Burden of phenylketonuria in Latin American patients: a systematic review and meta-analysis of observational studies

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Abstract

Background: Phenylketonuria (PKU) is an inborn error of metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase. If untreated, the complications of PKU lead to significant neuropsychiatric impairments, placing a burden on both the individual’s quality of life and on the healthcare system. We conducted a systematic literature review to characterize the impact of PKU on affected individuals and on healthcare resources in Latin American (LATAM) countries.

Methods: Searches of the global medical literature as well as regional and local medical literature up to September 2021. Observational studies on patients with PKU from any LATAM country. Pairs of reviewers independently screened eligible articles, extracted data from included studies, and assessed their risk of bias.

Results: 79 unique studies (47 cross-sectional studies, 18 case series, 12 case reports, and two cohort studies) with a total of 4090 patients were eligible. Of these studies, 20 had data available evaluating early-diagnosed PKU patients for meta-analysis of burden outcomes. Intellectual disability in the pooled studies was 18% [95% Confidence Interval (CI) 0.04–0.38; I² = 83.7%, p = 0.0133; two studies; n = 114]. Motor delay was 15% [95% CI 0.04–0.30; I² = 74.5%, p = 0.0083; four studies; n = 132]. Speech deficit was 35% [95% CI 0.08–0.68; I² = 93.9%, p < 0.0001; five studies; n = 162].

Conclusions: There is currently evidence of high clinical burden in PKU patients in LATAM countries. Recognition that there are many unmet neuropsychological needs and socioeconomic challenges faced in the LATAM countries is the first step in planning cost-effective interventions.

Keywords: Neurological disease, Attention deficit hyperactivity disorder, Overweight, Phenylketonuria, LATAM

Background

Phenylketonuria (PKU) is an inborn error of metabolism caused by a deficiency of the enzyme phenylalanine hydroxylase (PAH) which results in elevated levels of phenylalanine (Phe) and reduced levels of tyrosine [1]. The incidence within Latin American (LATAM) countries is estimated at 1 in 23,000 live births [2]. PKU presents a spectrum of severity, and there are several different classifications that have been proposed [2]. Several different classification schemes to determine clinical management have been proposed since PAH deficiency presents a spectrum of severity [1]. Individuals with classical PKU have a complete enzyme deficiency resulting in untreated blood Phe levels > 1200 μmol/L (an average...
normal Phe level is approximately 60 μmol/L), which is considered the severe form of this disorder [1].

The treatment for PKU is a lifelong dietary restriction of protein supplemented by a Phe-free amino acid fortified medical food [1], and ongoing monitoring of blood Phe levels to maintain a target range of 120–600 μmol/L for patients ≥12 years old, and up to 360 μmol/L for those <12 years old [3]. If left untreated, the disease can manifest as significant intellectual impairment, neuropsychiatric disorders, and seizures [4] which place a burden on the individual’s quality of life, their families, and on the public and private healthcare systems [4]. Even patients diagnosed and treated at an early age face significant challenges related to adherence with the Phe-restricted diet.

Latin America comprises of 20 countries that represent a great diversity not only in terms of geography but also demographics, economies, languages, ethnicities, and health care systems [5]. In a recent review from Borrajo [6], newborn screening (NBS) programs were distinctively implemented in Latin America. While some programs date back from the 1980’s, other countries are still implementing regional NBS programs. Additionally, the number of diseases covered varies significantly across programs. Specifically concerning PKU, this genetic disorder is included in the NBS program for 14 countries (Cuba, Costa Rica, Chile, Uruguay, Argentina, Mexico, Brazil, Guatemala, Paraguay, Panama, Ecuador, Peru, Bolivia and Honduras) [6] with on average 92.3% of newborns in those countries screened for PKU. Regarding the availability of PKU treatment, half of the Latin America countries have fully subsidized medical foods by the government through the special low-protein foods are not available in most of the countries [7].

Evaluating the unmet needs and burden of PKU on affected individuals is important to determine the impact on the LATAM public and private healthcare system. Recognition that there are many challenges that the patient with PKU faces is the first step in planning for cost-effective intervention scenarios. We therefore conducted a systematic literature review and meta-analysis to better characterize the impact of PKU in LATAM countries on selected patient-important outcomes as well as at the economic (socioeconomic, healthcare utilization) level.

**Material and methods**

Our review followed recommendations for systematic reviews and meta-analyses of observational studies in epidemiology (MOOSE) [8]. This systematic review has been registered in the PROSPERO (International Prospective Register of Systematic Reviews) database under the number CRD42020211417.

**Eligibility criteria**

We included any epidemiological observational study (ie, cohort, case-control, nested case-control, cross-sectional studies, case series, case reports, surveys) on patients with PKU or phenylalanine hydroxylase deficiency (PAH), regardless of disease severity, including classical, moderate, and mild forms of this disorder, from any LATAM country regardless of whether they reported on any of the pre-defined patient-important outcomes and/or economic burden outcomes as defined below. We also included studies on caregivers of PKU patients.

Studies that only reported disease prevalence or incidence as well as non-human studies and subjective reports of clinical or observational studies such as letters, editorials and commentaries were excluded.

**Pre-defined patient-important outcomes of interest included:**

- Neurological, neurocognitive and neuropsychiatric impairments: intellectual disability, mental disorders, autism spectrum disorder, motor deficits, speech deficits and language delay, tremor, Attention Deficit Hyperactivity Disorder (ADHD) and hyperactivity, mood, depression, anxiety, phobias, irritability and/or aggressiveness, frustration, social isolation;
- Executive function deficit: working memory, sustained attention, inhibitory control, processing speed impairments, impairment in visuomotor coordination;
- Other comorbidities such as overweight, osteopenia, osteoporosis, skin problems, headaches, fatigue and sleeping disorder;
- Quality of life measured by non-validated and validated questionnaires, as defined by the included studies; and
- **Patient adherence to clinical recommendations**, including frequency of blood testing (ideally biweekly to monthly with targeted Phe concentrations of 120–360 μmol/L as recommended by the American College of Medical Genetics and Genomics (ACMG) guidelines [1] and 120–600 μmol/L for those ≥12 years of age by the European guidelines [9] and dietary management including a Phe-restricted diet supplemented by Phe-free amino acid fortified medical foods as well as the use of sapropterin dihydroloride in patients who are responsive to this pharmacological treatment.

Symptoms of being late-treated for the disease, such as seizures, microcephaly, generalized rash, and peculiar-smelling urine, were not investigated as patient-important outcomes for the purposes of this review.

**Pre-defined economic outcomes of interest included:**
• Socioeconomic impact (eg, school/education level, work experience and productivity, marital status, personal independence, living situation, employment, social status);
• Impact of PKU on caregiver health-related quality of life; and
• Impact of PKU on the healthcare system (eg, direct and/or indirect costs, treatment costs, health care resource use, cost of comediations, hospitalizations).

