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1

Infant and Young Child Feeding Interventions Targeting Overweight and Obesity: A Narrative Review

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ABSTRACT

Introduction: Summary findings from systematic reviews into infant feeding and later adiposity are largely negative. WHO is auspicing HeLTI, a suite of trials aiming to prevent overweight/obesity in childhood. To inform planning, this narrative review sought to detail potentially effective components of nutrition-related interventions involving children aged 0-2 years.

Methods: Systematic searches of PubMed and the Cochrane Library (2006-2016) identified 108 systematic reviews. These included 31 randomised trials in the age group of interest. Of these, 11 reported ≥1 statistically significant ($p<.05$) benefit on body weight and/or composition.

Results: Six multi-component trials whose interventions incorporated education to promote breastfeeding (4 trials), responsive feeding (2 trials) and healthy diet (e.g. increasing fruit and vegetables, limiting unhealthy snack foods; 5 trials), delivered through home visits or at baby health clinics, reported relative reductions in body mass index at the end of intervention. Early benefits were not maintained in the two trials reporting followup 1-3 years later. Other potentially effective approaches included lower protein formulas in formula-fed infants and reducing sugar-sweetened beverages.

Conclusions: There is some evidence that infant feeding interventions can have a transient positive impact on a child's BMI. It is not known whether ongoing intervention can avoid the subsequent expected wash-out.

INTRODUCTION

The first few years of life present an important opportunity for intervention to reduce the long term risk of non-communicable diseases including obesity, type 2 diabetes and cardio-metabolic syndrome. There is epidemiological and biological evidence to suggest that interventions in this period may have longer term effects on weight and metabolism. Evidence from animal models shows prenatal and infant exposures can have lifelong effects on the offspring's adiposity and metabolism, mediated in part through epigenetic mechanisms [1]. Twin analyses suggest that weight gain in infancy is less susceptible to genetic influences than weight gain later in childhood, pointing towards infancy as a critical period when growth may be more easily modified by environmental factors [2]. Since rapid weight gain in infancy is associated with later childhood overweight [3], optimising growth trajectories in infancy could have lasting benefits. There are also practical advantages, since mothers and infants receive frequent routine medical care, improving the opportunity for delivery of interventions.

Infant and toddler feeding has been a key focus of many observational and intervention studies. Infant feeding could influence later adiposity either by optimising early growth and body composition, and/or by establishing early patterns of dietary patterns that then track to influence later growth and body composition [4]. In early infancy, studies focus on breastfeeding or infant formula composition, moving to how complementary foods are introduced (around 6 months). Thereafter, other issues come into play, including dietary composition (e.g. diet diversity, nutrient content, amounts of protein, fibre, fat and sugar consumed), how infants are fed (e.g. overfeeding, nonresponsive feeding), and establishment of taste preferences and eating behaviours [5].

Prevention may need to be tailored to meet the needs of low, middle and high income countries. Although obesity is more prevalent in high-income countries, in absolute numbers more overweight and obese children live in low and middle-income countries. Low-middle income countries may suffer a dual burden of undernutrition and over nutrition, as well as greater difficulties in accessing healthcare; differences in health literacy; availability and affordability of fresh fruit and vegetables; and issues around marketing and preferential availability and consumption of unhealthier foods and beverages. They also experience most of the burden of the 20 million low birthweight babies (preterm and/or small for gestational age) born annually [6] [7]. There is consistent epidemiological evidence that low birth weight is associated with an increased risk of metabolic and cardiovascular disorders in adulthood [8-10]. It is possible that some of this excess risk might be modifiable by optimising infant nutrition.

Numerous systematic reviews have therefore synthesised the evidence for a relationship between infant feeding and subsequent risk of overweight/obesity or intermediary risk factors for cardio-metabolic syndrome. Positive 'effects' seen in nutritional observational studies cannot be relied on, due to the likelihood of massive confounding and covariance [11]. Nor do systematic reviews of intervention trials provide much guidance for intervention due to their largely negative summary findings. However, these systematic reviews often lose important detail on the specific nature of exposures or interventions, the context in which interventions were implemented, outcomes measured, and methods for evaluation. These could be critical details for those designing new trials interventions targeting childhood overweight and obesity.

Thus major new intervention initiatives targeting early prevention of overweight/obesity and cardiometabolic risk face something of a planning vacuum. The World Health Organisation (WHO) and Canadian Institutes of Health are now auspicing HeLTI (Healthy Life Trajectories Initiative), a suite of cross-national trials aiming to prevent overweight/obesity in the early years. Faced with a largely negative summary literature, we were asked to provide a critical in depth analysis of exposures or interventions and outcomes *within* these negative systematic reviews that could inform selection of interventions for the Healthy Life Trajectories Initiative (HeLTI). In this review, we aim to identify nutrition-related exposures or interventions for infants and children aged 0-2 years for which there is some evidence of benefit on child outcomes. We also briefly summarise evidence for low-middle income countries and for low birth weight infants, and discuss issues specific for infant feeding interventions in these groups.

