Systematic Review:

The Prevalence and Incidence of Congenital Phenylketonuria in 59 Countries: A Systematic Review

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ABSTRACT

Background: Phenylketonuria (PKU) is the most frequent inborn error of metabolism, in which newborns cannot metabolize phenylalanine to tyrosine. Increased phenylalanine in untreated patients with PKU can cause serious intellectual disability; its onerous financial burden also falls on societies. This review study aimed to systematically indicate the frequency of PKU worldwide. We also intended to highlight the global prevalence of PKU, which might shed light on better clinical management and screening programs.

Methods: In this systematic review, two electronic databases, including PubMed and ScienceDirect were searched for the related literature using relevant keywords: "Phenylketonuria" or "PKU" and "Prevalence" or "Incidence" and "Iran" or "Middle East" or "Europe" or "America" or "Asia." Accordingly, 4306 reports conducted on PKU from January 2007 to December 2018 were retrieved. With the removal of 44 duplicated publications, 44 reports were included in the current systematic review. Prevalence and incidence rates were categorized based on different continents in which nations used various NBS programs to report the incidence and prevalence of PKU. Non-English, non-eligible, duplicated, animal, and in vitro studies are excluded.

Results: Based on the reported quantitative data, the prevalence of PKU diagnosed worldwide ranged from 0.00044% to 0.02736% in which Italy possessed the highest prevalence; however, Thailand manifested the lowest prevalence rate. However, for some countries, such as India or Finland, either the related data to the frequency of PKU was outdated or overlooked applying any newborn screening programs respecting PKU.

Conclusions: The current study revealed an elevated prevalence of PKU in Iran, compared with other Asian countries; thus, it demands a more serious management program. Moreover, the high prevalence of PKU in European countries should not be underestimated.

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1. Context

Phenylalanine Hydroxylase (PAH; EC 1.14.16.1) is a hepatic enzyme, which hydroxylates the side-chain of Phenylalanine (Phe) to form Tyrosine (Tyr). Furthermore, the deficiency of PAH leads to Phenylketonuria (PKU, OMIM #261600), an autosomal recessive disorder [1]. Besides, the PAH enzyme cofactor, tetrahydrobiopterin (BH4) decreases plasma Phe level in some patients with PKU. Therefore, the BH4 responsiveness must be monitored with a BH4 loading test. The 20%-29% reduction in blood Phe is defined as partial BH4 responsiveness; a >30% reduction is defined as the arbitrary BH4 responsiveness [2]. There exists no consensus concerning PKU phenotype classification [3] due to the large range of cut-off points [4], and the time of neonatal screening. This is because patients often initiate the treatment before reaching the maximal Phe blood level [5]. Moreover, Phe tolerance could not be applied to differentiate the PKU phenotypes. This is because due to the non-standard discrepancies and conditions between actual Phe that will be consumed and prescribed, it is controversial to determine the exact Phe tolerance. Recently, the PKU classification scheme has been simplified as follows: not requiring treatment; requiring diet, BH4, or both [6].

Most of the publications classified PKU based on its severity, which depends on the plasma Phe concentration; thus, we used the same previous scheme that categorized PKU in 3 classes, as follows: classic PKU (cPKU; Phe >1200 µmol/L), moderate PKU (modPKU; Phe 600-1200 µmol/L), and mild hyperphenylalaninemia (mHPA; 120-600 µmol/L) [7]. The prompt diagnosis of PKU after birth can lead to the prescription of a low Phe diet, which can prevent the irreversible Intellectual Disability (ID). Although PKU screening in newborns is being performed in various developed countries, in Iran, it has been started in 2007 [8]. PKU is the most frequent inborn error of amino acid metabolism affecting about 1 per 10000 Caucasians [9]. Due to the approximate high rate of consanguineous marriage in developing countries, like Iran, it is predicted that the frequency of PKU will grow higher [10].

In case PKU patients remain undetected during the first week after birth, due to the increased level of Phe in the brain and blood, ID, motor deficits, autism, seizures, and microcephaly may be developed [3, 11]. In this regard, it is of high importance to diagnose PKU shortly after birth. In this case, being equipped with an efficient screening program may prevent the development of PKU-induced complications in newborns. Therefore, throwing light on the frequency of PKU in various countries can raise awareness and lead to establishing an efficient NBS program. Therefore, it will be useful to recognize the most recent data on the worldwide prevalence of PKU as well as the prevalence of the disease in Iran; accordingly, these data could help to suggest new strategies for its prevention, diagnosis, and treatment. This systematic review explored the prevalence of PKU in different countries from January 2007 to December 2018. The relevant data could help to provide baseline information for the effective management of patients with PKU.

