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Review

Post-discharge formula feeding in preterm infants: A systematic review mapping evidence about the role of macronutrient enrichment

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SUMMARY

Background & aims: Preterm infants are a heterogeneous group and many accumulate growth deficits before and after initial hospital discharge. Although this is associated with worse cognitive outcome, recent meta-analyses suggest that nutrient fortification of breast milk, or the use of nutrient and energy rich formulae after discharge exert little effect on growth and neurodevelopment. However, the complexity of study design, inclusion criteria and outcome parameters, combined with differences in formula composition mean that meta-analysis may overlook important effects of differing interventions in sub-groups.

Methods: We systematically identified evidence and mapped the information on Participants, Intervention, Comparator, and Outcome (PICO) from 31 published studies illustrating the marked heterogeneity in study design and interventions next to outcomes on (quality of) growth and neurodevelopment.

Results: Despite significant heterogeneity in study design, we found that nutrient enriched diets after discharge show no negative effects but frequently improve growth parameters at some point in the course of the study, in particular for boys. The data indicates that when energy requirements are adequate, increased protein results in increased growth and lean mass (LM) accretion; In particular, higher protein to energy ratios lead to increased lean mass accretion, and increased head circumference (HC) at one year. However, improvements in neurodevelopmental outcome were rarely seen.

Conclusion: This comprehensive evidence mapping approach to the field provides a broad but detailed overview of the currently available evidence. Furthermore, we identified key gaps in existing knowledge on the role of nutrient enrichment in the post-discharge period.

1. Introduction

During their initial hospital stay many preterm infants accumulate significant nutrient deficits that result in growth restriction [28]. This malnutrition coincides with a period of functional organ development and intense brain growth that may, in part, explain why preterm infants have higher risks for cognitive impairment and low IQ scores in later life. In addition, preterm infants seem to be at higher risk for subsequent development of the metabolic syndrome, including insulin insensitivity, hypertension, and cardiovascular disease, which may be due to sub-optimal nutrition at sensitive time points in early life [42]. Whether the causation for the long-term risk factors relates to the abbreviated gestational period, the degree of intrauterine growth restriction, or extrauterine growth

Non-standard abbreviations: ADP, air displacement plethysmography; AGA, appropriate for gestational age; BIA, bioelectrical impedance analysis; BPD, bronchopulmonary dysplasia; CA, corrected age; CHO, carbohydrates; -e, protein and/or nutrient enriched formula(e); FM, fat mass; GA, gestational age; GMDS, Griffith mental developmental scale; KPS, Knobloch, Passamanick, and Sherrards' developmental screening inventory; LM, lean body or fat free mass; MAC, mid-arm circumference; NBAS, neonatal behavioral assessment scale; P:E ratio, protein:energy ratio; PDF, post-discharge formula; PICO (acronym), participant – intervention – comparator – outcomes; PRISMA (acronym), preferred reporting items for systematic reviews and meta-analyses; PTF, preterm formula; SFT, skinfold thickness; SGA, small for gestational age; STF, standard term formula.

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velocity has recently been discussed in detail but would exceed the scope of this paper [42]. Although current guidelines recommend aiming for a growth velocity approximating fetal growth prior to term corrected age (CA) [5], disproportional but accelerated growth in the first months after birth may result in worse metabolic outcomes later in life [39]. Some have recommended that preterm infants without growth faltering at discharge receive maternal breast milk or, a formula intended for term infants if breast milk is not available [1,35]. When infants exhibit poor growth at discharge additional nutrients and energy may better support growth; and for these infants fortification of breast milk or the use of nutrient enriched formulae has been recommended [1,35]. However, recent meta-analyses failed to show significant benefits from fortifying breast milk as available studies are few [68] and inconsistent benefits of enriched formulae such as preterm or specific post-discharge formulae [50] after discharge. Whilst meta-analyses are considered to provide the highest level of evidence, there are significant challenges in applying their outcomes to practice situations. This includes significant heterogeneity in study design and formulae composition, lack of homogeneity in patient population and markedly different risk factors for poor nutritional status.

We adopted an 'evidence mapping' approach to address these uncertainties. This emerging concept to assess clinical evidence is reproducible and more inclusive than strictly focused meta-analyses and provides insights into clearly-defined but broad-based topics by providing a comprehensive assessment of existing knowledge and its gaps [36]. Following the PICO strategy [24], we identified variation in Participant population – Intervention – Comparator – Outcomes of interventions where energy density and/or nutrient ratio of formulae differed from the comparator. We decided *a priori* to include all studies to the topic, but allow assessment of relevance by illustrating heterogeneity in addition to outcomes of these varying nutrient interventions on growth, body composition, and neurodevelopmental outcome.

2. Methods

2.1. Method of literature search

We followed the Preferred Reporting Items For Systematic Reviews And Meta-Analyses (PRISMA) guidance [49] and searched PubMED/MEDLINE, Web of Science and Dialog databases between 1980-present without language restriction but limited to "human" (Search strategy: "preterm infants" OR "premature infants" OR "low birth-weight" OR "low birthweight" OR LBW OR "very low birthweight" OR "very low birthweight" OR VLBW OR (extremely low birth weight) OR ELBW OR infant OR newborn OR neonat*) AND (nutrition OR formula* OR "infant formula" OR milk OR "preterm formula" OR growth OR "infant nutrition" OR fortif? OR supplement?) AND (post-discharge OR postdischarge OR "hospital discharge"). These were followed by hand searches on conference abstract databases from 2000 – 2012 and 2014 (www.pas-meetings.org (Abstract archive)) using search terms "Preterm + post + discharge" or "premature + post + discharge" and "discharge", respectively.

Recent reviews (from 2009 – present) or identified study publications were cross-checked for additional studies not found by electronic searches and specialty journals which were not included in the searched databases. We searched for follow-up publications by first and last name (senior author) and corresponding authors of identified studies in PubMED and conference abstract databases and cross-referenced our findings with the Cochrane review on "*Nutrient-enriched formula versus standard term formula for preterm infants following discharge*", from now on referred to as Cochrane 2012 [69].

The search was first executed in April 2013, and repeated in October 2013 (2010 – present), January 2014 (February 2013 – present) and December 2014 (January – present) using the same search strategy and allowing for overlap to ensure recent publications were not overlooked.