METHODS

Identification of Systematic Reviews: In May 2016, WHO conducted the initial systematic search of PubMed and the Cochrane Library to identify published systematic reviews, with and without meta-analyses, which investigated the effect of exposures or interventions to reduce the risk of overweight/obesity or intermediate risk factors for cardio-metabolic syndrome in children (see Supporting Information for search strategy). Although this search yielded both systematic reviews of observational studies and systematic reviews of intervention studies, we focus here only on intervention studies because of fundamental limitations associated with observational nutritional epidemiological research [11].

We screened the 108 systematic reviews retrieved by this search by title, abstract and full text (where necessary). To be included, all systematic reviews had to examine:

(i) an intervention related to infant feeding (reviews of multi-component interventions that included an infant feeding component were also included)

We excluded reviews if they:

(i) were not published in English (due to resource reasons)

(ii) did not capture any primary articles in the 0-2 year age group

Systematic Review Selection and Identification of Primary RCTs: Thirty-nine reviews met the above inclusion criteria. We next identified all relevant primary RCT papers included in the 39 systematic reviews.

We included primary RCTs that:

(i) incorporated at least one intervention targeting one or more aspects of infant feeding

(ii) included the 0-24 month age group

We identified 34 infant feeding RCTs (see supporting information Figure 1). Then, to better understand the individual characteristics of effective interventions, we extracted details of the intervention for all trials that reported evidence of a treatment benefit at a level of statistical significance of $p<0.05$ for one or more relevant outcomes.

We did not formally assess the quality of the randomised controlled trials as this was outside the scope of the review, and formal quality assessments had already been undertaken by the systematic reviews from which these trials were identified.

In reviewing these systematic reviews and primary papers the following intervention strategies to improve infant feeding were examined:

- Improve breastfeeding duration or exclusivity
- Adjust protein composition in infant formula
- Adjust the age at introduction of complementary foods
- Adjust forms and/or amount of polyunsaturated fatty acid intake
- Adjust sugar sweetened beverage intake
- Multi-component intervention strategies that included at least one nutrition-related component (e.g. nutritional guidance/education, education on responsive feeding, others from the list above)

Outcomes of interest were:

- Weight or BMI for age
- Overweight/obesity
- Measures of adiposity

The following subgroups were of particular interest and evidence for these was reviewed separately where available:

- Studies in low-middle income countries
- Pre-term, small for gestational age, low birth weight infants

RESULTS

Breastfeeding

A systematic review by Redsell et al. identified two intervention studies that included a breastfeeding promotion or breastfeeding support intervention and reported weight or related outcomes [12]. The cluster-randomised hospital-based PROBIT trial recruited 31 maternity hospitals and polyclinics in Belarus. Dyads contained healthy full-term singleton infants (≥ 37 weeks gestation, ≥5 Apgar score, ≥2 500 g birthweight) and mothers intending to breastfeed (n≈16 000 mother-infant dyads completed the 12-month follow up). Sixteen sites were randomly assigned to receive the intervention which was based on the WHO and UNICEF Baby-Friendly Hospital Initiative. At each intervention site the chief obstetrician and chief paediatrician completed an 18-hour lactation management training course which covered methods to maintain lactation, encourage exclusive and prolonged breastfeeding and resolve common breastfeeding problems. Training of all midwives, nurses and physicians providing care to the mother-infant dyads took 12-16 months. Dyads at control sites received usual care (i.e. continuing usual infant feeding practices and policies). Data were analysed based on intention-to-treat; at the 12-month follow up infants at the intervention sites were more likely to be breastfed (adjusted odds ratio (OR) 0.47, 95% confidence interval (CI) 0.32-0.69) and there were large increases in exclusive breastfeeding in the intervention group to 3 months of age (43% vs 6.4%, $p<0.001$). However, there were no significant difference in weight at 12 months, or in multiple anthropometric outcomes and blood pressure at 6.5 years of age (e.g., BMI mean difference 0.1, 95% CI -0.2, 0.3). [13, 14]

The other randomised intervention trial was conducted by Albernaz et al [15] in Brazil. 188 infants (singleton, 37-42 weeks gestation, lack of perinatal morbidity, no maternal smoking or economic constraints to growth) whose mothers intended to breastfeed were randomised to either no intervention (control) or home visits with trained lactation nurses. The nurses attended 40-hour lactation support training course (WHO endorsed) delivered by certified consultants. Nurse delivered counselling to the mothers in the intervention group in hospital and at home on day 5, 15, 30, 45, 60, 90 and 120. As well as providing a breastfeeding promotion leaflet and "how to" video, counselling topics included education about breastfeeding advantages, breastfeeding observation, correction of technique if needed, and manual breastmilk expression. Additional home visits and 24-hour phone support was offered to these mothers. The control group did not receive any home visits., Despite intervention mothers being twice as likely to continue breastfeeding to 4 months of age, there were no statistically significant differences in infant weight outcomes at any time point (e.g. mean difference at day 120 = 0.15 kg, p=.29).

Several other studies investigated the effect of modifying timing of introduction of complementary foods in exclusively breastfed infants – these are reviewed separately below.

