



Update and further development of the calculation of additional costs of low protein diets in children and adolescents with phenylketonuria (PKU)

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Abstract

Phenylketonuria (PKU) is a rare, congenital metabolic disorder in which the body is unable to break phenylalanine down into tyrosine. Elevated phenylalanine levels in the blood can lead to the accumulation of neurotoxic metabolites. Dietetic treatment can help keep blood phenylalanine levels low and prevent negative effects. The treatment is a diet that minimizes phenylalanine intake by limiting protein-rich or phenylalanine-rich foods. This creates a need for special low-phenylalanine amino acid preparations and special low-protein foods to enable patients to follow the diet on a day-to-day basis. Since health insurance companies in Germany do not cover the costs of these special low-protein foods, it can be assumed that there will be an additional cost burden for those affected. This study shows that the monthly costs of the PKU diet for children and adolescents up to and including the age of 18 can be more than twice as high as the costs of the Optimized Mixed Diet (OMD), depending on how the costs are calculated and what purchasing behavior is assumed.

Citation

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Introduction

Phenylketonuria (PKU), formerly also known as phenylalanine hydroxylase deficiency or Fölling's disease [1], is the most common congenital metabolic disorder screened for in newborn screenings in Germany. In 2020, 140 newborns in Germany were diagnosed with hyperphenylalaninemia, and 79 newborns were diagnosed with classic PKU. Of the 79 newborns with classic PKU, in 77 the underlying cause was phenylalanine hydroxylase (PAH) deficiency, whereas tetrahydrobiopterin (BH₄) deficiency was the underlying cause in the other two (cofactor; atypical PKU) [2]. The prevalence of PKU varies globally, but in Europe it averages at around 1:10,000 [3]. According to the ICD-10 (Chapter IV, E70.0) and ICD-11 (5C50.0), PKU is a disorder of aromatic amino acid (AA) metabolism [4].

The treatment for this condition is a strict diet – especially in childhood and adolescence. This diet can prevent the negative effects of the condition. Treatment should begin immediately after diagnosis, in infancy. The diet involves restricting phenylalanine intake, which requires severe restriction of native proteins. The use of phenylalanine-free AA preparations and low-protein foods is also characteristic of the diet. The purpose of the AA preparations used is to cover daily AA requirements, especially essential AA requirements. This diet can greatly reduce the concentration of phenylalanine in the body [3, 5, 6]. According to the European guideline, the target value for children and adolescents is 120–360 μmol/L (≤ 12 years) or 120–600 μmol/L (> 12 years) [3]. The phenylalanine-free AA preparations not only cover AA supply requirements, but

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also contain vitamins and minerals to compensate for possible nutritional deficiencies. The diet should be adhered to for life to ensure healthy brain development and prevent neurological damage [3, 7]. In adulthood or late adolescence, the diet can be relaxed a little because of the broader phenylalanine target values ($< 600 \mu\text{mol/L}$; $< 1200 \mu\text{mol/L}$) [3, 8].

This diet can have a severe impact on quality of life, and especially on the enjoyment of eating. Furthermore, besides being difficult to source, the special food products required for the diet are also much more expensive than normal, protein-rich products. Unlike the deficiency-specific AA preparations, which can be prescribed in accordance with Section 23 of the German Medicinal Products Directive (prescription-only standard and special products), health insurance companies in Germany do not reimburse the cost of special foods required for the diet [9]. At present, financial support for the additional costs of daily nutrition is only possible via the sickness supplements to citizen's benefit – if you are entitled to it – but the amount is not fixed for PKU (German Social Security Code volume II [SGB II], 2023). If a person is not entitled to social welfare benefits, the only limited help available is through tax benefits and applying for disability status [10, 11]. Fixed, basic compensatory payments to cover the additional cost of nutrition in the case of PKU are a positive way of relieving the already heavy burden on families and ensuring optimal development of the child by supporting treatment adherence and success.

The most recent assessment of the additional costs of nutrition in the case of PKU dates from 2018 [12]. Since then, events such as the coronavirus pandemic and the Ukraine war have led to strong inflation [13, 14], which means that the additional costs of nutrition in the case of PKU need to be updated. In addition, the first assessment of additional costs was a purely hypothetical calculation based on the optimized mixed diet (OMD). The calculation presented here includes a simplified extrapolation of the results of the first survey using the inflation factor as well as a comparison with patients' dietary records. The overarching objective here is to calculate the current additional costs of nutrition for PKU compared to the nutrition of a healthy child in the most realistic way possible, taking current inflation into account.