2.2. Study eligibility

A priori, we decided to include all studies whose intervention started at or extended into the post-discharge period, independent of the criteria that were applied to decide the circumstance under which a preterm infant (born < 37 complete weeks gestational age (GA)) was fit to be discharged from the hospital. Comparisons were either with a term formula, or between formulae with differing degrees of nutrient and/or energy enrichment. We applied no restrictions to formula composition, start, type, or duration of intervention, preterm infant population characteristics, sample size, methods of randomization, blinding, stratification, potential group bias, drop out, compliance or lack of follow-up. Studies were limited to those with measurements of relevant outcome growth parameters (weight, length, and HC), gains, z-scores or data related to body composition assessment or cognitive function. Investigations restricted to in-hospital interventions, mixed parenteral and enteral interventions or comparisons of formulae to fortified breast milk, between preterm and term infants, or with focus on bone parameters alone were excluded as were follow-up publications of included studies not reporting growth, body composition and/or neurodevelopment.

We chose the first authors' last name and year of the first publication as identifier for each study. Data was combined with subsequent publications including conference proceedings if these contained novel information. Otherwise, they were excluded.

2.3. Formula categories

Studies were grouped by energy density of test and comparator formulae only, irrespective of terminology used in the original publication. Infant formulae developed to meet term infant requirements contain between 60 to 70 kcal/100 ml [27]. In most studies, such standard term formula (STF) was used as comparator. Test formulae with similar energy density than the comparator but higher macro-/micro-nutrient concentrations were grouped in the category "enriched" standard term formulae (STF-e). For studies investigating effects of protein quantity or quality (e.g. whey vs casein), the isocaloric formula with highest protein and nutrient concentrations was considered "enriched". Formulae with highest energy density were grouped in the "Preterm formula" (PTF) category in line with terminology for in-hospital formulae, defined here as containing ≥80 kcal/100 ml.

Formulae with intermediate energy densities between 70 to 79 kcal/100 ml were grouped in the "Post-discharge" (PDF) category despite the name being somewhat misleading since these formulae are also provided before discharge in some hospitals.

In addition to higher energy density or increased protein concentrations, the test formulae most often also contained higher concentrations of lipids, carbohydrates, and selected minerals and/or vitamins. When using the term "enriched", we refer to these energy and nutrient differences between test and comparator formulae. Consequently, comparisons between isocaloric but energy-dense formulae differing in nutrient concentrations were also labeled "enriched" (PDF-e or PTF-e, respectively).

2.4. Data extraction and recalculation

We recalculated formula composition values to present concentrations per 100 kcal, converted nutrient units to IU, mg or μg, where applicable, and calculated ratios of protein:energy and

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calcium:phosphorus from base values. Data for inclusion criteria, mean birth weight, mean gestational age, anthropometrics and sample size was extracted from tables or text wherever possible and if the data was incomplete or unavailable from publication or authors, we used it from Cochrane 2012 [69]. In case of discrepancies, we applied publication information or direct correspondence with the author. When the data was presented as standard error of the mean, we calculated standard deviations [square root of (sample size minus one) multiplied by SEM].

Observations of volume intake, on gender or on auxological parameters, body composition and neurodevelopment were extracted from tables, figures, or from the text. As the intention of formula enrichments with energy, macro- and/or micronutrients was countering growth faltering, study outcomes are marked as (un)favorable in the overviews.

For a broad mapping of effects and understanding in how many studies favorable or unfavorable effects had been reported, we combined absolute measures, z-scores, gains and velocity not only as significant outcomes but also identified non-significant trends that were either described as such in the publication or were measures with statistical outcomes of $p < 0.1$. Effects on gains were ascribed to the end of the observation period, i.e. weight gain between term and three months CA is recorded at three months assessment time. Final study outcomes were captured as reported by original authors. In addition, we compiled observations at assessment times not only of the total population but also included those for subgroups (boys, SGA) whenever these were observed.

Since interpretation of changes in body composition is complicated by a lack of agreement on the parameters of greatest interest, we decided to capture the original author's interpretation in the course of the study. Most authorities agree that promotion of LM accretion whilst avoiding excessive adiposity is an important goal for preterm infants [5]. However, although often reported fat or lean mass percent (LM% or FM%) may not be the most reliable parameter to determine changes in body composition because it requires adjustment for linear size (for example the fat mass (FM) index) [15,16]. Despite these challenges we annotate the differences in LM or FM using the symbols [+/−] where body compositional changes had been assessed at study end.

3. Results

3.1. Identification and selection

The first search in 2013 resulted in 1260 hits which were screened for relevance. From these, 58 publications were identified (26 full text, 32 conference proceedings). The subsequent searches led to two further full-text publications. Searches on abstract databases and for author names resulted in identification of six additional conference proceedings. All were screened for eligibility and combined when relating to the same study. Conference proceedings were excluded when a related full-text publication contained the same information. The most recent search identified one follow-up publication but no novel study.

In total, 31 eligible studies that investigated effects of a feeding intervention in preterm infants after hospital discharge were included, 17 of which allowed extraction of growth data in relation to P:E ratio.

3.2. Data compilation

Many studies reported outcomes in subsequent publications. This section describes for which studies data was combined.

Data for Vengi 1997 [63] and Agosti 1999 [2] were extracted from a review [48] since the original publications could not be retrieved. Data for Cooke 1998 [20] was combined from three subsequent publications [18,19,21] and information from the authors (NDE). Data for Lucas 1992 [46] was combined with growth data from Bishop et al. 1993 [11] whereas their comparator formula composition was extracted from a subsequent review [32]. Lucas 2001 [47] was combined with Onyeador et al. 2011 [51]; Cooper 1985 [23] with Cooper et al. 1989 [22]; Roggero 2012 [58] with Gianni et al. 2014 [31] and data from the authors. Authors for Amesz 2010 [6] and Roggero 2011 [59] provided additional data. Pittaluga 2011 [56] was combined with a previously published conference abstract [55] whereas preliminary data for Roggero 2012 [58], Litmanovitz 2007 [45], and Picaud 2008 [54] previously published as conference abstracts, were excluded as were follow-up publications without reports of growth [62]. One study, only published as conference proceeding, investigated visual preference development (Fagan Test of Infant Intelligence) of 104 preterm infants (birth weight 725 − 1390 g) fed enriched formula from discharge to two months CA [65], However, due to lack of information on formula composition, it was excluded although results are briefly discussed in the Neurodevelopment section. Studies that were only published as conference proceedings are identified by the letter 'A' following the year [7,8,60].

3.3. Studies grouped by formula energy density

Of the 31 included studies, eight investigated effects of isocaloric but nutrient enriched STF (67 − 68 kcal/100 ml) [6,9,10,14,22,23,29,60,66]; Thirteen studies investigated effects of energy-nutrient enriched PDF (selection range 70 − 80 kcal/100 ml, in fact all studies used energy densities between 72 and 75 kcal/100 ml) [7,8,11,13,26,31,32,40,45–47,51,58,59,61,63,67], and six studies investigated effects of PTF continued after hospital discharge (selection range 80 − 90 kcal/100 ml) ([3,12,18–21,38,53,54], Fig. 1, Supplementary Table 1). One observational prospective cohort comparison [56] evaluated effectiveness of a national feeding program for preterm infants [55,56] and three studies evaluated enrichment of a single nutrient (group) such as either long-chain poly-unsaturated fatty acids [2] or predominantly minerals [44,57] in comparison to an isocaloric comparator. These were identified in separate categories.

