

## 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.

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### 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  $\leq 1000$   $\mu\text{mol/L}$ , Phe tolerance  $\geq 500$  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

combination with disease severity; and dietary adherence compared with dietary non-adherence.

Disease severity was defined according to the amount of natural protein (or Phe) allowed per day for an individual patient: patients who are allowed >10 g of natural protein (500 mg of Phe) per day were classified as 'mild'; patients who are allowed ≤10 g of natural protein (500 mg of Phe) per day were classified as 'severe'. For assessing adherence, patients were asked to provide the number of days in which they did not adhere to the diet over the preceding 100-day period; patients were regarded as showing good adherence if this totalled 30 days or fewer. Monetary costs for patients were reported as OOPCs.

The analyses were performed based on the available case principle, including only those patients for which the outcome and covariates are known. The total number included in the analyses will differ across parameter estimations. All outcomes were continuous outcomes (time and OOPC) and inferences were described in terms of medians, means, interquartile ranges and ranges. To test whether differences between subgroups were statistically significant (two sided *p*-value <0.05) the Wilcoxon Rank Tests for skewed outcome distributions were used.

### 3. Results

#### 3.1. Patient characteristics

A total of 69 participants from another web based PKU study in the Netherlands were invited to participate in the study; of these, 22 adult PKU patients and 24 caregivers of paediatric patients with PKU (67%) completed the survey and were included in the analyses. Adult patients had a median age of 28 years [interquartile range (IQR) 23–53] and paediatric patients of 11 years [IQR 9–14]. Of the adult patients, 15 reported to have a mild disease severity and 6 reported severe. Of the paediatric patients, 9 were mild and 12 severe. No patients were excluded from the analyses. The majority of patients (38/46) were on a protein restricted diet. Among the patients on a protein restricted diet, 30 patients took amino acid supplementation, 1 patient was treated with protein restriction and sapropterin, 3 patients were treated with sapropterin and amino acid supplementation, and 4 patients took no other treatment. Eight patients were not on a diet, of whom 3 were treated with sapropterin only, and 2 were treated with sapropterin and amino acid supplementation. One patient reported using amino acid supplements without dietary restriction. In total, 26 patients reported the use of low-protein food products (11 adults and 15 caregivers).

#### 3.2. Time burden of PKU

The primary components of the time burden of PKU are summarised in Table 1. On regular household tasks, not associated with PKU management, caregivers of patients with PKU spent a median of 312 h and adult patients a median of 208 h/year. The median total time burden associated specifically with managing PKU was 265 h [IQR 129–588]/year for the complete cohort, with a median 527 h for caregivers [IQR 213–826] and a median 175 h [IQR 125–300]/year for adult patients. (Fig. 1). Dietary management represented the greatest time burden, with 46% of the total PKU time burden consisting of cooking and preparing meals specifically for a Phe-restricted diet, and 11% on monitoring protein/Phe intake. The time spent on managing PKU was significantly lower for adults than for caregivers. Furthermore, severe (median 595 h [IQR 214–862]) PKU was associated with a significant greater time burden than mild PKU (median 235 h [IQR 123–353]) (Fig. 1). Neither adherence nor different age groups among adults or caregivers had a significant effect on the time spent of managing PKU.

**Table 1**

Time spent on PKU-related tasks, overall population.

| Activity                                     | Median [IQR] (mean)/h/year |
|--|----------------------------|
| Blood testing                                | 1 [0–1] (1)                |
| Keeping Phe records                          | 30 [0–30] (35)             |
| Cooking for Phe-restricted diet              | 121 [15–182] (131)         |
| Weighing foods                               | 0 [0–12] (13)              |
| Supervising protein intake (caregivers only) | 30 [8–61] (64)             |
| Baking bread                                 | 0 [0–104] (130)            |
| Food research                                | 2 [0–39] (39)              |
| Researching PKU                              | 0 [0–12] (20)              |
| Other PKU-related tasks                      | 0 [0–0] (19)               |
| PKU events                                   | 0 [0–9] (17)               |
| Preparing for social events                  | 3 [0–12] (11)              |
| Ordering amino acids                         | 1 [0–2] (1)                |
| Ordering low-proteins                        | 1 [0–2] (2)                |
| Ordering sapropterin                         | 0 [0–0] (0)                |
| Total time                                   | 265 [129–588] (420)        |

IQR, interquartile range.

