Review Article
The Prevalence of Phenylketonuria in Arab Countries, Turkey, and Iran: A Systematic Review

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Background/Objectives. This paper seeks to identify the prevalence of Phenylketonuria (PKU) in Arab countries, Turkey, and Iran. The study reviewed the existence of comprehensive national newborn screening programs and reported consanguinity rates.

Methods. A computer based literature search was conducted using relevant keywords to retrieve studies conducted on PKU. A total of 34 articles were included. Prevalence was categorized based on the type of screening method used for PKU diagnoses.

Results. The prevalence of classical PKU diagnosed through a comprehensive national newborn screening program ranged from 0.005% to 0.0167%. The highest prevalence was reported in Turkey at 0.0167%, whereas the lowest prevalence was reported in the UAE, 0.005%.

Conclusion. The findings of this review emphasize the need for the establishment of more efficient reporting systems in these countries that would help measure Disability-Adjusted Life Year (DALY) in order to estimate the overall societal burden of PKU.

1. Introduction
Phenylketonuria (PKU) (OMIM 261600) is an autosomal recessive inborn error of phenylalanine (Phe) metabolism, occurring in approximately 1:15,000 people. PKU is mainly caused by a deficiency of phenylalanine hydroxylase (PAH; 612349), the enzyme that catalyzes the hydroxylation of phenylalanine to tyrosine [1]. Hyperphenylalaninemia can also be due to defects in the regeneration or biosynthesis of the enzyme cofactor tetrahydrobiopterin (BH4). If untreated or undiagnosed, the neurotoxic effects of excess phenylalanine can lead to impaired postnatal cognitive development. Both types of hyperphenylalaninemia (PAH and BH4 deficient) are thought to be heterogeneous disorders that vary from severe, for example, classical phenylketonuria (PKU), to mild, benign, and transient forms. Enzyme deficiency yields a spectrum of disorders such as mild hyperphenylalaninemia, mild phenylketonuria, and classic phenylketonuria. Classic phenylketonuria is a result of near complete or complete deficiency of phenylalanine hydroxylase activity which will lead to profound and irreversible intellectual disability in the absence of dietary restriction of phenylalanine. Mild hyperphenylalaninemia and mild phenylketonuria are linked to a lower risk of impaired cognitive development if left untreated [2]. All of the aforementioned are included in OMIM 261640 with cytogenetic location: 12q23.2. Deficiency of BH4 is a rare disorder that changes the levels of various substances in the body, including phenylalanine [3]. Clinical manifestations of BH4 deficiency include intellectual disability, neurological deterioration, difficulty swallowing,
Electronic search using Pub Med, Embase, and Google Scholar was conducted to extract articles addressing the epidemiology of Phenylketonuria in Arab countries, Turkey, and Iran. Key words used for our search included Phenylketonuria or PKU or aminoacidopathies or metabolic disorders or inborn error metabolism and (prevalence or incidence or frequency) and (newborn screening program or selective screening or national neonatal screening or tandem mass spectrometry) and (Saudi or Kuwait or Oman or United Arab Emirates or Bahrain or Qatar or Egypt or Iraq or Syria or Jordon or Sudan or Libya or Tunisia or Algeria or Morocco or Palestine or Lebanon or Yemen).

2.1. Inclusion and Exclusion Criteria. Inclusion criteria were English language articles published in peer-reviewed journals from January 1982 to December 2017, studies focusing on prevalence/incidence of PKU and NBS programs in the countries mentioned above. Any case reports/series or articles tackling treatment, molecular mutation, and molecular diagnosis were excluded.

2.2. Selection and Data Extraction. Comprehensive search terms such as Phenylketonuria or PKU or aminoacidopathies or metabolic disorders or inborn error metabolism were systematically applied along with Boolean operators. A broad search of Pubmed and Embase databases yielded 2487 records. After removing duplicate records, a total of 1772 were identified in our search, of which, 1702 were irrelevant and were excluded based on title/abstract screening. Finally, 70 full-text articles were assessed for eligibility and were screened against the inclusion criteria (including 18 Arab countries). A total of 48 articles were further eliminated because PKU prevalence/incidence was neither mentioned nor were the researchers able to extract data or self-calculate prevalence. A secondary search was performed by cross-referencing and using the same keywords in Google Scholar that resulted in a total of (12) articles, which did not appear in our original PubMed and/or Embase search. Consequently, the total number of articles included in this systematic review was 34. The review was conducted by two professionals in the field of epidemiology and public health. Any disagreements between the two researchers were solved by consensus.