3.4. Heterogeneity of study population and design

The challenge in synthesizing data from multiple studies is illustrated when study feeding, design and population characteristics are considered (Fig. 1). Sixteen studies included infants with a birth weight below 2500 − 1620 g, twelve studies those with a birth weight ≤1500 g, and only two studies ≤1100 g (Agosti, 1999; Vegni, 1997) [2,63], although Carver 2001 [13] and Koo 2006 [40] stratified birth weight groups into this weight category. Mean gestational age ranged from 26 to 34.3 weeks and mean birth weights from 870 to 1990 g. Consequently, body weight at intervention start varied highly (1220 − 3210 g) with most values in the range of 2.0 − 2.5 kg.

Seven studies investigated small-for-gestational age (SGA) populations only, defined using differing criteria (Agosti, 2003; Amesz, 2010; Atkinson, 2004A; Roggero, 2011; Roggero, 2012; Taroni, 2009; Vegni, 1997) [3,6,7,58,59,61,63], but in other studies 10 − 45% of the study population was SGA (Chan, 1994; Jeon, 2011; Lucas, 2001; Picaud, 2008; Pittaluga, 2011; Raupp, 1997) [14,38,47,54,56,57]. One study included appropriate-for-gestational age (AGA) male subjects only (Agosti, 1999) [2]. Gender effects were reported in detail in six studies (Agosti, 2003; Amesz, 2010; Carver, 2001; Cooke, 1998; Lucas, 2001; Koo, 2006) [3,6,13,20,40,47].

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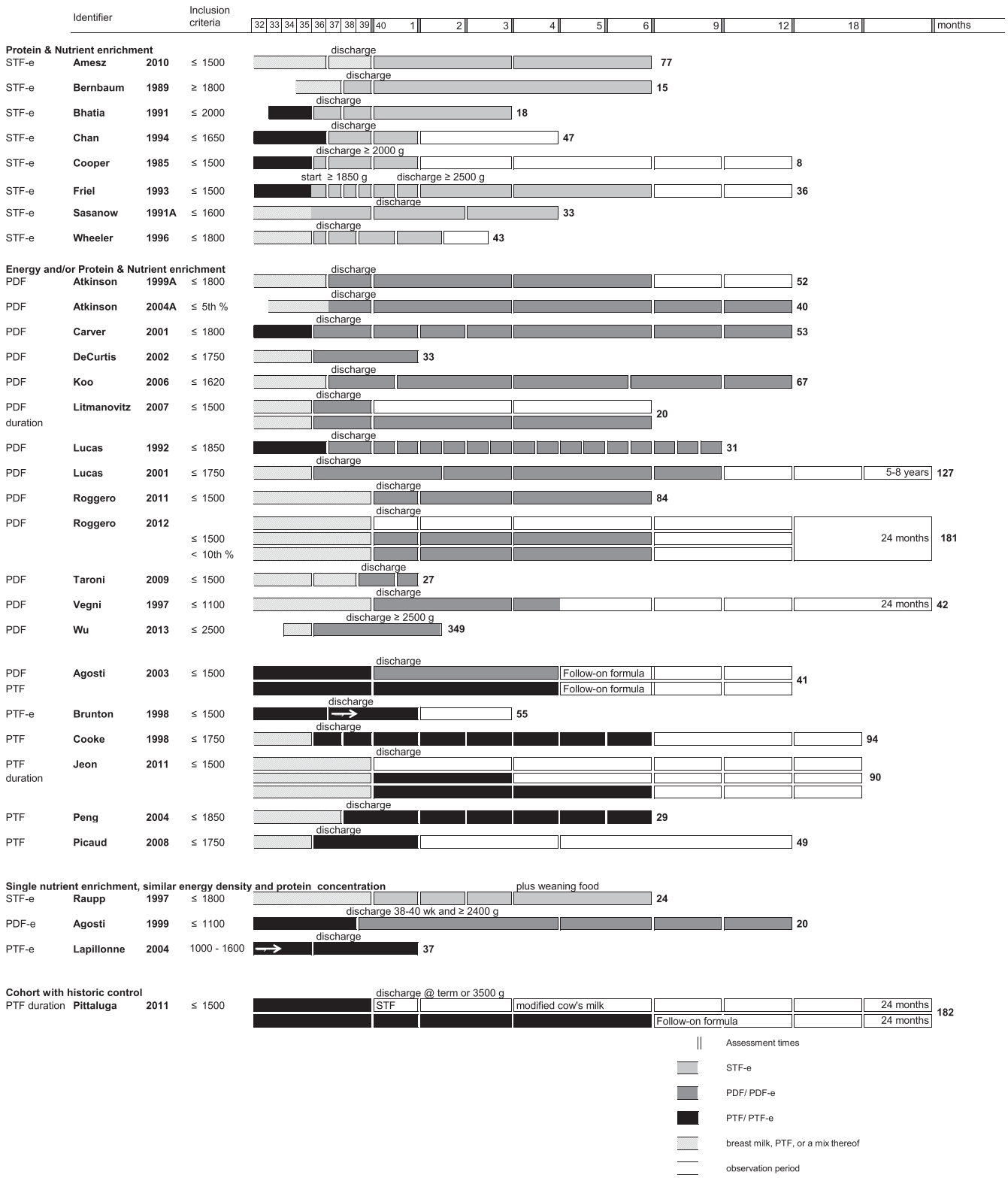

Fig. 1. Setup of 31 studies investigating effects of nutrition after discharge by alphabetical order per formula category. Observation period, intervention start and end are shown in months corrected age per study. When the comparator formula was started and provided as long as test formula, it is not specifically shown. Feeding prior to intervention is indicated between weeks 32 to intervention start (PTF – black, non-reported feeding or breast milk, PTF or a mix thereof – light grey), type of intervention is indicated by pattern and shades (STF-e – light grey, PDF – medium grey, PTF – black, feeding after intervention – white). The arrows at Brunton 1998 [12] and Lapillonne 2004 [44] indicate the intervention start with use of in-hospital PTF was extended post-discharge and used as comparator. Assessment times are breaks in flow and number of subjects at end of observational period are shown at study end. Time of discharge is indicated when differing from intervention start. Litmanovitz 2007 [45] and Jeon 2011 [38] investigated duration of exposure to enriched formula, Roggero 2012 [58] investigated effects of enriched diet on AGA and SGA populations, and Agosti 2003 [3] compared PDF with PTF. Abbreviations: PTF Preterm Formulae (80 – 90 kcal/100 ml); STF-e (enriched) Standard Term Formulae (60 – 70 kcal/100 ml: in fact all 67 – 68 kcal/100 ml); PDF Post-discharge Formulae (70 – 80 kcal/100 ml; in fact all had an energy density of 72 – 75 kcal/100 ml).

