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REVIEW ARTICLE

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Infant formula feeding practices associated with rapid weight gain: A systematic review

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Abstract

Excess or rapid weight gain during the first 2 years of life is associated with an increased risk of later childhood and adult overweight and obesity. When compared with breastfed infants, formula fed infants are more likely to experience excess or rapid weight gain, and this increased risk in formula fed infant populations may be due to a number of different mechanisms. These mechanisms include the nutrient composition of the formula and the way formula is prepared and provided to infants. This systematic literature review examines the association between formula feeding practice and excess or rapid weight gain. This review explores these different mechanisms and provides practical recommendations for best practice formula feeding to reduce rapid weight gain. Eighteen studies are included in this review. The findings are complicated by the challenges in study design and accuracy of measurements. Nevertheless, there are some potential recommendations for best practice formula feeding that may reduce excess or rapid weight gain, such as providing formula with lower protein content, not adding cereals into bottles, not putting a baby to bed with a bottle, and not overfeeding formula. Although further well designed studies are required before more firm recommendations can be made.

KEYWORDS

childhood obesity, infant feeding, infant feeding behaviours, infant formula, infant growth, systematic review

1 | INTRODUCTION

Rapid or excess weight gain (RWG)[1] in infancy is associated with higher risk of being overweight or obese in childhood (Baird et al., 2005; Koletzko, von Kries, Monasterolo, 2009; Monteiro & Victora, 2005; Zheng et al., 2017). In a comprehensive systematic review comprising 282 studies examining modifiable risk factors for childhood obesity (from the antenatal period until 2 years of age), RWG was one of the more consistent risk factors of overweight or obesity in later childhood with 45 out of 46 included studies finding a positive association (Woo Baidal et al., 2016). Another literature review and meta-analysis on RWG and subsequent obesity, including 17 studies (meta-analysis based on 14 of the included studies), found that, for those infants who experienced RWG, there was a 3.66 times increased odds for overweight or obesity in later life (Zheng et al., 2017). The proportion of infants experiencing rapid weight gain varied from approximately 10–50% across studies included in the review (Zheng et al., 2017). Infants fed formula, as opposed to infants fed breast milk, are more likely to experience RWG (Dewey, 1998; Koletzko, von Kries, Monasterolo, et al., 2009; Mihrshahi, Battistutta, Magarey, & Daniels, 2011).

It has been understood for some time that infants fed formula have different weight gain patterns to breastfed infants (Dewey, Heinig, Nommsen, Peerson, & Lonnerdal, 1993; Taitz, 1971; Yang & Huffman, 2013). Heinig, Nommsen, Peerson, Lonnerdal, and Dewey (1993) found that infants fed formula had higher: energy intake, protein intake, and weight gain compared with matched breastfed infants. These differences may be due to physiological and behavioural variances between breastfeeding and feeding formula from a bottle (Bartok & Ventura, 2009). Such as, the nutrient profile of breast milk and formula milk is different. And the feeding interaction between the mother and infant

[1]A widely agreed on definition of rapid weight gain is a change in weight for age Z score > 0.67 (Goodell et al., 2009; Ong et al., 2000) although studies measure and define excess and rapid weight gain in infancy in other ways—see Section 2. For simplicity throughout this paper, the acronym RWG will be used to refer to all measures of excess or rapid weight gain during the first 2 years of life.

when feeding from a breast or a bottle is different, where feeding via a bottle provides the adult with more control over the feeding situation than the breastfed infant (Bartok & Ventura, 2009).

Many infants are fed with some formula in their first year of life: In Australia, at least 50% of infants are fed with some formula milk in their first 6 months, and only 39% are exclusively breastfed to 3 months (Australian Institute of Health and Welfare, 2011). Similar proportions are found in the United States where, in 2014 the national rates of exclusive breastfeeding at 3 months were 40.7% (Centre for Disease Control and Prevention, 2014). Considering the high prevalence of formula feeding, is it possible to use formula in a way that best mimics breast milk and breastfeeding (Ryan & Hay, 2016) and prevents RWG?

Identifying how formula feeding practices (which include the type and preparation, the amount provided and consumed, and the way in which formula is provided) relates to RWG is important to inform public health and obesity prevention strategies. It is also important to improve the information and advice provided to parents who are feeding with formula to reduce the potential for RWG. This systematic review identifies and assesses the supporting evidence for a range of formula feeding practices associated with RWG in infancy. It explores the different mechanisms and provides practical recommendations on the basis of the current evidence for best practice formula feeding to prevent RWG.

Key messages

- Preventing early RWG in formula fed infants may reduce their risk of later overweight and obesity.
- There is some evidence to suggest that there are formula feeding practices, such as adding cereals in bottle, putting an infant to bed with bottle, overfeeding formula, and compositions, such as higher protein that contribute to RWG.
- Parents and health professionals should be provided with accurate evidence of these associations so they can implement best practice formula feeding.
- Much of the current evidence relies on theoretical links and further research is required to provide a solid evidence base.

2 | METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) (Moher, Liberati, Tetzlaff, & Altman, 2009) and guidance for systematic reviews in epidemiology (Denison et al., 2013) informed the methods. The study selection criteria for inclusion were based on three biologically plausible mechanisms by which breastfeeding may be protective and formula feeding may contribute to RWG. That is, epidemiological and experimental research suggests that the (a) composition of the milk (nutrient profile), (b) the mode of feeding (e.g., using a bottle, size of teat), and/or (c) the parent feeding practices may be important mechanisms. These three pathways help conceptualise how formula may be provided in ways which may closely imitate breast milk and breastfeeding (Ryan & Hay, 2016). These pathways do not work in isolation: They have overlapping effects. Nor are they simply unidirectional, for example, an infant's weight or weight gain may impact parents' feeding practices (Li, Fein, & Grummer-Strawn, 2008).

2.1 | Inclusion/exclusion criteria

Studies were selected for inclusion if they (a) addressed one of the pathways outlined above, (b) included a sample (or a portion of the sample) of infants who were fed with formula milk in their first year since birth, and (c) included RWG in the first two years as an outcome. Nutrient profile variables included studies where the composition of formula milks was differentiated. Mode of delivery variables included studies where the type of bottle or teat was investigated. Parent feeding practice variables included studies where the parent's preparation or provision of formula was measured.

