areas and 71.9% in rural areas of China [310], whereas the rate dropped to 18.1% and 19.4% in 2013 [55], respectively. The fact of the matter is an increasing number of Chinese parents give infant formula, either as the only food or as supplementary food, to their infants during the first few months of life. A population-based birth cohort study of China, involving 98,097 maternal-infant pairs (the data was collected from 2010 to 2016), showed that in the first month of life, infant formula exposure rate (FF and mix feeding) was 58.8%; in the third month, exposure rate was 66.6%; in the sixth month exposure rate was 72.0% [256].

Previous studies examining the effect of formula feeding on OW/OB just focused on comparing formula-fed with breastfed infants [306, 311]. A Chinese birth cohort indicated that compared with EBF, mix feeding (OR 1.54-1.57) or FF (OR 1.90-1.93) in the first month of life were associated with a higher risk of being overweight or obesity (OW/OB) at 2 years of age [312]. Another Chinese cohort study also found that having FF after birth was associated with a higher risk of being overweight and obesity at 2 years of age, compared with having infant formula or solids between 3 and 6 months of age (prevalence of overweight: 15.6% vs. 11.0%, $p<0.05$; prevalence of obesity: 4.4% vs. 1.4%, $p<0.05$) [313]. However, this study also showed that compared with EBF for 3 to 6 months, EBF for 6 months (introducing infant formula or solids after 6 months) was associated with a higher risk of being overweight and obesity at 2 years old (prevalence of overweight: 15.5% vs. 11.0%, $p<0.05$; the prevalence of obesity: 2.6% vs. 1.4%, $p<0.05$) [313]. An Australian cohort study showed a higher risk of OW/OB up to 11 years old among children introduced to formula or solids before 4 months of age compared to those introduced later (OR 1.95, 95%CI 1.10-3.47) [314]. These results suggested that the exposure to infant formula during the critical time windows of infant development (before 3 months, 3 to 6 months or after 6 months of age) might have different modulating effects on later OW/OB. Several factors related to the associations of infant formula feeding practices with rapid weight gain, including the amount of protein in the formula, protein-hydrolysed formula, energy density of the formula, the feeding bottle size, and parents' feeding practices (whether taking a bottle to bed, feeding on-demand or schedule, the amount of formula consumed, and whether the parents encouraged their infant to empty

the bottle), have been examined [10]. However, there was little evidence specially focused on the association of timing of formula introduction with the development of childhood OW/OB.

This study was aimed at assessing the association between the timing of formula introduction and early childhood growth to identify a critical exposure period for the development of childhood excess weight. In addition, whether this association is modified by breastfeeding duration and complementary food introduction was also examined.

Methods

Study Population

We analysed data from the Born in Guangzhou Cohort Study (BIGCS). 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 [174]. 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 pediatric 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 (**Figure 6.1**).

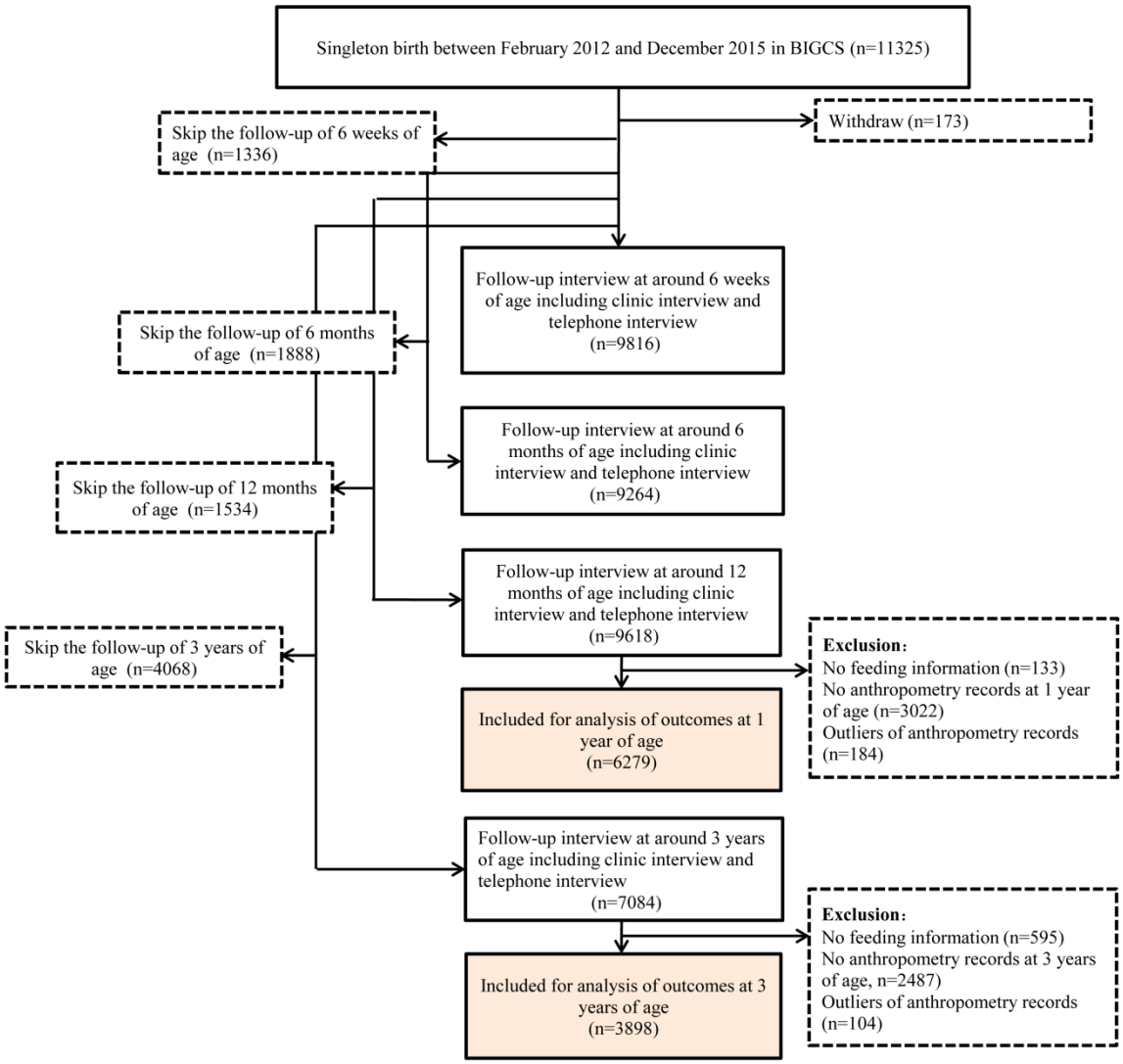


Figure 6.1 Flow chart of the study population

Exposures

Feeding Information

The age of first introduction of infant formula and other food, and duration of breastfeeding was defined from several variables reported in the self-administered questionnaire at age 6 weeks as well as 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 formula feed (standard cow's milk formula, hydrolyzed formula, preterm formula, other types of formulas) and the age when the child first had the 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 complementary food introduction.

Infant Outcomes

Anthropometric measurements were undertaken at each follow-up visit, at age 6 weeks, 6, 12, and 36 months, by trained fieldworkers. Abdomen circumference and upper arm circumference, in centimetres (cm), was measured in a supine position, using a measuring tape to the nearest 0.1 cm. Length (cm) was measured in a supine position using an electronic scale (Shekel Healthweigh™) to the nearest 0.1 cm. Bodyweight, in kilograms (kg), was measured without shoes and with light clothing (single layer clothes) in a supine position, using a stadiometer (Shekel Healthweigh™) to the nearest 0.01 kg. Body mass index (BMI) measures were also calculated using the formula kg/m^2. Children's gender and age-specific z-scores of BMI were recalculated through the SAS program (WHO-source-code.sas) based

on the 2006 WHO growth standards.[175] Obesity and overweight were defined as BMI-for-age z-score ≥2 and between 1 and 2, respectively. Since the number of obese children was insufficient for reliable analyses, overweight and obese children were combined as being overweight. Z-scores for a child's sex and age for weight and height (length-for-age z-score, LAZ; weight-for-age z-score, WAZ; weight-for-length z-score, WLZ) based on the WHO Growth Charts were also calculated. Extreme or biologically implausible values were removed.

In addition, based on the observation of the prevalence of overweight at 1 and 3 years of age, four mutually exclusive groups of overweight status were created: children who were never overweight before 3 years of age (**normal group**), children who were overweight at 1 year of age but transitioned to normal at 3 years (**early overweight**), children who were normal at 1 year of age but transitioned to overweight at 3 years (**later overweight**), and children who were overweight at 1 year and remained overweight at 3 years of age (**persistent overweight**).

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, Cary, NC, USA). The participants' characteristics stratified by the timing of infant formula introduction (≤3 months, 4-6 months, >6 months). The information on characteristics was presented as means and standard deviation (SD) for continuous variables or as percentages for categorical variables. The overall association between timing of infant formula introduction and abdomen circumference, upper arm circumference, BMI z-scores, LAZ, WAZ, and WLZ was analyzed with linear regression models and presented as β and 95% confidence intervals (95% CI). The overall association between timing of infant formula introduction and overweight status under 3 years old (early overweight, later overweight, persistent overweight) was analyzed with logistic regression models and presented as odds ratio (OR) and 95% confidence intervals (95% CI). The early overweight, later overweight and persistent overweight were modeled separately in the regression analysis. Each analysis included one of the three types of overweight status children and those who had never been overweight before 3 years of age. 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), maternal smoking during pregnancy (yes, no), passive smoking during pregnancy (yes, no), preterm birth (yes, no), parity (primiparous, multiparous), mode of delivery (vaginal labour, cesarean delivery), infant sex, birth weight (<2500g and ≥2500g), the duration of breastfeeding (0-6, >6 months) and age at

first introduction to complementary foods (≤3 months, 4-6 months, >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, the modification effects of breastfeeding duration and complementary food introduction were also examined by adding an interaction term of these variables and outcomes at 1 year and 3 years of age, respectively, in the models.

Given the proportion of missing data on confounder variables were 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 [176]. We used the fully conditional method (FCS) iterative method for imputation by using SAS 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 breastfeeding, and the timing of introduction of any complementary 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, 10 imputations were run. We ran a procedure call proc mianalyze which combines all the estimates (coefficients and standard errors) across all the imputed datasets and outputs one set of parameter estimates for the model of interest [177]. The fraction of missing information (FMI) analysis was performed to determine potential efficiency gains from MI (**Supplementary material S10 and S11**). Values of FMI range between 0 and 1. A smaller FMI (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 [262]. In addition, sensitivity analyses were performed by restricting to full-term infants with normal birth weight (2500-4000g).

Results

Characteristics of the study population

Characteristics of the participants based on the three infant formula introduction groups are shown in **Table 6.1**. Of the 6279 children, 5152 (82.1%) were introduced to infant formula within 3 months of age. Compared with the later introduction (>6 months) of infant formula group, the mothers in the earlier group (≤3 months) were more likely to be older, lower educated, multiparous, and have a caesarean delivery. The children in the earlier introduction group were more likely to be male, low birth weight (<2500g), breastfed less than 6 months, and overweight at 1 year and 3 years of age. Characteristics of included and excluded participants of this study are also shown in **supplementary material S12**.

Table 6.1 Baseline characteristics of participants in different timing of infant formula introduction groups in the BIGCS study

Characteristics	Timing of any infant formulas introduction, months			No. of cases missing out of 6279 (%)
	≤3 m (n=5152)	4-6 m (n=568)	> 6 m (n=559)	
Mother				
Age at delivery (y), mean (SD)	29.5 (3.4)	29.1 (3.1)	29.0 (3.1)	0 (0)
Educational level,n (%)				0 (0)
High school or below	412 (8.0)	41 (7.2)	39 (7.0)	
Vocational/technical college	1302 (25.3)	128 (22.5)	125 (22.4)	
Undergraduate	2868 (55.7)	316 (55.6)	316 (56.5)	
Postgraduate	570 (11.0)	83 (14.6)	79 (14.1)	
Pre-pregnancy BMI, n (%)				152 (2.4)
<18.5 kg/m^2	1216 (24.2)	127 (22.8)	116 (21.1)	
18.5-23.9 kg/m^2	3306 (65.9)	371 (66.6)	384 (69.8)	
24-27.9 kg/m^2	420 (8.4)	47 (8.4)	42 (7.6)	
≥28kg/m^2	78 (1.6)	12 (2.2)	8 (1.5)	
Height (cm), mean (SD)	160.0 (4.9)	159.7 (4.9)	160.1 (4.8)	49 (0.8)
Parity, n (%)				3 (0)
Primiparous	4575 (88.9)	514 (90.5)	478 (85.5)	
Multiparous	574 (11.1)	54 (9.5)	81 (14.5)	
Delivery mode, n (%)				7 (0.1)
Vaginal labor	3312 (64.4)	385 (67.8)	367 (65.8)	
Cesarean delivery	1834 (35.6)	183 (32.2)	191 (34.2)	
Smoking during pregnancy, n (%)	27 (0.5)	4 (0.7)	4 (0.7)	46 (0.7)
Passive smoking during pregnancy, n (%)	1593 (31.1)	181 (32.2)	159 (28.6)	44 (0.7)
Father				
BMI, n (%)				648 (10.3)
<18.5 kg/m^2	198 (4.3)	26 (5.3)	14 (2.7)	
18.5-23.9 kg/m^2	2592 (56.1)	278 (56.6)	303 (58.3)	
24-27.9 kg/m^2	1476 (31.9)	152 (31.0)	164 (31.5)	
≥28kg/m^2	354 (7.7)	35 (7.1)	39 (7.5)	
Height (cm), mean (SD)	172.7 (5.3)	172.6 (5.1)	172.8 (5.1)	113 (1.8)
Child				
Child's gender, n (%)				
Male	2756 (53.5)	264 (46.5)	282 (50.5)	0 (0)
Female	2396 (46.5)	304 (53.5)	277 (49.6)	
Birth weight <2500g, n (%)	203 (3.9)	21 (3.7)	19 (3.4)	6 (0.1)
Preterm birth, n (%)	247 (4.8)	28 (4.9)	21 (3.8)	0 (0)

Duration of any breastfeeding, n (%)				187 (3.0)
≤6 months	1443 (29.1)	106 (18.7)	2 (0.4)	
> 6 months	3523 (70.9)	462 (81.3)	556 (99.6)	
Timing of complementary food introduction				9 (0.1)
≤3 m	552	37	35	
4-6 m	4479	518	502	
> 6 m	113	13	21	

BMI: Body Mass Index

Timing of introduction of infant formula and anthropometric outcomes

Table 6.2 showed the anthropometric outcomes including abdomen circumference (cm), upper arm circumference (cm), BMI, and the prevalence of overweight, at 1 year and 3 years old, respectively.

Table 6.2 Anthropometric outcomes in different timing of infant formula introduction groups in the BIGCS study

Anthropometric outcomes	Timing of any infant formulas introduction, months		
	≤3 m	4-6 m	> 6 m
at 1 year of age, mean (SD)	(n=5152)	(n=568)	(n=559)
Abdomen circumference (cm)	42.9 (4.1)	42.8 (3.7)	42.9 (3.8)
Upper arm circumference (cm)	14.5 (1.2)	14.3 (1.1)	14.4 (1.2)
BMI	17.0 (1.4)	16.8 (1.4)	17.0 (1.4)
Overweight, n (%)	1107 (21.9)	95 (17.2)	116 (21.2)
at 3 years of age, mean (SD)	(n=3222)	(n=358)	(n=318)
Abdomen circumference (cm)	46.3 (4.5)	46.2 (4.2)	46.4 (4.1)
Upper arm circumference (cm)	14.9 (1.1)	14.8 (1.1)	14.9 (1.1)
BMI	15.6 (1.3)	15.4 (1.1)	15.5 (1.2)
Overweight, n (%)	389 (12.3)	27 (7.7)	33 (10.7)

Table 6.3 presents the associations between the timing of infant formula introduction and anthropometric outcomes at 1 year and 3 years of age. Compared with introducing infant formula within the first 3 months of age, introducing it later, particularly between 4 to 6 months, was associated with lower upper arm circumference (4-6 months: Adjusted β -0.15, 95%CI -0.25, -0.05; >6 months: Adjusted β -0.05, 95%CI -0.15, 0.06), BMI z-score (4-6m: Adjusted β -0.17, 95% -0.25, -0.08; >6m: Adjusted β -0.06, 95% -0.15, 0.03), length-for-age z-score (4-6m: Adjusted β -0.11, 95% CI -0.19, -0.03; >6m: Adjusted β -0.11, 95%CI -0.19, -0.03), weight-for-age z-score (4-6m: Adjusted β -0.22, 95% CI -0.30, -0.14; >6m: Adjusted β

-0.12, 95%CI -0.20, -0.04), weight-for-length z-score (4-6m: adjusted β -0.18, 95%CI -0.26, -0.09; >6m: Adjusted β -0.08, 95%CI -0.16, 0.01) at 1 year of age in multiple imputation models. For 3 years outcomes, introducing formula between 4 to 6 months seemed associated with lower BMI z-score (adjusted β-0.12, 95%CI -0.23, -0.02), weight-for-age z-score (adjusted β -0.12, 95%CI -0.23, -0.02), and weight-for-length z-score (adjusted β -0.14, 95%CI -0.24, -0.03) in multiple imputation models (**Table 6.3**).

Table 6.3 Linear regression models to evaluate the associations between timing of formula introduction and anthropometric outcomes at 1 year and 3 years of age (Before and after multiple imputation)

Anthropometric outcomes	Timing of formula introduction	Outcomes at 1 year of age			Outcomes at 3 years of age (n=3898)		
		Crude β (95% CI)	Adjusted β before MI (95% CI)	Adjusted β after MI (95% CI)	Crude β (95% CI)	Adjusted β before MI (95% CI)	Adjusted β after MI (95% CI)
Abdomen circumference[a]		n=5992	n=5041	n=5992	n=3707	n=3096	n=3707
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6 m	-0.17 (-0.53; 0.18)	0.00 (-0.38; 0.39)	-0.13 (-0.48; 0.23)	-0.02 (-0.51; 0.48)	0.17 (-0.37; 0.71)	-0.01 (-0.50 ; 0.48)
	>6 m	-0.06 (-0.42; 0.31)	-0.11 (-0.50; 0.27)	-0.11 (-0.48; 0.25)	0.23 (-0.30; 0.75)	-0.09 (-0.66; 0.48)	0.12 (-0.43 ; 0.66)
Upper arm circumference[a]		n=5925	n=4985	n=5925	n=3696	n=3088	n=3696
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6 m	-0.16 (-0.26; -0.06)	-0.14 (-0.25; -0.03)	-0.15 (-0.25; -0.05)	-0.10 (-0.22; 0.03)	-0.06 (-0.20; 0.07)	-0.09 (-0.22; 0.03)
	>6 m	-0.05 (-0.16; 0.05)	-0.06 (-0.17; 0.05)	-0.05 (-0.15; 0.06)	0.08 (-0.05; 0.21)	-0.02 (-0.15; 0.12)	0.06 (-0.07; 0.19)
BMI z-score[a]		n=6153	n=5176	n=6153	n=3839	n=3271	n=3839
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6 m	-0.15 (-0.24; -0.07)	-0.17 (-0.26; -0.08)	-0.17 (-0.25; -0.08)	-0.13 (-0.24; -0.03)	-0.12 (-0.23; -0.01)	-0.12 (-0.23; -0.02)
	>6 m	-0.01 (-0.10; 0.07)	-0.07 (-0.17; 0.02)	-0.06 (-0.15; 0.03)	-0.02 (-0.13; 0.10)	-0.10 (-0.22; 0.02)	-0.03 (-0.14; 0.08)
Length-for-age z-score[b]		n=6221	n=5315	n=6221	n=3849	n=3281	n=3849
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6m	-0.14 (-0.22; -0.05)	-0.11 (-0.19; -0.02)	-0.11 (-0.19; -0.03)	-0.05 (-0.15; 0.06)	-0.07 (-0.18; 0.05)	-0.06 (-0.15; 0.04)
	>6 m	-0.12 (-0.21; -0.03)	-0.10 (-0.18; -0.01)	-0.11 (-0.19; -0.03)	0.08 (-0.03; 0.19)	0.03 (-0.10; 0.15)	0.04 (-0.07; 0.14)
Weight-for-age z-score[a]		n=6206	n=5221	n=6206	n=3880	n=3243	n=3880
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6 m	-0.21 (-0.29; -0.12)	-0.23 (-0.32; -0.14)	-0.22 (-0.30; -0.14)	-0.12 (-0.22; -0.02)	-0.12 (-0.23; -0.01)	-0.12 (-0.23; -0.02)
	>6 m	-0.09 (-0.17; 0.00)	-0.12 (-0.21; -0.04)	-0.12 (-0.20; -0.04)	0.06 (-0.05; 0.17)	-0.02 (-0.14; 0.09)	0.03 (-0.08; 0.14)
Weight-for-length z-score[b]		n=6153	n=5257	n=6153	n=3839	n=3271	n=3839
	≤3 m	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	4-6 m	-0.17 (-0.26; -0.09)	-0.17 (-0.26; -0.08)	-0.18 (-0.26; -0.09)	-0.14 (-0.25; -0.04)	-0.14 (-0.25; -0.03)	-0.14 (-0.24; -0.03)
	>6 m	-0.03 (-0.12; 0.05)	-0.09 (-0.18; 0.00)	-0.08 (-0.16; 0.01)	-0.01 (-0.12; 0.10)	-0.10 (-0.21; 0.02)	-0.03 (-0.14; 0.08)

MI: Multiple Imputation

[a]Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI and paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, birth weight, the duration of breastfeeding, and age at first introduction to complementary foods

[b]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, preterm birth, parity, mode of delivery, infant sex, birth weight, the duration of breastfeeding, and age at first introduction to complementary foods

Timing of introduction of infant formula and weight status

Compared with introduction within the first 3 months of life, negative associations between introduction of infant formula between 4 to 6 months of age and the risk of overweight at 1 year (adjusted OR 0.71, 95% CI 0.56, 0.90) and 3 years of age (adjusted OR 0.62, 95% CI 0.41, 0.95) were observed in multiple imputation models (**Table 6.4**).

A comparison of overweight status between different infant introduction groups showed that compared to within the first 3 months of life, introducing infant formula between 4 to 6 months seems to be significantly associated with a lower risk of early overweight (adjusted OR 0.65, 95% CI 0.42, 0.99) and persistent overweight (adjusted OR 0.49, 95% CI 0.24, 1.00) (**Table 6.4**).

Table 6.4 Logistic regression models to evaluate the associations between timing of formula introduction and overweight at 1 year and 3 years of age

Timing of formula introduction	Case （n%）	Crude OR (95% CI)	Adjusted before MI OR (95% CI)	Adjusted after MI OR (95% CI)
Overweight at 1 year of age				
≤3 m	1107 (21.9)	1	1	1
4-6 m	95 (17.2)	0.74 (0.59-0.93)	0.71 (0.55-0.91)	0.71 (0.56-0.90)
> 6 m	116 (21.2)	0.96 (0.77-1.19)	0.84 (0.66-1.07)	0.87 (0.69-1.09)
Overweight at 3 years of age				
≤3 m	389 (12.3)	1	1	1
4-6 m	27 (7.7)	0.59 (0.40-0.89)	0.69 (0.45-1.07)	0.62 (0.41-0.95)
> 6 m	33 (10.7)	0.85 (0.58-1.24)	0.69 (0.44-1.09)	0.90 (0.61-1.33)
Overweight status from 1 to 3 years of age				
Early overweight				
≤3 m	378 (18.0)	1	1	1
4-6 m	27 (12.6)	0.65 (0.43-0.99)	0.79 (0.51-1.23)	0.65 (0.42-0.99)
> 6 m	46 (23.0)	1.36 (0.96-1.92)	1.27 (0.87-1.85)	1.21 (0.84-1.75)
Later overweight				
≤3 m	125 (6.8)	1	1	1
4-6 m	12 (6.0)	0.88 (0.48-1.62)	1.09 (0.56-2.11)	0.92 (0.48-1.76)
> 6 m	14 (8.3)	1.25 (0.70-2.23)	1.12 (0.57-2.20)	1.31 (0.72-2.39)
Persistent overweight				
≤3 m	172 (9.1)	1	1	1
4-6 m	9 (4.6)	0.48 (0.24-0.95)	0.54 (0.26-1.14)	0.49 (0.24-1.00)
> 6 m	9 (5.5)	0.58 (0.29-1.17)	0.46 (0.20-1.07)	0.63 (0.31-1.28)

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

MI: multiple imputation

When we restricted the analysis to the full-term infants with normal birth weight (2500-4000g), introducing infant formula between 4 to 6 months of age were significantly associated with lower risks of being overweight at 1 year (adjusted OR 0.68, 95% CI 0.53, 0.87) and 3 years of age (adjusted OR 0.49, 95% CI 0.30, 0.79), compared to introducing within the first 3 months of life in the multiple imputation models (**Table 6.5**). For weight status during the first 3 years, introduction infant formula between 4 to 6 months was significantly associated with the lower risks of early overweight (adjusted OR 0.60, 95% CI 0.38, 0.94) and persistent overweight (adjusted OR 0.36, 95% CI 0.16, 0.85) (**Figure 6.2**).

Table 6.5 Sensitivity analyses to evaluate the associations between timing of formula introduction and being overweight in full-term children with normal birth weight (2500-4000g)

Timing of introduction, months	Case （n%）	Normal birth weight & full term		
		Crude OR (95% CI)	Adjusted before MI OR (95% CI)	Adjusted after MI OR (95% CI)
1 year of age				
≤3 m	998 (21.7)	1	1	1
4-6 m	82 (16.2)	0.70 (0.55-0.89)	0.68 (0.52-0.89)	0.68 (0.53-0.87)
> 6 m	116 (20.7)	0.94 (0.75-1.18)	0.83 (0.65-1.07)	0.85 (0.67-1.08)
3 years of age				
≤3 m	350 (12.2)	1	1	1
4-6 m	20 (6.3)	0.48 (0.30-0.77)	0.48 (0.30-0.77)	0.49 (0.30-0.79)
> 6 m	30 (10.6)	0.86 (0.58-1.28)	0.86 (0.58-1.28)	0.91 (0.61-1.37)
Changes from 1 to 3 years of age				
Early overweight				
≤3 m	348 (18.1)	1	1	1
4-6 m	24 (12.1)	0.63 (0.40-0.97)	0.73 (0.45-1.16)	0.60 (0.38-0.94)
> 6 m	41 (22.5)	1.32 (0.91-1.90)	1.15 (0.76-1.72)	1.15 (0.78-1.69)
Later overweight				
≤3 m	118 (7.0)	1	1	1
4-6 m	9 (4.9)	0.69 (0.35-1.39)	0.84 (0.39-1.79)	0.68 (0.32-1.44)
> 6 m	13 (8.4)	1.23 (0.68-2.24)	1.23 (0.63-2.42)	1.32 (0.71-2.45)
Persistent overweight				
≤3 m	150 (8.7)	1	1	1
4-6 m	6 (3.3)	0.36 (0.16-0.83)	0.39 (0.15-0.97)	0.36 (0.16-0.85)
> 6 m	8 (5.4)	0.60 (0.29-1.24)	0.54 (0.23-1.27)	0.65 (0.31-1.38)

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, the duration of breastfeeding, and age at first introduction to complementary foods. MI: multiple imputation

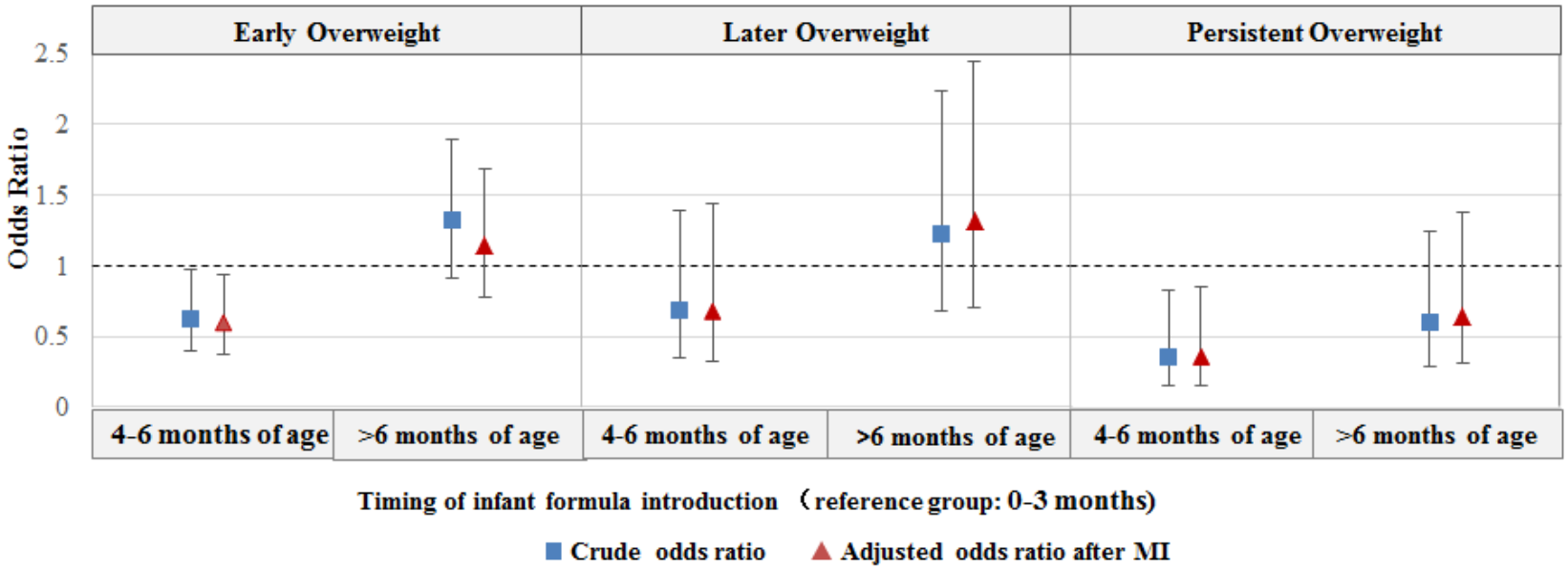


Figure 6.2 Logistic regression models to evaluate the associations between timing of formula introduction and overweight status from 1 to 3 years of age in full-term children with normal birth weight (2500-4000g)

Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI and paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, birth weight, the duration of breastfeeding, and age at first introduction to complementary foods

MI: multiple imputation

Discussion

Results of this prospective longitudinal cohort indicated that compared with the introduction at the first 3 months of life, infant formula introduction between 4-6 months was associated with the lower z-scores for BMI, weight-for-age and weight for length at both 1 year and 3 years of age. We also found that there may be a potential effect of early formula introduction on being persistently overweight from 1 year to 3 years old.

In our study population, most of the infants (82.1%) were introduced formula to their diet within the first 3 months of life, highlighting that early formula introduction is widespread in this urban area of China. A longitudinal cohort study indicated that the risk of OW/OB was significantly higher among infants introduced to formula or solids during the first 4 months of life compared to those introduced later [314]. In our study, we also found that infants exposed to infant formula between 4 to 6 months of life were more likely to have lower weight-for-age and weight-for-length z-scores at both 1 year and 3 years of age than those exposed earlier (≤3 months). In multiple imputation models for 1-year-old outcomes, the average weight-for-age z-scores of the infants who were introduced infant formula between 4 to 6 months of age was 0.22 lower than those introduced within the first 3 months, indicating that the average weight of children having formula between 4 to 6 months is 0.22 standard deviations lower than the average weight of those having formula within the first 3 months. These results suggest that compared to introduction within the first 3 months of life, delaying infant formula introduction to 4-6 months would reduce the weight-for-age percentile at 1 year old by about 10 points. The length-for-age z-scores of the infants who were introduced to infant formula between 4 to 6 months of age was 0.11 lower than those introduced within the first 3 months, indicating that the average length of children having formula between 4 to 6 months is 0.11 standard deviations lower than the average length of those having formula

within the first 3 months. These results suggest that compared to introduction within the first 3 months of life, delaying infant formula introduction to 4-6 months would reduce the length for age percentile at 1 year old by about 5 points. Similar associations were also found for 3 years old outcomes. Milk consumption augments additional growth, especially in height [315]. However, it is not clear whether this growth-promoting effect is caused by anabolic hormones, specific amino acids, or other factors in the milk [316]. The accelerated growth during early stage has been reported in association with later adverse health consequences, such as later obesity [113, 305], increased blood pressure [317], and a higher risk of diabetes [318]. Therefore, infant formula promotes growth velocity and greater attained weight and height in infants, which confer both benefits and risks.