3. Results

A total of 34 prevalence/incidence studies conducted in different years and regions were included in this review (see Table 2). In some of the prevalence/incidence studies, prevalence was self-calculated in 9 articles and corrected in 11 articles. Prevalence/incidence studies were further categorized to the type of study whether it was a national NBS program (n = 5 articles) [6, 15–18], regional/governorate NBS program (n = 6 articles) [19–24], selective screening for newborns (n = 6 articles) [25–30], selective screening of sick/symptomatic newborns and/or infants, children, and adults (n = 9 articles) [31–39], selective screening for both newborns and sick/symptomatic newborns and/or infants,
Table 2: Illustration categorization of the studies based on the type of screening used. Prevalence as % and rate per 100,000 neonates and or sick/symptomatic subjects were computed. NA: information is not available; ‘prevalence among citizen only,’ ‘self-calculated prevalence,’ and ‘corrected information. Remarks column indicates the way of prevalence/incidence estimated by articles if different from computed and states any self-computing prevalence and correction made in this review.

| Type | Study and country setting | Age at sampling | Sample size | Classical PKU (% of cases) | Prevalence | Consanguinity | Remarks |
|------|--------------------------|-----------------|-------------|----------------------------|------------|---------------|---------|
|      |                          |                 |             | Number of cases | Per 100,000 neonates/sick | Number of cases | Per 100,000 neonates/sick |        |
| [6]  | Saudi Arabia, 2017       | After 24 hr. of birth | 775000     | 53 | 0.0068 | 6.84 | NA — — | NA — — — | Incidence Rate reported in article as 1:14245 and should be corrected to 1:14623. |
| [5]  | United Arab Emirates, 2010, Ministry of Health, National screening center. Tawam Hospital | 3rd day for discharged newborns and before discharge for those admitted for >3 days | 138718     | 7 | 0.0050 | 5.05 | NA — — | NA — — — | No information |
| [6]  | United Arab Emirates, 2014, Ministry of Health, National screening center. Tawam Hospital | 3rd day after birth (≥48 hr) and before discharge for those admitted for >3 days | 752065     | 51 | 0.0068 | 6.80 | 1.00 | 0.00013 | 0.13 | NA — — — |
|      | National NBS program    |                 |             | Number of cases | Per 100,000 neonates/sick | Number of cases | Per 100,000 neonates/sick |        |
| [7]  | United Arab Emirates, 2016 & c, United Arab Emirates University, Al Ain, Tawam Hospital | 48 hr. of age and before discharge for those admitted for >3 days | 166049     | II | 0.0080 | 8.09 | NA — — | NA — — — | No information |
| [8]  | Turkey, 1995 c, Hacettepe University, Departments of Nutrition and Metabolism, Molecular Biology, Dietetics and Neonatology, Ankara | Samples collected before discharge & test repeated if collected <24 h | 576122     | 96 | 0.086 | 8.66 | 1.00 | 0.00017 | 0.17 | 46.0 | 0.008 | 798 | 45.7% of marriages among PKU families were consanguineous. 30.9% were first degree relative marriages, 5.6% second degree, 72 others and 54.3 were nonconsanguineous. |
### Table 2: Continued.

| Type | Study and country setting | Age at sampling | Sample size | Number of cases | Classical PKU (%) | Per 100,000 neonates/infant | Prevalence of homocystinuria (BH4) (%) | Per 100,000 neonates/infant | HPA (mild and moderate) (%) | Consonant/y | Remarks |
|------|---------------------------|-----------------|-------------|-----------------|-------------------|-----------------------------|-------------------------------------|-----------------------------|----------------------------|-------------|---------|
| [19] | Palestine Gaza Strip, 2015 | Average age 13.5 days | 102,207 | 65 | 0.0063 | 6.36 | NA | NA | NA | 60% of PKU parents were first cousins, while 7.7% with no consanguinity |
| [20] | Iraq, Sulaimani City, 2015 | 3–10 days | 825 | 1 | 0.0231 | 12.11 | NA | NA | NA | The parents of this case were consanguineous |
| [21] | Iraq, Baghdad/Al-Karkh Directorate, 2016 | Within 3–5 days up to 2 months | 80,049 | 6 | 0.0075 | 7.46 | NA | NA | NA | No information |
| [22] | Iran, Fars province, Shiraz, 2009 | 72 hours after birth | 70,077 | 15 | 0.0213 | 21.24 | NA | NA | NA | Incidence rate reported as 12.1/10,000 neonates |
| [23] | Iran, Fars province, 2010, Pediatric Endocrinologist, PKU Center, Naderkazemi Clinic | 3–5 days after birth | 175,335 | 28 | 0.0160 | 13.94 | NA | 10 | 0.001 | 0.57 | No information |
| [24] | Iran, Mazandaran Province, Department of Pediatrics, School of Medicine, Clinical Research Development Unit of Referral Laboratory | During days 3–5 after birth | 607,244 | 6 | 0.00147 | 1.47 | NA | 21 | 0.0005 | 5.16 | Parental relationship observed in 8 cases (53.6%) |