Methods

Updating the data

To determine the costs of the OMD adjusted for inflation, a simple extrapolation of the data collected in 2018 by John et al. (2019) was carried out using a cross-group inflation factor to obtain the estimated current costs for the respective age group [12]. The factor for price changes from December 2018 (time of the last calculation [12]) to March 2023 was calculated using German Federal Statistical Office data on the cost of living. The researched factor was additionally checked using two indicator foods ($N = 18$) per food group from the 2018 data collection, by directly comparing the prices from the two data collection periods. The indicator foods therefore performed a validation function.

In line with the 2018 approach [12], the costs of the PKU diet were calculated using a low-cost variant with products from cheaper supermarkets (known as “discounters” in Germany) and an expensive variant based on more expensive and branded products from a conventional supermarket. In addition, a mixed variant was calculated based on the average of the costs of the high-cost and low-cost variants. The food prices for the low-cost variant were determined primarily via websites, but also by visiting stores (ALDI Nord, LIDL, Netto) in the period from April to May 2023. Own-brand products or products with the lowest price per kilogram were selected wherever possible. Any products not available in these stores were purchased from conventional supermarkets (especially REWE) or drugstores. For the high-cost variant, the food prices were calculated based on various more expensive or branded products from conventional supermarkets (mainly REWE and EDEKA). Products with a price per kilogram in the middle of the price range were selected. Organic products were selected if no comparable conventionally produced product was available. The food prices and special food prices for the cost calculation were determined in the period from March to May 2023.

Use of dietary records

In order to compare the calculation based purely on the OMD with the costs of actual dietary patterns, an assessment of dietary records ($N = 27$) provided by PKU patients at Münster University Hospital was also carried out. This approach is intended to provide a more realistic assessment of the cost burden. The inclusion criteria for patients were an age of up to 18 years and the implementation of a classic low-protein diet – i.e., no use of cofactor-based drugs (sapropterin; Kuvan®) or enzyme replacement therapy (pegvaliase; Palynziq®). Up to five dietary records were available for each of the different age groups, and these were used to calculate the costs incurred. The exact number of records varied by age group, ranging from zero to five (0 = 7–9 age group; 5 = female 13–14 age group and female 15–18 age group). Drinks in the form of water were not recorded, so this was added in line with the German Nutrition Society/Austrian Nutrition Society reference values. The cost calculation for the weekly menus was based on the food prices per kilogram and the recorded intake levels. To do this, the daily costs were calculated by adding up the costs



of the food consumed and adjusting them to 100% of the energy requirement (according to the German Nutrition Society/Austrian Nutrition Society reference values with a Physical Activity Level [PAL] value of 1.4), in line with the actual energy intake. A flat-rate delivery charge has been added for speciality food orders of four per month with a delivery charge of €5.50 per order, giving a monthly delivery charge of €22. The resulting daily costs were then extrapolated to 30.5 days and, if several dietary records were available, the average value for the age group was calculated. Due to a lack of dietary records for the 7–9 years age group, the energy requirements were extrapolated from the data for 4–6 and 10–12 years age groups using the German Nutrition Society/Austrian Nutrition Society reference values. Low-cost, medium-cost and high-cost variants were calculated for all cases.

All data preparation, processing and evaluation was done using the Microsoft Office Excel program (version 16.72). The food costs were calculated as mean values per 30.5 days. To simplify presentation, separate gender groups were created that corresponded to the age categories of the German Nutrition Society/Austrian Nutrition Society reference values (12–14 and 15–18 years) and the average value in each case was then determined.

Results

Based on data from the German Federal Statistical Office, an inflation factor of 1.32 was established for food in the period from December 2018 to March 2023 [14]. This factor was confirmed by checking it against indicator foods (e.g. carrots, eggs, milk, butter), which resulted in an inflation factor of 1.29. The additional costs of the OMD were then calculated from the data from John et al. (2019) using an inflation factor of 1.32 [12].

A comparison of the monthly costs of the low-cost form of OMD and the costs of the low-cost variant according to the assessment of the dietary records for PKU shows that the costs are €37–79 (21–100%) higher per month for PKU, depending on the age group. A comparison of the costs of the high-cost variant of OMD and those of the PKU diet also shows increased costs for a

low-protein diet. Depending on the age group, the additional costs here are €26–85 (8–39%; ♦ Table 1).

In contrast to the data from the OMD calculation (♦ Figure 1), there was no linear relationship between the additional costs and the age groups in the dietary record evaluation. The average additional costs for all age groups are approx. 50% for the low-cost variant and approx. 26% for the high-cost variant. ♦ Figure 1 shows the average total monthly costs of the low-cost and high-cost variants of a low-protein PKU diet and the OMD diet as a function of age group.

