FOCUS

Despite the large literature on the effect of early diet in infancy and young childhood on health outcomes in childhood/adulthood, little evidence is available on the strength of the relationship between the timing of introduction of complementary food and the risk of disorders in later life

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Timing of Introduction of Complementary Food: Short- and Long-Term Health Consequences

by Hildegard Przyrembel

Key insights

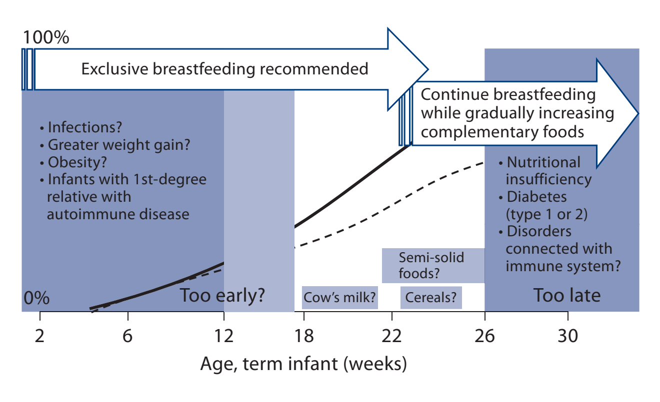
Although new foods in the first year of life are intended to support ongoing breast- or formula feeding, this is not always the case. In this article, an outline is given of how timing and nutritive content of such foods can have direct or later health consequences, based mostly on observational studies reporting the age at which complementary foods are introduced, regardless of whether the infant was breast- or formula fed.

Current knowledge

Studies demonstrate that the introduction of complementary food before the age of 4 months is inversely related to the level of maternal education, maternal age, socioeconomic status, maternal smoking, duration of breastfeeding and information on health care; these factors alone may have an impact on health consequences in later life. Both too early (<12 weeks) and too late introduction (>26 weeks) can have undesirable health consequences. Notably, complementary food may ameliorate the short-term consequences of stunting and infection rates, particularly in infants not receiving sufficient nutritive content from breast milk or formula. Current infant feeding patterns are too complex to find anything more than 'associational' relationships to possible long-term consequences.

Practical implications

In practice, complementary food should 'complement' breastfeeding when nutritionally needed and when the infant is ready for it.



Complexity and challenges in understanding the strength of relationship/causality between timing and outcomes. Too early or too late introduction can have adverse health consequences/bear an increased risk of disease: theoretical 'window' (unshaded area) and current feeding practices (curves; shape and percentages are approximate). Dotted curve = Formula feeding (may be fortified/supplemented); solid curve = liquids other than breast milk or formula (see text for details).

Recommended reading

EFSA Panel on Dietetic Products, Nutrition and Allergy (NDA): Scientific Opinion on the appropriate age for introduction of complementary feeding of infants. EFSA J 2009;7:1423–1460.

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Timing of Introduction of Complementary Food: Short- and Long-Term Health Consequences

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Key Messages

- Complementary food should 'complement' breastfeeding when nutritionally needed and when the infant is ready for it.
- Too early (before 12 weeks of age) and too late introduction (beyond 26 weeks) can have undesirable health consequences.
- Continuation of breastfeeding after the introduction of complementary food is beneficial.

Key Words

Breastfeeding · Complementary food · Formula feeding · Growth · Infectious disease

Abstract

Complementary food is needed when breast milk (or infant formula) alone is no longer sufficient for both nutritional and developmental reasons. The timing of its introduction, therefore, is an individual decision, although 6 months of exclusive breastfeeding can be recommended for most healthy term infants. The new foods are intended to 'complement' ongoing breastfeeding with those dietary items whose intake has become marginal or insufficient. Both breastfeeding and complementary feeding can have direct or later consequences on health. The evaluation of consequences of both early and late introduction of complementary food can neither disregard the effect of breastfeeding compared to formula feeding nor the composition or quality of the complementary food. Possible short-term health effects concern growth velocity and infections, and possible long-term effects may relate to atopic diseases, type 1 and 2 diabetes, obesity and neuromuscular development. On the basis of the currently available evidence, it is impossible to exactly determine the age when risks related to the start of complementary feeding are lowest or highest for most of these effects, with the possible exception of infections and early growth velocity. The present knowledge on undesirable health effects, however, is mainly based on observational studies, and although some mechanisms have been proposed, further prospective studies have to clarify these unsolved issues. Even less evidence on the consequences of the timing of complementary food introduction is available for formula-fed infants.

Introduction

A discussion of the consequences of the timing of the introduction of complementary food into the diet of infants on their health should neither be misunderstood as a discussion of the 'optimal' or desirable duration of breastfeeding nor as an assessment of the evidence for an appropriate age for the introduction of complementary feeding, both have been done already: the former in sys-

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tematic reviews [1, 2] with subsequent recommendations for a desirable length of exclusive (6 and 4–6 months) and partial breastfeeding (up to 2 years) [3, 4], and the latter in several reviews [5–7] concluding that some infants may need complementary food before the age of 6 months, preferably in addition to breastfeeding.