**Correction:** Article used the total population livebirth in calculating prevalence. However, it should be calculated using total number of newborns screened in 2000 which is mentioned as 13,756 in including the 11 cases that had been excluded due to death. So, corrected prevalence should be \((13,756/30) \times 100 = 0.57 \times \) 100,000.

**Correction:** Incidence rate reported in article as 1:4698.

**Correction:** Incidence rate was reported to be 0.66 in 10,000, while non-classic PKU cases were not detected.
| Type | Study and country setting | Age at sampling | Sample size | Classical PKU (%) | Per 100,000 neonate/sick | Prevalence | Number of cases | Number of BP H4 (%) | Per 100,000 neonate/sick | HPA (mild and moderate) (%) | Per 100,000 neonate/sick | Consanguinity | Remarks | Classi cal PKU | B H4 defect (BH4) |
|------|--------------------------|----------------|-------------|-------------------|--------------------------|------------|----------------|-------------------|--------------------------|-----------------------------|--------------------------|--------------|---------|----------------|----------------|
| PKU  | Saudi Arabia, Aramco, 2010 | Not indicated | 165330 | 12 | 0.0672 | 7.25 | 400 | 0.0024 | 2.8 | NA | — | — | Almost all of detected cases were consanguineous | Incidence Rate reported in article for classical PKU is 7:100,000 live births and for BH4 defect is 2:100,000 |
|      | Egypt, 2009, Pediatrics Department, National Liver Institute, Menoufiya University, Biomedical Genetics Department, National Research Center | Mean age 9.3 ± 2.43 days | 3000 | 1 | 0.333 | 33.33 | NA | — | — | NA | — | — | Positive consanguinity was found in 57% of the samples | Incidence Rate reported in article as 1:3000 (0.03%)
| PKU  | Turkey, 1996, Department of Metabolism and Department of Neonatology, Institute of Child Health, Hacettepe University, General Maternity Hospital, Ankara | Samples collected before discharge & test repeated if collected <24 h | 20979 | 8 | 0.381 | 38.13 | NA | — | — | 4.0 | 0.039 | 19.07 | No information | Article reported incidence of typical PKU as 1:2622 and that for HPA as 1:3243 and the overall is 1:7942 |
| PKU  | Lebanon, 2003a, Department of Pathology and Laboratory Medicine and Pediatrics, American University of Beirut | 2-3 days | 937 | 1 | 0.0130 | 10.97 | NA | — | — | 10 | 0.011 | 10.97 | No information | Article reported incidence of typical PKU as 1:2622 and that for HPA as 1:3243 and the overall is 1:7942 |
| PKU  | Lebanon, 2003b, Medical genetics Unit in Saint Joseph University, Epidemiology and Population Studies Department and Department Of Pediatrics and Adolescent Medicine at the American University of Beirut, Faculty of Science at the Lebanese University | Not indicated | 126000 | 18 | 0.0143 | 14.29 | 7.00 | 0.0015 | 5.55 | NA | — | — | No information | Reported incidence was 1:8000, should be corrected to 1:8633. Mild HPA cases normalized after retesting |
| Type | Study and country setting | Age at sampling | Sample size | Classical PKU (%) | Prevalence Biopsy defect (BH4) (%) | HPA (mild and moderate) (%) | Consanguinity | Remarks |
|------|--------------------------|----------------|-------------|------------------|--------------------------------|--------------------------|--------------|---------|
| [31] | Bahrain, 2013, Department of Molecular Medicine, College of Medicine and Medical Science, AGU, Manama | 3–90 days | 1986 | 3 | 0.1311 | 51.06 | NA | — | — |
| [32] | Kuwait, 1986, Department of Clinical Biochemistry, Al-Sabah Hospital | 13% neonates, 26% infants (<1 year of age), 43% older children and 18% adults (>12 years) | 800 | 9 | 1.1230 | 125.00 | NA | — | 10 | 0.125 | 125.0 |
| [33] | Oman, 2012, Department of Biochemistry, Department of Child Health, Sultan Qaboos University | No age | 100 | 8 | 0.7273 | 72.72 | 0.3727 | 27.22 | NA | — | — |
| [34] | Egypt, Cairo, 2014, Department of Pediatric Neurology, Department of Pediatric Genetics and Department of Clinical and Chemical Pathology in Cairo University, Inherited Metabolic Disease Unit, Cairo University Children Hospital | 2.5 months to 6 years | 3380 | 100 | 2.9586 | 29.58 | NA | — | — | — | — |
| [35] | Jordan, 2012, Department of Pediatrics, Metabolic Genetics Clinic, Queen Rania Al-Abdullah Children Hospital, King Hussein Medical Center | One to 50 months | 258 | 17 | 8.0189 | 801.87 | NA | — | NA | — | — |
| [36] | Lebanon, 2013, Department of Pediatrics and Adolescent Medicine and Department of Pathology and Laboratory Medicine at the American University of Beirut Medical Center | 2 months to 21 years | 2921 | 90 | 3.0411 | 3041.11 | NA | — | NA | — | — |
| [37] | Iraq, 2013, Department of Pediatrics, College of Medicine, Baghdad University and Children Welfare Teaching Hospital Medical City Complex | >1 year and <5 years | 61 | 7 | 11.11 | 111.11 | NA | — | NA | — | — |
| [38] | Iraq, 2016, Child Welfare Teaching Hospital and Al-Imran Al-Kadhemiyan Teaching Hospital, Baghdad | 9.3% neonates (<30 days of age), 34% (<1–5 years), 9.3% >5 years. | 1758 | 19 | 1.0807 | 1080.7 | NA | — | 10 | 0.057 | 56.88 |
| [39] | Iran, Shiraz, 2013, Department of Biochemistry, Department of Pediatric, Shiraz University of Medical Sciences | Not indicated | 1061 | 29 | 0.0273 | 2.73 | NA | — | 10 | 0.0009 | 9.42 |