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Most often, infants with feeding difficulties, in need of oxygen, or other complicating factors at discharge were excluded with exception of Bunton, 1998 [12] who focused on infants with chronic lung disease (bronchopulmonary dysplasia, BPD). The overall population for which data is available therefore reflects relatively healthy and clinically stable preterm infants.

Prior to the intervention, infants in 11 studies received a PTF whereas in the remaining studies, feeding type before intervention start was either not reported or infants received breast milk, a PTF or a mix thereof. Interventions started in hospital substantially before discharge, at discharge, or after discharge when term corrected age and/or a certain body weight was reached. To illustrate the variation in study setup, one study continued use of PTF from full enteral feeding (30 − 34 postconceptual age) into the discharge period till term CA (Lapillonne, 2004) [44] whereas others continued PTF or fortified HM until term CA before intervention start up to either 6 or 4 months CA, respectively (Amesz, 2010; Agost, 2003) [3,6], compared to Cooke 1998 [20] whose subjects intervention began at 36 weeks postconceptual age till 6 months CA (Fig. 1).

Overall, the intervention period varied from four weeks to 12 months, assessment times from biweekly to every three months, observation period ended with intervention or subjects were followed-up to 5 − 8 years. All factors of study variation we identified are summarized in Table 1. In addition, we compiled information on study formulae illustrating the high heterogeneity between interventions from energy density and protein concentration, fat quality, mineral densities and vitamin variations (Supplementary Table 2).

3.5. Broad evidence mapping of effects on weight, length, and head circumference

An overview of (un)favorable effects (Fig. 2) shows the end result reported for the study, but also trends and significances at assessment times that includes sub-populations. Most authors did not find differences in auxological parameters at study end. This is particularly apparent in the STF-e category where a few trends on the full or sub-populations were observed most often a few weeks before and after term CA, with exception of Wheeler 1996 [66].

When differences were observed at study end, they were most often favorable for the enriched diet group (Fig. 2). Only two studies report better growth in the comparator group (Koo, 2006; Pittaluga, 2011) [40,56]. Interestingly Pittaluga 2011 [56], first found higher weight and linear growth at term to six months CA that turned to be lower at 12 months CA in the enriched diet cohort, which received PTF/PDF till six months CA whereas the historic comparator cohort received STF from discharge on (Fig. 1). This indicates a fast early weight and length gain in the early months that slows at 18 months CA that is accompanied by a better metabolic profile.

Most differences occurred within the first six months (Fig. 2). However, 15 of the 31 studies did not publish their observations beyond this age so longer term effects (e.g. at one year) are uncertain. Differences in HC measures, especially in the PDF/PTF category, were often not seen at early assessment times but only from six months CA on. One study first observed a trend for smaller HC for their SGA population at term in the PTF group which changed to a larger HC at 12 months CA, indicating catch-up growth (Fig. 2, [3]).

3.6. Quality of growth

In eighteen studies, body composition was determined using different techniques (Fig. 3): One study measured mid-arm circumference (MAC), another bioelectrical impedance analysis (BIA); five measured skinfold thickness (SFT) and although differences early in the study were found, none detected differences at the end of the respective observation period. However, when dual-energy x-ray absorptiometry (DXA) and air displacement plethysmography (ADP) were used, differences in fat and lean mass accretion were observed in the course of seven studies.

Amesz 2010 [6] reported increased LM and decreased FM accretion related to body size in subjects that received PTF till term CA followed by a protein and nutrient-rich STF-e (protein:energy (P:E) ratio 2.54, Supplementary Table 2) till six months CA without affecting any of the growth parameters (Figs. 2 and 3).

Table 1
Heterogeneity of study design − major variation factors identified from evidence mapping.

Design characteristics	Key examples
Population inclusion criteria	1. Gestation or birth weight eligibility criteria
	2. Inclusion/exclusion of small for gestational age
	3. Previous nutritional exposures − breast milk, formula, a mix thereof
	4. Presence/absence of key neonatal pathologies
	5. Approach to inclusion and randomization of infants from multiple pregnancy
	6. Stratification to birth weight, gender and/or sub-populations
	7. Sample size
Interventions	8. Energy density of milk formula
	9. Macronutrient composition of formula
	10. Micronutrient and vitamin content of formula
	11. Differences in comparator formula
Trial related procedures	12. Blinding, masking and randomization processes
	13. Sample size determination
Study timing	14. Continuation of preterm formula, or change to test formula before, at, or after discharge
	15. Definition of discharge criteria (by weight and/or age)
Exposure to intervention	16. Continuation until specific post-menstrual age or weight was attained
Outcome assessments	17. Frequency and duration of outcome assessment during intervention period and follow-up period after intervention
Outcome parameters	18. Formula intake measured or reported
	19. Absolute measures vs gain defined differently (i.e. g/day, g/kg/day, g/week, or between study assessment times) vs change in parameter centiles (standard deviation scores)
	20. Body composition techniques e.g. skinfold thickness, dual X-ray absorptiometry or air-displacement plethysmography
	21. Definition of quality of growth
	22. Neurodevelopment e.g. different tools and ages of assessment

