RESEARCH ARTICLE

Phenylketonuria screening in Iranian newborns: a systematic review and metaanalysis

Mehdi Shokri¹, Parviz Karimi¹, Hadis Zamanifar², Fatemeh Kazemi³, Gholamreza Badfar⁴ and Milad Azami^{5*}

Abstract

Background: Phenylketonuria (PKU), which is characterized by a deficiency of phenylalanine hydroxylase activity, is an autosomal recessive disorder of phenylalanine (Phe) metabolism. Newborn screening is the main population-based public health screening program that allows successful identification and treatment of PKU with low-Phe diet. The aim of this study was to evaluate the epidemiology of PKU screening in Iranian newborns.

Methods: The present study was designed based on MOOSE protocol and reporting was done in accordance with the PRISMA guidelines. The protocol of this systematic review was published in PROSPERO before it was performed (CRD42020162626). A comprehensive search was done in 10/10/2019 to find related literature on international online databases Web of Science, Scopus, EMBASE, Science Direct, PubMed/Medline, EBSCO, CINAHL, Cochrane Library, national online databases and the Google Scholar search engine. Heterogeneity among studies was assessed by I^2 index and Q test. All meta-analyses were performed using Comprehensive Meta-Analysis Software ver. 2. P < 0.05 was considered significant.

Result: Finally, 18 studies with 3,339,327 Iranian neonates were included. The prevalence of suspected hyperphenylalaninemia (HPA) was estimated to be 45.6/100,000 (95% Cl: 23.9–87.1). The prevalence of suspected HPA in girls and boys infants in Iran was estimated to be 38.0/100,000 (95% Cl: 15.1-95.5) and 43.3/100,000 (95% Cl: 16.2-116.2), respectively. The prevalence of PKU was estimated to be 16.5/100,000 (95% Cl: 12.9–21.2). The prevalence of PKU in girls and boys infants was estimated to be 13.3/100,000 (95% Cl: 7.5–15.8) and 10.9/100,000 (95% Cl: 7.5–15.8), respectively. The prevalence of mild to moderate HPA was estimated 9.7/100,000 (95% Cl: 5.1–18.4) and the prevalence of classical PKU was estimated 4.4/100,000 (95% Cl: 2.5–7.8). Sensitivity analysis for all meta-analysis with the omission of one study showed that overall estimation is still robust.

Conclusion: The results of this meta-analysis showed that PKU is prevalent in Iranian neonates. It should be considered that for PKU there is a highly effective dietary treatment which can prevent the clinical symptoms of PKU if initiated early after detection by newborn screening.

Keywords: Phenylketonuria, Iran, Newborn, Meta-analysis



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Background

Phenylketonuria (PKU), which is characterized by a deficiency of phenylalanine hydroxylase (PAH) activity, is an autosomal recessive disorder of phenylalanine (Phe) metabolism [1]. If left untreated, high blood Phe concentrations pass through the blood brain barrier and cause harmful effects on the growth and function of brain [2].

The main treatment for PKU is low Phe diet. It is recommended that treatment be started as soon as possible and continue throughout life. Although a restricted diet is beneficial for PKU patients, long-term adherence to diet is a difficult challenge, especially for teenagers and those preparing for pregnancy [3].

If urine tyrosine and tetrahydrobiopterin levels are normal and Phe levels are above 20 mg/dl, between 10 and 20 mg/dl, and between 2 and 10 mg/dl, newborns are diagnosed with severe or classical PKU, mild PKU and hyperphenylalaninemia (HPA), respectively [4].

Nowadays, clinical manifestations of classical PKU are rarely reported in developed countries, where newborn screening (NBS) is common. NBS is the main population-based public health screening program that allows successful identification and treatment of PKU with low-Phe diet. Early dietary treatment leads to normal results for patients with this disorder [5]. The first NBS program appeared in the United States in the early 1960s [6] and then spread to most developed countries [7]. PKU can be easily detected in heel prick test 24 h after birth using novel diagnostic methods [8]. There are various methods for detecting PKU in dried blood spot (DBS) sampling, such as fluorometric and colorimetric methods [9], enzymatic method [10, 11], highperformance liquid chromatographic (HPLC) [10], and new methods such as Tandem Mass Spectrometry [12, 13].

Numerous studies have shown that the prevalence of PKU is inconsistent in different Iranian studies and is still a challenging issue [14–31]. Meta-analysis is a statistical method for combining the data of multiple studies with the same goal. When the effect size is consistent between studies, meta-analysis can be used to identify this common effect. Finally, meta-analysis results can provide a more accurate estimate of the impact of treatment or risk factors for disease or other outcomes by combining individual studies [32–34]. The aim of this study was to evaluate the epidemiology of PKU screening in Iranian newborns.

Method

Study protocol

The present study was designed based on Meta-analyses Of Observational Studies in Epidemiology (MOOSE) protocol [35] and reporting was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [34]. Given the type of study, the approval of the Ethics Committee was not required. All study phases were performed independently by two authors. In cases where there were disagreements, they were resolved through group discussion. The protocol of this systematic review was published in PROSPERO before it was performed (CRD42020162626). Available from: https://www.crd. york.ac.uk/prospero/display_record.php?RecordID= 162626.