Previous evidence has shown that compared with breastfed children, formula-fed children were typically fed an earlier introduction to complementary foods [96, 319]. In this study, we observed that the earlier infant formula was supplemented, the earlier complementary food was introduced to the infant diet (**Supplementary material S13**). The associations between formula feeding and risk of childhood excess weight are likely to be confounded by complementary food introduction [320-322]. Huh's study showed that introducing solid food before the first 4 months of life was associated with a higher risk of obesity among formula-fed infants, but not in breastfed infants [323]. When analyzing the association of infant formula introduction with the risk of overweight, the introduction of complementary food was included in the regression models. In addition, we examined the modification effects of breastfeeding duration and the timing of complementary food introduction on these associations and found the effects were non-significant (**Supplementary material S14**). Furthermore, in our study, there were fewer differences in the outcomes between the formula introduction within the first 3 months group and after 6 months group. One possible

explanation is that after 6 months, most infants begin to eat solid foods as a complement to breast-feeding or formula-feeding, whereas within the first 3 months, there are few infants introduced to complementary food. 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 breastfeeding over 6 months) [324]. Therefore, for formula introduction after 6 months, it is difficult to distinguish the impacts of formula or complementary foods on later excess weight. Furthermore, formula feeding and complementary feeding might be not independent decisions, and may jointly explain variances in later obesity [320-322]. However, there are no studies to assess the relationship of excess weight gain with the age of complementary foods introduction in different timing of formula introduction groups. Future research on the relationship between both of the timings of formula and complementary foods introduction and rapid weight gain and obesity are warranted.

Compared to introduction within the first 3 months of life, significant negative associations between infant formula introduction between 4 to 6 months and risk of overweight were observed. When the analysis was limited to the full-term infants with normal birth weight, negative associations between infant formula introduction at 4 to 6 months and risk of overweight became more prominent. These results suggest that the association between feeding practice and excess weight during early stage might be modified by birth weight [325]. However, in our study, the number of cases being persistently overweight was too small in abnormal birth weight groups to provide a reliable effect size assessment. Future studies should seek to elucidate the potential relationships between the timing of foods other than breast milk introduction and risk for excess weight among infants with varying weights of birth.

Our data showed that a large proportion of infants were given infant formula as the breast milk supplement during the early months of life. The aggressive marketing for infant formula and other breast milk substitutes has influenced the parents' preferences in China [57]. In addition, there is a limited number of existed recommendations focusing on infant formula feeding and only emphasized that formula feeding is an alternative feeding choice for children who cannot be breastfed [326]. Government and health professionals should provide more information on the differences of health benefits between breast milk and formula milk to let the parents understand that there's no better early food than breast milk for their young babies.

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 42 days, 6 months, and 1 year, allowing specific descriptions of dietary patterns during infancy. A wide range of confounders was adjusted or controlled in our multiple imputation 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 formula consumption. Limitations of this study should be considered. First, the high prevalence of formula feeding before 6 month of life in the study limits the power to study the subgroup who was introduced to infant formula after 6 months, but it provides a good opportunity to study the association between timing of formula introduction and growth of infants. In addition, the population size in 3 years age group was smaller than 1 year age group. Thus, there was relatively lower power to detect differences at 3 years of age as opposed to 1 year of age. Second, the assessment of feeding practice was based on parental self-report, but recall of infant feeding practices is regarded as sufficiently accurate [327]. Third, in this study, there

was missing data on some key confounding variables such as maternal and paternal BMI. We reported the percentage of missing confounder variables before imputation in the table of baseline characteristics of participants in each chapter (Table 6.1), which indicate that adjustments for these confounders might reduce the study population and effect size in the fully adjusted models. Therefore, we performed multiple imputation analyses to address missing data. The results from imputation analysis strengthened our main findings, including significant effect sizes observed with BMI z-score, weight for age z-score and weight for length z-score, with narrower confidence intervals. Moreover, for all imputed models, there was a reasonable low fraction of missing information (FMI) < 0.2 (**Supplementary S10 and S11**) which indicates low variability between imputed data sets and points at much of the "missing" information being captured by more completely observed variables [267]. Finally, the information on the specific quantity of formula and complementary food introduced was absent in this analysis. We also have no information on whether the consumption was sustained after the introduction. Further evidence is needed to explore the extent of timing and quantity of formula introduction during early infancy that is related to excess weight gain in later life.

Conclusion

Overall, the results indicate that compared to within the first 3 months of life, introducing infant formula between 4-6 months was associated with the lower z-scores for BMI, weight-for-age and weight for length at both 1 year and 3 years of age. In addition, the infants introduced to infant formula between 4 to 6 months of age were appeared less likely to be persistently overweight from 1 to 3 years of age than those introduced within the first 3 months. Although the results need to be replicated in other well-designed studies before more

firm recommendations can be made, avoiding the early introduction of infant formula, particularly in the first 3 months, should be promoted to reduce the possibility of excess or rapid weight gain during early age.

Chapter 7 Summary and Overall Conclusion

The primary aims of the research within this thesis were to examine the associations of early infant formula introduction and risks of development of allergic diseases and obesity or overweight in young children. This chapter will summarize the key findings, implications of our findings and the potential direction of future research.

7.1 Summary of the findings

7.1.1 Early formula introduction and allergic diseases

The evidence on the effects of early cow's milk (CM) or cow's milk formula (CMF) introduction on the risk of developing atopic diseases in children was systematically reviewed in **Chapter 3**. The review found that there was limited high-quality evidence to allow for definitive conclusions on the associations of early CM or CMF introduction with the risk of childhood allergic diseases. Specific gaps in information for public recommendations regarding the optimal timing of infant formula introduction during infancy existed. In addition, I found limited evidence on the specific question of the effects of feeding practice on the development of allergic diseases outside Western countries [5, 7-9, 72, 252, 328]. In **Chapter 4**, I examined whether early introduction of infant formula, particularly within the first 3 months of life, would influence the development of atopic disease in infants base on a large prospective birth cohort study in China [174]. I found that compared with introducing infant formula after 6 months of age, introducing it within the first 3 months was significantly associated with the higher risk of eczema during the first year of life within multiple imputation and fully adjusted model. However, the high prevalence of formula introduction within the first 3 months of life in the study limits the power to study the subgroup who was introduced between 4 to 6 months.

Except for infant formula, there is substantial evidence for an association between

complementary food introduction and development of allergic diseases [7, 9, 328]. However, all of these studies mainly focused on the impacts of particular foods or dietary characteristic on the development of atopic diseases, and may have oversimplified the synergistic effects and complex interrelationships between many foods. Therefore, I further looked at the patterns of food introduction, including infant formula introduction, during early infancy instead of focusing on single food introduction in order to better inform about interactions of known or unknown effects between many foods and nutrients (**Chapter 5**). Four patterns of food introduction were identified in our population based on the average age of months at which infant formula and complementary foods were first introduced to the infant diet. I found that compared with the 'late formula' introduction pattern, infants who were introduced to infant formula at a relatively early age (mean age <1 month) had a higher risk of eczema during the first 3 years of life regardless of whether complementary foods were introduced early or late. In Chapter 5, after excluding the infants who were diagnosed with allergic diseases before food introduction, the prevalence of asthma (1.23%), allergic rhinitis (5.81%) or food allergy (4.22%) was much lower than eczema (9.42%) in our population. In addition, the high prevalence of early formula introduction in the study limits the power to study the subgroup who was introduced to infant formula after 6 months. Thus, we had a more modest power to detect a relationship with these outcomes. These associations need to be further confirmed by other larger cohort studies.

7.1.2 Early formula introduction and Z-scores of growth and being overweight in children

Evidence accumulates that formula feeding has an impact on being overweight and obesity in Chinese children [256, 312, 313, 329, 330]. A cohort study from Australia indicated that the risks of being overweight or obesity were significantly higher among infants introduced to

formula or solids before 4 months compared to those introduced lately [314]. Thus, feeding events during a critical time window of infant development have marked modulating effects on later health. In **Chapter 6** I assessed the association of the timing of formula introduction with early childhood growth to identify a critical exposure period for the development of childhood excess weight gain. The findings suggest that compared with early introduction of infant formula within the first 3 months of life, later introduction between 4 to 6 months was likely to be associated with lower BMI, weight-for-age and weight-for-length z-scores at both 1 year and 3 years of age. We also found that there may be a potential effect of early formula introduction on being persistently overweight from 1 year to 3 years old.

The accelerated growth during early stage has been reported in association with later adverse health consequences, including later obesity [113, 305], increased blood pressure [317], and a higher risk of diabetes [318]. In addition, commencing infant formula feeding during the first 3 months of life might increase the risk of being persistently overweight from 1 to 3 years of age. Rapid weight gain during the first two years of life has been suggested as a risk of later obesity [92, 331]. In promoting growth velocity and greater attained weight and height in infants, infant formula may confer both benefits and risks. The effects of these associations on long term health in our population need further exploration.

7.2 Implication and conclusion

The most recent national survey on influencing factors of breastfeeding in China reported that the commercial promotion of breast milk substitutes is one of the biggest obstacles to breastfeeding [62]. The dramatic increase in commercial infant formula sales in China raises serious concerns for child health and calls into question the efficacy of current policy on promoting optimal feeding in infants and young children. The primary research studies presented in this thesis were based on a large prospective cohort study in China. The results

showed that early introduction of infant formula within the first 3 months of life might contribute to the increased risk of eczema and being persistently overweight before 3 years of age. Our findings contribute to the evidence for public health policy and regulatory regimes on improving the health of children. Furthermore, it called for evidence of higher quality to inform the formulation of guidelines on improving exclusive breastfeeding and avoiding formula consumption during the first months of life.

Follow-up of the BIGCS cohort is still on-going. This would allow extended evaluation of the association between feeding practice and long-term health effects in the study population.

7.3 Strengths and limitations

One of the main strengths is that the BIGCS is a prospective birth cohort study with multiple follow-up time points which can provide continuously updated information. The birth cohort study design is considered to be an essential tool for understanding the development and life course of diseases, enabling the possibility to develop preventive strategies [332]. The BIGCS has a large population and can provide a wide range of variables used in our research. We anticipate having more power than estimated by using the large population from BIGCS. In addition, for allergic outcomes in Chapter 4 and 5, considering the reverse causation between the introduction of infant formula and early skin or allergic symptoms, we have attempted to avoid reverse causation in our analysis as follows: first, we limited the analysis to children who had further information on the age at which eczema was first diagnosed (collected by questionnaire at 3 years old), resulting in cases that were "at-risk" for developing allergic diseases after the formula introduction (Table 4.4). Second, we excluded all infants with reported symptoms of itchy red rash (Table 4.5) and wheezing (Table 4.6) between 0 and 6 months, resulting in cases that were "at-risk" for developing the symptoms between 7 and 12 months (Chapter 4). In the same way, in Chapter 5, we excluded all infants with reported

itchy red rash in the first year of life (0–12 months), considering that parents of infants with early skin symptoms might delay the introduction of infant formula or other foods. Unfortunately, we were not able to exclude infants who developed wheezing in the first year for the sensitivity analysis on asthma due to the limited cases available for the analysis.

Several limitations of BIGCS need to be considered. The high prevalence of formula feeding within the first 3 months of life in the study limits the power to study the subgroup who was introduced to infant formula between 4 to 6 months, but it provides a good opportunity to study the timing of formula introduction. The information on the timing of infant formulas and complementary foods introduction was collected retrospectively when the child was 6 weeks, 6 and 12 months old. Thus, misclassification due to differential recall was possible but unlikely as the parents and interviewers were not informed of the specific research questions. The allergic outcomes were collected by questionnaires based on parental report. Although the clinical diagnosis of allergic diseases would be more accurate, misclassification due to parental reports was unlikely to have influenced the effect of timing of food allergen introduction on the outcomes. In this study, we used logistic regression to explore the relationships between timing of formula feeding and outcomes of interest, however, logistic regression for binary outcome data produces an odds ratio (OR), not a relative risk (RR). If the risk of an outcome event is rare, under 10%, and the OR is small, the OR approximates the RR. But with more common outcomes (>10%), the OR is likely an overestimate of the relative risk for the outcomes. Another limitation of this study is the missing data on some key confounding variables such as the parental history of allergy, use of antibiotic before 12 months of age, and paternal BMI. We reported the percentage of missing confounder variables before imputation in the table of baseline characteristics of participants in each chapter (Table 4.1, Table 5.2, Table 6.1), which indicate that adjustments for these

confounders might reduce the study population and effect size in the fully adjusted models. To examine the impact of missing confounders, we performed multiple imputation analyses addressing this. The results from imputation analysis strengthened our main findings, including significant effect sizes observed with early eczema (**Table 4.2**, **Figure 5.3**), BMI z-scores, weight-for-age z-scores and weight-for-length z-scores (**Table 6.3**), with a narrower confidence interval. Moreover, for all imputed models, there was a reasonable low fraction of missing information (FMI) < 0.2 (**Supplementary material S7, S8, S10 and S11**), which indicates low variability between imputed data sets and points at much of the "missing" information being captured by more completely observed variables [267]. Though multiple social, behavioural and environmental factors were adjusted in our analyses, the possibility of residual confounding in our observational study cannot be excluded. In addition, the population of BIGCS is not representative of the Guangzhou population. Mothers included in BIGCS are likely to be more affluent, older and have higher education than women in Guangzhou, hence limiting the generalizability of the findings [174]. However, a relatively widespread across all social-economic status indicators can be still observed within the participants of BIGCS, hence enabling us to explore the differences in health consequences across different social-economic status strata. Finally, our population was limited to 3 years old, extended follow-up will be important since other cohorts have reported time-dependent associations with discrepant results for the impact of feeding practice on allergic diseases during infancy versus later in childhood [206, 333].

References

1. Collaboration NCDRF. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. Lancet. 2017;390(10113):2627-42.
2. Platts-Mills TA. The allergy epidemics: 1870-2010. The Journal of allergy and clinical immunology. 2015;136(1):3-13.
3. Flynn MA, McNeil DA, Maloff B, Mutasingwa D, Wu M, Ford C, et al. Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2006;7 Suppl 1:7-66.
4. Kauffmann F, Demenais F. Gene-environment interactions in asthma and allergic diseases: challenges and perspectives. The Journal of allergy and clinical immunology. 2012;130(6):1229-40; quiz 41-2.
5. Yuan M, Tan M, Moore D, Shen S, Qiu X, Thomas GN, et al. Timing of Cow's Milk or Cow's Milk Formula Introduction to the Infant Diet and Atopic Risk in Children: a Systematic Review and Meta-analysis. Clinical reviews in allergy & immunology. 2020;59(1):46-60.
6. van Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LA, et al. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966-2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy. 2003;58(9):833-43.
7. Obbagy JE, English LK, Wong YP, Butte NF, Dewey KG, Fleischer DM, et al. Complementary feeding and food allergy, atopic dermatitis/eczema, asthma, and allergic rhinitis: a systematic review. The American journal of clinical nutrition. 2019;109(Supplement_7):890S-934S.
8. Lodge CJ, Tan DJ, Lau MX, Dai X, Tham R, Lowe AJ, et al. Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatr. 2015;104(467):38-53. doi: 10.1111/apa.13132.
9. Ierodiakonou D, Garcia-Larsen V, Logan A, Groome A, Cunha S, Chivinge J, et al. Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis. Jama. 2016;316(11):1181-92.
10. Appleton J, Russell CG, Laws R, Fowler C, Campbell K, Denney-Wilson E. Infant formula feeding practices associated with rapid weight gain: A systematic review. Matern Child Nutr. 2018;14(3):e12602-e.
11. Zhang J, Li X, Hawley N, Zheng Z, Zou Z, Tan L, et al. Trends in the Prevalence of Overweight and Obesity among Chinese School-Age Children and Adolescents from 2010 to 2015. Childhood obesity. 2018;14(3):182-8.
12. Wong GWK, Li J, Bao YX, Wang JY, Leung TF, Li LL, et al. Pediatric allergy and immunology in China. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2018;29(2):127-32.

13. Halken S. Prevention of allergic disease in childhood: clinical and epidemiological aspects of primary and secondary allergy prevention. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2004;15 Suppl 16:4-5, 9-32.
14. Spergel JM. From atopic dermatitis to asthma: the atopic march. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology. 2010;105(2):99-106; quiz 7-9, 17.
15. National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (EPR-3). http://www.nhlbi.nih.gov/guidelines/asthma/index.htm. Accessed May 16, 2020. 2007.
16. Weidinger S, Novak N. Atopic dermatitis. Lancet. 2016;387(10023):1109-22.
17. Greiner AN, Hellings PW, Rotiroti G, Scadding GK. Allergic rhinitis. Lancet. 2011;378(9809):2112-22.
18. Sicherer SH. Food allergy. Lancet. 2002;360(9334):701-10.
19. Zhang Y, Li B, Huang C, Yang X, Qian H, Deng Q, et al. Ten cities cross-sectional questionnaire survey of children asthma and other allergies in China. Chinese Science Bulletin. 2013;58(34):4182-9.
20. Li J, Wang H, Chen Y, Zheng J, Wong GW, Zhong N. House dust mite sensitization is the main risk factor for the increase in prevalence of wheeze in 13- to 14-year-old schoolchildren in Guangzhou city, China. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2013;43(10):1171-9.
21. Wong GW, Hui DS, Chan HH, Fok TF, Leung R, Zhong NS, et al. Prevalence of respiratory and atopic disorders in Chinese schoolchildren. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2001;31(8):1225-31.
22. Wang S, Jiang J, Wang Y, Wang Z, Wang T, Wang H. Survey on prevalence of allergic symptoms among 0 to 24 months old children in Chinese cities. Chinese Journal of Child Health Care. 2016;24(2):119-22.
23. Stratakis N, Roumeliotaki T, Oken E, Ballester F, Barros H, Basterrechea M, et al. Fish and seafood consumption during pregnancy and the risk of asthma and allergic rhinitis in childhood: a pooled analysis of 18 European and US birth cohorts. International journal of epidemiology. 2017;46(5):1465-77.
24. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. The Journal of allergy and clinical immunology. 2017;140(1):145-53 e8.
25. Loo EXL, Ong L, Goh A, Chia AR, Teoh OH, Colega MT, et al. Effect of Maternal Dietary Patterns during Pregnancy on Self-Reported Allergic Diseases in the First 3 Years of Life: Results from the GUSTO Study. International archives of allergy and immunology. 2017;173(2):105-13.
26. Miyake Y, Tanaka K. Lack of relationship between birth conditions and allergic disorders in Japanese children aged 3 years. The Journal of asthma : official journal of the Association for the Care of Asthma. 2013;50(6):555-9.
27. Cai M, Loy SL, Tan KH, Godfrey KM, Gluckman PD, Chong YS, et al. Association of

Elective and Emergency Cesarean Delivery With Early Childhood Overweight at 12 Months of Age. JAMA network open. 2018;1(7):e185025.
28. Kuniyoshi Y, Kikuya M, Matsubara H, Ishikuro M, Obara T, Kure S, et al. Association of Feeding Practice with Childhood Overweight and/or Obesity in Affected Areas Before and After the Great East Japan Earthquake. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2019;14(6):382-9.
29. Hill DA, Grundmeier RW, Ram G, Spergel JM. The epidemiologic characteristics of healthcare provider-diagnosed eczema, asthma, allergic rhinitis, and food allergy in children: a retrospective cohort study. BMC pediatrics. 2016;16:133.
30. Uphoff EP, Bird PK, Anto JM, Basterrechea M, von Berg A, Bergstrom A, et al. Variations in the prevalence of childhood asthma and wheeze in MeDALL cohorts in Europe. ERJ open research. 2017;3(3).
31. Grimshaw KE, Bryant T, Oliver EM, Martin J, Maskell J, Kemp T, et al. Incidence and risk factors for food hypersensitivity in UK infants: results from a birth cohort study. Clinical and translational allergy. 2015;6:1.
32. Schmidt F, Hose AJ, Mueller-Rompa S, Brick T, Hamalainen AM, Peet A, et al. Development of atopic sensitization in Finnish and Estonian children: A latent class analysis in a multicenter cohort. The Journal of allergy and clinical immunology. 2019;143(5):1904-13 e9.
33. Ballardini N, Kramer MS, Oken E, Henderson AJ, Bogdanovich N, Dahhou M, et al. Associations of atopic dermatitis and asthma with child behaviour: Results from the PROBIT cohort. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2019;49(9):1235-44.
34. Kaneko M, Miyoshi T, Miyashita Y, Onogi K, Okano Y, Shimizu A, et al. Food allergy in nursery children of Kawasaki city, Japan. Asian Pacific journal of allergy and immunology. 2019.
35. Tham EH, Lee BW, Chan YH, Loo EXL, Toh JY, Goh A, et al. Low Food Allergy Prevalence Despite Delayed Introduction of Allergenic Foods-Data from the GUSTO Cohort. Journal of Allergy and Clinical Immunology: In Practice. 2018;6(2):466-75.e1.
36. World Health Organization. Obesity and overweight. Available from: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight. Accessed 13 April 2020.
37. Group WHOMGRS. WHO Child Growth Standards based on length/height, weight and age. Acta paediatrica. 2006;450:76-85.
38. Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. Bmj. 2000;320(7244):1240-3.
39. Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Archives of disease in childhood. 1995;73(1):25-9.
40. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, et al. 2000 CDC Growth Charts for the United States: methods and development. Vital and health statistics Series 11, Data from the National Health Survey. 2002(246):1-190.
41. Zong XN, Li H, Zhang YQ, Wu HH. Child nutrition to new stage in China: evidence from a series of national surveys, 1985-2015. BMC public health. 2019;19(1):402.

42. Guo Y, Yin X, Wu H, Chai X, Yang X. Trends in Overweight and Obesity Among Children and Adolescents in China from 1991 to 2015: A Meta-Analysis. International journal of environmental research and public health. 2019;16(23).
43. Li N, Liu E, Sun S, Guo J, Pan L, Wang P, et al. Birth weight and overweight or obesity risk in children under 3 years in China. American journal of human biology : the official journal of the Human Biology Council. 2014;26(3):331-6.
44. Jones RE, Jewell J, Saksena R, Ramos Salas X, Breda J. Overweight and Obesity in Children under 5 Years: Surveillance Opportunities and Challenges for the WHO European Region. Frontiers in public health. 2017;5:58.
45. Lang IA, Kipping RR, Jago R, Lawlor DA. Variation in childhood and adolescent obesity prevalence defined by international and country-specific criteria in England and the United States. European journal of clinical nutrition. 2011;65(2):143-50.
46. Hoffmann SW, Ulrich R, Simon P. Refined analysis of the critical age ranges of childhood overweight: implications for primary prevention. Obesity. 2012;20(10):2151-4.
47. Nichols MS, Silva-Sanigorski A, Cleary JE, Goldfeld SR, Colahan A, Swinburn BA. Decreasing trends in overweight and obesity among an Australian population of preschool children. International journal of obesity. 2011;35(7):916-24.
48. Yu DM, Ju LH, Zhao LY, Fang HY, Yang ZY, Guo HJ, et al. [Prevalence and characteristics of overweight and obesity in Chinese children aged 0-5 years]. Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi. 2018;39(6):710-4.
49. Biro S, Barber D, Williamson T, Morkem R, Khan S, Janssen I. Prevalence of toddler, child and adolescent overweight and obesity derived from primary care electronic medical records: an observational study. CMAJ open. 2016;4(3):E538-E44.
50. Ramasubramanian L, Lane S, Rahman A. The association between maternal serious psychological distress and child obesity at 3 years: a cross-sectional analysis of the UK Millennium Cohort Data. Child: care, health and development. 2013;39(1):134-40.
51. Jabakhanji SB, Pavlova M, Groot W, Boland F, Biesma R. Social class variation, the effect of the economic recession and childhood obesity at 3 years of age in Ireland. European journal of public health. 2017;27(2):234-9.
52. Rajput N, Tuohy P, Mishra S, Smith A, Taylor B. Overweight and obesity in 4-5-year-old children in New Zealand: results from the first 4 years (2009-2012) of the B4School Check programme. Journal of paediatrics and child health. 2015;51(3):334-43.
53. Schmidt Morgen C, Rokholm B, Sjoberg Brixval C, Schou Andersen C, Geisler Andersen L, Rasmussen M, et al. Trends in prevalence of overweight and obesity in danish infants, children and adolescents--are we still on a plateau? PloS one. 2013;8(7):e69860.
54. Neves PAR, Gatica-Dom ńguez G, Rollins NC, Piwoz E, Baker P, Barros AJD, et al. Infant Formula Consumption Is Positively Correlated with Wealth, Within and Between Countries: A Multi-Country Study. The Journal of nutrition. 2020;150(4):910-7.
55. Duan Y, Yang Z, Lai J, Yu D, Chang S, Pang X, et al. Exclusive Breastfeeding Rate and Complementary Feeding Indicators in China: A National Representative Survey in 2013. Nutrients. 2018;10(2).
56. Wu HH, Zhang YQ, Zong XN, Li H. Changes of feeding patterns in Chinese city children under 2 years from 1985 to 2015: results from a series of national cross-sectional surveys.

World journal of pediatrics : WJP. 2019;15(2):176-81.
57. Tang L, Lee AH, Binns CW, Yang Y, Wu Y, Li Y, et al. Widespread usage of infant formula in China: a major public health problem. Birth. 2014;41(4):339-43.
58. Wei X, Li Q. A survey of feeding practive in 4537 infants at 42 days old from 1996 to 2007. Chin J Child Heal Care. 2009;17(1):106-8.
59. UNICEF. An Atlas of Social Indicators of Children in China 2018. Available from https://www.unicef.org/china/atlas-2018-cn. Accessed 14th January 2020.
60. Chen YC, Chang JS, Gong YT. A Content Analysis of Infant and Toddler Food Advertisements in Taiwanese Popular Pregnancy and Early Parenting Magazines. Journal of human lactation : official journal of International Lactation Consultant Association. 2015;31(3):458-66.
61. Zhang Y, Carlton E, Fein SB. The association of prenatal media marketing exposure recall with breastfeeding intentions, initiation, and duration. Journal of human lactation : official journal of International Lactation Consultant Association. 2013;29(4):500-9.
62. China Development Research Foundation. A report on the influencing factors of breastfeeding in China, 2019. https://cdrf.org.cn/jjh/pdf/mu.pdf. Accessed Feburary 20, 2020.
63. Piwoz EG, Huffman SL. The Impact of Marketing of Breast-Milk Substitutes on WHO-Recommended Breastfeeding Practices. Food and nutrition bulletin. 2015;36(4):373-86.
64. Baker P, Smith J, Salmon L, Friel S, Kent G, Iellamo A, et al. Global trends and patterns of commercial milk-based formula sales: is an unprecedented infant and young child feeding transition underway? Public health nutrition. 2016;19(14):2540-50.
65. Etowa J, MacDonald S, Hannan J, Phillips JC, Boadu NY, Babatunde S. Sociocultural factors influencing infant-feeding choices among African immigrant women living with HIV: A synthesis of the literature. Journal of the American Association of Nurse Practitioners. 2018;30(4):208-35.
66. Bolton KA, Kremer P, Hesketh KD, Laws R, Kuswara K, Campbell KJ. Differences in infant feeding practices between Chinese-born and Australian-born mothers living in Australia: a cross-sectional study. BMC pediatrics. 2018;18(1):209.
67. Brown A. Breastfeeding as a public health responsibility: a review of the evidence. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2017;30(6):759-70.
68. Bonia K, Twells L, Halfyard B, Ludlow V, Newhook LA, Murphy-Goodridge J. A qualitative study exploring factors associated with mothers' decisions to formula-feed their infants in Newfoundland and Labrador, Canada. BMC public health. 2013;13:645.
69. Gurka KK, Hornsby PP, Drake E, Mulvihill EM, Kinsey EN, Yitayew MS, et al. Exploring intended infant feeding decisions among low-income women. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2014;9(8):377-84.
70. Zhang K, Tang L, Wang H, Qiu L, Binns CW, Lee AH. Why do mothers of young infants choose to formula feed in China? Perceptions of mothers and hospital staff. International journal of environmental research and public health. 2015;12(5):4520-32.
71. Sheehan A, Schmied V, Cooke M. Australian women's stories of their baby-feeding decisions in pregnancy. Midwifery. 2003;19(4):259-66.

72. Griebler U, Bruckmuller MU, Kien C, Dieminger B, Meidlinger B, Seper K, et al. Health effects of cow's milk consumption in infants up to 3 years of age: a systematic review and meta-analysis. Public health nutrition. 2016;19(2):293-307.
73. Calder PC, Albers R, Antoine JM, Blum S, Bourdet-Sicard R, Ferns GA, et al. Inflammatory disease processes and interactions with nutrition. The British journal of nutrition. 2009;101 Suppl 1:S1-45.
74. Calder PC, Krauss-Etschmann S, de Jong EC, Dupont C, Frick JS, Frokiaer H, et al. Early nutrition and immunity - progress and perspectives. The British journal of nutrition. 2006;96(4):774-90.
75. Basha S, Surendran N, Pichichero M. Immune responses in neonates. Expert review of clinical immunology. 2014;10(9):1171-84.
76. Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. The Journal of allergy and clinical immunology. 2005;115(6):1109-17; quiz 18.
77. Melnik BC. The potential mechanistic link between allergy and obesity development and infant formula feeding. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology. 2014;10(1):37.
78. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. Journal of immunology. 1986;136(7):2348-57.
79. Gandhi GR, Neta M, Sathiyabama RG, Quintans JSS, de Oliveira ESAM, Araujo AAS, et al. Flavonoids as Th1/Th2 cytokines immunomodulators: A systematic review of studies on animal models. Phytomedicine : international journal of phytotherapy and phytopharmacology. 2018;44:74-84.
80. Warner JA, Jones AC, Miles EA, Warner JO. Prenatal sensitisation. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 1996;7(9 Suppl):98-101.
81. Melnik BC, John SM, Schmitz G. Milk: an exosomal microRNA transmitter promoting thymic regulatory T cell maturation preventing the development of atopy? Journal of translational medicine. 2014;12:43.
82. Enke U, Seyfarth L, Schleussner E, Markert UR. Impact of PUFA on early immune and fetal development. The British journal of nutrition. 2008;100(6):1158-68.
83. World Health Organization. Feeding and nutrition of infants and young children: Guidelines for the WHO European region, with emphasis on the former Soviet countries. 2003. Available from: http://wwwwhoint/nutrition/publications/infantfeeding/9289013540/en/. Accessed September 25, 2020.
84. Lynch SV, Pedersen O. The Human Intestinal Microbiome in Health and Disease. The New England journal of medicine. 2016;375(24):2369-79.
85. Penders J, Stobberingh EE, van den Brandt PA, Thijs C. The role of the intestinal microbiota in the development of atopic disorders. Allergy. 2007;62(11):1223-36.
86. Marques TM, Wall R, Ross RP, Fitzgerald GF, Ryan CA, Stanton C. Programming infant gut microbiota: influence of dietary and environmental factors. Current opinion in biotechnology. 2010;21(2):149-56.
87. Kashtanova DA, Popenko AS, Tkacheva ON, Tyakht AB, Alexeev DG, Boytsov SA.

