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Review

# Optimising growth in phenylketonuria: Current state of the clinical evidence base

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SUMMARY

Patients with phenylketonuria (PKU) must follow a strict low-phenylalanine (Phe) diet in order to minimise the potentially disabling neuropsychological sequelae of the disorder. Research in this area has unsurprisingly focussed largely on managing blood Phe concentrations to protect the brain. Protein requirements in dietary management of PKU are met mostly from Phe-free protein substitutes with the intake of natural protein restricted to patient tolerance. Several reports have suggested that growth in early childhood in PKU is sub-optimal, relative to non-PKU control groups or reference populations. We reviewed the literature searching for evidence regarding PKU and growth as well as possible links between dietary management of PKU and growth. The search retrieved only limited evidence on the effect of PKU and its dietary management on growth. Physical development in PKU remains an under-studied aspect of this disorder.
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## 1. Introduction

The introduction of routine neonatal screening for hyperphenylalaninaemia from the 1960s onwards permitted early diagnosis of phenylketonuria (PKU).[1] Prompt intervention with a phenylalanine (Phe)-restricted diet within the first weeks, or even days, of life has prevented most, of the adverse effects of this disorder on cognitive function.[2,3] Maintaining adequate nutrition to support normal physical development for patients with PKU, is challenging, given the nature of the Phe-restricted diet, which restricts natural protein to patient tolerance and requires supplementation with a Phe-free protein substitute and specially manufactured low-protein foods.[4] The relationship between diet and growth in PKU has been little studied compared with the large database of publications on the neuropsychological sequelae of PKU, especially in recent years. Little is also known about the development of obesity. The purpose of this review is to summarise the current state of the literature regarding physical development in patients with PKU; we provide our interpretation of this evidence base and also highlight future areas for research.

## 2. The evidence base for growth and diet in PKU

### 2.1. Publications

Publications were identified from a PubMed search using the terms "growth" and "phenylketonuria". Other publications came from the reference list of other publications, and from the personal reference databases of the authors. A brief summary of key study features and results is given in Table 1.[5–20] Other publications of interest that are less clearly relevant to physical development (e.g. published as a letter only, or dealing with overweight/obesity) are discussed separately.

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**Table 1**
Overview of studies of diet and growth in patients with phenylketonuria.