"Excess" or "rapid" weight gain is defined and measured a number of different ways in the literature. A widely agreed upon definition of RWG is a change in weight for age *z*-score > 0.67 (Goodell, Wakefield, & Ferris, 2009; Ong, Ahmed, Dunger, Emmett, & Preece, 2000). However, some studies measure and define "excess" or "rapid" weight gain in other ways—for example, specific percentile cut offs are used to define excess weight, for example, body mass index (BMI) above the 85th percentile defined as overweight (Gubbels, Thijs, Stafleu, Buuren, & Kremers, 2011). Studies were included regardless of the measure or definition used. Studies of infants or parents afflicted by conditions that may impact on infant feeding or growth were excluded.

2.2 | Search strategy

Searches were conducted in five electronic databases (Medline, PsycINFO, CINAHL, MIDIRS, and Scopus) followed by a snowball search strategy through citation searching, hand-searching, and visual scanning of reference lists of sentinel papers and relevant systematic reviews. For database searches, keywords were used in conjunction with subject heading in CINAHL and PsycINFO and MeSH terms in Medline (full search terms are available in the Supporting Information). Limits were set to English language, human subjects, and those published from 1990. The primary search was conducted between August and November 2016 and repeated in July 2017 that revealed no further studies for inclusion.

2.3 | Study selection

All papers were imported into an Endnote database and duplicates removed. One researcher (JA) screened titles and abstracts using a screening checklist (see Supporting Information). Any uncertainties were discussed with a second researcher (EDW). After the initial screen, full text of the included articles were retrieved and analysed according to the eligibility criteria (see Supporting Information).

2.4 | Data extraction and narrative synthesis

One researcher (JA) extracted data from the included studies using a data extraction checklist which included study description, participant characteristics, exposure definition and measure, outcome definition and measure, statistical data and results, was derived with guidance from Denison et al. (2013). This formed a structured table of the included studies organised according to the three pathways of interest, established a priori. Studies within each pathway were then summarised in groups reporting on the same exposure (e.g., the parent feeding practice of feeding on demand or schedule). The characteristics, study designs and findings within each group were described, compared, and synthesised.

2.5 | Quality assessment

The Mixed Methods Appraisal Tool (MMAT)—Version 2011 (Pluye et al., 2011) was used to assess study quality. This tool assesses a range of study designs including randomised, nonrandomised, and descriptive quantitative studies. Two researchers (JA and EDW) independently assessed each of the included studies, and any discrepancies in the scores were discussed and consensus drawn.

3 | RESULTS

Overall, 3,881 papers were retrieved, and one additional paper was found via snowball searching. Title and abstract screening excluded 3,796 papers, leaving 86 papers. Full text review of these 86 papers excluded a further 68 papers, leaving 18 for inclusion in the review (Figure 1).

3.1 | Study characteristics

Eight[2] papers addressed nutrient profile, two addressed mode of delivery and nine[2] addressed parent feeding practices (Tables 1–3). The study designs included randomised controlled trials (RCT—six studies), nonrandomised trials (one study), longitudinal cohort studies (eight studies), and cross section studies (three studies). The RCTs varied in size, from very large multi-national studies (Koletzko, von Kries, Closa, 2009), to small single site studies (Mennella, Ventura, & Beauchamp, 2011). The longitudinal studies varied in length of follow up period and size, with five having greater than 1,000 participants. For most studies, the samples were taken from general populations defined within a geographical area, or some were sampled nationwide. A small number of studies included specific populations such as overweight mothers only (Inostroza et al., 2014), those with a family history of atopic disease (Roche, Guo, Siervogel, Khamis, & Chandra, 1993; Rzehak et al., 2009), and a Women, Infant, and Children (WIC) population in the United States (Cartagena, McGrath, & Masho, 2016; Worobey, Lopez, & Hoffman, 2009).

[2]One paper involves exposure variables in both the nutrient profile and parent feeding practices section and is included in the parent feeding practice table (Table 3).

3.2 | Quality assessment

The MMAT scores ranged from 25% (*) to 100% (****; Table 1–3). The strongest evidence was found in the nutrient profile pathway, which comprised five RCTs which may suggest a directional association, one nonrandomised trial, and one longitudinal study. Although this section included five RCTs, their MMAT scores varied: In three of the studies, lower scores were a result of participant attrition (Inostroza et al., 2014; Koletzko, von Kries, Closa, et al., 2009; Rzehak et al., 2009). The mode of delivery pathway included only two studies: one RCT and one longitudinal study. A longitudinal design may provide evidence of directional association, however, further validation of this association is required. The parent feeding practice pathway included nine studies of either cross sectional or longitudinal study design. The cross sectional studies provide the most limited evidence as directional association cannot be assumed. Many of the studies also relied on parent reported data that can be limited due to social desirability bias and incorrect measurement or reporting (e.g., of infants' weight or height). However, many studies included used a sampling technique that minimised bias, controlled for differences between groups, and controlled for known factors associated with RWG in infancy (e.g., infant birth weight and maternal BMI).

3.3 | Synthesis of study results

3.3.1 | Nutrient profile

The amount of protein

Two studies address the amount of protein. The first showed that the amount of protein is linked with weight outcomes in a large European multicentre randomised control trial including 1,090 formula fed infants (540 randomised to the low protein formula group, 550 to the high protein group, and a breastfed comparison group; Koletzko, von Kries, Closa, et al., 2009). This trial found that formula with a higher protein content (2.05 g/100 ml—standard then 3.2 g/100 ml—follow on) lead to more RWG, compared with both a formula with lower protein content (1.25 g/100 ml—standard then 1.6 g/100 ml—follow on) and breastfed infants (Koletzko, von Kries, Closa, et al., 2009). Likewise, the second study suggested that low protein content formula may attenuate some of the risk for RWG (Inostroza et al., 2014). This study was conducted in Chile with 172 infants with mothers who were overweight or obese (86 to an experimental low protein formula with probiotics and 86 to a control standard formula and a breastfed comparison group). However, the study design of including a specific population and the inclusion of probiotics in the experimental formula limits our capacity to directly attribute this difference to protein (Inostroza et al., 2014).