Association between the gut microbiota and diet: Fetal life, early childhood, and further life. Nutrition. 2016;32(6):620-7.
88. Hart AL, Lammers K, Brigidi P, Vitali B, Rizzello F, Gionchetti P, et al. Modulation of human dendritic cell phenotype and function by probiotic bacteria. Gut. 2004;53(11):1602-9.
89. Sievers E, Oldigs HD, Santer R, Schaub J. Feeding patterns in breast-fed and formula-fed infants. Annals of nutrition & metabolism. 2002;46(6):243-8.
90. Agras WS, Kraemer HC, Berkowitz RI, Hammer LD. Influence of early feeding style on adiposity at 6 years of age. The Journal of pediatrics. 1990;116(5):805-9.
91. WHO. Feeding and nutrition of infants and young children Guidelines for the WHO European region, with emphasis on the former Soviet countries. 2003 [cited 2018 October 23]. Available from: http://www.euro.who.int/__data/assets/pdf_file/0004/98302/WS_115_2000FE.pdf?ua=1.
92. Koletzko B, von Kries R, Monasterolo RC, Subias JE, Scaglioni S, Giovannini M, et al. Infant feeding and later obesity risk. Advances in experimental medicine and biology. 2009;646:15-29.
93. Koletzko B, Broekaert I, Demmelmair H, Franke J, Hannibal I, Oberle D, et al. Protein intake in the first year of life: a risk factor for later obesity? The E.U. childhood obesity project. Advances in experimental medicine and biology. 2005;569:69-79.
94. Grote V, Theurich M, Luque V, Gruszfeld D, Verduci E, Xhonneux A, et al. Complementary Feeding, Infant Growth, and Obesity Risk: Timing, Composition, and Mode of Feeding. Nestle Nutrition Institute workshop series. 2018;89:93-103.
95. Kronborg H, Foverskov E, Vaeth M. Breastfeeding and introduction of complementary food in Danish infants. Scandinavian journal of public health. 2015;43(2):138-45.
96. Schiess S, Grote V, Scaglioni S, Luque V, Martin F, Stolarczyk A, et al. Introduction of complementary feeding in 5 European countries. Journal of pediatric gastroenterology and nutrition. 2010;50(1):92-8.
97. Fewtrell MS, Lucas A, Morgan JB. Factors associated with weaning in full term and preterm infants. Archives of disease in childhood Fetal and neonatal edition. 2003;88(4):F296-301.
98. Papoutsou S, Savva SC, Hunsberger M, Jilani H, Michels N, Ahrens W, et al. Timing of solid food introduction and association with later childhood overweight and obesity: The IDEFICS study. Matern Child Nutr. 2018;14(1):10.1111/mcn.12471.
99. O'Sullivan A, He X, McNiven EM, Haggarty NW, Lönnerdal B, Slupsky CM. Early diet impacts infant rhesus gut microbiome, immunity, and metabolism. Journal of proteome research. 2013;12(6):2833-45.
100. Bezirtzoglou E, Tsiotsias A, Welling GW. Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). Anaerobe. 2011;17(6):478-82.
101. Pihl AF, Fonvig CE, Stjernholm T, Hansen T, Pedersen O, Holm JC. The Role of the Gut Microbiota in Childhood Obesity. Childhood obesity. 2016;12(4):292-9.
102. Maruvada P, Leone V, Kaplan LM, Chang EB. The Human Microbiome and Obesity: Moving beyond Associations. Cell host & microbe. 2017;22(5):589-99.
103. Indiani C, Rizzardi KF, Castelo PM, Ferraz LFC, Darrieux M, Parisotto TM.

Childhood Obesity and Firmicutes/Bacteroidetes Ratio in the Gut Microbiota: A Systematic Review. Childhood obesity. 2018;14(8):501-9.
104. Boulangé CL, Neves AL, Chilloux J, Nicholson JK, Dumas ME. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome medicine. 2016;8(1):42.
105. Gao X, Jia R, Xie L, Kuang L, Feng L, Wan C. Obesity in school-aged children and its correlation with gut E.coli and Bifidobacteria: a case-control study. BMC pediatrics. 2015;15:64.
106. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. The American journal of clinical nutrition. 2008;87(3):534-8.
107. Kelishadi R, Roufarshbaf M, Soheili S, Payghambarzadeh F, Masjedi M. Association of Childhood Obesity and the Immune System: A Systematic Review of Reviews. Childhood obesity. 2017;13(4):332-46.
108. Lang JE, Bunnell HT, Lima JJ, Hossain MJ, Wysocki T, Bacharier L, et al. Effects of age, sex, race/ethnicity, and allergy status in obesity-related pediatric asthma. Pediatric pulmonology. 2019;54(11):1684-93.
109. Pan CX, Jee YH, Moore KJ, Kraft P, Asgari MM. Relationship Between Body Mass Index and Atopic Dermatitis: Critical Appraisal of a Mendelian Randomization Approach in Exploring Causality. The British journal of dermatology. 2020.
110. Anderson EL, Fraser A, Martin RM, Kramer MS, Oken E, Patel R, et al. Associations of postnatal growth with asthma and atopy: the PROBIT Study. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2013;24(2):122-30.
111. Pike KC, Crozier SR, Lucas JS, Inskip HM, Robinson S, Southampton Women's Survey Study G, et al. Patterns of fetal and infant growth are related to atopy and wheezing disorders at age 3 years. Thorax. 2010;65(12):1099-106.
112. Loo EX, Goh A, Aris IBM, Teoh OH, Shek LP, Lee BW, et al. Effects of infant weight gain on subsequent allergic outcomes in the first 3 years of life. BMC pediatrics. 2017;17(1):134.
113. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al. Can infant feeding choices modulate later obesity risk? The American journal of clinical nutrition. 2009;89(5):1502S-8S.
114. WHO, UNICEF. Global strategy for infant and young child feeding 2003. Available from: http://www.who.int/nutrition/publications/infantfeeding/9241562218/en/. Accessed 2020 August 24.
115. American Academy of Pediatrics Committee on Nutrition. In: Kleinrnan RE, Greer FR, eds Pediatric Nutrition 7th ed. 2014.
116. CNS. Chinese Nutrition Society. Feeding Guidelines for Infant Under Six Months. Journal of clinical pediatrics. 2016;34(4):287-91.
117. FSAI. Scientific Recommendations for a National Infant Feeding Policy, 2nd Edition 2011 [cited 2018 October 26]. Available from: https://www.fsai.ie/resources_publications/national_infant_feeding_policy/.
118. GOC. Goverment of Canada. Nutrition for Healthy Term Infants: Recommendations

from Birth to Six Months 2015. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/infant-feeding/nutrition-healthy-term-infants-recommendations-birth-six-months.html#a4.
119. IAP. India academy of pediatrics. Infant and Young Child Feeding Guidelines 2016 [cited 2018 October 26]. Available from: https://www.iapindia.org/wp-content/uploads/2018/08/Infant-and-Young-Child-Feeding-Guidelines-2016.pdf.
120. MH. Ministry of Health. Food and Nutrition Guidelines for Healthy Infants and Toddlers (Aged 0–2)A background paper 2012 [cited 2018 October 26]. Available from: https://www.health.govt.nz/system/files/documents/publications/food-and-nutrition-guidelines-healthy-infants-and-toddlers-revised-dec12.pdf.
121. NHMRC. National Health and Medical Research Council. Infant Feeding Guidelines 2012 [cited 2020 October 26]. Available from: https://nhmrc.gov.au/about-us/publications/infant-feeding-guidelines-information-health-workers.
122. NICE. The National Institute for Health and Care Excellence. Maternal and child nutrition 2008 [cited 2020 October 26]. Available from: https://www.nice.org.uk/guidance/ph11/resources/maternal-and-child-nutrition-pdf-1996171502533.
123. World Health Organization. Infant and young child feeding. Model Chapter for textbooks for medical students and allied health professionals 2009. Available from: http://www.who.int/nutrition/publications/infantfeeding/9789241597494/en/. Accessed 2020 August 24.
124. SACN. Scientific Advisory Committee on Nutrition. SACN report on Feeding in the First Year of Life 2018 [cited 2018 October 26]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/725530/SACN_report_on_Feeding_in_the_First_Year_of_Life.pdf.
125. USDA. Guidelines for Feeding Healthy Infants (for WIC staff) 2017 [cited 2018 26 October]. Available from: https://wicworks.fns.usda.gov/sites/default/files/media/document/Guidelines%20for%20Feeding%20Healthy%20Infants%20Job%20Aid%20FINAL_rev6-2017_508c.pdf.
126. Fewtrell M, Wilson DC, Booth I, Lucas A. Six months of exclusive breast feeding: how good is the evidence? Bmj. 2010;342:c5955.
127. Ssemukasa EL, Kearney J. Six months of exclusive breastfeeding recommendation: how applicable is the universal exclusive breastfeeding recommendation policy? African Journal of Food Agriculture Nutrition & Development. 2014;14.
128. Klingberg S, Brekke HK, Ludvigsson J. Introduction of fish and other foods during infancy and risk of asthma in the All Babies In Southeast Sweden cohort study. European journal of pediatrics. 2019;178(3):395-402.
129. van Ginkel CD, van der Meulen GN, Bak E, Flokstra-de Blok BMJ, Kollen BJ, Koppelman GH, et al. Retrospective observational cohort study regarding the effect of breastfeeding on challenge-proven food allergy. European journal of clinical nutrition. 2018;72(4):557-63.

130. Lossius AK, Magnus MC, Lunde J, Stordal K. Prospective Cohort Study of Breastfeeding and the Risk of Childhood Asthma. Journal of Pediatrics. 2018;195:182-9.e2.
131. Filipiak-Pittroff B, Koletzko S, Kramer U, Standl M, Bauer CP, Berdel D, et al. Full breastfeeding and allergies from infancy until adolescence in the GINIplus cohort. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2018;29(1):96-101.
132. El-Heneidy A, Abdel-Rahman ME, Mihala G, Ross LJ, Comans TA. Milk Other Than Breast Milk and the Development of Asthma in Children 3 Years of Age. A Birth Cohort Study (2006(-)2011). Nutrients. 2018;10(11).
133. Tran MM, Lefebvre DL, Dai D, Dharma C, Subbarao P, Lou W, et al. Timing of food introduction and development of food sensitization in a prospective birth cohort. Pediatric Allergy and Immunology. 2017;28(5):471-7.
134. Klopp A, Vehling L, Becker AB, Mandhane PJ, Turvey SE, Lefebvre DL, et al. Modes of Infant Feeding and the Risk of Childhood Asthma: A Prospective Birth Cohort Study. Journal of Pediatrics. 2017;190:192-9.e2.
135. Azad MB, Vehling L, Lu Z, Dai D, Subbarao P, Becker AB, et al. Breastfeeding, maternal asthma and wheezing in the first year of life: a longitudinal birth cohort study. The European respiratory journal. 2017;49(5).
136. Teele DW, Klein JO, Rosner B. Epidemiology of Otitis Media During the First Seven Years of Life in Children in Greater Boston: A Prospective, Cohort Study. Journal of Infectious Diseases. 1989;160(1):83-94.
137. GOC. Goverment of Canada. Nutrition for Healthy Term Infants: Recommendations from Six to 24 Months 2015. Available from: https://www.canada.ca/en/health-canada/services/food-nutrition/healthy-eating/infant-feeding/nutrition-healthy-term-infants-recommendations-birth-six-months/6-24-months.html.
138. Wright CM, Parkinson KN, Drewett RF. Why are babies weaned early? Data from a prospective population based cohort study. Archives of disease in childhood. 2004;89(9):813-6.
139. Wallenborn JT, Ihongbe T, Rozario S, Masho SW. Knowledge of Breastfeeding Recommendations and Breastfeeding Duration: A Survival Analysis on Infant Feeding Practices II. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2017;12:156-62.
140. Tarrant RC, Younger KM, Sheridan-Pereira M, White MJ, Kearney JM. Factors associated with weaning practices in term infants: a prospective observational study in Ireland. The British journal of nutrition. 2010;104(10):1544-54.
141. Nelson JM, Li R, Perrine CG, Scanlon KS. Public Opinions About Infant Feeding in the United States. Birth (Berkeley, Calif). 2016;43(4):313-9.
142. MHLW. Ministry of Health, Labour and Welfare. Breast feeding and weaning assistance Guide 2007 [cited 2018 October 26]. Available from: https://www.mhlw.go.jp/shingi/2007/03/dl/s0314-10.pdf.
143. DH. Department of Health. Infant feeding recommendation 2003 [cited 2018 October 26]. Available from: http://webarchive.nationalarchives.gov.uk/_http_/webarchive.nationalarchives.gov.uk/201205

03221049/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4097197.
144. CNS. Feeding Guidelines for Infant From Seven to 24 Months. Journal of clinical pediatrics. 2016;34(5):381-7.
145. Ministry of Health & Family Welfare, Government of India. Guidelines for Enhancing Optimal Infant And Young Child Feeding Practices 2013 [cited 2018 October 26]. Available from: http://www.nrhmorissa.gov.in/writereaddata/Upload/Documents/Guideline%20-%20IYCF.pdf.
146. Ministry of Women and Child Development (Food and Nutrition Board), Government of India. National Guidelines On Infant And Young Child Feeding 2006 [cited 2018 October 26]. Available from: http://motherchildnutrition.org/india/india-national-guidelines.html.
147. MH. Ministry of Health. Guidelines for New Zealand Health Workers 1997 [cited 2018 October 26]. Available from: http://www.moh.govt.nz/notebook/nbbooks.nsf/0/ca92a08467ba57c94c2565d70018c999/$FILE/infant1.pdf.
148. IYCF. India academy of pediatrics. Infant and Young Child Feeding Guidelines 2016 [cited 2018 October 26]. Available from: https://www.iapindia.org/wp-content/uploads/2018/08/Infant-and-Young-Child-Feeding-Guidelines-2016.pdf.
149. Kramer MS, Kakuma R. Optimal duration of exclusive breastfeeding. The Cochrane database of systematic reviews. 2012(8):CD003517.
150. Onayade AA, Abiona TC, Abayomi IO, Makanjuola RO. The first six month growth and illness of exclusively and non-exclusively breast-fed infants in Nigeria. East African medical journal. 2004;81(3):146-53.
151. Khadivzadeh T, Parsai S. Effect of exclusive breastfeeding and complementary feeding on infant growth and morbidity. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit. 2004;10(3):289-94.
152. Kramer MS, Guo T, Platt RW, Sevkovskaya Z, Dzikovich I, Collet JP, et al. Infant growth and health outcomes associated with 3 compared with 6 mo of exclusive breastfeeding. The American journal of clinical nutrition. 2003;78(2):291-5.
153. Chantry CJ, Howard CR, Auinger P. Full breastfeeding duration and associated decrease in respiratory tract infection in US children. Pediatrics. 2006;117(2):425-32.
154. Sauls HS. Potential effect of demographic and other variables in studies comparing morbidity of breast-fed and bottle-fed infants. Pediatrics. 1979;64(4):523-7.
155. Lanigan JA, Bishop J, Kimber AC, Morgan J. Systematic review concerning the age of introduction of complementary foods to the healthy full-term infant. European journal of clinical nutrition. 2001;55(5):309-20.
156. EFSA. Scientific Opinion on the appropriate age for introduction of complementary feeding of infants. EFSA Journal. 2009;7(12):1423.
157. Chantry CJ, Howard CR, Auinger P. Full breastfeeding duration and risk for iron

deficiency in U.S. infants. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2007;2(2):63-73.
158. Flohr C, Henderson AJ, Kramer MS, Patel R, Thompson J, Rifas-Shiman SL, et al. Effect of an Intervention to Promote Breastfeeding on Asthma, Lung Function, and Atopic Eczema at Age 16 Years: Follow-up of the PROBIT Randomized Trial. JAMA pediatrics. 2018;172(1):e174064.
159. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. Jama. 2001;285(4):413-20.
160. Kramer MS, Fombonne E, Igumnov S, Vanilovich I, Matush L, Mironova E, et al. Effects of prolonged and exclusive breastfeeding on child behavior and maternal adjustment: evidence from a large, randomized trial. Pediatrics. 2008;121(3):e435-40.
161. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, et al. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 y: evidence from a large randomized trial. The American journal of clinical nutrition. 2007;86(6):1717-21.
162. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, et al. A randomized breast-feeding promotion intervention did not reduce child obesity in Belarus. The Journal of nutrition. 2009;139(2):417S-21S.
163. Kramer MS, Vanilovich I, Matush L, Bogdanovich N, Zhang X, Shishko G, et al. The effect of prolonged and exclusive breast-feeding on dental caries in early school-age children. New evidence from a large randomized trial. Caries research. 2007;41(6):484-8.
164. Martin RM, Patel R, Kramer MS, Vilchuck K, Bogdanovich N, Sergeichick N, et al. Effects of promoting longer-term and exclusive breastfeeding on cardiometabolic risk factors at age 11.5 years: a cluster-randomized, controlled trial. Circulation. 2014;129(3):321-9.
165. Skugarevsky O, Wade KH, Richmond RC, Martin RM, Tilling K, Patel R, et al. Effects of promoting longer-term and exclusive breastfeeding on childhood eating attitudes: a cluster-randomized trial. International journal of epidemiology. 2014;43(4):1263-71.
166. Yang S, Martin RM, Oken E, Hameza M, Doniger G, Amit S, et al. Breastfeeding during infancy and neurocognitive function in adolescence: 16-year follow-up of the PROBIT cluster-randomized trial. PLoS medicine. 2018;15(4):e1002554.
167. Kramer MS, Matush L, Bogdanovich N, Aboud F, Mazer B, Fombonne E, et al. Health and development outcomes in 6.5-y-old children breastfed exclusively for 3 or 6 mo. The American journal of clinical nutrition. 2009;90(4):1070-4.
168. Renfrew MJ, McGuire W, McCormick FM. When to wean. Analysis article on breast feeding was misleading. Bmj. 2011;342:d987.
169. Wright CM. When to wean. Infection more important than anaemia or allergy. Bmj. 2011;342:d1000.
170. Parry JE, Ip DK, Chau PY, Wu KM, Tarrant M. Predictors and consequences of in-hospital formula supplementation for healthy breastfeeding newborns. Journal of human lactation : official journal of International Lactation Consultant Association. 2013;29(4):527-36.
171. Kim E, Hoetmer SE, Li Y, Vandenberg JE. Relationship between intention to

supplement with infant formula and breastfeeding duration. Canadian journal of public health = Revue canadienne de sante publique. 2013;104(5):e388-93.
172. Perez-Escamilla R, Pollitt E, Lonnerdal B, Dewey KG. Infant feeding policies in maternity wards and their effect on breast-feeding success: an analytical overview. American journal of public health. 1994;84(1):89-97.
173. Chien PF, Howie PW. Breast milk and the risk of opportunistic infection in infancy in industrialized and non-industrialized settings. Advances in nutritional research. 2001;10:69-104.
174. Qiu X, Lu JH, He JR, Lam KH, Shen SY, Guo Y, et al. The Born in Guangzhou Cohort Study (BIGCS). European journal of epidemiology. 2017;32(4):337-46.
175. World Health Organization. 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.WHO, Geneva. 2006.
176. Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. Bmj. 2009;338:b2393.
177. UCLA. 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 2021 January 18.
178. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet. 2006;368(9537):733-43.
179. Gomez-Gallego C, Garcia-Mantrana I, Salminen S, Collado MC. The human milk microbiome and factors influencing its composition and activity. Seminars in fetal & neonatal medicine. 2016;21(6):400-5.
180. Friedman NJ, Zeiger RS. The role of breast-feeding in the development of allergies and asthma. The Journal of allergy and clinical immunology. 2005;115(6):1238-48.
181. Hoppu U, Kalliomaki M, Laiho K, Isolauri E. Breast milk--immunomodulatory signals against allergic diseases. Allergy. 2001;56 Suppl 67:23-6.
182. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.
183. The World Bank In China 2018. www.worldbank.org/en/country/china/overview. Accessed 13 May 2020.
184. Ram FSF, Scarlett JF. Development of childhood asthma and formula milk. British Journal of Midwifery. 2004;12(4):221-30.
185. Peters RL, Koplin JJ, Dharmage SC, Tang MLK, McWilliam VL, Gurrin LC, et al. Early Exposure to Cow's Milk Protein Is Associated with a Reduced Risk of Cow's Milk Allergic Outcomes. The journal of allergy and clinical immunology In practice. 2019;7(2):462-70 e1.
186. Smith HA. Formula supplementation and the risk of cow's milk allergy. British

Journal of Midwifery. 2012;20(5):345-50.
187. Chen M, Welch M, Laubach S. Preventing Peanut Allergy. Pediatric allergy, immunology, and pulmonology. 2018;31(1):2-8.
188. Fleischer DM, Sicherer S, Greenhawt M, Campbell D, Chan E, Muraro A, et al. Consensus communication on early peanut introduction and the prevention of peanut allergy in high-risk infants. The Journal of allergy and clinical immunology. 2015;136(2):258-61.
189. Prescott SL, Smith P, Tang M, Palmer DJ, Sinn J, Huntley SJ, et al. The importance of early complementary feeding in the development of oral tolerance: concerns and controversies. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2008;19(5):375-80.
190. Halken S, Host A. Prevention of allergic disease. Exposure to food allergens and dietetic intervention. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 1996;7(9 Suppl):102-7.
191. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. Bmj. 2015;349:g7647.
192. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Health Research Institute. 2014.
193. Higgins J, Altman DG. Chapter 8: assessing risk of bias in included studies. http://handbook.cochrane.org/. Accessed 15 December 2018.
194. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? The American journal of gastroenterology. 2011;106(11):1911-21; quiz 22.
195. Chilaka VN, Konje JC. HIV in pregnancy - An update. European journal of obstetrics, gynecology, and reproductive biology. 2021;256:484-91.
196. Nwaru BI, Takkinen HM, Niemela O, Kaila M, Erkkola M, Ahonen S, et al. Timing of infant feeding in relation to childhood asthma and allergic diseases. Journal of Allergy and Clinical Immunology. 2013a;131(1):78-86.
197. Juvonen P, Månsson M, Andersson C, Jakobsson I. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life. A three-year prospective follow-up. Acta paediatrica. 1996;85(9):1047-52.
198. Lindfors AT, Danielsson L, Enocksson E, Johansson SG, Westin S. Allergic symptoms up to 4-6 years of age in children given cow milk neonatally. A prospective study. Allergy. 1992;47(3):207-11.
199. Gustafsson D, Lowhagen T, Andersson K. Risk of developing atopic disease after early feeding with cow's milk based formula. Archives of disease in childhood. 1992;67(8):1008-10.
200. Nwaru BI, Craig LC, Allan K, Prabhu N, Turner SW, McNeill G, et al. Breastfeeding and introduction of complementary foods during infancy in relation to the risk of asthma and atopic diseases up to 10 years. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2013;43(11):1263-73.
201. Strassburger SZ, Vitolo MR, Bortolini GA, Pitrez PM, Jones MH, Stein RT.

Nutritional errors in the first months of life and their association with asthma and atopy in preschool children. J Pediatr (Rio J). 2010;86(5):391-9.
202. Tariq SM, Matthews SM, Hakim EA, Stevens M, Arshad SH, Hide DW. The prevalence of and risk factors for atopy in early childhood: a whole population birth cohort study. The Journal of allergy and clinical immunology. 1998;101(5):587-93.
203. Kemeny DM, Price JF, Richardson V, Richards D, Lessof MH. The IgE and IgG subclass antibody response to foods in babies during the first year of life and their relationship to feeding regimen and the development of food allergy. The Journal of allergy and clinical immunology. 1991;87(5):920-9.
204. Marini A, Agosti M, Motta G, Mosca F. Effects of a dietary and environmental prevention programme on the incidence of allergic symptoms in high atopic risk infants: Three years follow-up. Acta Paediatrica, International Journal of Paediatrics, Supplement. 1996;85(414):1-22.
205. Simon MR, Havstad SL, Wegienka GR, Ownby DR, Johnson CC. Risk factors associated with transient wheezing in young children. Allergy and Asthma Proceedings. 2008;29(2):161-5.
206. Snijders BE, Thijs C, van Ree R, van den Brandt PA. Age at first introduction of cow milk products and other food products in relation to infant atopic manifestations in the first 2 years of life: the KOALA Birth Cohort Study. Pediatrics. 2008;122(1):e115-22.
207. Van Asperen PP, Kemp AS, Mellis CM. Relationship of diet in the development of atopy in infancy. Clinical allergy. 1984;14(6):525-32.
208. Zutavern A, von Mutius E, Harris J, Mills P, Moffatt S, White C, et al. The introduction of solids in relation to asthma and eczema. Archives of disease in childhood. 2004;89(4):303-8.
209. Tromp, II, Kiefte-de Jong JC, Lebon A, Renders CM, Jaddoe VW, Hofman A, et al. The introduction of allergenic foods and the development of reported wheezing and eczema in childhood: the Generation R study. Arch Pediatr Adolesc Med. 2011;165(10):933-8.
210. Lindfors A, Enocksson E. Development of atopic disease after early administration of cow milk formula. Allergy. 1988;43(1):11-6.
211. Fergusson DM, Horwood LJ, Shannon FT. Early solid feeding and recurrent childhood eczema: a 10-year longitudinal study. Pediatrics. 1990;86(4):541-6.
212. Ito J, Fujiwara T. Breastfeeding and risk of atopic dermatitis up to the age 42 months: A birth cohort study in Japan. Annals of Epidemiology. 2014;24(4):267-72.
213. Moore WJ, Midwinter RE, Morris AF, Colley JR, Soothill JF. Infant feeding and subsequent risk of atopic eczema. Archives of disease in childhood. 1985;60(8):722-6.
214. Poysa L, Remes K, Korppi M, Juntunen-Backman K. Atopy in children with and without a family history of atopy. I. Clinical manifestations, with special reference to diet in infancy. Acta paediatrica Scandinavica. 1989;78(6):896-901.
215. Ruiz RGG, Kemeny DM, Price JF. Higher risk of infantile atopic dermatitis from maternal atopy than from paternal atopy. Clinical and Experimental Allergy. 1992;22(8):762-6.
216. Saarinen KM, Juntunen-Backman K, Jarvenpaa AL, Kuitunen P, Lope L, Renlund M, et al. Supplementary feeding in maternity hospitals and the risk of cow's milk allergy: A

prospective study of 6209 infants. Journal of Allergy and Clinical Immunology. 1999;104(2 I):457-61.
217. Soto-Ramirez N, Kar S, Zhang H, Karmaus W. Infant feeding patterns and eczema in children in the first 6 years of life. Clinical and Experimental Allergy. 2017;47(10):1285-98.
218. Sariachvili M, Droste J, Dom S, Wieringa M, Hagendorens M, Stevens W, et al. Early exposure to solid foods and the development of eczema in children up to 4 years of age. Pediatric Allergy and Immunology. 2010;21(1 PART I):74-81.
219. Turati F, Bertuccio P, Galeone C, Pelucchi C, Naldi L, Bach JF, et al. Early weaning is beneficial to prevent atopic dermatitis occurrence in young children. Allergy. 2016;71(6):878-88.
220. Kumar R, Caruso DM, Arguelles L, Kim JS, Schroeder A, Rowland B, et al. Early life eczema, food introduction, and risk of food allergy in children. Pediatric, Allergy, Immunology, and Pulmonology. 2010;23(3):175-82.
221. Saarinen UM, Kajosaari M, Backman A, Siimes MA. Prolonged breast-feeding as prophylaxis for atopic disease. Lancet (london, england). 1979;2(8135):163-6.
222. Elbert NJ, Kiefte-de Jong JC, Voortman T, Nijsten TEC, De Jong NW, Jaddoe VWV, et al. Allergenic food introduction and risk of childhood atopic diseases. PloS one. 2017;12 (11) (no pagination)(e0187999).
223. Roduit C, Frei R, Loss G, Buchele G, Weber J, Depner M, et al. Development of atopic dermatitis according to age of onset and association with early-life exposures. The Journal of allergy and clinical immunology. 2012;130(1):130-6.e5.
224. Cogswell JJ, Mitchell EB, Alexander J. Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. Archives of disease in childhood. 1987;62(4):338-44.
225. Batool T, Reece PL, Schulze KM, Morrison KM, Atkinson SA, Anand SS, et al. Prenatal and early-life predictors of atopy and allergic disease in Canadian children: results of the Family Atherosclerosis Monitoring In earLY life (FAMILY) Study. Journal of developmental origins of health and disease. 2016;7(6):665-71.
226. Luccioli S, Zhang Y, Verrill L, Ramos-Valle M, Kwegyir-Afful E. Infant feeding practices and reported food allergies at 6 years of age. Pediatrics. 2014;134 Suppl 1:S21-8.
227. Nwaru BI, Erkkola M, Ahonen S, Kaila M, Haapala AM, Kronberg-Kippila C, et al. Age at the introduction of solid foods during the first year and allergic sensitization at age 5 years. Pediatrics. 2010;125(1):50-9.
228. Grimshaw KEC, Maskell J, Oliver EM, Morris RCG, Foote KD, Clare Mills EN, et al. Introduction of complementary foods and the relationship to food allergy. Pediatrics. 2013;132(6):e1529-e38.
229. Host A. Importance of the first meal on the development of cow's milk allergy and intolerance. Allergy proceedings : the official journal of regional and state allergy societies. 1991;12(4):227-32.
230. Katz Y, Rajuan N, Goldberg MR, Eisenberg E, Heyman E, Cohen A, et al. Early exposure to cow's milk protein is protective against IgE-mediated cow's milk protein allergy. The Journal of allergy and clinical immunology. 2010;126(1):77-82.e1.
231. Onizawa Y, Noguchi E, Okada M, Sumazaki R, Hayashi D. The Association of the

Delayed Introduction of Cow's Milk with IgE-Mediated Cow's Milk Allergies. The journal of allergy and clinical immunology In practice. 2016;4(3):481-8.e2.
232. Garcia-Garcia ML, Calvo Rey C, Del Rosal Rabes T. Pediatric Asthma and Viral Infection. Archivos de bronconeumologia. 2016;52(5):269-73.
233. Melendi GA, Coviello S, Bhat N, Zea-Hernandez J, Ferolla FM, Polack FP. Breastfeeding is associated with the production of type I interferon in infants infected with influenza virus. Acta Paediatr. 2010;99(10):1517-21.
234. Bogahawaththa D, Chandrapala J, Vasiljevic T. Modulation of milk immunogenicity by thermal processing. International Dairy Journal. 2017;69:23-32.
235. Miciński J, Kowalski IM, Zwierzchowski G, Szarek J, Pierożyński B, Zabłocka E. Characteristics of cow's milk proteins including allergenic properties and methods for its reduction. Polish Annals of Medicine. 2013;20(1):69–76.
236. Savilahti E, Kuitunen M. Allergenicity of cow milk proteins. The Journal of pediatrics. 1992;121(5 Pt 2):S12-20.
237. Boner AL, Benedetti M, Spezia E, Piacentini GL, Bellanti JA. Evaluation of the allergenicity of infant formulas in a guinea pig model. Annals of allergy. 1992;68(5):404-6.
238. Alexander DD, Schmitt DF, Tran NL, Barraj LM, Cushing CA. Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature. Nutrition reviews. 2010;68(4):232-45.
239. Flodstrom C, Berge I, Bergstrom A, Nopp A, Lilja G, Kull I. Associations between early infant feeding with soy formula and allergic disease in adulthood. Allergy: European Journal of Allergy and Clinical Immunology. 2017;72 (Supplement 103):554.
240. Sanz Ceballos L, Sanz Sampelayo MR, Gil Extremera F, Rodriguez Osorio M. Evaluation of the allergenicity of goat milk, cow milk, and their lactosera in a guinea pig model. Journal of dairy science. 2009;92(3):837-46.
241. Lara-Villoslada F, Olivares M, Jimenez J, Boza J, Xaus J. Goat milk is less immunogenic than cow milk in a murine model of atopy. Journal of pediatric gastroenterology and nutrition. 2004;39(4):354-60.
242. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. The Journal of allergy and clinical immunology. 2003;112(6 Suppl):S118-27.
243. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. The journal of allergy and clinical immunology In practice. 2013;1(1):29-36.
244. Yang YW, Tsai CL, Lu CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. The British journal of dermatology. 2009;161(2):373-83.
245. Lin B, Dai R, Lu L, Fan X, Yu Y. Breastfeeding and Atopic Dermatitis Risk: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. Dermatology. 2019:1-16.
246. Flohr C, Nagel G, Weinmayr G, Kleiner A, Strachan DP, Williams HC, et al. Lack of evidence for a protective effect of prolonged breastfeeding on childhood eczema: lessons from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two. The British journal of dermatology. 2011;165(6):1280-9.

