Breast feeding in infants diagnosed with phenylketonuria (PKU): a scoping review

Jahnavi Kalvala,1,2 Lydia Chong,1,2 Neil Chadborn,1,3 Shalini Ojha 2,4

ABSTRACT

Background Phenylketonuria (PKU) is the most common inherited disease of amino acid metabolism, characterised by elevated levels of phenylalanine (Phe). There is a lack of infant feeding guidance for those with PKU. From birth to 6 months of age, breast feeding is the optimal nutrition for an infant and continuing breast feeding for infants with PKU is recommended by European guidelines. However, human breast milk contains Phe in varying quantities, and therefore, the effects breast feeding might have on infants with PKU needs careful consideration.

Aim To assess the effects of breast feeding (exclusive or partial) compared with low-Phe formula feeding in infants diagnosed with PKU, on blood Phe levels, growth and neurodevelopmental scores.

Methods The Cochrane Inborn Errors of Metabolism Trials Register, MEDLINE and Embase were searched (date of latest search: 9 August 2022). Studies were included if they looked at the effects of breast feeding in infants diagnosed with PKU compared with formula feeding. Predetermined outcomes included blood Phe levels, growth in the first 2 years of life and neurodevelopmental scores.

Results Seven observational studies (282 participants) met the inclusion criteria. All studies compared continuation of breast feeding with low-Phe formula versus formula feeding only. While most studies concluded that there was no difference in mean serum Phe levels in their follow-up period, two reported that breastfed infants were more likely to have a normal mean Phe level. Two studies described no difference in mean weight gain after birth, while one found that breastfed infants were more likely to have higher mean weight gain. Two studies commented that breastfed infants achieved higher developmental scores in childhood as compared with formula fed infants.

Conclusion Although there are no randomised trials, observational evidence suggests that continuation of breast feeding and supplementation with low-Phe formula is safe and may be beneficial for infants diagnosed with PKU.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Infants diagnosed with phenylketonuria (PKU) need dietary management to maintain safe serum phenylalanine (Phe) levels.
- Usually, breast feeding is the best form of nutrition and care for babies between birth and 6 months.
- Human breast milk contains Phe and infants with PKU who continue to breast feed may need supplementation to prevent high serum Phe levels.

WHAT THIS STUDY ADDS

- Observational studies suggest that continuing breast feeding along with supplementation with low-Phe formula is safe and possibly beneficial in infants diagnosed with PKU.
- There are no randomised trials to compare continuation of breast feeding with formula feeding only and no studies investigating exclusive breast feeding in infants with PKU.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Parents of infants diagnosed with PKU should be supported to continue to breast feed after diagnosis.
- National policy should recommend continuation of breast feeding after diagnosis to ensure infants with PKU gain the benefits of breast feeding while maintaining safe Phe levels.

INTRODUCTION

Phenylketonuria (PKU) is the most common inherited disease of amino acid metabolism, characterised by elevated levels of phenylalanine (Phe) which affect the fetal brain, heart and nervous system development in the newborn infant.1 Dietary restriction of Phe is the mainstay of treatment and as soon as the condition is suspected or diagnosed, restricting protein intake by lowering the amount of milk containing Phe, such as breast milk or standard infant formula, and supplementing the diet with low-Phe protein substitutes is recommended.1

Human breast milk has low Phe content, containing approximately 46mg per 100mL.2 From birth to 6 months of age, breast feeding is the optimal nutrition for most infants. It is optimal for infant growth and development and has other advantages, such as lower risk of sudden infant death, fewer infections (such as otitis media), as well as long-term benefits of lower risk of obesity, diabetes and an association with higher performance on intelligence tests.3
There is no agreed approach to optimal feeding methods for newborn babies and infants with PKU and no clear guidance given in the UK (National Institute of Health and Care Excellence (NICE)), although the European guidelines recommend that in infants with PKU, breast feeding in combination with specialised formula should be encouraged. These European guidelines also recommend treatment should start as early as possible to prevent neurological damage. Due to variability in the concentration of Phe in human milk and because the volume of milk consumed cannot be measured accurately for a baby feeding directly on the breast, the effects of breast feeding might have on infants with PKU needs careful monitoring, especially in the early weeks of life to accurately obtain Phe results. Infants with PKU are often offered low-Phe milk to ensure that their Phe intake can be controlled.