Protein-hydrolysed formula

Three studies considered the effects of protein-hydrolysed formula (Mennella et al., 2011; Roche et al., 1993; Rzehak et al., 2009), in which the protein has been either partially or extensively broken down into smaller peptides (Vandenplas et al., 2016) on weight gain. An RCT found infants (*n* = 250) fed extensively hydrolysed casein formula had a lower BMI (WHO Multicentre Growth Reference population [2006] charts) growth to 11 months than those fed partially hydrolysed whey

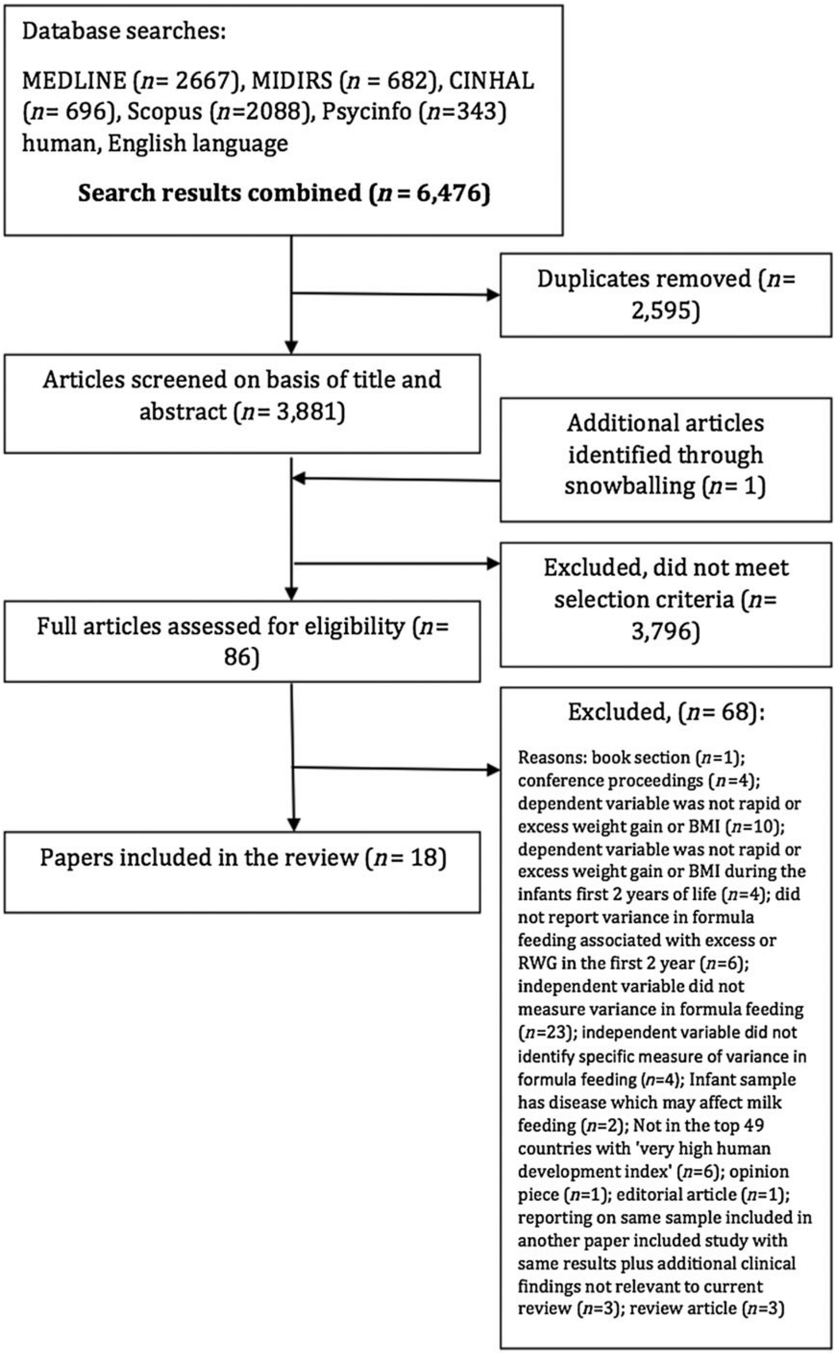

FIGURE 1 PRISMA flow diagram

(pHF-W; n = 253), extensively hydrolysed whey (eHF-W; n = 265) and cow's milk formula (n = 276; Rzehak et al., 2009). Although, there was no difference in BMI at follow up (measured up to 6 years; Rzehak et al., 2009). In another small RCT (n = 64), infants fed cow's milk formula had statistically significant higher weight for age and length z-scores compared with those fed extensively hydrolysed formula between 3.5 and 7.5 months (Mennella et al., 2011). Another nonrandomised study comparing cow's milk formula to soy formula, a hydrolysed formula, and breastfeeding found that infant boys fed with a cow's milk formula were more likely to have weights above the 95th percentile between birth and 6 months (Roche et al., 1993). The generalisability of this study is limited given that the growth reference comparison group was a local national study (from Canada), and the sample was of infants with a family history of atopic disease (Roche et al., 1993).

Energy density

Three studies considered how the energy density of formulas (one is included in the parent feeding practice table) related to weight gain. A small RCT (n = 42) compared powdered and ready to feed formula. The study hypothesised that powdered formula may be incorrectly made up and, thus, provide a more energy dense feed than the ready to feed formulas (Lucas, Lockton, & Davies, 1992). They found in the powdered feeding group that bottles that were reconstituted to a higher energy concentration (i.e., more concentrated) were associated with higher weight at 6 months. They also found a significantly higher body weight change in powdered formula group between 1 and 6 weeks (p = .003) and 1–12 weeks (p = .03); but not at 1–26 weeks (p = .06). Another paper reported on a large (n = 2666) prospective longitudinal cohort study which considered the use of a milk cereal drink

TABLE 1 Included studies nutrient profile (n = 7)