**Table 2: Continued.**

| Type | Study and country setting | Age at sampling | Sample size | Classical PKU (%) | Prevalence Biopsy defect (BH4) (%) | HPA (mild and moderate) (%) | Consanguinity | Remarks |
|------|--------------------------|----------------|-------------|------------------|--------------------------------|--------------------------|--------------|---------|
| [31] | Bahrain, 2013, Department of Molecular Medicine, College of Medicine and Medical Science, AGU, Manama | 3–90 days | 1986 | 3 | 0.1311 | 51.06 | NA | — | — |
| [32] | Kuwait, 1986, Department of Clinical Biochemistry, Al-Sabah Hospital | 13% neonates, 26% infants (<1 year of age), 43% older children and 18% adults (>12 years) | 800 | 9 | 1.1230 | 125.00 | NA | — | 10 | 0.125 | 125.0 |
| [33] | Oman, 2012, Department of Biochemistry, Department of Child Health, Sultan Qaboos University | No age | 100 | 8 | 0.7273 | 72.72 | 0.3727 | 27.22 | NA | — | — |
| [34] | Egypt, Cairo, 2014, Department of Pediatric Neurology, Department of Pediatric Genetics and Department of Clinical and Chemical Pathology in Cairo University, Inherited Metabolic Disease Unit, Cairo University Children Hospital | 2.5 months to 6 years | 3380 | 100 | 2.9586 | 29.58 | NA | — | — | — | — |
| [35] | Jordan, 2012, Department of Pediatrics, Metabolic Genetics Clinic, Queen Rania Al-Abdullah Children Hospital, King Hussein Medical Center | One to 50 months | 258 | 17 | 8.0189 | 801.87 | NA | — | NA | — | — |
| [36] | Lebanon, 2013, Department of Pediatrics and Adolescent Medicine and Department of Pathology and Laboratory Medicine at the American University of Beirut Medical Center | 2 months to 21 years | 2921 | 90 | 3.0411 | 3041.11 | NA | — | NA | — | — |
| [37] | Iraq, 2013, Department of Pediatrics, College of Medicine, Baghdad University and Children Welfare Teaching Hospital Medical City Complex | >1 year and <5 years | 61 | 7 | 11.11 | 111.11 | NA | — | NA | — | — |
| [38] | Iraq, 2016, Child Welfare Teaching Hospital and Al-Imran Al-Kadhemiyan Teaching Hospital, Baghdad | 9.3% neonates (<30 days of age), 34% (<1–5 years), 9.3% >5 years. | 1758 | 19 | 1.0807 | 1080.7 | NA | — | 10 | 0.057 | 56.88 |
| [39] | Iran, Shiraz, 2013, Department of Biochemistry, Department of Pediatric, Shiraz University of Medical Sciences | Not indicated | 1061 | 29 | 0.0273 | 2.73 | NA | — | 10 | 0.0009 | 9.42 |
Table 2: Continued.