Search strategy

A comprehensive search was done in 10/10/2019 to find related literature on international online databases Web of Science, Scopus, EMBASE, Science Direct, PubMed/ Medline, EBSCO, CINAHL, Cochrane Library (Cochrane Database of Systematic Reviews - CDSR), and national online databases Barakat Knowledge Network System (http://health.barakatkns.com), Magiran (http://www. magiran.com/), Regional Information Center for Science and Technology (RICST) (http://en.ricest.ac.ir/), Scientific Information Database (SID) (http://www.sid.ir/), Civilica (https://www.civilica.com/), Iranian Research Institute for Information Science and Technology (IranDoc ((https://irandoc.ac.ir), Iranian National Library (http:// www.nlai.ir/) and the Google Scholar search engine. The search was carried out without limitation in time and language. Keywords were: "Metabolism, Inborn Errors" [Mesh], "Metabolic Diseases" [Mesh], "Amino Acid Metabolism, Inborn Errors" [Mesh], "Phenylketonurias" [Mesh] and "Iran" [Mesh].

The keywords were combined using boolean operator "AND" and "OR". An example of a combined search in the Pubmed database was as follows: (((("Metabolism, Inborn Errors" [Mesh]) OR "Metabolic Diseases" [Mesh]) OR "Amino Acid Metabolism, Inborn Errors" [Mesh]) OR "Phenylketonurias" [Mesh]) AND "Iran" [Mesh].

Search keywords were regulated based on minor specifications and differences in the syntax rules of each database. Reference lists of all retrieved articles were manually reviewed to identify all potential studies.

Inclusion and exclusion criteria

PICO (Patient, Population, or Problem; Intervention, Prognostic Factor, or Exposure; Comparison or Intervention (if appropriate); Outcome) [36] for inclusion and exclusion criteria were determined as follows: Inclusion criteria were all epidemiological studies about the prevalence of PKU that have been peer-reviewed at least in the form of abstract. Exclusion criteria were: 1) duplicate studies; 2) sample size other than infants (over 28 days of age); 3) non-random sample size; 4) non-Iranian studies; 5) being irrelevant; 6) sample size smaller than 200 participants; 7) participants with certain diseases (e.g. mental retardation and etc); 8) unknown diagnostic intervention; 9) poor quality qualitative evaluation; 10), case reports, review articles, and letters to the editor without quantitative data.

Study selection

The title and abstract of all identified documentations were screened. Then, we evaluated the full text of the articles according to the inclusion and exclusion criteria. Finally, the raised disagreements were discussed and resolved in the presence of all authors.

Definitions

Suspected cases of HPA were defined as Phe serum levels in primary NBS (in some sources 2 mg/dl and in some 4 mg/dl), and PKU was diagnosed in suspected cases of HPA after confirmatory tests. In this study, PKU it relates to all degrees of HPA, and PKU was classified into two categories: 1. Phe concentrations between (2 or 4) and 20 were considered as mild to moderate HPA, and 2. Phe concentrations above 20 were considered as classical PKU [4].

Data extraction

Data extracted by the authors included first author's name, email of the corresponding author or the first author, year of publication, region/province, year of study, sample size (total, boys and girls), data collection method, diagnostic criteria, prevalence for each variable (suspected HPA, PKU, and types of PKU), and finally the extracted data were entered into Excel software (XP professional edition; Microsoft, Redmond, Washington, USA).

For duplicate publications, we contacted the corresponding author or the first author to clarify the original publication, and if we did not receive a response, we selected the study with the largest number of participants for overlapping cases. We also contacted the corresponding author when the article data was incomplete or ambiguous and resolved the problem.

Quality evaluation

As all studies eventually included the prevalence, so the quality of the studies was evaluated using a checklist for cross-sectional/prevalence studies by the modified Newcastle-Ottawa Scale (NOS) [37]. The quality of articles was classified into three categories of low, medium and high. Scoring was considered 0–5, 6–7, and 8–9, respectively, and studies with poor quality excluded.

Statistical analysis

Heterogeneity among studies was assessed by I^2 and Q tests. Interpretation of heterogeneity based on I^2 Index

is as follows: less than 25% (low heterogeneity), 25-49% (moderate heterogeneity) and 50-75% (considerable heterogeneity), and greater than 75% (high heterogeneity), and *P*-value less than 0.10 is statistically significant [38, 39]. In cases of low heterogeneity, the fixed effects model was used, and in other cases, the random effects model was used for data integration. Girls-boys Odds Ratio (OR) was used to indicate the effect of gender on suspected HPA and PKU, using HPA and PKU positive cases in both genders and the total sample size. To explore the cause of heterogeneity, subgroup analysis was done based on the region and the province of study, and sensitivity analysis was used to measure the overall estimation power by omitting one study at a time. Mixedeffects meta-regression was used to investigate the association between continuous variables such as the effect of time of study on prevalence. Publication bias was assessed by a visual survey of the funnel plot for skewed distribution, and using the Begg and Egger's tests [40, 41]. All meta-analyses were performed using Comprehensive Meta-Analysis Software (CMA) ver. 2. P < 0.05was considered significant in all tests.

Results

Search results and the features of studies included the meta-analysis

Figure 1 shows the flowchart of the selection of studies. Systematic search on databases and references identified 2126 related papers. Subsequently, 421 duplicate articles and 1672 unrelated articles were removed by reviewing the title and abstract. Then, 56 studies were excluded after reviewing the full-text since they did not meet the eligibility criteria. Finally, 18 studies with 3,339,327 Iranian neonates were included (Fig. 1).

Studies by Abbaskhanian A. et al. [16], Motamedi N. et al. [18], and Ganji F. et al. [28] were considered as more than one study each since they reported information in more than one population. All studies had appropriate quality to enter the meta-analysis (Table 1).