First author year location/setting study name	Design	Sample *N* & key descriptions	Exposure & measurement	Outcome/s, reference population & measurement	Key findings	MMAT score (*, **, ***, ****)[a]
•Lucas et al., 1992 •UK	•Randomised control trial	•*N* = 42 •21 Per group dropped to 19 per group by 6 months •Approx. evenly gendered groups •Infants from one postnatal ward of parents already decided to feed formula	•Powdered versus ready to feed formula •Randomised at enrolment within 2 days of birth	•Weight, change in weight, & standardised weight *z*-score •Local reference population (Cambridge reference growth centiles) •Directly measured at birth, 1, 2 4, 6, 10, 12, & 26 weeks	•Higher body weight in powdered formula group (non-significant) •Higher body weight change in powdered formula group (1–6 weeks, 1–12 weeks significant, 1–26 weeks non-significant) •Powdered formula group standardised weight from 6 to 26 weeks around 0.6 compared with ready to feed group around 0.1	****
•Roche et al., 1993 •Canada	•Nonrandomised control trial	•*N* = 288 •72 Per group. *N* = 263 with complete data—uneven between groups •52% Female infants •Infants with family history of atopic disease	•Whey hydrolysate versus soy based formula versus standard cow's milk based, breast fed group. •Allocated formula used from birth to 6 months	•Absolute weight gain & standardised weight percentile •Local reference population (Fels Longitudinal Study using Epi Info program) •Directly measured at birth, 2, 4, & 6 months	•Some small differences in weight between groups •Most infants weights ranged within 5th–95th percentile with all groups similar •Cow's milk based formula fed boys were more likely (p < .025) to be greater than 95th percentile for weight	*
•Koletzko, von Kries, Closa, et al., 2009 •Belgium, Germany, Italy, Poland, & Spain •European childhood obesity trial study	•Randomised control trial	•*N* = 1,138 Enrolled & randomised; *N* = 1,090 Commenced allocated formula 540 low protein group; 550 high protein group Final at 24 months after loss to follow & weight or length measures *N* = 635 (313 low; 322 high), •Approx. evenly gendered groups •Infants of healthy mother and parents already decided to feed formula	•Higher (2.05 g/100 ml then 3.2 g/100 ml) versus lower (1.25 g/100 ml then 1.6 g/100 ml) protein content cow's milk casein predominant formulas (breast fed observation group, not included in *N*) •Allocated formula commenced at enrolment & randomisation which took place up to infant age of 8 weeks	•Absolute weight gain & standardised weight for length *z*-score •WHO (World Health Organisation) multicentre growth reference population (2006) using WHO software •Directly measured at 3, 6, 12, & 24 months	•High protein group had higher weight gain from 3 months through to 24 months (statistically significant) •At 24 months adjusted weight for length *z*-scores were 0.20 greater in the high protein group compared to low protein group	**
•Rzehak et al., 2009 •Germany •German infant nutritional intervention study	•Randomised control trial	•*N* = 2,252 enrolled & randomised, Final after dropouts/non-compliance *n* = 1,840 Includes those randomised to 4 different formulas (*n* = 1, 044) + a breast fed	•Partially hydrolysed whey (pHF-W) versus extensively hydrolysed whey (eHF-W) versus extensively hydrolysed casein (eHF-C) versus cow's milk formula (CMF)	•Absolute BMI (body mass index) change & BMI *z*-score •WHO multicentre growth reference population (2006)	•eHF-C group had lower BMI compared with other formula groups (statistically significant) up to Month 11 of life but not beyond.	***

(Continues)

TABLE 1 (Continued)

First author year location/setting study name	Design	Sample N & key descriptions	Exposure & measurement	Outcome/s, reference population & measurement	Key findings	MMAT score (*, **, ***, ****)[a]
		observation group (n = 796). •48% Female infants •Infants with family history of atopic disease	and breastfed observation group •Allocated formula randomised at birth & commenced any time from birth to 16 weeks	•Medical records for weight at birth, 4 days, 5 weeks, 3.5, 6.5, 11.5, & 23 months		
•Mennella et al., 2011 •The United States	•Randomised control trial	•N = 64 enrolled & randomised (CMF 35, PHF 29) final after dropout n = 56 (CMF 32, PHF 24), •50% (CMF); 41.7% (PHF) female •Infants without family history of allergy or atopic all fully formula fed with exception of 3 mixed fed with formula and breast milk	•Extensively protein hydrolysed formula (PHF) versus cow's milk formula (CMF) •Allocated formula randomised & commenced at 0.5 months	•Weight for age z-score and weight for length z-score •Standardised using WHO multicentre growth reference population (2006) with Anthro software & CDC (Centers for Disease Control and Prevention) growth reference (2000) with Epi Info software •Directly measured monthly from 0.5 to 7.5 months	•Infants in the CMF group had higher weight for age and length z-scores (both WHO and CDC) compared with PHF group between 3.5 and 7.5 months (statistically significant)	***
•Almquist-Tangen et al., 2013 •Sweden	•Prospective, longitudinal, population-based, birth cohort study	•N = 2,666 At baseline, at 18 months N = 2,241 •At 4 months 21.3% formula fed, 4.3% mixed fed with breast and formula milk	•Use of milk cereal drink (MCD—"gruel") measured via self-reported questionnaire at 6 months	•BMI, high BMI defined at above 1 SD in study population •No reference population •Directly measured at 12 & 18 months	•Use of MCD at 6 months associated with higher BMI at 12 &18 months (statistically significant)	****
•Inostroza et al., 2014 •Chile	•Randomised control trial	•N = 172 enrolled & randomised at 3 months (86 experimental formula; 86 control formula) Final at 12 months after loss to follow N = 120 (54 experimental formula; 66 control formula), •47% Female •Infants of overweight mothers only BMI >25 kg/m^2	•Low protein with probiotics (experimental formula—protein 1.65 g/100 kcal) versus standard formula (protein 2.7 g/100 kcal) both whey predominant formula (breast fed observation group, not included in N). •Allocated formula commenced at 3 months	•Weight gain per day between 3 and 6 months, weight for age, length & BMI z-scores •Standardised to WHO multicentre growth reference population (2006) •Directly measured at 3, 4, 6, 9, & 12 months	•Lower weight gain between 3 and 6 months in experimental formula group compared to standard formula group (statistically significant) •At 24 months BMI lower in experimental formula group & breast fed group compared with standard formula group (statically significantly)	**

[a]The MMAT provides a quality score based on four pertinent criteria for each study design, studies receive one * per each criteria met. Therefore, studies may meet the following:

*One criterion.