| Type | Study and country setting | Age at sampling | Sample size | Number of cases | Classical PKU (%) | Prevalence of hypoxanthine (BH4) (%) | HPA (mild and moderate) (%) | Consanguinity | Remarks |
|------|--------------------------|-----------------|-------------|-----------------|------------------|--------------------------------------|----------------------------|--------------|---------|
|      |                          |                 |             |                 |                  |                                      |                            |              |         |
|      | Kuwait, 2007<sup>a</sup>, Department of Pharmaceutical Chemistry and Pharmacy Practice, Faculty of Pharmacy at Kuwait University and Department of Pediatrics at Sabah Hospital |                  |             |                 |                  |                                      |                            |              |         |
|      | Among newborns | Not indicated | 1520<sup>b</sup> | 362 <sup>c</sup> | 0 | 0.000 | 2.00 | NA | — | 3.0 | 0.197 | 197.37 | No information |
|      | Among sick | | | | 0 | 0.000 | 7.86 | NA | — | 3.0 | 0.197 | 197.37 | No information |
|      | Self-calculated prevalence among sick subjects. Article did not report prevalence of PKU. Data extracted from table and calculated. Not all those screened (sick or newborns). Overall classical PKU prevalence can be estimated as (1/1520) * 100 = 0.066% |
|      | | | | | | | | | | | | | |
|      | Egypt, 2009<sup>b</sup>, Clinical and Chemical Pathology and Pediatric Departments, Faculty of Medicine, Cairo University and Ministry of Health and Population | | | | | | | | | | | | | |
|      | Among newborns | 3–7 days | 1600 | 350 | 4 | 0.029 | 25.0 | NA | — | 25.0 | 2545.4 | NA | No information |
|      | Among sick | 3 months to 15 years | | | | | | | | | | | |
|      | Article stated that PKU cases among newborns are 1:5000. Also, estimated birth prevalence among newborns and sick subjects as percent from number of abnormal cases not total screened is 38.5% and 49.3%, respectively. Corrected estimates should be done using total number screened as calculated in table |
|      | | | | | | | | | | | | | |
|      | Egypt, 2016<sup>c</sup>, Clinical and Chemical Pathology and Department of Pediatrics in Cairo University, Inherited Metabolic Disease Unit, Cairo University Children Hospital | | | | | | | | | | | | | |
|      | Among newborns | 3–7 days | 25276 | 3900 | 5 | 0.019 | 24.3 | NA | — | 24.3 | 245.7 | NA | No information |
|      | Among sick/symptomatic | 1 week to 15 years | | | | | | | | | | | |
|      | | | | | | | | | | | | | |
|      | Turkey, Ankara, 1999<sup>d</sup>, Institute of Child Health, Department of Metabolism, Hacettepe University, Ankara, Department of Pediatrics, Free University of Berlin | | | | | | | | | | | | | |
|      | Among newborns | Not indicated | 6050 | 170466 | 116 | 1.974 | 25.0 | NA | — | 25.0 | 2545.4 | NA | No information |
|      | Among healthy newborns | | | | | | | | | | | | | |
|      | | | | | | | | | | | | | |
|      | Reported incidence of typical PKU among newborns as 1:4500 prevalent HPA = 1.9741 and overall incidence as 1:29.74. The total should be corrected to 1:29.39 |

<sup>a</sup> Department of Pharmaceutical Chemistry and Pharmacy Practice, Faculty of Pharmacy at Kuwait University and Department of Pediatrics at Sabah Hospital.