Age at introduction of complementary foods (solids)

One systematic review of RCTs [16] assessed the relationship between timing of introduction of first complementary foods and weight outcomes. This review only included studies of healthy, full-term, exclusively breastfed infants and assessed short term impact on weight. Three RCTs were identified, with none showing any evidence of a difference between introduction of complementary food at 4 months vs 6 months of age on BMI or fat mass at age 6 months (single RCT, n=100) or growth/weight measures at 6 months (3 RCTs, n=100-200 per study) [17-19].

Protein composition of infant formula

One systematic review was specifically designed to examine the relationship between protein concentration in milk formula, growth and later risk of obesity [20]. Several other reviews also considered infant formula composition as part of a broader review of early life nutrition exposures [12, 21].

Twelve randomised controlled trials (RCTs) in infants from the general population who were fed cow milk-based infant formulas with variations in protein concentration were included in the systematic review by Patro-Golab [20]. No significant differences were found for mean weight at 3 months of age (pooled results from 4 RCTs, n=998). Only the EU Childhood Obesity Program (CHOP) study (n=1138) conducted within Belgium, Germany, Italy, Poland and Spain reported data on mean BMI and BMI z-scores at later ages. This double-blind intervention trial randomly assigned healthy formula-fed infants to receive formula with a higher or lower protein content for their first year of life. This formula was free of charge for the 12-months intervention period. The two formulas were identical in energy content, but differed in cow milk protein content. Infant formula was used for the first 6-months (cow milk protein 2.05 g/dL vs 1.25 g/dL), followed by the introduction of follow-up formula to complement solids food introduction (cow milk protein 3.2 g/dL vs. 1.6 g/dL). BMI was consistently higher in the higher protein formula group at all time points (6, 12 and 24 months and 6 years: mean difference 0.51, 95% CI 0.13, 0.90), as well as an increased risk developing obesity at 6 years of age (OR 2.43, 95% CI 1.12, 5.27) [22, 23]. However, the CHOP study was at high risk of bias due to low follow up to 6 years (46%) and per protocol analysis.

Two additional studies comparing hydrolysed protein formula milk with standard cow's milk formula were identified from the two systematic reviews that reviewed early life nutrition more broadly [12, 21]. A large randomized trial in Germany (GINI) compared BMI trajectories in infants fed either partially hydrolysed whey formula, extensively hydrolysed whey formula, extensively hydrolysed casein formula or cow's milk formula (combined n=1172) and infants exclusively breastfed (n=889) for the first 16 weeks of life. There were no significant differences in BMI trajectories up to the age of

10 years, except for a slower sex-adjusted BMI gain in infancy in those fed extensively hydrolysed casein formula (8th to 48th week of life), which was not maintained beyond the first year of life [24, 25]. The second small trial (60 infants) in the US randomly assigned formula-fed infants to receive cow-milk formula or extensively protein hydrolysate formula (35% more protein) between 0.5 and 7.5 months of age. These formulas were equivalent in energy content, but the hydrolysed formula contained 35% more protein (1.9 vs 1.4 g/100mL) and more small peptides and free amino acids. The infants fed partially hydrolysed formula had lower weight-for-age ($F(1, 42) = 4.72$, $p<.05$), weight-for-length ($F(1, 42) = 8.52$, $p<.01$) z scores and slower weight gain ($F(1, 44) = 6.60$, $p<.05$) from 2.5 to 7.5 months of age (i.e. during the intervention period) than cow's milk formula fed infants [26]. Across the study period, infants fed the hydrolysed formula consumed less to satiation than did those consuming the cow's milk formula. The authors note that the observed differences in growth could be due to the difference in protein content or amino acid profile.

Other aspects of diet composition

Other aspects of diet composition that were reviewed in one or more systematic reviews were protein intake, fat intake, energy intake, fruit and vegetable intake, polyunsaturated fatty acid intake and vitamin D intake [27-33]. However, RCTs in the age group of interest were identified only for polyunsaturated fatty acid intake.

Two systematic reviews [31, 32] and one systematic review of systematic reviews [34] assessed the intake and status of LCPUFA in infancy on later obesity, BMI or body composition. These reviews identified eight interventional and observational studies assessing different forms of PUFA intake or status (fish oils, dietary supplements, dietary intake or measured levels of n-3 and n-6 fatty acids). Two RCTs compared infant formula with and without supplementation with n-3 LCPUFA (docasahexaenoic and arachidonic acid) given from the first few days of life to 2-4 months of age.

They are not reviewed in detail here because neither showed any difference in body composition, BMI or overweight (at 12 months/9 years of age) [31, 35].