**Two criteria.

***Three criteria.

****All criteria.

TABLE 2 Included studies mode of delivery (n = 2)

First author year location/setting study name	Design	Sample N & key descriptions	Exposure & measurement	Outcome/s, reference population & measurement	Key findings	MMAT score (*, **, ***, ****)[a]
•Fewtrell et al., 2012 •UK	•Randomised control trial	•N = 63 enrolled & randomised after dropout N = 54 at 4 weeks •43% female •Infants all formula fed from enrolment	•Bottle antivacuum design (2 types of bottles) •Randomised at birth through to 15 days	•Absolute weight gain & weight gain z-score to 4 weeks •Standardised to UK reference data (1990) •Directly measured at enrolment, 2, 4 weeks & 3 months	•No statistically significant difference in weight or formula consumed between the two bottle groups	**
•Wood et al., 2016 •The United States •Greenlight intervention study	•Longitudinal data from a cluster randomised control trial	•N = 386 (45% of all study participants), •53% female •Infants fully formula feeding at 2 months	•Feeding formula from "large" ≥ 6 oz (~177 ml), or "regular" bottles <6 oz (~177 ml) •Measured at 2 month clinic visit through providing study staff a sample of the usual bottle used to feed infant.	•Change in weight (2–6 months), weight for length and age z-scores •Standardised using WHO multicentre growth reference population (2006) •Directly measured at 2 & 6 months	•Higher weight for length (and weight for age) in those infants fed with the large bottle compared to those with the regular bottle (statistically significant)	****

[a]The MMAT provides a quality score based on four pertinent criteria for each study design, studies receive one * per each criteria met. Therefore, studies may meet the following:

*One criterion.

**Two criteria.

***Three criteria.

****All criteria.

TABLE 3 Included studies parent feeding practices (n = 9)

First author year location/setting study name	Design	Sample *N* & key descriptions	Exposure & measurement	Outcome/s, reference population & measurement	Key findings	MMAT score (*, **, ***, ****)[a]
•Saxon et al., 2002 •The United States	•Cross section	•*N* = 48 •41% female Infants •54% of infants full formula fed	•Feeding infant by demand or by schedule •Measured via self-reported questionnaire at 6 months (asked consider the feeding routine from birth to 6 months)	•Weight percentile •Standardised using National Centre for Health Statistics (1979) reference population using ANTHRO software •Medical records for weight at 2, 4, & 6 months	•Feeding by demand or schedule had no effect on weight percentile	**
•Li et al., 2008 •The United States •Infant feeding practice Study II	•Longitudinal postal survey	•*N* = 1,896 •35.9% of infants has "low" (<20% of all milk feeds) breastfeeding intensity	•Bottle emptying, "infant initiated" and "mother initiated" •Measure via self-reported at 2, 3, 4, 5, & 6-month survey	•Weight for age *z*-score, *z*-score > 1 defined as excess weight •Standardised using CDC reference population •Weight reported by mother at 3, 6, 7, & 12-month survey	•Multiple logistic regression (*n* = 1,187) found infants that frequently emptied the bottle were 69% more likely (odds ratio) to have excess weight than those that rarely did •Infants of mothers who frequently encouraged baby to finish the bottle were less likely to have excess weight gain that those that rarely did	***
•Worobey et al., 2009 •The United States	•Longitudinal study	•*N* = 242 recruited after loss to follow up over the 6 months *N* = 96 •48% female, •100% of infants full formula fed, recruited from one WIC (women, infants, and children) Centre	•Number of formula feeds per day & maternal sensitivity to infant cues while feeding •Measured with NCAST at home visit at 6 months	•Absolute weight gain (6–12 months) •Not standardised. •Weight directly measured at 3, 6, & 12 months	•Lower maternal sensitivity to infant cues (statistically significant in forward & backward regression) and higher number of feeds (only statistically significant in backward regression model) per day associated with more weight gain between 6 and 12 months	***
•Gubbels et al., 2011 •The Netherlands •KOALA birth cohort study	•Prospective longitudinal cohort study	•*N* = 2,834 •49% female •15.5% of infants never breast fed; 33.3% breast fed for 1–3 months	•Feeding infant by demand or by schedule •Measured via self-reported questionnaire at 3 months	•Absolute weight gain (birth—12 months), standardised BMI *z*-score (at 1, 2 years) BMI *z*-score > 85th percentile defined as overweight •Standardised to local reference population •Weight reported by parent at 3 months, 1 year, & 2-year survey	•No difference between the schedule or demand group in terms of weight gain from birth—12 months or BMI.	***
•Mihrshahi et al., 2011 •Australia •Nourish randomised control trial	•Cross section baseline data of a randomised control trial	•*N* = 612 •50% female	•Feeding infant by demand or by schedule	•Rapid weight gain defined as weight for age *z*-score above 0.67 *SD* from birth to baseline	•Feeding on schedule was associated with rapid weight gain (statistically significant)	****

(Continues)

TABLE 3 (Continued)