Our previous systematic review searched for randomised controlled trials (RCT) and found zero publications. We now aim to conduct a scoping review of ‘non-RCT’ (or a broad range of study types) literature to assess the effects of breast feeding (exclusive or partial) compared with feeding low-Phe formula milk only in infants with PKU in the first 6 months after birth.

**METHODS**

We performed this scoping review with a similar protocol as our review protocol for a systematic review for the same research question, except in the plan to include all study types and not restrict the review to RCTs as was previously done. We included all studies where the participants were infants diagnosed with PKU (via newborn screening programme or later) in the first 6 months after birth and their mothers. We excluded studies on infants born to mothers who have PKU, regardless of whether the infants themselves have PKU.

We included studies where exclusive or partial breast feeding (as defined by the WHO) was compared with low-Phe formula feeding. Exclusive breast feeding is defined as when the infant receives only breast milk. No other liquids or solids are given—not even water—except oral rehydration solutions, or drops or syrups of vitamins, minerals or medicines. Partial breast feeding means that an infant continues to breast feed but is also receiving other milk.

Our predetermined outcomes were blood Phe levels (at 6 and/or 12 months after birth); growth in the first 2 years of life (measured as changes in weight-for-age z scores, height-for-age z scores, head circumference-for-age z scores or weight-for-height z scores); neurodevelopmental scores in children aged 12 months or older based on validated assessment tools, such as the Bayley Scale Index.

In addition, we included studies that reported any adverse psychological effects in the child or the mother due to infant feeding choices and practice as measured by standardised methods such as the Infant and Toddler Quality of Life Questionnaire or mother–infant bonding measured using standardised methods such as the Post-partum Bonding Questionnaire.

We planned to include all types of studies. We have previously published a systematic review of RCTs which found no published studies (Cochrane review, in press). For this review of diverse study types, we did not expect sufficient data for meta-analysis, but instead planned a narrative analysis.

A systematic search was conducted (date of latest search: 9 August 2022) of the following electronic databases: PubMed, Embase, Cochrane Library, CINAHL and MEDLINE. Searches were conducted on all relevant published and unpublished studies without restrictions on language, year or publication status using criteria and standard methods as described by Cochrane.

The search terms included:
- Condition or disease: PKU OR phenylketonuria OR PAH OR hyperphenylalaninemia OR phenylalanine hydroxylase deficiency.
- Other terms: breast OR breastfeed OR breastfeeding OR breastfed OR “chest feed” OR “chest feeding” OR “chest fed” OR chestfeed OR chestfeeding OR chestfed OR milk.

Two independent reviewers (LC and JK) screened the titles and abstracts of all identified studies for eligibility and reviewed the full text articles for inclusion in the review. Data from the included articles were extracted using a standardised data extraction form by two independent reviewers (LC and JK). The extracted data included study characteristics (eg, study design, sample size, study population), intervention details (eg, duration, frequency, exclusions), and outcome data (eg, means, SD, effect sizes). Any discrepancies between the two reviewers were resolved through discussion and consensus. A third reviewer (NC or SO) was consulted if there were any disagreements.

A narrative synthesis approach was used to summarise the findings of the included studies. The results of the review were presented in a descriptive summary and a tabular format, including study characteristics, intervention details and outcome data.

We followed a similar search strategy as performed for our systematic review with the Cochrane Collaboration. We searched the following databases and trial registries: MEDLINE Ovid (1946 to present); Embase Ovid (1974 to present); US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov); WHO International Clinical Trials Registry Platform (trialssearch.who.int/). We checked the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials. We contacted experts in the field to obtain additional information on relevant trials, where applicable. The date of the latest search was 9 August 2022. We removed duplicates using Covidence software prior to title and abstract screening and removed any additional duplicates during the screening process.
RESULTS

The electronic searches yielded 86 articles of which seven were selected for inclusion (figure 1).

The description of the included studies is given in table 1. Publication dates ranged from 1996 to 2018 including two studies published in the last decade; (Kose et al and Aksoy). We found four studies from Europe, two from South America and one from the USA.