This article only considers the available studies on the health effects of age at which complementary food has been introduced regardless of breastfeeding or formula feeding. Such studies are scarce and are mostly observational; furthermore, these studies have often been performed retrospectively and, with a few exceptions, for short follow-up periods, i.e. only into early childhood.

In this article, complementary food is defined as any food, solid or (semi-) liquid, besides breast milk or its substitutes, i.e. infant (or follow-on) formula. This definition of complementary food was chosen because not all infants are breastfed or are only breastfed for short periods [8]. This is different from the World Health Organization (WHO) definition [9]: any food or liquid given along with breast milk. Nevertheless, it has been shown that the introduction of complementary food before the age of 4 months is inversely related to the level of maternal education, maternal age, socioeconomic status, maternal smoking, duration of breastfeeding and information on health care [5, 10–12], and these factors by themselves may have an impact on health consequences in later life. When such consequences are assessed, the nature and composition of the complementary food cannot be disregarded, because this varies in different regions of the world due to tradition, food availability and socioeconomic status of the parents. Moreover, the pattern of introduction of other food than human milk (or formula), as shown in figure 1 [adapted from ref. 13], is so complex that it is impossible to find meaningful associations with health consequences for each food item separately. Furthermore, each pattern may be associated with health consequences by itself: this should be investigated in more detail in the future. In low- and middle-income countries, infants are at the greatest risk of malnutrition and stunting during the period when breast milk is complemented or replaced by other food [14].

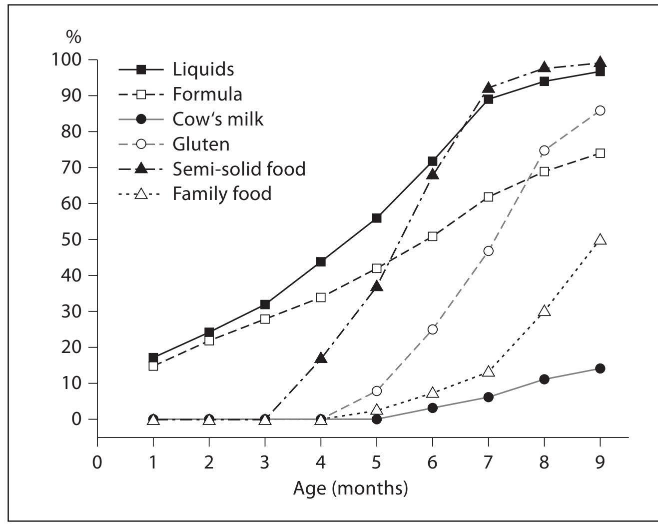

Fig. 1. Making sense of complex feeding practices. Prospective birth cohort study throughout Bavaria, Germany: cumulative percentage of consumption of other foods than human milk in 3,092 infants aged 1–9 months [modified from ref. 13]. Observed differences in growth and infection rates from feeding practice patterns or interventions should be further investigated.

Nutritional Inadequacy of Prolonged Exclusive Breastfeeding

The time span that exclusive breastfeeding is adequate to meet the infants' requirements for proteins, most vitamins and essential minerals has been found to be 6 months in the case of healthy term infants of well-nourished mothers [15, 16].

There are few data on health effects of exclusive breastfeeding prolonged beyond the first 6 months. In one prospective longitudinal study on 193 healthy term infants born to non-smoking mothers, 116 were exclusively breastfed beyond 6 months of life (7 infants for >9 months). Length velocity lagged slightly but progressively behind, and the weight for length was higher for infants exclusively breastfed more than 6 months compared to infants receiving both breast milk and complementary food (6–9 months). This may indicate stunting related to insufficient intake of energy and some nutrients [17]. Both serum iron and serum ferritin were significantly lower in infants exclusively breastfed beyond 6 months than in weaned infants [18].

The iron, zinc and vitamin D requirements of young infants cannot be provided by human milk alone. There is a higher risk of iron deficiency in infants exclusively breastfed for 6 months compared to infants exclusively breastfed for 3–4 months [2]. The risk for iron deficiency anemia at 6 months of age is increased by male sex, birth weight 2,500–2,999 g and weight gain above the reference value since birth [19]. Iron deficiency anemia is a risk factor for long-term adverse effects on motor, mental and social development [20, 21]. The risk of zinc deficiency was found to be increased after 6 months of exclusive breastfeeding, and zinc deficiency may contribute to a deceleration in growth of some fully breastfed infants [22, 23]. Rickets can be a consequence of prolonged breastfeeding without vitamin D supplements and has been observed in 1 of the 3 infants exclusively breastfed up to the age of 9 months who participated in Clara Davis' 1928 historical experiment on nutritional adequacy of self-selected complementary food in late infancy [24]. However, vitamin D insufficiency of human milk should be compensated by supplements and not by the early introduction of complementary food.