#### 3.3. Out of pocket costs for PKU

The primary components of OOPCs for patients with PKU are summarised in Table 2. The median OOPC per patient was €604 [IQR €28–€1206] annually, and there was also a median one-off OOPC of €50 [IQR €30–€250]. The majority (99%) of OOPCs were due to expenditure on low-protein food products. Other costs consisted of the postage cost for the Phe blood test, taking extra holiday luggage to accommodate equipment for PKU testing or dietary management, and PKU-related events such as specialised cookery classes. OOPCs were significantly higher for patients with severe PKU (daily allowed intake of natural protein ≤10 g) versus mild PKU (daily allowed intake of natural protein >10 g), €1309 [IQR €716–€1755] and €393 [IQR €3–€698] respectively. In addition caregivers taking care of a child with severe PKU (€1309 [IQR €1054–€1793]) also had significantly more OOPCs than those who were caring for a child with mild PKU (€5 [IQR €0–€486]) (Fig. 2). Neither adherence nor different age groups among adults or caregivers had a significant effect on OOPCs.

#### 3.4. Other findings

Six adult patients and 6 caregivers reported receiving tax credits towards PKU products. Loss of productivity was reported by 3 adult patients; additionally 3 patients indicated that health affected their performance at work. Caregivers did not report any production loss, although 2 caregivers reported leaving their employment in order to care for a PKU child and 1 changed their employment because of PKU.

### 4. Discussion

This is the first study to investigate the time burden and costs resulting from having PKU or caring for a child with PKU.

The most important outcome of our study is the considerable time burden posed on patients and families with PKU. As presented earlier in the results, the median time burden associated with managing PKU was 527 h/year (1 h and 24 min/day) for caregivers and 175 h/year (30 min/day) for adult patients. Time was mostly spent on cooking and preparing meals specifically for a Phe-restricted diet, followed by monitoring protein intake. The significantly higher time burden for caregivers versus adult patients suggests that less time is required for PKU management as patients enter adulthood and begin caring for themselves. Also, this fits with the idea that many adult patients tend to somewhat relax their diet [21]. Furthermore, the higher time burden associated with severe versus mild PKU is to be expected as greater disease severity necessitates more stringent dietary control and PKU monitoring.

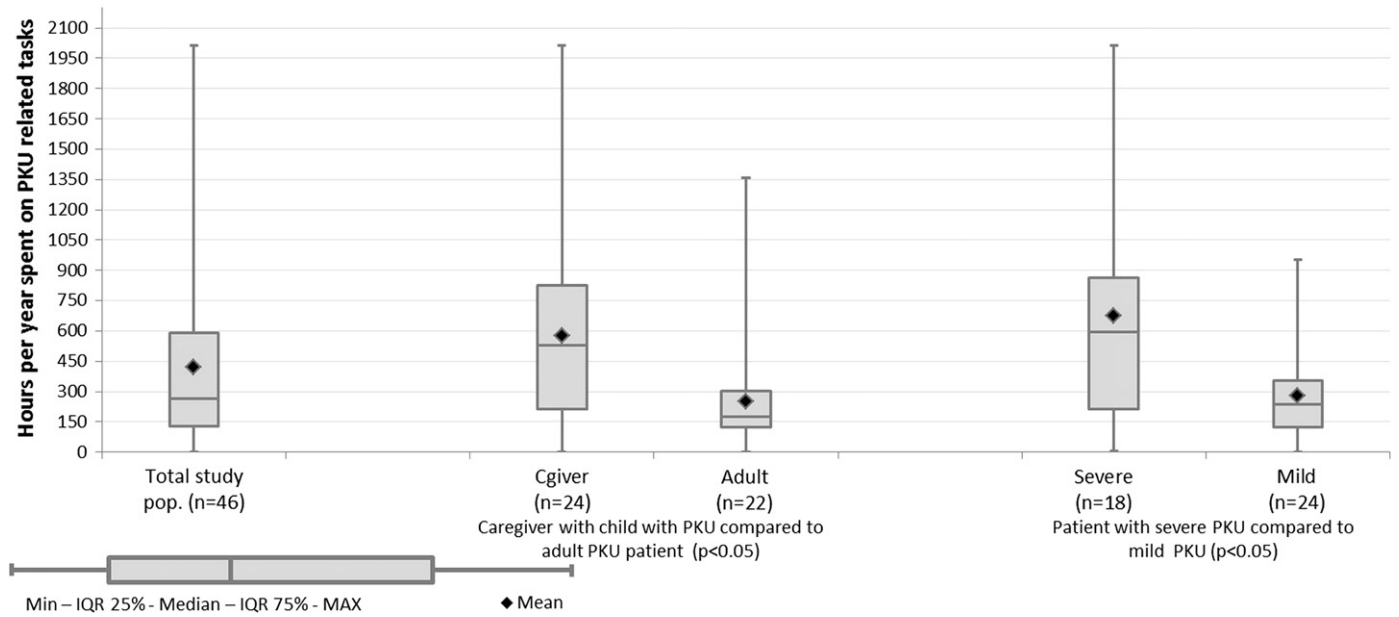


Fig. 1. Time burden for different subgroups of participants.

