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# The time consuming nature of phenylketonuria: A cross-sectional study investigating time burden and costs of phenylketonuria in the Netherlands

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ABSTRACT

*Background:* Phenylketonuria (PKU) is a rare inborn error of metabolism that affects the ability of patients to metabolise phenylalanine (Phe). Lifelong management of blood Phe levels is required in order to avoid the complications associated with PKU. This constitutes a severely protein restricted diet, and regular monitoring of Phe levels. Management of PKU may be costly and time-consuming for adult patients or caregivers of PKU-affected children. A cross-sectional study was performed with patients or their caregivers in the Netherlands to gain insight into the personal time burden and cost of living with PKU.
*Methods:* A systematic literature review was performed to identify all aspects of PKU management that may pose a financial or time burden on patients or caregivers. Findings were confirmed through interviews with PKU experts and feedback from patients and caregivers, and consolidated into a questionnaire that aimed to evaluate the impact of each of these factors. Early and continuously treated adult patients and caregivers from seven metabolic centres were recruited to complete the questionnaire online.
*Results:* 22 adult patients and 24 caregivers participated in the study. Managing a Phe-restricted diet represented an extra time burden of 1 h and 24 min for caregivers and 30 min for adult patients per day. Caregivers reported a significantly higher time burden than adult patients. The median total out-of-pocket cost (OOPC) for patients was €604 annually, with 99% of expenditure on low-protein food products. Greater disease severity was significantly associated with increased OOPC and time burden for both adult patients and caregivers.
*Conclusions:* Management of PKU is associated with a considerable time burden for both caregivers of children with PKU and adult patients. Caregivers of PKU-affected children reported a significantly higher time burden than adult patients. The OOPC of caregivers and patients was mainly driven by the expenditure on low protein food.


## 1. Introduction

Phenylketonuria (PKU, ORPHA79254, MIM 261600) is a genetic disorder that arises due to mutations in the gene that codes for phenylalanine hydroxylase (PAH; EC 1.14.16.1), a hepatic enzyme necessary for the metabolism of the essential amino acid phenylalanine (Phe) to tyrosine [1]. The resulting PAH deficiency leads to chronic increases in blood and tissue Phe concentrations, with toxic effects on the brain. PKU is an orphan disease with a mean prevalence in Europe of 1:10,000 [2]. If left untreated, it will lead to severe mental retardation, with additional symptoms such as autism, epilepsy and eczema. Since the 1960s, in most European countries, these severe complications can effectively be prevented by detection through newborn screening and early start of treatment, usually within the first two weeks of life [3].

Treatment of PKU consists of a very strict and unpalatable diet that severely restricts intake of natural protein, with supplementation of other amino acids in a mixture with vitamins and minerals [2,4]. Energy is provided by food that is naturally low in protein such as fruit and non-starchy vegetables, as well as specially formulated products such as pastas, breads, imitation cheese and baking mixes designed for low-protein diets [5]. Some patients may benefit from treatment with BH4 (sapropterin), the cofactor of the PAH enzyme, which increases PAH activity and consequently lowers Phe blood concentrations in responsive PKU patients [6,7].

Disease severity can be classified by the Phe blood level at the time of diagnosis, or be based on the tolerance for the dietary intake of Phe during treatment. Several classifications are used in the literature; one of the common classifications describes patients as having classical PKU (untreated Phe level > 1000 μmol/L, Phe tolerance < 500 mg/day)

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or mild PKU (untreated Phe level ≤ 1000 μmol/L, Phe tolerance ≥ 500 mg/day) [2,4,8,9].

Even if treatment is started early, patients may suffer from executive deficits and mood disturbances. As these effects are strongly associated with concurrent Phe levels, a diet for life is usually advised [10–12]. Poor executive functions may lead to "hidden disabilities" such as difficulties in planning, organising and reduced processing speed, thereby affecting treatment adherence, social relationships, and job performance [13]. Most studies report a normal health related quality and course of life in patients who are treated early and continuously, even though patients often report having certain restrictions with an evident lack of spontaneity in their lives [14–17]. This reporting of "normal" health related quality of life (HRQoL) is probably due to the fact that the generic questionnaires available for measuring HRQoL do not evaluate specific PKU related problems. However, the authors are currently aware of a disease specific questionnaire being developed for PKU and this will hopefully provide more insight into the HRQoL of PKU patients.

The PKU diet is considered a heavy burden by both patients and professionals [18] and the management of PKU can be time-consuming for both adult patients and caregivers of PKU-affected children. Patients and caregivers need to obtain low-protein food products, plan the daily Phe intake, prepare the daily menu (that often involves extra cooking), and prepare and take (or supervise the intake of) supplements. Furthermore, Phe intake has to be closely monitored with regular blood testing of Phe levels. The Dutch Guidelines recommend once weekly testing during the first year of life, twice monthly from age 1, monthly after age 4, and twice weekly during pregnancy if the mother has PKU [12].