<sup>b</sup> Self-calculated prevalence among sick subjects. Article did not report prevalence of PKU. Data extracted from table and calculated. Not all those screened (sick or newborns). Overall classical PKU prevalence can be estimated as (1/1520) * 100 = 0.066%.

<sup>c</sup> Among newborns (sick or newborns, children and adults).

<sup>d</sup> Article stated that PKU cases among newborns are 1:5000. Also, estimated birth prevalence among newborns and sick subjects as percent from number of abnormal cases not total screened is 38.5% and 49.3%, respectively. Corrected estimates should be done using total number screened as calculated in table.
| Type |
| --- |
| Selective screening for sick children and adults from mental retardation institutes |

| Study and country setting | Age at sampling | Sample size | Number of cases Classical PKU (Per 100,000 neonates/sick) | Number of cases HPA (mild and moderate) (Per 100,000 neonates/sick) |
| --- | --- | --- | --- | --- |
| **Turkey, Ankara, 1990.** Institute of Child Health, Department of Metabolism, Hacettepe University, Ankara, Department of Pediatrics, Free University of Berlin | Not indicated | 10800 | 530 4.72 | 4722.2 NA —— NA —— |
| **Kuwait, 1987.** Kuwait Medical Genetics Center, Maternity Hospital | 5-45 Years | 451 | 7 1.55 | 1552.1 NA —— NA —— |
| **Iran, Isfahan, 2003.** | Not indicated | 611 | 26 4.25 | 4255.3 NA —— 8.0 13 130.9 |
| **Iran, Tehran, 2009.** Department of Biology, Grand Valley State University, Genetic Center, Beheshti University of Medical Science in Tehran, Iran, Department of Epidemiology, School of Health and Nutrition, Shiraz University of Medical Science, Student Research Center, Tehran University of Medical Science, Department of statistics, Grand Valley State University, Allendale, MI, USA, Tehran Province Welfare and Rehabilitation Organization | Average age 13.5 days | 4963 | 104 2.09 | 2095.5 NA —— 210 0.42 42.13 |

**Remarks:**

- Among mentally retarded children, 45% of cases had parental consanguinity and the rest were not.
- Consanguinity in all 7 patients. In six cases parents were first cousins and in one case distant relatives but from the same tribe.
- Article stated the prevalence of all HPA as (34/611) × 100 = 5.56%.
- Article stated the prevalence of all HPA as (34/1541) × 100 = 2.2%.
- Article reported prevalence of classical PKU among all mentally retarded individuals in Iran as 2.8% and prevalence of severe HPA as 0.44%. The prevalence among inmates deprived in Tehran only was 2.81% and other cities were 1.68%.
children, and adults ($n = 4$ articles) [40–43], or selective screening for sick/symptomatic children and adults from institutions for mentally challenged ($n = 3$ articles) [44–46]. In addition, a study conducted in Turkey addressed PKU prevalence among newborns, sick/symptomatic subjects, and mentally challenged individuals. For all selected studies, prevalence of classical PKU, BH4 dependent PKU, and mild–moderate HPA were calculated as a percentage, and as a rate per 100,000 population, also presented in Table 2 [43]. Furthermore, consanguinity rate is indicated wherever available.

To conduct a reliable comparison of PKU prevalence, and as most of the studies reported prevalence and/or incidence in different ways, we first sought to unify the prevalence calculation in the form of percentage and rate per 100,000 of the screened population. Then, we categorized the studies by the population used to estimate prevalence into either national, regional, and selective screening programs or studies conducted in institutions for the mentally challenged. Moreover, a comparison was conducted using classical PKU prevalence as the most severe form in addition to the fact that not all (only few studies) gave estimates for BH4 dependent PKU (6 studies) and mild/moderate HPA (13 studies). Prevalence of self- calculation for PKU (including classical type or BH4 dependent PKU and HPA) was generated by extraction of the available information from articles included in this study by dividing the number of cases by the number of life births or sample size in the study during a specific year. Prevalence calculations were tabulated and expressed as percentage or as rate per 100,000 of population screened. Though we calculated PKU prevalence for all studies considered, only national programs will yield solid estimates.