Data source and searches
Using “phenylketonuria” and “phenylalanine” (Additional file 1: Table 1) we performed the search in the global medical literature using Medical Literature Analysis and Retrieval System Online (MEDLINE, via PubMed, from 1946 to September 2021), Excerpta Medica Database (EMBASE, via Elsevier, from 1974 to September 2021), and Web of Science (to September 2021).

In the regional and local medical literature, both Spanish and English terms were used to search in Latin American and Caribbean Health Sciences Literature (LILACS, 1982 to September 2021), Scientific Electronic Library Online (SciELO, 1997 to September 2021), SciVerse Scopus via Elsevier (to September 2021), the Spanish Bibliographic Index of the Health Sciences (IBECS, 1983 to September 2021), National Bibliography in Health Sciences Argentina (BINACIS, to September 2021), Caribbean Health Sciences Literature (MedCarib, to September 2021), National Medical Sciences Information Center of Cuba (CUMED, to September 2021), Brazilian Bibliography of Dentistry (BBO, to September 2021), Health Information Locator (LIS, to September 2021), and the WHO Institutional Repository for Information Sharing (WHO IRIS, to September 2021). The date the search was conducted was September 24, 2021 and no starting date restrictions, or language restrictions, were imposed. The search strategy was adapted for each database to achieve more specificity and sensitivity. Duplicate records across databases were removed.

We searched the gray literature including the Brazilian Digital Library of Theses and Dissertations (BDTD). In addition, reference lists of relevant primary studies were hand searched and experts in the field were contacted to obtain additional unpublished data where feasible.

Selection of studies
Reviewers independently screened all titles and abstracts identified by the literature search using online software Covidence (https://www.covidence.org), obtained full-text articles of all potentially relevant studies, and evaluated them against the eligibility criteria. Reviewers resolved disagreement by discussion or, if necessary, with third party adjudication. We also considered studies reported only as abstracts and we attempted to contact study authors for additional information where needed. We recorded the selection process and documented via a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Fig. 1).

Data synthesis and statistical analysis
We performed a systematic review of studies with pooled analysis of proportions [10, 11], using the method of Stuart-Ord (inverse double arcsine square root) with their respective 95% confidence intervals (CI). Only case series and cross-sectional studies were considered for quantitative analysis; case reports were excluded. To avoid bias related to the effect of delayed implementation of dietary management in late treated patients, only early-diagnosed patients (ie, diagnosed within first three months of life) were included. Studies that did not report whether the treatment was implemented at an early or late age were excluded from the meta-analysis as well as those that did not separate data for the early- or late-diagnosed patients.

Since we expected that there were both clinical and methodological differences among the included studies, a random-effects model [12] was used to perform the pooled analysis of proportions [10, 11]. The meta-analysis was performed with the StatsDirect software, version 2.8.0. (StatsDirect Ltd, Altrincham, Cheshire, UK).

Results

Study selection
Our initial searches identified 3917 citations (n=3854 from electronic searches; n=63 identified through the gray literature). After removing duplicates from different databases, 3081 potentially relevant articles were further assessed using title and abstract review. A total of 202 articles were identified for full text assessment. After screening the full texts, we included 79 studies with 11 further publications (ie, multiple publications of the same set of patients) (47 cross-sectional studies, 18 case series, 12 case reports, and two retrospective cohort studies) with a total of 4090 patients [7, 18-17-106]. The reasons for exclusion are listed in the PRISMA flow diagram.
Six of the included studies were published only as an abstract [13–19], ten studies as a thesis [20–29], and the majority (n=57) were published as full-text in peer-reviewed journals [14, 28, 30–74]. Seven further studies [27, 29, 75–79] were published initially as a thesis followed by a full-text publication [34, 43, 80–83]. When information regarding risk of bias or other aspects related to study criteria were unavailable in the methods, we attempted to contact study authors for additional information.