247. Laubereau B, Brockow I, Zirngibl A, Koletzko S, Gruebl A, von Berg A, et al. Effect of breast-feeding on the development of atopic dermatitis during the first 3 years of life--results from the GINI-birth cohort study. The Journal of pediatrics. 2004;144(5):602-7.
248. Kull I, Wickman M, Lilja G, Nordvall SL, Pershagen G. Breast feeding and allergic diseases in infants-a prospective birth cohort study. Archives of disease in childhood. 2002;87(6):478-81.
249. Benn CS, Wohlfahrt J, Aaby P, Westergaard T, Benfeldt E, Michaelsen KF, et al. Breastfeeding and risk of atopic dermatitis, by parental history of allergy, during the first 18 months of life. Am J Epidemiol2004. p. 217-23.
250. Miyake Y, Yura A, Iki M. Breastfeeding and the prevalence of symptoms of allergic disorders in Japanese adolescents. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2003;33(3):312-6.
251. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J, et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. The New England journal of medicine. 2016;374(18):1733-43.
252. Gungor D, Nadaud P, LaPergola CC, Dreibelbis C, Wong YP, Terry N, et al. Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. The American journal of clinical nutrition. 2019;109(Suppl_7):772S-99S.
253. Oddy WH, Holt PG, Sly PD, Read AW, Landau LI, Stanley FJ, et al. Association between breast feeding and asthma in 6 year old children: findings of a prospective birth cohort study. BMJ. 1999;319(7213):815-9. doi: 10.1136/bmj.319.7213.815.
254. Stoody EE, Spahn JM, Casavale KO. The Pregnancy and Birth to 24 Months Project: a series of systematic reviews on diet and health. The American journal of clinical nutrition. 2019;109(Suppl_7):685s-97s.
255. Wright AL, Holberg CJ, Martinez FD, Halonen M, Morgan W, Taussig LM. Epidemiology of physician-diagnosed allergic rhinitis in childhood. Pediatrics. 1994;94(6 Pt 1):895-901.
256. Yang S, Mei H, Mei H, Yang Y, Li N, Tan Y, et al. 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. Science China Life sciences. 2019;62(12):1580-9.
257. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. The European respiratory journal. 1995;8(3):483-91.
258. Chen C, Lu FC. The guidelines for prevention and control of overweight and obesity in Chinese adults. Biomedical and environmental sciences : BES. 2004;17 Suppl:1-36.
259. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutrition reviews. 2017;75(12):951-70.
260. El-Heneidy A, Abdel-Rahman ME. Milk Other Than Breast Milk and the Development of Asthma in Children 3 Years of Age. A Birth Cohort Study (2006⁻2011). 2018;10(11).
261. Kusunoki T, Morimoto T, Nishikomori R, Yasumi T, Heike T, Mukaida K, et al.

Breastfeeding and the prevalence of allergic diseases in schoolchildren: Does reverse causation matter? Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology. 2010;21(1 Pt 1):60-6.
262. Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, et al. The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. The Journal of allergy and clinical immunology. 2004;113(5):925-31.
263. Basra MK, Gada V, Ungaro S, Finlay AY, Salek SM. Infants' Dermatitis Quality of Life Index: a decade of experience of validation and clinical application. The British journal of dermatology. 2013;169(4):760-8.
264. Afzal B, Elberson V, McLaughlin C, Kumar VH. Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age. Pediatric Allergy and Immunology. 2017;10(1):109-12. doi: 10.3233/NPM-1616.
265. Chiu CY, Yang CH, Su KW, Tsai MH, Hua MC, Liao SL, et al. Early-onset eczema is associated with increased milk sensitization and risk of rhinitis and asthma in early childhood. J Microbiol Immunol Infect. 2019;8(19):30044-1.
266. von Kobyletzki LB, Bornehag CG, Hasselgren M, Larsson M, Lindstrom CB, Svensson A. Eczema in early childhood is strongly associated with the development of asthma and rhinitis in a prospective cohort. BMC dermatology. 2012;12:11.
267. Madley-Dowd P, Hughes R, Tilling K, Heron J. The proportion of missing data should not be used to guide decisions on multiple imputation. J Clin Epidemiol. 2019;110:63-73.
268. Chatkin J, Correa L, Santos U. External Environmental Pollution as a Risk Factor for Asthma. Clinical reviews in allergy & immunology. 2021:1-18.
269. Lehtimäki J, Thorsen J, Rasmussen MA, Hjelmsø M, Shah S, Mortensen MS, et al. Urbanized microbiota in infants, immune constitution and later risk of atopic diseases. The Journal of allergy and clinical immunology. 2020.
270. Li C, Chen Q, Zhang X, Li H, Liu Q, Fei P, et al. Early Life Domestic Pet Ownership, and the Risk of Pet Sensitization and Atopic Dermatitis in Preschool Children: A Prospective Birth Cohort in Shanghai. Frontiers in pediatrics. 2020;8:192.
271. Foote KD, Marriott LD. Weaning of infants. Archives of disease in childhood. 2003;88(6):488-92.
272. Hill VL, Wood PR. Asthma epidemiology, pathophysiology, and initial evaluation. Pediatrics in review. 2009;30(9):331-5; quiz 5-6.
273. Cosme-Blanco W, Arroyo-Flores E, Ale H. Food Allergies. Pediatrics in review. 2020;41(8):403-15.
274. Wyness L. Nutrition in early life and the risk of asthma and allergic disease. British journal of community nursing. 2014;Suppl:S28-32.
275. Chmielewska A, Piescik-Lech M, Shamir R, Szajewska H. Systematic review: Early infant feeding practices and the risk of wheat allergy. Journal of paediatrics and child health. 2017;53(9):889-96.
276. Pacheco-Gonzalez RM, Garcia-Marcos L, Morales E. Prenatal vitamin D status and respiratory and allergic outcomes in childhood: A meta-analysis of observational studies. Pediatric allergy and immunology : official publication of the European Society of Pediatric

Allergy and Immunology. 2018;29(3):243-53.
277. Best KP, Gold M, Kennedy D, Martin J, Makrides M. Omega-3 long-chain PUFA intake during pregnancy and allergic disease outcomes in the offspring: a systematic review and meta-analysis of observational studies and randomized controlled trials. The American journal of clinical nutrition. 2016;103(1):128-43.
278. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Current opinion in lipidology. 2002;13(1):3-9.
279. Grimshaw KE, Maskell J, Oliver EM, Morris RC, Foote KD, Mills EN, et al. Diet and food allergy development during infancy: birth cohort study findings using prospective food diary data. The Journal of allergy and clinical immunology. 2014;133(2):511-9.
280. Lu MS, Chen QZ, He JR, Wei XL, Lu JH, Li SH, et al. Maternal Dietary Patterns and Fetal Growth: A Large Prospective Cohort Study in China. Nutrients. 2016;8(5).
281. Lu MS, He JR, Chen Q, Lu J, Wei X, Zhou Q, et al. Maternal dietary patterns during pregnancy and preterm delivery: a large prospective cohort study in China. Nutrition journal. 2018;17(1):71.
282. Osborn DA, Sinn JK, Jones LJ. Infant formulas containing hydrolysed protein for prevention of allergic disease and food allergy. The Cochrane database of systematic reviews. 2017;3(3):CD003664-CD.
283. Tucker KL. Dietary patterns, approaches, and multicultural perspective. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2010;35(2):211-8.
284. Apfelbacher CJ, Diepgen TL, Schmitt J. Determinants of eczema: population-based cross-sectional study in Germany. Allergy. 2011;66(2):206-13.
285. Guo X, Li Z, Ling W, Long J, Su C, Li J, et al. Epidemiology of childhood asthma in mainland China (1988-2014): A meta-analysis. Allergy Asthma Proc. 2018;39(3):15-29.
286. Subspecialty Group of Respiratory Diseases, Society of Pediatrics, Chinese Medical Association ; Editorial Board. Guideline for the diagnosis and optimal management of asthma in children (2016). Chinese Journal of Pediatrics. 2016;54(3):167-81.
287. du Toit G, Tsakok T, Lack S, Lack G. Prevention of food allergy. The Journal of allergy and clinical immunology. 2016;137(4):998-1010.
288. Videhult FK, West CE. Nutrition, gut microbiota and child health outcomes. Current opinion in clinical nutrition and metabolic care. 2016;19(3):208-13.
289. Timmerman HM, Rutten N, Boekhorst J, Saulnier DM, Kortman GAM, Contractor N, et al. Intestinal colonisation patterns in breastfed and formula-fed infants during the first 12 weeks of life reveal sequential microbiota signatures. Scientific reports. 2017;7(1):8327.
290. Pannaraj PS, Li F, Cerini C, Bender JM, Yang S, Rollie A, et al. Association Between Breast Milk Bacterial Communities and Establishment and Development of the Infant Gut Microbiome. JAMA pediatrics. 2017;171(7):647-54.
291. Oozeer R, van Limpt K, Ludwig T, Ben Amor K, Martin R, Wind RD, et al. Intestinal microbiology in early life: specific prebiotics can have similar functionalities as human-milk oligosaccharides. The American journal of clinical nutrition. 2013;98(2):561S-71S.
292. Matsuyama M, Gomez-Arango LF, Fukuma NM, Morrison M, Davies PSW, Hill RJ.

Breastfeeding: a key modulator of gut microbiota characteristics in late infancy. J Dev Orig Health Dis. 2019;10(2):206-13.
293. Forbes JD, Azad MB, Vehling L, Tun HM, Konya TB, Guttman DS, et al. Association of Exposure to Formula in the Hospital and Subsequent Infant Feeding Practices With Gut Microbiota and Risk of Overweight in the First Year of Life. JAMA pediatrics. 2018;172(7):e181161.
294. Thompson AL, Monteagudo-Mera A, Cadenas MB, Lampl ML, Azcarate-Peril MA. Milk- and solid-feeding practices and daycare attendance are associated with differences in bacterial diversity, predominant communities, and metabolic and immune function of the infant gut microbiome. Frontiers in cellular and infection microbiology. 2015;5:3.
295. Bergstrom A, Skov TH, Bahl MI, Roager HM, Christensen LB, Ejlerskov KT, et al. Establishment of intestinal microbiota during early life: a longitudinal, explorative study of a large cohort of Danish infants. Applied and environmental microbiology. 2014;80(9):2889-900.
296. Azad MB, Konya T, Guttman DS, Field CJ, Sears MR, HayGlass KT, et al. Infant gut microbiota and food sensitization: associations in the first year of life. Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2015;45(3):632-43.
297. Thijs C, Muller A, Rist L, Kummeling I, Snijders BE, Huber M, et al. Fatty acids in breast milk and development of atopic eczema and allergic sensitisation in infancy. Allergy. 2011;66(1):58-67.
298. Wijga AH, van Houwelingen AC, Kerkhof M, Tabak C, de Jongste JC, Gerritsen J, et al. Breast milk fatty acids and allergic disease in preschool children: the Prevention and Incidence of Asthma and Mite Allergy birth cohort study. The Journal of allergy and clinical immunology. 2006;117(2):440-7.
299. Silverberg JI, Patel N, Immaneni S, Rusniak B, Silverberg NB, Debashis R, et al. Assessment of atopic dermatitis using self-report and caregiver report: a multicentre validation study. The British journal of dermatology. 2015;173(6):1400-4.
300. Yang B, Huang X, Liu Q, Tang S, Story M, Chen Y, et al. Child Nutrition Trends Over the Past Two Decades and Challenges for Achieving Nutrition SDGs and National Targets in China. International journal of environmental research and public health. 2020;17(4).
301. Di Cesare M, Sorić M, Bovet P, Miranda JJ, Bhutta Z, Stevens GA, et al. The epidemiological burden of obesity in childhood: a worldwide epidemic requiring urgent action. BMC medicine. 2019;17(1):212.
302. Umer A, Kelley GA, Cottrell LE, Giacobbi P, Jr., Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC public health. 2017;17(1):683.
303. Simmonds M, Burch J, Llewellyn A, Griffiths C, Yang H, Owen C, et al. 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 technology assessment. 2015;19(43):1-336.
304. Llewellyn A, Simmonds M, Owen CG, Woolacott N. Childhood obesity as a

predictor of morbidity in adulthood: a systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2016;17(1):56-67.
305. Simmonds M, Llewellyn A, Owen CG, Woolacott N. Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2016;17(2):95-107.
306. Owen CG, Martin RM, Whincup PH, Smith GD, Cook DG. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics. 2005;115(5):1367-77.
307. Pearce J, Taylor MA, Langley-Evans SC. Timing of the introduction of complementary feeding and risk of childhood obesity: a systematic review. International journal of obesity. 2013;37(10):1295-306.
308. Brockway M, Benzies K, Hayden KA. Interventions to Improve Breastfeeding Self-Efficacy and Resultant Breastfeeding Rates: A Systematic Review and Meta-Analysis. Journal of human lactation : official journal of International Lactation Consultant Association. 2017;33(3):486-99.
309. Walters D, Eberwein JD, Sullivan LM, D'Alimonte MR, Shekar M. Reaching the Global Target to Increase Exclusive Breastfeeding: How Much Will It Cost and How Can We Pay for It? Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2016;11:413-5.
310. Ten provinces rural children physical development investigation cooperation group. Feeding situation of 63387 infants in ten provinces of China. Chinese Journal of Practical Pediatrics. 1990;4(2):100-1.
311. Owen CG, Martin RM, Whincup PH, Davey-Smith G, Gillman MW, Cook DG. The effect of breastfeeding on mean body mass index throughout life: a quantitative review of published and unpublished observational evidence. The American journal of clinical nutrition. 2005;82(6):1298-307.
312. Zhang J, Himes JH, Guo Y, Jiang J, Yang L, Lu Q, et al. Birth weight, growth and feeding pattern in early infancy predict overweight/obesity status at two years of age: a birth cohort study of Chinese infants. PloS one. 2013;8(6):e64542.
313. Tian Q, Gao X, Sha T, Chen C, Li L, He Q, et al. Effect of feeding patterns on growth and nutritional status of children aged 0-24 months: A Chinese cohort study. PloS one. 2019;14(11):e0224968.
314. Mannan H. 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. International journal of environmental research and public health. 2018;15(8).
315. de Beer H. Dairy products and physical stature: a systematic review and meta-analysis of controlled trials. Economics and human biology. 2012;10(3):299-309.
316. Willett WC, Ludwig DS. Milk and Health. The New England journal of medicine. 2020;382(7):644-54.
317. Bansal N, Ayoola OO, Gemmell I, Vyas A, Koudsi A, Oldroyd J, et al. Effects of early growth on blood pressure of infants of British European and South Asian origin at one year of age: the Manchester children's growth and vascular health study. Journal of

hypertension. 2008;26(3):412-8.
318. Dunger DB, Salgin B, Ong KK. Session 7: Early nutrition and later health early developmental pathways of obesity and diabetes risk. The Proceedings of the Nutrition Society. 2007;66(3):451-7.
319. Ong KK, Emmett PM, Noble S, Ness A, Dunger DB, Team AS. Dietary energy intake at the age of 4 months predicts postnatal weight gain and childhood body mass index. Pediatrics. 2006;117(3):e503-8.
320. Binns CW. Introduction of solids before 4 months is associated with obesity at 3 years among formula-fed infants but not among breast-fed infants. Evid Based Med. 2011;16(6):177-8.
321. Pluymen LPM, Wijga AH, Gehring U, Koppelman GH, Smit HA, van Rossem L. Early introduction of complementary foods and childhood overweight in breastfed and formula-fed infants in the Netherlands: the PIAMA birth cohort study. Eur J Nutr. 2018;57(5):1985-93.
322. Iguacel I, Monje L, Cabero MJ, Moreno Aznar LA, Samper MP, Rodr ǵuez-Palmero M, et al. Feeding patterns and growth trajectories in breast-fed and formula-fed infants during the introduction of complementary food. Nutr Hosp. 2019;36(4):777-85.
323. Huh SY, Rifas-Shiman SL, Taveras EM, Oken E, Gillman MW. Timing of solid food introduction and risk of obesity in preschool-aged children. Pediatrics. 2011;127(3):e544-e51.
324. Papoutsou S, Savva SC, Hunsberger M, Jilani H, Michels N, Ahrens W, et al. Timing of solid food introduction and association with later childhood overweight and obesity: The IDEFICS study. Matern Child Nutr. 2018;14(1).
325. Goetz AR, Mara CA, Stark LJ. Greater Breastfeeding in Early Infancy Is Associated with Slower Weight Gain among High Birth Weight Infants. The Journal of pediatrics. 2018;201:27-33 e4.
326. Zalewski BM, Patro B, Veldhorst M, Kouwenhoven S, Crespo Escobar P, Calvo Lerma J, et al. Nutrition of infants and young children (one to three years) and its effect on later health: A systematic review of current recommendations (EarlyNutrition project). Critical reviews in food science and nutrition. 2017;57(3):489-500.
327. Launer LJ, Forman MR, Hundt GL, Sarov B, Chang D, Berendes HW, et al. Maternal recall of infant feeding events is accurate. Journal of epidemiology and community health. 1992;46(3):203-6.
328. Al-Saud B, Sigurdardottir ST. Early Introduction of Egg and the Development of Egg Allergy in Children: A Systematic Review and Meta-Analysis. International archives of allergy and immunology. 2018;177(4):350-9.
329. Mei H, Guo B, Yin B, Liang X, Adair L, Thompson A, et al. Interactive Effects of Early Exclusive Breastfeeding and Pre-Pregnancy Maternal Weight Status on Young Children's BMI - A Chinese Birth Cohort. PloS one. 2015;10(12):e0144357.
330. Jingxiong J, Rosenqvist U, Huishan W, Koletzko B, Guangli L, Jing H, et al. Relationship of parental characteristics and feeding practices to overweight in infants and young children in Beijing, China. Public health nutrition. 2009;12(7):973-8.
331. Baird J, Fisher D, Lucas P, Kleijnen J, Roberts H, Law C. Being big or growing fast: systematic review of size and growth in infancy and later obesity. Bmj. 2005;331(7522):929.

332. Westman M, Asarnoj A, Hamsten C, Wickman M, van Hage M. Windows of opportunity for tolerance induction for allergy by studying the evolution of allergic sensitization in birth cohorts. Seminars in immunology. 2017;30:61-6.
333. Sears MR, Greene JM, Willan AR, Taylor DR, Flannery EM, Cowan JO, et al. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet. 2002;360(9337):901-7.

Appendices

Supplementary material S1 in Chapter 3: PRISMA statement

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	42
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	43
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	44-45
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	45
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	45
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	46
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	45
Search	8	Present full electronic search strategy for at least one database, including any limits used,	Supplementary material S2

		such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	46
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	47
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	47-48
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	46-47
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	47-48
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	47-48
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	48
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	48
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	48, Figure 3.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 3.1-3.3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary material S3: Table S3.1-S3.3

Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary material S3: Table S3.4-S3.6 Supplementary material S4: Supplemental Figure 1-20
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 3.2-3.3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Supplementary material S4: Supplemental Figure 21
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Figure 3.4-3.5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	67-68
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	71
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	72
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Supplementary material S2 in Chapter 3: Search Strategies

Databases	
Embase	1. infant/ 2. exp baby/ 3. child/ 4. newborn/ 5. breast feeding.ab,ti. 6. breastfeeding.ab,ti. 7. breast fed.ab,ti. 8. breastfed.ab,ti. 9. breast feeding/ 10. breast milk/ 11. formula$.ab,ti. 12. bottlefed.ab,ti. 13. bottle fed.ab,ti. 14. artificial milk/ 15. bottle feeding/ 16. baby food$.ab,ti. 17. baby food/ 18. infant nutrition/ 19. exp infant feeding/ 20. milk.ti,ab. 21. milk/ 22. diet/ 23. diet.ti,ab. 24. diets.ti,ab. 25. dietetic.ab,ti. 26. dietary.ab,ti. 27. allerg$.ab,ti. 28. asthma$.ab,ti. 29. wheeze.ab,ti. 30. wheezing.ab,ti.

	31. eczema.ab,ti. 32. rhinitis.ab,ti. 33. rhinoconjunctivitis.ab,ti. 34. conjunctivitis.ab,ti. 35. atopic disease.ab,ti. 36. atopic dermatitis.ab,ti. 37. atopy.ab,ti. 38. hypersensitiv$.ab,ti. 39. exp hypersensitivity/ 40. asthma/ 41. wheezing/ 42. eczema/ 43. rhinitis/ 44. rhinoconjunctivitis/ 45. conjunctivitis/ 46. obesity.ab,ti. 47. overweight.ab,ti. 48. BMI.ab,ti. 49. body mass index.ab,ti. 50. exp obesity/ 51. exp body mass/ 52. iron stauts.ab,ti. 53. iron deficiency anemia.ab,ti. 54. iron deficiency anemia/ 55. exp iron blood level/ 56. exp food allergy/ 57. exp milk allergy/ 58. 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 59. exp cohort analysis/ 60. exp longitudinal study/ 61. exp prospective study/

	62. exp follow up/ 63. cohort$.tw. 64. exp case control study/ 65. (case$ and control$).tw. 66. 59 or 60 or 61 or 62 or 63 or 64 or 65 67. (random$ or placebo$ or single blind$ or double blind$ or triple blind$).ti,ab. 68. RETRACTED ARTICLE/ 69. 67 or 68 70. (animal$ not human$).sh,hw. 71. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/ 72. (random sampl$ or random digit$ or random effect$ or random survey or random regression).ti,ab. not exp randomized controlled trial/ 73. 69 not (70 or 71 or 72) 74. 66 or 73 75. 1 or 2 or 3 or 4 76. complementary food$.ab,ti. 77. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 76 78. 58 and 74 and 75 and 77 79. 78 not animals.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
Pubmed	((((("child"[MeSH Terms] OR "infant"[MeSH Terms])) AND (((((((("milk, human"[MeSH Terms] OR "milk"[MeSH Terms]) OR "dairy products"[MeSH Terms]) OR ("infant formula"[MeSH Terms] OR "infant formula"[MeSH Terms])) OR "breast feeding"[MeSH Terms]) OR "infant nutritional physiological phenomena"[MeSH Terms]) OR "bottle feeding"[MeSH Terms])))) AND ((((((((((("obesity"[MeSH Terms] OR "overweight"[MeSH Terms]) OR "body mass index"[MeSH Terms]) OR ("body height"[MeSH Terms] OR "body weight"[MeSH Terms])) OR "anthropometry"[MeSH Terms]) OR ("hypersensitivity"[MeSH Terms] OR "allergy and immunology"[MeSH

	Terms])) OR "eczema"[MeSH Terms]) OR "asthma"[MeSH Terms]) OR "respiratory sounds"[MeSH Terms]) OR "dermatitis, atopic"[MeSH Terms]) OR "food hypersensitivity"[MeSH Terms]) OR "milk hypersensitivity"[MeSH Terms]) OR ("anemia"[MeSH Terms] OR "anemia, iron-deficiency"[MeSH Terms]))))) AND (((((((((cohort studies[mesh:noexp] OR longitudinal studies[mesh:noexp] OR follow-up studies[mesh:noexp] OR prospective studies[mesh:noexp] OR retrospective studies[mesh:noexp] OR cohort[TIAB] OR longitudinal[TIAB] OR prospective[TIAB] OR retrospective[TIAB])))) OR "Epidemiologic Studies"[Mesh:noexp]) OR (("Clinical Trial" [PT:NoExp] OR "clinical trial, phase i"[pt] OR "clinical trial, phase ii"[pt] OR "clinical trial, phase iii"[pt] OR "clinical trial, phase iv"[pt] OR "controlled clinical trial"[pt] OR "multicenter study"[pt] OR "randomized controlled trial"[pt] OR "Clinical Trials as Topic"[mesh:noexp] OR "clinical trials, phase i as topic"[MeSH Terms:noexp] OR "clinical trials, phase ii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iii as topic"[MeSH Terms:noexp] OR "clinical trials, phase iv as topic"[MeSH Terms:noexp] OR "controlled clinical trials as topic"[MeSH Terms:noexp] OR "randomized controlled trials as topic"[MeSH Terms:noexp] OR "early termination of clinical trials"[MeSH Terms:noexp] OR "multicenter studies as topic"[MeSH Terms:noexp] OR "Double-Blind Method"[Mesh] OR ((randomised[TIAB] OR randomized[TIAB]) AND (trial[TIAB] OR trials[tiab])) OR ((single[TIAB] OR double[TIAB] OR doubled[TIAB] OR triple[TIAB] OR tripled[TIAB] OR treble[TIAB] OR treble[TIAB]) AND (blind*[TIAB] OR mask*[TIAB])) OR ("4 arm"[tiab] OR "four arm"[tiab])))))) OR ("Case-Control Studies"[Mesh:noexp] OR "retrospective studies"[mesh:noexp] OR "Control Groups"[Mesh:noexp] OR (case[TIAB] AND control[TIAB]) OR (cases[TIAB] AND controls[TIAB]) OR (cases[TIAB] AND controlled[TIAB]) OR (case[TIAB] AND comparison*[TIAB]) OR (cases[TIAB] AND comparison*[TIAB]) OR "control group"[TIAB] OR "control groups"[TIAB]))))
Cochrane CENTRAL	**#1:** child:ti,ab,kw (Word variations have been searched) **#2:** "infant":ti,ab,kw (Word variations have been searched) **#3:** "newborn":ti,ab,kw (Word variations have been searched) **#4:** "baby":ti,ab,kw (Word variations have been searched) **#5:** #1 or #2 or #3 or #4 **#6:** "breastfeeding":ti,ab,kw (Word variations have been searched)

	#7: "breast feeding":ti,ab,kw (Word variations have been searched) **#8:** "milk":ti,ab,kw (Word variations have been searched) **#9:** formula*:ti,ab,kw (Word variations have been searched) **#10:** "bottle feeding":ti,ab,kw (Word variations have been searched) **#11:** breast fed:ti,ab,kw (Word variations have been searched) **#12:** breastfed:ti,ab,kw (Word variations have been searched) **#13:** bottlefed:ti,ab,kw (Word variations have been searched) **#14:** complementary food:ti,ab,kw (Word variations have been searched) **#15:** MeSH descriptor: [Breast Feeding] explode all trees **#16:** MeSH descriptor: [Milk, Human] explode all trees **#17:** MeSH descriptor: [Bottle Feeding] explode all trees **#18:** (introduc* near/2 food*):ab,ti **#19:** #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 **#20:** allerg*:ti,ab,kw (Word variations have been searched) **#21:** "atopic disease":ab,ti **#22:** hypersensitiv*:ab,ti **#23:** atopy:ab,ti **#24:** asthma*:ti,ab,kw (Word variations have been searched) **#25:** wheeze:ti,ab,kw (Word variations have been searched) **#26:** "wheezing":ti,ab,kw (Word variations have been searched) **#27:** eczema:ti,ab,kw (Word variations have been searched) **#28:** "atopic dermatitis":ab,ti **#29:** rhinitis:ti,ab,kw (Word variations have been searched) **#30:** rhinoconjunctivitis:ab,ti **#31:** conjunctivitis:ab,ti **#32:** rhinoconjunctivitis:ti,ab,kw (Word variations have been searched) **#33:** MeSH descriptor: [Dermatitis, Atopic] explode all trees **#34:** MeSH descriptor: [Asthma] explode all trees **#35:** MeSH descriptor: [Eczema] explode all trees **#36:** MeSH descriptor: [Rhinitis, Allergic] explode all trees **#37:** MeSH descriptor: [Food Hypersensitivity] explode all trees **#38:** "cow's milk allergy":ti,ab,kw (Word variations have been searched)

	#39: MeSH descriptor: [Anemia, Iron-Deficiency] explode all trees **#40:** MeSH descriptor: [Anemia] explode all trees **#41:** MeSH descriptor: [Obesity] explode all trees **#42:** MeSH descriptor: [Overweight] explode all trees **#43:** MeSH descriptor: [Body Mass Index] explode all trees **#44:** MeSH descriptor: [Body Height] explode all trees **#45:** MeSH descriptor: [Body Weight] explode all trees **#46:** MeSH descriptor: [Growth] explode all trees **#47:** #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 **#48:** #5 and #19 and #47
CINAHL	S1 (MH "Infant+") S2 (MH "Child+") S3 (MH "Breast Feeding+") S4 (MH "Infant Feeding+") S5 (MH "Infant Nutritional Physiology+") S6 (MH "Milk+") S7 (MH "Dairy Products+") S8 S1 OR S2 S9 S3 OR S4 OR S5 OR S6 OR S7 S10 (MH "Asthma+") S11 (MH "Eczema") S12 (MH "Respiratory Sounds+") S13 (MH "Dermatitis, Atopic") S14 (MH "Rhinitis, Allergic, Perennial") OR (MH "Rhinitis, Allergic, Seasonal") S15 (MH "Food Hypersensitivity+") S16 (MH "Milk Hypersensitivity") S17 (MH "Obesity+") S18 (MM "Body Mass Index") OR (MH "Body Weights and Measures+") S19 (MH "Body Weight+") S20 (MM "Body Height") S21 (MH "Anemia+") OR (MM "Anemia, Iron Deficiency")

	S22 S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 S23 S8 AND S9 AND S22
CNKI	(“婴儿” OR “新生儿” OR “儿童”) AND (“牛奶”OR “奶粉”OR “母乳”OR “奶制品”OR “乳制品”OR “喂养”OR “辅食”) AND (“过敏”OR“哮喘”OR“喘息”OR“过敏性鼻炎”OR“特异性皮炎”OR“湿疹”OR“食物过敏”OR“牛奶过敏”OR“肥胖”OR“超重”OR“缺铁性贫血”) AND (“临床试验”OR“对照试验”OR“随机”OR“临床观察”OR“临床研究”OR“随机对照试验”OR“队列”OR“观察性研究”OR“病例对照”)

Supplementary material S3 in Chapter 3: Quality assessment and data extraction forms

Table S3.1 Risk of bias of randomized clinical trials using the Cochrane Collaboration Risk of Bias Tool

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Overall
Juvonen 1996	High risk	High risk	Unclear	Unclear	Low risk	Unclear	High risk
Lindfors 1988	High risk	High risk	High risk	Low risk	Unclear risk	Unclear	High risk
Lindfors 1992	High risk	High risk	High risk	Low risk	Unclear risk	Unclear	High risk
Saarinen 1999 Saarinen 2000	High risk	High risk	Low risk	Low risk	Unclear risk	Unclear	High risk

Table S3.2 Quality ratings for the 37 cohort studies included on the basis of Newcastle-Ottawa quality assessment scale

Outcomes	Study ID	Representative of exposed cohort	Selections of non-exposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up period	Adequacy of follow-up (≥70%)	Total Score
Wheeze	Azad 2017	1	1	0	1	2	1	1	1	8
FA	Batool 2016	1	1	1	1	0	0	1	1	6
Eczema	Cogswell 1987	0	1	1	1	0	1	1	1	6
Eczema/ FA	Elbert 2017	1	1	0	1	2	1	1	1	8
Eczema	Fergusson 1990	1	1	0	1	1	0	1	1	6
Asthma/ Eczema/ Rhinitis	Filipiak-Pittroff 2018	0	0	1	1	0		1	1	4
Asthma/ Rhino-conj / Eczema	Gustafsson 1992	1	1	1	1	0	1	1	1	7
CMA	Host 1991	1	1	0	1	1	1	1	1	7
AD	Ito 2014	1	1	0	1	2	0	1	1	7
CMA	Katz 2010	1	1	0	1	1	1	1	1	7
Wheeze/ Eczema/ CMA	Kemeny 1991	1	1	0	1	0	1	1	1	6
Asthma	Kilingberg 2019	1	1	1	1	2	1	1	0	8
Asthma	Klopp 2017	1	1	0	1	2	1	1	1	8
FA	Kumar 2010	1	1	0	0	2	1	1	1	7
Eczema		1	1	0	0	2	0	1	1	6
Asthma	Lossius 2018	1	1	0	1	2	1	1	0	7
FA	Luccioli 2014	1	1	0	1	2	0	1	1	7
Wheeze /AD /Allergic rhino-conj	Marini 1996	0	1	0	1	0	1	1	1	5
Eczema	Moore 1985	0	1	1	1	0	1	1	1	6

FA	Nwaru 2010	0	1	0	1	1	1	1	1	6
Outcomes	Study ID	Representative of exposed cohort	Selections of non-exposed cohort	Ascertainment of exposure	Absence of outcome at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow-up period	Adequacy of follow-up (≥70%)	Total Score
Asthma/ Eczema/ Rhinitis	Nwaru 2013a	0	1	0	1	1	1	1	1	6
Asthma/ Wheeze/ Eczema	Nwaru 2013b	1	1	1	1	2	1	1	0	8
CMA	Peters 2019	1	1	0	1	1	1	0	0	5
Eczema	Poysa 1989	0	1	0	1	0	1	1	1	5
AD	Roduit 2012	0	1	1	1	2	1	1	1	8
AD	Ruiz 1992	0	1	0	1	0	1	1	1	5
AD/ FA	Saarinen 1979	0	1	0	1	0	1	1	1	5
Wheeze	Simon 2008	0	1	0	1	2	0	1	0	5
Wheeze/ Eczema	Snijders 2008	1	1	0	1	2	0	1	1	7
AD/ CMA		1	1	0	1	2	1	1	1	8
Eczema	Soto-Ramirez 2017	1	1	0	1	2	0	1	1	7
Asthma/ Wheeze	Strassburger 2010	1	1	0	1	2	1	1	1	8
Asthma	Tariq 1998	1	1	0	1	1	1	1	1	7
CMA	Tham 2018	1	1	0	1	2	1	1	1	8
CMA	Tran 2017	1	1	0	1	2	1	1	0	7
Eczema/ Wheeze	Tromp 2011	1	1	0	1	2	1	1	1	8
AD	Van Asperen 1984	0	1	0	1	0	1	1	1	5
Wheeze/ Rhinitis		0	1	0	1	0	0	1	1	4
Rhinitis	Wright 1994	1	1	0	1	1	0	1	0	5
Wheeze/ Eczema	Zutavern 2004	1	1	0	1	2	0	1	1	7

AD atopic dermatitis; **CMA** cow's milk allergy; **FA** food allergy; **Rhino-conj** rhinitis+conjunctivitis

Table S3.3 Quality ratings for the 5 case-control studies included on the basis of Newcastle-Ottawa quality assessment scale

Study ID	Selection (score)				Comparability (score)	Exposure (score)			Total Score
	Case definition	Representative of cases	Selections of controls	Definition of controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for participants	Nonresponse rate	
Grimshaw 2013	1	1	1	1	1	0	1	1	7
Onizawa 2016	1	1	0	1	1	0	1	1	6
Sariachvili 2010	1	1	1	1	1	0	1	1	7
Turati 2016	1	1	0	1	1	0	1	1	6

Table S3.4 Original data extracted from the included clinical trial studies for each outcome.