Prevalence of classical PKU extracted or self-calculated from articles using comprehensive national NBS programs ranged between 0.005% and 0.0167%. The corresponding range for regional/governorate NBS programs was 0.0015% to 0.0213%. Selective screening programs of newborns gave prevalence of 0.0072% to 0.0381%. However, in articles estimating PKU via selective screening of sick/symptomatic subjects [newborns, infants, children, and adults], the prevalence was reported to be between 0.0273% and 11.1%. Prevalence in institutions caring for mentally challenged individuals ranged from 1.55% to 4.722%. Four articles reported prevalence based on selective screening of both apparently healthy newborns and sick/symptomatic newborns (i.e., neonates who have missed newborn screening, thus, becoming symptomatic or acting abnormally in any way). Prevalence for selectively screened newborns was 0.0198%–0.0250% and prevalence for sick/symptomatic subjects ranged from 1.917% to 2.974%.

### 4. Discussion

The review addressed and sought to shed light on the epidemic of PKU in the Arab countries, Turkey, and Iran. To our knowledge, this is the first systematic review conducted to summarize the prevalence of PKU in these countries. Despite the lack of published data on PKU prevalence in many Arab countries such as Algeria, Syria, Libya, Sudan, and Yemen, most likely due to the absence or limitation of comprehensive screening programs [47], our review still reflects the high prevalence of PKU in Saudi Arabia, United Arab Emirates (UAE), Turkey, Gaza Strip, Sulaimani, the Baghdad region in Iraq, and the Fars region in Iran. Our results show that prevalence of classical PKU in countries having national newborn screening programs ranges from 0.005% to 0.0167%. The highest prevalence was reported for Turkey in 1995 (0.0167%) [18] and the lowest one for the UAE in 2003 (0.005%) [15]. In regions conducting NBS, prevalence ranged from 0.0015% in the Mazandaran Province [24] to 0.02% in the Fars region in south-central Iran [22].

The prevalence of classical PKU among selective NBS studies ranged between 0.0072% and 0.038%. The lowest prevalence was reported for the Aramco Province in Eastern Saudi Arabia (0.0072%) [25] and the highest for Ankara (0.038%) [27]. Other studies estimated prevalence through selective screening for sick/symptomatic newborns and/or infants, children, and adults such as the ones conducted in Bahrain, Kuwait, Oman, Egypt, Jordan, Lebanon, and Iran. PKU prevalence among sick/symptomatic newborns was highest in the Jordan study (8%) [35] (due to relatively a small sample size) and the lowest in the study was conducted by Golbahar et al. with 0.0273% [31]. Among mentally challenged individuals, the highest prevalence was noted in Turkey during 1990 (4.722%) [43] and the lowest in Kuwait (1.55%) [44]. Prevalence among sick/symptomatic subjects was the highest in Egypt during 2009 (2.5%) and the lowest in Turkey in 1990 (0.02%).

To date, only a few countries such as Saudi Arabia, UAE, Qatar, and Turkey in the region have implemented comprehensive national NBS programs with relatively high coverage that aim for early detection of PKU along with other treatable disorders in an attempt to reduce disability rates. The percentage uptake (or coverage) of newborn screening in the UAE was increased from 50% in 1998 to reach 95% in 2010, with a prompt increase in the year 2003 [16]; however, these levels are still below the international coverage standards (99%) [48].

Unfortunately, our search failed to find any published data showing the prevalence of PKU in Qatari. The prevalence of PKU in Saudi Arabia was 0.0068%. In UAE, PKU prevalence was 0.0081% analogous to the prevalence (~0.0073%) for the Aramco Province in Eastern Saudi Arabia. Consecutive studies on PKU prevalence in UAE have demonstrated an increase in prevalence with time from 0.005% in 2003 to 0.0068 in 2014, and finally 0.008% in 2016.