It needs to be discussed whether the time spent on PKU management will truly pose a burden on the lives of patients and caregivers. On regular household tasks the caregivers reported to spend a mean of 2 h and 3 min/day (median 52 min), which is comparable to the mean 2 h and 10 min spent on household tasks in the general population by a Dutch parent of a family with a youngest child age 6–12 [22]. Patients and caregivers were explicitly asked to report the extra time spent on PKU management. Our study showed that management of PKU poses a considerable additional time burden on adults (30 min/day) and caregivers (1 h and 24 min), which could have been spent more valuable when not having to deal with PKU. As such, the time spent on managing PKU could take away time from other daily activities. As few caretakers reported change of employment or production loss as a result of having a child with PKU, the extra time needed to manage PKU will probably be taken away from leisure time. The time burden for adult patients is significantly less

than for the caregivers; however, as “hidden disabilities” such as difficulties in planning and organising have been reported in patients with PKU, this time burden may affect their daily lives as well.

The additional time spent by PKU patients for managing their disease can be considered as a loss of valuable time that could have been spent more beneficial. When this time loss is expressed as a monetary burden (using the gross hourly earnings of a cleaner €13.40 [23] per hour as recommended by the Dutch Healthcare Insurance Board [24]) on society, this would amount to €7066 for caregivers of PKU-affected children and to € 2341 annually for adult PKU patients.

There is a lack of published information on the time burden for other metabolic diseases; therefore comparison to other metabolic disorders is not feasible. However, a US study on the burden of patients with diabetes mellitus type I, found that patients spent on average 28.3 min a day managing their condition [25]. Additionally they spent 4.4 min/week researching the internet on diabetes and

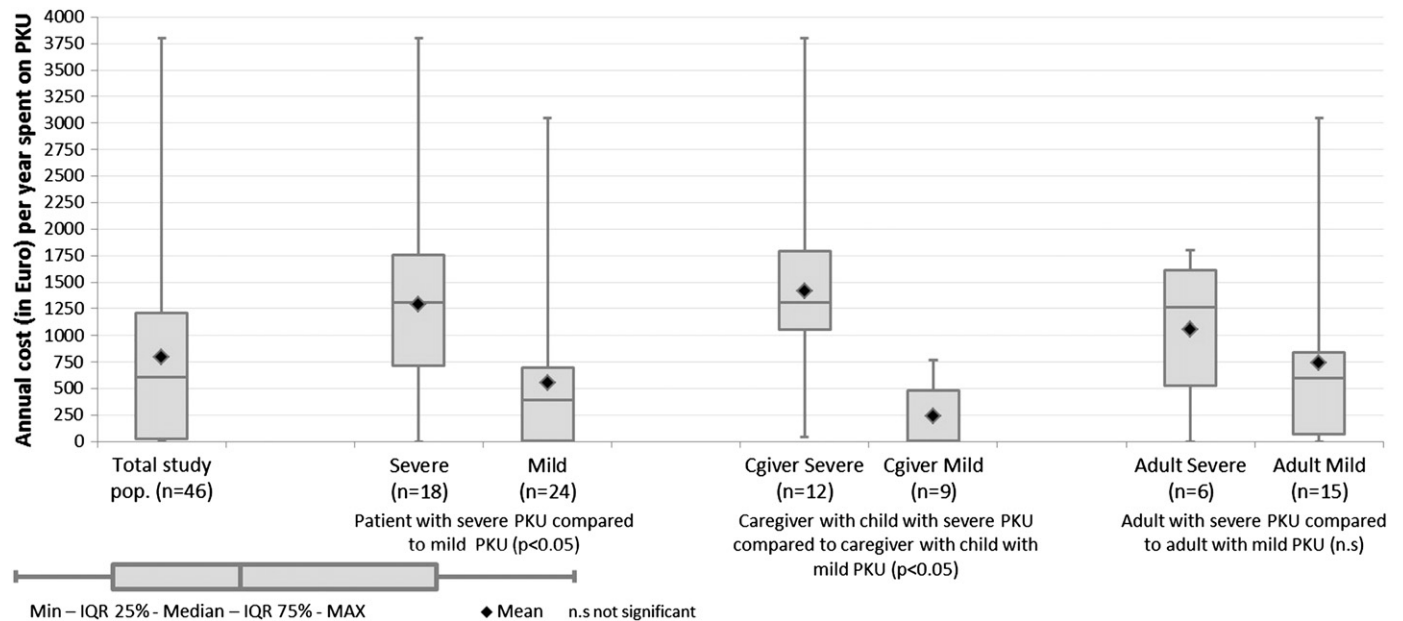


Fig. 2. OOPC for different subgroups of participants.