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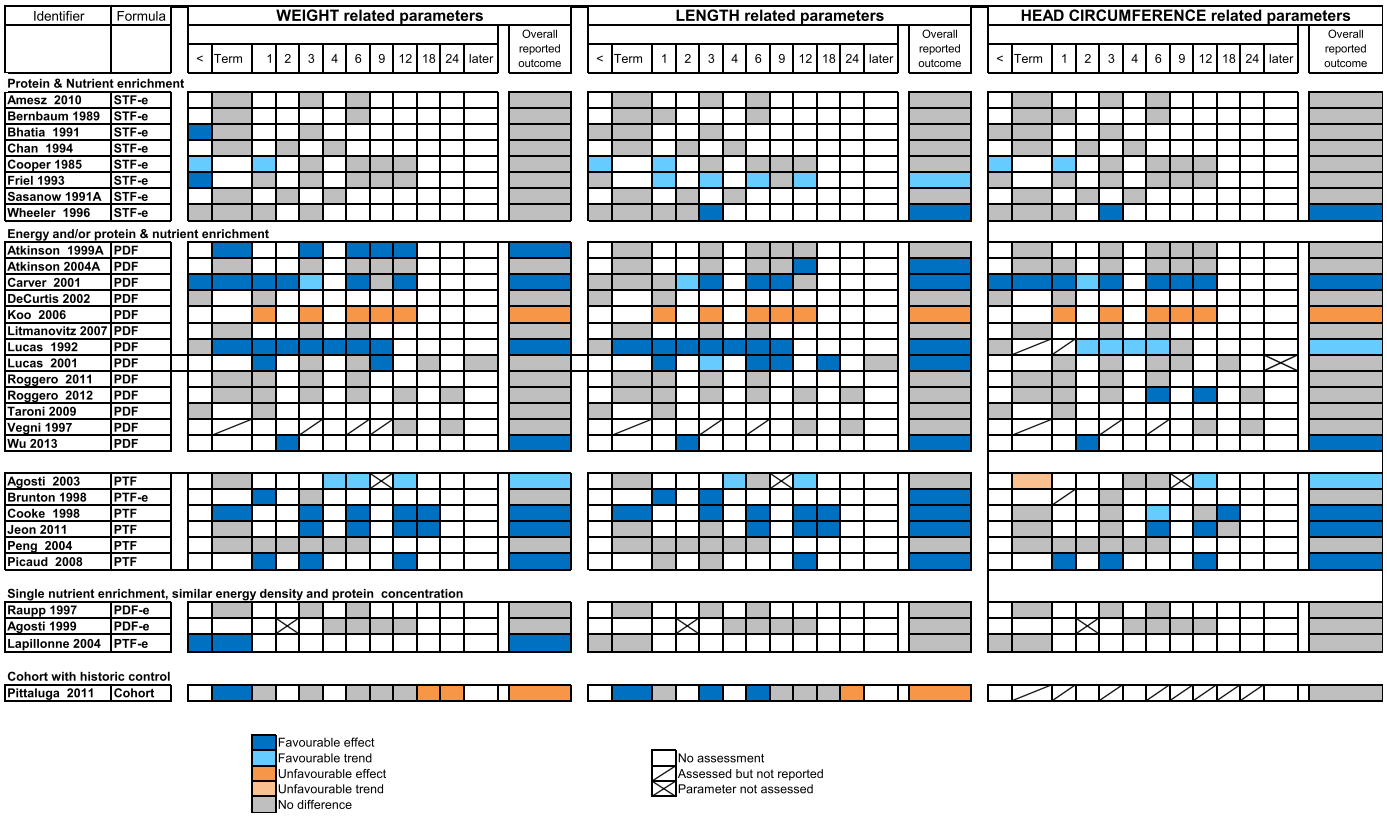

Fig. 2. Overview Growth parameters at the end and during the studies. Any effect of enriched formula on either absolute measures, gains, z-scores of weight, length, or head circumference as reported by the original authors was captured in this overview and identified as unfavorable (orange), favorable (blue) or 'not different' (grey). Trends as reported in text or as $p < 0.1$ are identified by lighter shade. A diagonal line indicates that assessments were made but not reported. A crossed out section indicates that a visit took place but that this particular parameter was not assessed.

Roggero 2012 [58] achieved proportional increases of LM and lower FM accretion after supplying PDF (P:E ratio 2.7) for six months also without reporting effects on growth.

Although subjects in the Chilean cohort [56] were lighter and shorter than their historic control peers that had not received PDF or PTF for six months (P:E ratio 2.8 – 3.0), they accrued similar lean mass percentages and were less fat.

Cooke 1998 [20] and Lapillonne 2004 [44] proportionally increased LM and FM with their respective interventions of six months PTF (P:E ratio 2.75) or a higher protein calcium-phosphorus rich PTF-e (P:E ratio 2.72) that was provided till one month CA using the same assessment method.

Only one study identified unfavorable body composition (Koo, 2006) [40]. In line with their observations on lighter, shorter subjects with lower HC after one year of supplying PDF (P:E ratio 2.6), they found less accretion of either LM or FM (Figs. 2 and 3).

3.7. Neurodevelopment

Neurodevelopmental outcomes up to 24 months or later were assessed in ten studies either by the Neonatal Behavioral Assessment Scale (NBAS), Griffith Mental Developmental Scale (GMDS), Bayley Scales of Infant Development (BSID) or the Fagan Test of Infant Intelligence [65]. Two of these identified significant benefits of enriched formula (Vegni, 1997) [63], and Werkman et al. [65], and one further study described a beneficial trend (Agosti, 1999) [2]. Both Agosti 1999 [2] and Vegni 1997 [63] included infants born ≤1100 g and analyzed SGA infants separately.

Interestingly, the preliminary analysis of the 24 months follow-up of Roggero, 2012 [58] identified improved cognitive measures via GMDS in the PDF group (Gianni et al., 2013) [30]. Unfortunately, this effect was no longer present in the complete population [31]. No unfavorable effects were identified applying any of the enriched formulae (Fig. 4).

3.8. Volume intake and P:E ratio

Twenty-one studies published data on volume intake (Fig. 5). Eight of these found a higher intake for the less energy-dense comparator formula. Ten of the thirteen studies that did not find any consistent difference were comparing isocaloric formulae, suggesting that infants adjusted their volume intake based on energy intake.

In line with this observation, we calculated the P:E ratio of test and comparator formulae (Supplementary Table 2) and plotted these against absolute measures of weight, length and head circumference at three, six, and 12 months CA (Fig. 6 and Supplemental Figures).

Although it should be noted that the studies do not allow a direct comparison because of variation in study population and setting (Table 1, Fig. 1), all three growth parameters increased when a higher P:E ratio was provided. In particular, length and head circumference at 12 months CA appear greater with a higher P:E ratio.

3.9. Gender

Fourteen studies reported gender effects (Fig. 5). Of these, nine reported that males responded more sensitively to the enriched diet whereas five found no difference between formula groups. Two studies reported a higher quality of growth