This systematic review was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [12]. Eligible literature was extracted from PubMed and ScienceDirect databases from January 2007 to December 2018 to identify studies reporting the global status of PKU prevalence.

2. Study selection and data extraction

Studies were screened using the following keywords: “Phenylketonuria”, “PKU”, “Phenylketonuria” or “PKU” and “Prevalence” or “Incidence” and “Iran” or “Middle East” or “Europe” or “America” or “Asia”. The exclusion criteria of the studies were as follows: studies not written in English; animals and in vitro studies; non-eligible publications, which included out-of-date data or PKU genotype frequency; duplicate reports, and studies presenting irrelevant data to PKU prevalence.

After a comprehensive search by two investigators (Sh. Ghazanfari, N. Mojibi) for PKU prevalence, 4306 (PubMed=1332, ScienceDirect=2974) relevant articles were identified, and 44 duplicates were removed. The relevance of remained 4262 studies was evaluated based on the titles/abstracts alone; of them, 223 studies were subjected to full-text review by authors based on the inclusion and exclusion criteria. Eventually, 44 of them were eligible to be included in the present systematic review (Figure 1). The references of the selected studies were also screened to obtain the relevant reports. Eventually, the authors independently evaluated selected studies to extract the required data. Any controversies were settled by consensus.

3. Results and Discussion

By searching the aforementioned databases, 4306 applicable articles were identified. Consequently, after removing 44 duplicates and 4039 non-eligible publica-

tions based on their language, the type of study, the date of publication, etc., the full texts and abstract of 223 publications were screened. Eventually, by the exclusion of 185 papers based on the inclusion/exclusion criteria, 44 publications were identified as qualified for the present systematic review (Figure 1).

The flow chart of the selection process of eligible studies is shown in Figure 1. We identified 44 studies addressing the prevalence of PKU in 59 countries, including 15 Asian (Bahrain, China, India, Iran, Iraq, Japan, Korea, Lebanon, Saudi Arabia, Singapore, India, Taiwan, Thailand, Turkey, & United Arab Emirates; UAE), 36 European (Austria, Belarus, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Moldova, Netherlands, Norway, Poland, Portugal, Romania, Russia, Scotland, Serbia, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom; UK, Ukraine, & Wales), two African (Egypt & Tunisia), and 6 American (the United States of America; U.S.A, Argentina, Brazil, Chile, Costa Rica, & Cuba) countries. The quantitative data derived from eligible studies are summarized in Tables 1-4.

These studies were conducted based on recent surveys among opinion leaders in these 59 countries, i.e., in the majority members of the International Society for Neonatal Screening (ISNS). For Asian countries, such as Iran, Saudi Arabia, and Thailand, e.g., the reported