Intake of sugar sweetened beverages (SSB)

In the age group up to 3 years of age, we identified a single RCT. This RCT in a high risk for obesity population of American Indians/Alaskan Natives assigned three tribes to one of two community-based interventions to promote breastfeeding and reduce consumption of SSB. Participants were randomly assigned to interventions with or without family involvement from birth to age 18-24 months (n=205). Intervention outcomes were compared to a pre-test sample of American Indians/Alaskan Native children born in the same tribes two years earlier experiencing similar rates of childhood obesity. The intervention aimed to increase breastfeeding initiation and duration, limit SSB, and promote water consumption. The community intervention component was mostly media based, utilising videos, newspapers, brochures etc. to promote the three intervention aims (above). The intervention used five strategies: 1) raising awareness, 2) providing health education, 3) facilitating behaviour change, 4) augmenting public health practice, 5) environment and/or policy modification (e.g. working with hospitals to become more baby friendly (including the cessation of free formula provision, improving access to lactation consultants), allowing mothers longer breaks before returning to work for tribal employers, placing water vending machines next to soda vending machines, passing tribal resolutions to ban the purchase of SSB with tribal money, subsiding the cost of providing water in tribal health facilities). Those assigned to also receive the family component were visited in their home 7-21 times (dependent on family need) by community health workers who had been trained by tribal staff and the research team to support breastfeeding mothers, provide counselling to reduce SSB consumption and promote water intake using techniques such as motivation enhancement and behaviour change principles. This community intervention with the family component was associated with a lower BMI z-score rise (-0.75, p=.02) in toddlers at the age of 2 years compared with the community-alone intervention [36]. This was a pilot study, with a larger study currently underway.

Multi-component intervention trials with infant feeding-related components

Twelve multi-component RCTs were identified which included at least one infant feeding intervention component. Of these, 6 showed some evidence of a beneficial effect ($p<0.05$) on relevant outcomes for at least one time point. The interventions trialled in these studies [37-43] are described in Table 1. Trial outcomes are detailed in Table 2.

Interventions related to infant feeding included education aimed at promoting breastfeeding, advice on age at introduction of solid foods, healthy diet patterns (promoting fruit and vegetables), exposing infant repeatedly to healthy foods to promote the development of healthy food preferences, avoidance of follow-on infant formula after 12 months of age, recognising infant cues for hunger and satiety, avoiding using food as a reward and settling infants without feeding (see Table 1 for more information on strategies used in each trial). Interventions were delivered through home visits (3 trials) or community child health clinics or well-baby clinics (3 trials). The person targeted also differed between trials: 2 had interventions for the infant only and 4 for the infant along with other family members.

Navarro et al.'s quasi-experimental community-based trial of mother-child dyads (n=452) in the Dominican Republic [41] recruited pregnant women and involved educational meetings every 2-weeks, followed by post-birth home visits fortnightly for the first 6-weeks to encourage and support breastfeeding. Following this, monthly educational group meetings and home visits continued and focused on breastfeeding, complementary feeding, growth monitoring, micronutrient supplementation and other health-related topics. During the intervention period, the infants' growth was monitored against growth curves during home visits; advice and counselling were offered if the infants growth deviated from the growth curves from >2 consecutive home visits. At the end of the trial (between 13 and 24 months of age), children in the intervention group recorded more favourable BMI z-score (adjusted mean difference -0.31, 95% CI -0.49, -0.12) and a lower risk of overweight (adjusted odds ratio BMI-for-age>85th percentile 0.43, 95% CI 0.23, 0.77).

The *Nourish* trial (n=698) and *Healthy Beginnings* trial (n=667) were both conducted in Australia and involved first time mothers [37, 40]. *Nourish* involved two 6-session group education modules delivered at community child health clinics when the child was 4-6 months and 13-15 months of age. Sessions focused on healthy eating patterns and growth, and promoted neutral exposure to unfamiliar foods and limiting exposure to unhealthy foods to promote the development of healthy food preferences and responsive feeding that recognises and responds appropriately to infant cues of hunger and satiety to maintain infants' innate capacity to self-regulate intake and avoid overfeeding. At 13-15 months of age (after the first module but before commencement of the second module), children in the intervention group had a lower BMI-for-age Z-score (0.42+/-0.85 vs 0.23 +/-0.93, p=0.009). However, there were no differences in BMI or prevalence of overweight/obesity at age 2 years [44], or at 5 years of age [45]. *Healthy Beginnings* recruited pregnant women from socially and economically disadvantaged areas of Sydney, Australia, and involved 8 home visits starting prenatally and up to 24 months postpartum. Interventions promoted breastfeeding, delaying solids to age 6 months, eating a variety of fruit and vegetables, drinking water and active play for the infants. Wen et al. reported a slightly lower mean BMI in the intervention group at conclusion of the intervention at 24 months of age (16.49 vs 16.87, p<0.05) but no evidence of a difference in BMI or BMI z score at follow up at 5 years of age [46].

A pilot cluster-randomised controlled trial by Verbestel and colleagues in Belgium (n=156) recruited six communities: two matched for low SES, two for medium SES and two for high SES [38]. One community from each matched pair was allocated to either control or intervention group. In the intervention group, parents of all children aged 9-24 months attending day-care centres were invited to participate in a family-based lifestyle intervention which aimed to increase water (vs. soft drink), milk, fruit and vegetable consumption, increase physical activity and decrease daily unhealthy snacks and screen-time. Children with obesity at baseline were excluded. This intervention was theory-based and guided by well-known behaviour change models (e.g. elaboration likelihood model). Information about the translation of strategies from the theoretical models is available in the RCT paper itself. The intervention included poster-presented guidelines and tips for parents animated with a colourful sticker for each target behaviour. Stickers were given to parents every two months with an information letter about the target behaviour (e.g. screen-time reduction). Parents also received a tailored feedback form about their children’s diet and physical activity. After 12-months of intervention, there were no between-group differences in the target behaviours, yet BMI z-score decreased in both groups, and more so among the intervention children (-0.95 in the intervention group vs. -0.44 in the control group, $p<.05$).