We performed a systematic search but did not find RCTs using our search strategy. Lamônica et al collected data prospectively, where as all others were retrospective. Most studies compared infants who were breastfed...
<table>
<thead>
<tr>
<th>Study ID/Country</th>
<th>Study design</th>
<th>No of infants</th>
<th>Infant characteristic</th>
<th>Mother’s characteristics</th>
<th>Method of diagnosis</th>
<th>Duration of Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aksoy 2015⁹</td>
<td>Retrospective case series</td>
<td>25</td>
<td>15</td>
<td>Age at study entry: 25±8 days BW: NR GA: NR Feeding before diagnosis: 40 breastfed; 1 formula fed</td>
<td>Age: NR Ethnicity: NR SE factors: NR</td>
<td>National Neonatal Screening Programme</td>
</tr>
<tr>
<td>Banta-Wright et al 2012¹³</td>
<td>Retrospective case series</td>
<td>75</td>
<td>22</td>
<td>Age at study entry: mean (range) in days Breastfed 15 (5–56) Formula fed 17 (6–44) BW: Breastfed=3.46 kg (2.05–5.3), Formula fed = 3.66 kg (1.5–5.2) GA: NR</td>
<td>Age: NR Ethnicity: NR SE factors: NR</td>
<td>PKU screening postpartum, Guthrie cards</td>
</tr>
<tr>
<td>Lamônica et al 2012¹⁰</td>
<td>Prospective case series</td>
<td>10</td>
<td>0</td>
<td>Age at start of mixed diet, mean (range) days 17.8 (7–30)* BW: NR GA: NR</td>
<td>Age: NR Ethnicity: NR SE factors: NR</td>
<td>Neonatal screening, blood tests via venepuncture</td>
</tr>
<tr>
<td>van Rijn et al 2003¹⁠</td>
<td>Non-randomised controlled study</td>
<td>9</td>
<td>9</td>
<td>Age at diagnosis: median (range) in days; Breastfed=7 (6–8); Formula-fed =12 (9–16) BW mean (SD) z-score: breastfed=−0.52 (−1.37 to 0.65); formula fed = −0.33 (−1.79 to 3.11) GA: NR</td>
<td>Age: NR Ethnicity: Dutch n=13; Turkish n=4; Georgian; n=1 SE factors: NR</td>
<td>Neonatal screening</td>
</tr>
<tr>
<td>Riva et al 1996⁷</td>
<td>Retrospective case series</td>
<td>13</td>
<td>13</td>
<td>Age at diagnosis mean in days: Breastfed; 28.1; formula fed; 27.6 BW=NR GA mean (SD) in weeks: Breastfed, 39.8 (0.8); formula fed, 39.5 (1.2)</td>
<td>Age in year, mean (SD): Breastfed, 26.6 (5.4); Formula fed, 28.6 (4.4) Ethnicity: NR SE factors: mother with lower education status: Breastfed, 8; formula fed, 9 Fathers with lower work position: Breastfed, 6; Formula fed, 7</td>
<td>Neonatal screening</td>
</tr>
<tr>
<td>Kose et al 2018⁸</td>
<td>Retrospective case series</td>
<td>25</td>
<td>16</td>
<td>Age at diagnosis: mean (range) in days: Breastfed, 18.8 (3–36); Formula fed, 21.1 (10–34) BW=NR—given as ‘no statistically significant difference was found in terms of birth weight and birth weight percentile’ GA=NR</td>
<td>Age: NR Ethnicity: NR SE factors: no difference in family income, urban vs rural, maternal education, parity or previous breastfeeding experience</td>
<td>Neonatal screening</td>
</tr>
<tr>
<td>Kanufre et al 2007¹²</td>
<td>Non-randomised controlled study</td>
<td>35</td>
<td>35</td>
<td>Age at screening test, median (range) in days: breastfed, 7 (4–25); control: 6 (4–19) BW median (range) in kg=Breastfed, 3.2 (2.6–4.2); control 3.0 (2.5–3.9) GA=NR</td>
<td>Age: NR Ethnicity: NR SE factors: NR</td>
<td>Neonatal screening programme</td>
</tr>
</tbody>
</table>

*Calculated from individual patient data reported.