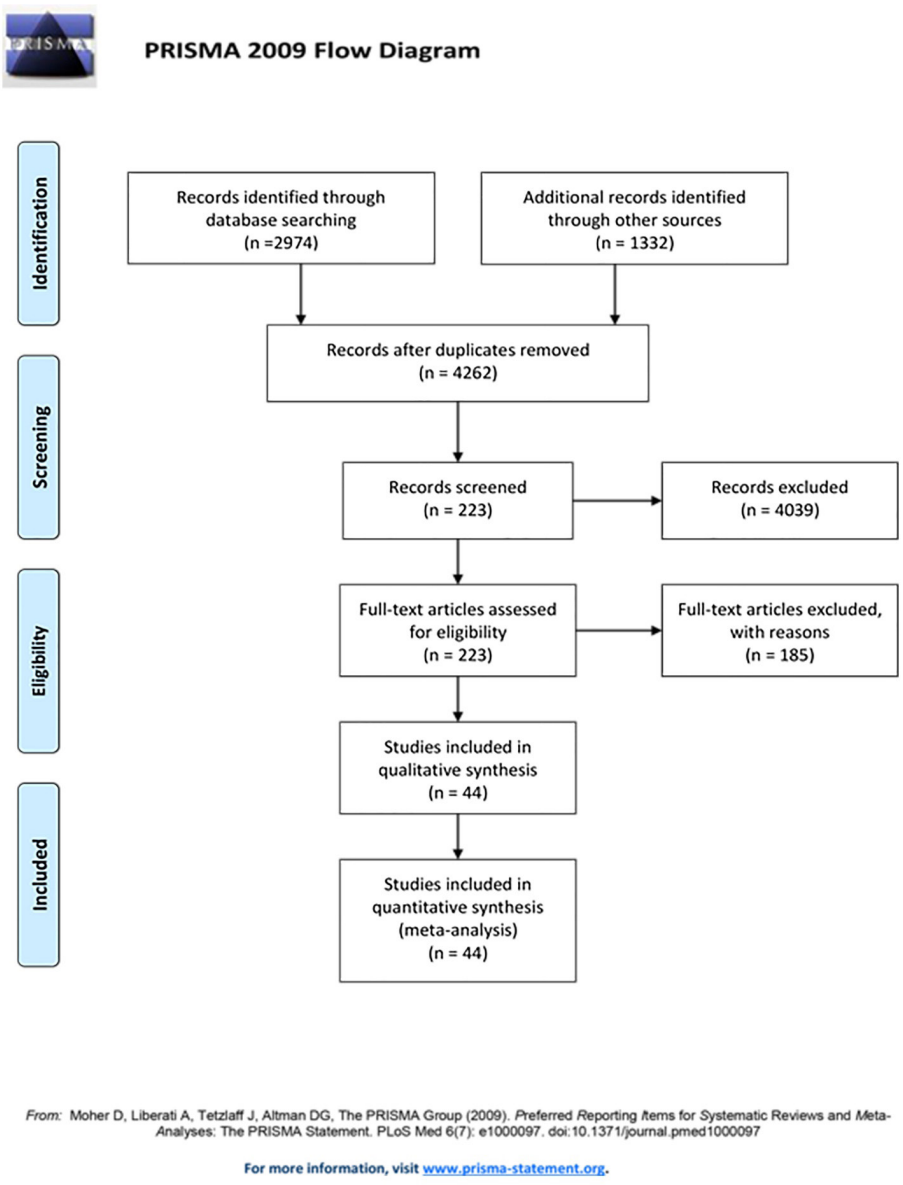

Figure 1. The flowchart of the study selection process

Table 1. The distribution of PKU reported in publications from Asian countries

Asia				
Country	**Period of Data Collection**	**Incidence or Prevalence (%)**	**PKU Phenotype (%)**	**References**
Bahrain	2008-2011	0.0045 I	N.A.	Golbahar J et al. [36]
China	2003-2007	0.00862 I	HPA (0.0085 [BH4 (0.00012)])	Gu X et al. [16]
India	2000	0.00546 I	N.A.	Rama Devi AR et al. [34]
Iran	2010	0.02 I	mHPA rt a(0.00376 [BH4 (0.003384)]), mPKU (0.00528 [BH4 (0.00188)]), modPKU (0.0068 [BH4 (0.00038)]), cPKU (0.00416)	Setoodeh A et al. [2]
Iran (Fars)	2004-2007	0.01597 I	HPA (0.0154 [BH4 (0.00057)])	Habib A et al. [25]
Iran (Fars)	2007-2008	0.01169 I	mHPA (0.0073), cPKU (0.00438), [BH4 (0.00129)]	Karamifar H et al. [26]
Iran (Mazandaran)	2007 to 2015	0.0067 I	HPA (0.00294), cPKU (0.00147), mPKU (0.0022)	Abbaskhanian A et al. [13]
Iraq	2013-2014	0.01211 I	N.A.	Hamawandi et al. [33]
Japan	2001	0.0008 I	N.A.	El-Metwally A et al. [39]
Korea	2000-2015	0.00072 I	HPA (0.00333), PKU (0.005), [BH4(0.0025)]b	Shibata N et al. [41]
Lebanon	1998-2007	0.01258 I	N.A.	Karam PE et al. [21]
Lebanon	2007-2010	0.02613 I	N.A.	Karam PE et al. [21]
Lebanon	2007-2013	0.01984 I	PKU (0.01428 [BH4 (0.00555)])	Khneisser I et al. [28]
Saudi Arabia	2005-2012	0.00702 I	HPA nrt a/ cPKU	Alfadhel M et al. [14]
Singapore	2006-2014	0.00112 I	HPA (0/00112 [BH4 (0.00056)])	Lim JS et al. [38]
Southern India	2007–2009	34.5% of IEM	N.A.	Nagaraja D et al. [35]
Taiwan	2000-2009	0.00167 I	mHPA(0.00268), cPKU (0.00033), mPKU(0.00134)	Niu DM et al. [37]
Thailand	2000-2009	0.00044 P	N.A.	Banpavichit A et al. [15]
Turkey	2007	0.01538 P	mHPA (0.00646), mPKU (0.00507), cPKU (0.00384), [BH4 (0.00676)]	Dobrowolski SF et al. [29]
UAE	1995-2011	0.00687 I	cPKU (0.00674 [BH4 (0.00013)])	Al Hosani H et al. [31]
UAE	2011-2014	0.01323 P	HPA (0.00073), PKU (0.01249)	Al-Jasmi FA et al. [32]

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I: Incidence; P: Prevalence; N.A.: Not available; HPA: hyperphenylalaninemia; BH4: tetrahydrobiopterin responsive; mHPA: mild hyperphenylalaninemia; mPKU: mild phenylketonuria; modPKU; moderate phenylketonuria; cPKU: classic phenylketonuria; PKU: phenylketonuria.