First author year location/setting study name	Design	Sample *N* & key descriptions	Exposure & measurement	Outcome/s, reference population & measurement	Key findings	MMAT score (*, **, ***, ****)[a]
		•26.5% of infants formula fed only; 16.3% mixed fed with breast and formula milk	•Measured via self-reported questionnaire at 4–7 months	•Standardised by WHO multicentre growth reference population (2006) •Weight directly measured at baseline (4–7 months), birth weight collected from hospital records at recruitment		
•Gaffney et al., 2012 •The United States •Infant feeding practice Study II	•Longitudinal postal survey	•*N* = 691 •51% female •52.1% of infants has "low" (<20% of all milk feeds) breastfeeding intensity for the period of 6–12 months infant age	•Bottle to bed practice •Measured via self-reported questionnaire at 6, 7, 9, 10, & 12 months	•Weight for age *z*-score •Standardised using CDC reference population (2000) •Weight reported by mother at 12 month survey	•Did not find a statistically significant result between bottle to bed and weight for age *z*-score	***
•Gibbs & Forste, 2014 •The United States •Early childhood •Longitudinal study	•Nationally representative longitudinal study	•*N* = 8,030 (original sample 10,500—excluded case of missing variables) •49% Female •31% Infants predominately formula fed; 54% mixed with breast and formula milk to 6 months	•Bottle to bed practice •Measured via home interview survey at 9 months	•Weight for age percentile, weight for age > 98th percentile defined as early obesity •Standardised using WHO reference population (2006) •Weight directly measured at 24 months	•Bottle to bed practice was associated with an increased odds ratio of early obesity at 24 months (statistically significant)	****
•Hopkins et al., 2015 •UK •Child in focus sub study of the Avon longitudinal study of parents and children	•Longitudinal study	•*N* = 1,112 (82% of child in focus sub study that had full dietary data), (*N* = 845 for 18 month outcome data) •45% Female •74.1% Of infants formula fed at 8 months	•Amount of formula consumed at 8 months considered low if <600 ml/day or high if ≥600 ml/day •Measured by a 3-day unweighed food diary completed by parent	•Weight for age & BMI *z*-scores, rapid weight gain *z*-score above 0.67 *SD* from birth to 2 years •Standardised using the UK (1990) growth reference •Weight directly measured at 4, 8, & 18 months	•Compared with breast fed infants, infants in low formula group were 0.27 *SD* heavier and high formula group 0.41 *SD* heavier at 18 months •Similar proportion of children experiencing rapid weight gain in the formula milk high group (30.7%) and formula milk low groups (29%)	***
•Cartagena et al., 2016 •The United States	•Cross sectional	•*N* = 62 •55% female •72% of sample formula fed purposeful recruitment from WIC immigrant Latina population	•Bottle to bed practice and rice cereal in bottle practice •Measured at home visit infant age 4–12 months	•Weight for length •Standardised using WHO reference population (2006) •Weight directly measured at 4–12 months	•Did not find a statistically significant result between bottle to bed or rice cereal in bottle and greater weight for length	**

[a]The MMAT provides a quality score based on four pertinent criteria for each study design, studies receive one * per each criteria met. Therefore, studies may meet the following:

*One criterion.

**Two criteria.

***Three criteria.

****All criteria.

("gruel") at 6 months in relation to BMI at 12 and 18 months (Almquist-Tangen, Dahlgren, Roswall, Bergman, & Alm, 2013). This study found a positive association between use of milk cereal drink at 6 months and higher BMI at 12 and 18 months after controlling for parental obesity and education, maternal smoking, gestational age, birth weight, gender, and BMI at 1, 4, and 6 months but not other dietary intake. This study did not use a growth reference group to standardise their sample weights and used a unique definition of "high BMI" as one standard deviation above their study population mean (Almquist-Tangen et al., 2013). Another small (*n* = 62) cross sectional study (included in the parent feeding practice table) reported no statistically significant relationships between putting rice cereal in the bottle of four to 12-month olds and higher weight for length in a WIC immigrant Latina population (Cartagena et al., 2016).

3.3.2 | Mode of delivery

The type of bottle used to feed formula was considered in only two studies. A small (*n* = 63) RCT compared two bottles, one with, a "partial antivacuum" design and another with a "full antivacuum" design (Fewtrell, Kennedy, Nicholl, Khakoo, & Lucas, 2012). The hypothesis was that a partial antivacuum design would require more effort to extract the milk from the bottle which would lead to lower milk intake and hence lower weight gain (Fewtrell et al., 2012). However, this study found no statistically significant difference in consumption or weight gain between the two groups (Fewtrell et al., 2012). Another longitudinal study (*n* = 386) compared the size of the bottle used to feed formula (Wood et al., 2016). This study recorded the size (volume) of bottles used by participants who were fully formula feeding their infants at 2 months. After adjusting for a number of confounders (such as child's gender, age, family ethnicity, education, household income, and household size), infants fed with a 'large'- 6 oz (~177 ml) bottle had more weight gain between 2 and 6 months compared with infants fed with a smaller bottle (< 6 oz or ~177 ml; Wood et al., 2016).

3.3.3 | Parent feeding practices

Nine papers were included in this section, measuring various aspects of parents' feeding practices including feeding on demand or schedule, taking a bottle to bed, the amount of formula provided and whether an infant was encouraged to empty the bottle.

Feeding on demand or schedule

Three studies (two cross sectional and one longitudinal) measured feeding on demand or on schedule, with differing results. One small (*n* = 48) cross sectional study found no weight difference at 6 months between groups who were fed on demand versus on a schedule (Saxon, Gollapalli, Mitchell, & Stanko, 2002). Another large prospective longitudinal cohort study (*n* = 2,834), which controlled for pertinent confounders (such as child gender, birth weight, maternal age, prepregnancy BMI, and smoking in pregnancy) also found no difference between their schedule or demand groups in terms of weight gain from birth to 12 months (Gubbels et al., 2011). Another cross sectional study (*n* = 612), which also controlled for pertinent confounders (such as mother's age, smoking in pregnancy, BMI, and education, infant birth weight and gender) found feeding to schedule was positively associated with RWG between birth and 4–7 months (Mihrshahi et al., 2011). These studies measured demand or schedule feeding at different time periods, with different tools, used a different reference population to standardise their sample growth and used different definitions of RWG.

Bottle to bed

Three studies measured whether parents put their infants to bed with a bottle of formula. All papers measured this practice at various time points in the first year and as a dichotomous variable (i.e., they did not consider frequency of this practice). Two found no association between putting an infant to bed with a bottle and greater weight (Cartagena et al., 2016; Gaffney, Kitsantas, & Cheema, 2012). The other study did find a positive association between putting an infant to bed with a bottle, measured at 9 months via an interview survey, and "early obesity" (weight for age > 98th percentile) at 24 months (Gibbs & Forste, 2014).

