Health economic burden of patients with phenylketonuria (PKU) – A retrospective study of German health insurance claims data

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ABSTRACT

This retrospective matched-cohort analysis compared health-economic burdens of adults (≥18 years; n = 377) with phenylketonuria (PKU) and age/gender-matched non-PKU controls (n = 3770) in Germany. Healthcare costs and resource-utilization were analyzed for the year 2015. Differences between groups were tested using 95% CI of mean differences (MD). PKU patients had significantly higher mean costs in total (MD €3307, 95% CI €1736–€4879), for pharmaceuticals (MD €1912, 95% CI €1195–€2629) [including dietary amino-acid supplements (MD €1268, 95% CI €864–€1672)], and outpatient costs (MD €395, 95% CI €115–€675). Inpatient costs (MD €904, 95% CI €293 to €2100) and costs for aids and remedies (MD €97, 95% CI –€10 to €203) were also higher in PKU patients. PKU patients had more outpatient visits and stayed longer in hospital. Adult PKU patients incurred higher total healthcare costs than non-PKU controls, especially regarding pharmaceuticals and outpatient costs, and more frequent resource-utilization, resulting in higher health-economic burden for the statutory healthcare system.

1. Introduction

Phenylketonuria (PKU) is an inherited metabolic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase (PAH), which results in elevated levels of phenylalanine (Phe) and reduced levels of tyrosine [1]. PKU is caused by over 1,000 different gene variants of PAH [2] and the severity of the resulting disease ranges from mild to severe based on the level of Phe in the blood and tissues [1,3]. Poorly managed PKU in childhood can result in a variety of symptoms including intellectual disability, seizures, behavioral problems, and mental disorders [4].

Management of PKU should start within the first 10 days of life (requiring timely diagnosis via newborn screening programs) to prevent irreversible damage (e.g. neurological impairment and mental retardation) and should be maintained throughout life to control neuropsychological and neurocognitive symptoms (e.g. slow reaction times and impaired inhibition, attention, and working memory) [5]. Strict control of blood Phe levels is of primary importance for optimal outcomes, particularly during the first years of life [5,6]. The dietary management of PKU comprises the reduction of dietary intake of Phe from natural sources, Phe-free amino acid supplements, and/or low-protein supplements/foods. Additionally, sapropterin dihydrochloride (a synthetic version of tetrahydrobiopterin [BH4], the natural co-factor of PAH) can be used in responsive patients to increase residual PAH activity [7,8]. Dietary management options are ineffective in many adults with PKU due to long-term adherence issues [9–11] or inadequate Phe-lowering effects [7]. Moreover, a long-term PKU diet is associated with vitamin and/or mineral deficiencies [12–14] and an increased risk of low bone density [5]. Also, it is reported that women with PKU appear particularly vulnerable to excess weight gain and are more often obese...
than men with PKU [15]. Nevertheless, treatment for life is recommended for any patient with PKU, even though dietary management is associated with a significant patient burden [5].

The impact of this disease on individual patients and the healthcare system can only be understood when considering all involved healthcare domains and healthcare resources utilized by patients with PKU. As PKU is often associated with neurological, neuropsychiatric, behavioral, and cognitive symptoms, as well as a variety of somatic comorbidities [16], these conditions can also have a major impact on the health economic burden of patients with PKU.

The aim of this study was to assess the healthcare resource utilization and the associated costs of adult patients with PKU in Germany to gain insights into the health economic burden of adult patients with PKU.

2. Methods

2.1. Study design

This study was designed as a retrospective, matched-cohort analysis comparing adult patients with PKU (ICD-10 E70.0) and controls without PKU. The study utilized German statutory health insurance (SHI) claims data.

2.2. Data source

The Institut für angewandte Gesundheitsforschung Berlin (InGef) database contains anonymized healthcare claims of approximately 4,000,000 individuals. It is adjusted to the overall German population in terms of age and gender and is considered to be in good accordance to the overall German population for measures of morbidity, mortality, and drug usage [17]. The InGef database includes a geographically well-distributed population from all federal states of Germany. Approximately 70 (out of 120) different insurance companies contribute to the database, which includes verified claims data as originally used for reimbursement purposes. These claims data were used in this study in accordance with German Social Law. Data on patients and physicians is anonymized, as are the providers and the health insurances, before data is made available to the InGef, ensuring compliance with the strict data protection regulations in Germany.

