

The Economic Burden of Phenylketonuria among Patients and their Caregivers: A Systematic Literature Review from a Global Perspective

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BACKGROUND

- Phenylketonuria (PKU) is an autosomal recessive metabolic disorder characterized by an inborn error of phenylalanine (Phe) metabolism, caused by pathogenic variants in the phenylalanine hydroxylase (PAH) gene^{1,2}.
- Early treatment is critical to prevent severe and irreversible neurological damage; and lifelong maintenance of low plasma Phe concentrations is required to minimize behavioral and social dysfunction in adolescents and adults^{1,2}.
- Significant healthcare resource utilization (HCRU) and treatment costs are associated with PKU management³⁻⁴.
- No prior comprehensive systematic literature reviews (SLR) were available to assess the economic burden of disease.

OBJECTIVE

- This SLR aimed to identify and to systematically analyze published evidence on the humanistic and economic burden of PKU among patients and their caregivers.
- This presentation summarized findings related to the economic burden of PKU.

METHODS

- The literature search was conducted across the following databases: Medline (via PubMed), Embase, Cochrane Library, PROSPERO, Econlit, and CEA Registry on 12 January 2024 with no prior date restriction.
- Articles written in English involving patients or their caregivers with hyperphenylalaninemia (HPA), including in those with PKU, were included.
- Screening, full-text review, data extraction and quality assessment were performed independently by two researchers.
- Research findings were narratively synthesized.
- Costs were converted and adjusted to 2023 US dollars.

RESULTS

Results of the literature search

- A total of 1,102 articles related to the humanistic and economic burden of HPA, including PKU, were screened.
- Thirty-nine studies, including 18 studies for HCRU and 34 studies for costs, published from 1973 to 2023, were included in the SLR (Figure 1).