**Table 2**  
Out-of-pocket costs, overall population.

| Expense type  | Median [IQR] (mean)/€/year |
|---|----------------------------|
| Amino acid supplements                              | 0 [0–0] (75)               |
| Low-protein foods                                   | 600 [0–1200] (680)         |
| Postal cost for Phe blood test                      | 2 [0–5] (5)                |
| Extra holiday luggage for PKU equipment             | 0 [0–0] (54)               |
| PKU events  | 0 [0–8] (34)               |
| One off-expenses (PKU equipment)                    | 50 [30–250] (189)          |
| Annual total direct OOPCs (medical and non-medical) | 604 [28–1206] (798)        |

IQR, interquartile range.

30.8 min/week on reading for diabetes. This would indicate a total time burden of 203 h/year for diabetes management, compared with 265 h/year PKU management in the present study. Although diabetes is not a metabolic disorder, the diabetes study can be used for comparison with this study as they both involve dietary restrictions and regulation, and close disease monitoring. However, comparison between the two studies should be interpreted with caution as the activities that contributed to the time burden were different in each of the two studies; furthermore, the diabetes study reported mean values instead of median values as reported in the present study.

The median OOPC per patient (€604 annually) was comparable for both patients and caregivers. These costs were mainly due to expenditure on low-protein food products and for a small part on costs related to PKU testing equipment, postage of Phe blood tests, taking extra luggage on holiday to accommodate PKU equipment and attending PKU events. It can be easily explained that OOPCs are higher for patients with severe PKU than for those with mild PKU by the fact that greater disease severity necessitates more stringent protein restriction with a higher intake of low-protein food products. An important point to consider is whether these additional PKU-related costs are offset by the potentially cheaper natural diet imposed upon PKU patients that contains very little or no regular bread, dairy products or meat. In comparison to the general population: a Dutch adult on a normal diet has been demonstrated to spend a mean amount of €1200 annually on meat, cheese, milk, yoghurt and bread [26]. For patients with PKU this expenditure is replaced by the costs of the low protein products. It may be expected that costs between protein containing and low protein food products will balance out in patients depending on disease severity and the need for low protein food products. Taking this into account, it is unlikely that there will be a large burden of extra OOPCs for families of patients with PKU.

It must be stressed, however, that the costs of the Phe free protein supplements in a mixture with vitamins and minerals, which are an essential part of the diet of patients with PKU, vary per country but may be as high as €30,000 annually [19]. In most European countries these costs are reimbursed by the government, or as is the case in the Netherlands, by health insurance. To guarantee proper dietary treatment of patients with PKU and to avoid a disproportionate financial burden for patients and families, it is essential that costs of the Phe free protein supplements are reimbursed in all countries.

A limitation of our study was the low sample size, especially when results were analysed within subgroups. However, this is a consequence of the rarity of this disease, with approximately 550 early-treated PKU patients in the Netherlands at present, a true orphan disease. Another limitation was the age limit used in our study. Since our questionnaire was joined on to an existing registry, patients aged 0–4 years were excluded. Furthermore, many participants were unwilling to reveal certain details such as their income, so it was not possible to formally analyse the impact of the cost of living on these patients according to their socio-economic status. Nevertheless, the main objective of the study to gain insight into the time burden and cost of living with PKU overall (rather than comparison between patient subgroups) was achieved.

## 5. Conclusions

With an extra daily time burden of 1 h and 24 min/day for caregivers of children with PKU and 30 min/day for adult patients, PKU management is highly time consuming. As was expected, the time burden was significantly higher for severe versus mild patients. For both the caregivers and the adult patients the OOPC mainly consisted of the cost related to low protein foods.

## Conflict of interest

IE, TAS, and JVL are employed by MAPI Consultancy. MAPI Consultancy received funding of the study from Merck Serono S.A., Geneva, Switzerland. SL is employed by Merck Serono S.A., Geneva, Switzerland. SD and AB did not receive funding. AB is a member of advisory boards for Merck Serono and for Danone.

## Authors' contributions

IE, AS, JVL, AB and SL contributed to the conception and design of the study. IE and AS developed the questionnaire and this was reviewed by the other authors. AB and SD contributed to acquiring the data, together with IE and AS who also performed the data analysis. AS and SL conducted the expert interviews. All authors were involved in the interpretation of the data. IE coordinated the writing of the manuscript. All authors reviewed the manuscript content and approved the final manuscript.

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