A: mHPA rt: mHPA requiring treatment; HPA nrt: HPA not requiring treatment. B: Data is related to 2001-2004.

Table 2. The distribution of PKU reported in publications from European countries

Europe				
Country	**Period of Data Collection**	**Incidence or Prevalence (%)**	**PKU Phenotype (%)**	**References**
Austria	2002-2009	0.00883 I	HPA (0.00803), PKU (0.00931)	Kasper DC et al. [52]
Belarus	2004	0.01368 P	N.A.	Loeber JG et al. [18]
Belgium Wallonia	2004	0.00645 P	N.A.	Loeber JG et al. [18]
Belgium Flanders	2004	0.00305 P	N.A.	Loeber JG et al. [18]
Bosnia – Rep Srpska.	1986-2007	0.00287 I	cPKU	Zerjav Tansek M et al. [17]
Bosnia-Herzegovina	2004	0.01024 P	N.A.	Loeber JG et al. [18]
Bulgaria	2004	0.003 P	N.A.	Loeber JG et al. [18]
Bulgaria	1979	0.00352 I	cPKU	Zerjav Tansek M et al. [17]
Croatia	N.A.	0.01208 P	mHPA (0.0012), mPKU (0.00277), cPKU (0.00809), [BH4 (0.00435)]	Karačić I et al. [49]
Cyprus	1989-2010	0.00765 P	mHPA (0.00437), mPKU (0.00218), 0.00109 left the study, [BH4 0.00191]	Georgiou T et al. [70]
Czech Republic	2004	0.00716 P	N.A.	Loeber JG et al. [18]
Denmark	2004	0.00744 P	N.A.	Loeber JG et al. [18]
Estonia	1974-2016	0.01492 I	N.A.	Lillevali H et al. [47]
Federation of Bosnia and Herzegovina (without SarajevoCanton)	2001-2005	0.00333 I	cPKU	Zerjav Tansek M et al. [17]
Finland	2005	0.0007 I	N.A.	Autti-Rämö I et al. [56]
France	2011	0.01168 P	N.A.	Wiedemann A et al. [50]
Germany	2002-2015	0.02 I	N.A.	Shibata N et al. [41]
Greece	2004	0.00281 P	N.A.	Loeber JG et al. [18]
Hungary	2004	0.00788 P	N.A.	Loeber JG et al. [18]
Ireland	2004	0.01612 P	N.A.	Loeber JG et al. [18]
Italy	2004	0.02736 P	N.A.	Loeber JG et al. [18]
Latvia	2004	0.01474 P	N.A.	Loeber JG et al. [18]
Lithuania	2004	0.01029 P	N.A.	Loeber JG et al. [18]
Moldova	2013-2014	0.01365 I	HPA cumulatively	Zerjav Tansek M et al. [17]
Netherlands	2004	0.0077 P	N.A.	Loeber JG et al. [18]
Norway	2004	0.00872 P	N.A.	Loeber JG et al. [18]
Poland	2004	0.01239 P	N.A.	Loeber JG et al. [18]
Portugal	2010	0.00822 I	HPA (0.00379), PKU (0.00822)	Vilarinho L et al. [53]
Romania	2013	0.01 I	N.A.	Gemperle-Britschgi C et al. [55]
Russia	2004	0.01296 P	N.A.	Loeber JG et al. [18]

Europe				
Country	**Period of Data Collection**	**Incidence or Prevalence (%)**	**PKU Phenotype (%)**	**References**
Scotland	2004	0.01281 P	N.A.	Loeber JG et al. [18]
Serbia	2004	0.00875 P	N.A.	Loeber JG et al. [18]
Slovak Republic	2012	0.01694 I	mHPA (0.00237), mPKU (0.0022), cPKU (0.0113), [BH4 0.00626]	Polak E et al. [45]
Slovenia	1993-2012	0.01477 I	mPKU(0.00382), modPKU (0.00101), cPKU (0.00967)	Šmon A et al. [46]
Spain	2000-2010	0.00808 P	HPA (0.01665) PKU (0.00791)	Couce ML et al. [54]
Sweden	2004	0.00788 P	N.A.	Loeber JG et al. [18]
Switzerland	2004	0.01318 P	N.A.	Loeber JG et al. [18]
UK	2015	0.01 I	mPKU (0.00075), modPKU (0.00349), cPKU (0.00566)	MacDonald A et al. [51]
Ukraine	N.A.	0.01428 P	N.A.	Pampukha V et al. [48]
Wales	2004	0.00934 P	N.A.	Loeber JG et al. [18]
Total (Europe)	2004	0.01244 P	N.A.	Loeber JG et al. [18]