2.3. Study period

The study period was from January 1, 2010, to December 31, 2015. PKU patients were enrolled within this time frame (enrollment period) and the outcomes were analyzed for a 1-year period from January 1, 2015, to December 31, 2015 (observation period).

2.4. Study population

Adult PKU patients were identified by using International Statistical Classification of Diseases and Related Health Problems, 10th revision, German Modification (ICD-10-GM) codes E70.0 [Classic phenylketonuria] or E70.1 [Other hyperphenylalaninemas]) in the inpatient (main or secondary discharge diagnoses) and/or outpatient setting (verified diagnoses) during the enrollment period. They were excluded if they were younger than 18 years of age on January 1, 2015, or if they were lost to follow-up due to a sickness fund switch within the outcomes observation period.

2.5. Subgroups

Adult PKU patients were divided into cohorts of early-diagnosed and late-diagnosed patients, based on their birth year in relation to the implementation of newborn screening for PKU in Germany between 1969 and 1970 [18]. Thus, adult PKU patients born prior to January 1, 1969 were defined as late-diagnosed.

2.6. Matching

For each adult PKU patient, ten controls were drawn from the InGef database via direct, exact matching, without replacement on age and sex. Non-PKU controls (no PKU diagnosis code in the enrollment period) were required to be continuously enrolled in the database during the enrollment and observation periods, except for patients who died in the observation period.

2.7. Outcomes

Total annual healthcare costs were analyzed in the observation period and also stratified by the different cost domains: inpatient care, outpatient care, pharmaceuticals (including dietary amino acid supplements), and devices and aids. Healthcare resource utilization was analyzed in terms of hospitalizations and length of stay of hospitalizations, as well as for outpatient visits by physician specialty.

All-cause mortality was analyzed in 2015 and was described as an annual rate. All-cause mortality was defined as any reason for death, as the database did not contain the cause of death.

Prevalence ratios (PR) were calculated for categorical variables and mean differences (MD) between study groups were calculated for continuous variables. Differences between the groups were tested using 95% confidence intervals (95% CI) of PR and MD values.

3. Results

3.1. Study population

Overall, 3,723,345 individuals in the InGef database were continuously enrolled during the study period from January 1, 2015, until December 31, 2015. Of these, 377 adult individuals with PKU were identified, resulting in a period prevalence of 10.13 per 100,000 individuals in 2015.

The majority of adult PKU patients was female (58.1%) and the mean age ± standard deviation (SD) of adult PKU patients in 2015 was 50.9 ± 20.4 years. Of the 377 patients in the adult PKU cohort, 161 (42.7%) patients were born after the implementation of newborn screening in 1969 (early-diagnosed) and 216 (57.3%) patients were born prior to the implementation of newborn screening (late-diagnosed). The mean age of early-diagnosed and late-diagnosed patients was 30.7 ± 8.2 years and 65.9 ± 12.1 years, respectively. There was a higher proportion of females in the early-diagnosed cohort (n = 101; 63%) than in the late-diagnosed cohort (n = 118; 55%) (Table 1).

| Table 1 | Age and gender of adult PKU patients. |
|---------|-------------------------------------|
|         | **Adult PKU patients** | **Early-diagnosed adult PKU patients** | **Late-diagnosed adult PKU patients** |
| N       | 377 (100%)              | 161 (42.7%)                            | 215 (57.3%)                            |
| Age, years | Mean (SD)              | 50.9 (20.4)                             | 30.7 (8.2)                             | 65.9 (12.1)                             |
|         | Median (range)          | 51 (18–96)                              | 30 (18–46)                             | 65 (46–96)                              |
| Interquartile range (Q1–Q3) | 33–67                   | 24–37                                  | 56–76                                  |
| Gender  |                       |                                        |                                        |                                        |
| Female, n (%) | 219 (58.1%)           | 101 (62.7%)                            | 118 (54.6%)                           |
| Male, n (%)       | 158 (41.9%)            | 60 (37.3%)                             | 98 (45.4%)                            |

PKU, phenylketonuria; Q, quartile; SD, standard deviation.

a Both the maximum age of the early-diagnosed patients and the minimum age of the late-diagnosed patients was 46 years since age was determined on January 1, 2015, and dates of birthday are set to the first day of a quarter (January 1, April 1, July 1, October 1) in the database.
3.2. Mortality

The overall mortality of adult PKU patients in 2015 was 2.4% (n = 9) versus 1.3% (n = 43) in the matched controls. The difference between the two cohorts was not statistically significant (PR 1.9; 95% CI 0.93–3.79). All deceased patients were late-diagnosed PKU patients; no early-diagnosed PKU patients died in 2015.