BW, birth weight; GA, gestational age at birth; NR, not reported; PKU, phenylketonuria; SE, Socioeconomic.
versus formula fed after diagnosis except Riva et al\textsuperscript{7} who compared those breastfed versus formula fed before diagnosis; only 5 of 13 infants in this study continued to breastfeed after diagnosis. Most studies reported a series of cases except van Rijn et al\textsuperscript{10} and Kanufre et al\textsuperscript{12} which were non-randomised controlled studies (retrospective controls). Two studies\textsuperscript{10,13} were single centre. Others did not describe the setting.

The age of diagnosis or study entry of infants is given in table 1, all were diagnosed in early infancy via neonatal screening programmes in all studies.

The total number of participants in all included studies was 282 with study sample sizes ranging from 10 to 97 (median, 40). Lamôñica et al\textsuperscript{11} included only breastfed infants while the others included both breastfed and non-breastfed infants with the number of breastfed infants (total=192) ranging from 9 to 75 (median, 25). The duration of follow-up was not specified in Banta-Wright et al\textsuperscript{13} and Lamôñica et al.\textsuperscript{11} The other studies ranged from 51 days to 12 months except Riva et al\textsuperscript{7} which reported outcomes at a median age of 9.5 years.

Maternal and infant characteristics
Reported maternal characteristics are given in table 1. Riva et al\textsuperscript{7} reported age and socioeconomic characteristics. This was also described in Kose et al\textsuperscript{8} while van Rijn et al\textsuperscript{10} categorised mothers into Dutch, Turkish and Georgian ethnicities. Infants’ birth weight was reported in Banta-Wright et al,\textsuperscript{13} van Rijn et al\textsuperscript{10} and Kanufre et al\textsuperscript{12} while Kose et al\textsuperscript{8} reported that there was no difference in birth weight between the two groups. Gestational age at birth was reported in Riva et al\textsuperscript{7} only.

The duration of breast feeding was reported by all studies (online supplemental table 1). There were wide variations: in Riva et al\textsuperscript{7} only 5 of 13 mothers in the breastfed group continued breast feeding after diagnosis and breastfed for 2 weeks. In the other studies, all mothers in the breastfed group continued to breastfeed with mean durations ranging from 10 weeks\textsuperscript{10} to 7.4 months.\textsuperscript{9} Plasma Phe levels at the time of diagnosis were reported in five studies.\textsuperscript{7,10–13}

Outcomes
Online supplemental table 1 summarises the results of the included studies.

Risk of bias
The risk of bias assessment was done according to the ROBINS-I tool. The results are shown in figures 2 and 3. All articles were graded as moderate risk of bias, apart from Aksoy\textsuperscript{9} where there was not enough information to make a judgement.

Quality of evidence: limitations of studies
Most included studies\textsuperscript{7,8,10–13} were based in high resource settings. This reduces the generalisability of our results. It is not clear if families in low-income and middle-income settings would continue breast feeding particularly if regular Phe-level monitoring was not accessible.

![Risk of bias assessment](image_url)
The Phe levels of formula and breast milk were not reported in the majority of studies. Aksoy\(^9\) had mentioned a Phe-free amino acid-based protein substitute, while Banta-Wright\(^13\) noted that a Phe-free formula was used along with a dietician assessment. Lamônica \(et\ al\)\(^11\) and van Rijn \(et\ al\)\(^10\) did not give any details. Kose \(et\ al\)\(^8\) reported the use of two commercial Phe-free formula (PKU Anamix Infant from Nutrica and Comida PKU A from ComidaMed) and Kanufre\(^12\) reported ‘special formula’ free from Phe was used.

**Effects of breast feeding**

Blood or serum Phe levels at 6 and/or 12 months after birth

No study reported Phe levels at specifically 6 or 12 months of age. van Rijn \(et\ al\)\(^10\) reported that there were no differences in Phe levels in the first 6 months. Phe-level differences were reported at the end of the follow-up period by most studies. As given in online supplemental table 1, there was no difference in blood Phe levels between breastfed and non-breastfed infants in Aksoy, van Rijn \(et\ al\) and Riva \(et\ al\)\(^7\)\(^9\)\(^10\) Banta-Wright \(et\ al\)\(^13\) found that breastfed infants were more likely to have normal mean Phe while formula fed infants were more likely to have low mean Phe levels. Kose \(et\ al\) and Kanufre \(et\ al\)\(^8\)\(^12\) also found that breastfed infants were more likely to have normal mean Phe levels with Kose \(et\ al\) reporting a mean blood Phe of 280±163 µmol/L and 490±199 µmol/L in the breastfed and non-breastfed group respectively (p<0.001).\(^8\) Kanufre \(et\ al\) reported that 87% of the breastfed group had normal Phe assay results compared to 74% in the control group.\(^12\)