**Study characteristics**

Sixty-four of the 79 included studies reported at least one patient-important outcome at individual or population level, and they are displayed in Table 1 for study characteristics. Regarding study design, 18 were case series [22, 23, 33, 34, 40–42, 45, 54, 55, 58, 60, 70, 84–87], 47 cross-sectional studies [6, 7, 13–15, 17–21, 24, 26, 29, 30,
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|--------------|---------------|------------------|------------|---------------|------------------|---------------------------------------|------------------------|------------------|-------------------------|------------------------------|-----------------------------|-----------------|---------------------------------|
| Benítez et al. 2001 [32] | Uruguay | 2 | 12 | 0.0 | NR | NR | Individual and economic | Neurological, neurocognitive and neuropsychiatric impairments | Mental disorders—repetitive behaviors (rocking, flapping, etc.); motor deficits—march with aid; speech deficits—only emits a word | NR | NR | NR | NR | Not included as did not report whether the treatment was implemented at an early or late age |
| Bernal, 2017 [33] | Argentina | 3 | NR | 100.0 | NR (66.66) and classic (33.33) | NR | Individual and economic | Patient adherence to clinical recommendations | Neurological, neurocognitive and neuropsychiatric impairments | Neurological, intellectual disability, aggressiveness, low frustration tolerance | NR | Early (66.7%) and late (33.3%) | Phe-restricted diet | 3.80** | NR | Not included as did not report data separately for early versus late treated |
| Cornejo et al. 1995 [42] | Chile | 17 | 18.8 | NR | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Slight retardation, normal mental development | Early | Phe-restricted diet and education program | 19.9** | 6 | Included in Fig. 3E |
| Cornejo et al. 2003 [41] | Chile | 19 | 19.9 | 52.63 | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Low motor development | Early | Direct breast feeding and a special formula without Phe | 20.3** | NR | Included in Fig. 3D |
| Cornejo et al. 2012 [40] | Chile | 184 | 0 to 20€ | 46.73 | NR | Classic and moderate (NR) | Individual | Overweight and obesity | Neurological, neurocognitive and neuropsychiatric impairments | Average total IQ in preschoolers, schoolers and teenagers | Early | Phe-restricted diet and education program | 18 | NR | Included in Fig. 4A and B |
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|--------------------------------------|------------------------|-----------------|-----------------------------|------------------|----------------------------------|
| Diament & Lefevre, 1967 [45] | Brazil | 6 | 4.36 | 66.66 | NR | NR | Individual | Neurological, neurocognitive, and neuropsychiatric impairments | Irritability; language delay; mental retardation; hyperactive patient | Late | Phe-restricted diet | NR | Not included as population was not early diagnosed/treated |
| Figueira, 2018 [22] | Brazil | 78 | 9.2 | 59.0 | Classic (100.0) | NR | Individual | Patient adherence to clinical recommendations | Neurological, neurocognitive, and neuropsychiatric impairments | Non-adherence to Phe-restricted diet | Early (56.4%) and late (43.6) | Phe-restricted diet | NR | Included in Figs. 3C, E, F, and 4E Not included as did not report data separately for early versus late treated |
| Gelvez et al. 2016 [54] | Colombia | 4 | 13 | 75.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive, and neuropsychiatric impairments | Speech deficits; neuropsychomotor development delay; aggression; anxiety; attention deficit symptoms; executive function deficit | Late | Phe-restricted diet and education program | 13** | Not included as population was not early diagnosed/treated |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|------------------|----------------------|----------------------|-----------------|-----------------------------|---------------------------|--------------------------|---------------------------|------------------------------------------------------------------|
| Jiménez-Pérez et al. 2015 [55] | Mexico | 6 | 7 | 33.3 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Skin problems | Late | NR | 690 | NR | Included in Fig. 4C | Not included as population was not early diagnosed/treated |
| Lamônica et al. 2012 [58] | Brazil | 10 | NR | 40.0 | NR | Chronic disease | Individual | Executive function deficit | Executive function deficit | Early | Phe-restricted diet and mixed formula | Before 30 days of life | NR | Included in Figs. 3A, C, 4D, and 5 |
| Mahfoud et al. 2008 [60] | Venezuela | 5 | NR | 40.0 | Classic (60.0) and mild (40.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Early | Phe-restricted diet and special formula | 480 | NR | Included in Figs. 3A, C, F, and 4D |
| Martins, 2007 [23] | Brazil | 15 | 9 to 29€ | 66.7 | NR | NR | Individual | Overweight and obesity | Osteopenia | NR | Phe-restricted diet | NR | 6 | Not included as did not report whether the treatment was implemented at an early or late age |
| Queiroz & Pondé, 2015 [84] | Brazil | 8 | NR | 37.5 | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Hyperactivity; attention deficit; aggressive behavior; intellectual disability; autism | Early (50%) Late (50%) | Phe-restricted diet | 3,698** | NR | Not included as did not report data separately for early versus late treated |
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|--------------|-------------------|------------|---------------|-------------------|----------------------------------------|----------------------------|-----------------|--------------------------|-------------------------------|-----------------------------|--------------------------|--------------------------------------------------|
| Sánchez-Peña et al. 2008 [85] | Mexico | 3 | 5.6 | 100.0 | Classic (66.6) and moderate (33.3) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Personal-social development delay; adaptive-motor delay; language delay; hyperactivity; aggressiveness; irritability; autistic behaviour | Early (86.7%) Late (33.3%) | Phe-restricted diet and special formula | 2,044** | At least 3 | Not included as did not report data separately for early versus late treated |
| Silva et al. 2016 [70] | Brazil | 36 | NR | 52.77 | NR | NR | Individual | Patient adherence to clinical recommendations | Noncompliance to treatment | Early (80.55%) | Phe-restricted diet | NR | NR | Not included as quantitative data on outcome of interest not provided in paper |
| Steiner et al. 2007 [86] | Brazil | 3 | 17.33 | 33.33 | NR | NR | Individual and economic | Neurological, neurocognitive and neuropsychiatric impairments | Socio-economic impact | Early | Phe-restricted diet | NR | NR | Not included as quantitative data on outcome of interest not provided in paper |
Table 1 (continued)