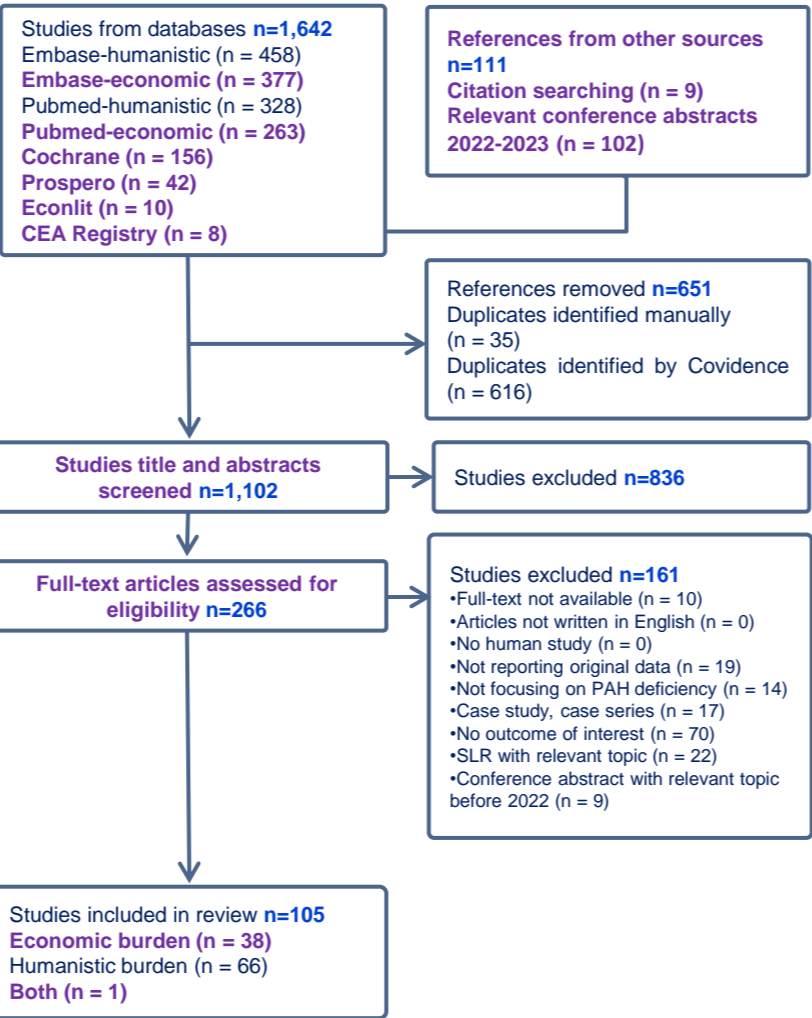
Characteristics of identified studies

- Most of the studies (n=38) focused on patients with PKU, while only one study involved patients with HPA.
- Six studies assessed caregiver burden.
- Studies from 37 countries were included, such as United States (US=9), United Kingdom (UK=8), and 3 each in France, Spain, and China (Figure 2).
- Among the included patients, 32 studies involved children, 18 included adolescents, and 20 featured adults (Figure 3).
- Sixteen publications provided cost data from health economic evaluations of newborn screening programs, nine reported HCRU and costs, nine examined diet-related HCRU and costs, and five addressed caregiver time burden and out-of-pocket (OOP) expenses (Figure 4).

CONCLUSIONS

- Despite being a rare disease, a substantial body of literature exists highlighting significant economic burden associated with PKU among patients and their caregivers.
- The HCRU and costs were mainly driven by the increased outpatient visits, greater use of pharmacological treatments, including dietary supplements, and a significant time burden associated with PKU management-related activities.
 - Among patients with early-diagnosed PKU, approximately half of the healthcare costs were attributed to medications, with dietary supplements comprising the majority of the pharmaceutical expense, while the remaining costs were related to inpatient and outpatient services.
 - In contrast, for late-diagnosed patients, overall healthcare costs were higher, with inpatient care representing the half proportion of total healthcare expenditures.
- The reviewed studies showed that the overall burden was more pronounced among patients diagnosed later in life or those with severe forms of PKU. However, further research is needed to quantify the HCRU and associated costs by disease severity, age group, and among patients currently on pharmacotherapies.

Figure 1. PRISMA Diagram of Identified Studies in the Humanistic and Economic Burden of PKU*



*This presentation summarized findings related to the economic burden of PKU. Purple colour indicates records related to the economic burden of PKU.

Figure 2. Geographical Coverage



Figure 3. Study Populations by Age

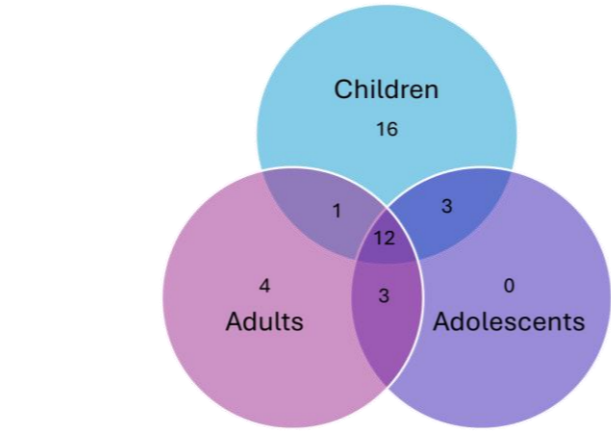
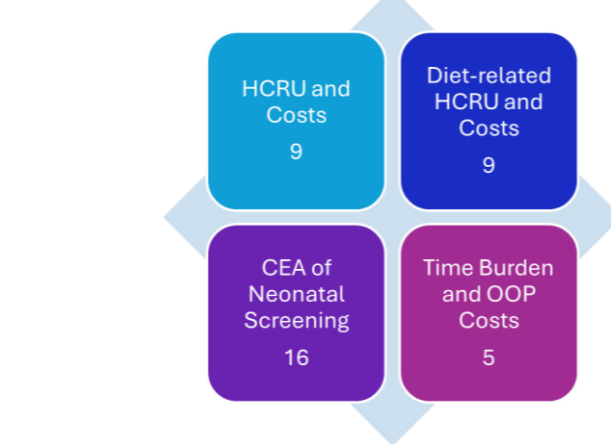


Figure 4. Types of Included Studies



HCRU, healthcare resource utilization; CEA, cost-effectiveness analysis; OOP, out-of-pocket

HCRU results

- Six studies assessed HCRU among patients with PKU and reported a mean number of hospitalizations ranging from 0.12 to 1.18 per patient per year (PPPY), with an associated mean length of stay from 0.96 to 365 days PPPY (Table 1).