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I: Incidence; P: Prevalence; N.A.: Not available; HPA: hyperphenylalaninemia; PKU: phenylketonuria; cPKU: classic phenylketonuria; BH4: tetrahydrobiopterin responsive; mHPA: mild hyperphenylalaninemia; mPKU: mild phenylketonuria; modPKU; moderate phenylketonuria.

Table 3. The distribution of PKU reported in publications from African countries

Africa				
Country	**Period of Data Collection**	**Incidence or Prevalence (%)**	**PKU Phenotype (%)**	**References**
Egypt	2008-2013	0.00909 P	PKU/HPA	Selim LA et al. [22]
Egypt	2008	0.01978 P	cPKU/mPKU	Hassan FA et al. [57]
Tunisia	1988-2008	0.0131 I	mPKU (0.00019), modPKU (0.00172), cPKU (0.01117)	Khemir S et al. [19]

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I: Incidence; P: Prevalence; HPA: hyperphenylalaninemia; mPKU: mild phenylketonuria; modPKU; moderate phenylketonuria; cPKU: classic phenylketonuria; PKU: phenylketonuria.

data were provided by the Ministry of Health [13-15]; in China, the same was reported by the National Neonatal Screening Quality Control, National Center for Clinical Laboratories (NCCL) [16] according to the national evaluation of PKU. Additionally, in Europe, previous international studies on the management of PKU mostly focused on the developed parts of Europe, while data about the large parts of southeastern and eastern Europe are scarce. In this regard, various eligible studies used in the present report, particularly the report by Zerjav Tansek et al. (2015), have meticulously covered PKU prevalence and incident in the southeastern Europe region (i.e., Balkan Peninsula) [17, 18].

In Tunisia, the related data were collected in association with the Association Tunisienne d'Etude des Maladies métaboliques héréditaires (ATEMMH), i.e., English is Tunisian association for the study of inherited metabolic diseases [19]. Reported data for the U.S.A contributed to the Council of Regional Networks for Genetic Services (CORN) and the National Newborn Screening and Genetics Resource Center (now the National Newborn Screening & Global Resource Center; NNSGRC) reports through the National Newborn Screening Information System (NNSIS) [20]. Although in other countries, like Lebonan NBS has not yet been covered by any national healthcare system, eligible tertiary care facili-

Table 4. The distribution of PKU reported in publications from American countries

America				
Country	**Period of Data Collection**	**Incidence or Prevalence (%)**	**PKU Phenotype (%)**	**References**
Argentina (Buenos Aires)	2001-2005	0.03333 P	N.A.	Penchaszadeh VB [60]
Brazil	2005	0.003 P	N.A.	Georgiou T et al. [71]. MLPA analysis and real-time PCR. Results: Among 22 independent alleles thirteen previously described mutations were detected (detection rate 100%)
Chile	1992-2008	0.00528 I	mHPA (0.0098), PKU (0.00528)	Cornejo V et al. [72]
Costa Rica	2005	0.002 P	N.A.	Georgiou T et al. [71]. MLPA analysis and real-time PCR. Results: Among 22 independent alleles thirteen previously described mutations were detected (detection rate 100%)
Cuba	2000-2007	0.00191 I	N.A.	González EC et al. [61]
North America	N.A.	0.00625 I	N.A.	Hamman KJ et al. [62]
US	1991-2000	0.00524 I	HPA (0.00192)	Therrell BL et al. [20]
US	2001-2010	0.00433 I	HPA (0.00171)	Therrell BL et al. [20]

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I: Incidence; P: Prevalence; mHPA: mild hyperphenylalaninemia; PKU: phenylketonuria; HPA: hyperphenylalaninemia.

ties, like various national and international universities. Concerning Lebonan, the American University of Beirut Medical Center (AUBMC), and Saint Joseph University (USJ) [21] or in Egypt, Cairo University Children's Hospital (CUCH) [22], are responsible for national biochemical genetic investigations.