| Author, year        | LATAM country | #of patients | Age, Mean* (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|---------------------|---------------|--------------|--------------------|------------|---------------|-------------------|----------------------------------------|------------------------|-----------------|----------------------------|-------------------------------|-----------------------------|---------------------|----------------------------------------------------------------------------|
| Tanaka et al. 2018  | Brazil        | 18           | 10                 | 39.0       | NR            | Patients who did not adhere to the dietary treatment (evaluated by the food anamnesis) associated with no intake of elemental formula free of Phe in the recommended amount and those who were receiving a drug supplement of calcium | Individual              | Overweight or obese              | NR              | Phe-restricted diet and special formula | NR                           | 34*                         |                     | Not included as did not report whether the treatment was implemented at an early or late age |
| Valle et al. 2019   | Argentina     | 133          | 2 months to adulthood | NR         | Moderate (50%), mild (67%), and HPA (33.0%) | Neurological, neurocognitive and neuropsychiatric impairments Others | Individual              | Neurocognitive evaluation Successful pregnancies Patient adherence to clinical recommendations | Early (24.06%) and late (5.75%) | Phe-restricted diet + protein substitute (5.13%); Phe-restricted diet + glyco-macropeptides (1.50%); and diet counselling (3.15%); BH4 (9.77%) | Until age five and monthly thereafter |                     | Not included as did not report data separately for early versus late treated |
| Andere et al. 1988E | Brazil        | 35           | 4* to 11*          | 48.57      | Classic (100.0%) | Skin problems | Keratosis pilaris, ammonia dermatitis, dry skin, reticular livedo and dermographism, during the dietary treatment darkening of skin, hair and eyes; lightening of the skin and hair | NR                     | Phe-restricted diet | NR                           | NA                          | Included in Fig. 4C |                     |                                                                 |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
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| Beckhauser et al. 2020 [31] | Brazil | 34 | 12 | 47.0 | NR | Patient who started treatment after 60 days of age, who failed to maintain Phe levels below 6 mg/dL or who failed to adhere to regular medical follow-ups | Individual | Neurological, neurocognitive and neuropsychiatric impairments | ADHD | Early | Regularly treated since birth according to the "Brazilian Phenylketonuria Clinical and Therapeutic Guidelines," consisting of a diet and protein formula diet, with Phe restrictions | Before 60 days of life (treated since birth) | NA | Included in Fig. 3A |
| Brandalize, 2004 [75, 88] | Brazil | 32 | 0 to 6 months | 56.3 | NR (84.40) and moderate (16) | Children who started early treatment in the pioneering program of the Association of Parents and Friends of the Exceptional of São Paulo (APAE-SP), late diagnoses, and early diagnosis due to age above the rest of the group (11, 13 and 14 years) | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Low development of gross motor function; mean gross motor function of PKU and HPAP children; for PKU and HPAP low development of gross motor function | Early | Phe- restricted diet | For PKU, 8 days to 30 days after born (n = 23 patients) and 31 days to 60 days after born (n = 4 patients); for HPAP, 2 months to 1 year after born (n = 5 patients) | NA | Not included as quantitative data on outcomes of interest not provided in paper |
| Author et al. | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|--------------|------------------|------------|---------------|--------------------|-------------------------------|---------------------|------------------|----------------------|-------------------------|-------------------------|-------------------------|------------------------------------------------------------------|
| Pardo-Campos et al. [35–37] | Argentina | 30 | 8 to 11 | 10.4 | NR | NR | Individual and economic | Executive function deficit | Impact of PKU on caregiver health-related quality of life | Coping strategies (facing conflicts, relationship with impulsivity), cognitive profile, organization, IQ, memory, visuospatial skills, reaction times, processing speed or in language | Parenting styles perceived by the children | Early | NR | NR | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Chiesa et al. 2012 [38] | Argentina | NR | NR | NR | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | NR | NR | Phe-restricted diet, and free animal food | NR | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Camatta, 2020 [76, 80] | Brazil | 94 | 14 | 53.0 | NR | Tetrahydrobiopterin (BH4) deficiency, use of pacemaker, pregnancy, growth-related disorder, and abandonment of treatment over the two previous years | Individual and obese | Overweight and obese | Early | Phe-restricted diet and special formula | Up to 30 days of life | NA | Included in Fig. 4A |
| Author, year | LATAM country | #of patients | Age, Mean\(\text{SD}\), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|--------------|--------------------------|-------------|---------------|------------------|-------------------------------------|------------------------|-----------------|--------------------------------|-----------------------------|-----------------------------|--------------------------|--------------------------------------------------|
| Castro et al. 2012 [77, 81] | Brazil | 63 | 6 to 12\(\text{EC}\) | 52.4 | Classic (82.5) and mild (17.5) | Not having a free and informed consent form; child's disagreement; and lack of information on Phe dosages of the transferred patients | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Intellectually disabled from total IQ | Early | Phe-restricted diet | Up to 90 days after born | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Cerqueira, 2004 [20] | Brazil | 101 | 34.23\(\text{S}\) | 84.2 | NA | NR | NR | NR | NR | NR | NR | NR | NA | Not included as did not report whether the treatment was implemented at an early or late age |
| Colombo et al. 1988 [39] | Chile | 44 | 3.11 | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Language delay; isolated psychomotor developmental delay; mental retardation; hyperactivity; irritability; psychomotor or mental retardation; psychometric evaluation; MRI | Late | Phe-restricted diet | 3 years 11 months | NA | Included in Fig. 3A, C, and D Not included as population was not early diagnosed/treated |
| Author, year | LATAM country | #of patients | Age, Mean* (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|--------------|------------------|------------|--------------|-------------------|---------------------------------------|------------------------|-----------------|---------------------|---------------------------|-----------------------------|-------------------|------------------------------------------------|
| Da Silva et al. 2020 [43] | Brazil | 31 | 17.4 | 51.6 | Classic (30.8) and mild (69.2) | To be in an irregular clinical follow-up in the last 12 months; (2) to have a clinical diagnosis of intellectual disability or diagnosis of other associated genetic, psychiatric, or neurological diseases which compromise the assessment of ADHD | Individual | Neurological, neurocognitive and neuropsychiatric impairments | ADHD Late | Late | Phen-restricted diet and special formula | 26** | NA | Not included as population was not early diagnosed/treated |
| Dutra et al. 2013£ [21] | Brazil | 21 | 9.52 | 42.9 | Classic (4.76) and mild (57.16) and HPAP (38.1) | Children and adolescents whose parents or legal guardians have not signed the ICF; with confirmed diagnosis of neurological and / or psychiatric illness or other syndromes that cause delays in cognitive development | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Neuropsychological assessment; executive function of IQ, verbal of IQ, verbal comprehension index; perceptual organization index; distraction resistance index; Snoop Executive function deficit | Early | NR | Up to 90 days after born | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|------------------|----------------------------------------|-------------------------------|-------------------|----------------------|----------------------------|------------------------|-----------------|------------------------------------------|
| Gejão et al. 2009 [53] | Brazil | 25 | 1 to 10 | NR | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Alterations in fine motor adaptative, gross motor, language, and personal-social behaviour; motor alterations; language alterations; cognitive alterations; self-care alterations; socialization alterations; alterations in expressive auditory, receptive auditory, and visual auditory; LDES alterations in PPVT, and Total Score ABPW Child Language Test-phonology; alterations in Visual reception, auditory association, visual association, auditory memory, visual memory, auditory closure, grammatical closure, visual closure, verbal expression, manual expression, sounds combination; difficulty in attention time maintenance; hyperactivity | Early | According to national guidelines | Up to 30 days of life | NA | Included in Figs. 3A, E, and F |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|---------------|-------------------|------------|---------------|-------------------|---------------------------------------|-----------------------|----------------|----------------------|---------------------------|-----------------------------|----------------------|-----------------------------------------------------|
| Kanufre et al. 2015 [56] | Brazil | 58 | 9.15 | 48.27 | NR | NR | Individual | Overweight | Overweight | NR | Phe-restricted diet | NR | NA | Not included as did not report whether the treatment was implemented at an early or late age |
| Keselman 2005 et al. [17] | Argentina | 11 | 8.7 to 13 | 18.28 | Classic (100.0) | NR | Individual | Osteopenia | Bone mineralization and lumbar spine | Early | Phe-restricted diet | NR | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Lamônica et al. 2015 [59] | Brazil | 17 | 10.2 | 36.0 | Classic (100.0) | NR | Individual and economic | Neurological, neurocognitive and neuropsychiatric impairments | ADHD; IQ; low Reading School Performance Test—Number of patients classified as Inferior; low Writing School Performance Test—Number of patients classified as Inferior; irritability; Peabody Picture Vocabulary Test—Number of patients classified as Low; Sleeping disorder; Poor school performance | Executive function deficit | ADHD, IQ, low Reading School Performance Test—Number of patients classified as Inferior; low Writing School Performance Test—Number of patients classified as Inferior; irritability; Peabody Picture Vocabulary Test—Number of patients classified as Low; Sleeping disorder; Poor school performance | 76.47% before 30 days of life and 23.53% after 30 days of life | NA | Included in Figs. 3A, C, 4D and 5 |
| Malloy-Diniz et al. 2004 [61] | Brazil | 21 | 274 | 61.9 | NR | Average phe level below 120 μmol/l | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Executive function deficit | A not B task | Piaget | Phe-restricted diet | 27.5** | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|---------------|-------------------|-------------|---------------|-------------------|--------------------------------------|------------------------|-----------------|-------------------------|--------------------------|-----------------------------|------------------|---------------------------------------------------|
| Mancini et al. 2010 [62] | Brazil       | 33            | 7.67              | 52.38       | NR            | NR               | Individual and/or population outcomes | Serum PKU              | Early           | Phe-restricted diet | Financial impact related to the PKU management; stop working to care for the PKU patient; need to hire a caregiver to assist the PKU patient; absence of neuropsychological care; did not receive the support of a day-to-day psychologist; limitation on social activities; impact on professional life; and effect on self-esteem |
| Martins et al. 2020 [30]   | Brazil       | 228           | Newborn, 90%; between 1 and 5 years old, 8%; and over 10 years old (2%) | 21.49       | NR            | NR               | Individual and/or population outcomes | Neurological, neurocognitive and neuropsychiatric impairments; Socio-economic impact; the impact of PKU on the daily lives of patients and caregivers; the main difficulties faced by PKU patients and their caregivers; cognitive and emotional symptoms | Irritability, anxiety, and lack of concentration | Early (89.92%) and late (10.08%) | Phe-restricted diet and supplements | Not included as did not report data separately for early versus late treated | NA              | NA                                               | Included in Fig. 4E |