3.3. Healthcare costs and resource utilization

Healthcare costs were analyzed as a total for 2015 and stratified by cost domains: inpatient care, outpatient care, pharmaceuticals including dietary amino acid supplements, and devices and aids.

3.4. Overall adult PKU population

Mean total healthcare costs per subject incurred in 2015 by adult PKU patients were 2.3 times higher than those of the matched controls: mean for PKU patients (mean\(^{\text{PKU}}\) €5932; MD €3307, 95% CI €1736–€4879). Furthermore, mean costs for PKU patients were significantly higher for pharmaceutical costs (mean\(^{\text{PKU}}\) €2533; MD €1912, 95% CI €1195–€2629) and outpatient costs (mean\(^{\text{PKU}}\) €1063; MD €395, 95% CI €115–€675) (Fig. 1). Mean costs for inpatient resources (mean\(^{\text{PKU}}\) €2054; MD €904, 95% CI €293 to €2100) and for aids and remedies (mean\(^{\text{PKU}}\) €282; MD €97, 95% CI €110 to €203) also tended to be higher in the PKU cohort than in controls although the differences were not significant (Fig. 1). The greatest difference between the two cohorts was for pharmaceutical costs (including dietary amino acid supplements), which accounted for 57.8% of the MD in total costs. Although only 13.8% of the PKU patients were prescribed and filled a prescription for dietary amino acid supplements in 2015, 50.1% of the pharmaceutical costs were for dietary amino acid supplements (mean costs: €1268). Sapropterin dihydrochloride was prescribed for fewer than five PKU patients (<1.3%).

Overall, 22.8% of the adult PKU patients were hospitalized in 2015 compared with 17.3% of matched controls (PR 1.3; 95% CI 1.08–1.60). Hospitalized PKU patients had a longer mean length of stay compared with their matched controls (mean 16.9 versus 14.2 days; MD 2.7 days, 95% CI -0.63 to 5.89 days). Adult PKU patients had a mean of 0.5 hospital stays in 2015 (MD 0.2, 95% CI 0.05–0.31).

In total, the mean number of all-cause outpatient visits for adult PKU patients in 2015 was 24.6 versus 17.3 visits in the matched controls (MD 7.3, 95% CI 4.56–10.04). Looking at outpatient visits by physician specialty, those with statistically significant MD between adult PKU patients and controls were primary care physicians (mean\(^{\text{PKU}}\) 8.5; MD 2.8, 95% CI 1.74–3.81), other physicians (e.g. dermatologists, anesthetists, ophthalmologists, etc.) (mean\(^{\text{PKU}}\) 5.5; MD 1.3, 95% CI 0.53–2.07), and orthopedists (mean\(^{\text{PKU}}\) 1.2; MD 0.3, 95% CI 0.03–0.66). See Table S1 for a complete list of outpatient visits by physician specialty.

3.5. Early-diagnosed adult PKU patients

Mean total healthcare costs per subject incurred by early-diagnosed adult PKU patients were 4.0 times higher compared with those of the matched controls (mean\(^{\text{PKU}}\) €5443; MD €4070, 95% CI €2544–€5597). Costs for pharmaceutical therapy (mean\(^{\text{PKU}}\) €3646; MD €3313, 95% CI €1987–€4639) accounted for the majority of this difference (81.4%). Fewer than five early-diagnosed PKU patients (<3.1%) received a prescription for sapropterin dihydrochloride and only 29.2% filled a prescription for dietary amino acid supplements (~70% were not receiving dietary amino acid supplements). Nevertheless, dietary amino acid supplements were responsible for 67.8% of pharmaceutical costs (mean dietary amino acid supplement costs: €2473). Compared with matched controls, mean costs for early-diagnosed PKU patients were also higher for inpatient costs (mean\(^{\text{PKU}}\) €815, MD €295, 95% CI €165 to €755), outpatient costs (mean\(^{\text{PKU}}\) €752; MD €302, 95% CI €165–€438), and costs for aids and remedies (mean\(^{\text{PKU}}\) €230; MD €160, 95% CI €7 to €328) (Fig. 2).

Overall, 18.0% of the early-diagnosed adult PKU patients were hospitalized in 2015, compared with 10.4% of matched controls (PR 1.7; 95% CI 1.21–2.49). Hospitalized PKU patients had a shorter mean duration of stay compared with their matched controls (mean\(^{\text{PKU}}\) 10.8 days; MD 4.7 days, 95% CI 1.33–8.01 days). However, early-diagnosed PKU patients had a mean of 0.3 hospital stays in 2015 compared to 0.2 among their matched controls (MD 0.1, 95% CI 0.02–0.27).