Prevalence of suspected hyperphenylalaninemia

Heterogeneity was high for these studies (I² = 98.41%; P < 0.001). The prevalence of suspected HPA in 873,174 Iranian neonates was estimated to be 45.6/100,000 (95% CI: 23.9–87.1) (Fig. 2 a). The lowest prevalence was related to the study of Soori in 2016–2017 (8.8/100,000) and the highest prevalence was related to the study of Abbaskhanian in 2017 (600.1/100,000).

Prevalence of suspected hyperphenylalaninemia based on gender

The prevalence of suspected HPA in 285,331 girls infants and 297,347 boys infants in Iran was estimated to be 38.0/100,000 (95% CI: 15.1-95.5) and 43.3/100,000





(95% CI: 16.2-116.2), respectively (Fig. 2 b-c). The girlsboys OR of suspected HPA was not significant (OR = 0.90 (95% CI: 0.75–1.08; P = 0.259) (Fig. 2-d).

Subgroup analysis of the prevalence of suspected hyperphenylalaninemia

Subgroup analysis of the prevalence of suspected HPA based on five geographical regions and provinces in Iran showed significant differences with P < 0.007 and P < 0.001, respectively, but it was not significant in terms of the quality of studies (P = 0.241) (Fig. 3).

Prevalence of phenylketonuria

Heterogeneity was high for the studies ($I^2 = 82.56\%$; P < 0.001). The prevalence of PKU in 3,000,917 Iranian neonates was estimated to be 16.5/100,000 (95% CI: 12.9–21.2). The lowest and highest prevalence was related to the studies of Abbaskhanian et al. (2.3/100,000) and Badiee et al. (144.3/100,000) (Fig. 4), respectively.

Prevalence of phenylketonuria based on gender

The prevalence of PKU in 285,331 girls and 297,347 boys infants was estimated to be 13.3/100,000 (95% CI: 9.3-19.0) and 10.9/100,000 (95% CI: 7.5–15.8), respectively. The girls-boys OR of PKU prevalence was not significant (OR = 1.58 (95% CI: 0.66–2.02, P = 0.606) (Fig. 5).

Subgroup analysis of phenylketonuria prevalence

The prevalence of PKU in West, East, North, South and Center of Iran was estimated to be 19.4/100,000 (95% CI: 15.1–24.9), 31.9/100,000 (95% CI: 9.0–113.3), 7.9/100,000 (95% CI: 4.7–13.1), 17.2/100,000 (95% CI: 13.6–21.8) and 21.3/100,000 (95% CI: 10.2–44.6), respectively, and the differences in subgroup analysis were significant (P < 0.001). In subgroup analysis based on province, the lowest and highest prevalence of PKU was in Golestan (5.4/100,000) and Isfahan (58.4/100,000) provinces, respectively and the difference was significant (P < 0.001).

In subgroup analysis based on the quality of studies, the prevalence of PKU in medium and high-quality studies was estimated to be 22.2/100,000 (95% CI: 15.6-31.5)

				`									
Ref	First author, Published Year	Year	Place	Design	Age (day)	Method	Sample size		Suspected HPA ^a	PKU p	Classic PKU	HPA 0	Quality
							Female	Male All					
[14]	Senemar S, 2009	2000-5	Fars	Screening program	m	Fluorometric		70,477		15	Ν	13 13	Aedium sk
[15]	Habib A, 2010	2004-7	Fars	Screening program	3-5	Colorimetric and HPLC	87,091	88,143 175,235	30	28		< '	Aedium sk
[16]	Abbaskhanian A, 2017	2007– 2015	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	193,229	214, 407,244 015				< '	Aedium sk
[16]	Abbaskhanian A, 2017	2007	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	20,759	21,569 42,328	254	2	-	- 2	Aedium sk
[16]	Abbaskhanian A, 2017	2008	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	22,506	23,197 45,703	99	2	0	~ <u>-</u>	Aedium sk
[16]	Abbaskhanian A, 2017	2009	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	22,050	23,392 45,442	92	7	-	6 L	ow risk
[16]	Abbaskhanian A, 2017	2010	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	21,447	22,973 44,420	19	e	1	~ '2	Aedium sk
[16]	Abbaskhanian A, 2017	2011	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	21,168	23,374 44,342	11	. 	0	1	ow risk
[16]	Abbaskhanian A, 2017	2012	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	21,719	22,633 44,352	7	2	-	7 12	Aedium sk
[16]	Abbaskhanian A, 2017	2013	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	22,738	23,256 45,994	IJ	e	0	3 L	ow risk
[16]	Abbaskhanian A, 2017	2014	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	22,672	24,548 47,220	Q	4	1	∼ :⊑	Aedium sk
[16]	Abbaskhanian A, 2017	2015	Mazandaran	Screening program	3-5	Colorimetric method and HPLC technique	23,181	24,262 47,443	IJ	e	1	2 L	ow risk
[1]	Ordooei M, 2015	2010-11	Yazd	Screening program	m	Colorimetric method and HPLC technique		22,131		4	1	~ :⊑ M	Aedium sk
[18]	Motamedi N, 2017	2006	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		33,284		4		< '⊑	Aedium sk
[18]	Motamedi N, 2017	2007	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		33,890		-2		2 12	Aedium sk
[18]	Motamedi N, 2017	2008	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		34,045		7		2 12	Aedium sk
[18]	Motamedi N, 2017	2009	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		35,969		-2		< '⊑	Aedium sk
[18]	Motamedi N, 2017	2010	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		35,011		9		∠ ⊑	Aedium sk
[18]	Motamedi N, 2017	2011	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		35,799		10		< 1	Aedium sk
[18]	Motamedi N, 2017	2012	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique		37,154		9			ow risk