Developmental Aspects

The initiation of feeding food with a spoon or cup involves a number of important changes, including oral motor development, new tastes, new textures and new interaction between the infant and the caregiver. This occurs in parallel to greater stability and strength of the trunk, shoulder and neck musculature, which allows the infant to sit up and control his head position [25]. Some authors suggest that there is a critical window for introducing lumpy solid food into an infant's diet and that introduction after the age of 10 months becomes more difficult [26], particularly in infants who had been tube fed or only fed purees throughout the first year of life [27].

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Food Acceptance and Feeding Problems

Early exposure to a variety of flavors with complementary food in addition to the flavors provided by breast milk has a positive effect on the acceptance of new food [28]. The effect of age at the introduction of lumpy food on subsequent feeding difficulties was assessed in the large cohort of the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC). An introduction later than 9 months of age resulted in a greater incidence of feeding problems at 15 months [29] and in a dislike of fruit and vegetables and being more choosy with food at 7 years of age compared to the group that had been introduced to lumpy food between 6 and 9 months. An introduction below the age of 6 months had no detrimental effects and, on the contrary, increased the likelihood of consumption of more varied vegetables more often [30].

Growth (Weight Gain)

Rapid weight gain during the first months of life may have negative implications on risk markers of other noncommunicable diseases in later life (i.e. high blood pressure, obesity, non-insulin-dependent diabetes or coronary heart disease), but no associations with growth during the period from 6 to 12 months have been found [7, 31]. Compared to formula-fed infants, breastfed infants gain weight more rapidly during the first 2 months and more slowly thereafter, i.e. between 3 and 12 months [32, 33].

This observation has been proposed to be the consequence of the higher protein content of most infant formulae than of human milk, but the evidence from both observational and interventional studies is inconsistent for the first months. A lower protein intake in infancy was found to be associated with lower linear growth during the first 2 years of life and in children and adolescents [34 and references therein]. The introduction of complementary food may lead to an increase in the total protein intake, but this is not necessarily the case and depends on the food selected. The composition of the diet of infants early in life may have long-lasting implications on body fat, for example, but this does not imply an effect of the timing of complementary food introduction. In the WHO Multicenter Growth Study [35], the prevalence of consumption of various food groups, i.e. cereals, legumes and nuts, tubers, milk/milk products, meat (fish), eggs, vitamin A-rich and other fruits and vegetables, fat/oil, juices, sweet beverages and soups, at different ages up to 24 months in the 903 children participating is also revealing: cereals were most frequently part of the first complementary food, followed by dairy products, whilst meat, poultry and fish, which are good protein sources, were introduced relatively late, and only more than half of the infants received them between 9 and 12 months of age. Total breastfeeding duration was 14.3 ± 7.9 months and mean age at the introduction of complementary [(semi)solid] food was 5.4 ± 0.7 months (mean ± SD) [35]. Notably, the anthropometric data of this growth study group form the basis of the WHO growth reference standard [36].

The available studies [9, 37–44] that provide data on the effect of age at the introduction of complementary food on growth are listed in table 1. The demonstration

Table 1. Effect of age at the introduction of complementary food on growth

Setting/authors	Study description	Outcome	Comments
Dundee/ Forsyth et al. [37], 1993 Wilson et al. [38], 1998	prospective, observational, longitudinal cohort study 671 term infants 455 at the 2-year follow-up 545 at the 7.3-year follow-up	2 years: solid food <12 vs. >12 weeks higher weight in first half year of life ($p < 0.01$) but not at 52 and 104 weeks 7 years: solid food <15 vs. >15 weeks higher weight ($p < 0.025$) and higher percent body fat (skinfold thickness and bioelectrical impedance; $p < 0.01$)	two possible interpretations: – early feeding programs for late manifestation of effects on weight and body fat – post-hoc analysis with statistical manipulation of data
Honduras/ Cohen et al. [39], 1994 Cohen et al. [40], 1995	randomized intervention study 152 breastfed AGA term infants 16 weeks old – continue exclusive BF – continue BF and add CF at 16–26 weeks, follow-up to 52 weeks	no difference in weight, length and head circumference changes between groups	no advantage or disadvantage for growth of breastfed AGA infants for CF at 16–26 weeks
Honduras/ Dewey et al. [41], 1999	randomized intervention study 128 breastfed SGA term infants 16 weeks old – continue exclusive BF – continue BF and add CF at 16–26 weeks, follow-up to 52 weeks	despite higher increase in energy intake in the BF/CF group, there was no difference in weight, length, head circumference changes between groups and similar weight-for-age and length-for-age z-scores until 52 weeks	no advantage or disadvantage for growth of breastfed SGA infants for CF at 16–26 weeks
WHO Multinational Study of Breastfeeding and Lactational Amenorrhea/ WHO [9], 2002	observational, longitudinal study 1,252 term infants from urban sites in Sweden, Australia, China, Chile, India predominantly breastfed ≥16 weeks	length and weight smaller at 1–16 weeks in those with CF <17 vs. at 17–24 weeks ($p < 0.002$ and $p < 0.001$) no significant difference in length and weight between CF at 17–24 and 25–32 weeks absolute differences in length and weight velocities (0.2 mm/week and 7 g/week) between <17 and >17 weeks were small	reverse causality, i.e. earlier introduction of CF in slow-growing infants? 'too small to be likely of biological significance'
Morgan et al. [42], 2004	evaluation of data from >1,600 infants (AGA/SGA term and preterm) participating in 5 randomized trials between 1993 and 1997 comparison: solid food <12 and >12 weeks, follow-up to 18 months for term and to 9 months for preterm infants	term infants weaned <12 weeks were heavier at 12 weeks of age than infants weaned >12 weeks their growth velocity at 12–78 weeks was lower than in infants weaned >12 weeks no significant difference in size between groups at 18 and 9 months, respectively	reverse causality, i.e. earlier introduction of CF in fast-growing infants? early feeding programming for late manifestation of effects on weight and body fat cannot be excluded
Danish National Birth Cohort/ Baker et al. [43], 2004	prospective observational study 3,768 term infants	CF <16 weeks compared to ≥16 weeks: higher weight gain until 1 year but only when associated with BF <20 weeks	infant weight gain is associated with other maternal and infant factors besides CF timing
Mehta et al. [44], 1998	prospective randomized intervention 165 formula-fed infants age <3 months solid food at 3–12 and 6–12 months	anthropometry and body composition (by DXA) at 3, 6 and 12 months showed no difference between early and late introduction of CF no difference in energy intake	no growth difference at 52 weeks associated with early (≤12 weeks) or late (≥26 weeks) CF introduction