In total, early-diagnosed adult PKU patients had a mean of 18.5 all-cause outpatient visits in 2015, whereas the matched controls had a mean of 11.5 all-cause outpatient visits (MD 6.9, 95% CI 4.01–9.85). Looking at outpatient visits by physician specialty, those with statistically significant MD between early-diagnosed PKU patients and the controls were primary care physicians (mean\(^{\text{PKU}}\) 5.1 visits; MD 1.6, 95% CI 0.70–2.59), gynecologists (mean\(^{\text{PKU}}\) 2.8; MD 0.8, 95% CI 0.02–1.53), internists working as a primary care provider (mean\(^{\text{PKU}}\) 2.1; MD 1.1, 95% CI 0.41–1.70), and pediatricians (mean\(^{\text{PKU}}\) 0.7; MD 0.4, 95% CI 0.14–0.68). See Table S2 for a complete list of mean outpatient visits by physician specialty.

3.6. Late-diagnosed adult PKU patients

Mean total healthcare costs per subject incurred by late-diagnosed adult PKU patients were 1.8 times higher than those of the matched controls (mean\(^{\text{PKU}}\) €6296; MD €2738, 95% CI €241–€5236). Inpatient costs (mean\(^{\text{PKU}}\) €2977; MD €1358, 95% CI €0–€695 to €3441) accounted for the largest part of this difference (49.6%). Furthermore, mean...
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Discussion

At present, there is very limited information on the health economic burden of adult PKU patients, in terms of costs and resource utilization, in Germany. This study demonstrates that PKU in adults is associated with a high health economic burden in Germany. Compared with age- and gender-matched controls without PKU, the PKU patients incurred 2.3 times higher annual healthcare costs. Pharmaceutical costs were the main cost driver in PKU patients and contributed 57.8% to the MD in total costs. More than half of the pharmaceutical costs were attributable to dietary amino acid supplements, even though the proportion of patients on dietary amino acid supplements was unexpectedly low (13.8%). Costs for inpatient care were shown to be the second cost driver in PKU patients, contributing 27.3% to the mean difference in total costs.

The high health economic burden was particularly evident in early-diagnosed PKU patients who had 4.0 times higher annual costs than their matched controls. Late-diagnosed PKU patients had 1.8 times higher annual costs than their matched controls. The burden was higher for early-diagnosed PKU patients because of strongly increased costs for pharmaceuticals (MD €3313 for early-diagnosed PKU patients versus MD €867 for late-diagnosed PKU patients), even though late-diagnosed PKU patients incurred higher inpatient costs than early-diagnosed PKU patients when compared with matched controls (MD €295 for early-diagnosed PKU patients versus MD €1358 for late-diagnosed PKU patients). The higher inpatient costs for the late-diagnosed cohort are likely being driven up by their older age.

An exploratory study of the costs and reimbursement of special dietary foods used in the management of PKU in ten European specialist PKU centers confirms our findings that the most expensive items in the dietary management of PKU are dietary amino acid supplements [19]. As more than half of the pharmaceutical costs were attributable to dietary amino acid supplements, but only 13.8% of our study population received at least one prescription for dietary amino acid supplements, they can be defined as an important cost driver regarding the health economic burden of PKU. Other drugs that contributed to the pharmaceutical costs included those acting on the cardiovascular system, alimentary tract and metabolism, and nervous system. These drugs were prescribed significantly more often in PKU patients than in matched controls [16].

There are a few published studies that concentrate on the (cost-)effectiveness of newborn screening for metabolic diseases in Germany and in Europe [20, 21]. A study from the United Kingdom (UK) using The Health Improvement Network database assessed the levels of healthcare resource use and corresponding costs over the first 36 years of life in PKU patients [22]. Comparisons of our findings to results of Guest et al. [22] are limited as this study assessed cumulative lifetime costs associated with PKU (versus annual costs in our study), and there are inherent differences in the healthcare system and reimbursement between Germany and the UK.