Growth in the first 2 years of life

Aksoy\(^9\) described mean weight gain for a month after birth to be higher in breastfed infants, while van Rijn \(et\ al\)\(^10\) found no difference in growth in the first 6 months between the two groups. Kose \(et\ al\)\(^8\) is the only study that described weight at both 6 and 12 months and showed that there were no differences between breastfed and non-breastfed infants. While it is not explicitly mentioned at what time this was done, Kanufre \(et\ al\)\(^12\) also reported no differences at the end of the follow-up.

Neurodevelopmental scores in children aged 12 months or older

Two studies, Lamônica \(et\ al\) and Riva \(et\ al\)\(^7\)\(^11\) reported neurodevelopmental scores. Eight of 10 infants who continued to breast feed for 30 days after diagnosis had adequate developmental scores in Lamônica \(et\ al\).\(^11\) Riva \(et\ al\) reported that breastfed infants had a higher overall IQ as determined by the Wechsler Intelligence Scale for Children-Revised scale after adjustment for social class and maternal education with a mean difference (95% CI) of 12.9 (1.6 to 24.3).

Any adverse psychological effects in the child or the mother or measures of quality of life and/or psychosocial bonding

No studies reported adverse psychological effects in the child or mother, and none of the studies described any measures of quality of life and/or psychosocial bonding.

**DISCUSSION**

We found that although there are no RCTs investigating the effect of exclusive or partial breast feeding in infants with PKU, observational studies report that continuing breast feeding is not harmful and may be beneficial. We found seven studies including 282 infants. None reported any harm and some demonstrated better growth and development in the breastfed group.

In all studies, the breastfed group practised mixed feeding with continued breast feeding and supplementation with low-Phe infant formula. We did not find any studies where exclusive breast feeding was continued after diagnosis. The duration of continued breast feeding was variable and reasons for discontinuing were not reported. No studies reported on the mother’s experience of breast feeding and difficulties that they may have faced. There was no report of long-term follow-up in adolescence or adulthood.

In the absence of evidence from randomised trials, it is not possible to ascertain a causal relationship, and it is possible that mothers who chose to breast feed had other characteristics that impacted their infant’s outcome positively. However, the studies that reported maternal

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**Figure 3** Summary of risk of bias assessment.
socioeconomic characteristics did not show any difference in such variables between the groups. The positive effects of breast feeding on infant health and development are well accepted and infants with PKU are likely to benefit similarly. In addition to the benefits it provides to the infant, it is beneficial to the mother, protecting against later cancer and cardiovascular disease. Another important consideration is the effect of breast feeding on mother-infant bonding. Breast feeding positively influences factors such as maternal sensitivity and secure attachment which promote mother-infant bonding. At times of stress such as when a new diagnosis of an inherited metabolic disorder is received, being able to continue breast feeding may be beneficial in supporting the mother’s mental health. The importance of breast feeding is emphasised through the well-known benefits to both the mother and the infant, and international guidance that recommends the same. Although we did not find any studies that explored these outcomes, further research investigating the impact of continuing breast feeding on parental and infant well-being could be informative, especially in supporting mothers to continue breast feeding and in helping healthcare professionals support them.

The European guidelines on diagnosis and management of PKU stress that treatment must be started as soon as possible, quoting studies that demonstrated that every 4 weeks’ delay in starting treatment caused a decline of IQ score by approximately 4 points. With the introduction of newborn screening and early treatment, infants with PKU no longer develop intellectual disability and research is focusing on how their lifelong management can be refined to enable good health with minimal impact. The guideline recommends giving a measured volume of a Phe-free infant formula before breast feeds or alternating feeds between breast feeding and formula feeding as in the study by van Rijn et al.