The selected reports were published between January 2007 to December 2018. Ten studies had a case-control design, one was a cohort research, and the remainings were cross-sectional studies on PKU frequency. The age of the study participants ranged between 2 days and 11 years, with the sample sizes ranging from 3627 to 1100000 subjects. Except for 19 countries, which used tandem Mass Spectroscopy (MS/MS), 4 countries implemented bacterial inhibition assay. Besides, 4 studies applied High-Pressure Liquid Chromatography (HPLC) and ELISA. Information on the applied methodology for 9 countries was unavailable; all other countries used a variety of the aforementioned methods to measure the blood Phe concentration.

Initially, unifying the calculation of prevalence rate per 100000 screened population and in the form of percentage was sought to obtain a dependable comparison of PKU prevalence/incidence. Then, studies were categorized via the population used to reckon PKU prevalence in national screening programs. The self-calculated prevalence/incidence of PKU (including BH4 dependent, classical type PKU, & HPA) was provided by the available information. The relevant extraction from included publications by dividing the number of cases by the sample size or the number of births from January 2007 to December 2018. Prevalence calculations were tabulated and expressed as the rate per 100000 of the screened population or as a percentage. We calculated PKU prevalence for all considered studies; however, only national programs yielded solid estimates. To report a reliable comparison, we converted PKU prevalence proportions, which in different studies were reported in various units, by percentage. Due to our calculation, Thailand presented the least percentage of PKU prevalence (0.00044%) and Italy faced the most prevalence of PKU, i.e., approximately 0.02736%. Moreover, the prevalence of PKU among patients with ID in Iran was reported by 2.1% in 2009.

A summary of the whole prevalence and incidence of PKU in numerous countries is presented in Tables 1-4. Most of the cases included in this study are not only cPKU, but also Hyperphenylalaninemia (HPA) not requiring treatment. Data related to all PKU variants frequency are listed in Tables 1-4; however, the relevant frequency of different PKU variants was not calculated in some of the references. Thus, we assumed the PKU frequency in these publications was related to all PKU phenotypes. In the case of the data availability related to the percentage of BH4 responsiveness among the

different HPA and PKU variants in the eligible publications that were investigated for this study, this percentage is reported in Tables 1-4, as well. Extensive studies are available on the prevalence of PKU in Iran. The incidence of PKU in Iran in 1982 was estimated as 0.011% [23]; however, this rate had raised to 0.02757% in 2002 [24], and it had later reduced to 0.02% of live births in 2015. Among these cases, 18.8%, 26.4%, 34%, and 20.8%, respectively presented mHPA (360-600 µmol/L blood Phe), mild PKU (mPKU; 600-900 µmol/L blood Phe), modPKU (900-1200 µmol/L blood Phe), and cPKU (blood Phe >1200 µmol/L) [2]. Using HPLC in Fars Province, the south of Iran, the incidence of PKU from 2004 to 2007 was reported to be 0.01597% [25]; however, this proportion reduced to 0.01169% from 2007 to -2008 by the screening of a total of 76966 newborns (62.5% mHPA &d 37.5% PKU) [26].

In a descriptive retrospective study in Mazandaran Province, northern Iran, 0.00662% of newborns were diagnosed with PKU from 2007 to 2015 using ELISA and HPLC as the confirmation methods. HPA phenotypes in Mazandaran was reported as 22.2% for cPKU, 33.3% for mPKU, and 44.5% for HPA [13]. Another study in patients with ID (except Down syndrome) in Tehran and 31 other cities of Iran exhibited the %2.1 prevalence of cPKU and %0.44 of mHPA cases [27]. These studies revealed that despite the implementation of the Newborn Screening (NBS) programs for an Inborn Error of Metabolism (IEM) in most cities of Iran, the prevalence of PKU remained significant.

The frequency of the disease in Asian countries

According to our findings, based on the Ministry of Health, PKU was highly prevalent in Iran (0.02%), particularly in Fars Province with a prevalence of 0.01597% from 2004 to 2007 [25]. This rate was respectively higher than Turkey, UAE, Lebanon, Iraq, China, Saudi Arabia, Mazandaran (Iran), India, Bahrain, Taiwan, Singapore, Japan, Korea, and Thailand. Nevertheless, PKU occurrence experienced a reduction to 0.01169% in Fras Province in the following years (2007-2008) [26], i.e., less than PKU incidence in Iraq, Lebanon, UAE, and Turkey. Although in Lebanon from 1998 to 2007, only 18 cases of PKU variants were detected by screening 143000 newborns (0.01258%); after introducing expanded NBS by MS/MS in 2007, the incidence of PKU equaled 0.02613%. This rate reduced to 0.01984% of newborns by 2013 [21, 28]; the PKU disorders were of the highest prevalence in this country among the other Asian countries. After Lebanon and Iran, the highest PKU prevalence belonged to Turkey with 0.01538% of newborns in 2007 [29]. In the UAE however, the incidence of PKU from 1998 to 2000 was nearly close to Thailand, which had raised from 0.00498% [30] to 0.00687% (89% cPKU & 1.75% PKU) in 1995-2011 [31]. PKU prevalence reached 0.01323 % (only cPKU) in 2011-2014; UAE was ranked fourth for having a high prevalence of PKU in the investigated Asian countries (Table 1) [32]. Besides, 0.01211% of newborns presented PKU in Sulaimani City in Iraq. Accordingly, Hamawandi et al. claimed that using Iranian kit materials and lab equipment, as well as the similar ethnicity of Fars and Kurdish population might be the possible explanations for this similarity [33].