Table 1 Summary of characteristics in studies into a meta-analysis

Table	1 Summary of ch	aracteristi	cs in studies into a r	neta-analysis (Co	ontinued)									
Ref Fi Y€	rst author, Published sar	Year	Place	Design	Age (day)	Method	Sample size		Susp HPA	ected	PKU ^b CI	lassic KU	HPA (Quality
[18] M	lotamedi N, 2017	2013	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique			37,944		4			Medium isk
[18] M.	iotamedi N, 2017	2014	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique			39,388		15			ow risk
[18] M	lotamedi N, 2017	2015	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique			38,585		Ŋ			Medium isk
[18] M	lotamedi N, 2017	2016	Lorestan	Screening program	Infancy	Colorimetric, ELISA and HPLC technique			36,585		7			ow risk
[19] Aj	iami A, 2013	2012-13	Isfahan	Screening program	Infancy	Colorimetric method and HPLC technique			77,000		45	12	33 1	Medium isk
[20] N	asiri Sh, 2013	2012-13	South Khorasan	Screening program	m	Colorimetric method and HPLC technique			26,455	31	23		_	-ow risk
[<mark>2</mark> 1] M 20	lodares Sadrani N,)13	2012-13	Ardebil	Screening program	m	Colorimetric method and HPLC technique			44,232		13	00	- 1	Medium isk
[22] M	iorovatdar N, 2015	2013	Razavi Khorasan	Screening program	Infancy	Colorimetric method and HPLC technique			69,347		4			Medium isk
[<mark>23</mark>] S¿	aadatinasab Z, 2015	2012-14	South Khorasan	Screening program	Neonatal	Colorimetric method and HPLC technique			30,103	55	e			Medium isk
[24] Bč	adiee M, 2014	2011–13	Torbat Heydariy	Screening program	Neonatal	Colorimetric method and HPLC technique	5390	5701	11,091		16	-	15	Medium isk
[25] K _č	aramifar H, 2010	2007–8	Fars	Screening program	3-5	Colorimetric method and HPLC technique	35,470	41,496	76,966	6	Ø	m	5	Medium isk
[26] Sc	oori M, 2018	2016–17	Nahavand	Screening program	Neonatal	Immuno-enzymatic method			5704	0	0	0	0	Medium isk
[27] H.	eydari A, 2016	2013	All Iran	Screening program	Neonatal	Colorimetric method and HPLC technique			1,356, 132		322			Medium isk
[<mark>28</mark>] G	anji F, 2018	2012	Chaharmahal and Bakhtiari	Screening program	1-5	Colorimetric method and HPLC technique			13,022		-		_	-ow risk
[<mark>28</mark>]	anji F, 2018	2013	Chaharmahal and Bakhtiari	Screening program	1-5	Colorimetric method and HPLC technique			19,612		4			Medium isk
[28] 1	anji F, 2018	2014	Chaharmahal and Bakhtiari	Screening program	1-5	Colorimetric method and HPLC technique			19,753		e			-ow risk
[<mark>28</mark>] C	anji F, 2018	2015	Chaharmahal and Bakhtiari	Screening program	1-5	Colorimetric method and HPLC technique			20,893		ς.		~ 1	Medium isk
[29] M.	lahmoodi M, 2013	2012-13	Golestan	Screening program	Neonatal	Colorimetric method and HPLC technique			74,000	32	4			ow risk
[30] B¢	ehineh M, 2015	2007– 2014	Khonj	Screening program	3-5	Fluorometric			6399		2			Medium isk
[31] R¢ 2(ezabigidavarani E,)18	2012– 2016	Kerman	Screening program	At birth	Colorimetric method and HPLC technique			77,467	85	15	2	13 1	-ow risk
^a hyper ^b Pheny	phenylalaninemia /lketonuria													

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Heterogeneity: I²= 2.51; P=0.416

leta Analysi

Fig. 2 Prevalence of suspected hyperphenylalaninemia in all (a), girls (b), and boys (c) and girls to boys odds ratio (d) in national neonate screening program in Iran

0.01

0.1

100

10

Study name	Subgroup within geographical regions		Statist	ics for eac	ch study		_ <u>Ev</u>	ent rate and 95% CI	
		Event rate	Lower limit	Upper limit	Z-Value	p-Value			Relative
Nasiri Sh, 2013	East	0.001172	0.000824	0.001666	-37.549	0.000	1 4	1	46.44
Saadatinasab Z, 2015	East	0.001827	0.001403	0.002379	-46.703	0.000			53.56
		0.001487	0.000963	0.002294	-29.344	0.000	•		
Abbaskhanian A, 2017 (2)	North	0.006001	0.005308	0.006783	-81.193	0.000			10.45
Abbaskhanian A, 2017 (3)	North	0.001444	0.001135	0.001838	-53.083	0.000			10.39
Abbaskhanian A, 2017 (4)	North	0.002025	0.001651	0.002483	-59.412	0.000	-		10.41
bbaskhanian A, 2017 (5)	North	0.000428	0.000273	0.000670	-33.803	0.000	-		10.19
bbaskhanian A, 2017 (6)	North	0.000248	0.000137	0.000448	-27.530	0.000	-		9.99
Abbaskhanian A, 2017 (7)	North	0.000158	0.000075	0.000331	-23.159	0.000			9.73
Abbaskhanian A, 2017 (8)	North	0.000109	0.000045	0.000261	-20.407	0.000	•		9.46
Abbaskhanian A, 2017 (9)	North	0.000127	0.000057	0.000283	-21.972	0.000	-		9.62
Abbaskhanian A, 2017 (10)	North	0.000105	0.000044	0.000253	-20.476	0.000	-		9.46
Mahmoodi M, 2013	North	0.000432	0.000306	0.000611	-43.807	0.000	-		10.30
		0.000443	0.000186	0.001056	-17.422	0.000	•		
labib A, 2010	South	0.000171	0.000120	0.000245	-47.497	0.000			33.67
Karamifar H, 2010	South	0.000117	0.000061	0.000225	-27.160	0.000			32.25
Rezabigidavarani E, 2018	South	0.001097	0.000887	0.001357	-62.786	0.000			34.08
		0.000285	0.000063	0.001293	-10.579	0.000			
oori M, 2018	West	0.000088	0.000005	0.001400	-6.606	0.000			100.00
		0.000088	0.000005	0.001400	-6.606	0.000			