AGA = Appropriate for gestational age; BF = breastfeeding; CF = complementary feeding; SGA = small for gestational age; DXA = dual-emission X-ray absorptiometry.

of an independent effect of the timing of the introduction of complementary feeding on growth (and other health outcomes) should include adjustment for factors which might influence growth, which is seldom done. Body weight was found to be positively associated with maternal height, birth weight and male sex from 8 to 104 weeks of age [37].

In developed countries, age at the introduction of complementary food does not seem to have a significant impact on body weight during infancy and in the second year of life either in breastfed or formula-fed infants; in developing countries, however, it may prevent growth faltering related to the transition of exclusive breastfeeding to mixed feeding, provided that breastfeeding is continued and hygiene and composition of the complementary food are adequate. On the contrary, Peruvian infants breastfed >12 months whose complementary food was deficient both in amount and nutrient density showed growth faltering in the second half of the first year of life when compared to US infants of similar breastfeeding duration [45]. According to one study in 94 white US infants, gender explained 10% of the variance in weight gain during the period from 2 to 8 months of life, and weight prior to 12 months predicted 54% of the variance of weight gain from 12 to 24 months of life, whilst the timing of supplementary feeding was not statistically associated [46]. However, due to the lack of longitudinal studies of longer duration, the long-term effects on body weight and composition of this temporary acceleration in weight gain during the first year of life, associated in some studies with the introduction of complementary food at ages <12 weeks, cannot be excluded.

Infection

Whilst breastfed infants have a lower risk for gastrointestinal and respiratory infections than formula-fed infants [47], with the effect depending on the duration and intensity of breastfeeding (≤3 vs. ≥6 months; exclusive vs. partial) [48–53], data on the effect of the timing of the introduction of complementary food on infectious disease incidence are scarce. The available studies and their results are summarized in table 2. In a population-based survey in the UK Millennium Cohort Study involving 15,890 healthy singleton term infants, exclusive breastfeeding compared to no breastfeeding protected against diarrhea and lower respiratory tract infection hospitalizations during the first 8 months of life. After breastfeeding cessation, the protective effect weakened immediately for respiratory tract infections and did not persist beyond 1 month for diarrhea [51]. The monthly risk for hospitalization was not significantly higher for those who received solid food than for those who did not, and the risk did not vary significantly according to the age of starting solid food [54], indicating that there is a protective effect of breastfeeding against infectious diseases but no effect related to age at the introduction of complementary feeding.

The impact of age at the introduction of complementary food is inconsistent with regard to the type of illness but also with regard to its occurrence. An introduction of complementary food before the age of 12–14 weeks (3 months) may increase the risk for gastrointestinal and respiratory tract infections, whilst an introduction at or after the age of 17 weeks (4 months) does not increase the risk.

Obesity

Obesity or the accumulation of excessive fat in the body in childhood has adverse consequences on health and is related to adult obesity, type 2 diabetes, hypertension, dyslipidemia, some cancer types and fatty liver disease, for example, in addition to psychosocial consequences [55]. A protective effect of breastfeeding against the risk of obesity has been demonstrated in a number of observational studies and meta-analyses/systematic reviews. Other studies did not find an effect of breastfeeding on obesity [56–58]. A 6.5-year follow-up study investigating cluster-randomized breastfeeding promotion also found no difference in the body mass index (BMI) between 3 and 6 months of exclusive breastfeeding [59]. These inconsistencies may be due to the parameters used to define obesity or overweight and the absence or presence of correction of the data for relevant confounders.