The *SLIMTIME* trial (n=110) was also a pilot study for a 2x2 design in which mother-newborn dyads were randomised to receive both a soothe/sleep and nutrition-related intervention, only one of those interventions or no intervention [39]. Mothers and infants (singleton, >34 weeks gestation, without morbidities affecting sleeping/feeding) were recruited from a medical centre in Pennsylvania. All mothers received routine care, breastfeeding support and a parenting book with traditional advice and a standard handout on complementary feeding. First, the soothe/sleep intervention was delivered during the first home visit by the research nurse 2-3 weeks after the infants birth. Together with support from the attending nurse, parents were provided handouts and videos that taught strategies, other than feeding, to soothe distressed infants and how to discriminate infant hunger from other sources of distress. Second, parents receiving the nutrition-related intervention centred on complementary feeding were guided not to introduce solid foods until at least 4 months and to call the research nurse when they felt the infant was ready to begin. The nurse visited the participants within 2-weeks and explained the importance of repeated exposure to healthy foods, developmental signs of readiness, hunger and fullness cues. In addition, across four successive week's parents were provided with pureed vegetable portions to offer the infant each week for 6 consecutive days – green beans, peas, squash and carrot. Parents were instructed to offer cereal, breast milk or formula if the vegetable was refused on three successive attempts. At one year, infants receiving both interventions had lower weight-for-length percentiles (33^{rd} percentile vs. $\geq 50^{th}$ percentile in three other conditions, p=.009). Moreover, those in the soothe/sleep intervention (vs control) gained weight at a slower rate than infants in the control group did (weight-for-age z-score -.39 vs. -.08, p=.02).

The *STRIP* trial in Finland (n=1062) had the longest intervention period of all included trials [43]. The intervention started at age 7 months and involved individualised counselling focused on achieving a healthy diet and physical activity, delivered at 1-3 month intervals to age 2 years then twice a year up to age 10 years. Breastfeeding was encouraged, as was consumption of vegetables, fruits, berries and whole-grain products. At 10 years of age, females in the intervention group were less likely to be overweight or obese (10.2% versus 18.8%, p=0.04), while there was no difference in males.

Intervention trials in low birthweight infants

None of the systematic reviews or trials identified in this review focussed on preterm, small for gestational age or low birth weight infants, and in fact many of the systematic reviews and the primary intervention studies that they included specifically excluded these groups of infants.

Intervention trials in low-middle income countries

Of the studies reviewed above, very few were conducted in low-middle income countries - the two breastfeeding promotion trials were conducted in Belarus [13, 14] and Brazil [15], one early introduction of complementary foods trial was conducted in Honduras [17] and one multi-component intervention study was conducted in the Dominican Republic [41], all classified as upper-middle income countries except for Honduras (low middle-income).

DISCUSSION

Summary of results: Six multi-component trials whose interventions incorporated education aimed at promoting breastfeeding (4 trials), responsive feeding (2 trials) and a "healthy diet" (6 trials; e.g. increasing fruit and vegetables, reducing sugar-sweetened beverages and limiting unhealthy snack food), delivered through home visits or education at baby health clinics, reported relative reductions in body mass index at the end of the intervention (generally age 1-2 years). Early benefits were not maintained in the two trials reporting followup 1-3 years later. Other potentially effective approaches included lower protein formulas in formula-fed infants (one trial) and education around reducing sugar-sweetened beverages (one trial).

Recommendations for future intervention trials: Targeting a reduction in sugar sweetened beverages for the infant and family may be a beneficial addition to any intervention trial. Breastfeeding promotion, which was included as a component of most of the effective multi-component trials, did not appear to be effective as a sole intervention in two other trials. However, breastfeeding promotion may be considered for inclusion as part of any intervention trial because of the consistent association between breastfeeding and a reduced risk of overweight and obesity in observational studies [47]. Prolonged breastfeeding may also have benefits in reducing the consumption of sugar-sweetened beverages. For infants who are formula fed, use of lower protein formulas could be trialled.

Other potentially beneficial interventions could include education around responsive feeding and recognising and responding appropriately to infant cues of hunger and satiety, as well as alternative strategies to feeding to respond to infant distress. The Nourish trial, which included a responsive feeding component, reported a decrease in self-reported use of non-responsive feeding practices that persisted up to 3 years after the intervention [40]. Education around promoting development of healthy food preferences and acceptance of unfamiliar foods through appropriate (repeated) exposure to a variety of fruit and vegetables in infancy resulted in a (small) increase in vegetable consumption [37] and increase in acceptance of new healthy foods [39] and appear a worthwhile addition to future intervention trials.