A global comparison of incidence rates between countries with nationwide NBS programs shows that Japan, among Asian countries, reports the lowest rate with 1:125,000, whereas incidence in China is 1:17,000 [10]. Saudi Arabia is close to the PKU incidence of Japan at 1:14,623 [6] and UAE 1:12,369 [17]. On the other hand, the incidence rate among Caucasians in North America (1:10,000) is lower than those reported for Japan and China [49]. A similar study gave reported incidence for Australia [10]. Among European countries, incidence rates among Saudis are higher than the rate of 1:4,500 reported for Ireland [11] but comparable to rates recorded in Denmark 1:12,000, France 1:13,500, Norway 1:14,500, and finally UK 1:14,300 [10].
The consanguinity rate is very high in Arab countries as reported by most of the articles in our search. For example, 9 out of 11 PKU patients in Oman [33] and 8 out of 9 PKU patients in Kuwait had consanguineous parents [32]. Other studies conducted in Iraq [37] indicated that all 7 cases detected with PKU had consanguineous parents. These findings were consistent with previous studies where 57% of PKU patients in Egypt [26], 60% of PKU cases in Gaza Strip [19], 86.6% of PKU patients in Iran [22], and 34 patients out of 43 PKU cases from Iran [31] had consanguineous parents. Similarly, a recent study conducted in 2017 in Mazandaran Province in Iran indicated that parental family relationships among confirmed PKU cases were 53.6% [24]. Congruently, another study from Iraq, Sulaimani city [20], reported only one case diagnosed with PKU being a product of consanguineous parents.

Addressing some recent articles, consanguinity rates among all cases with different metabolic disorder including PKU were reported. For example, a Jordanian study [35] reveals that out of 151 families, 137 cases had parental consanguinity. Similarly, Al-Jasmi et al. [17] in UAE declared that, among all metabolic disorders detected including PKU, consanguinity was 81.5%. Alternatively, Selim et al. [34] showed that 88% of patients were born to consanguineous parents in Egypt. These results concur with Moammar et al. [25] findings in Saudi Arabia revealing all detected cases to have consanguineous parents. A study conducted in Gaza in contrast confirmed that some PKU cases were not consanguineous [19]. Nevertheless, it fails to mask the fact that most of the studies reporting the cases arose from consanguineous marriages.

5. Limitations

There were certain limitations to this review. First, our search was limited to publications in English. However, most if not all research conducted in the Arab world is published in English. One major drawback was attributed to the study design itself, in particular for prevalence/incidence studies where data from most of the articles were based on retrospective data collection either from medical records or registries. This kind of routine data has its own disadvantages such as incompleteness or inaccuracy. Other limitations include small sample size (63 samples from sick/symptomatic children in Iraq) in Rabab Thijeel study [37]. There is still an ambiguity with regard to the high prevalence of PKU (11.1%) that cannot be generalized. Likewise, another possible limitation involved the way prevalence/incidence calculations were reported in some studies, where some articles used the denominator as a number of all live births during the study period and not the actual number of screened subjects. Others perform PKU estimations by using a total number of abnormal cases as a denominator instead of total number screened. For those incorrect estimates, corrections were made and documented in Table 2.

6. Implications for Future Research

PKU if not detected and treated early will lead to disability which presents a great socioeconomic burden for any country. Unfortunately, only few countries in the region including Saudi Arabia, UAE, Qatar, and Turkey have established active and comprehensive national NBS programs for PKU along with other disorders. More studies are needed in the region to monitor and study PKU. At the public level, and since consanguinity is the main factor of having the disorder in our region, continuous awareness campaigns through media, schools, and universities are recommended to educate the public about potential health risks posed by marriage between close relatives. Genetic counselors also play a big role in educating and helping the parents and affected siblings in not having another affected child during future pregnancy by introducing them to primary prevention such as prenatal diagnosis or Preimplantation Genetic Diagnosis (PGD). Issuing a policy through governments to mandate the screening test for every newborn is one effective approach to reduce PKU. Due to the rarity of specialized experts in this field, physicians, scientist, lab technologist, and governments should support training programs to compensate for this inadequacy.

7. Conclusion

In light of this review, our search demonstrated the need for establishment of more research work so as to investigate the true prevalence of PKU in our region using comprehensive population screening tests. The data in regard to prevalence, follow-up, and identification of other possible risk factors or other disease spectrum associated with PKU is scarce in our region. Our research through PubMed, Embase, and Google Scholar failed to find published data about reliable or recent PKU prevalence in many Arab countries such as Syria, Yemen, Libya, Morocco, Algeria, Tunisia, and Sudan.

Future research should also focus on measuring the Disability-Adjusted Life Year (DALY) to demonstrate overall burden of this disease as well as other genetic diseases. Estimating DALY is another successful measure to estimate years of life lost due to premature mortality (YLL) and years of life lived with disability (YLD). Providing such data will definitely give true estimates of this problem and allow for effective intervention programs to reduce disease burden.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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