| Ref. | Year (*N*) | Ages (y) | Follow-up | Where? | Measured growth parameters | Study design and key findings |
|---|---|---|---|---|---|---|
| 5 | 1979 (693) | 0–17 | NA[a] | USA | Height, head circ. | *Retrospective cross-sectional survey*. Significant ↓ ($p < 0.01$ to $p < 0.001$) height (−0.7 to −0.8 SD) vs. normal controls at 1.3–1.4 y; head circ. was ↓ 0.78 SD vs. normal controls at 1.2 y ($p < 0.01$).[b] |
| 16 | 1979 (124) | 0–4 | 4 y | USA | Height, wt, head circ | *Longitudinal study*. No significant difference in height, weight, head circ. between PKU and normal controls at any age. However, there was a significant trend towards weight gain over time in girls with PKU ($p < 0.005$), but not in other groups. Overall, growth in PKU was as expected. |
| 10 | 1984 (67) | 0–6 | 6 y | USA | Height, head circ. wt | *Longitudinal study of early diet-treated children*. Normal growth was observed in children with PKU, compared with the general population. |
| 18 | 1991 (133) | 2–10 | 8 y | USA | Height, head circ. wt | *Longitudinal study of early diet-treated children*. No significant differences for height of head circ. for PKU vs. reference population. Weight was significantly ($p < 0.05$) higher for PKU vs. reference standards for the general population at most ages. |
| 7 | 1994 (25) | 'Infants' | 6 months | USA | Length,[c] head circ., wt | *Comparison of growth parameters in children receiving different protein supplements (38% difference in protein intake between study groups)*. Higher protein intake was associated with higher growth percentiles for length (55 vs. 28), head circ. (50 vs. 29), weight (73 vs. 39). |
| 13 | 1994 (137) | 0–10 | 10 y | NL | Height, head circ., wt | *Longitudinal study*. PKU infants were 141 g smaller at birth, on average, than reference control; *z* scores for height remained significantly smaller for PKU vs. control, though there were no significant differences in *z* scores for height for age ≥1 y, and no differences for weight. |
| 19 | 1994 (82) | 0–6 | 6 y | Germany | Height, head circ., wt | *Longitudinal study*. Height declined up to age 2.5 y in boys and girls, and head circ. decreased in boys up to 2.5 y, compared with a reference population. Weight-for-height SD score remained close to zero for boys and girls. |
| 11 | 1995 (94) | 0–8 | 8 y | France | Height, head circ., wt/BMI | *Longitudinal study at a single centre*. The *z* score for height-by-age was decreased vs. normal values at ages up to 8 y (only seen for patients born after 1981). Above this age, height-by-age and weight-by age increased to above normal values by 10 years. |
| 20 | 1995 (30) | Mean 9.6 | NA[a] | AUS | Wt | *Cross-sectional comparison of children with PKU and control children*. No excess weight, and no difference in resting energy expenditure was observed between groups. |
| 14 | 1997 (103) | 0–3 | NA[a] | NL | Height (*z* score) | *Study correlated the strictness of diet treatment (blood Phe levels) with growth parameters*. No effect on growth was associated with the strictness of dietary control. |
| 8 | 1998 (35) | 'Infants' | 6 months | USA | Length,[c] head circ., wt | *Longitudinal study*. Intake of protein, energy and Tyr correlated with growth indices at 3 months; neither Phe nor Tyr concentrations in the blood correlated with growth. |
| 9 | 2002 (38) | Mean 8.9 | NA[d] | USA | BMI, height | *Chart review of early and continuously diet-treated children with PKU*. Mean height was at the 46th percentile; protein insufficiency (low pre-albumin) correlated with impaired growth. |
| 6 | 2003 (58) | 2–12 | 1 y | USA | Height, BMI[e] | *One-year non-randomised comparison of three medical foods*. All children received adequate nutrition; normal growth was observed. BMI *z* scores were ≥+0.5 in 40/58 children at study end, suggesting many were overweight. |
| 12 | 2003 (20) | 1–7 | NA[a] | France | Height, wt, FFM | *Cross-sectional study*. Patients with PKU were shorter (mean height-for-age *z*-score −0.49) and lighter (mean wt-for-age *z*-score −0.471) than the French reference population. There were no effects of PKU on body composition, IGF1, IGFBP3, or thyroid hormone. Plasma Phe did not predict growth. |
| 15 | 2005 (174) | 0–3 | NA[a] | NL | Height, head circ. | *Retrospective analysis*. Head circ. increased in line with natural or total protein intake (regression coefficients adjusted for Phe and energy intake of 0.28 and 0.22, respectively), but not with intake of protein substitute (adjusted regression coefficient 0.07). Height did not vary with intake of protein from natural sources, substitute, or both. |
| 17 | 2007 (34) | Mean 8.7 | 1 y | Austria | Height, wt | *Longitudinal study*. No difference in growth or body composition for PKU vs. reference population. |

AUS: Australia; FFM: fat-free mass; NA: not applicable; NL: Netherlands; Wt: body weight. All studies measured Phe intake in addition to parameters shown. 'Year' refers to year of publication. N: total number of patients.

[a] Cross-sectional or retrospective study.

[b] Data shown for treated PKU only (data on untreated PKU not shown as this is not relevant to current management of PKU), and deficits in growth parameters are for a subset of patients with measurements before and after treatment.

[c] Crown–heel length.

[d] Regression analysis based on retrospective analysis of the most recent nutritional assessment.

[e] *z*-scores for length/height or body mass index (BMI).

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