Two of the effective multi-component trials included education around delaying the introduction of solids to beyond 4 months or "around 6 months", however there is evidence from other trials included in this review that changing the age of introduction of complementary foods (solids) in breastfed infants does not alter BMI or fat mass [17-19]. A more recent large randomised controlled trial in the UK, designed as an allergy prevention study, supports these findings [48]. Exclusively breastfed infants (n=1303) were randomised to either follow current UK guidelines (Standard Introduction Group [SIG]: Exclusive breastfeeding to around 6 months; no consumption of allergenic foods before 6 months) or to introduce a range of solid foods from 3 months of age alongside continued breastfeeding (Early introduction group [EIG]: give low-allergen weaning food first (e.g. rice, fruits or vegetables) followed by sequential introduction of 6 allergenic foods (cow's milk yoghurt, peanut butter, egg, sesame paste, whitefish and wheat-based cereal biscuits)). At 12 months of age, the EIG group had modest evidence of greater weight-for-length z-score, BMI z-score, weight-for-age z-score, triceps skin fold-for-age z-score (all p values between 0.05 and 0.15), but no differences were seen in any of the anthropometry measures at 36 months of age (all $p>0.4$).

There is no clear evidence for whether intervention trials should target only the infant diet, or involve both the child and the mother or family. However, it is possible that interventions aimed at improving the diet of the infant will have flow-on effects for improving the diet of the family. Conversely, interventions which improve the diet of the family are likely to improve the diet of the infant when complementary feeding commences. Future trials could potentially directly compare infant versus maternal interventions to determine which is more effective in improving family diet as well as for improving anthropometry outcomes in the child. Similarly, there is currently little evidence to guide the appropriate location of education-based interventions – both home visits and group education sessions appeared to be effective in changing infant feeding behaviours.

Recommendations for research into feeding of low birthweight infants: We found limited evidence to guide nutrition interventions for reducing intermediary risk factors for cardio-metabolic syndrome in low birth weight infants. None of the systematic reviews identified by the HeLTI search specifically focussed on this group, and many of the systematic reviews and the primary studies that they included specifically excluded preterm, small for gestational age or low birth weight infants. This will be an important group for future intervention trials. For low birth weight infants, measuring intermediary risk factors for cardio-metabolic syndrome such as insulin resistance [10] as well as changes in weight in response to dietary interventions will be crucial.

A small number of trials in low birth weight infants have measured weight outcomes in childhood following different early feeding methods. Quigley et al. conducted a systematic review comparing formula versus donor breast milk for feeding preterm or low birth weight infants that examined a range of outcomes including longer term effects on growth [49]. Only two small trials (30 and 56 infants per arm) followed up infants into later childhood. Both trials reported no statistically significant differences in weight, length or head circumference to 8 years post-term, despite both finding a higher rate of early weight gain for formula fed infants. A more recent follow up of one of these trials showed no difference in BMI, BP, insulin, glucose, triglycerides, cholesterol, in 46 participants who were followed up to adulthood (30 exclusively fed human milk, 16 exclusively formula) [50]. Fenton et al. conducted a systematic review comparing higher versus lower protein intake in formula fed low birth weight infants [51], which reported improved weight gain in early infancy with higher protein intake from formulas (5 studies). Longer term effects on weight, obesity or cardio-metabolic risk factors were not reported.

Even less is known about optimal feeding once low birth weight infants leave hospital. Observational studies of feeding practices for low birthweight infants might be warranted as a first step to characterise whether low birth weight infants are fed differently from infants with a higher birthweight. For example, parents might overfeed or use high calorie food in childhood for low birthweight infants if they are perceived as being underweight, and if so these behaviours could be targeted in future intervention studies. Many of the interventions described above (e.g. education to promote healthy diet patterns, increasing vegetable consumption and responsive feeding practices) may also be appropriate for low birth weight infants once they are no longer exclusively breast- or formula-fed.

It has been hypothesised that the increased risk of adverse cardio-metabolic outcomes in low birth weight infants may be driven by accelerated postnatal catch-up growth, which is a common compensatory mechanism for low birth weight that appears to have beneficial effects for infants in the short term. Martin et al. (2016) conducted a systematic review to examine the role of accelerated postnatal ‘catch-up growth’ in individuals with low birth weight and the risk of future health outcomes [53], concluding that there was some evidence of a beneficial effect of catch up growth in the short term relative to no catch up growth, while three studies of longer term health outcomes found catch-up growth was associated with higher body mass, BMI or cholesterol (mean age 11.1 years) but the quality (by GRADE assessment) and quantity of the evidence was limited. Future RCTs may wish to consider collecting data for multiple growth points in infancy and beyond to better measure and define growth trajectories and adiposity rebound, and how these respond to intervention. Interventions will also need to balance the benefits of

Finally, low birth weight infants includes both babies born preterm and infants born small for gestational age (SGA). These components of low birthweight have different causes and might have different risks of non-communicable diseases in later life, as well as different feeding needs. However, there is currently insufficient evidence to provide separate recommendations for SGA and preterm infants, as recognised in the WHO guidelines for optimal feeding of low birth weight infants [52].