The rate of PKU incidence in China and Saudi Arabia were more than in Mazandaran Province in Iran and measured as 0.00862% [16] and 0.00702% [14], respectively. In some countries, we only could find outdated data, e.g., the latest PKU incidence report in India was published in 2004 (0.00546%) [34]; however, this rate in Southern India was reported as 34.5% of IEM in 2007-2009 [35]. The United Kingdom of Bahrain reported the PKU incidence of 0.0045% [36]. In Taiwan, from 2001 to 2014, 0.00167% of Taiwanese live births were detected with PKU [37]. An 8-year study in Singapore revealed an incidence of 0.00112% for PKU [38]. This rate was 0.0008% in Nagasaki, Japan, in 2001 [39]. The reason for the low incidence of PKU in Japan was claimed to be because of genetic drift in the founder population of Japanese islands [40]. In South Korea, NBS on 3.44 million in 2000-2015 indicated 0.00072% of newborns with PKU [41]. Among Asian countries, Thailand possessed the least prevalence of PKU (0.00044%) [15] after Korea. We can suggest the high rate of the heterogeneity of PAH locus [42, 43] and consanguineous marriages among the Iranian and Turkish population [10, 27, 44] as remarkable causes of the high occurrence of PKU; thus, these countries are of high rank in PKU frequency in Asia.

The frequency of the disease in European countries

In Europe, apart from Malta and Finland (because of their known low PKU incidence), all countries use a national program for PKU; although in some countries, these programs fail to have 100% coverage. Italy (0.02736%) [18], and Germany (0.02%) [41] presented the highest frequency of PKU among European countries. Slovak Republic (Bratislava, Banska Bystrica, & Kosice centers) in 2012 and Ireland in 2004 with 0.01694% PKU incidence [45, 46] and 0.01612% PKU prevalence [18] detected among newborns, respectively possessed the highest PKU frequency after Germany and Italy. The incidence of PKU had an estimated 0.01492% of newborns in Estonia from 1974 to 2016 [47], i.e., almost

close to Slovenia (0.01477%, cPKU=0.0098%) [46] and PKU prevalence in Latvia (0.01474%) [18]. However, the ethnic origin of the reported subjects in Estonia was 26% of Slavic (Russian), 7% of mixed-origin, and the rest were Estonian. Furthermore, as per the State Expert Center MoH, PKU prevalence was reported to be 0.01428% in Ukrainians [48]. Moreover, PKU prevalence was documented as 0.01318% for Switzerland [18]. This rate is almost close to PKU frequency in Russia (0.01296%), Scotland (0.01281%), Poland (0.01239%), and Croatia (0.01208%; 10% of the patients were classified as mHPA, 23% were assigned to mPKU, and 67% to cPKU) [18, 49].

In other European countries, PKU frequency was reported as 0.01168% in France [50], 0.01% in UK [51], 0.00833% in Austria [52], 0.00872% in Norway [18], 0.00822% in 2010 in Portugal [53], 0.00808% in Spain (HPA=0.016%) [54], 0.00788% in Sweden [18], 0.00788% in Hungary, 0.0077% in Netherlands [18], and 0.00744 in Denmark [18]. Although the official incidence of PKU in Romania remains unpublished, it has been reported by Bucharest National Authority for neonatal screening diagnostic confirmation and specific treatment in PKU and congenital hypothyroidism as 0.01% of live births in 2013 [55]. PKU incidence in some other European countries is summarized in Table 2. Among European countries, Finland experienced the lowest PKU frequency by an incidence of 0.001-0.0005; however, this is the latest incidence we could find in our database, i.e., related to 2005 [56]. Due to our investigation, the highest and lowest rate of PKU distribution belonged to Italy (0.027%) and Finland (0.0007%), respectively. Notably, the incidence of PKU in Germany was respectively 25- and 45-fold higher than that in Japan and Thailand; however, it was equal to the occurrence of this disorder in Iran.