Prolonged breastfeeding may be associated with a later introduction of complementary food and vice versa. Several studies on the impact of age at the introduction of complementary food on the risk for obesity in childhood and adolescence found no effect [5, 60]. In addition, an intervention study with formula-fed infants who were introduced to complementary food either at 3–4 or 6 months found no differences between the groups in percentage body fat at 12 months [44].

The results of several longitudinal observational or cohort studies with follow-ups of 7–42 years indicate an inverse association between age at the introduction of complementary food and the risk of adiposity [38, 58, 61]. The risk of obesity from an early introduction of complementary food (i.e. <17 weeks) may differ for breastfed and

Table 2. Effect of age at the introduction of complementary food on infectious morbidity

Setting/authors	Compared ages at introduction weeks	Gastrointestinal disease	Observation period (age) weeks	Respiratory disease	Observation period (age) weeks	Effect of age at the introduction and duration of the effect
Dundee/ Forsyth et al. [37], 1983	<8 (n = 65) vs. >12 (n = 274) 8–12 (n = 332) vs. >12 (n = 274	no difference adjusted for maternal age, socioeconomic class formula-feeding	14–39	increased $p < 0.05$ persistent cough increased $p > 0.05$	14–26 14–39	positive effect of a later introduction (>12 weeks) on respiratory tract disease at age 14–39 weeks not persistent at age 40–104 weeks
Dundee/ Wilson et al. [38], 1998	<15 (n = 401) vs. >15 (n = 144)	no difference	0 to ≥310	adjusted for socioeconomic group, atopy in family, sex, wheeze 21 vs. 9.7% ($p < 0.01$)	0 to ≈ 6 years	positive effect of a later introduction (>15 weeks) on wheeze of unknown etiology at age 6 years
Honduras/ Cohen et al. [39], 1994	≤17 (n = 91) vs. ≥26 (n = 50)	no difference	17–26 26–52	no difference	17–26 26–52	no difference during and after intervention with complementary food
PROBIT Belarus/ Kramer et al. [48], 2003	>26 (n = 621) vs. <14 (n = 2,862)	adjusted incidence ratio 0.35 (95% CI 0.13–0.96) adjusted incidence ratio 0.90 (95% CI 0.46–1.78	14–26 26–52	not reported	0–52	protective effect of a late introduction in the first 6 months does not persist in the second half of the first year
Millennium Baby UK/ Wright et al. [52], 2004	<13 (n = 146) vs. >17 (n = 41)	diarrhea odds ratio 1.65 (95% CI 1.09–2.5) no difference	6–17 17–44	no difference	6–44	later age (>17 weeks) at introduction decreases risk for diarrhea, but the effect does not persist
Morgan et al. [42], 2004	≤12 (n = 715) vs. >12 (n = 428)	no difference	0–72	no difference	0–72	data from 5 prospective randomized dietary intervention studies did not demonstrate an effect of age at introduction
Millennium Cohort Study/ Quigley et al. [51], 2007 Quigley et al. [54], 2009	introduced ± BF vs. not introduced ± BF	monthly risk for hospitalization with diarrhea 1.14 (95% CI 0.76–1.70) no significant difference	0–32	monthly risk for hospitalization with lower respiratory tract infection 1.39 (95% CI 0.75–2.59) no significant difference	0–32	effect of BF but no effect of age at introduction

BF = Breastfeeding ; CI = confidence interval.

formula-fed infants according to a prospective cohort study with a follow-up of 3 years. In children who had been breastfed for at least 4 months, the timing of solid food introduction was not associated with the odds for obesity, whilst formula-fed children (never breastfed or stopped before the age of 4 months) had a 6-fold increased likelihood for obesity (odds ratio after adjustment for weight-for-age z-score 6.6; 95% confidence interval 2.3–6.9) [62]. Table 3 summarizes the relevant studies and their results.

Few studies have been done on the influence of composition or constituents of complementary food on the risk for adiposity, as the introduction of complementary food may mean an increase in protein intake. In the Dortmund Nutrition and Longitudinally Designed Study, a high protein intake at 6 months (about 12% of energy intake) was not associated with adiposity at age 7 years, yet, an association with adiposity was found for a high protein intake (about 14% of energy) at the age of 12 months and throughout the second year of life [63].

The weight gain rate in the first 6–24 months of life has been shown to be more strongly associated with fat mass than with fat-free mass during childhood and adolescence [64, 65]. A relationship between a higher weight-for-length z-score at birth and a greater change in weight-for-length z-score or BMI from birth to 6 months and 6–24 months with an increased risk of obesity at 3–4 years of age was found in two prospective cohort studies, but there was no effect of an introduction of complementary food before the age of 4 months [66, 67].