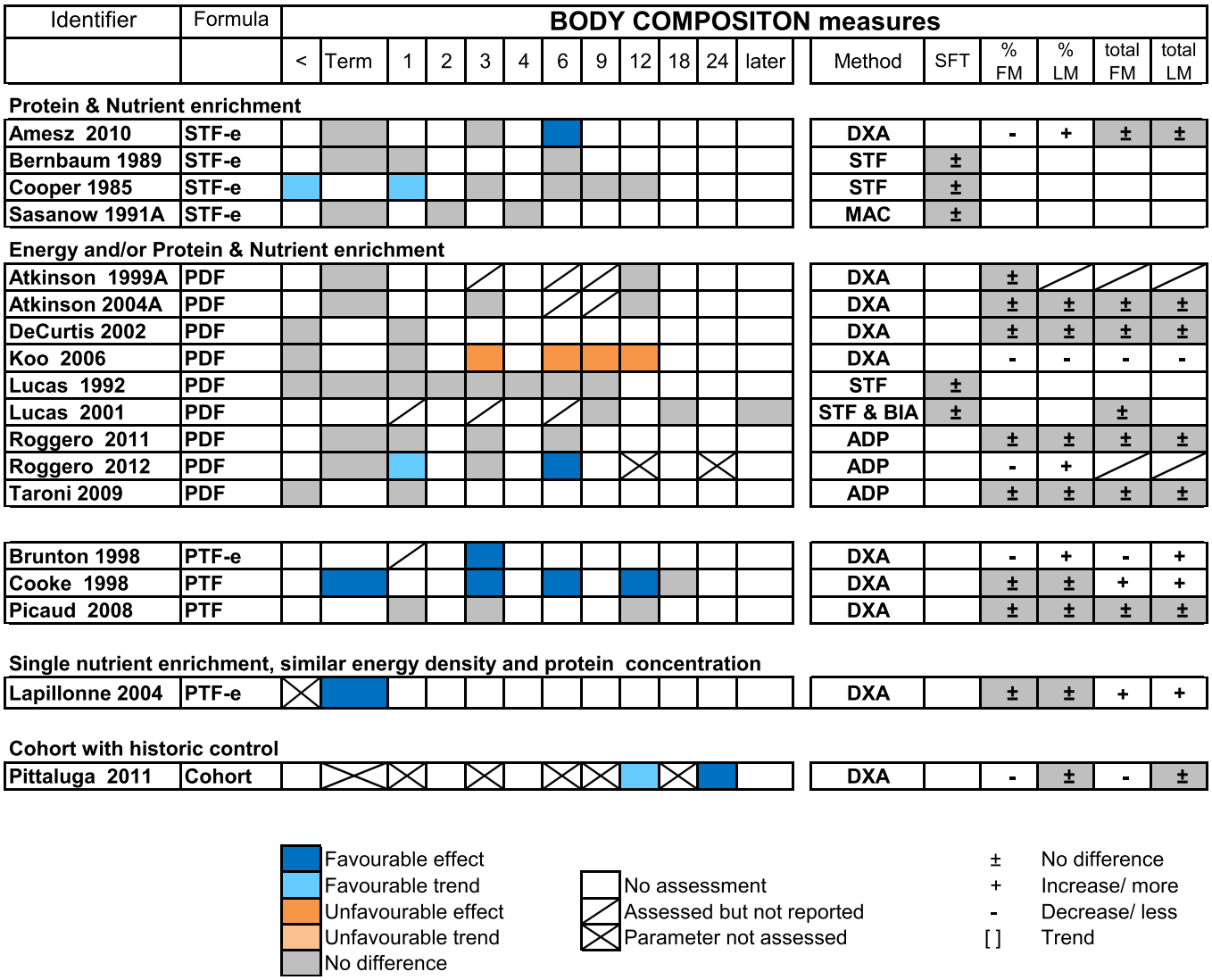

Fig. 3. Overview Body Composition assessed by different methods. Left panel: Reported outcomes in the course of the study were identified by original author as unfavorable (orange), favorable (blue) or 'not different' (grey). Trends as reported in text or as $p < 0.1$ are identified by lighter shade. Right panel: Outcome at study end. Symbols + and − indicate less and more accretion of the respective tissue mass; the symbol ± indicates no difference thereof. A diagonal line indicates that assessments were made but not reported. A crossed out section indicates that a visit took place but that this parameter was not assessed.

particularly for males (Cooke, 1998; Amesz, 2010) [6,20], that was not observed in Roggero 2012 [58]. Agosti 2003 [3] found higher GMDS scores in boys at 6 and 9 months CA.

3.10. Specific populations

Several studies analyzed data on SGA subjects but found variable effects (Figs. 2, 3 and 4): Neither Taroni 2009 [61] nor Roggero [59] or [58] reported differences in any of the auxological parameters for the SGA population. In Roggero 2012 [58] both AGA and SGA populations in the PDF intervention group showed more LM gain especially between three to six months CA. However, only for the AGA group were these findings significant. Atkinson 2004A [7] found greater linear growth whereas Amesz 2010 [6] found weight and length gain as well as a higher quality of growth (less FM accretion) in the SGA population. Vegni 1997 [63] significantly improved GMDS scores at two years, and Agosti 2003 [3] improved GMDS scores at six months CA together with greater linear growth.

Only Brunton 1998 [12] investigated subjects with BPD and they observed greater linear growth, less accretion of total and relative fat mass in parallel to increased accretion of total and relative lean mass applying a PTF intervention enriched in protein and minerals but not in energy (Figs. 2 and 3, Supplementary Table 2).

4. Discussion

This review highlights the marked heterogeneity between studies examining effects of post-discharge formula intervention following the PICO strategy of evidence mapping [24,36]. The lack of similarities between studies (Table 1, Supplementary Table 2, and Fig. 1) with regard to population characteristics, inclusion criteria, formula composition, initiation and duration of intervention, and several other potential confounders of later growth undermines efforts of meta-analyses. In addition, many of these studies relate to infants born more than 10 − 20 years ago, where antenatal steroid use, perinatal mortality and nutritional care were very different. The high variations in pre- and post-discharge intervention periods make identification of the most sensitive window of plasticity for nutrient enrichment difficult. This variation is in part due to the arbitrary nature of "post-discharge": age and stage at which an infant is sent

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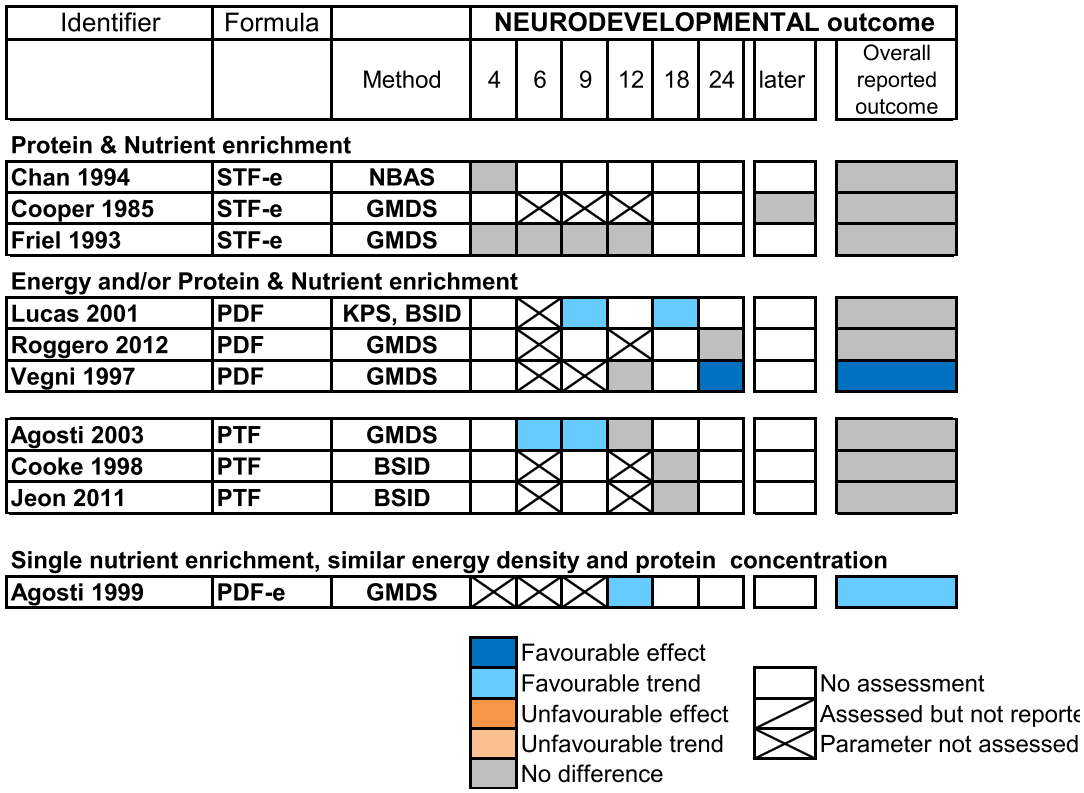