The frequency of the disease in African countries

The prevalence of PKU in Egypt was evaluated as 0.01978% of infants in 2008 [57], by 2013 this rate reduced to 0.00909%. In 2012, PKU was the most common aminoacidopathies disorder among Tunisians as another African country [58]. Khemir et al. estimated the incidence of PKU in Tunisia as 0.0131% from 1988 to 2008 [19]. Insufficient diagnostic capabilities in Africa might obstruct revealing the actual rate of PKU frequency; in general, the occurrence of PKU has been reported as low in Africa [59]. In this regard, the high frequency of PKU in the north of Africa might be owed to the high level of consanguineous marriage (Table 3).

The frequency of the disease in American countries

In 2005, Buenos Aires in Argentina (0.03333%) [60] possessed the highest, and Cuba (0.00191) [61] had the lowest rate of PKU incidence among Latin American countries. Based on the calculated occurrence of IEM in the U.S.A through NBS by the National Newborn Screening Information System (NNSIS), the US witnessed a decrease in PKU incidence from 0.00524% in 1991-2000 to 0.00433% in 2001-2010 [20]. By 2014, 10000 individuals in the US were diagnosed with PKU. In 2001-2010, Hawaii was the US state with the least prevalence of PKU (0.00054%) and Wyoming presented the most PKU prevalence (0.016%) [20]. In northern America, the PKU incidence rate was reported as 0.00625% [62]. Moreover, PKU occurs in 0.01% of Caucasians [9] and 0.00191% of African Americans in the US [63] (Table 4).

Certain restrictions have affected this review. First, the main search was limited to the publications in English. A major disadvantage of this review concerned its design, in particular for prevalence/incidence studies in which data from most of the reports are based on the collection of the retrospective data either from registries or medical records. Such routine data possess some pitfalls, such as imprecision or deficiency. Another possible limitation included the small sample sizes. Other limitations involved the method for calculating PKU prevalence/incidence in the reports. Some reports applied the divisor as several whole live births and not the actual number of screened cases; however, others performed PKU prevalence/incidence evaluation using a total number of abnormal cases instead of total screened subjects. However, in the case of these reports using self-calculations, we tried to provide more precise data of PKU prevalence/incidence.

4. Conclusion

Advances in science and technology drive the evolution of methods, which allow the accurate measurements of acylcarnitines, amino acids, and other critical metabolites in the diagnosis of metabolic disorders, like MS/MS [64]. Due to its sensitivity, selectivity, the ability to screen several diseases simultaneously, and short-term analysis, MS/MS has been widely used for NBS [65]. Moreover, the widespread use of MS/MS can significantly be contributed to the estimating of the frequency of incidence of each IEM in our population; reports from countries that have incorporated NBS indicated that the occurrence of some disorders is higher than expected [38, 66]. Overall, the prevalence of PKU worldwide in 2015 was claimed to be 0.00641% of live births [67]. This review aimed to report the PKU prevalence in different countries to raise awareness and leads

to establishing an efficient NBS program. Surprisingly, the highest and lowest relevant rates belonged to Asia and a European country, respectively. Therefore, with a slight difference between Iran, Germany, and Italy, the highest rate of incidence of PKU belonged to Italy with approximately 0.02736% of total live newborns. In contrast, the lowest rate of PKU distribution in Asia belonged to Thailand (about 0.0004%), and in Europe, it concerned Finland. Although we could not conclude the prevalence of PKU in Africa just based on two studies, this prevalence in Tunisia was about the same as some European and Asian countries. In conclusion, in the investigated studies, PKU had covered more than 50% of IEMs in Germany and Italy [68, 69], while this rate for Asian countries (Oman, Japan, Bahrain, India, China) ranged between 6% and 20% of IEMs (data not presented) [70]. These findings indicated that the incidence rates of amino acids differ between European and Asian populations.

Our research demonstrated the necessity of conducting further investigations on PKU prevalence, especially in Iran and other countries in the Middle East. Thus, the priority is to assist the countries where the basic screening programs encompass less than 100% coverage. Additionally, continuous monitoring of the NBS program could help to decrease the variation in design and methodology using the available knowledge and expertise in the literature. The considerable difference in recalling the PKU incidence rates represents one important and obvious area for the refinement of NBS program performances, globally. Since treatment depends on the early diagnosis of the disorder, the implementation of neonatal screening for PKU is crucial. Moreover, the estimation of the exact prevalence of the disorder is required to implement effective policies and strategies for controlling the disease occurrence.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

All authors equally contributed to preparing this article.

Conflicts of interest

The authors declared no conflicts of interest.

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