Volume of formula

Two studies considered the volume of formula infants consumed by measuring the number of feeds per day or the amount consumed over a day. Both found weak positive associations between the amount of formula consumed and weight gain. One small (*n* = 96) longitudinal study based in a WIC population found a higher number of feeds per day, measured at 6 months, was associated with greater absolute weight gain between 6 and 12 months (Worobey et al., 2009). However, this study only considered weight change over time—They did not standardise infants' weight to length, nor compare their sample to a reference population or control for other foods consumed. The other larger (*n* = 1,112) longitudinal study measured the amount of formula consumed at 8 months, dichotomising into low (<600 ml formula/day) or high (≥600 ml formula/day; Hopkins, Steer, Northstone, & Emmett, 2015). Relative to a breastfeeding comparator group both formula intake groups and gained more weight when measured to 18 months although actual differences were small (the low formula group were 0.27, and the high formula group was 0.41, standard deviations heavier [Hopkins et al., 2015] than the breastfed group). On the other hand, there were a similar proportion of children experiencing RWG in the formula milk high group (30.7%) and formula milk low group (29%) with a low proportion in the breastfed group (19.7%; Hopkins et al., 2015).

Bottle emptying

One study considered the frequency of an infant finishing a bottle of milk related to weight gain. In a longitudinal postal survey (*n* = 1,896), this study asked about the frequency at which an infant finished all the milk in their bottle (infant initiated bottle emptying) and the frequency at which the carer encouraged the infant to finish all the milk (mother initiated bottle emptying; Li et al., 2008). They found that infants who frequently "infant initiated" emptied their bottle were more likely to have excess weight gain, which was defined as a standardised weight for age score of more than one standard deviation above the mean using CDC charts (Li et al., 2008). This study also found that infants of mothers who frequently encouraged their baby to finish the milk in their bottle ("mother initiated" bottle emptying) were less likely to have excess weight gain than those who rarely did (Li et al., 2008).

4 | DISCUSSION

This review aimed to examine the evidence on associations between formula feeding practices and RWG with a view to providing practical recommendations to parents and health professionals on formula feeding to promote healthy weight gain. Overall, limited evidence identified which, if any, formula feeding practices are likely to be associated with RWG in infancy. All three of the explored pathways relied heavily on theoretical links and require further research to provide a solid evidence base.

The nutrient profile pathway provided strong but limited evidence. This review found it is plausible that a lower protein content formula (e.g., 1.25 g/100 ml for formula from birth; Koletzko, von Kries, Closa, et al., 2009) can reduce the likelihood of an infant experiencing RWG. By comparison, the average amount of protein found in breast milk is lower at 1.03 g/100 ml (although this varies), and the range of protein currently available in infant formula (e.g., on the Australian market 1.3–1.9 g/100 ml) and "follow on" formula to use from 6 months (e.g., on the Australian market 1.3–2.5 g/100 ml; Blair, Frazer, & Gaskin, 2014). Advising that "follow on" formula is not required may be an appropriate intervention to reduce protein intake (Redsell et al., 2016).

However, caution should be observed as the current review included only two RCTs. Although two recent systematic reviews of RCTs that focused specifically on protein content of infant formula and general infant growth found while there is some evidence to support lower protein content, further research is necessary, including long term research of not only weight outcomes but also neurodevelopment outcomes (Abrams, Hawthorne, & Pammi, 2015; Patro-Gołąb et al., 2016). Further limitations in applying this to the "real world" are the diversity of the composition of formula available: Both studies only considered cow's milk formula although other formulas based on different sources of protein are available (e.g., goats milk or soy plant).

Three studies in this review provided some evidence that hydrolysed infant formula may have a positive effect on reducing RWG in formula fed infants. The potential mechanism is that hydrolysed protein may promote greater satiation than intact protein (Ventura, Beauchamp, & Mennella, 2012). Further larger studies with samples from the general population (two studies included populations of family history of atopic disease) are required, however, before any firm conclusions can be drawn. Further research is also required to understand the short and long term effects of hydrolysed infant formulas (Vandenplas et al., 2016) which are typically used for infants with a family atopic history or gastrointestinal complaints (Vandenplas et al., 2016).

In the first weeks after birth, formula fed infants generally have higher energy intakes than their breastfed peers (Hester, Hustead, Mackey, Singhal, & Marriage, 2012). The energy density of formula is a theoretically interesting point because parents may make up the formula at a higher density than the manufacturer's recommendations or add cereal (in the belief it may enhance sleep or satiety; Baughcum, Burklow, Deeks, Powers, & Whitaker, 1998; Lucas et al., 2017). Interestingly, recent research in Australia has found around 20% of infant bottles have inaccurate measurements, which could lead to over or under concentrated formula (Gribble, Berry, Kerac, & Challinor, 2016). The present review found the consumption of milk with cereals may have positive association with excess weight gain (Almquist-Tangen et al., 2013) but further evidence is required, as not all studies found a positive association (Cartagena et al., 2016). Nevertheless, feeding recommendations generally do not support providing milk with cereal added in the bottle due to other risks such as choking.

The bottle alone (irrespective of the milk inside the bottle, i.e., formula or expressed breast milk) may be an important factor in RWG: In a large longitudinal survey, infants fed by bottle (compared with those fed at the breast) gained more weight per month regardless if the milk was formula or expressed breast milk (Li, Magadia, Fein, & Grummer-Strawn, 2012). A similar more recent analysis of this same large longitudinal survey also showed a higher frequency of feeds provided by a bottle (irrespective of the milk inside the bottle) in the first 3 months was associated with higher weight gain in the first year (Ventura, 2017). In the current review, the type of bottle was investigated in only two studies, with only one finding a positive association. Although replication is required, this study provided an interesting and potentially useful intervention—that of using smaller bottles (less than 6 oz, ~177 ml; Wood et al., 2016). It may be that the size of the bottle reduced the chance of overfeeding (Wood et al., 2016). Overfeeding may not only lead to more RWG but may also impact the development of an infant's satiety responsiveness and self-regulation (DiSantis, Hodges, Johnson, & Fisher, 2011). Generally, it is theorised that overfeeding may occur when a caregiver is less responsive to an infant's signals (cues) of satiety (DiSantis et al., 2011). There is strong evidence that infants are generally consistent in sending signals of satiety (Bartok & Ventura, 2009; DiSantis et al., 2011; Ventura, Inamdar, & Mennella, 2015; Ventura & Mennella, 2017). However, a range of factors including infant temperament and the external environment may influence the communication of the cues and caregiver interpretation and response to these cues (McNally et al., 2015). A smaller sized bottle may indeed adjust a part of the external environment to have a positive effect in this regard.