Averaging the low-cost and high-cost variants shows that the average additional costs for PKU nutrition are between €29 and €82, depending on the age group. The average percentage increase in costs for all age groups combined is around 35%. This means that a mixed shopping strategy, i.e. shopping in a combination of low-cost supermarkets (known in Germany as “discounters”) and conventional supermarkets, is also associated with additional costs for the diet of children and adolescents with PKU.

A direct comparison with the costs of nutrition in the case of PKU according to John et al. (2019) before the inflation-related increase in food costs based solely on calculations, i.e. without using dietary records, shows an inconsistent picture for both the low-cost and high-cost variants. Some of the costs identified in the previous study were lower, some were higher [12]. For the low-cost variant, the difference is between –24% and +14%. In the case of the expensive variant, the differences range from –35% to +3%.

Age group	Additional costs for low-cost variant	Additional costs for high-cost variant
1 year	€67 (100%)	€31 (26%)
2–3 years	€51 (61%)	€52 (37%)
4–6 years	€73 (70%)	€69 (39%)
7–9 years	€76 (64%)	€74 (36%)
10–12 years	€54 (39%)	€52 (22%)
13–14 years	€79 (52%)	€85 (32%)
15–18 years	€37 (21%)	€26 (8%)

Tab. 1: Absolute and relative comparison of the additional costs of the low-cost and the high-cost variant of a low-protein diet for PKU based on dietary records summarized for both genders (rounded to the full euro) (own presentation)

Discussion

The OMD is designed to ensure the health, proper development and physical well-being of children and adolescents. It is based on the German Nutrition Society/Austrian Nutrition Society reference values, but is also intended to take culturally based habits and the actual eating habits of children and adolescents into account [15]. In John et al (2019), the OMD was chosen as the basis for the calculation of the cost of the diet of healthy children and adolescents and those with PKU because it is the only available food-based dietary recommendation for children

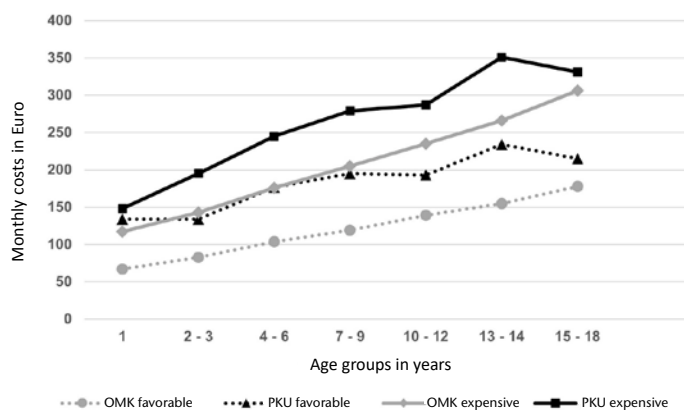


Fig. 1: Costs of the low-cost and high-cost variants of OMD and a low-protein diet for PKU summarized for both sexes (own presentation)

and adolescents [12]. Although the OMD concept provides a good basis for calculation because its recommendations for the different age groups are based on foods, the question of whether this concept is comparable to the actual diet of children and adolescents remains controversial. For instance, both the EsKiMo I and II studies showed that actual diets deviated significantly from the OMD [16, 17]. The approach of extrapolating energy requirements from the recommendations for the age group of 4-year-olds to the other age groups and using these extrapolations to set recommendations for food intake has been criticized time and again. The recommendations only meet the nutritional and food composition requirements of the individual age groups to a limited extent. In the analysis of actual eating habits, which were taken into account in the OMD, only ten dietary records with the highest dietary quality were selected from the DONALD study, whose subjects had a relatively high socio-economic status. This means that these data cannot be considered representative of the population on average. In summary, the OMD concept provides a good basis for meeting the nutrient requirements of the respective age groups, but is not always applicable to individual dietary behaviors or habits [15]. Based on the aforementioned criticisms, it was assumed even at the time of the first calculation that the calculation would deviate significantly from the diet of real people – whether healthy or disease sufferers. This assumption was confirmed in a study by von der Weiden et al. (2022). A comparison of 15 PKU patients with a control group showed that nutritional status and quality of nutrition among the patients were comparable to those of the metabolically healthy control group of the same age, which meant there was room for improvement [18].