Outcomes	Study ID	Cases in each comparative group	
		All population	High-risk population
Wheeze	Lindfors 1988	CMF: 6/109, HM: 8/98	CMF:3/50, HM:5/57
Eczema	Juvonen 1996	HM: 3/53, CMF: 3/39	
	Lindfors 1988	CMF: 10/109, HM: 18/98	CMF:3/50, HM:11/57
Asthma	Lindfors 1992	CMF: 9/95, HM: 8/88	CMF: 6/53, HM:7/56
Allergic rhinitis/ conjunctivitis	Lindfors 1992	CMF: 9/95, HM: 2/88	CMF: 7/53, HM: 1/56
Cow's milk allergy	Lindfors 1992	CMF:3/80, HM: 2/74	
	Saarinen 1999 Saarinen 2000	CMF: 43/1758, HM: 32/1844	
Food allergy	Lindfors 1992	CMF: 3/80, HM: 0/74	
	Perkin 2016	3-6m: 42/595, >6m: 32/567	

CMF: cow's milk formula; **HM**: human milk

Table S3.5 Original data extracted from the included cohort studies for each outcome.

Outcomes	Study ID	Exposure time	Cases in each comparative group / Unadjusted OR (95%CI), N				Adjusted OR (95%CI), N
Asthma	Filipiak-Pittroff 2018	<4m (RG), ≥4m	0.94 (0.60- 1.47), N=2252				1.05 (0.67- 1.66), N=2252
	Gustafsson 1992	≤8d, >8d	≤8d: 8/240	>8d: 10/496			
	Kilingberg 2019	< 14 weeks Never (RG)	1.30 (1.00–1.70), N=9229				1.27 (0.95–1.71), N=8797
	Klopp 2017	0m, <3m, ≥3m	0m:56/354	<3m: 98/659	≥3m: 165/1521		
	Lossius 2018	<4m, 4-5.9m, ≥6m	<4m: 426/8351	4-5.9m: 168/3261	≥ 6m: 854/20318		
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Nwaru 2013b	CM: <5.75m (RG), ≥5.75m	0.99 (0.73–1.34)，N=934				0.91 (0.66–1.25)，N=934
		CMF: <0.5m (RG), ≥0.5m	0.70 (0.51–0.94)，N=934				0.72 (0.47–1.12)，N=934
	Strassburger 2010	<4m, ≥4m	<4m:12/119	≥4m:15/174			
	Tariq 1998	<3m, ≥3m	<3m:114/667	≥3m:43/419			1.8 (1.2-2.6), N=1086
Wheeze	Azad 2017	<3m, ≥3m (RG)	1.28 (1.07-1.53), N=2366				1.16 (0.97-1.39), N=2366
	Azad 2017	<6m, ≥6m (RG)	1.64 (1.38-1.96), N=1214				1.47 (1.23-1.75), N=1214
	Kemeny 1991	0m, <3m, ≥3m	0m:14/60	<3m:18/64	≥3m:8/65		
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 9/53	<4m: 4/41	≥4m: 6/127		
		CMF: 0m, <4m, ≥4m (hig risk)	0m: 5/38	<4m:1 /22	≥4m: 3/98		
		CM: <6m, ≥6m (RG) (normal children)					0.5 (0.1-1.1), N=62
	Nwaru 2013b	CM: <5.75m (RG), ≥5.75m	0.98 (0.70, 1.39)，N=934				0.97 (0.68–1.39)，N=934

		CMF: <0.5m (RG), ≥0.5m	0.75 (0.54–1.05) , N=934				0.75 (0.47–2.00) , N=934
	Simon 2008	0m, <4m, ≥4m	0m: 49/103	<4m:44/101	≥4m:35/99		
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0-3m: 127/730	4–6m: 83/589	7-9m: 44/519	>9m: 5/56	
	Strassburger 2010	<4m, ≥4m	<4m: 28/119	≥4m: 34/174			
	Tromp 2011	<6m, ≥6m (RG)	0.96 (0.77-1.21), N=6905				0.96 (0.77-1.19) , N=6905
	Van Asperen 1984	<4m, ≥4m	<4m: 16/51	≥4m: 6/28			
	Zutavern 2004	<6m, ≥6m	<6m 120/407	≥6m 69/213			
Eczema/Atopic Dermatitis	Cogswell 1987	<4w, 4-13w, ≥14w	<4w:7/33	4-13w: 6/31	≥14w: 2/9		
	Elbert 2017	<6m, ≥6m (RG)					0.82 (0.63, 1.07), N=3692
	Fergusson 1990	<4m, ≥4m	<4m: 79/998	≥4m: 11/212			
	Filipiak-Pittroff 2018	<4m (RG), ≥4m	0.80 (0.61- 1.05), N=2252				0.73 (0.55- 0.97), N=2252
	Gustafsson 1992	≤8d, >8d	≤8d: 17/240	>8d: 22/496			
	Ito 2014	0m, <6m, ≥6m	0m: 502/2217	<6m:7213/27861	≥6m:2474/8679		
	Kemeny 1991	0m, <3m, ≥3m	0m:10/60	<3m:15/64	≥3m:11/65		
	Kumar 2010	<6m, ≥6m	<6m: 236/464	≥6m:155/325			
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 16/53	<4m: 10/41	≥4m: 17/127		
		CMF: 0m, <4m, ≥4m (hig risk)	0m: 9/38	<4m:3/22	≥4m: 3/98		
		CM: <6m, ≥6m (RG) (normal children)					4.2 (1.1- 14.5), N=68
	Moore 1985	1-4w, 5-8w, 9-12w, >12w	1-4w : 37/162 (0w: 7/35)	5-8w: 4/39	9-12w:3/26	>12w:34/248	
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Nwaru 2013b	CM: <5.75m (RG), ≥5.75m	1.15 (0.92–1.43), N=934				1.16 (0.92–1.46), N=934

		CMF: <0.5m (RG), ≥0.5m	0.97 (0.78–1.22), N=934				0.93 (0.68–1.29), N=934
	Poysa 1989	<3m, 3-6m, >6m	<3m: 6/25	3-6m: 4/14	>6m: 7/31		
	Roduit 2012	3-12m, >12m (RG)					Normal: 0.68 (0.44,1.05)
							High risk:0.86 (0.51,1.45)
	Ruiz 1992	<4m, ≥4m	<4m:4/22	≥4m: 7/17			
	Saarinen 1979	All: <2m, 2-6m, >6m	<2m: 21/105	2-6m:13/77	>6m:5/54		
		High risk: <2m, 2-6m, >6m	<2m: 10/38	2-6m:8/38	>6m:3/25		
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0-3m:297/976	4–6m: 239/800	7-9m: 219/664	>9m: 28/70	
	Soto-Ramirez 2017	0m, <1m, 1-3m, ≥4m	0m: 84/487	<1m: 83/323	1-3m: 20/122	≥4m: 88/447	
	Tromp 2011	<6m, ≥6m (RG)	0.95 (0.77-1.17), N=6905				0.95 (0.77-1.15), N=6905
	Van Asperen 1984	<4m, ≥4m	≤4m: 22/51	>4m: 16/28			
	Zutavern 2004	<6m, ≥6m	≤6m 131/407	>6m 88/213			
Allergic rhinitis/ conjunctivitis	Filipiak-Pittroff 2018	<4m, ≥4m (RG)	0.95 (0.71- 1.27), N=2252				0.94 (0.70- 1.26), N=2252
	Gustafsson 1992	≤8d, >8d	≤8d: 6/240	>8d: 19/496			
	Marini 1996	CMF: 0m, <4m, ≥4m (all children)	0m: 4/53	<4m: 2/41	≥4m: 4/127		
		CMF: 0m, <4m, ≥4m (high risk)	0m: 2/38	<4m: 1/22	≥4m: 2/98		
		CM: <6m, ≥6m (RG) (normal children)					0.4 (0.1- 1.1), N=62
	Nwaru 2013a	<0.92m, 0.92-4m, >4m	No data				
	Van Asperen 1984	≤4m, >4m	≤4m: 27/51	>4m: 17/28			
	Wright 1994	<6m, ≥6m	<6m:244/571	≥6m:57/176			
Food allergy	Batool 2016	<6m, ≥6m (RG)	<6m: 58/143	≥6m: 271/675			1.30 (0.90–1.88), N=642
	Elbert 2017	<6m, ≥6m (RG)					1.44 (0.76, 2.73), N=3006

	Kumar 2010	<6m, ≥6m	<6m: 249/464	>6m:162/325			
	Luccioli 2014	All: 4m, 4–5m, 6–12m	<4m:60/899	4–5m: 4/59	6–12m:16/300		
		High risk: 4m, 4–5m, 6–12m	<4m: 53/530	4–5m: 4/42	6–12m:14/180		
	Nwaru 2010	<0.92m (RG), 0.92-4m, >4m	0.92-4m: 1.09 (0.72-1.65)				0.92-4m: 1.25 (0.77-2.03)
			>4m: 1.20 (0.80-1.81) , N=994				>4m: 1.51 (0.93-2.46), N=994
	Saarinen 1979	All: <2m, 2-6m, >6m	<2m: 25/81	2-6m:10/56	>6m:8/40		
		High risk: <2m, 2-6m, >6m	<2m: 11/28	2-6m:4/27	>6m:4/20		
Cow's milk allergy	Katz 2010	<1m (RG), ≥1m	12.2 (5.2-28.6), N=11633				
	Kemeny 1991	0m, <3m, ≥3m	0m: 0/60	<3m:1/64	≥3m:1/65		
	Host 1991	<1m, 1-3m, ≥4m	0m: 2/145	<1m: 0/190	1-3m:4/505	≥4m:10/909	
	Perters 2019	<3m, ≥3m (RG)		<3m:3/784	≥3m: 18/1399		0.30 (0.09-1.02), N=2183
	Snijders 2008	0–3m, 4–6m, 7–9m, >9m	0-3m: 50/270	4–6m: 54/235	7-9m: 44/255	>9m: 2/22	
	Tham 2018	<10m, ≥10m	<10m: 2/687	≥10m:1/183			
	Tran 2017	≤6m, 7-12m (RG)					0.29 (0.10,0.70), N=2124

CM: cow's milk**; CMF**: cow's milk formula; **d**: day; **m**: month; **RG**: reference group; **w**: week

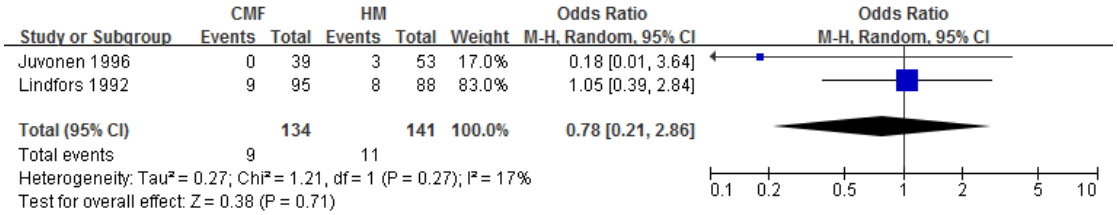
Table S3.6 Original data extracted from the included case-control studies for each outcome.

Outcomes	Study ID	Sample size	Timing of introduction	Cases in each comparative group / OR 95%CI
Food allergy	Grimshaw 2013	123 Case:41 Control:82	Median age of weeks	Case:22w Control:26w
Cow's milk allergy	Onizawa 2016	153 Case:51 Control:102	≤1m	Case: 6/51 Control: 60/102
Eczema/Atopic Dermatitis	Sariachvili 2010	Case: 252 Control: 305	<4m	Case:169/252 Control: 240/305
	Turati 2016	Case: 329 Control: 329	No cow's milk before 5 m(RG) at 1m at 2m at 3m at 4m at 5m	at 1m: 0.62 (0.40–0.96) at 2m: 0.64 (0.41–1.00) at 3m: 0.57 (0.37–0.89) at 4m: 0.64 (0.38–1.09) at 5m: 0.61 (0.28–1.30)

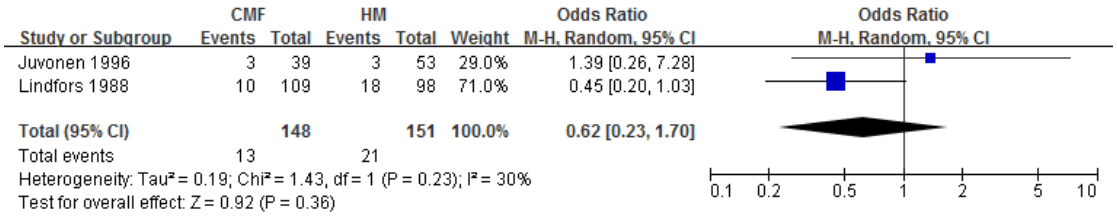
m: month; **w:** week

Supplementary material S4 in Chapter 3: Forest plots of the effect sizes for individual studies included in the meta-analyses

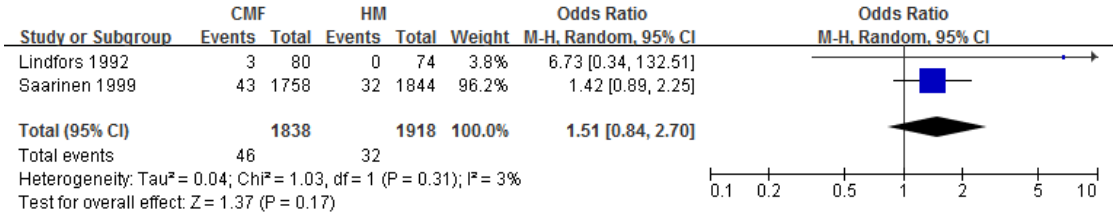
A



B

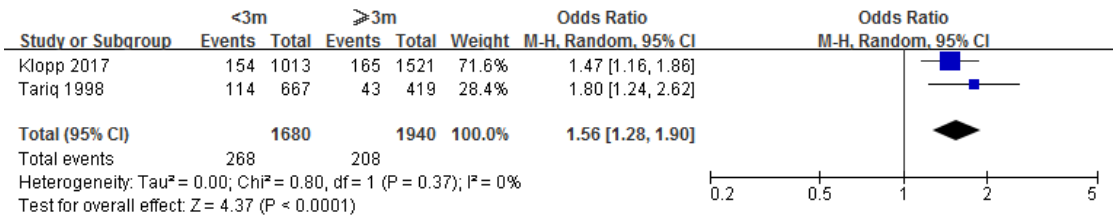


C

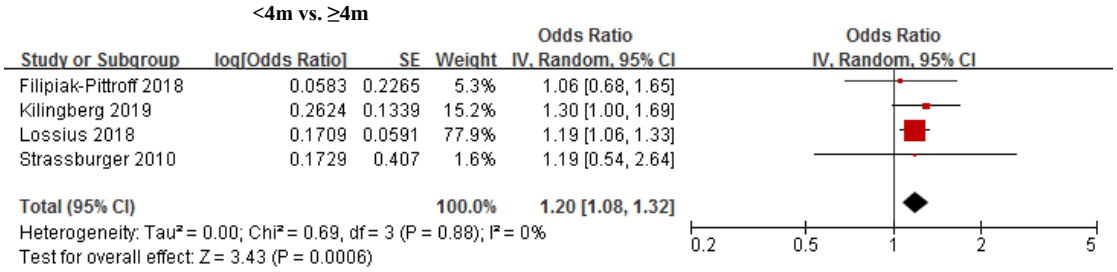


Supplemental Figure 1. Summary of risk of allergic diseases for introducing cow's milk formula versus human milk during the first days of life from clinical trials: **(A)** asthma **(B)** eczema/atopic dermatitis **(C)** cow's milk allergy**.** CMF: cow's milk formula; HM: human milk.

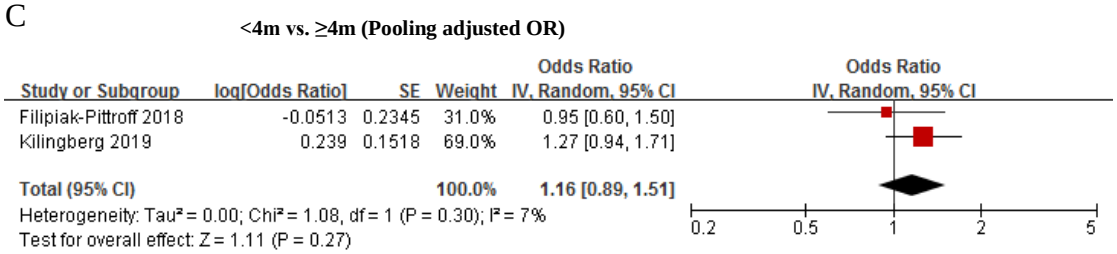
A



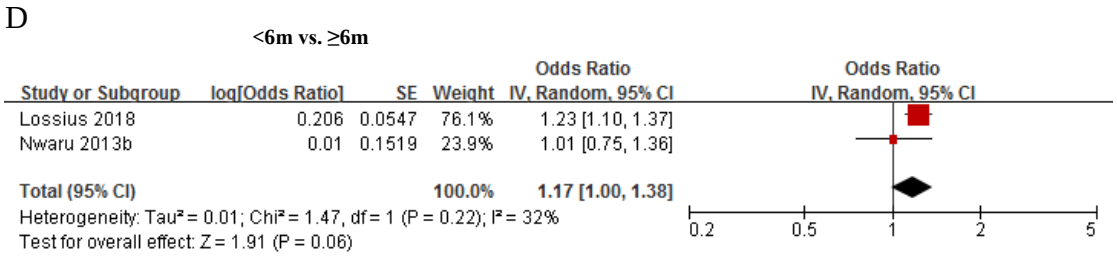
B



C

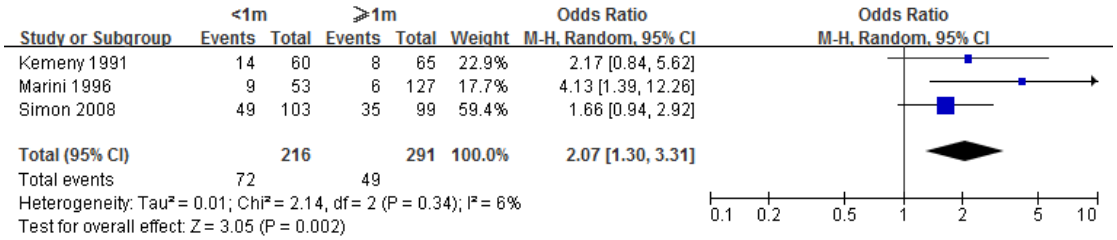


D

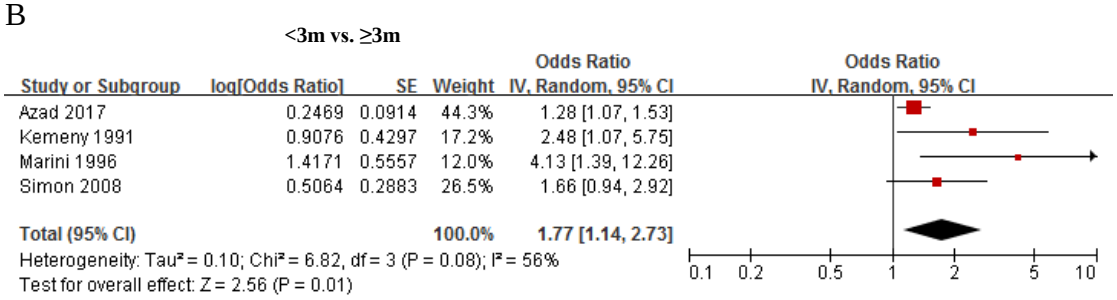


Supplemental Figure 2. Summary of risk of asthma for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <3 vs. ≥3 months; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <4 vs. ≥4 months, pooling adjusted OR; **(D)**exposure time <6 vs. ≥6 months.

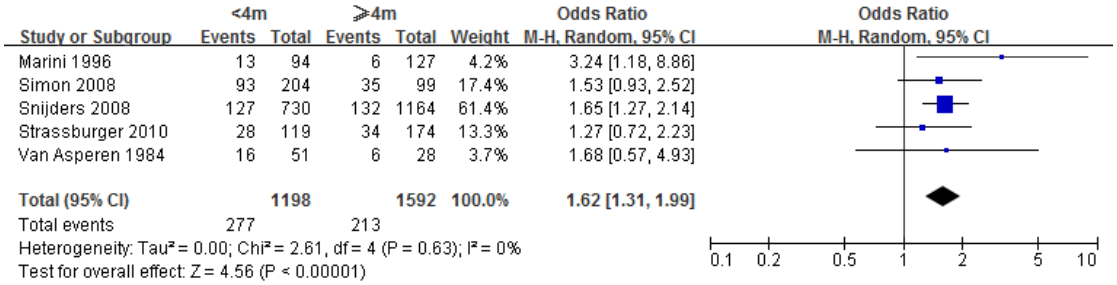
A



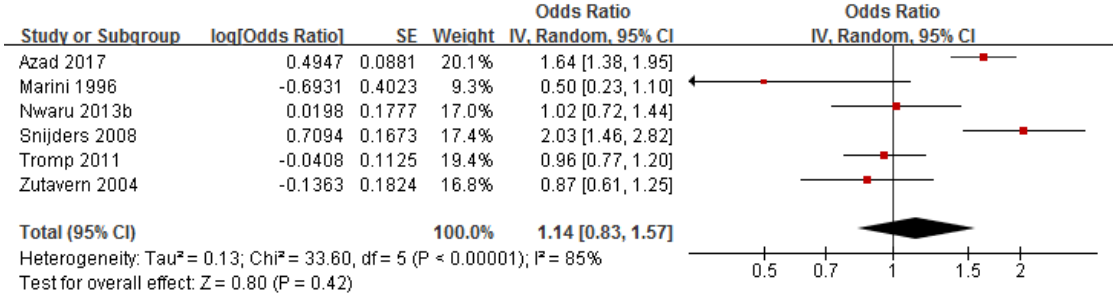
B



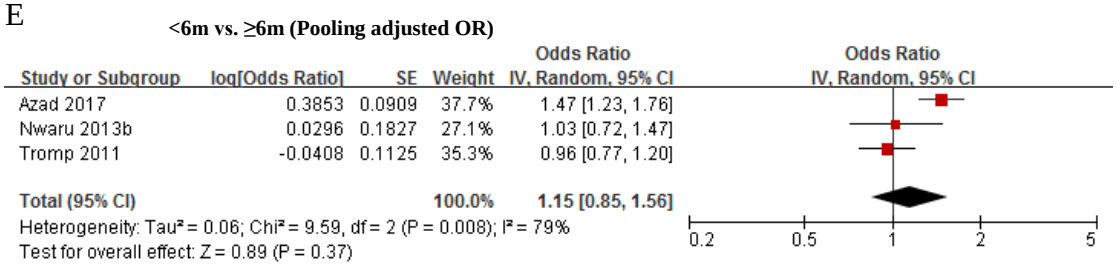
C



D

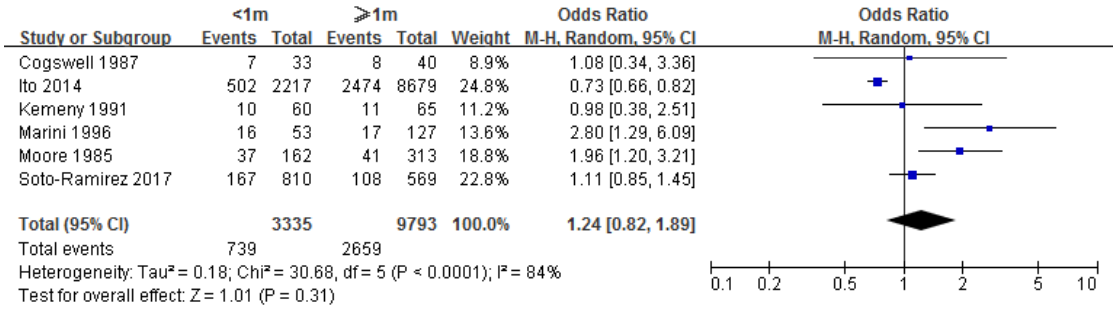


E

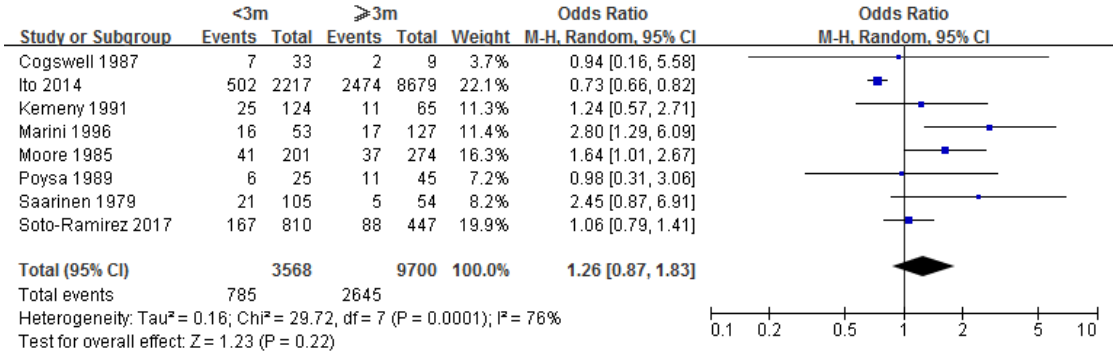


Supplemental Figure 3. Summary of risk of wheeze for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

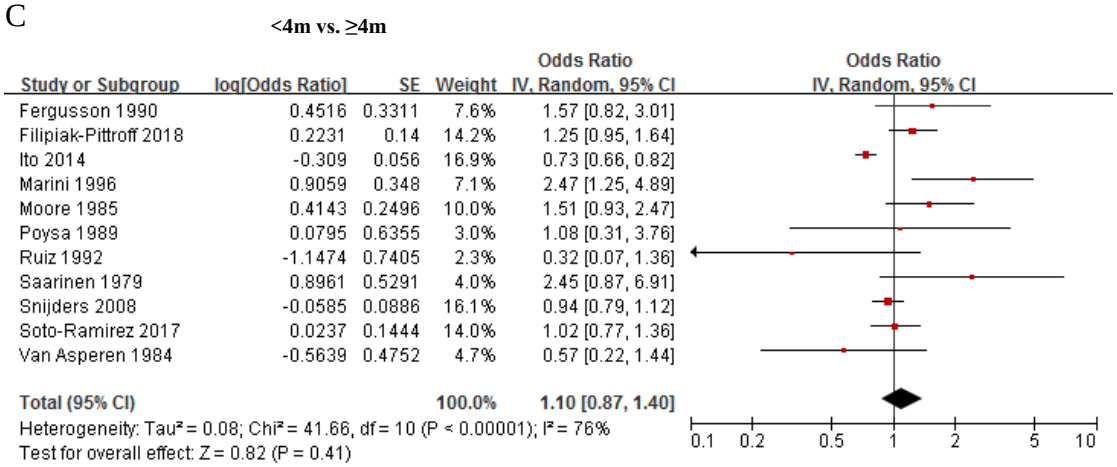
A


<1m
≥1m
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Cogswell 1987 7 33 8 40 8.9% 1.08 [0.34, 3.36]
Ito 2014 502 2217 2474 8679 24.8% 0.73 [0.66, 0.82]
Kemeny 1991 10 60 11 65 11.2% 0.98 [0.38, 2.51]
Marini 1996 16 53 17 127 13.6% 2.80 [1.29, 6.09]
Moore 1985 37 162 41 313 18.8% 1.96 [1.20, 3.21]
Soto-Ramirez 2017 167 810 108 569 22.8% 1.11 [0.85, 1.45]
Total (95% CI) 3335 9793 100.0% 1.24 [0.82, 1.89]
Total events 739 2659
Heterogeneity: Tau² = 0.18; Chi² = 30.68, df = 5 (P < 0.0001); I² = 84%
Test for overall effect: Z = 1.01 (P = 0.31)
0.1 0.2 0.5 1 2 5 10