Table 1 (continued)
| Author, year | LATAM country | # of patients | Age, Mean\(^{\text{a}}\) (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed\(^{**}\) | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|-------------------------------|------------|---------------|-------------------|----------------------------------------|------------------------|----------------|-----------------------------|---------------------------------|---------------------------|----------------|--------------------------------------------------|
| Mendes, 2006 [19] | Brazil | 17 | NR | 70.58 | NR | NR | Individual | Osteopenia | Osteopenia | NR | Phe-restricted diet | NR | NR | NA | Not included as did not report whether the treatment was implemented at an early or late age |
| Morão, 2017 [19] | Brazil | 20 | NR | NR | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Verbal fluency test, Children Behavior Checklist 6'18, Wechsler Intelligence Scale for Children (WISC-IV); Word and Pseudoword Reading Competency Test, Snap automatic naming test, SNAP—IV (attention deficits) | NR | NR | NR | NA | Not included as did not report whether the treatment was implemented at an early or late age |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|---------------|------------------|------------|---------------|-------------------|-------------------------------|------------------------|-----------------|---------------------|---------------------------|-----------------------------|-----------------|------------------------------------------------------------------|
| Nalin et al 2010 [66] | Brazil | 45 | 11 | 49.0 | NR (18.0) and classic (53.0) and mild (29.0) | NR | Individual | Patient adherence to clinical recommendations | Patient adherence to treatment | Early | Phe-restricted diet and special formula | 90 | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Viera Neto et al. 2018 [67] | Brazil | 51 | 6 to 17 | 43.13 | NR (2.0) and classic (64.7) and mild/moderate (33.3) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Intellectual capacity classified as below average or intellectual defective | Total score; physical health; emotional functioning; social functioning; school functioning; psychosocial health | Adequate serum PKU levels | 48 | NA | Included in Figs. 38 and 4E |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|-------------|---------------|---------------|-------------------|------------|---------------|-------------------|----------------------------------------|------------------------|-----------------|--------------------------|---------------------------------|-----------------------------|-----------------|--------------------------------------------------|
| Paneque et al. 2013 [68] | Cuba | 12 | NR | NR | NR | NR | Individual and economic | Neurological, neurocognitive and neuropsychiatric impairments | Intelligence test, group attention test, and psychometric test (Weil's non-verbal intelligence test) | Overweight | Overweight according to the growth and development tables of the Cuban population (weight for height, height for age and weight for age) | Skin problems | Skin alterations | Osteopenia | Bone alterations | Socio-economic impact | Normal worker | Not included as did not report whether the treatment was implemented at an early or late age |
| Peredo et al. 2010 [89] | Chile | 20 | 13.4 | 1000 | Classic (1000) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | IQ | Early | Special milk-based formula | 17.9** | NA | Not included as quantitative data on outcome of interest not provided in paper |
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|---------------------------------------|------------------------|----------------|--------------------------|-----------------------------|-----------------------------|-------------------|----------------------------------|
| Pérsico et al. 2019 [97] | Brazil | 15 | 16 | 53.33 | Classic (53.3) and mild (46.7) | Presence of associated comorbidities and/or use of medications unrelated to specific diet therapy with the possibility of interfering with bone metabolism | Individual | Overweight | Overweight | NR | NR | Not included as did not report whether the treatment was implemented at an early or late age |
| Poloni et al. 2021 [7] | Brazil, Argentina, Colombia, Venezuela, Costa Rica, Chile, Mexico, Paraguay, Peru, Dominican Republic, Panama, Uruguay, and Cuba | NR | NR | NR | NR | Poor adherence | Overweight | Overweight | NR | NR | PhE-restricted diet, unflavored powdered amino acid substitutes | NR | NA | Not included as did not report whether the treatment was implemented at an early or late age |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|----------------------------------------|------------------------|----------------|--------------------------|---------------------------|-----------------------------|------------------|--------------------------------------------------|
| Sena, 2018   | Brazil        | 31            | 6.5              | 48.4       | NR            | Individual        | Overweight               | Overweight             | NR            | Pre-restricted diet       | NR                        | NA                          | Not included as did not report whether the treatment was implemented at an early or late age |
| Silva, 2010* | Brazil        | 10            | 5.18             | 50.0       | Classic (100.0) | Individual        | Neurological, neurocognitive and neuropsychiatric impairments | Hyperactivity, attention deficit below average for personal-social area; below average for adaptive, language, gross motor, and fine motor; vocabulary classified as below average; mild to moderate speech disorder; deficit for personal-social area, fine motor-adaptive area, language, and gross motor area | Early | Pre-restricted diet       | 5.18**                    | NA                          | Included in Fig. 3A, E, and F |

**Specify the type of treatment**
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|---------------------------------------|-------------------------|---------------------|------------------------|------------------------------|----------------------------|------------------------|---------------------------------|
| Silva, 2016  | Brazil        | 24            | 15.8             | 50.0       | Classic (50.0) and mild (50.0) | There was no exclusion criterion for samples | Individual Neurological, neurocognitive and neuropsychiatric | Neuropsychomotor impairment; behavioral alterations | Early | Phe-restricted diet and special formula | 92.29** | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Silva, 2018  | Brazil        | 31            | 17.4             | 51.6       | Classic (51.6) and mild (48.4) | Have a clinical diagnosis of mild, moderate, severe or profound intellectual disability; have a diagnosis of other associated genetic diseases; depression, bipolar mood disorder or epileptic encephalopathy | Individual Neurological, neurocognitive and neuropsychiatric | ADHD Osteopenia | Early | Phe-restricted diet and special formula | 26  | NA | Included in Fig. 3A |
| Silveira et al. 2021 | Brazil | 101           | 14.0             | 45.5       | Classic (56.4) and mild (45.6) | Patients with late diagnosis and patients diagnosed with tetrahydrobiopterin (BH4) deficiency | Individual Overweight and obesity | – | Early | NR | NR | NA | Included in Fig. 4A, and B |
| Teruya, 2019  | Brazil        | 23            | 18               | 39.0       | Classic (47.8) and mild (52.2) | NA | Not included as quantitative data on outcome of interest not provided in paper | Patient adherence to clinical recommendations | Poor current adherence to Phe-restricted diet, poor current median adherence to Phe-restricted diet | Early (65.2%) | Phe-restricted diet and special formula | Up to 90 days after born |
| Tonon et al. 2019 | Brazil | 25            | 19.3             | 52.0       | Classic (52.0) and mild (48.0) | NR | Individual Overweight or obese | – | Early | Phe-restricted diet and special formula | 52.8** | NA | Not included as quantitative data on outcome of interest not provided in paper |
| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|------------------|--------------------------------------|------------------------|----------------|------------------------|-------------------------------|-----------------------------|--------------------------|--------------------------------|
| Vieira, 2010 [29] | Brazil | 56 | 12 | 55.35 | NR (12.5), classic (58.9) and mild (28.6) | NR | Individual and economic | Neurological, neurocognitive and neuropsychiatric | Mental retardation, learning disability, hyperactivity, aggressiveness, attention deficit | Patient adherence to clinical recommendations | Nonadherent to treatment | Special Education | Restricted diet and special formula | 60 | NA | Included in Figs. 3A, C, D, 4E, and S |
| Blanco et al. 2012 [34] | Argentina | 1 | 34 | 100.0 | Mild (100.0) | NR | Individual | Executive function deficit | Mental retardation and moderate cognitive impairment | Autism; psychomotor retardation | Delayed severe mental developmental delay | Pneumothorax | Restricted diet | 34 years | 3 | Not included due to design |
| De Lucca et al. 2017 [44] | Ecuador | 1 | 15 | 100.0 | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Executive function deficit | Irritability; focal hyperactivity; seizures | Musty smell; hair hypopigmentation | Eczema | Restricted diet | 3 years and 11 months | NR | Not included due to design |
| Escaf, 2003 [48] | Colombia | 1 | NR | NR | HPAP (100.0) | NR | Individual | Neurological, neuropsychiatric and neuropsychiatric impairments | Skin problems | Irritability; sporadic seizures | Eczema | Restricted diet | NR | NR | Not included due to design |
Table 1 (continued)