Another facet to the relationship between the bottle, the amount of formula consumed and potential overfeeding was the parent feeding practices, and if a parent encouraged or pressured an infant to finish all the milk in the bottle. This review found one study that conceptualised two types of bottle emptying scenarios: infant led and mother led (Li et al., 2008). Surprisingly, the relationship with RWG gain was only found in the infant led scenario, which may be an indicator of bottle fed infants' diminished response to internal cues of satiety (Li et al., 2008). The mother led scenario was not associated with RWG (Li et al., 2008). The authors suggest it may be that parents feed in response to infant size or feeding behaviour; for example, a small infant is encouraged to finish the bottle (Li et al., 2008). Conversely, it may be that the self-reported questionnaire did not accurately reflect what was happening in practice.

Considering the potential impact of overfeeding on both RWG and also an infant's satiety responsiveness and self-regulation (DiSantis et al., 2011), there was surprisingly little research considering formula intake and RWG. This review found two studies showing a positive association between amount of formula consumed and RWG. However, the measures of "amount of formula" consumed in both these studies had questionable validity and reliability with one counting only the number of feeds per day and the other an average amount of formula consumed over a 3-day period, and both relying on parent reported data (Hopkins et al., 2015; Worobey et al., 2009). Further studies with validated measures are necessary.

Two other parent feeding practices considered were feeding to schedule or demand and putting an infant to bed with a bottle. Three studies investigated the associations between RWG and demand versus scheduled type feeding, with only one finding a positive association. It is unclear if either method (demand or schedule) is associated with RWG. It may be that other factors, such as those noted above, including an infant's temperament/appetitive traits and other external environment influences (McNally et al., 2015), and the parent's response to infant cues that are more influential than this one particular practice. Although it is argued that feeding on demand theoretically should foster a style of feeding more responsive to infant cues (DiSantis et al., 2011; Saxon et al., 2002) but this is contingent on the infant and parent communicating effectively via feeding cues and response.

The practice of putting a baby to sleep with a bottle was associated with RWG in one of three included studies. Two studies considered bottle to bed practice during the second 6 months of infancy, one with more directly measured data (at infant age of 9 months) found an association (Gibbs & Forste, 2014) whereas the other, with self-reported data (at infant age 6–12 months) did not (Gaffney et al., 2012). This difference may be due to variation in data collection tools and timing. Previous studies have found an association between bottle to bed use during the toddler years and increased risk of overweight and obesity (Bonuck, Huang, & Fletcher, 2010; Kimbro, Brooks-Gunn, & McLanahan, 2007). However, regardless of age, it is a practice that is considered inadvisable as it is a choking hazard (NHMRC, 2013) and is also one of the risk factors for dental carries (Harris, Nicoll, Adair, & Pine, 2004).

This review examined formula feeding practices that may increase the risk of formula fed infants experiencing RWG based on the three pathways of nutrient profile, mode of delivery, and parents' feeding practices. Overall, there is some limited evidence to support the nutrient profile of formula (specifically lower protein) and certain parent feeding practices (not adding cereals in bottle, not putting a baby to bed with bottle, and not overfeeding) are important to reduce RWG. However, this evidence is very limited in scope and quality, and further studies are required before firm recommendations can be made.

Many of the included studies were based on self-reported data of unknown validity that may not be accurately measuring formula feeding practices or infant weights due to social desirability bias and incorrect reporting (e.g., of infants' weight or height). There is a need for improved measures of parental milk feeding practices and parent intentions and beliefs during this period as predictors of these to accurately assess which practices contribute to RWG. In addition, not all studies controlled for important confounders such as when the infant commenced solid foods. Further research providing evidence from which health professionals may advise parents on how best to use formula is needed.

Further research is required to provide evidence for best practice formula feeding, yet there are prominent ethical considerations for studies in the area. First, studies should ensure that breastfeeding is promoted and continues to be the first option for infant feeding (Binns, Lee, & Kagawa, 2017). Second, as it is now clear that RWG has lifelong implications for the risk of later overweight and obesity (Woo Baidal et al., 2016; Zheng et al., 2017), studies of infant feeding should monitor for these early signs of overweight and obesity (Binns et al., 2017). This has implications for future prospective studies that hypothesise that certain formula feeding practices will contribute to RWG.

This review is limited by a focus only on studies that specifically considered RWG in the first 2 years, leading to exclusion of papers that looked at weight gain or growth more generally or those looking at infants at ages beyond 2 years. In addition, this review examined three theoretical differences between breastfeeding and formula feeding (nutrient profile, the mode of feeding, and the parent feeding practices). Forthcoming research has conceptualised additional mechanisms by which formula feeding may contribute to weight gain such as the development of the microbiome (Binns et al., 2017; Mischke & Plösch, 2013) and taste preferences (Trabulsi & Mennella, 2012). However, presently, these aspects are infrequently measured so were not included in the review. This review did not include studies of parent feeding style as the aim was to identify specific formula feeding practices rather than theoretical feeding styles—which may be important for weight gain but are important across all modes of feeding, that is, breastfeeding, formula feeding, and introducing solids foods. Studies of feeding style are important considerations for infant feeding no matter which type of milk or food, and merit their own review, of which one was recently published related to the theory of responsive feeding (DiSantis et al., 2011).

5 | CONCLUSION

Although it is imperative that breastfeeding is promoted, many parents use infant formula. Health professionals and parents need high quality evidence to inform their infant feeding practice. Available evidence indicates that some formula feeding practices (such as adding cereals in bottle, putting a baby to bed with bottle, and overfeeding formula) and compositions (higher protein) that may contribute to RWG. This review contributes to the discourse in this area by highlighting both the evidence and the gaps in our understanding of how formula feeding may contribute to RWG and the opportunities for promoting those practices that promote healthy weight gain.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

CONTRIBUTIONS

JA led the study, drafted the protocol, undertook the searches, screened the abstracts, read the full-text papers, undertook data entry, performed quality assessment (MMAT), and drafted the paper. EDW refined the protocol, read the full-text papers, performed quality assessment (MMAT) and co-wrote the paper. GR, RL, CF, and KC refined the protocol and co-wrote the paper.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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