Further cost assessments on the burden of PKU in children, adolescents, and adults concentrated on the out-of-pocket costs for PKU patients, as well as for caregivers [23–26]. Most of the out-of-pocket costs were due to expenditures on low-protein food products [23]. The database used in this study did not contain out-of-pocket costs, but dietary amino acid supplements are reimbursable in German SHI. Besides out-of-pocket expenditures, PKU is associated with a high societal burden for caregivers in terms of invested time and financial loss due to lost earnings [24]. The utilized database in this study provides only very limited information on societal costs; therefore, we had to focus on the SHI perspective of the health economic burden of PKU.

A notable finding of this study was that 86.2% of adult PKU patients did not follow a dietary amino acid supplements diet, which could be reimbursed by the SHI, especially if they were late-diagnosed and, by definition, older (70.8% for early-diagnosed and 97.7% for late-diagnosed PKU patients). Even fewer patients were treated with sapropterin dihydrochloride (<1.3% of PKU patients). These findings are in line with results from Miloch et al. [27] who found that compliance with low-protein foods decreased with increasing age. This trend might indicate decreasing compliance as a strict diet imposes a burden on patients, but it could also be caused by decreasing management of older PKU patients due to former recommendations not to treat adult PKU [11, 28]. Many adult PKU patients become lost to follow-up in their transition from pediatric to adult care [29] and many of these may be taken care of by general practitioners, who might be reluctant to prescribe dietary amino acid supplements because of lack of knowledge about PKU treatment and because of budget considerations (F. Rutsch, personal communication). Regarding the treatment of PKU patients with sapropterin dihydrochloride, it needs to be considered that sapropterin dihydrochloride is only effective in BH4-responsive PKU patients [30], about 20–56% of PKU patients [31, 32]. However, as we saw in the results, only <5 patients of our study population were treated with sapropterin dihydrochloride. This might suggest that other reasons besides the responsiveness to BH4 are decisive factors for the treatment with sapropterin dihydrochloride. In a recent expert survey on the use of...
sapropterin in PKU patients ≥16 years in Germany, only 11.8% of patients who were followed at a metabolic center were reported to be on sapropterin therapy [29]. In the current study, it is likely that a substantial proportion of patients was not continuously followed by a specialized center in Germany. General practitioners in Germany are more reluctant to prescribe sapropterin due to budget limitations (F. Rutsch, personal communication). Both of these factors may account for the low number of sapropterin prescriptions in the current study population.

In this study, more PKU patients required a hospital stay in 2015 compared with their matched non-PKU controls (22.8% versus 17.3%). Hospitalized PKU patients stayed an average 2.7 days longer in the hospital than the controls. Interestingly, early-diagnosed PKU patients had a higher chance of getting hospitalized in 2015 than late-diagnosed PKU patients compared with their matched controls (PR 1.7 in early-diagnosed versus PR 1.2 in late-diagnosed).

On average, PKU patients had 7.3 more outpatient visits in 2015. In early-diagnosed as well as in late-diagnosed PKU patients, a primary care physician was visited more often by PKU patients than their matched controls. Experience from a physician treating children with PKU confirms the suggestion that primary care physicians are crucial for the ongoing medical care of PKU patients besides the management in specific PKU centers [33]. On the other hand, a survey assessing the health-related quality of life of PKU patients in northern Germany found that frequency of annual physician visits in PKU patients does not significantly differ from the general population [34].

Early-diagnosed patients on average saw a pediatrician 0.7 times in 2015. As we only included PKU patients who are at least 18 years old, this is an interesting result. This indicates that the transition from pediatric care to adult care in Germany is lacking, due to a scarcity of adult specialists who treat PKU [35]. It is reasonable to assume that some patients might be followed up by their pediatrician since birth.

Moreover, early-diagnosed female PKU patients had visited a gynecologist more often compared with their matched controls. As 62.7% of the early-diagnosed PKU patients are female and are on average 30.7 years old, it is reasonable that early-diagnosed patients see a gynecologist more often than late-diagnosed PKU patients (on average 65.9 years old and 54.6% female). As maternal PKU is considered a high-risk pregnancy, the European PKU guidelines [5] recommend outpatient physician visits at least once during each trimester, but the intensity of monitoring should depend on individual needs and metabolic control, which is based on weekly Phe blood spots pre-conception and at least twice weekly during pregnancy. Maternal PKU is associated with two main risks for fetal development: growth retardation and birth defects including congenital heart defects. Therefore, a detailed follow-up by ultrasound examination is highly recommended from the very early beginning of pregnancy [5].