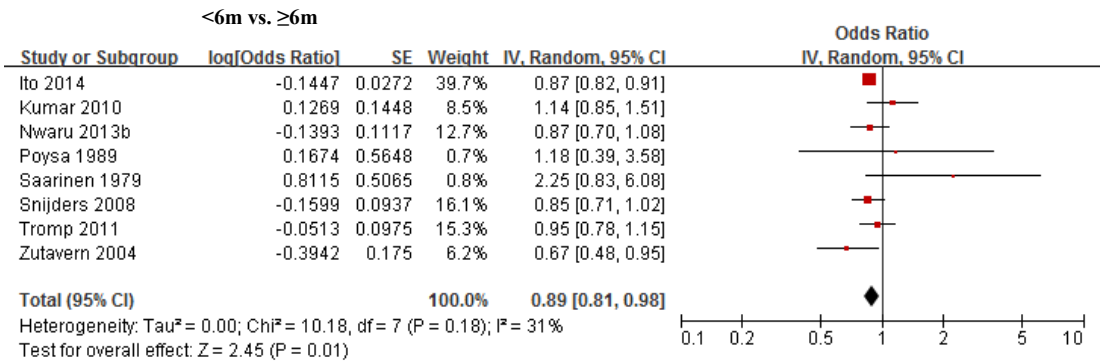
B


<3m
≥3m
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Cogswell 1987 7 33 2 9 3.7% 0.94 [0.16, 5.58]
Ito 2014 502 2217 2474 8679 22.1% 0.73 [0.66, 0.82]
Kemeny 1991 25 124 11 65 11.3% 1.24 [0.57, 2.71]
Marini 1996 16 53 17 127 11.4% 2.80 [1.29, 6.09]
Moore 1985 41 201 37 274 16.3% 1.64 [1.01, 2.67]
Poysa 1989 6 25 11 45 7.2% 0.98 [0.31, 3.06]
Saarinen 1979 21 105 5 54 8.2% 2.45 [0.87, 6.91]
Soto-Ramirez 2017 167 810 88 447 19.9% 1.06 [0.79, 1.41]
Total (95% CI) 3568 9700 100.0% 1.26 [0.87, 1.83]
Total events 785 2645
Heterogeneity: Tau² = 0.16; Chi² = 29.72, df = 7 (P = 0.0001); I² = 76%
Test for overall effect: Z = 1.23 (P = 0.22)
0.1 0.2 0.5 1 2 5 10

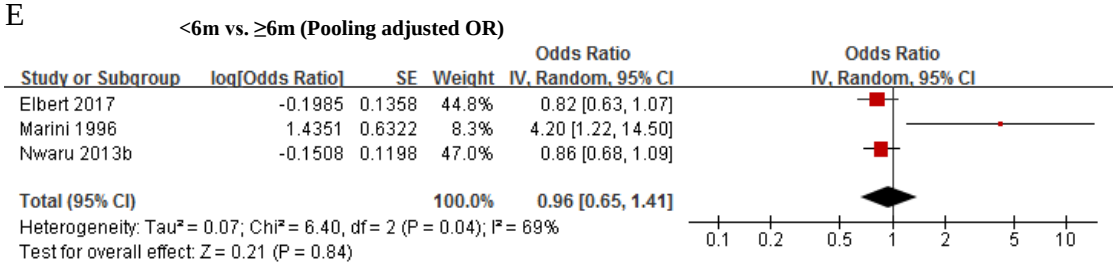
C


<4m vs. ≥4m
Odds Ratio
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Fergusson 1990 0.4516 0.3311 7.6% 1.57 [0.82, 3.01]
Filipiak-Pittroff 2018 0.2231 0.14 14.2% 1.25 [0.95, 1.64]
Ito 2014 -0.309 0.056 16.9% 0.73 [0.66, 0.82]
Marini 1996 0.9059 0.348 7.1% 2.47 [1.25, 4.89]
Moore 1985 0.4143 0.2496 10.0% 1.51 [0.93, 2.47]
Poysa 1989 0.0795 0.6355 3.0% 1.08 [0.31, 3.76]
Ruiz 1992 -1.1474 0.7405 2.3% 0.32 [0.07, 1.36]
Saarinen 1979 0.8961 0.5291 4.0% 2.45 [0.87, 6.91]
Snijders 2008 -0.0585 0.0886 16.1% 0.94 [0.79, 1.12]
Soto-Ramirez 2017 0.0237 0.1444 14.0% 1.02 [0.77, 1.36]
Van Asperen 1984 -0.5639 0.4752 4.7% 0.57 [0.22, 1.44]
Total (95% CI) 100.0% 1.10 [0.87, 1.40]
Heterogeneity: Tau² = 0.08; Chi² = 41.66, df = 10 (P < 0.00001); I² = 76%
Test for overall effect: Z = 0.82 (P = 0.41)
0.1 0.2 0.5 1 2 5 10

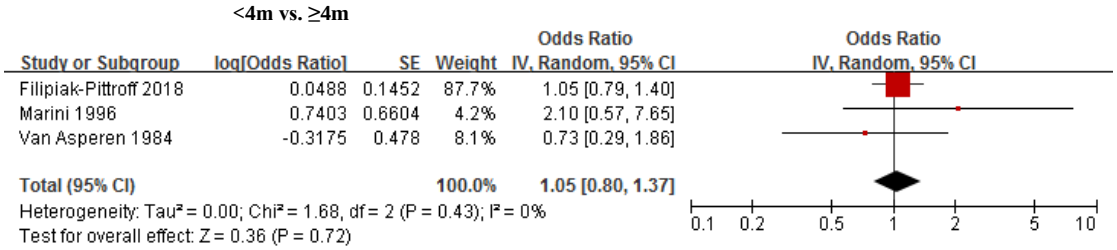
D


<6m vs. ≥6m
Odds Ratio
Study or Subgroup log[Odds Ratio] SE Weight IV, Random, 95% CI
IV, Random, 95% CI
Ito 2014 -0.1447 0.0272 39.7% 0.87 [0.82, 0.91]
Kumar 2010 0.1269 0.1448 8.5% 1.14 [0.85, 1.51]
Nwaru 2013b -0.1393 0.1117 12.7% 0.87 [0.70, 1.08]
Poysa 1989 0.1674 0.5648 0.7% 1.18 [0.39, 3.58]
Saarinen 1979 0.8115 0.5065 0.8% 2.25 [0.83, 6.08]
Snijders 2008 -0.1599 0.0937 16.1% 0.85 [0.71, 1.02]
Tromp 2011 -0.0513 0.0975 15.3% 0.95 [0.78, 1.15]
Zutavern 2004 -0.3942 0.175 6.2% 0.67 [0.48, 0.95]
Total (95% CI) 100.0% 0.89 [0.81, 0.98]
Heterogeneity: Tau² = 0.00; Chi² = 10.18, df = 7 (P = 0.18); I² = 31%
Test for overall effect: Z = 2.45 (P = 0.01)
0.1 0.2 0.5 1 2 5 10

E

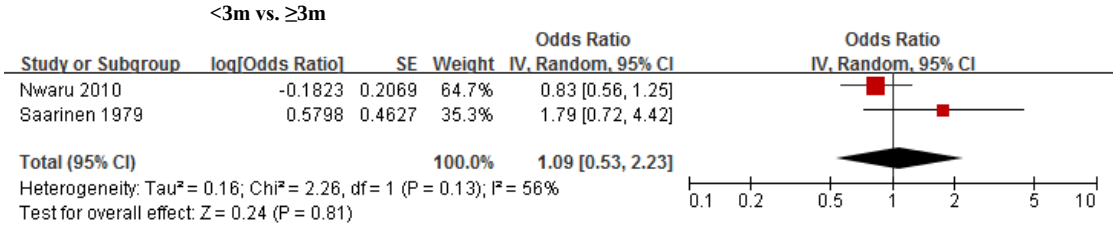


Supplemental Figure 4. Summary of risk of eczema/atopic dermatitis for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

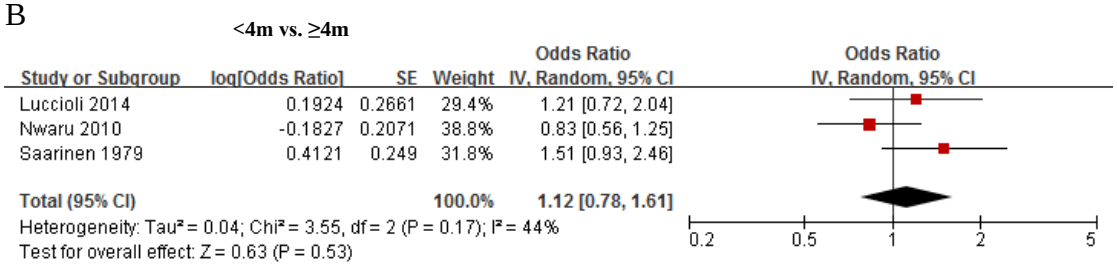


Supplemental Figure 5. Summary of risk of allergic rhinitis and/ or conjunctivitis for timing of cow's milk or cow's milk formula introduction from cohort studies: exposure time <4 vs. ≥4 months.

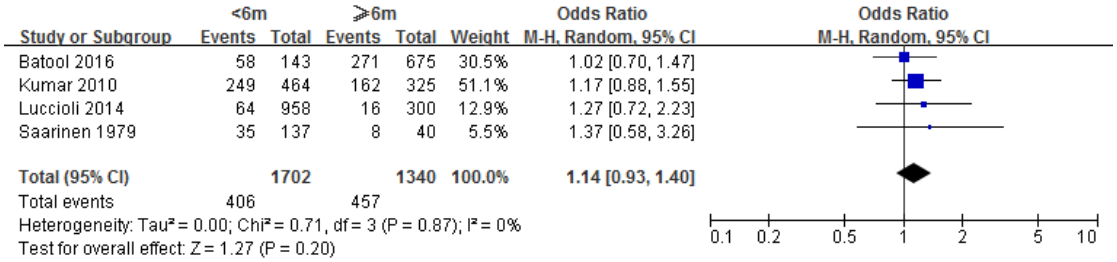
A



B

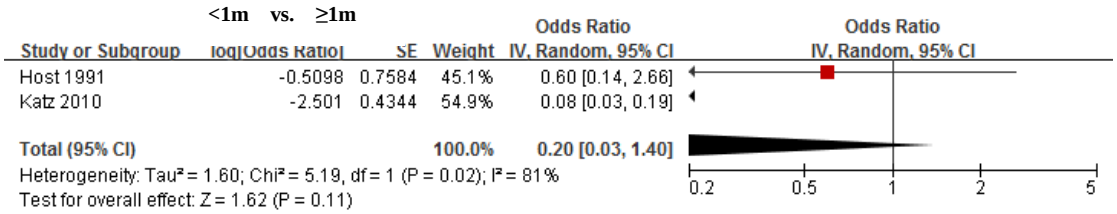


C

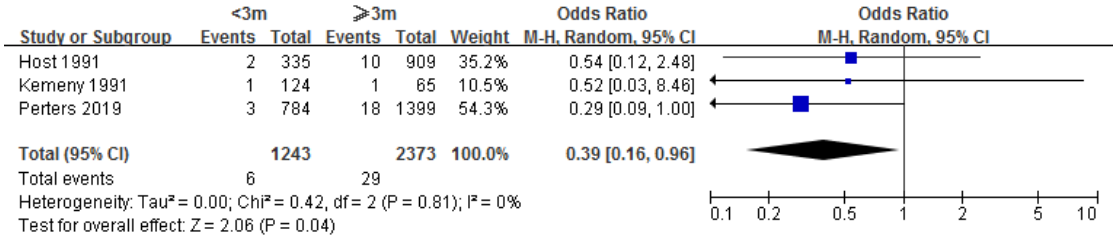


Supplemental Figure 6. Summary of risk of food allergy for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <3 vs. ≥3 months; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <6 vs. ≥6 months.

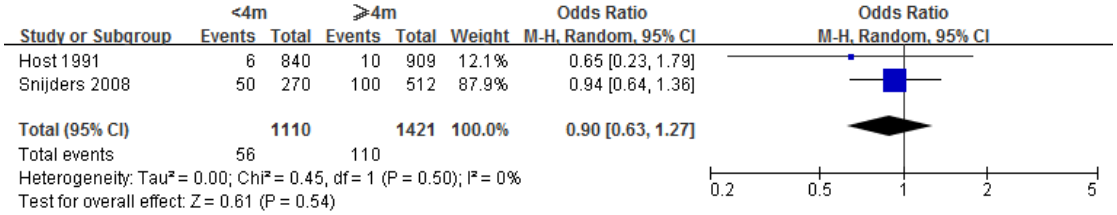
A



B

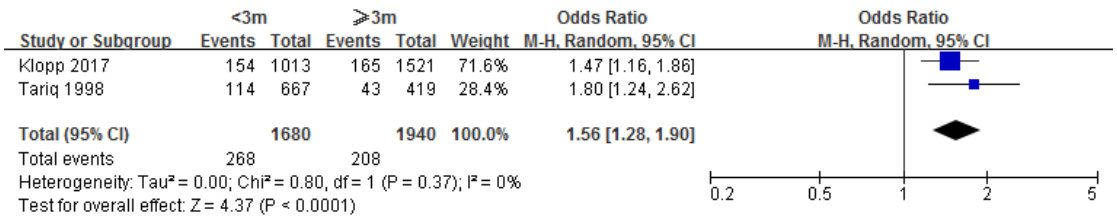


C

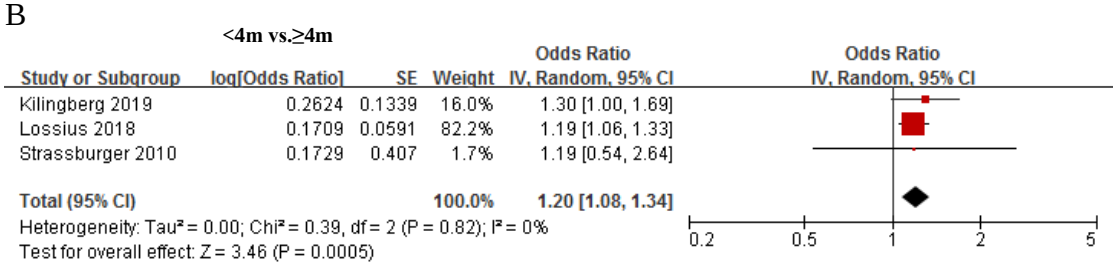


Supplemental Figure 7. Summary of risk of cow's milk allergy for timing of cow's milk or cow's milk formula introduction from cohort studies: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months.

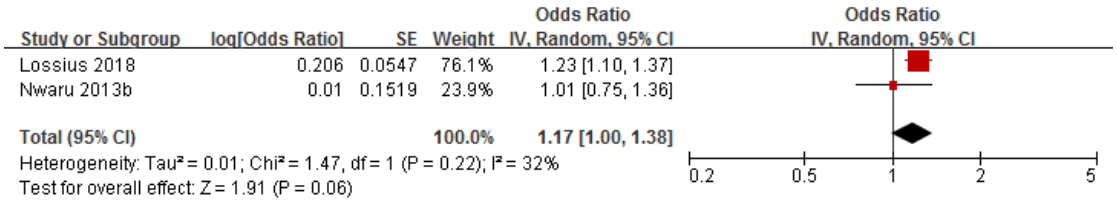
A



B

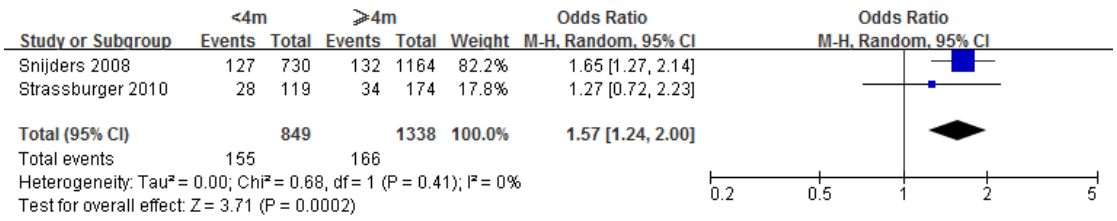


C

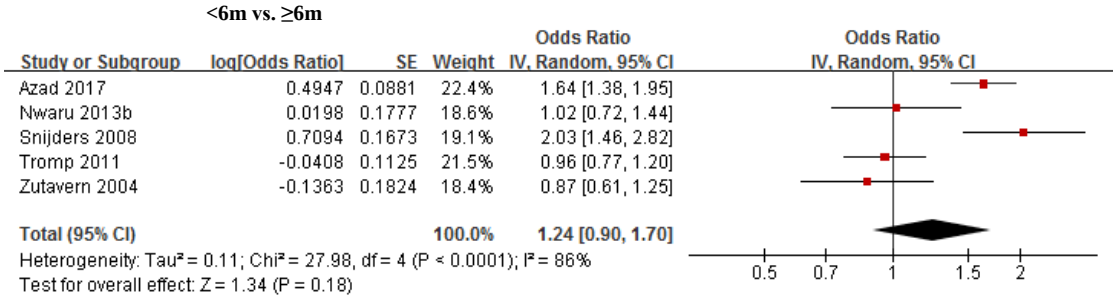


Supplemental Figure 8. Sensitivity analyses of the cohort studies with high-quality scores on timing of CM or CMF introduction and risk of asthma: **(A)** exposure time <3 vs. ≥3 month; **(B)** exposure time <4 vs. ≥4 months; **(C)** exposure time <6 vs. ≥6 month.

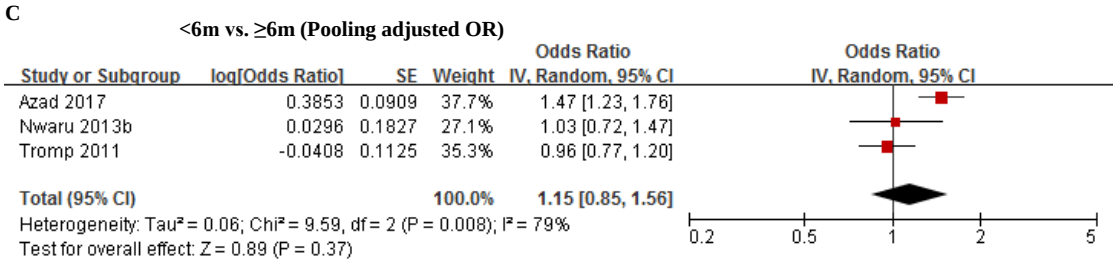
A



B

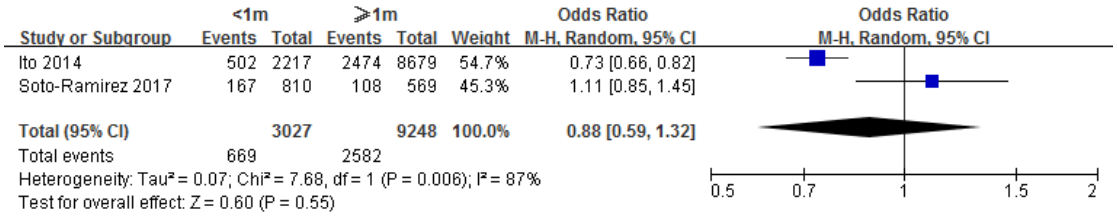


C

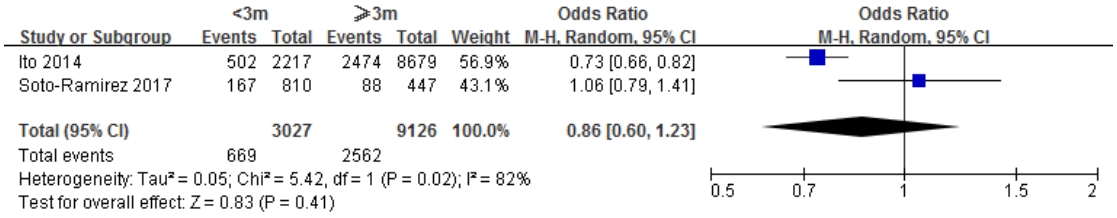


Supplemental Figure 9. Sensitivity analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of wheeze: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <6 vs. ≥6 months; **(C)** exposure time <6 vs. ≥6 months, pooling adjusted OR

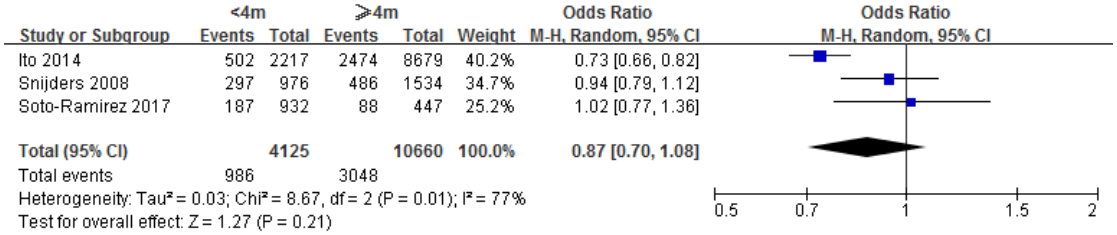
A



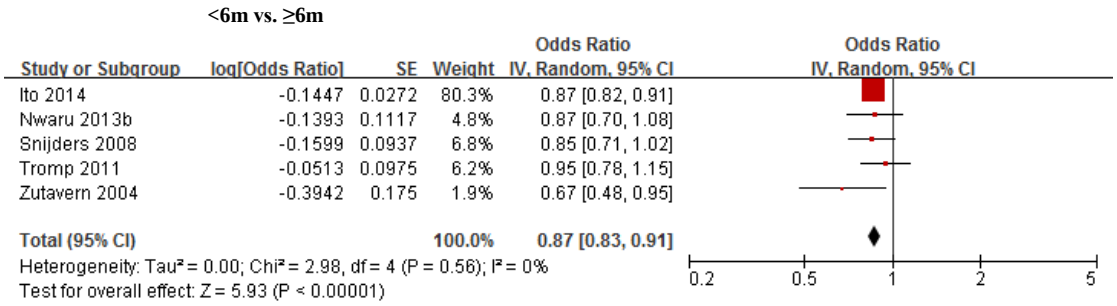
B



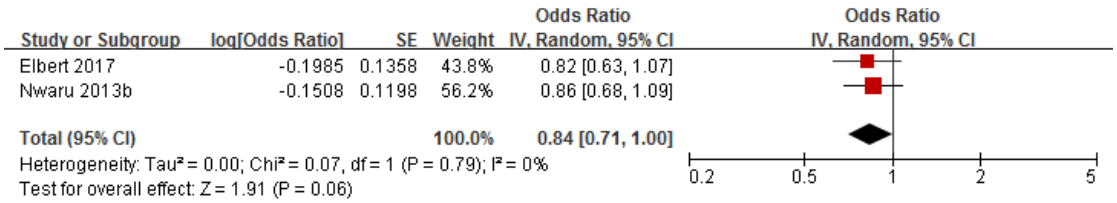
C



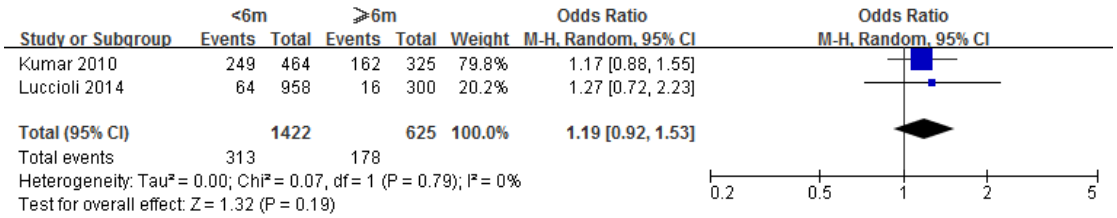
D



E

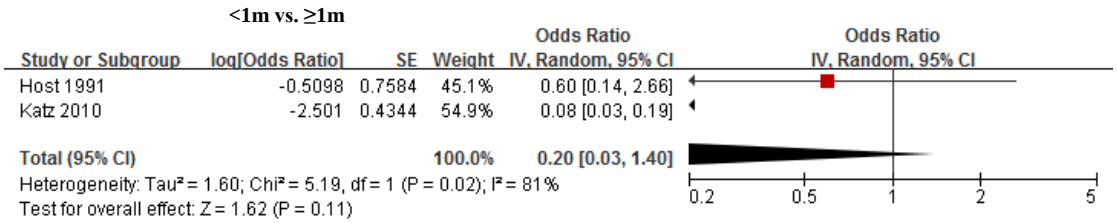


Supplemental Figure 10. Sensitivity analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of eczema/atopic dermatitis: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months; **(E)** exposure time <6 vs. ≥6 months, pooling adjusted OR

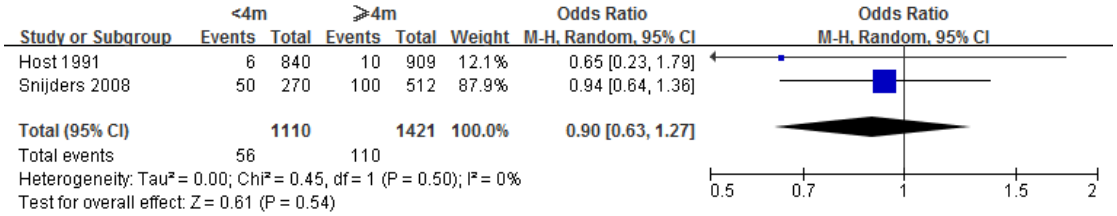


Supplemental Figure 11. Sensitivity analysis of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of food allergy: exposure time <6 vs. ≥6 months.

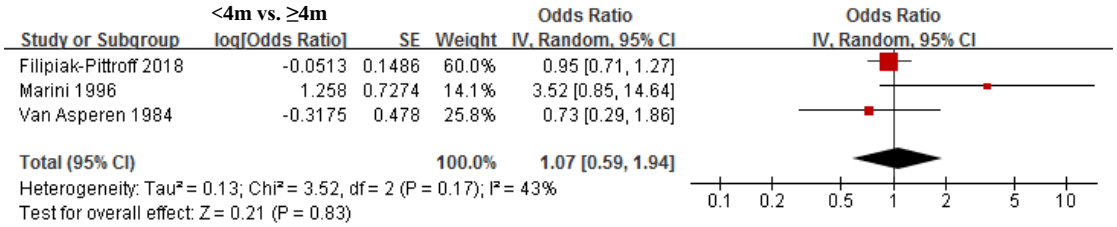
A



B

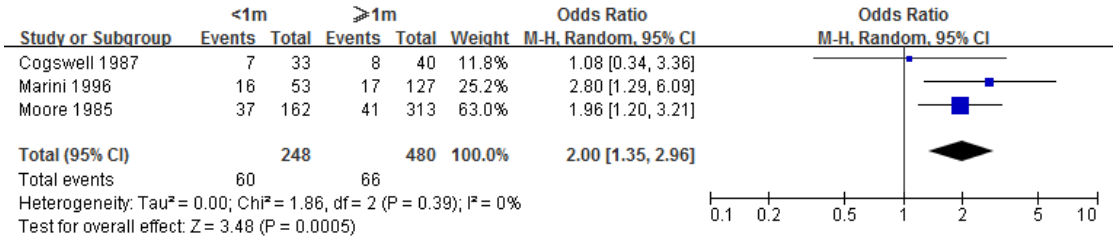


Supplemental Figure 12. Sensitivity analyses of the cohort studies with high quality scores on timing of CM or CMF introduction and risk of cow's milk allergy: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <4 vs. ≥4 months.

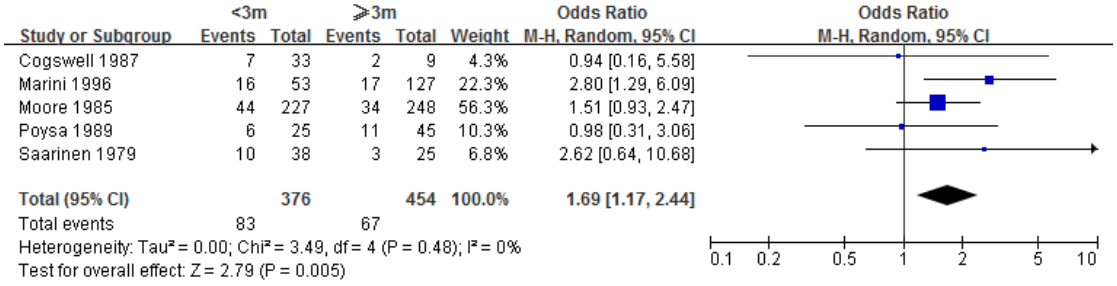


Supplemental Figure 13. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of wheeze: exposure time <4 vs. ≥4 months.

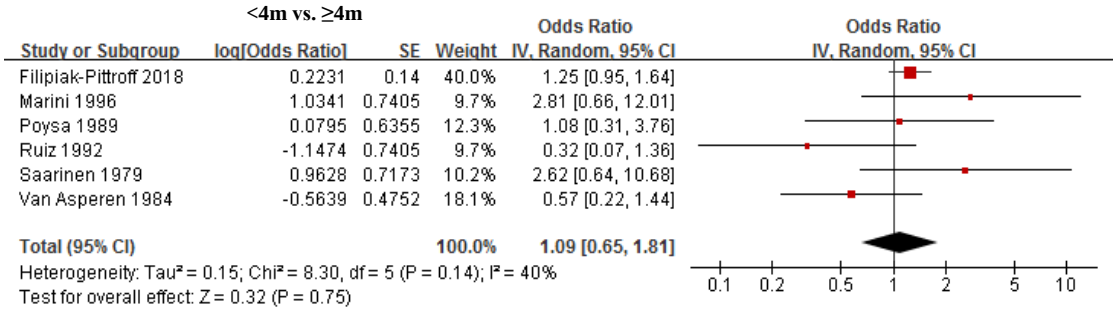
A



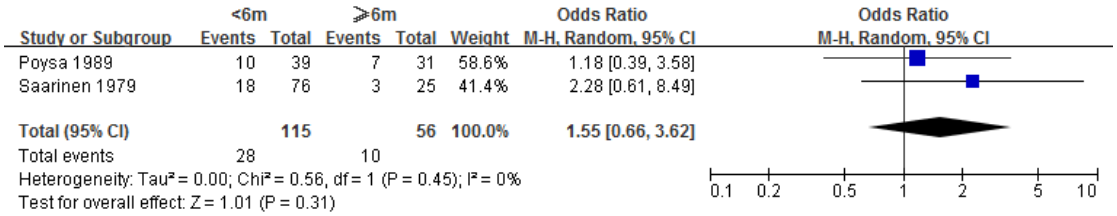
B



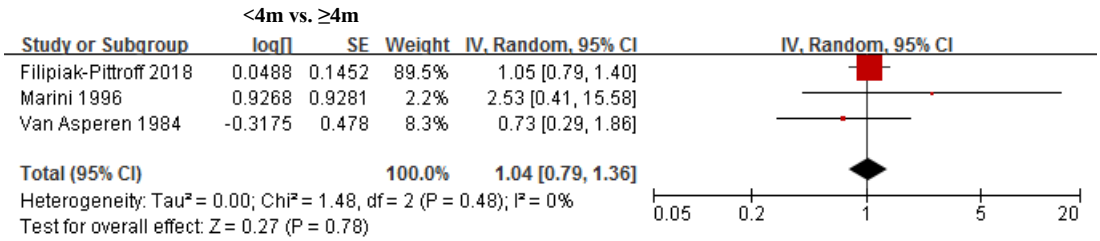
C



D

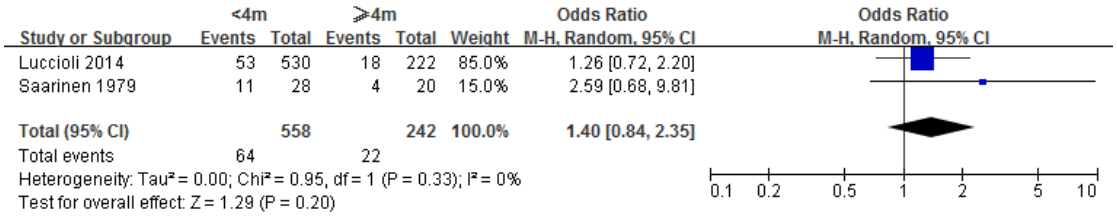


Supplemental Figure 14. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of eczema/atopic dermatitis: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4 months; **(D)** exposure time <6 vs. ≥6 months.