B

Study name	Subgroup within provinces		Statis	tics for ea	ach study	-	_	Event rate and 95% CI	_	
		Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Habib A, 2010	Fars	0.000171	0.000120	0.000245	-47.497	0.000		1	1	76.76
Karamifar H, 2010	Fars	0.000117	0.000061	0.000225	-27.160	0.000	•			23.24
		0.000157	0.000114	0.000215	-54.403	0.000				
Mahmoodi M, 2013	Golestan	0.000432	0.000306	0.000611	-43.807	0.000				100.00
		0.000432	0.000306	0.000611	-43.807	0.000	•			
Soori M, 2018	Hamadan	0.000088	0.000005	0.001400	-6.606	0.000	-			100.00
		0.000088	0.000005	0.001400	-6.606	0.000				
Rezabigidavarani E, 2018	Kerman	0.001097	0.000887	0.001357	-62.786	0.000				100.00
		0.001097	0.000887	0.001357	-62.786	0.000	•			
Abbaskhanian A, 2017 (2)	Mazandaran	0.006001	0.005308	0.006783	-81.193	0.000				11.67
Abbaskhanian A, 2017 (3)	Mazandaran	0.001444	0.001135	0.001838	-53.083	0.000	-			11.60
Abbaskhanian A, 2017 (4)	Mazandaran	0.002025	0.001651	0.002483	-59.412	0.000	-	-		11.63
Abbaskhanian A, 2017 (5)	Mazandaran	0.000428	0.000273	0.000670	-33.803	0.000	-			11.37
Abbaskhanian A, 2017 (6)	Mazandaran	0.000248	0.000137	0.000448	-27.530	0.000	-			11.14
Abbaskhanian A, 2017 (7)	Mazandaran	0.000158	0.000075	0.000331	-23.159	0.000	-			10.84
Abbaskhanian A, 2017 (8)	Mazandaran	0.000109	0.000045	0.000261	-20.407	0.000				10.53
Abbaskhanian A, 2017 (9)	Mazandaran	0.000127	0.000057	0.000283	-21.972	0.000	•			10.71
Abbaskhanian A, 2017 (10)	Mazandaran	0.000105	0.000044	0.000253	-20.476	0.000				10.53
		0.000446	0.000182	0.001093	-16.839	0.000	-			
Nasiri Sh, 2013	South Khorasan	0.001172	0.000824	0.001666	-37.549	0.000	-			46.44
Saadatinasab Z, 2015	South Khorasan	0.001827	0.001403	0.002379	-46.703	0.000		-		53.56
		0.001487	0.000963	0.002294	-29.344	0.000		•		
Test for subgroup differen	ann 0-122 874 df(0)-	5 D < 0.0	01				0.00	0.01	0.01	

Test for subgroup differences: Q=122.874, df(Q)=5, P< 0.001

С

Study name	Subgroup within quality of studies	_	Statisti	cs for each	study			Event rate and 95% CI	_	
		Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Habib A, 2010	High	0.000171	0.000120	0.000245	-47.497	0.000			1	8.54
Abbaskhanian A, 2017 (2)	High	0.006001	0.005308	0.006783	-81.193	0.000				8.67
Abbaskhanian A, 2017 (3)	High	0.001444	0.001135	0.001838	-53.083	0.000	•			8.62
Abbaskhanian A, 2017 (4)	High	0.002025	0.001651	0.002483	-59.412	0.000	•			8.64
Abbaskhanian A, 2017 (5)	High	0.000428	0.000273	0.000670	-33.803	0.000				8.46
Abbaskhanian A, 2017 (6)	High	0.000248	0.000137	0.000448	-27.530	0.000				8.31
Abbaskhanian A, 2017 (7)	High	0.000158	0.000075	0.000331	-23.159	0.000				8.11
Abbaskhanian A, 2017 (8)	High	0.000109	0.000045	0.000261	-20.407	0.000	•			7.90
Abbaskhanian A, 2017 (9)	High	0.000127	0.000057	0.000283	-21.972	0.000				8.02
Abbaskhanian A, 2017 (10)	High	0.000105	0.000044	0.000253	-20.476	0.000	•			7.90
Saadatinasab Z, 2015	High	0.001827	0.001403	0.002379	-46.703	0.000				8.61
Karamifar H, 2010	High	0.000117	0.000061	0.000225	-27.160	0.000	•			8.23
		0.000414	0.000183	0.000937	-18.667	0.000	1			
Nasiri Sh, 2013	Moderate	0.001172	0.000824	0.001666	-37.549	0.000				31.17
Soori M, 2018	Moderate	0.000088	0.000005	0.001400	-6.606	0.000	±			4.02
Mahmoodi M, 2013	Moderate	0.000432	0.000306	0.000611	-43.807	0.000				31.28
Rezabigidavarani E, 2018	Moderate	0.001097	0.000887	0.001357	-62.786	0.000				33.53
		0.000756	0.000419	0.001365	-23.830	0.000				
								1	1	
Test for subgroup diffe	erences: Q=1.374, df(Q)=	=1, P= ().241				0.00	0.50	1.00	