4.1. Strengths and limitations

In general, claims data analyses are subject to limitations, as they are primarily collected for reimbursement purposes and do not necessarily cover clinical parameters. Therefore, the study had to rely on the information that is coded in the utilized coding systems, namely the ICD-10-GM catalog. The ICD-10-GM catalog provides information about the disorders of aromatic amino-acid metabolism such as classical phenylketonuria (E70.0) and other hyperphenylalaninemias (E70.1) but contains no specific codes for severity of PKU. Therefore, we might see cases in the database with a very mild form of PKU, where no specific treatment or dietary management is necessary.

The stratification of the study population into early-diagnosed and late-diagnosed adult PKU patients was based exclusively on the year of birth in relation to the implementation of newborn screening for PKU, which was established in 1969/1970 in Germany. Individuals born prior to January 1, 1969 were classified as late-diagnosed PKU patients. This approach does not account for patients who were born in 1969/1970 who may or may not have undergone screening or patients who may have been born in other countries. It also does not account for newborns born prior to 1969 whose siblings already suffered from PKU and who therefore may have been tested and diagnosed early. Due to a disparity in the timing of the implementation of newborn screening between West Germany and the German Democratic Republic (GDR), the early-treated population from the united Germany may include some late-diagnosed patients originally from the GDR.

German claims data contains no direct information about the reason of death. Nevertheless, the data source provides sufficient information on overall mortality and the time of death.

Societal costs and patient individual costs were not considered in this study, as their assessment is strongly limited with claims data. On the other hand, this study has some major strengths. First, the utilized data source allows the generalization of the results to the German SHI population. Second, participants of the German SHI system benefit from nearly full coverage of all healthcare services. Only small copayments exist in the German SHI. German claims data therefore provides a virtually comprehensive picture of all direct healthcare utilization. Furthermore, due to the large sample of approximately 4 million individuals in the InGef database, we identified a rather robust PKU patient sample size, which can sometimes be challenging concerning the rareness of the disease.

4.2. Generalizability

The InGef database is based on claims data from the SHI system, but is adjusted to the German overall population in terms of age and gender. The proportion of females in the SHI population is higher than in the overall German population because proportionately more males choose private health insurance in Germany. Moreover, the prevalence of PKU shows regional differences among the federal states in Germany. The adjusted age and sex distribution of the InGef database does not account for these regional differences [36].

5. Conclusions

This retrospective matched cohort analysis utilizing German SHI claims data demonstrated that PKU is associated with a high health economic burden in Germany. Costs for pharmaceuticals, especially dietary amino acid supplements, were revealed to be the cost driver, despite relatively few patients receiving dietary amino acid supplements and almost none receiving sapropterin dihydrochloride. Late-diagnosed (by definition, older) PKU patients were especially at risk of not receiving dietary amino acid supplements, indicating they are not being treated by a Phe-restricted diet as suggested by the European PKU treatment guidelines. Looking at early- and late-diagnosed PKU patients separately, most costs for late-diagnosed PKU patients were produced in the inpatient sector, whereas pharmaceuticals are the main cost driver in early-diagnosed PKU patients. PKU patients were hospitalized more often and stayed longer in the hospital compared with their matched controls. Also, in the outpatient sector, PKU patients utilized more healthcare resources regarding physician visits compared with their matched controls. Besides primary care physicians, gynecologists were visited significantly more often by early-diagnosed and therefore younger PKU patients. Overall, this study revealed the high health economic burden of PKU patients for the statutory healthcare system. Further research is needed to investigate the individual or societal economic burden of PKU.

Authors’ contributions

KMS, JA, and CJ analyzed the dataset. All authors interpreted the data. KMS and PL were responsible for drafting an initial outline of the manuscript for review by all authors prior to development of a first draft. All authors provided critical review, revision of drafts, and approval of
the final manuscript.

Availability of data and materials

The utilized database in this study is available from the Institut für angewandte Gesundheitsforschung Berlin (InGef) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data tables showing all included analyses are included in the supplementary materials.

Conflicts of interest

FT received honoraria for presentations from BioMarin. ACM has been a member of scientific advisory boards supported by BioMarin Europe Ltd. and has received honoraria as a speaker for BioMarin Europe Ltd. KMS, JA, CJ, and SB are full-time employees of Xcenda, acting as contractors of BioMarin Europe Ltd. for the execution of this study. AJ and MJ are employees and stockholders of BioMarin Europe Ltd. IA and PL were employees of BioMarin Europe Ltd. at the time of the study. CZ is an employee and stockholder of BioMarin Deutschland GmbH. FR has received speaker and consulting honoraria from BioMarin Europe Ltd. WG declares no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2021.100764.

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