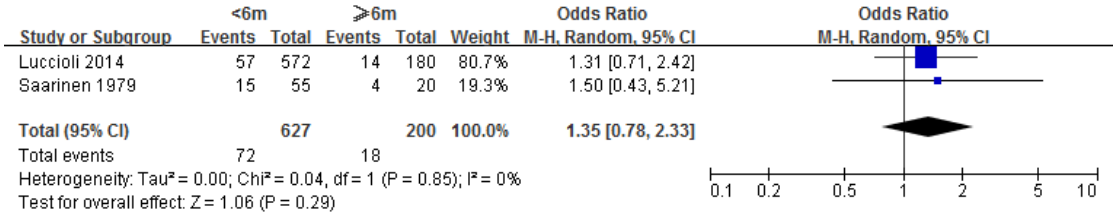


Supplemental Figure 15. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of allergic rhinitis and/ or conjunctivitis: exposure time <4 vs. ≥4 months.

A

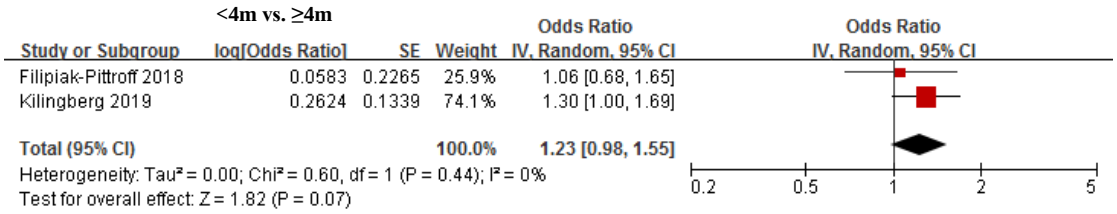


B

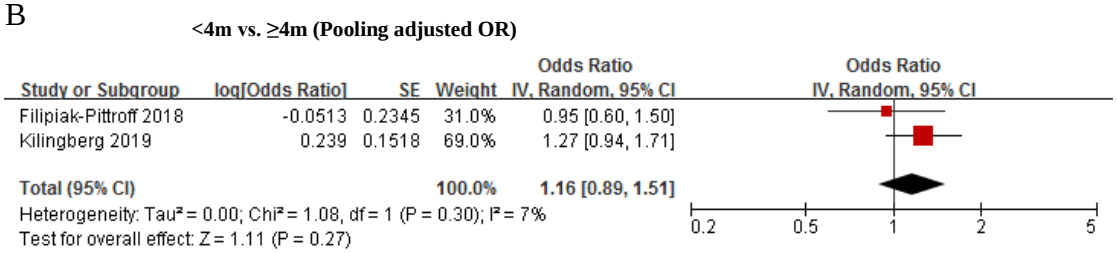


Supplemental Figure 16. Subgroup analysis of the cohort studies with children at high risk of allergic diseases on timing of CM or CMF introduction and risk of food allergy: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <6 vs. ≥6 months.

A

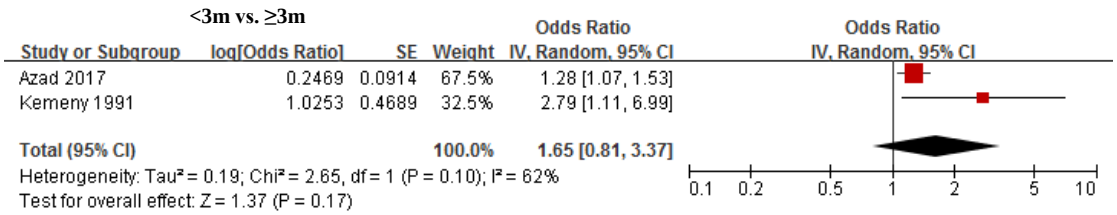


B

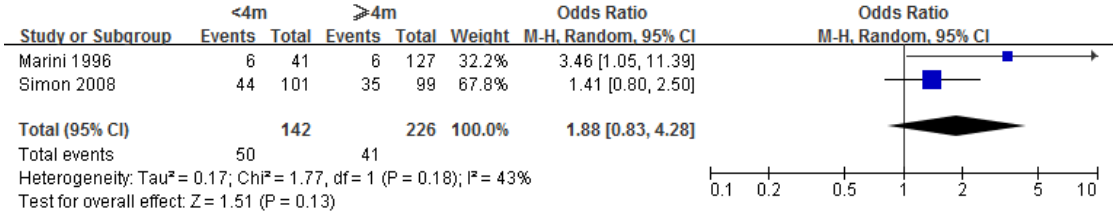


Supplemental Figure 17. Subgroup analysis on risk of asthma by excluding exclusive formula feeding children: **(A)** exposure time <4 vs. ≥4 month; **(B)** exposure time <4 vs. ≥4 months, pooling adjusted OR.

A

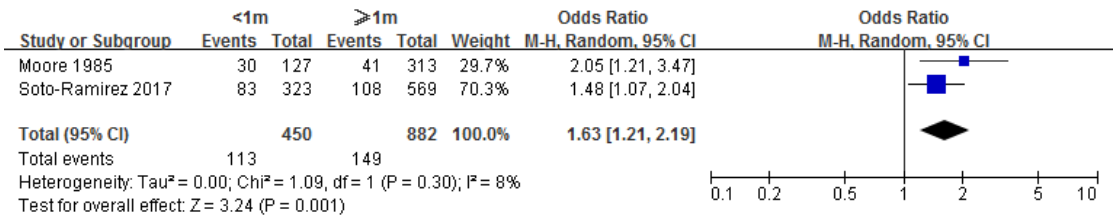


B

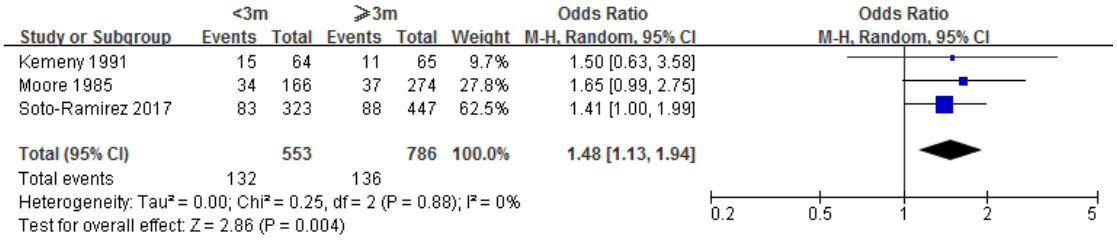


Supplemental Figure 18. Subgroup analysis on risk of wheeze by excluding exclusive formula feeding children: **(A)** exposure time <3 vs. ≥3 month; **(B)** exposure time <4 vs. ≥4 months.

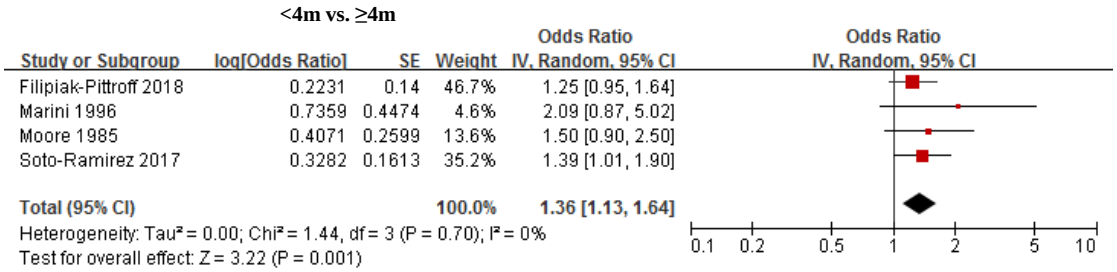
A



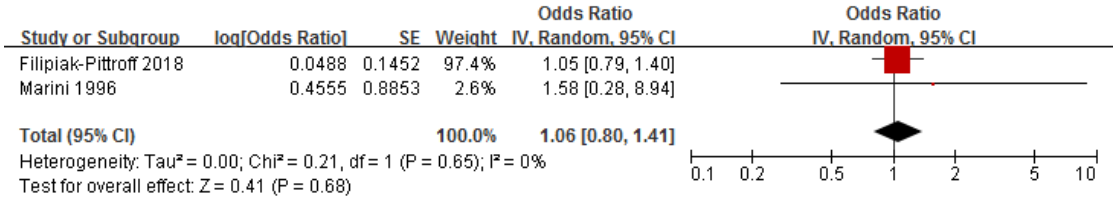
B



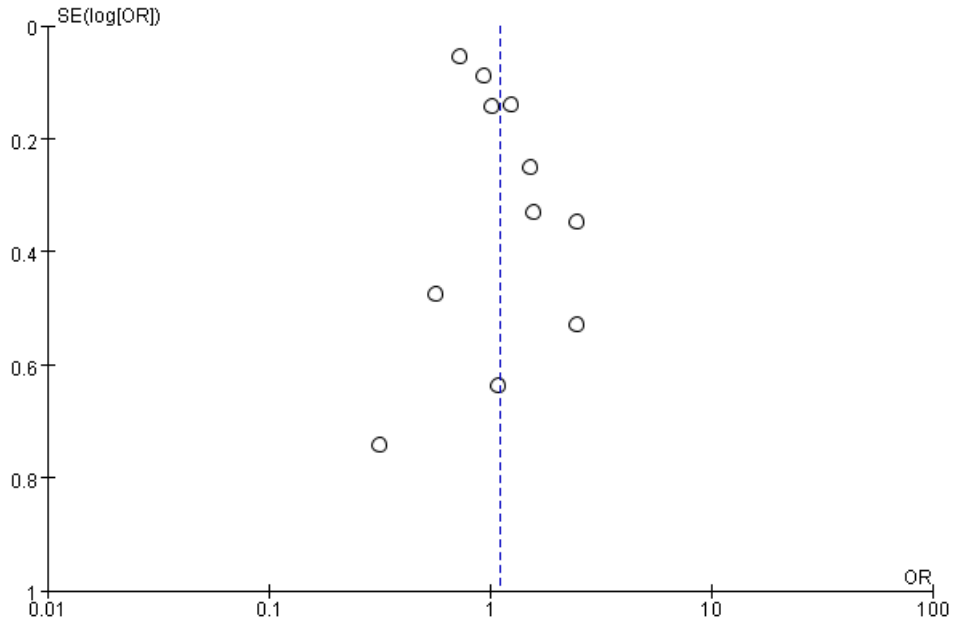
C



Supplemental Figure 19. Subgroup analysis on risk of eczema/atopic dermatitis by excluding exclusive formula feeding children: **(A)** exposure time <1 vs. ≥1 month; **(B)** exposure time <3 vs. ≥3 months; **(C)** exposure time <4 vs. ≥4months.



Supplemental Figure 20. Subgroup analysis on risk of allergic rhinitis and/ or conjunctivitis by excluding exclusive formula feeding children: exposure time <4 vs. ≥4 month

Funnel Plots	**P value for Begg's test**
Effects of introducing CM or CMF before 4 months of age on risk of eczema or or atopic dermatitis from 11cohort studies including 19276 subjects.	
	0.876

Supplemental Figure 21. Evaluation of small study effects using funnel plots and Begg' tests.

Supplementary material S5 in Chapter 4: Baseline characteristics of included and not included participants of this study

Variables	Clinic measurement (N=6334)	Telephone call interview (N=3146)
Mother		
Age at delivery (y), mean (SD)	29.4 (3.4)	29.1 (3.4)
Educational level,n (%)		
High school or below	498 (7.9)	366 (11.6)
Vocational/technical college	1571 (24.8)	804 (25.6)
Undergraduate	3528 (55.7)	1587 (50.4)
Postgraduate	737 (11.6)	389 (12.4)
Pre-pregnancy BMI, n (%)		
<18.5 kg/m^2	1474 (23.9)	834 (27.4)
18.5-23.9 kg/m^2	4097 (66.3)	1921 (63.2)
24-27.9 kg/m^2	509 (8.2)	236 (7.8)
≥28kg/m^2	101 (1.6)	49 (1.6)
Parity, n (%)		
Primiparous	5616 (88.7)	2582 (82.2)
Multiparous	715 (11.3)	560 (17.8)
Delivery mode, n (%)		
Vaginal labor	4102 (64.8)	2040 (65.0)
Cesarean delivery	2225 (35.2)	1098 (35.0)
Smoking during pregnancy, n (%)	35 (0.6)	9 (0.3)
Passive smoking during pregnancy, n (%)	1949 (31.0)	860 (27.6)
Child		
Child's gender, n (%)		
Male	3339 (52.7)	1598 (50.8)
Female	2995 (47.3)	1548 (49.2)
Birth weight <2500g, n (%)	245 (3.9)	159 (5.1)
Preterm birth, n (%)	299 (4.7)	150 (4.8)
Duration of any breastfeeding, n (%)		
≤6 months	1562 (25.4)	905 (29.7)
> 6 months	4583 (74.6)	2146 (70.3)
Parental history of allergy, n (%)	1776 (31.2)	877 (30.5)
Antibiotic use before 12 months, n (%)	1509 (28.8)	630 (28.0)
Timing of any infant formulas introduction, months n (%)		
≤3 m	5196 (82.0)	2169 (71.8)
4-6 m	575 (9.1)	427 (14.1)
> 6 m	563 (8.9)	426 (14.1)

Supplementary material S6 in Chapter 4: Modification effects of timing of complementary food introduction and breastfeeding duration on associations of formula introduction with eczema and wheeze before 1 year of age.

	Modification effects*	P-value
Eczema		
	Complementary foods introduction * Infant formula introduction	0.087
	Cereal introduction* Infant formula introduction	0.362
	Vegetable introduction * Infant formula introduction	0.680
	Fruit introduction * Infant formula introduction	0.765
	Meat introduction * Infant formula introduction	0.481
	Offal introduction * Infant formula introduction	0.741
	Fish introduction * Infant formula introduction	0.890
	Other seafood introduction * Infant formula introduction	0.779
	Eggyolk introduction * Infant formula introduction	0.251
	Eggwhite introduction * Infant formula introduction	0.963
	Breastfeeding duration * Infant formula introduction	0.221
Itchy rash		
	Complementary foods introduction * Infant formula introduction	0.246
	Cereal introduction* Infant formula introduction	0.951
	Vegetable introduction * Infant formula introduction	0.842
	Fruit introduction * Infant formula introduction	0.447
	Meat introduction * Infant formula introduction	0.632
	Offal introduction * Infant formula introduction	0.992
	Fish introduction * Infant formula introduction	0.192
	Other seafood introduction * Infant formula introduction	0.698
	Eggyolk introduction * Infant formula introduction	0.456
	Eggwhite introduction * Infant formula introduction	0.974
	Breastfeeding duration * Infant formula introduction	0.587
Wheezing		
	Complementary foods introduction * Infant formula introduction	0.884
	Cereal introduction* Infant formula introduction	0.784
	Vegetable introduction * Infant formula introduction	0.964
	Fruit introduction * Infant formula introduction	0.900
	Meat introduction * Infant formula introduction	0.998
	Offal introduction * Infant formula introduction	0.980
	Fish introduction * Infant formula introduction	0.771
	Other seafood introduction * Infant formula introduction	0.999
	Eggyolk introduction * Infant formula introduction	0.828
	Eggwhite introduction * Infant formula introduction	0.977
	Breastfeeding duration * Infant formula introduction	0.655

Adjusted for maternal age at conception, maternal education, pre-pregnancy body mass index, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, parental history of atopic diseases, antibiotic usage before 12

months of age, the duration of breastfeeding, and the timing of introduction any complementary food.

Supplementary material S7 in Chapter 4: The variance information between imputed data sets.

Variance Information					
Parameter	**Variance**			**Relative Increase in Variance**	**Fraction Missing Information (FMI)**
	Between	Within	Total		
Eczema					
Maternal_age_≤25 years	0.000054575	0.010835	0.010896	0.006	0.006
Maternal_age_ 26-30 years	0.000017028	0.003733	0.003752	0.005	0.005
Maternal_age_31-35 years	0.000021135	0.004224	0.004247	0.006	0.005
Maternal_edu_high school or below	0.000126	0.009381	0.009519	0.015	0.015
Maternal_edu_vocational/technical college	0.000020148	0.004212	0.004235	0.005	0.005
Maternal_edu_undergraduate	0.000013603	0.003034	0.003049	0.005	0.005
pre-pregnancy_BMI_<18.5 kg/m^2	0.000156	0.008277	0.008448	0.021	0.020
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.00023	0.006642	0.006895	0.038	0.037
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000154	0.011994	0.012164	0.014	0.014
Smoking during pregnancy	0.000064517	0.092233	0.092304	0.001	0.001
Passive smoking during pregnancy	0.000013356	0.001278	0.001293	0.011	0.011
Parity	0.000020052	0.003221	0.003243	0.007	0.007
Delivery mode	0.000005777	0.001255	0.001262	0.005	0.005
Preterm birth	0.000002688	0.006398	0.006401	0.000	0.000
Child's gender	0.000003176	0.001138	0.001142	0.003	0.003
Parental history of allergy	0.000196	0.001248	0.001464	0.173	0.151
Antibiotic use before 12 months	0.00022	0.001331	0.001573	0.182	0.158
Duration of any breastfeeding	0.000045983	0.001486	0.001537	0.034	0.033
Timing of complementary food introduction≤3 m	0.000041098	0.060437	0.060482	0.001	0.001
Timing of complementary food introduction 4-6 m	0.000024629	0.051598	0.051625	0.001	0.001
Itchy red rash					
Maternal_age_≤25 years	0.000005668	0.007742	0.007748	0.001	0.001
Maternal_age_ 26-30 years	0.000000935	0.002686	0.002687	0.000	0.000
Maternal_age_31-35 years	0.000000913	0.003087	0.003088	0.000	0.000
Maternal_edu_high school or below	0.000004137	0.006917	0.006922	0.001	0.001
Maternal_edu_vocational/technical college	0.00000264	0.002976	0.002979	0.001	0.001
Maternal_edu_undergraduate	0.000005006	0.002155	0.00216	0.003	0.003
pre-pregnancy_BMI_<18.5 kg/m^2	0.000192	0.005858	0.006069	0.036	0.035
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000152	0.004673	0.004841	0.036	0.035
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000232	0.008638	0.008893	0.030	0.029
Smoking during pregnancy	0.000041216	0.038168	0.038213	0.001	0.001
Passive smoking during pregnancy	0.000009724	0.000916	0.000927	0.012	0.012
Parity	0.000008698	0.002351	0.002361	0.004	0.004
Delivery mode	0.000001428	0.0009	0.000901	0.002	0.002
Preterm birth	0.000001599	0.004654	0.004656	0.000	0.000
Child's gender	0.000001355	0.000794	0.000796	0.002	0.002
Parental history of allergy	0.000126	0.000894	0.001032	0.155	0.138

Antibiotic use before 12 months	0.000112	0.000958	0.001081	0.129	0.117
Duration of any breastfeeding	0.000020247	0.001062	0.001085	0.021	0.021
Timing of complementary food introduction≤3 m	0.000015964	0.039884	0.039902	0.000	0.000
Timing of complementary food introduction 4-6 m	0.000012144	0.033204	0.033217	0.000	0.000
Wheezing					
Maternal_age_≤25 years	0.000159	0.021786	0.021961	0.008	0.008
Maternal_age_ 26-30 years	0.000063654	0.007802	0.007872	0.009	0.009
Maternal_age_31-35 years	0.00007727	0.008811	0.008896	0.010	0.010
Maternal_edu_high school or below	0.000101	0.0206	0.020711	0.005	0.005
Maternal_edu_vocational/technical college	0.000059624	0.008631	0.008697	0.008	0.008
Maternal_edu_undergraduate	0.000035045	0.006586	0.006625	0.006	0.006
pre-pregnancy_BMI_<18.5 kg/m^2	0.000252	0.026816	0.027093	0.010	0.010
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.00016	0.021405	0.021581	0.008	0.008
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000826	0.034531	0.035439	0.026	0.026
Smoking during pregnancy	0.000378	0.137937	0.138354	0.003	0.003
Passive smoking during pregnancy	0.000018932	0.002953	0.002974	0.007	0.007
Parity	0.000022137	0.00534	0.005364	0.005	0.005
Delivery mode	0.000021355	0.002701	0.002724	0.009	0.009
Preterm birth	0.000025833	0.01074	0.010768	0.003	0.003
Child's gender	0.000008353	0.002647	0.002656	0.003	0.003
Parental history of allergy	0.000242	0.002669	0.002936	0.100	0.092
Antibiotic use before 12 months	0.000541	0.002491	0.003086	0.239	0.199
Duration of any breastfeeding	0.000289	0.003114	0.003432	0.102	0.094
Timing of complementary food introduction≤3 m	0.000189	0.12713	0.127339	0.002	0.002
Timing of complementary food introduction 4-6 m	0.00023	0.105772	0.106026	0.002	0.002

*FMI: range between 0-1, a large FMI (close to 0) indicates low variability between imputed data sets

Supplementary material S8 in Chapter 5: The variance information between imputed data sets.

Variance Information					
Parameter	**Variance**			**Relative Increase in Variance**	**Fraction Missing Information (FMI)***
	Between	Within	Total		
Eczema					
Maternal_age_≤25 years	0.000017838	0.044105	0.044125	0.000	0.000
Maternal_age_ 26-30 years	0.000006693	0.01563	0.015637	0.000	0.000
Maternal_age_31-35 years	0.000006853	0.017049	0.017056	0.000	0.000
Maternal_edu_high school or below	0.000019849	0.042698	0.04272	0.001	0.001
Maternal_edu_vocational/technical college	0.000007036	0.018145	0.018153	0.000	0.000
Maternal_edu_undergraduate	0.000005191	0.01235	0.012356	0.000	0.000
pre-pregnancy_BMI_<18.5 kg/m^2	0.000774	0.039405	0.040256	0.022	0.021
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000111	0.031099	0.031221	0.004	0.004
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000539	0.05645	0.057043	0.010	0.010
Smoking during pregnancy	0.000080298	0.106399	0.106487	0.001	0.001
Passive smoking during pregnancy	0.000010706	0.005559	0.005571	0.002	0.002
Parity	0.000007664	0.013304	0.013312	0.001	0.001
Delivery mode	0.00000224	0.004912	0.004914	0.001	0.001
Preterm birth	0.000010177	0.034954	0.034965	0.000	0.000
Child's gender	0.000000717	0.00448	0.004481	0.000	0.000
Parental history of allergy	0.000375	0.005116	0.005528	0.081	0.076
Duration of any breastfeeding	0.000193	0.006158	0.00637	0.034	0.033
Antibiotic use before 12 months	0.002882	0.02296	0.02613	0.138	0.124
Asthma					
Maternal_age_≤25 years	0.00024	0.175636	0.1759	0.002	0.002
Maternal_age_ 26-30 years	0.000022503	0.0766	0.076625	0.000	0.000
Maternal_age_31-35 years	0.000166	0.098556	0.098739	0.002	0.002
Maternal_edu_high school or below	0.000198	0.219835	0.220053	0.001	0.001
Maternal_edu_vocational/technical college	0.000033989	0.082869	0.082907	0.000	0.000
Maternal_edu_undergraduate	0.000119	0.06276	0.062891	0.002	0.002
pre-pregnancy_BMI_<18.5 kg/m^2	0.007295	30518	30518	0.000	0.000
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.007403	30518	30518	0.000	0.000
pre-pregnancy_BMI_24-27.9 kg/m^2	0.050197	30519	30519	0.000	0.000
Smoking during pregnancy	0.000371	424378	424378	0.000	0.000
Passive smoking during pregnancy	0.001108	0.032137	0.033355	0.038	0.037
Parity	0.000038733	0.097392	0.097435	0.000	0.000
Delivery mode	0.000017597	0.02639	0.026409	0.001	0.001
Preterm birth	0.000050567	0.259508	0.259563	0.000	0.000
Child's gender	0.000014571	0.024589	0.024605	0.001	0.001
Parental history of allergy	0.001517	0.023441	0.02511	0.071	0.067

Duration of any breastfeeding	0.001735	0.024788	0.026696	0.077	0.073
Antibiotic use before 12 months	0.020933	0.094955	0.117981	0.242	0.202
Allergic rhinitis					
Maternal_age_≤25 years	0.000045731	0.060716	0.060766	0.001	0.001
Maternal_age_ 26-30 years	0.000006219	0.017184	0.017191	0.000	0.000
Maternal_age_31-35 years	0.000008772	0.021715	0.021725	0.000	0.000
Maternal_edu_high school or below	0.000032817	0.061165	0.061201	0.001	0.001
Maternal_edu_vocational/technical college	0.000012586	0.02288	0.022894	0.001	0.001
Maternal_edu_undergraduate	0.000015307	0.015572	0.015589	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000403	0.03461	0.035054	0.013	0.013
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000217	0.026597	0.026836	0.009	0.009
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000453	0.054066	0.054563	0.009	0.009
Smoking during pregnancy	0.000132	0.147096	0.147241	0.001	0.001
Passive smoking during pregnancy	0.000008249	0.006071	0.00608	0.001	0.001
Parity	0.00001645	0.019219	0.019237	0.001	0.001
Delivery mode	0.00000329	0.005631	0.005635	0.001	0.001
Preterm birth	0.000007981	0.026012	0.026021	0.000	0.000
Child's gender	0.000003656	0.005143	0.005147	0.001	0.001
Parental history of allergy	0.000883	0.005528	0.006498	0.176	0.154
Duration of any breastfeeding	0.000224	0.006292	0.006539	0.039	0.038
Antibiotic use before 12 months	0.003287	0.023251	0.026866	0.155	0.138
Food allergy					
Maternal_age_≤25 years	0.00001605	0.082572	0.082589	0.000	0.000
Maternal_age_ 26-30 years	0.000014182	0.032626	0.032641	0.000	0.000
Maternal_age_31-35 years	0.000007802	0.035884	0.035892	0.000	0.000
Maternal_edu_high school or below	0.000033612	0.208811	0.208848	0.000	0.000
Maternal_edu_vocational/technical college	0.000010217	0.057058	0.057069	0.000	0.000
Maternal_edu_undergraduate	0.000024566	0.042214	0.042241	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.00049	0.097828	0.098366	0.006	0.005
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.00014	0.083558	0.083712	0.002	0.002
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000135	0.134903	0.135052	0.001	0.001
Smoking during pregnancy	0.000072114	0.293057	0.293137	0.000	0.000
Passive smoking during pregnancy	0.000004396	0.012021	0.012026	0.000	0.000
Parity	0.000022026	0.042272	0.042296	0.001	0.001
Delivery mode	0.000003299	0.012935	0.012938	0.000	0.000
Preterm birth	0.000007712	0.131039	0.131048	0.000	0.000
Child's gender	0.000004136	0.010129	0.010133	0.000	0.000
Parental history of allergy	0.000944	0.010527	0.011566	0.099	0.091
Duration of any breastfeeding	0.000491	0.012757	0.013297	0.042	0.041
Antibiotic use before 12 months	0.00773	0.047949	0.056453	0.177	0.155

*FMI: range between 0-1, a large FMI (close to 0) indicates low variability between imputed data sets

Supplementary material S9 in Chapter 5: Baseline characteristics of included and not included participants of this study

Variables	Clinic measurement (N=4346)	Telephone call interview (N=2635)	*P*-value
Mother			
Age at delivery (y), mean (SD)	29.5 (3.3)	29.1 (3.4)	**<0.001**
Educational level,n (%)			**<0.001**
High school or below	286 (6.6)	303 (11.5)	
Vocational/technical college	1006 (23.2)	694 (26.3)	
Undergraduate	2508 (57.7)	1346 (51.1)	
Postgraduate	546 (12.5)	292 (11.1)	
Pre-pregnancy BMI, n (%)			0.280
<18.5 kg/m^2	1002 (23.6)	646 (25.2)	
18.5-23.9 kg/m^2	2825 (66.4)	1677 (65.6)	
24-27.9 kg/m^2	357 (8.4)	191 (7.5)	
≥28kg/m^2	70 (1.6)	44 (1.7)	
Parity, n (%)			**0.001**
Primiparous	3834 (88.2)	2251 (85.6)	
Multiparous	511 (11.8)	379 (14.4)	
Delivery mode, n (%)			0.056
Vaginal labor	2871 (66.1)	1678 (63.9)	
Cesarean delivery	1471 (33.9)	949 (36.1)	
Smoking during pregnancy, n (%)			0.576
Yes	19 (0.4)	14 (0.5)	
No	6389 (99.6)	3111 (99.5)	
Passive smoking during pregnancy, n (%)			0.250
Yes	1253 (28.9)	791 (30.2)	
No	3075 (71.1)	1824 (69.8)	
Child			
Child‘s gender, n (%)			0.936
Male	2280 (52.5)	1385 (52.6)	
Female	2066 (47.5)	1250 (47.4)	
Birth weight <2500g, n (%)			0.895
Yes	189 (4.4)	116 (4.4)	
No	4155 (95.6)	2510 (95.6)	
Preterm birth, n (%)			0.992
Yes	213 (4.9)	129 (4.9)	
No	4133 (95.1)	2506 (95.1)	
Duration of any breastfeeding, n (%)			**<0.001**
≤6 months	1163 (28.4)	906 (37.5)	
> 6 months	2931 (71.6)	1512 (62.5)	
Parental history of allergy, n (%)			**0.029**

Yes	1315 (33.2)	693 (30.5)	
No	2644 (66.8)	1577 (69.5)	
Antibiotic use before 12 months, n (%)			**0.002**
Yes	947 (27.7)	570 (31.9)	
No	2470 (72.3)	1215 (68.1)	

Supplementary material S10 in Chapter 6: The variance information between imputed data sets for outcomes at 1 year of age.