| Author, year | LATAM country | #of patients | Age, Mean\(^\text{a}\) (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed\(^{**}\) | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|--------------|-------------------------------|------------|---------------|-------------------|---------------------------------------|-------------------------|-----------------|-------------------------------|-----------------------------|--------------------------|-----------------------------|------------------------------------------------|
| Figueiró-Filho et al., 2004 [51] | Brazil | 1 | 22 | 100.0 | NR | NR | Individual | Others | Maternal PKU | Late | Phe-restricted diet and supplementation with protein hydrolyzate | 22 | NR | Not included due to design |
| Mariño & Zarzalejo, 2000 [63] | Venezuela | 1 | 0.1 | 0.0 | HPA (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Skin problems | Motor deficits; mental development | Early Breastfeeding and special formula | 28 | 9 | Not included due to design |
| Menezes et al. 2019 [64] | Brazil | 1 | 82\(^\text{c}\) | 100.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Executive function deficit | Psychomotor retardation; language impairment | Early Phe-restricted diet and special formula associated with the milk formula | 40 | NR | Not included due to design |
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|----------------------------------------|----------------------------|----------------|----------------------------|---------------------------------|-----------------------------|---------------------|------------------------------------------------|
| Patricio & Maritza, 2018 [92] | Ecuador | 1 | 29* | 0.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Seizures, neurological complications | Early | NR | 30 | 6 | Not included due to design |
| Pereda-Torales et al. 2008 [93] | Mexico | 1 | 0.2 | 0.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Axial hypotonia | Early | NR | 60 | 12 | Not included due to design |
| Rasner et al. 2014 [90] | Uruguay | 1 | 10* | 0.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Losing the cephalic support; irritability; myoclonia of all four members; hypotonia | Early | NR | 10 months | NR | Not included due to design |
Table 1 (continued)

| Author, year | LATAM country | # of patients | Age, Mean (SD), y | Female (%) | Phenotype (%) | Exclusion criteria | Individual and/or population outcomes | Type of burden outcomes | Specific outcomes | Early or late diagnosed** | Specify the type of treatment | Age (days) at start of treatment | Follow-up (months) | Reasons why the study was excluded from the analysis |
|--------------|---------------|---------------|------------------|------------|---------------|-------------------|---------------------------------------|------------------------|----------------|----------------------------|--------------------------------|-------------------------------|-------------------|----------------------------------|
| Santos & Haack, 2013 [94] | Brazil | 1 | 5 | 100.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Seizures | Early | Pheno-restricted diet and special formula | 20 | 60 | Not included due to design |
| Schmidt et al. 2016 [69] | Brazil | 1 | 13 | 0.0 | NR | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Hypoactivity | Early | Pheno-restricted diet | NR | NR | Not included due to design |
| Urbanes et al. 2006 [74] | Colombia | 1 | 8 | 0.0 | Classic (100.0) | NR | Individual | Neurological, neurocognitive and neuropsychiatric impairments | Restless; aggressive; inconsistent language; neuromotor restriction; intellectual deterioration; poor socialization | Late | NA | NA | NR | Not included due to design |

ADHD: Attention Deficit Hyperactivity Disorder, HPA: hyperphenylalaninemia, HPAP: hyperphenylalaninemia persistent, IQ: intelligence quotient, LATAM: Latin America, LDES: Total Score Language Development Evaluation Scale, NR: not reported, NA: not applicable, Phe: phenylalanine, PKU: phenylketonuria, PPVT: alterations in Total Score Peabody Picture Vocabulary Test, RAVLT: Rey auditory verbal learning test, RVDLT: Rey visual design learning test, SD: standard deviation, TMT: Trail making test (partes A e B), USP: Universidade de São Paulo, UFMG: Universidade Federal de Minas Gerais, y: years

**We considered that late diagnosed refers to children diagnosed between the ages of 3 months to 7 years (≥ 3 months to < 7 years); untreated PKU refers to patients untreated by 7 years of age and over

- Days
- Months
- Mean
- Only in two was it done after 30 days
- # Number
- ☞ Range
- ☞ Comparative cross-sectional studies
- ☞ Weeks of gestational age
- ☞ Caregiver's age
- ☞ For the case reports, age is expressed as absolute number
- ☞ Included in the analysis
Forty of the included studies were conducted in Brazil [14, 19–24, 26, 27, 29, 31, 43, 45, 51, 56, 58, 59, 62, 64, 67, 69–73, 75–78, 80, 81, 83, 84, 86, 88, 91, 94, 97, 98], seven in Argentina [15, 17, 18, 33–38, 46, 47], five in Chile [39–42, 89], three each in Colombia [48, 54, 74] and Mexico [55, 85, 93], two each in Ecuador [44, 92], Venezuela [60, 63] and Uruguay [32, 90], and one in Cuba [68]. One study [87] was a multicenter conducted in Ecuador, Bolivia, and Paraguay. The case series and cross-sectional studies sample size ranged from two [32] to 420 patients [46, 47]. Patients’ ages ranged from a mean of 3.11 [20] to 19.3 [73] years old (Table 1).

Risk of bias assessment

Figure 2 and Additional files 4 and 5: Tables 4 and 5 describe the risk of bias assessment. Overall, the included studies presented a low risk of bias in the majority of the domains. In the cross-sectional studies (Fig. 2, panel A), at least one of the following domains of sample size, statistical significance, statistics methods, or demographic data were rated as “high risk of bias” in five studies (12.8%) [7, 38, 39, 43, 96]. In the case series studies (Fig. 2, panel B), three domains (ie, clear description of both patient’s history and post-intervention clinical condition, and description of a takeaway lesson) were rated as “high risk of bias” in three studies (25.0%) [32, 58, 86].