The dietary records analyzed in this study showed that as expected, dietary requirements and situations differed within the age groups in some cases. For example, some of the 15–18 age group consumed alcoholic beverages. Furthermore, the dietary records were found to be very different from individual to individual, resulting in a high degree of variation within age groups and between age groups, thus impairing direct comparability. The data reflect this as there is no linear relationship between additional costs and rising age group. Only some of the dietary records included special foods, which have the greatest impact on the total cost of nutrition due to their high prices (♦ Table 2). Since special food products are essential for a balanced and enjoyable diet in

people with PKU and are needed to achieve an appropriate or simplified daily meal plan, the omission of special food products reduced the additional costs to an unrealistic level. In addition, the food quantities and energy intakes in the dietary records varied. In some cases, the recorded energy intakes were far above or far below the German Nutrition Society/Austrian Nutrition Society reference values, which in turn affected the costs. To compensate for these variations, the costs were adjusted to the energy requirement on the basis of the energy supplied by the foods. This raises the question of whether nutritional requirements would be met and whether sufficient individual satiety would be achieved. Overall, the patients' diets deviated considerably from the OMD, so the extent to which the costs of this diet are comparable to those of the OMD in healthy children and adolescents is questionable. Due to the confounding factors described, the low additional costs calculated based on dietary records should be viewed with caution, as they have resulted in a contradiction between the lower costs calculated in this study and the theoretically proven higher financial costs from previous studies [12, 19].

Fundamentally, the increased costs of a PKU diet compared to OMD are attributable to various factors. Grain products such as bread, pasta and rice are considered relatively inexpensive, but they are rich in phenylalanine, which means that comparatively expensive low-phenylalanine or phenylalanine-free special products must be used in the case of PKU. Other foods requiring substitution include meat, fish and dairy products, which can be replaced by vegan alternatives or special low-phenylalanine products, for example. Vegan alternative products may expand the range of options for PKU patients depending on their composition, but they are also usually more expensive than their animal-derived counterparts. However, when directly compared with special low-phenylalanine foods, vegan alternative products are often cheaper (see examples in ♦ Table 2). In addition, the vegan alternative products can be bought in local shops and do not have to be purchased online, which is usually how PKU patients have to source special PKU foods. Vegan alternative products were used in a total of 67% of the dietary records evaluated, accounting for 0.3–12.8% of the amount of food consumed and 1.8–19.4% of the total costs in the affected dietary records. This is indicative of the impact



of the use of vegan alternative products on total dietary costs in the case of PKU. In clinical practice, patients who only include a few special low-protein products in their diet are often found to have poorer metabolic control.

However, an additional aspect of these substitute/special products that should be examined in addition to their costs and their ability to simplify everyday nutrition is their composition. For example, low-phenylalanine pasta is made of extracted starch, thickeners, emulsifiers and colorants [21]. This is an example of a food that would benefit from an adjustment in composition. From a nutritional point of view, the addition of dietary fiber would increase nutritional quality while maintaining a low phenylalanine content. Further research is needed into the composition of special low-protein products to investigate their nutritional quality.

Food category	Liver sausage	Smoked salmon	Milk	Vienna sausages
“Original“	€11.95/kg (Keunecker)	€35.27/kg (Krone)	€1.69/L (Weihenstephan)	€13.45/kg (Wiesenhof)
Vegan alternative product	€15.92/kg (+33%) (Rügenwalder)	€49.90/kg (+41%) (Veganz)	€2.39/L (+41%) (Alpro Hafer)	€16.51/kg (+23%) (Rügenwalder)
Special product	€24/kg (+101%) (Walter Schott)	–	€7.27/L (+330%) (Taranis)	€24.30 (+81%) (Loprofin)

Tab. 2: Cost comparison comparing meat, fish and dairy products with vegan alternatives and special low-phenylalanine products (data source: [20–23]; authors’ own presentation)

In terms of both absolute additional costs in euros and percentage additional costs, the additional costs of the PKU diet are higher for the low-cost variant than for the high-cost variant across almost all age groups. This means that there is less difference in costs between the OMD and actual food intake in the case of PKU in the high-cost variant. Furthermore, this shows that even when the cheapest possible food is selected for the PKU diet, the additional costs can only be reduced to a limited extent and can even increase compared to an equally inexpensive food selection strategy when consuming the OMD. According to research by the Munich Market Research Institute [24], a strict distinction between the two variants is unrealistic. The average variant, which is a combination of the low-cost and high-cost variants, seems to best reflect reality in this comparison.