Comparison with other literature: The comprehensive report from the Commission on Ending Childhood Obesity (ECHO) provided a series of recommendations relating to both behaviour change and regulatory change for preventing childhood obesity [53]. Recommendations relevant to infants and young children included regulations on marketing of complementary foods and beverages to limit consumption of foods and beverages high in fat, sugar and salt by infants and young children, guidance and support to caregivers to encourage consumption of a wide variety of health foods and to avoid specific categories of foods (e.g. sugar-sweetened drinks or energy-dense, nutrient-poor foods), and guidance on appropriate nutrition, diet and portion size, as well as several recommendations aimed at improving breastfeeding rates. Our review also found some evidence to support a potential benefit of education for caregivers around strategies to encourage consumption of a variety of healthy foods for infants, and avoiding sugar-sweetened beverages and snack foods high in salt and sugar. Regulatory changes were not assessed in any of the trials included in our review and their effects are more difficult to assess in a randomised trial.

Strengths and weaknesses: Strengths of this review include the systematic search and approach to selection of articles and our attempt to understand the key elements of successful interventions. Consequently our evidence is restricted to trials that obtained at least one beneficial outcome effect. Thus, the positive findings on which this review selectively focused may represent the extreme positive end of a spectrum of efficacy for each strategy, with other trials that generated null findings for the same strategy excluded by our criteria. We acknowledge that similarly-designed trials in the literature have produced null findings. Nonetheless, endeavours such as the HeLTI trials need some positive starting point on which to build their future rigorous trials.

There are also some limitations to the included studies that affect the conclusions that can be drawn from this review. Few studies included follow up beyond the period of intervention, so it is unclear whether effects would be maintained in the medium-long term. Several of the studies had a small sample size, including 3 which were pilot studies for planned larger trials. Finally, some of the effective multi-component intervention trials targeted both nutrition-based and non-nutrition components (e.g. sleep, active play education, decreasing screen time), thus it is not clear which component/s are responsible for the reported benefits.

In conclusion, there is some evidence that nutrition or feeding interventions in the first two years of life can have a transient positive impact on a child's BMI, but maintaining this benefit may require continued intervention and sustainable environmental change.

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Table 1: Description of multi-component interventions which included a nutrition component and had some effect on child weight/BMI or related outcomes

Study/ country	Population	Age at intervention	Setting	Breast-feeding promotion	Info on age at intro of solids	Responsive feeding		Other nutrition components	Family components	No co
Daniels 2012 *Nourish* Australia [40]	N=698 healthy term infants of first-time mothers *RCT*	4-6 months and 13-15 months	Two 6-session group education modules – community child health clinic	No	No	Responsive feeding, recognise/ responds appropriately to infant cues of hunger and satiety to maintain infants' innate capacity to self-regulate intake and avoid overfeeding.		Repeated neutral exposure to unfamiliar foods and limiting exposure to unhealthy foods to promote the development of healthy food preferences.	No	No
Wen 2012 *Healthy Beginnings* Australia [37]	N=667 first-time mothers *RCT*	Prenatally and up to 24 months postpartum	Eight home visits of 1-2 hours antenatally & at 1, 3, 5, 9, 12, 18, 24 mths	Yes	Yes (around 6 months)	Not specific focus		Eat variety of fruit and vegetables, drink water, no formula after 12 mths	Family physical activity and nutrition, and social support	Ac ed
Navarro 2013 *Maternal-child pastoral* Dominican Republic	N=452 mother-infant dyads *Paired quasi-experimental trial*	Pregnancy and infancy	Monthly home visits + group activities biweekly in pregnancy and monthly after birth	Yes	Not stated	No		Micronutrient supplementation, complementary feeding, *Nutritional Advice Based on the Growth Curve*	Maternal diet	Ne pre tre inf dis gro mo

[41]								protocol		ea sti pre ac
Hakanen 2006 STRIP Finland [43]	N=1062 infants RCT	7 months – 10 years	Individual counselling at 7, 8, 10 and 13 months, biannually until 7 years old, annually until 10 years old - community well-baby clinic	Yes	No	No		Individualised counselling (no defined diet). The optimal diet was defined to contain energy without any restrictions, protein 10–15% of energy (E%), carbohydrates 50–60 E%, and fat 30 E% after the age of 2 years (30–35 E% between 1 and 2 years) with unsaturated to saturated fatty acid ratio (U:S) of 2:1. Encouraged vegetables, fruits, berries and whole-grain products.	Family physical activity and diet	Pa sm av

Paul 2011 SLIMTIME US [39]	N=160 mother-infant dyads RCT with a 2x2 intervention design	Pregnancy to 6 months	2 home visits: first visit 2-3 weeks after birth; second visit at 4-6 months	Yes	Yes (delay until 4 months)	Alternate strategies to feeding as an indiscriminate first response to infant distress, identify hunger and fullness cues, review developmental signs for solid food readiness, feed when calm and alert, not crying or fussing		Repeated exposure to healthy foods to improve acceptance of unfamiliar foods, provision of vegetable portions	No	So tec
Verbestel 2013 Belgium [38]	N=203 pilot cluster-randomised controlled trial	9-24 months	Community – child day-care centres (intervention materials distributed via child day-care centres and mailed)	No	No	No		Increase consumption of water (instead of soft drink), milk, fruit and vegetables and decrease consumption of sweets and savoury snacks	Family physical activity and diet	De da tin