Fig. 4. Overview Neurodevelopment assessed by different methods between four months up to three years. Favorable impact of enriched formulae (trend $p < 0.1$ or stated in the text by original author) is indicated in blue; statistically significant outcomes in the darker shade. Grey indicates no difference. A diagonal line indicates that assessments were made but not reported. A crossed out section indicates that a visit took place but that this parameter was not assessed. Note: Bayley Scales of Infant Development II; DXA, Dual-energy X-ray absorptiometry; FM, Fat mass; LM, Lean body or fat-free mass; NBAS test.

home depends on local policies and will also vary depending on illness severity. Not all studies shared in-hospital feeding practices, which especially in case of older studies may have resulted in study populations having been fed unfortified maternal milk and those having received PTF, which may have affected the magnitude of affects, especially if groups were not stratified to previous feeding. Similarly, the variation in formulae composition limits conclusion about the highest effect of rate limiting nutrients. Drawing clear conclusions from such heterogenous data is difficult. Despite these predicaments, there appears to be an association between the protein and nutrient concentrations, when energy is secured, with growth, particularly on HC, and body composition, more so than with a particular formula type itself (Fig. 6).

Identifier	Formula	Volume Intake	Effect boys > girls
Protein & Nutrient enrichment			
Amesz 2010	STF-e	STF = STF-e	>
Chan 1994	STF-e	STF = STF-e	>
Friel 1993	STF-e	STF = STF-e	>
Energy and/or Protein & Nutrient enrichment			
Carver 2001	PDF	STF > PDF	>
DeCurtis 2002	PDF	STF = PDF	=
Koo 2006	PDF		=
Lucas 2001	PDF		>
Roggero 2011	PDF	STF > PDF	=
Roggero 2012	PDF	STF > PDF	=
Agosti 2003	PTF	PDF > PTF	>
Brunton 1998	PTF-e	PTF = PTF-e	>
Cooke 1998	PTF	STF > PTF	>
Jeon 2011	PTF		
Peng 2004	PTF	STF = PTF	
Picaud 2008	PTF	STF > PTF	=
Cohort with historic control			
Pittaluga 2011	Cohort		>

Fig. 5. Volume Intake observations and effect by gender are shown for comparator and intervention formula per study as reported by the original authors or extracted from text. Symbols indicate effects that are equal to (=), above (>), or below (<) the intervention formula or other gender.

The benefit of providing protein and energy at a ratio ≥2.5 to 3.0 until 6 months corrected age on growth and quality of growth is worthy of note (Figs. 2, 3 and 6), (Amesz, 2010; Cooke, 1998; Roggero, 2012; Pittaluga, 2011) [6,20,56,58]. Linear growth seems to be most responsive to an increased P:E ratio as higher absolute measures are apparent from three months onwards; weight and HC are visibly affected at 12 months (Fig. 6). However, the 5 – 8 year follow-up of Lucas 2001 [51] indicates that these or similar effects may only be transitory.

Quality of growth measures has not been firmly established [43]. Accretion of less visceral fat mass, increased LM or FM deposition in the extremities rather than the trunk may all be indicators of a more favorable distribution (Amesz et al., 2010; Cooke et al., 2001; Koo et al., 2006; Pittaluga et al., 2011) [6,17,40,56]. Interestingly, the cohort study that reported lighter and shorter children in the energy and nutrient enriched group at one and two years of age also observed these children to accumulate less FM, including trunk fat, but similar LM. This was paralleled by lower fasting serum insulin concentrations, which indicates a better metabolic profile for the cohort having received a P:E ratio of 2.8 – 3.0 for six months [55,56]. Interestingly, the study of Koo 2006 [40] showed very different results for growth and quality of growth parameters