Meta-analysis results

The results were pooled from case series and cross-sectional studies that reported data only on early-diagnosed patients to avoid bias related to the effects of delayed implementation of dietary management in late-diagnosed patients. Studies that did not provide quantitative data on outcome of interest in papers were also excluded from analysis as well as studies that did not report whether the treatment was implemented at an early or late age. Therefore, out of 67 included studies [14, 16, 19–29, 31–34, 39–45, 48–50, 52–57, 59–70, 72–86, 88–101], 20 studies [22, 29, 31, 39–42, 52, 55, 59, 60, 62, 66, 67, 76, 77, 78, 80, 83, 96, 98] qualified for the quantitative analysis described below. None of the included studies evaluating early-diagnosed PKU patients reported symptoms including headache and fatigue, quality of life, or the impact of PKU on the healthcare system.

Neurological, neurocognitive, and neuropsychiatric impairments

Attention deficit hyperactivity disorder (ADHD) and hyperactivity The pooled proportion of ADHD and hyperactivity was 40% [95% CI 0.21 to 0.61; I² = 89.2%, p < 0.0001] from eight studies [29, 31, 39, 53, 59, 60, 78, 83, 98] with a total of 222 patients (Fig. 3A). There was significant statistical heterogeneity in the analyses.
Fig. 2  Risk of bias assessment. (A) cross-sectional studies (B) case series studies
Autism, intellectual disability, irritability and aggressiveness. A single study [49] evaluated early-diagnosed PKU patients who were reported to have autism. Out of 78 patients assessed, two were diagnosed with autistic behaviour.

The pooled proportion of intellectual disability was 18% [95% CI 0.04–0.38;  \( I^2 = 83.7\% \),  \( p = 0.0133 \)] from two studies [67, 77, 81] including a total of 114 patients (Fig. 3B). There was significant statistical heterogeneity in the analyses.

The pooled proportion of irritability and aggressiveness was 44% [95% CI 0.12–0.80;  \( I^2 = 96.2\% \),  \( p < 0.0001 \)] from five studies [22, 29, 39, 59, 60, 83] with a total of 200 patients (Fig. 3C). There was significant statistical heterogeneity in the analyses.
Mental disorders  The pooled proportion of mental disorder was 16% [95% CI 0.01–0.42; \( I^2 = 89.7\% \), \( p < 0.0001 \)] from three studies [29, 39, 42, 83] with a total of 115 patients (Fig. 3 D). A study [42] that reported slight retardation was 15% [95% CI 0.04–0.30; \( I^2 \) = 83.7%, \( p < 0.0001 \)] from five studies [22, 29, 62, 66, 67, 83] with a total of 260 patients (Fig. 4E). There was significant statistical heterogeneity in the analyses.

Motor delay  The pooled proportion of motor delay was 15% [95% CI 0.04–0.30; \( I^2 = 74.5\% \), \( p = 0.0083 \)] from four studies [22, 27, 41, 53, 98] with a total of 132 patients (Fig. 3E). There was significant statistical heterogeneity in the analyses. Any report of motor delay such as low motor development, neuromotor restriction [22], and deficit for gross motor area [27, 98] was considered.

Speech and language deficits  The pooled proportion of speech and language deficits was 35% [95% CI 0.08–0.68; \( I^2 = 93.9\% \), \( p < 0.0001 \)] from five studies [22, 27, 39, 53, 60, 98] with a total of 162 patients (Fig. 3F). There was significant statistical heterogeneity in the analyses. Additional reports of speech delay included speech deficits such as "only emits a word" [32], alterations in language [53], and mild to moderate speech disorder [27, 98] were reported.

Other comorbidities

Obesity and overweight  The pooled proportion of obesity was 12% [95% CI 0.09–0.15; \( I^2 = 0\% \), \( p = 0.6129 \)] from three studies [40, 71, 76, 80] with a total of 123 patients (Fig. 4, panel A). There was no significant statistical heterogeneity in the analyses.

The pooled proportion of overweight was 11% [95% CI 0.07–0.16; \( I^2 = 47.2\% \), \( p = 0.1504 \)] from three studies [40, 71, 76, 80] with a total of 379 patients (Fig. 4B). There was no significant statistical heterogeneity in the analyses.

Osteopenia  Only one study [43, 78] evaluating early-diagnosed PKU patients reported on osteopenia. Out of 31 patients, three were diagnosed with osteopenia.

Skin alterations  The pooled proportion of skin alterations was 34% [95% CI 4.9E-3 to 0.85; \( I^2 = 85.7\% \), \( p = 0.0081 \)] from two studies [55, 96] with a total of 40 patients (Fig. 4 C). Both included studies reporting lightening of the skin. There was significant statistical heterogeneity in the analyses.

Sleeping disorders  The pooled proportion of sleeping disorders was 71% [95% CI 0.13–0.99; \( I^2 = 86.2\% \), \( p = 0.007 \)] from two studies [59, 60] with a total of 22 patients (Fig. 4D). There was significant statistical heterogeneity in the analyses.

Patient adherence to clinical recommendations after treatment  The pooled proportion of patient adherence to clinical recommendation was 53% [95% CI 0.38 to 0.67; \( I^2 = 89.7\% \), \( p = 0.0083 \)] from four studies [22, 29, 62, 66, 67, 83] with a total of 260 patients (Fig. 4E). There was significant statistical heterogeneity in the analyses.

Socioeconomic impact  The pooled proportion of socioeconomic impact was 37% [95% CI 0.07–0.75; \( I^2 = 88.5\% \), \( p = 0.0032 \)] from two studies [29, 59, 83] with a total of 73 patients (Fig. 5). There was significant statistical heterogeneity in the analyses. The included studies reported the following socioeconomic impact: poor school performance [18], and special education [29, 83].

Impact of phenylketonuria on caregiver health-related quality of life  The pooled proportion of impact of PKU on caregiver health-related quality of life (ie, did not acquire toilet training [32, 86]) was 42% [95% CI 0.09–0.80; \( I^2 = 0\% \), \( p = 0.7519 \)] from two studies [32, 86] with a total of five patients. There was no significant statistical heterogeneity in the analyses.