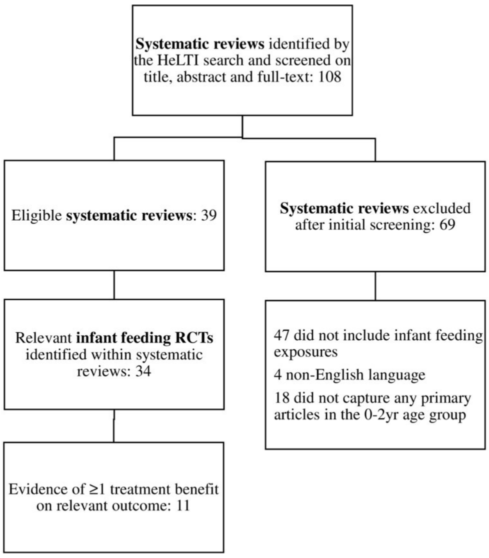
Table 2: Effect of interventions on infant feeding and weight-related outcomes

Study/ country	Duration/ exclusivity of breastfeeding	Age at intro of solids	Responsive feeding	Diet composition	Other infant feeding outcomes	Maternal/family diet	Weight-related outcomes
Daniels 2012 Nourish Australia [40]			Control group mothers more likely to report using non-responsive feeding practices: using food as reward (15% vs 4%, p=0.001); using games (67% vs 29%, p<0.001) (13-15 months). From age 2 to 5 years, intervention mothers reported less nonresponsive feeding techniques (P < .05)				**Age 13-15 months:** BMI-for-age Z-score: Intervention vs control 0.23 (±0.93) vs. 0.42 (±0.85); p=0.009 (13-15 months) **Age 2 and 5 years:** No differences in BMI in intervention vs control
Wen 2012 Healthy Beginnings Australia [37]	The intervention group had a significantly higher median duration of breastfeeding at 12 months than the control group (17 weeks (95% confidence interval,	Introduction of solid foods before 6 months reduced by 12% (95% confidence interval, 4%-20%) from 74% to 62%; P= < .001	Given food for reward in intervention - control: (62% v 72%, P=0.03)	One or more servings of vegetables per day in intervention - control: (89% v 83%, P=0.03).		Two or more servings of vegetables per day in intervention - control (mothers) (52% v 36%; P<0.001)	**Age 2 years:** BMI: Mean BMI in intervention (16.53) vs control (16.82); with a difference of 0.29 (95% Cl 0.02,0.55); P=0.04 **Age 5 years:** No

	13.9-20.4 weeks) vs 13 weeks (95% confidence interval, 10.1-15.0 weeks); P = .03)						differences in BMI between control and intervention groups
Navarro 2013 Maternal-child pastoral Dominican Republic [41]	Prevalence of exclusive breastfeeding through to 6 months of age in control group 2.34% and intervention group 7.29% (P=0.017), OR (95%Cl) 3.28 (1.24; 8.69)			Higher proportion of children in intervention consumed five or more solid or semisolid food items over past 24 hours (27.46% vs 18.53% in the control group, P=0.037)	Higher consumption of vitamin A and iron supplements by children in intervention group, resulting in lower prevalence of anaemia with adjusted odds ratio of 0.57 (P=0.011) for Hb < 11.0 g/dl and 0.46 (P<0.001) for Hb < 10.0 g/dl		**Age 13-24 months:** BMI-for-age Z score: Intervention −0.31, 95%CI −0.49; -0.12), P=0.001 BMI-for-age >85th percentile: OR (95% Cl) 0.43 (0.23;0.77); P=0.005
Hakanen 2006 STRIP Finland [43]							**Age 10 years:** Prevalence of overweight and obesity (weight for height more than 20% above the Finnish mean): <u>Females:</u> intervention group 10.2% vs. control group 18.8%; P=0.0439; no

							difference for males
Paul 2011 SLIMTIME US [39]		Mothers giving cereal before 4 months in “Introduction of Solids” intervention vs. control (13% vs. 29%, P=0.02)		Significant increase in acceptance of new foods in infants receiving “Introduction of Solids” intervention from days 1 to 6: green beans (P=0.001), peas (P=0.02), and squash (P=0.04)			**Age 1 year:** Weight-for-length percentiles: Intervention group receiving both Soothe/Sleep and Introduction of solids: 33%; Soothe/Sleep only 50%; Introduction of solids only 56%, control group 50% (P=0.009)
Verbestel 2013 Belgium [38]					No intervention effects were found for dietary-related behaviours targeted by intervention		Decrease in BMI Z score from baseline to follow-up: intervention 1.33 to 0.38, control 0.74 to 0.30; P<0.05

Figure 1: Screening of systematic reviews for inclusion in the narrative review



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