The simplified approach to the extrapolation of the costs for a PKU diet and the OMD according to John et al. (2019) using an inflation factor of 1.32 results in a significant discrepancy in additional costs. The main reason for this is that the dietary records indicate a higher intake of high-fat and high-sugar foods and a lower intake of fruit and vegetables, resulting in a higher energy density together with a lower micronutrient density [18]. Because the costs of nutrition were re-calculated based on energy requirements, there was a significant cost reduction here compared to previous studies [12, 19]. In the optimized calculation from 2019, significantly more substitute products were used than is the case in the actual dietary records. In addition, the maximum recommended amounts of phenylalanine and protein were strictly ad-

hered to, which is likely not always the case in everyday life. It can therefore be assumed that although an optimized calculation model deviates from current practice, it is in line with the desired objective, and that providing support in line with the optimized model will enable this objective to be implemented in practice and make its achievement more likely. In summary, the main reasons for the variation in additional costs are the costs of alternative products, differences in compliance and unfavorable dietary patterns.

A direct comparison of the present results with earlier studies by Peul (2007) and John et al. (2019) clearly shows that the additional costs have risen sharply across all age groups based on the simple extrapolation calculation method. Regarding the dietary record evaluations carried out in the present study, the trend was partly in the opposite direction, although this can be explained by the limitations of the dietary record evaluation mentioned above (♦ Table 3). The increase is between €23 (4–6 years) and €71 (15–18 years) and varies between the age groups. When considering this, it is important to bear in mind that the Peul study and the present study and calculation method have different limitations [12, 19].

Comparing the costs of the PKU diet based on the simple extrapolation for the low-cost variant with the standard rates of the citizen’s benefit shows that 59–85% of the standard rate of the citizen’s benefit is spent just on food, leaving a maximum of €71–130 for all other living costs, depending on the age group. The Act on the Determination of Standard Needs pursuant to Section 28 of the Twelfth Volume of the German Social Code from 2021 onwards states that the estimated percentage of the citizen’s benefit designated for food, beverages and tobacco is approximately 30% based on the information for individual households (Section 5) [25]. It is important to note that the low-protein diet, including low-protein substitute products, is a form of nutrition that is medically necessary, meaning that the people affected do not have a choice about whether to follow it. The available data therefore directly indicate that a compensatory payment is needed.

Due to the present limitations (which are mainly due to unfavorable diets, limited comparability with an optimized diet in healthy people and limited access to special foods), future calculations should be optimized by using



Age group	Peul (2007) [19]	John et al. (2019) [12]	Average variant of the extrapolated results based on the data according to [12] for the year 2023	Average variant of own assessment obtained through dietary records (2023)
1 year	€35	€79	€97	€48
2–3 years	€75	€94	€114	€52
4–6 years	€105	€105	€128	€70
7–9 years	€105	€119	€147	€77
10–12 years	€115	€131	€163	€58
13–14 years	€135	€143	€179	€82
15–18 years	€135	€164	€206	€32

Tab. 3: Comparison of the additional costs of a low-protein diet for PKU in 2007, 2019 and 2023 combined for both sexes (rounded to the full euro) (modified according to [12, 19])

several patient dietary records for each age group together with appropriate use of special and substitute products. This approach is intended to achieve the lowest possible phenylalanine intake and at the same time reduce the everyday burden as much as possible. Regularly calculating the additional costs of a low-protein diet is important because food prices are constantly changing. Based on the present study and the previous studies, it can be concluded that there is an urgent need for lump-sum payments and sufficient sickness supplements for recipients of citizens' benefit. In order to determine the sickness supplements, the additional costs extrapolated using the inflation factor according to John et al. (2019) for the average purchase variant (♦ Table 3) should be taken as the minimum. This will help ensure that a balanced, PKU-appropriate diet is affordable for PKU sufferers and therefore promote a high level of treatment adherence. The use of substitute products and special products is a key and necessary cost factor here. Furthermore, discussions about reimbursing the costs of these products should be reopened, since reimbursement is standard in other countries [26, 27].

Conclusion

In summary, it is clear that the costs of a PKU diet are significantly higher than the costs of a standard diet according to the OMD concept. The extent of the additional costs mainly depends on how strictly the diet is adhered to, including the amount of special low-protein products used. There is an urgent need for financial support for the additional costs in the form of sickness benefits for those receiving the citizen's income, and this should be set at a flat rate. The additional costs of the average purchase variant, which were extrapolated using the inflation factor based on previous data, would be the best basis for determining the sickness benefits. Basing assessment and cost calculation purely on dietary records would not be an entirely suitable approach to answering the cost question due to limitations. Future studies will need to combine real dietary behavior based on dietary records with optimization according to OMD or other target group-specific, food-related dietary recommendations.

Disclosures on Conflicts of Interest and the use of AI

The authors declare that there is no conflict of interest and that no AI applications were used in the preparation of the manuscript.

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