Variance Information					
Parameter	**Variance**			**Relative Increase in Variance**	**Fraction Missing Information (FMI)***
	Between	Within	Total		
Abdomen circumference					
Maternal_age_≤at years	0.00221	0.052899	0.05533	0.046	0.044
Maternal_age_ 26-30 years	0.001964	0.05283	0.05499	0.041	0.040
Maternal_age_31-35 years	0.011256	0.087838	0.100219	0.141	0.126
Maternal_edu_high school or below	0.001262	0.034785	0.036173	0.040	0.039
Maternal_edu_vocational/technical college	0.000341	0.027575	0.02795	0.014	0.013
Maternal_edu_undergraduate	0.002006	0.06049	0.062697	0.036	0.035
pre-pregnancy_BMI_<18.5 kg/m^2	0.007476	0.168916	0.17714	0.049	0.047
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.009814	0.195594	0.206389	0.055	0.053
pre-pregnancy_BMI_24-27.9 kg/m^2	0.006738	0.177189	0.184601	0.042	0.040
Parity	0.000594	0.029807	0.03046	0.022	0.022
Delivery mode	0.000409	0.012067	0.012517	0.037	0.036
Smoking during pregnancy	0.003351	0.464849	0.468536	0.008	0.008
Passive smoking during pregnancy	0.000368	0.012435	0.01284	0.033	0.032
Paternal_BMI_<18.5 kg/m^2	0.003156	0.039325	0.042797	0.088	0.082
Paternal_BMI_18.5-23.9 kg/m^2	0.004732	0.042796	0.048	0.122	0.111

Paternal_BMI_24-27.9 kg/m^2	0.042296	0.096341	0.142867	0.483	0.341
Child's gender	0.000292	0.010559	0.01088	0.030	0.030
Preterm birth	0.0016	0.058758	0.060518	0.030	0.029
Duration of any breastfeeding ⩽6 m	0.00252	0.014652	0.017423	0.189	0.164
Timing of complementary food introduction sets	0.017692	0.116286	0.135748	0.167	0.147
Timing of complementary food introduction 4-6 m	0.015104	0.14	0.156614	0.119	0.108
Upper arm circumferencea					
Maternal_age_≤25 years	0.000006855	0.004331	0.004339	0.002	0.002
Maternal_age_ 26-30 years	0.000003807	0.00433	0.004334	0.001	0.001
Maternal_age_31-35 years	0.00001668	0.007254	0.007272	0.003	0.003
Maternal_edu_high school or below	0.000003951	0.002907	0.002912	0.001	0.001
Maternal_edu_vocational/technical college	0.000000396	0.002311	0.002311	0.000	0.000
Maternal_edu_undergraduate	0.00000419	0.005016	0.005021	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.00061	0.013675	0.014346	0.049	0.047
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000822	0.015921	0.016825	0.057	0.054
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000542	0.014354	0.01495	0.041	0.040
Parity	0.000002579	0.002463	0.002465	0.001	0.001
Delivery mode	0.000002471	0.000996	0.000998	0.003	0.003
Smoking during pregnancy	0.000529	0.03679	0.037372	0.016	0.016
Passive smoking during pregnancy	0.000011731	0.001021	0.001034	0.013	0.013
Paternal_BMI_<18.5 kg/m^2	0.000397	0.003257	0.003693	0.134	0.121
Paternal_BMI_18.5-23.9 kg/m^2	0.000377	0.003542	0.003957	0.117	0.107

Paternal_BMI_24-27.9 kg/m^2	0.00113	0.008039	0.009282	0.155	0.137
Child's gender	0.000000616	0.000872	0.000873	0.001	0.001
Preterm birth	0.00000762	0.004869	0.004877	0.002	0.002
Duration of any breastfeeding	0.000059147	0.001216	0.001281	0.054	0.051
Timing of complementary food introduction 4-6	0.000008695	0.009652	0.009662	0.001	0.001
Timing of complementary food introduction 4-6 m	0.000023401	0.011593	0.011619	0.002	0.002
BMI z-score					
Maternal_age_≤25 years	0.000006982	0.003027	0.003034	0.003	0.003
Maternal_age_ 26-30 years	0.000007413	0.003021	0.003029	0.003	0.003
Maternal_age_31-35 years	0.000020498	0.005047	0.00507	0.004	0.004
Maternal_edu_high school or below	0.00000064	0.001997	0.001997	0.000	0.000
Maternal_edu_vocational/technical college	0.000000473	0.001582	0.001582	0.000	0.000
Maternal_edu_undergraduate	0.000003743	0.003463	0.003467	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000146	0.009658	0.009819	0.017	0.016
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000255	0.011195	0.011476	0.025	0.025
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000169	0.010132	0.010318	0.018	0.018
Parity	0.000006761	0.001707	0.001714	0.004	0.004
Delivery mode	0.000001978	0.000695	0.000697	0.003	0.003
Smoking during pregnancy	0.000514	0.026479	0.027044	0.021	0.021
Passive smoking during pregnancy	0.000007766	0.000715	0.000723	0.012	0.012
Paternal_BMI_<18.5 kg/m^2	0.000262	0.00226	0.002548	0.127	0.116
Paternal_BMI_18.5-23.9 kg/m^2	0.000371	0.002458	0.002866	0.166	0.146

Paternal_BMI_24-27.9 kg/m^2	0.000261	0.0056	0.005888	0.051	0.049
Child's gender	0.000000527	0.000607	0.000607	0.001	0.001
Preterm birth	0.000002315	0.003372	0.003374	0.001	0.001
Duration of any breastfeeding	0.000026885	0.000843	0.000873	0.035	0.034
Timing of complementary food introduction 4-6	0.000042882	0.00665	0.006697	0.007	0.007
Timing of complementary food introduction 4-6 m	0.000044204	0.008013	0.008062	0.006	0.006
Length-for-age z-score					
Maternal_age_≤25 years	0.000006756	0.002733	0.002741	0.003	0.003
Maternal_age_ 26-30 years	0.000007494	0.002724	0.002733	0.003	0.003
Maternal_age_31-35 years	0.000009532	0.00457	0.004581	0.002	0.002
Maternal_edu_high school or below	0.000002969	0.001811	0.001814	0.002	0.002
Maternal_edu_vocational/technical college	0.000002397	0.001431	0.001434	0.002	0.002
Maternal_edu_undergraduate	0.000010152	0.003143	0.003154	0.004	0.004
pre-pregnancy_BMI_<18.5 kg/m^2	0.000275	0.008809	0.009112	0.034	0.033
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000235	0.010194	0.010453	0.025	0.025
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000207	0.009231	0.009459	0.025	0.024
Maternal height	3.76E-08	6.28E-06	6.32E-06	0.007	0.007
Parity	0.000004618	0.001526	0.001531	0.003	0.003
Delivery mode	0.000001857	0.000631	0.000633	0.003	0.003
Smoking during pregnancy	0.000059167	0.024278	0.024343	0.003	0.003
Passive smoking during pregnancy	0.00000225	0.000642	0.000644	0.004	0.004
Paternal_BMI_<18.5 kg/m^2	0.00023	0.002049	0.002302	0.124	0.113

Paternal_BMI_18.5-23.9 kg/m^2	0.000351	0.002226	0.002612	0.173	0.152
Paternal_BMI_24-27.9 kg/m^2	0.000822	0.005025	0.00593	0.180	0.157
Paternal height	6.58E-08	5.32E-06	5.39E-06	0.014	0.013
Child's gender	0.000000987	0.000546	0.000547	0.002	0.002
Preterm birth	0.000016634	0.00303	0.003048	0.006	0.006
Duration of any breastfeeding ⩽6 m	0.000027001	0.000759	0.000789	0.039	0.038
Timing of complementary food introduction 4-6	0.00000843	0.005988	0.005998	0.002	0.002
Timing of complementary food introduction 4-6 m	0.000016539	0.007217	0.007235	0.003	0.003
Weight-for-age z-score					
Maternal_age_≤25 years	0.000012689	0.002882	0.002896	0.005	0.005
Maternal_age_ 26-30 years	0.000009276	0.002878	0.002888	0.004	0.004
Maternal_age_31-35 years	0.000011638	0.004786	0.004799	0.003	0.003
Maternal_edu_high school or below	0.00000312	0.001894	0.001898	0.002	0.002
Maternal_edu_vocational/technical college	0.000002196	0.001503	0.001505	0.002	0.002
Maternal_edu_undergraduate	0.000004137	0.003298	0.003303	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000349	0.009285	0.00967	0.041	0.040
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.00039	0.01074	0.011169	0.040	0.039
pre-pregnancy_BMI_24-27.9 kg/m^2	0.00044	0.00974	0.010224	0.050	0.048
Parity	0.000008835	0.001623	0.001633	0.006	0.006
Delivery mode	0.000001414	0.000658	0.000659	0.002	0.002
Smoking during pregnancy	0.000395	0.025188	0.025622	0.017	0.017
Passive smoking during pregnancy	0.000008695	0.000678	0.000687	0.014	0.014

Paternal_BMI_<18.5 kg/m^2	0.000247	0.002145	0.002417	0.127	0.115
Paternal_BMI_18.5-23.9 kg/m^2	0.000205	0.002337	0.002562	0.097	0.090
Paternal_BMI_24-27.9 kg/m^2	0.000625	0.005259	0.005947	0.131	0.118
Child's gender	0.000001239	0.000575	0.000577	0.002	0.002
Preterm birth	0.000005951	0.003202	0.003209	0.002	0.002
Duration of any breastfeeding	0.00004338	0.000799	0.000847	0.060	0.057
Timing of complementary food introduction 4-6	0.000014072	0.006341	0.006356	0.002	0.002
Timing of complementary food introduction 4-6 m	0.000020002	0.007634	0.007656	0.003	0.003
Weight-for-length z-score					
Maternal_age_≤25 years	0.000007191	0.002952	0.00296	0.003	0.003
Maternal_age_ 26-30 years	0.000009031	0.002943	0.002952	0.003	0.003
Maternal_age_31-35 years	0.000015895	0.004925	0.004942	0.004	0.004
Maternal_edu_high school or below	0.000003879	0.001953	0.001958	0.002	0.002
Maternal_edu_vocational/technical college	0.000001973	0.001543	0.001545	0.001	0.001
Maternal_edu_undergraduate	0.00000344	0.003396	0.0034	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000571	0.009358	0.009987	0.067	0.064
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000708	0.010847	0.011626	0.072	0.068
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000657	0.009821	0.010544	0.074	0.070
Maternal height	6.49286E-08	6.77E-06	6.85E-06	0.011	0.010
Parity	0.00000432	0.001661	0.001665	0.003	0.003
Delivery mode	0.000001224	0.000681	0.000683	0.002	0.002
Smoking during pregnancy	0.000494	0.025806	0.026349	0.021	0.021

Passive smoking during pregnancy	0.000010752	0.000695	0.000707	0.017	0.017
Paternal_BMI_<18.5 kg/m^2	0.000203	0.002228	0.002452	0.100	0.093
Paternal_BMI_18.5-23.9 kg/m^2	0.000256	0.002418	0.0027	0.117	0.107
Paternal_BMI_24-27.9 kg/m^2	0.000677	0.005381	0.006126	0.138	0.125
Paternal height	0.000000245	5.74E-06	6.01E-06	0.047	0.045
Child's gender	0.000001839	0.00059	0.000592	0.003	0.003
Preterm birth	0.00000354	0.003281	0.003285	0.001	0.001
Duration of any breastfeeding ⩽6 m	0.000019848	0.00082	0.000842	0.027	0.026
Timing of complementary food introduction 4-6	0.000007504	0.006485	0.006493	0.001	0.001
Timing of complementary food introduction 4-6 m	0.000011337	0.007812	0.007824	0.002	0.002

*FMI: range between 0-1, a large FMI (close to 0) indicates low variability between imputed data sets

Supplementary material S11 in Chapter 6: The variance information between imputed data sets for outcomes at 3 years of age

Variance Information					
Parameter	**Variance**			**Relative Increase in Variance**	**Fraction Missing Information (FMI)***
	Between	Within	Total		
Abdomen circumference					
Maternal_age_≤25 years	0.001698	0.098301	0.10017	0.019	0.019
Maternal_age_ 26-30 years	0.000438	0.098989	0.099471	0.005	0.005
Maternal_age_31-35 years	0.005645	0.171018	0.177227	0.036	0.035
Maternal_edu_high school or below	0.002101	0.064105	0.066416	0.036	0.035
Maternal_edu_vocational/technical college	0.002321	0.049204	0.051757	0.052	0.050
Maternal_edu_undergraduate	0.003663	0.121007	0.125037	0.033	0.032
pre-pregnancy_BMI_<18.5 kg/m^2	0.024832	0.320031	0.347347	0.085	0.080
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.025504	0.370539	0.398594	0.076	0.071
pre-pregnancy_BMI_24-27.9 kg/m^2	0.025874	0.335355	0.363817	0.085	0.079
Parity	0.00161	0.056344	0.058114	0.031	0.031
Delivery mode	0.000312	0.023186	0.023529	0.015	0.015
Smoking during pregnancy	0.222821	1.17815	1.423253	0.208	0.178
Passive smoking during pregnancy	0.00049	0.024277	0.024815	0.022	0.022
Paternal_BMI_<18.5 kg/m^2	0.003832	0.075303	0.079518	0.056	0.054
Paternal_BMI_18.5-23.9 kg/m^2	0.007523	0.081477	0.089752	0.102	0.094
Paternal_BMI_24-27.9 kg/m^2	0.024956	0.190672	0.218123	0.144	0.129

Child's gender	0.001091	0.019913	0.021114	0.060	0.058
Preterm birth	0.000451	0.110369	0.110865	0.004	0.004
Duration of any breastfeeding ≤6 m	0.002243	0.028334	0.030801	0.087	0.081
Timing of complementary food introduction≤3 m	0.002137	0.264837	0.267188	0.009	0.009
Timing of complementary food introduction 4-6 m	0.002823	0.312962	0.316068	0.010	0.010
Upper arm circumferencea					
Maternal_age_≤25 years	2.8078E-05	0.006227	0.006258	0.005	0.005
Maternal_age_ 26-30 years	2.2502E-05	0.006279	0.006304	0.004	0.004
Maternal_age_31-35 years	2.8716E-05	0.011076	0.011107	0.003	0.003
Maternal_edu_high school or below	1.8323E-05	0.004192	0.004212	0.005	0.005
Maternal_edu_vocational/technical college	0.00000912	0.003223	0.003234	0.003	0.003
Maternal_edu_undergraduate	2.7129E-05	0.007757	0.007786	0.004	0.004
pre-pregnancy_BMI_<18.5 kg/m^2	0.000295	0.020691	0.021016	0.016	0.016
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000511	0.023962	0.024525	0.023	0.023
pre-pregnancy_BMI_24-27.9 kg/m^2	0.00038	0.021689	0.022107	0.019	0.019
Parity	1.7314E-05	0.003566	0.003585	0.005	0.005
Delivery mode	1.0747E-05	0.001498	0.001509	0.008	0.008
Smoking during pregnancy	0.000104	0.069948	0.070063	0.002	0.002
Passive smoking during pregnancy	5.858E-06	0.001572	0.001579	0.004	0.004
Paternal_BMI_<18.5 kg/m^2	0.000833	0.004775	0.005691	0.192	0.166
Paternal_BMI_18.5-23.9 kg/m^2	0.00099	0.005168	0.006256	0.211	0.180
Paternal_BMI_24-27.9 kg/m^2	0.002034	0.01234	0.014578	0.181	0.158

Child's gender	5.841E-06	0.001286	0.001293	0.005	0.005
Preterm birth	6.417E-06	0.006842	0.006849	0.001	0.001
Duration of any breastfeeding	7.5362E-05	0.00182	0.001902	0.046	0.044
Timing of complementary food introduction≤3 m	4.5334E-05	0.017263	0.017312	0.003	0.003
Timing of complementary food introduction 4-6 m	0.000278	0.02036	0.020666	0.015	0.015
BMI z-score					
Maternal_age_≤25 years	1.2538E-05	0.004669	0.004683	0.003	0.003
Maternal_age_ 26-30 years	1.3828E-05	0.004709	0.004724	0.003	0.003
Maternal_age_31-35 years	2.4522E-05	0.008145	0.008172	0.003	0.003
Maternal_edu_high school or below	6.455E-06	0.003061	0.003068	0.002	0.002
Maternal_edu_vocational/technical college	4.786E-06	0.002348	0.002353	0.002	0.002
Maternal_edu_undergraduate	7.141E-06	0.00577	0.005778	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000335	0.015459	0.015827	0.024	0.023
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000327	0.017844	0.018204	0.020	0.020
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000388	0.016187	0.016613	0.026	0.026
Parity	1.5894E-05	0.002686	0.002704	0.007	0.006
Delivery mode	3.938E-06	0.001108	0.001112	0.004	0.004
Smoking during pregnancy	0.001324	0.054817	0.056273	0.027	0.026
Passive smoking during pregnancy	0.00001631	0.001155	0.001173	0.016	0.015
Paternal_BMI_<18.5 kg/m^2	0.00043	0.003522	0.003995	0.134	0.121
Paternal_BMI_18.5-23.9 kg/m^2	0.000601	0.003822	0.004483	0.173	0.152
Paternal_BMI_24-27.9 kg/m^2	0.001442	0.008906	0.010491	0.178	0.155

Child's gender	3.398E-06	0.000948	0.000951	0.004	0.004
Preterm birth	1.3307E-05	0.005268	0.005283	0.003	0.003
Duration of any breastfeeding	6.4411E-05	0.001349	0.00142	0.053	0.050
Timing of complementary food introduction≤3 m	0.000143	0.012782	0.012939	0.012	0.012
Timing of complementary food introduction 4-6 m	0.000117	0.015066	0.015194	0.009	0.008
Length-for-age z-score					
Maternal_age_≤25 years	1.1465E-05	0.003905	0.003917	0.003	0.003
Maternal_age_ 26-30 years	7.442E-06	0.003931	0.003939	0.002	0.002
Maternal_age_31-35 years	1.9817E-05	0.006836	0.006858	0.003	0.003
Maternal_edu_high school or below	8.173E-06	0.002558	0.002567	0.004	0.004
Maternal_edu_vocational/technical college	7.249E-06	0.001958	0.001966	0.004	0.004
Maternal_edu_undergraduate	1.4644E-05	0.004822	0.004838	0.003	0.003
pre-pregnancy_BMI_<18.5 kg/m^2	9.9047E-05	0.012765	0.012874	0.009	0.008
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000192	0.014751	0.014963	0.014	0.014
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000149	0.013379	0.013543	0.012	0.012
Maternal height	8.45E-08	8.971E-06	9.064E-06	0.010	0.010
Parity	7.124E-06	0.002227	0.002234	0.004	0.004
Delivery mode	3.368E-06	0.000931	0.000934	0.004	0.004
Smoking during pregnancy	0.000288	0.047055	0.047371	0.007	0.007
Passive smoking during pregnancy	0.00001334	0.00096	0.000975	0.015	0.015
Paternal_BMI_<18.5 kg/m^2	0.000414	0.002919	0.003374	0.156	0.138
Paternal_BMI_18.5-23.9 kg/m^2	0.000452	0.003165	0.003663	0.157	0.139

Paternal_BMI_24-27.9 kg/m^2	0.000885	0.007443	0.008417	0.131	0.118
Paternal height	2.88E-07	6.879E-06	7.196E-06	0.046	0.044
Child's gender	5.34E-07	0.000788	0.000788	0.001	0.001
Preterm birth	0.00000318	0.004409	0.004413	0.001	0.001
Duration of any breastfeeding ≤6 m	4.6209E-05	0.001123	0.001173	0.045	0.044
Timing of complementary food introduction≤3 m	6.1773E-05	0.010737	0.010805	0.006	0.006
Timing of complementary food introduction 4-6 m	9.7678E-05	0.012652	0.012759	0.008	0.008
Weight-for-age z-score					
Maternal_age_≤25 years	8.364E-06	0.004244	0.004253	0.002	0.002
Maternal_age_ 26-30 years	6.572E-06	0.004274	0.004281	0.002	0.002
Maternal_age_31-35 years	1.1809E-05	0.007382	0.007395	0.002	0.002
Maternal_edu_high school or below	1.4486E-05	0.002769	0.002785	0.006	0.006
Maternal_edu_vocational/technical college	6.188E-06	0.002125	0.002132	0.003	0.003
Maternal_edu_undergraduate	0.00003746	0.005226	0.005268	0.008	0.008
pre-pregnancy_BMI_<18.5 kg/m^2	0.000263	0.014043	0.014331	0.021	0.020
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000404	0.016219	0.016664	0.027	0.027
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000218	0.014701	0.014941	0.016	0.016
Parity	1.8636E-05	0.002434	0.002455	0.008	0.008
Delivery mode	3.815E-06	0.001001	0.001005	0.004	0.004
Smoking during pregnancy	0.000815	0.0492	0.050097	0.018	0.018
Passive smoking during pregnancy	0.00000721	0.001048	0.001056	0.008	0.008
Paternal_BMI_<18.5 kg/m^2	0.000801	0.00322	0.004101	0.274	0.223

Paternal_BMI_18.5-23.9 kg/m^2	0.00074	0.003486	0.0043	0.234	0.196
Paternal_BMI_24-27.9 kg/m^2	0.001466	0.008214	0.009826	0.196	0.169
Child's gender	2.729E-06	0.00086	0.000863	0.003	0.003
Preterm birth	2.8124E-05	0.004765	0.004796	0.006	0.006
Duration of any breastfeeding	4.9129E-05	0.001224	0.001278	0.044	0.043
Timing of complementary food introduction≤3 m	6.7555E-05	0.011495	0.011569	0.006	0.006
Timing of complementary food introduction 4-6 m	6.5674E-05	0.013575	0.013647	0.005	0.005
Weight-for-length z-score					
Maternal_age_≤25 years	1.3969E-05	0.004516	0.004531	0.003	0.003
Maternal_age_ 26-30 years	1.0935E-05	0.004547	0.004559	0.003	0.003
Maternal_age_31-35 years	3.1465E-05	0.007878	0.007912	0.004	0.004
Maternal_edu_high school or below	4.849E-06	0.002954	0.002959	0.002	0.002
Maternal_edu_vocational/technical college	2.788E-06	0.002256	0.002259	0.001	0.001
Maternal_edu_undergraduate	6.713E-06	0.005539	0.005546	0.001	0.001
pre-pregnancy_BMI_<18.5 kg/m^2	0.000467	0.014844	0.015357	0.035	0.034
pre-pregnancy_BMI_18.5-23.9 kg/m^2	0.000537	0.017141	0.017732	0.034	0.034
pre-pregnancy_BMI_24-27.9 kg/m^2	0.000503	0.015539	0.016092	0.036	0.035
Maternal height	9.35E-08	1.0369E-05	1.0472E-05	0.010	0.010
Parity	8.802E-06	0.002589	0.002599	0.004	0.004
Delivery mode	4.652E-06	0.001079	0.001084	0.005	0.005
Smoking during pregnancy	0.001999	0.053062	0.055261	0.041	0.040
Passive smoking during pregnancy	9.768E-06	0.00111	0.00112	0.010	0.010

Paternal_BMI_<18.5 kg/m^2	0.000348	0.003373	0.003755	0.113	0.104
Paternal_BMI_18.5-23.9 kg/m^2	0.000426	0.003658	0.004126	0.128	0.116
Paternal_BMI_24-27.9 kg/m^2	0.000738	0.008612	0.009423	0.094	0.088
Paternal height	1.63E-07	7.937E-06	8.117E-06	0.023	0.022
Child's gender	2.191E-06	0.00091	0.000912	0.003	0.003
Preterm birth	8.123E-06	0.005057	0.005066	0.002	0.002
Duration of any breastfeeding ≤6 m	0.00004924	0.001298	0.001352	0.042	0.040
Timing of complementary food introduction≤3 m	7.2826E-05	0.012334	0.012415	0.006	0.006
Timing of complementary food introduction 4-6 m	0.000157	0.014541	0.014714	0.012	0.012

*FMI: range between 0-1, a large FMI (close to 0) indicates low variability between imputed data sets

Supplementary material S12 in Chapter 6: Baseline characteristics of participants with and without anthropometry information at 1 and 3 years of age

Variables	With Anthropometry Data at 1 year of age（N=6279）	No Anthropometry Data at 1 year of age（N=3146）	With Anthropometry Data at 3 years of age（N=3898）	No Anthropometry Data at 3 years of age（N=3101）
Mother				
Age at delivery (y), mean (SD)	29.4 (3.4)	29.1 (3.4)	29.5 (3.3)	29.2 (3.4)
Educational level,n (%)				
High school or below	492(7.8)	366 (11.6)	260(6.7)	323(10.7)
Vocational/technical college	1555(24.8)	804 (25.6)	906(23.2)	776(25.7)
Undergraduate	3500(55.7)	1587 (50.4)	2248(57.7)	1573(52.2)
Postgraduate	732(11.7)	389 (12.4)	484(12.4)	344(11.4)
Pre-pregnancy BMI, n (%)				
<18.5 kg/m^2	1459(23.8)	834 (27.4)	897(23.5)	733(25.0)
18.5-23.9 kg/m^2	4061(66.3)	1921 (63.2)	2544(66.6)	1917(65.5)
24-27.9 kg/m^2	509(8.3)	236 (7.8)	317(8.3)	224(7.7)
≥28kg/m^2	98(1.6)	49 (1.6)	61(1.6)	53(1.8)
Parity, n (%)				
Primiparous	5567(88.7)	2582 (82.2)	3472(89.1)	2553(84.8)
Multiparous	709(11.3)	560 (17.8)	425(10.9)	458(15.2)
Delivery mode, n (%)				
Vaginal labor	4064(64.8)	2040 (65.0)	2575(66.1)	1924(64.0)
Cesarean delivery	2208(35.2)	1098 (35.0)	1319(33.9)	1084(36.0)
Smoking during pregnancy, n (%)	35(0.6)	9 (0.3)	16(0.4)	17(0.6)
Passive smoking during pregnancy, n (%)	1933(31.0)	860 (27.6)	1125(29.0)	904(30.2)

Child				
Child's gender, n (%)				
Male	3302(52.6)	1598 (50.8)	2041(52.4)	1586(52.6)
Female	2977(47.4)	1548 (49.2)	1857(47.6)	1430(47.4)
Birth weight <2500g, n (%)	243(3.9)	159 (5.1)	170(4.4)	135(4.5)
Preterm birth, n (%)	296(4.7)	150 (4.8)	184(4.7)	156(5.2)
Duration of any breastfeeding, n (%)				
≤6 months	1551(25.5)	905 (29.7)	918(24.1)	784(26.7)
> 6 months	4541(74.5)	2146 (70.3)	2885(75.9)	2154(73.3)
Parental history of allergy, n (%)	1758(31.1)	877 (30.5)	1169(33.2)	818(31.0)
Timing of any infant formulas introduction, months n (%)				
≤3 m	5152(82.1)	2169 (71.8)	3222(82.7)	2238(78.3)
4-6 m	568(9.1)	427 (14.1)	358(9.2)	321(11.2)
> 6 m	559(8.9)	426 (14.1)	318(8.2)	298(10.4)

BMI: Body Mass Index

Supplementary material S13 in Chapter 6: The association between timing of formula introduction and complementary food introduction

Complementary foods introduction	Time of starting formula feeding (N=6279)			
	≤3 m	4-6 m	> 6 m	**P value**
Introduction of rice/cereal				**<0.001**
≤3 m	359 (7.0)	20 (3.5)	13 (2.3)	
4-6 m	4583 (89.1)	527 (92.8)	508 (91.1)	
> 6 m	202 (3.9)	21 (3.7)	37 (6.6)	
Introduction of vegetables				**0.003**
≤3 m	50 (1.0)	5 (0.9)	2 (0.3)	
4-6 m	3196 (63.2)	343 (61.0)	310 (55.8)	
> 6 m	1811 (35.8)	214 (38.1)	244 (43.9)	
Introduction of fruits				**0.025**
≤3 m	124 (2.4)	11 (1.9)	10 (1.8)	
4-6 m	3887 (75.9)	438 (77.7)	396 (71.0)	
> 6 m	1108 (21.7)	115 (20.4)	152 (27.2)	
Introduction of meat				**<0.001**
≤3 m	16 (0.3)	1 (0.2)	4 (0.7)	
4-6 m	1410 (28.9)	149 (27.4)	108 (19.7)	
> 6 m	3448 (70.7)	394 (72.4)	436 (79.6)	
Introduction of offals				0.216
≤3 m	14 (0.4)	0 (0)	2 (0.4)	
4-6 m	719 (19.4)	77 (18.1)	73 (16.2)	
> 6 m	2978 (80.3)	348 (81.9)	376 (83.4)	
Introduction of fish				**<0.001**
≤3 m	21 (0.4)	3 (0.6)	2 (0.4)	
4-6 m	1206 (25.1)	113 (21.1)	84 (15.7)	
> 6 m	3576 (74.4)	420 (78.4)	448 (83.9)	
Introduction of other seafood				0.330
≤3 m	14 (0.7)	4 (1.8)	2 (0.7)	
4-6 m	174 (8.4)	23 (10.3)	21 (7.6)	
> 6 m	1872 (90.9)	196 (87.9)	255 (91.7)	
Introduction of egg yolk				**0.001**
≤3 m	86 (1.7)	7 (1.3)	2 (0.4)	
4-6 m	3259 (65.0)	377 (67.8)	323 (59.4)	
> 6 m	1668 (33.3)	172 (30.9)	219 (40.2)	
Introduction of egg white				
≤3 m	21 (0.7)	3 (0.8)	2 (0.5)	0.248
4-6 m	400 (12.8)	47 (12.7)	32 (8.7)	
> 6 m	2692 (86.5)	320 (86.5)	333 (90.8)	

Supplementary material S14 in Chapter 6: Modification effects of timing of complementary food introduction and breastfeeding duration on associations of formula introduction with overweight at 1 year and 3 years of age.

	Modification effects*	P-value
Overweight at 1 year of age		
	Complementary foods introduction * Infant formula introduction	0.198
	Cereal introduction* Infant formula introduction	0.352
	Vegetable introduction * Infant formula introduction	1.000
	Fruit introduction * Infant formula introduction	0.600
	Meat introduction * Infant formula introduction	0.972
	Offal introduction * Infant formula introduction	0.542
	Fish introduction * Infant formula introduction	0.240
	Other seafood introduction * Infant formula introduction	0.853
	Egg yolk introduction * Infant formula introduction	0.982
	Egg white introduction * Infant formula introduction	0.969
	Breastfeeding duration * Infant formula introduction	0.201
Overweight at 3 years of age		
	Complementary foods introduction * Infant formula introduction	0.089
	Cereal introduction* Infant formula introduction	0.801
	Vegetable introduction * Infant formula introduction	0.539
	Fruit introduction * Infant formula introduction	0.264
	Meat introduction * Infant formula introduction	0.777
	Offal introduction * Infant formula introduction	0.649
	Fish introduction * Infant formula introduction	0.844
	Other seafood introduction * Infant formula introduction	0.896
	Egg yolk introduction * Infant formula introduction	0.288
	Egg white introduction * Infant formula introduction	0.300
	Breastfeeding duration * Infant formula introduction	0.271
Changes from 1 to 3 years of age		
	Early overweight	
	Complementary foods introduction * Infant formula introduction	0.465
	Cereal introduction* Infant formula introduction	0.669
	Vegetable introduction * Infant formula introduction	0.862
	Fruit introduction * Infant formula introduction	0.998
	Meat introduction * Infant formula introduction	0.796
	Offal introduction * Infant formula introduction	0.743
	Fish introduction * Infant formula introduction	**0.005**
	Other seafood introduction * Infant formula introduction	0.850
	Egg yolk introduction * Infant formula introduction	1.000
	Egg white introduction * Infant formula introduction	0.329

Breastfeeding duration * Infant formula introduction	0.781
Later overweight	
Complementary foods introduction * Infant formula introduction	0.933
Cereal introduction* Infant formula introduction	0.996
Vegetable introduction * Infant formula introduction	0.961
Fruit introduction * Infant formula introduction	0.403
Meat introduction * Infant formula introduction	0.548
Offal introduction * Infant formula introduction	0.606
Fish introduction * Infant formula introduction	0.606
Other seafood introduction * Infant formula introduction	0.709
Egg yolk introduction * Infant formula introduction	0.318
Egg white introduction * Infant formula introduction	0.088
Breastfeeding duration * Infant formula introduction	0.924
Persistent overweight	
Complementary foods introduction * Infant formula introduction	0.154
Cereal introduction* Infant formula introduction	0.165
Vegetable introduction * Infant formula introduction	0.985
Fruit introduction * Infant formula introduction	0.746
Meat introduction * Infant formula introduction	0.998
Offal introduction * Infant formula introduction	0.992
Fish introduction * Infant formula introduction	0.984
Other seafood introduction * Infant formula introduction	0.949
Egg yolk introduction * Infant formula introduction	0.942
Egg white introduction * Infant formula introduction	0.999
Breastfeeding duration * Infant formula introduction	0.529

Adjusted for maternal age at delivery, maternal education, maternal pre-pregnancy BMI and paternal BMI, maternal smoking during pregnancy, passive smoking during pregnancy, preterm birth, parity, mode of delivery, infant sex, birth weight and the duration of breastfeeding