Table 1. Hospitalization and Length of Stay among Patient with PKU

	Country	Study period	No. of Patients	Mean No. of Hospitalization PPPY	Mean Length of Stay (days) PPPY
Sellos-Moura 2020 ⁵	USA	2010-2016	5,120	0.12 ^a	NR (0.96 ^c)
Trefz 2021 ⁶	Germany	2010-2015	377	0.5	16.9 ^d ED: 10.8 LD: 20.0
Okhuoya 2022 ⁷	France	2018	1,911	0.97 ^b	7.3
Darbà 2019a ⁸	Spain	1997-2015	594	1.18	4.04
Darbà 2019b ⁹	Spain	2007-2017	289	0.23	NR
Brown 1999 ⁴	UK	NR	8	NR	365 ^e

a: Reported: mean 0.01 per patient per month; b: Reported: mean 3.3 if at least one hospitalization (n=559); c: Reported: mean 0.08 total days of hospitalizations per PKU patient per month; d: ED= Early-diagnosed PKU patients (n=161); LD=Late-diagnosed PKU patients (n=216); e: Length of long-term hospital stay

- In Germany, the mean number of primary care visits PPPY was 8.5 for patients with PKU, with a significant difference between early-diagnosed (5.1) and late-diagnosed patients (11.1)⁶. In Spain, the mean was slightly higher at 8.78 PPPY⁹.
- The mean number of outpatient visits PPPY was 24.6 for patients with PKU, differing between early-diagnosed (18.5) and late-diagnosed patients (29.2) in Germany⁶.
- Adult patients with PKU reported significantly higher usage of various medications compared to the control group, including dietary supplements, sapropterin (tetrahydrobiopterin), and a wide range of drugs for non-PKU chronic conditions^{10,11}.
- Caregivers and patients with severe PKU spent approximately three times more time on PKU management related activities than patients with mild PKU. The mean time spent on diet-related activities ranged from 233 to 359 hours PPPY^{12,13}.

Cost results

- Six studies reported the mean cost PPPY for inpatient, outpatient and total healthcare in the range of \$1,086-4,884, \$1,002-1,954, and \$3,253-25,476, respectively (Table 2).

Table 2. Healthcare Costs among Patients with PKU (USD 2023)

Study	Country	Study Period	No. of Patients	Mean Cost PPPY		
				Inpatient	Outpatient	Total Healthcare
Burton 2018 ¹⁰	USA	1998-2014	3,691	NR	NR	\$5,330
Darbà 2019a ⁸	Spain	1997-2015	594			\$3,253 - \$5,647 ^e
Min 2019 ¹⁴	China	2013-2015	40			\$4,087
Okhuoya 2022 ⁷	France	2018	1,911	\$3,278	\$1,954	\$12,782
Sellos-Moura 2020 ⁵	USA	2010-2016	5,120	\$4,884 ^a	\$1,068 ^b	\$25,476 ^c
Trefz 2021 ⁶	Germany	2010-2015	377	\$2,736 ^d ED: \$1,086 LD: \$3,966	\$1,416 ^d ED: \$1,002 LD: \$1,724	\$7,902 ^d ED: \$7,251 LD: \$8,387

a: Reported: \$407 per month; no year costing data; b: Reported: \$89 per month; no costing year data; c: Reported: \$2,123 per month; no costing year data; d: Early-diagnosed PKU patients (n=161); Late-diagnosed PKU patients (n=216); e: Total healthcare cost was reported annually, which increased between 1999 and 2015.

- The mean cost of a protein substitute diet treatment PPPY ranged from \$6,211 to \$31,381, and the mean cost of protein substitutes increased with age (e.g., 2 years old: \$7,971; 30 years old: \$27,292)³.
- The OOP costs for PKU increased with disease severity and decreased with patient age. The mean OOP cost PPPY ranged from \$1,173 to \$2,137 for low-protein foods, and from \$30 to \$370 for sapropterin¹².
- Diet management imposed a significant burden, with mean costs ranging from \$1,546 to \$31,381 PPPY^{3,4,7,12,15,16}.

LIMITATIONS

- Studies were heterogeneous in terms of study design, patient populations and their characteristics, resulting in a wide range of published data. Hence, meta-analysis was not feasible, and findings were summarized narratively.
- Studies reporting HCRU and cost data were mainly conducted in the US, UK and EU countries, hence the generalizability of the findings is limited.

DISCLOSURES

- This study was funded by Moderna, Inc. SP and VS are employees of Moderna, Inc. who owns stock/options in the company. SV is an employee of HealthEcon Consulting, Inc. and an external consultant for Moderna, Inc. TZ, DM, HV, MH, KGy, and JJH are employees of Syreon, which received research funding from Moderna, Inc.

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