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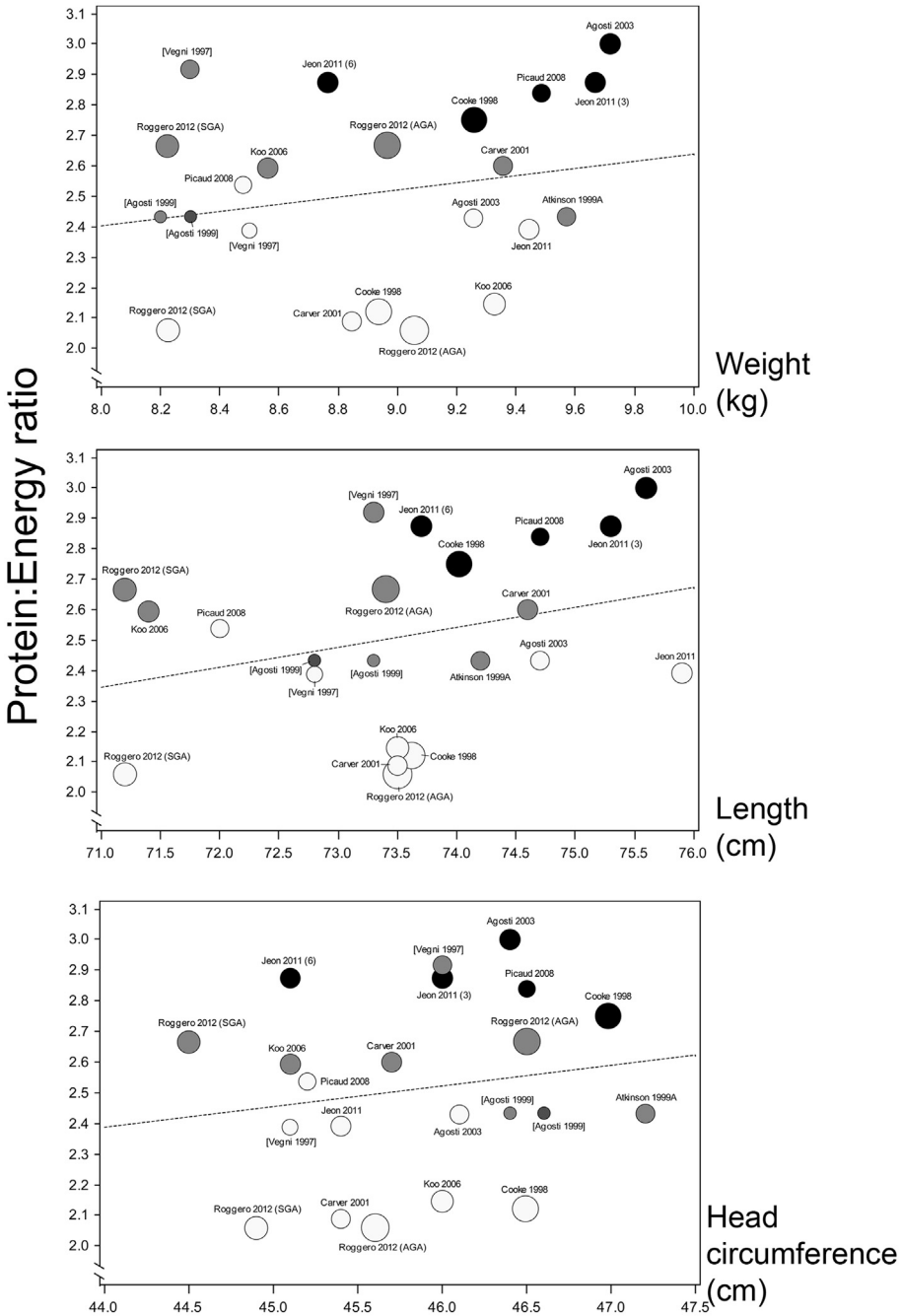

Fig. 6. Absolute measures of weight, length, head circumference at 12 months CA were plotted against the protein:energy ratio of study formulae and comparators. STF formulae are marked in white, STF-e in light grey, PDF/PDF-e in medium grey, and PTF/PTF-e in black. The circle circumference indicates study population size. Specific study population characteristics are added in brackets i.e. AGA/SGA for Roggero 2012 [58] or the two conditions of 3 and 6 months intervention with the same PTF for Jeon 2011 [38]. The simple regression line indicates increases for all three growth parameters when a higher P:E ratio was provided, especially at 12 months CA. Linear growth seems to be most sensitive to a high P:E ratio. Data at three and six months is provided as Supplementary material.

compared to the other studies. Unfortunately, there is no scientific explanation for the findings in this study and the majority of the other studies found quite consistent trends towards results in favor of the postdischarge formulas. In addition, there are no possibilities to further explore what could have been the reason for these very different results in the study of Koo 2006 [40].

Head circumference is a marker for brain growth and development and is correlated to later cognitive function [25,33,34,52], but we only identified one study (in growth restricted very low birth weight infants) that suggested a persisting benefit at 24 months of age from an enriched diet [63]. Developmental assessment methods used in most studies e.g. BSID, are not designed to be tests of cognitive function, and neither are they sufficiently sensitive to detect nutrient effects unless such effects are large. None of the studies were sufficiently powered to detect a realistic difference in a global measure of development. MRI based techniques may indicate effects on the brain [37], as might the developing technique of tractography. In one study a measure of corticospinal tract function (MagSTim) suggested benefits for brain damaged preterm and term children, although the study was terminated early because of the significantly increased head growth from enhanced caloric and protein intake over one year [25].

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It is possible that the window of plasticity to influence neurocognitive outcomes is less sensitive to nutritional interventions as proposed [31]. However, findings such as those of Dabydeen and colleagues [25] indicate differently and suggest the importance of the first year. It is as likely that the lack of long-term effects including on neurodevelopmental outcomes may be related to the majority of data having been collected from relatively healthy and stable preterm infants. Subjects with feeding difficulty and comorbidities were generally excluded [31,41]. We observed that certain populations such as boys, SGA, and those with BPD particularly benefit from protein and nutrient enrichment with regard to growth and its quality.

Determining which specific nutrient exerts effects is virtually impossible as nutritional studies are very different from most pharmaceutical studies: Nutrition may be considered a 'package' intervention although in some specific studies a single nutrient (e.g. iodine [48], predominantly minerals [44], or docosahexanoic acid [2,48]) may be key drivers of any effects observed when protein and energy requirements are met. It is likely that the first limiting nutrient will set the ceiling for outcomes: other nutrients may be important in affecting the outcome (e.g. neurodevelopment) but their effects will not be apparent if other nutrients are also impacting on development.

Our evidence mapping identified several research gaps that include (1) the definition of healthy growth in the post-discharge period, the questions (2) the window of highest plasticity for intervention, (3) how compromised preterm infants with comorbidities, feeding difficulties, and growth faltering at discharge are affected by a high protein:energy and/or nutrient:energy ratio, (4) which nutrients besides protein are particularly relevant for healthy growth and neurodevelopment, and (5) which techniques, approaches, and measures are sensitive enough to capture subtle developmental improvements on neurocognitive function and behavior by nutritional interventions.

Overall, this review highlights the marked heterogeneity of studies examining effects of post-discharge formula. Despite these variables, we found that preterm infants in the post-discharge period are able to adjust their volume intake by caloric density and that the provision of a high P:E ratio seems beneficial especially for certain sub-populations. A high P:E ratio ($\geq 2.5 - 2.7$) provided for six months CA seems to support growth and quality thereof. Considering the heterogeneity of available data it seems prudent to carefully monitor proportional growth of length and weight avoiding overfeeding once a steady growth velocity has been achieved.

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Statement of authorship

ICT, NDE, RVE designed the research which was conducted by ICT in form of study identification, data extraction, and figure generation. ICT, IJG, and NDE analyzed the data. All authors contributed equally to manuscript writing and take equal responsibility for final content.

Conflict of interest

RvE and ICT are employees of Nutricia Research, Utrecht, The Netherlands. NDE has previously conducted research with support from manufacturers of infant formula including Nestec SA (Switzerland), Wyeth UK and Nutricia UK but did not receive any payment, support, or benefit in kind for contribution to this manuscript and has no ongoing personal, consultancy or financial relationships with Nutricia or other relevant commercial interest. IJG has nothing to declare.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2015.08.006.

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