Overall, the evidence for an independent impact of age at the introduction of complementary food on the risk of obesity or overweight is insufficient. Some longitudinal observational studies suggest that an early, i.e. age <12–17 weeks, introduction of complementary food may increase the risk of overweight/obesity or body fat in child- and adulthood, compared to an introduction at age >17 weeks, and the risk may be smaller for breastfed than non-breastfed infants. Manifestation may be delayed to occur in childhood or even in adulthood only, which would argue for a lasting modification of factors regulating metabolism or the hormonal system. However, in the 30 years in which the studies have been performed, significant changes in infant feeding have occurred (lower protein content of infant formula, changes in breastfeeding duration and intensity in many countries, and changes in the composition and sequence of introduction of complementary food), all of which may be relevant factors by themselves for the risk of obesity.

Type 2 Diabetes

Breastfeeding protects against type 2 diabetes in later life according to a large review including >75,000 subjects [68]. Breastfed infants have lower insulin, glucose and insulin-like growth factor (IGF)-I levels than formula-fed infants early in life [68, 69] but have higher IGF-I levels and are taller in later life [70]; a negative correlation between IGF-I levels at 9 months and 17 years was demonstrated in Danish children [71]. It is presently not known when and why this change occurs and whether it is related to the time of introduction of complementary food, independent of the nature of that complementary food. It is conceivable that the observed changes in hormone levels influence the risk for type 2 diabetes later in life. From epidemiological studies, it is apparent that infants with a low birth weight followed by a rapid increase in BMI in childhood, as well as those who gain weight most rapidly in infancy or who are at the upper end of the BMI distribution, appear to be at an increased risk of impaired glucose tolerance and type 2 diabetes in adult life [31].

Coronary Heart Disease

There is no evidence that the risk for coronary heart disease is influenced by age at which complementary food is introduced. There is some evidence that the risk is modified by growth rates during certain periods in infancy and childhood. Low weight in infancy with a rapid BMI increase in early childhood was associated with the greatest risk [31].

Type 1 Diabetes

Type 1 diabetes is the consequence of a destructive autoimmune process that destroys insulin-producing pancreatic islet cells. Antibodies to insulin, glutamic acid decarboxylase GAD65, the tyrosine phosphatase-like insulinoma antigen and tissue transglutaminase precede the development of type 1 diabetes. Among other factors, weight gain expressed as weight z-score and BMI z-score at 2 years and change in weight z-score between birth and 2 years, but not dietary intake, predicted the risk of islet autoimmunity in 548 infants with a first-degree relative with type 1 diabetes followed up for 5.7 ± 3.2 years [72].

A negative effect of the early introduction (<3 months) of cow milk-derived complementary food [73], which appeared from observational studies and two meta-analyses of case-control studies [74, 75], has not been confirmed by case-control studies, e.g. in the high-risk population of Sardinia [76], or in cross-sectional studies [77],

Table 3. Effect of age at the introduction of complementary food on the risk of obesity

Setting/authors	Study description	Outcome	Comments
Dundee/ Forsyth et al. [37], 1993 Wilson et al. [38], 1998	prospective, observational, longitudinal cohort study 671 term infants 455 at the 2-year follow-up 545 at the 7.3-year follow-up	introduction of CF at <12 vs. >12 weeks: no difference in body weight at age 2 years (n = 392) introduction of CF at <15 vs. >15 weeks: body fat (by impedance) at 7 years 16.5 and 18.5%, respectively ($p < 0.01$) (n = 397)	support for a programming effect of early nutrition?
Mehta et al. [44], 1998	prospective randomized intervention 165 formula-fed infants aged <3 months solid food 3–12 and 6–12 months	anthropometry and body composition (by DXA) at 3, 6 and 12 months showed no difference between early and late CF introduction no difference in energy intake	no growth difference at 52 weeks associated with early (≤12 weeks) or late (≥26 weeks) introduction of CF
Systematic review/ Lanigan et al. [5], 2001	33 randomized controlled trials on healthy full-term infants related to health effects of age at CF introduction	no consistent results	no clear evidence to support one recommendation on length of breastfeeding
Morgan et al. [42], 2004	evaluation of data from >1,600 infants (AGA/SGA term and preterm) participating in 5 randomized trials between 1993 and 1997 comparing introduction of solid food <12 and >12 weeks, follow-up to 18 months for term and to 9 months for preterm infants	introduction of solid food <12 vs. >12 weeks: greater gain in subscapular (but not triceps) skinfold thickness at 9 months in preterm infants	small effect with unknown meaning
Burdette et al. [60], 2006	prospective cohort study on changes in body fat during development in relation to feeding pattern in 1st year of life assessed by DXA 313 children at age 5 years	introduction of CF before or after 16 weeks did not result in differences in fat mass	no association between timing of CF and adiposity at age 5 months
Melbourne Atopy Cohort Study/ Seach et al. [58], 2010	prospective longitudinal cohort study of children at risk of atopy 307 children at age 10 years	delayed introduction of solid food was associated with reduced odds of being overweight/obese (defined by BMI) at age 10 years children with a BMI in the normal range were introduced to solid food at the mean age of 20.5 (95% CI 19.96–21.0) weeks, children with a BMI above normal at 18.7 (95% CI 17.7–19.7) weeks	comparison of groups defined by BMI at age 10 years (normal or above normal) and relation to feeding practices during the first 2 years of life subjects at risk for atopy may not be representative for the normal population with respect to infant diets
Copenhagen Perinatal Cohort/ Schack-Nielsen et al. [61], 2010	observational longitudinal cohort study set up in 1959 with 5,068 subjects followed-up to age 42 years for effect of age at introduction of CF on BMI	age at introduction of vegetables ($p = 0.014$), meat ($p = 0.044$) and firm food ($p = 0.012$) is inversely related to adult BMI and waist circumference	support for a programming effect of early nutrition?
Project Viva/ Huh et al. [62], 2011	prospective pre-birth cohort 847 children obesity at 3 years of age according to age at introduction of CF (<16, 17–24 and >24 weeks)	no association of timing of introduction of CF with adiposity in breastfed infants odds ratio for adiposity in formula-fed infants with introduction <16 weeks was 6.3 (95% CI 2.3–6.9)	breastfed and formula-fed infants may react differently to early (<16 weeks) introduction of CF formula-fed infants are at risk of later obesity