Meta Analysis

Fig. 3 Subgroup analysis of suspected hyperphenylalaninemia prevalence based on geographical regions (a), provinces (b) and the quality of studies (c) in national neonate screening program in Iran

Event Intel Lower Intel Upper Intel Value Mediation Senemar S, 2009 0.000120 0.000121 0.000231 48.252 0.000 3.36 Habb A, 2017 (2) 0.000140 0.00011 0.000175 1-14.194 0.000 1.77 Abbashanian A, 2017 (3) 0.000144 0.0000175 1-14.194 0.000 1.77 Abbashanian A, 2017 (5) 0.000022 0.00029 1-6.632 0.000 1.77 Abbashanian A, 2017 (7) 0.00023 0.000020 0.0000 1.77 Abbashanian A, 2017 (7) 0.00024 0.00021 0.00022 16.682 0.000 1.77 Abbashanian A, 2017 (7) 0.00045 0.00021 0.000220 16.682 0.000 2.44 Abbashanian A, 2017 (10) 0.00045 0.00021 1.7225 0.000 2.44 Abbashanian A, 2017 0.00045 0.00024 1.8722 0.000 2.44 Abbashanian A, 2017 0.000148 <td< th=""><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th><th></th></td<>									
Senemar S, 2008 0.000128 0.000213 -82.742 0.000 3.33 Habib A, 2010 0.000160 0.000110 0.000121 -46.252 0.000 3.66 Abbashknian A, 2017 (2) 0.000147 0.000175 -14.194 0.000 17.77 Abbashknian A, 2017 (3) 0.000168 0.000010 -14.194 0.000 17.77 Abbashknian A, 2017 (6) 0.000043 0.00022 -16.632 0.000 17.71 Abbashknian A, 2017 (7) 0.000045 0.000010 -14.191 0.000 17.71 Abbashknian A, 2017 (1) 0.000065 0.000022 -16.682 0.000 17.71 Abbashknian A, 2017 (1) 0.000065 0.000202 -16.752 0.000 12.16 Abbashknian A, 2017 (1) 0.000065 0.000120 -16.752 0.000 12.16 Oridooil M, 2015 0.000161 0.00026 -16.752 0.000 12.16 Abbashknian A, 2017 (1) 0.000161 0.000381 -18.752 0.000 2.46 Motarmedi N, 2		Event rate	Lower limit	Upper limit	Z-Value	p-Value			Relative weight
Habib A, 2010 0.000160 0.000110 0.000231 -46.252 0.000 17.7 Abbaskhanian A, 2017 0.000047 0.00012 0.00012 0.00012 0.00013 1.48.95 0.000 17.7 Abbaskhanian A, 2017 0.000068 0.000023 -23.223 0.000 17.7 Abbaskhanian A, 2017 0.000068 0.000023 -0.00023 -23.223 0.000 12.11 Abbaskhanian A, 2017 0.000068 0.000023 -0.0002 16.632 0.000 12.11 Abbaskhanian A, 2017 0.000065 0.000022 -16.572 0.000 17.7 Abbaskhanian A, 2017 0.000068 0.000022 -16.746 0.000 12.11 Abbaskhanian A, 2017 0.000068 0.000021 -16.746 0.000 12.11 Abbaskhanian A, 2017 0.000170 0.000184 0.000021 -18.722 0.000 12.12 Abbaskhanian A, 2017 0.000170 0.000184 0.000018 0.00018 0.00018 0.00018 0.00018 0.00018 <	Senemar S, 2009	0.000213	0.000128	0.000353	-32.742	0.000			3.37
Abbaskhanian A, 2017 (2) 0.000012 0.00018 14.085 0.000 17.7 Abbaskhanian A, 2017 (3) 0.000014 0.000175 1.41.194 0.000 2.9 Abbaskhanian A, 2017 (4) 0.000013 0.00022 2.32.23 0.000 2.9 Abbaskhanian A, 2017 (6) 0.000023 0.00022 0.0000 0.0000 2.11 Abbaskhanian A, 2017 (7) 0.000023 0.000120 1.6682 0.000 2.11 Abbaskhanian A, 2017 (7) 0.000085 0.00022 1.6892 0.000 2.14 Abbaskhanian A, 2017 (10) 0.00022 0.00022 1.8592 0.000 2.44 Abbaskhanian A, 2017 (10) 0.00018 0.00022 1.852 0.000 2.44 Motamedi N, 2017 (1) 0.00014 0.00034 1.7235 0.000 2.44 Motamedi N, 2017 (1) 0.00014 0.00034 1.7245 0.000 2.44 Motamedi N, 2017 (1) 0.00015 0.00034 1.7235 0.000 2.44 Motamedi N, 2017 (6) 0.00017 0.00034 1.2485 0.000 2.44 Mota	Habib A, 2010	0.000160	0.000110	0.000231	-46.252	0.000			3.60