Given the lack of RCTs on this subject, current guidelines are not informed by high quality evidence. We found no reported adverse events of continuing breast feeding but did not find any high-quality evidence to answer the question. We were unable to perform any quantitative evidence synthesis because the studies were too heterogeneous. However, we have summarised evidence that support the current European recommendations and provide conclusions for clinicians and families of infants with PKU to enable them to continue to breast feed after diagnosis.

The European Guidelines published in 2017 currently recommends alternating breast feeding with Phe-free formulas to achieve ‘acceptable’ blood Phe control along with regular follow ups and blood tests, however, this is yet to be reflected in the UK guidelines (NICE). Our review of observational data supports the European guidelines. There is insufficient robust evidence for or against continuing breast feeding in infants with PKU. We aim to at raise awareness that breast feeding should be continued and parents need more information and support to do so.

Our findings also have research implications. Although randomised trials of breast feeding are usually ethically challenging because random allocation of a mother who wants to breastfeed to partial or full formula feeding is unacceptable in most circumstances, with a diagnosis of PKU, randomisation to no or partial breast feeding may be acceptable if parents understand the implications and provide full informed consent as continuing full breast feeding could be perceived as harmful to the infant. The other challenge is the rarity of the condition however collaborative efforts as supported by the National Centre for Advancing Translational Sciences-Office of Rare Diseases Research, that can surmount protocol harmonisation, ethical approvals, indemnity, differences in clinical service setups and standards of care, and cultural differences could enable such studies so that scientific advances can benefit those with PKU and other rare disease.

We found that observational evidence suggests that continuing to breast feed is safe and possibly beneficial for infants with PKU. In view of the many advantages of breast feeding for both the baby and the mother, parental choice to continue breast feeding should be respected and families should be encouraged and supported to breast feed.
REFERENCES

Title: Breastfeeding in infants diagnosed with Phenylketonuria (PKU): a scoping review

Supplementary Table 1. Study summary and results

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Methods, co-interventions</th>
<th>Duration of breastfeeding Mean (range, in months)</th>
<th>Plasma Phe levels at diagnosis (μmol/L)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aksoy 2015</td>
<td>Breastfed infants had Phe-free protein supplement</td>
<td>Mean (SD, range) = 7.4 (4.0, 1 to 15)</td>
<td>NR</td>
<td>Serum Phe level, total mean (SD): 456±180 μmol/L ND between breast-fed and non-breast fed; Malnutrition (7.3%) did not differ between the two groups. Did not define how nutrition assessed. Mean weight gain for a month was higher in breastfed infants (p&lt; 0.05). Values of weight gain NR.</td>
</tr>
<tr>
<td>Banta-Wright 2012</td>
<td>Phe levels: every other day to twice a week when levels were stable within range (120–360 μmol/l)</td>
<td>Mean, 6.8 months</td>
<td>Mean (range) Breastfed = 1126 (240 to 3534), Formula fed = 1339.8 (480 to 2802)</td>
<td>Mean Phe levels 120–360μmol/l: breastfed, 59 (80%); bottle-fed, 22 (77%) Breastfed: more likely to have a normal mean Phe level. Bottle-fed: more likely to have a low mean Phe level Both were equal in their distribution in the high mean Phe level category.</td>
</tr>
<tr>
<td>Lamonica 2012</td>
<td>Usual policy to discontinue breastfeeding at diagnosis. Participants continued to breastfeed for at least 30 days. Early Language Milestone Scale and Basic Steps of Development</td>
<td>*Median (range) in months, 4.5 (1-14)</td>
<td>**Mean (range) 1239.2 (605.4 to 2312.5)</td>
<td>8/10 maintained adequate developmental scores. *Median Phe levels mean (range) was 320.8 (193.7 to 466.1) μmol/L</td>
</tr>
<tr>
<td>van Rijn 2003</td>
<td>Breast-fed alternating breastfeeding and Phe-free</td>
<td>10 weeks (7-33)</td>
<td>Median (range) in weeks: Breast-fed, 10 (7 to 33); Formula-fed = 181 (114 to 257) (P = 0.86).</td>
<td>Plasma Phe levels, Mean (range) in μmol/L: Breast fed, 170 (137 to 243); Formula-fed = 181 (114 to 257) (P = 0.86).</td>
</tr>
<tr>
<td>Study</td>
<td>Method of Feeding</td>
<td>Description</td>
<td>Results</td>
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<tr>
<td><strong>Riva 1996</strong> [7]</td>
<td>Bottle fed: no breastfeeding before or after diagnosis</td>
<td>Breast fed: exclusively breast fed until diagnosis; 8 discontinued after diagnosis and 5 received 100 ml/day breast milk after diagnosis</td>
<td>Mean (SD) Breast fed, 1750 (341); Formula fed, 2060 (573)</td>
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<tr>
<td></td>
<td>Formula fed: stopped at diagnosis</td>
<td>No difference in number of infants with normal, low, or high Phe levels in the first 6 months. No difference in growth in the first 6 months, z-scores, median (range): Length: Breast fed, 0.33 (-0.98 to 2.42); Formula fed, 0.68 (-0.11 to 2.43). Weight: Breast fed, 0.30 (-1.46 to 2.16); Formula fed, 0.51 (-0.12 to 2.43). Head circumference: Breast fed, -0.15 (-1.54 to 0.36); Formula fed, 0.87 (-1.70 to 2.19).</td>
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<tr>
<td><strong>Kose 2018</strong> [8]</td>
<td>Breastfed group: Phe-free protein substitute given after each breastfeed. Amount of Phe consumed 40-70 mg/kg/day</td>
<td>Non-breastfed: combination of usual infant formula and Phe-free protein substitute Only one was formula fed prior to diagnosis.</td>
<td>Mean (SD, range) in months, 7.4 (4.0, 1 to 15)</td>
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<td></td>
<td>Mean (SD, range) in μmol/l: Breast fed, 570 (286); Formula fed, 456 (276)</td>
<td>At IQ testing: mean (SD) Age in years: Breast fed, 9.8 (2.2); Formula fed, 9.2 (1.6) Plasma Phe levels in μmol/l: Breast fed, 570 (286); Formula fed, 456 (276) Mean (SD) Overall IQ (WISC-R scale): Breast fed, 105.8 (10.2); Formula fed, 91.8 (16.8); mean difference (95% CI) after adjustment for social class and maternal education, 12.9 (1.6 to 24.3)</td>
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</table>