CF = Complementary food; DXA = dual-emission X-ray absorptiometry; AGA = appropriate for gestational age; SGA = small for gestational age; BF = breastfeeding; CI = confidence interval.

other (nested) case-control studies [78, 79] or in several prospective trials [80, and references therein].

Table 4 lists studies investigating the relationship between age at the introduction of complementary food and the risk for type 1 diabetes in unselected cohorts [81, 82], prospective studies in children at increased risk for type 1 diabetes [83–85] and a randomized study on different timing of introduction of gluten into the diet (26 vs. 52 weeks) [86].

There may be a difference in the reaction according to age at the introduction of certain complementary food in infants at genetic risk for type 1 diabetes and infants not at risk. Gluten-containing cereals have been implicated in the development of type 1 diabetes. Some studies suggest a time window for the low susceptibility to the diabetogenic effect of gluten or cereals between 17 and 26 weeks, which has not been confirmed by others to date. Continuation of breastfeeding with the introduction of cereals may reduce the risk.

Allergy

A prospective Finnish study [87] on 256 term infants who all received complementary food from 3.5 months of age showed that 'prolonged' breastfeeding up to 1–3 years of age and exclusive breastfeeding until 6 months of age decreased both the incidence of atopic dermatitis at 3 years of age in infants generally and the incidence of food allergy in infants from families with a history of atopy, compared to infants with no or short breastfeeding and with formula feeding. This study does not provide data on the effect of timing of complementary food but it raises the possibility that the effect of an early introduction on the manifestation of atopic disease may be attenuated by breastfeeding [87]. A recent analysis of retrospective data on breastfeeding duration and exclusivity in the cross-sectional ISAAC Phase Two Study [88] involving 51,119 randomly selected 8- to 12-year-old children from 21 countries did not find a protective effect of breastfeeding and delayed weaning on eczema risk. There was even a positive association between breastfeeding and total occurrence of eczema in affluent countries when breastfeeding was prolonged and weaning delayed, which disappeared when early-onset eczema was excluded. This could be due to 'reverse causation' in that mothers whose child developed eczema in early infancy were breastfeeding longer [88]. The risk of wheat allergy was increased in children who were first exposed to cereals after 6 months of age compared with children first exposed to cereals before 6 months of age (after controlling for confounders) [89]. It is hypothesized that this is due to a deficient development of oral tolerance to food allergens in infants sensitized to these allergens via other pathways, e.g. the skin [90]. The 'time window' for inducing tolerance is suggested to be 4–6 months, whilst an introduction of solids before 3–4 months increases the risk of allergy [91].

In infants at high risk of developing atopy, however, there is evidence that exclusive breastfeeding for 4 months decreases the risk of atopic dermatitis compared to partial breastfeeding, but exclusive breastfeeding beyond 3–4 months in infants not at risk does not have an impact on the incidence of atopic eczema [2].

The European Society for Pediatric Gastroenterology, Hepatology and Nutrition concluded that there was no evidence that avoiding or delaying an introduction of allergenic food beyond 17 weeks reduced the incidence of allergies both in infants at risk and in infants not at risk [6]. The American Academy of Pediatrics has revised its earlier recommendations for the prevention of atopic disease and states that there is little evidence that delaying the introduction of complementary food beyond the age of 4–6 months prevents the occurrence of atopic disease and that there is insufficient evidence for the effectiveness of dietary interventions beyond 4–6 months [92]. Continuation of breastfeeding while complementary feeding is gradually introduced is probably advantageous.

Conclusions

Despite the large literature on the effect of early diet in infancy and young childhood on health outcomes in childhood/adulthood, little evidence is available on the strength of the relationship between the timing of the introduction of complementary food and the risk of disorders in later life. There is some evidence that an introduction of complementary food before the age of 12 weeks in breastfed infants is associated with greater weight gain, at least temporarily during infancy; one study implies an effect on increased weight at a later age (7 years). Continuation of breastfeeding after the introduction of complementary food may attenuate the effect on weight gain.