Abbaskhanian A, 2017 (3) 0.000011 0.000175 -1.1194 0.000 17.7 Abbaskhanian A, 2017 (4) 0.000073 0.00022 -23.223 0.000 2.11 Abbaskhanian A, 2017 (5) 0.000028 0.00022 -16.632 0.000 2.11 Abbaskhanian A, 2017 (7) 0.000045 0.000021 0.00022 -16.632 0.000 1.11 Abbaskhanian A, 2017 (8) 0.000045 0.00022 -16.692 0.000 2.11 Abbaskhanian A, 2017 (9) 0.000085 0.00022 -18.692 0.000 2.11 Abbaskhanian A, 2017 (1) 0.000085 0.00022 -18.692 0.000 2.11 Abbaskhanian A, 2017 (1) 0.000085 0.00022 -18.692 0.000 2.12 Abbaskhanian A, 2017 (1) 0.000120 0.00041 -17.25 0.000 2.44 Motamedi N, 2017 (1) 0.000148 0.00031 -2.2488 0.000 2.44 Motamedi N, 2017 (3) 0.00026 0.000381 -2.239 0.000 2.75 Motamedi N, 2017 (5) 0.000171 0.000278 -2.2873 0.000 2.	Abbaskhanian A, 2017 (2)	0.000047	0.000012	0.000189	-14.085	0.000			1.77
Abbaskhanian A, 2017 (4) 0.000173 0.000223 22.223 0.000 2.97 Abbaskhanian A, 2017 (5) 0.000086 0.00022 0.000229 -16.632 0.000 2.16 Abbaskhanian A, 2017 (7) 0.000085 0.000021 0.000160 -14.151 0.000 2.16 Abbaskhanian A, 2017 (7) 0.000085 0.000222 -16.692 0.000 2.14 Abbaskhanian A, 2017 (10) 0.000085 0.000220 -16.692 0.000 2.44 Abbaskhanian A, 2017 (10) 0.000181 0.000086 0.000411 1.72.25 0.000 2.44 Motamedi N, 2017 (1) 0.000181 0.000086 0.000411 1.24.85 0.000 2.44 Motamedi N, 2017 (2) 0.000181 0.000261 -18.552 0.000 2.44 Motamedi N, 2017 (3) 0.000270 0.000381 -22.89 0.000 2.44 Motamedi N, 2017 (4) 0.000170 0.000371 -22.89 0.000 2.47 Motamedi N, 2017 (6) 0.000170 0.000281 -22.89 0.000 2.47 Motamedi N, 2017 (7) 0.000170 0	Abbaskhanian A, 2017 (3)	0.000044	0.000011	0.000175	-14.194	0.000	■		1.77
Abbaskhanian A, 2017 (5) 0.00008 0.00003 0.000180 -16.632 0.000 1.14 Abbaskhanian A, 2017 (7) 0.000045 0.00011 0.000180 -14.151 0.000 2.11 Abbaskhanian A, 2017 (7) 0.000045 0.000022 -16.692 0.000 2.14 Abbaskhanian A, 2017 (1) 0.000085 0.00022 -16.746 0.000 2.14 Abbaskhanian A, 2017 (1) 0.000145 0.00022 -16.746 0.000 2.44 Abbaskhanian A, 2017 (1) 0.000145 0.00020 -16.746 0.000 2.44 Motarmedi N, 2017 (1) 0.000145 0.00045 -19.724 0.000 2.64 Metarmedi N, 2017 (2) 0.00148 0.00058 -19.724 0.000 2.64 Metarmedi N, 2017 (3) 0.000279 0.00058 -12.248 0.000 2.75 Metarmedi N, 2017 (6) 0.000719 0.00028 -12.249 0.000 2.76 Metarmedi N, 2017 (7) 0.000279 0.00028 -2.2483 0.000 2.76 Metarmedi N, 2017 (10) 0.000150 0.000219 -2.6673 0.00	Abbaskhanian A, 2017 (4)	0.000154	0.000073	0.000323	-23.223	0.000			2.91
Abbaskhanian A, 2017 (6) 0.000023 0.000160 -10.700 0.000 11.11 Abbaskhanian A, 2017 (7) 0.000045 0.00011 0.000180 -14.151 0.000 12.71 Abbaskhanian A, 2017 (9) 0.000085 0.000020 0.000220 -16.692 0.000 2.44 Abbaskhanian A, 2017 (9) 0.000180 0.000120 0.000220 -16.746 0.000 2.44 Abbaskhanian A, 2017 (10) 0.000180 0.000220 0.000220 -18.652 0.000 2.44 Motamedi N, 2017 (1) 0.000180 0.000241 -12.725 0.000 2.44 Motamedi N, 2017 (2) 0.000180 0.000320 -18.652 0.000 2.44 Motamedi N, 2017 (3) 0.000270 0.000371 -2.248 0.000 2.64 Motamedi N, 2017 (5) 0.000171 0.000359 -2.1385 0.000 2.77 Motamedi N, 2017 (6) 0.000290 0.000211 -2.8173 0.000 2.44 Motamedi N, 2017 (7) 0.00161 0.000141 -2.248 0.000 2.77 Motamedi N, 2017 (10) 0.000170 0.	Abbaskhanian A, 2017 (5)	0.000068	0.000022	0.000209	-16.632	0.000			2.16