Descriptive analysis of single studies reporting the outcomes of interest

Four studies [24, 58, 59, 61] reported executive function outcomes with 41% being classified as below average in the assessment of receptive vocabulary using the Peabody Image Vocabulary Test [59]. Malloy-Diniz et al. [61] reported that PKU children with high blood Phe levels (ie, mean Phe levels between 360 and 600 \( \mu \text{mol/L} \)) performed significantly worse than both the PKU children with low blood Phe levels and the control children on tasks that assess executive functioning. Morão et al. [24] found that the patients also showed a loss in the score of the Children Gambling Task. Lamônica et al. [58] reported that out of 10 patients, two of them presented outside the normality standards in the development scales. The skills were related to performance in motor, linguistic and cognitive activities. Furthermore, Poloni et al. [7] reported that most LATAM countries did not have low-protein foods, including Phe-free amino acid fortified, and no alternative treatments available. Also, they found that low purchasing power, limited/insufficient availability of low-protein foods, poor adherence, and lack of technical resources to manage the diet were major barriers to treatment. And last, Martins et al. [30] reported that half of the parents and caregivers who completed the survey had financial burden related to PKU management, some had to stop working to care for the PKU patient, and others had to hire a caregiver to assist...
the PKU patient. With regards to patient’s complaints, irritability was the most reported affected symptom accounting for 78% of the patients, followed by anxiety (67%), and lack of concentration (58%). Despite these findings, 70% of the patients have never undergone a cognitive and/or executive function assessment, and limitation on social activities, impact on professional life, and the effect on self-esteem were also listed as barriers to receive appropriate assessments.

**Discussion**

**Main findings**

PKU is a genetic inborn error in the metabolism of Phe. The pathogenic variants that cause PKU are present in high frequency in some LATAM countries such as Brazil and Chile [102].

Based on pooled data from 21 case series and cross-sectional studies [19, 22–24, 26, 29, 31–33, 39, 40, 42, 44, 52, 56, 59, 60, 67, 70, 71, 78, 80–82, 84–86, 88, 96–98]
including 1224 patients, we found evidence demonstrating the impact of PKU on affected individuals in LATAM, with pooled proportions of burden ranging from 9% with osteopenia to 53% with speech and language deficits. Furthermore, only 53% of patients were adherent to clinical recommendations with 37% of patients experiencing socioeconomic impact of PKU. These are higher rates as compared to what we were expecting given that there is the ability to effectively diagnose and treat PKU.

### Strengths and limitations

**Strengths**

Strengths of our review include a comprehensive search; assessment of eligibility, risk of bias and data abstraction independently and in duplicate; and an assessment of risk of bias that included a sensitivity analysis addressing homogeneity of study designs.

The primary limitation of our study is the highly heterogeneous nature of study samples in all studied clinical burden outcomes, except for the outcomes of obesity (Fig. 4, Panel A), osteopenia, and impact of PKU on caregiver health-related quality of life. Sources of this heterogeneity include both clinical and methodological diversities. The studies differed considerably in their mean age of patient selection, phenotype, modalities of implementation of the treatment (eg, newborn screening, access to treatment, lack of knowledgeable caregivers), and study designs (ie, case series and cross-sectional).

Furthermore, out of the 79 studies that met selection criteria, we were only able to include data in the meta-analysis from 21 of them (26.6%). The majority of the studies provided data on only one pre-specified outcome of interest, resulting in small sample sizes for many of the pooled analyses. In addition, there were studies that reported on late diagnosis patients and they were not included in the meta-analysis.

### Relation to prior research

One systematic review [103] identified in the literature corroborates our findings showing that even with dietary treatment, long-term physical growth (ie, body weight, height/recumbent length, and body mass index) are not attained in PKU. Another systematic review [104] showed that bone mineral density was lower in PKU patients compared with a control group. With regards to the latter outcome, four studies [105–109] reported a prevalence of osteopenia and osteoporosis ranging from 5 to 14%, which encompass our findings. Although we did not evaluate anthropometric variables in our review, we found a reasonable high prevalence of overweight individuals (11%) and of obesity (12%).

Furthermore, a frequent prevalence of being overweight was described in another systematic review [110] ranging from 7.8 to 32.6% in children and adolescents with PKU, which is also consistent with our findings (23%).

A very high prevalence of ADHD and hyperactivity (40%) and a moderate rate of intellectual disability (19%) were found in our review, which is consistent with others systematic reviews [111, 112] indicating that they are more common in both children and adults with PKU, despite being early diagnosed.

One study [113] conducted in the United States (US) showed that compared to the general population, PKU was associated with a significantly higher prevalence for intellectual disability, autism spectrum disorder, Tourette/tic disorders, eating disorders and behavior/conduct disorder in adult population. Of note, increased prevalence of these comorbidities persisted even when the sample was restricted to younger adults (aged 20–38 years), a subgroup with high probability of being diagnosed at birth and had the opportunity for continuous treatment throughout life. In parallel, a German study [114] not only corroborated that adults PKU patients suffered with neuropsychological disease burden, but also revealed that this population presented additional comorbidities such as cardiometabolic risk factors. Also, these authors reported a higher intake of prescriptions for gastrointestinal agents, analgesics, antipyretics, statins, and antidepressants. Despite the methodological differences (both studies evaluated adult populations from a single country and were based on data retrieved from their respective healthcare systems), both studies are in line with our findings that PKU potentially increases the neuropsychological comorbidities.
Conclusions
LATAM PKU patients presented with a high prevalence of clinical complications, regardless of whether there is the possibility of residual confounding due to publication bias and the high heterogeneity in the analysis. Although it is widely accepted that PKU treatment is needed for life, the current approach in LATAM is primarily by using dietary management, which does not seem sufficient to avoid the disease burden outcomes investigated in this research. Furthermore, this review showed that there is a high degree of poor adherence to clinical recommendations. This study also highlights the need to address well-conducted burden of illness studies in PKU patients in LATAM to further elucidate the full spectrum of complications seen in this disease, to inform the healthcare providers taking care of these patients as well as the public health authorities on the ongoing and significant complications of this genetic disorder. [115–118]

Abbreviations
ADHD: Attention deficit hyperactivity disorder; ACMG: American College of Medical Genetics and Genomics guidelines; HPA: Hyperphenylalaninemia; LATAM: Latin American; PRISMA: Preferred reporting items for systematic review and meta-analysis; MOOSE: Meta-analysis of observational studies in epidemiology; PAH: Phenylalanine hydroxylyase deficiency; PKU: Phenylketonuria; PROSPERO: International prospective register of systematic reviews; MeSH: Medical subject headings; MEDLINE: Medical literature analysis and retrieval system online; EMBASE: Excerpta medica database; CENTRAL: Cochrane central register of controlled trials; LILACS: Latin American and Caribbean Health Sciences Literature; SciELO: Scientific electronic library online; IBECs: Spanish bibliographic index of the health sciences; BINACIS: National bibliography in health sciences Argentina; MedCarib: Caribbean health sciences literature; CUMED: National Medical Sciences Information Center of Cuba; BBO: Brazilian bibliography of dentistry; ANVISA: National health surveillance agency; BDTD: Brazilian digital library of theses and dissertations; BMI: Body mass index; JBI: Joanna Briggs Institute; CI: Confidence interval; PROSPERO: (International Prospective Register of Systematic Reviews).

Supplementary Information
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