An introduction of complementary food before the age of about 15 weeks in breastfed infants may increase the risk for obesity in later life, particularly when breastfeeding is discontinued at the same time. However, in formula-fed infants, the timing of introduction of complementary feeding (12–17 vs. 26 weeks) did not change the risk for obesity in one study.

Table 4. Effect of age at the introduction of complementary food on the risk of type 1 diabetes

Setting/authors	Study description	Outcome	Comments
Savilahti and Saarinen [81], 2009	follow-up to 11–12 years of a full-term newborn cohort (n = 6,209) 45 had type 1 diabetes	age at introduction of CF similar in diabetics and non-diabetics	no impact of age at introduction of CF in the general population
All Babies in Southwest Sweden Cohort/ Wahlberg et al. [82], 2006	prospective longitudinal 657 of 7,207 had type 1 diabetes-associated antibodies at age 2.5 years	early (≤8 weeks) cow's milk formula combined with introduction of gluten after 6 months increased likelihood 6-fold for antibodies at age 1 and 2.5 years	Increased risk for antibodies only in infants not or shortly breastfed and introduced to gluten after 26 weeks in the general population
Diabetes Autoimmunity Study in the Young (DAISY)/ Norris et al. [83], 2003	birth cohort study with a mean follow-up of 4 years (9 months to 9 years) 1,183 children at increased risk for type 1 diabetes	introduction of cereals between < 4 and ≥7 months increased likelihood to develop autoantibodies 4–5 times compared to when introduced at age 4–6 months (after adjustment for HLA genotype, family history of type 1 diabetes, ethnicity and maternal age) continued BF with introduction of cereals reduced the risk significantly and independent of age	increased risk for islet autoimmunity both at early (<4 months) and late (≥7 months) introduction of cereals in at-risk populations risk reduced when cereals introduced while BF
BABYDIAB/ Ziegler et al. [84], 2003	prospective birth cohort study of infants of parents with type 1 diabetes (n = 1,709) with a median follow-up of 6.5 years (9 months to 12.5 years)	introduction of gluten-containing foods at <3 months significantly increased the likelihood of diabetes-associated antibodies to be present compared to BF for 3 months (adjusted hazard ratio, 4.0; 95% CI 1.4–11.5; p = 0.01) no increased risk with gluten introduced after 6 months	increased risk for islet autoimmunity at early (<3 months) introduction of gluten, not at age >6 months in at-risk populations
Virtanen et al. [85], 2006	prospective birth cohort of 3,565 infants with HLA-DQB1-conferred susceptibility to type 1 diabetes in Finland diabetes-associated antibodies measured at 3–12-month intervals	early introduction (≤4 months) of fruits, berries and roots increased the risk of developing islet autoimmunity compared to introduction >4 months	introduction of other food than (gluten-containing) cereals at age <4 months increases the risk of developing diabetes-associated antibodies in at-risk populations
BABYDIET Study/ Hummel et al. [86], 2011	prospective cohort of 150 infants at high risk for type 1 diabetes randomized to first gluten exposure either at age 6 or 12 months follow-up >3 years	no significant differences in islet autoimmunity or incidence of type 1 diabetes autoimmunity	late introduction of gluten (12 months of age) does not reduce the risk for islet autoimmunity

CF = Complementary feeding; HLA = human leukocyte antigen; BF = breastfeeding; CI = confidence interval.

Although not consistent in all studies, the introduction of complementary food before the age of 12–15 weeks appears to increase the risk for infections of the gastrointestinal and the respiratory tract. The effect on the gastrointestinal tract may be short term only; however, in another study, a negative effect on the respiratory tract could be demonstrated to persist until the age of 7 years.

The introduction of complementary food before 12 weeks of age appears to increase the risk for (atopic) eczema in later life and the risk for food allergy in high-risk populations. A late introduction of complementary food beyond 26 weeks has been shown to increase the risk of wheat allergy in one study.

The timing of the introduction of complementary food does not appear to influence the incidence of type 1 diabetes mellitus in the general population. In high-risk populations, the introduction of complementary food, including cereals, before the age of 12–17 weeks as well as an introduction beyond 26 weeks increases the risk for diabetes-associated antibodies to be present.

Overall, the available evidence is far from sufficient to define the exact age at which complementary food should be introduced in infants, and, certainly not in an individual infant, to minimize the risk of adverse health effects (or optimize potential benefits for health) in later life: this clearly needs to be enforced by comprehensive prospective longitudinal studies. The available data can be considered to be sufficient (1) to strongly advise against the introduction of complementary food before the age of 12 weeks, and (2) to conclude that an introduction before the age of 17 weeks may be associated with adverse health consequences in later life and is not associated with any apparent health benefit. Delaying the introduction of complementary food beyond the age of 26 weeks is associated with the risk of nutritional insufficiency, particularly in low-income populations, and such delays may be associated with an increased risk for disorders connected with the immune system. Several studies point to the importance of the continuation of breastfeeding while gradually introducing complementary food according to the original meaning and intention of the term, namely, 'food to complement' the feeding of human milk.

Disclosure Statement

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