Plasma Phe levels in μmol/l: Breast fed, 280 (163, 90 to 720); Non-breastfed, 490 (199, 210 to 900) (p<0.001). Breastfed infants more likely to have normal mean Phe levels. Weight at 6 months, mean (SD, range) in kg: Breast fed, 7.3 (0.9, 6.0 to 9.6); non-breastfed, 7.9 (0.98, 6.1 to 10.5) Weight at 1 year, mean (SD, range) in kg: Breast fed, 10.3 (1.1, 8.2 to 12.9); non-breastfed, 9.6 (0.83, 8.5 to 11.5); p =0.02
<table>
<thead>
<tr>
<th>Kanufre 2007 [12]</th>
<th>Controls selected from historical cohort, randomly, Paired for sex and age of weaning. Breastfed: breastmilk on demand between 3hrly bottle feeds with formula free from Phe 24 infants in the breast-fed group also received formula milk</th>
<th>Median (range) in days = 199 (35 to 365)</th>
<th>Median (range) Breast fed, 1144.1 (320.8 to 2742.3); control = 1138.1 (363.2 to 2905.7)</th>
<th>Phe levels (μmol/L)</th>
<th>&lt;121.1</th>
<th>121.1 to 363.2</th>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>breastfed (695 tests),</td>
<td>30.9%</td>
<td>56.1%</td>
<td>13.8%</td>
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<td></td>
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<td></td>
<td></td>
<td>control (704 tests)</td>
<td>34.9%</td>
<td>39.5%</td>
<td>25.6%</td>
</tr>
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<td>No difference in growth measures at the end of breastfeeding WHZ: breastfed = 0.11; control = 0.19 WAZ: breast fed = -0.14; control = 0.13 HAZ: breast fed = -0.29; control = -0.02 Head circumference: breastfed = 44.0 cm; control = 44 cm</td>
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</tr>
</tbody>
</table>

*calculated from individual patient data reported; †Phe levels converted as 1 mg/dL = 60.55 μmol/L CI, confidence interval; NR, not reported; HAZ, height for age z-score; SD, standard deviation; WAZ, weight for age z-score; WHZ, weight for height z-score; WISC-R, Wechsler Intelligence Scale for Children-Revised