PKU may additionally present an economic burden to patients and caregivers. This includes direct costs of living with PKU, which relates to resource utilisation in managing their condition, such as low-protein foods, supplements, medications, laboratory monitoring, and healthcare visits. There may also be indirect costs such as those arising from the loss of productivity. Costs and reimbursement of diet therapy vary widely between different countries [19]. In the Netherlands patients with PKU and caregivers of PKU-affected children receive tax credits and amino acid supplements are reimbursed. Although information is available on the burden of PKU to the healthcare system [20], there is not much information available on the personal time burden and cost of living with PKU for patients.

To gain insight into the personal time burden and cost of living with PKU in the Netherlands, we conducted a cross-sectional study that assessed the impact of PKU on adult patients and caregivers of PKU-affected children. Our aim was to measure the time spent on activities related to PKU management and also to measure the out-of-pocket costs (OOPCs). The OOPC refers to those PKU-related expenses that are not reimbursed by the healthcare system. Any differences in OOPC and time burden according to different categories of patients (adult patients, caregivers, age, disease severity and adherence to diet) were also evaluated. Medical costs of PKU to the healthcare system are not considered in this study as the study focuses solely on the personal burden of PKU on affected individuals.

## 2. Methods

### 2.1. Study design and study population

We conducted a cross-sectional study to evaluate the costs and time burden of living with PKU in the Netherlands from the perspectives of the patient or the caregiver. Different aspects of the PKU lifestyle that present any potential monetary costs were presented to participants in an internet-based questionnaire through which respondents could indicate their OOPCs and time spent on managing a PKU lifestyle. Patients were recruited from seven metabolic centres in the Netherlands. Early and continuously treated adult patients and caregivers of paediatric patients (who were already participating in another internet-based PKU study including patients age 4 years and older) were invited to participate in this study as well.

### 2.2. Development of the questionnaires

A systematic literature review was performed to identify all available data on costs associated directly with PKU and aspects of PKU that affect HRQoL. This was to gain insight into the PKU lifestyle that would facilitate preparing a script for expert interviews. The search was specific for costs borne by patients and their families rather than the healthcare system. This included the costs of treating the symptoms of PKU as well as any costs associated with managing the disease or looking after patients with PKU. Information was categorised into disease subgroups, such as severe versus mild; this was to enable assessment of how the burden of PKU varied for different patient characteristics. A second literature search was performed in order to obtain guidance in the creation of the questionnaire, including the identification of any suitable pre-validated questionnaires that captured information on productivity loss and healthcare resource use that could be incorporated into the survey. The findings of the literature reviews were confirmed through interviews with six opinion leaders in the field of PKU, three of whom were from the UK and three from the Netherlands, who detailed the various costs associated with the management of PKU. This ensured that all potential OOPCs and time expenditure associated with living with PKU were captured in the study questionnaires.

Similar but separate questionnaires were created for completion by adult PKU patients and caregivers of paediatric patients with PKU. Each questionnaire consisted of five sections covering background information on the patient, treatment and clinical history, general life, the effect of their health on labour, and various aspects of the Phe-restricted diet. They assessed patients' experience over weekly, monthly and annual time frames retrospectively. The Short Form Health & Labour Questionnaire (SF-HLQ), which is validated in both Dutch and English, was included to gather data on productivity loss. The questionnaires, which were created in English and then translated to Dutch, were reviewed by four experts. They were appraised at the Dutch National PKU event by four caregivers and one adult patient who were asked to provide feedback on their ease-of-understanding as well as any possible suggestions for further areas that may be covered. The questionnaires were reviewed based on feedback obtained, with further input from two experts.

### 2.3. Data collection

Patients were recruited on an ongoing basis through the database of the Academic Medical Center (AMC), Amsterdam, from mid-December 2011 to early-April 2012. Participants were sent two reminders over a three-month period to complete the questionnaire. Informed consent was obtained from all participants, and confidentiality was assured. Participation was voluntary and there were no implications on treatment for participants. Participants received a fee after completing the questionnaire, of which they were not informed prior to filling out the questionnaire. Patient data sets were coded and ethical approval was requested from the Ethical Committee of the AMC who deemed that their approval was not necessary for this study.

### 2.4. Data analysis

In addition to the overall time burden and cost of living with PKU, demographic and disease data were used for creating subgroups to compare the time burden and financial cost of living for different categories of patients within each subgroup: adult patient versus caregiver; age; severity of disease; adult patient versus caregiver in