Abbaskhanian A, 2017 (7) 0.000045 0.00011 0.000180 -14.151 0.000 17.7 Abbaskhanian A, 2017 (8) 0.00028 0.000226 -16.692 0.000 2.14 Abbaskhanian A, 2017 (10) 0.000083 0.00026 -16.772 0.000 2.44 Abbaskhanian A, 2017 (10) 0.00045 0.000320 -16.672 0.000 2.44 Motamedi N, 2017 (10) 0.00045 0.000320 -16.652 0.000 2.44 Votamedi N, 2017 (2) 0.000148 0.000320 -18.052 0.000 2.64 Votamedi N, 2017 (3) 0.00026 0.000384 -19.857 0.000 2.64 Votamedi N, 2017 (5) 0.000171 0.000374 -19.857 0.000 2.76 Votamedi N, 2017 (6) 0.000779 0.000381 -21.239 0.000 2.77 Votamedi N, 2017 (7) 0.000150 0.000731 -20.014 0.000 2.77 Votamedi N, 2017 (10) 0.000164 0.000731 -20.014 0.000 2.77 Votamedi N, 20	Abbaskhanian A, 2017 (6)	0.000023	0.000003	0.000160	-10.700	0.000	•		1.14
Abbaskhanian A, 2017 (8) 0.00025 0.00022 -16.692 0.000 2.16 Abbaskhanian A, 2017 (9) 0.00025 0.000228 -18.752 0.000 2.44 Abbaskhanian A, 2017 (10) 0.000218 0.000228 -18.752 0.000 2.44 Abbaskhanian A, 2017 (11) 0.000120 0.000248 -16.752 0.000 2.44 Mctarmedi N, 2017 (2) 0.000141 0.000354 -19.724 0.000 2.66 Mctarmedi N, 2017 (4) 0.000179 0.000354 -19.724 0.000 2.64 Mctarmedi N, 2017 (5) 0.000170 0.000374 -21.239 0.000 2.75 Mctarmedi N, 2017 (6) 0.000170 0.000379 -21.385 0.000 2.75 Mctarmedi N, 2017 (7) 0.000161 0.000279 0.000159 -21.385 0.000 2.44 Mctarmedi N, 2017 (7) 0.000140 0.000281 -18.314 0.000 2.44 Mctarmedi N, 2017 (10) 0.000191 0.00041 -22.649 0.000 2.44 Mctarmedi N, 2017 (11) 0.000191 0.000194 0.000141 -22.649 <td< td=""><td>Abbaskhanian A, 2017 (7)</td><td>0.000045</td><td>0.000011</td><td>0.000180</td><td>-14.151</td><td>0.000</td><td>•</td><td></td><td>1.77</td></td<>	Abbaskhanian A, 2017 (7)	0.000045	0.000011	0.000180	-14.151	0.000	•		1.77
Abbaskhanian A, 2017 (9) 0.000085 0.000022 -18.752 0.000 244 Abbaskhanian A, 2017 (10) 0.000083 0.000020 0.000186 -16.746 0.000 244 Abbaskhanian A, 2017 (10) 0.000180 0.000084 1.77.235 0.000 244 Motamedi N, 2017 (12) 0.000148 0.000084 1.77.245 0.000 244 Motamedi N, 2017 (14) 0.000198 0.000084 1.72.488 0.000 269 Motamedi N, 2017 (15) 0.000171 0.000058 0.000334 -19.757 0.000 269 Motamedi N, 2017 (16) 0.000170 0.000381 -24.458 0.000 217 Motamedi N, 2017 (17) 0.000150 0.00059 -25.673 0.000 217 Motamedi N, 2017 (10) 0.000150 0.00059 -25.733 0.000 217 Motamedi N, 2017 (10) 0.000150 0.000220 0.0000 217 217 Motamedi N, 2017 (10) 0.000150 0.000230 0.0000 216 217	Abbaskhanian A, 2017 (8)	0.000065	0.000021	0.000202	-16.692	0.000			2.16
Abbaskhanian A, 2017 (10) 0.000063 0.000196 -16.746 0.000 216 Ordose M, 2015 0.000181 0.000045 0.000320 -18.052 0.000 244 Wotamedi N, 2017 (1) 0.000141 0.000045 0.000320 -18.052 0.000 244 Wotamedi N, 2017 (3) 0.000266 0.000384 -19.724 0.000 264 Wotamedi N, 2017 (4) 0.000198 0.000384 -19.857 0.000 264 Wotamedi N, 2017 (5) 0.000170 0.000399 -21.385 0.000 277 Wotamedi N, 2017 (7) 0.000161 0.000279 0.000159 -21.385 0.000 311 Wotamedi N, 2017 (7) 0.000161 0.000281 -18.314 0.000 277 Wotamedi N, 2017 (10) 0.000130 0.000281 -30.485 0.000 333 Wotamedi N, 2017 (10) 0.000130 0.000278 0.00141 -22.494 0.000 264 Wotamedi N, 2013 0.000278 0.000150 -23.716 0.000 264 333 Wotamedi N, 2017 (10) 0.000171 0.000384	Abbaskhanian A, 2017 (9)	0.000085	0.000032	0.000226	-18.752	0.000			2.44
Drdozei M, 2015 0.000181 0.000088 0.000481 -17.235 0.000 244 Wdarmedi N, 2017 (1) 0.000120 0.0000354 -19.052 0.000 244 Wdarmedi N, 2017 (2) 0.000180 0.000354 -19.774 0.000 246 Wdarmedi N, 2017 (4) 0.000170 0.000354 -19.774 0.000 256 Wdarmedi N, 2017 (5) 0.000171 0.000371 -22.458 0.000 266 Wdarmedi N, 2017 (7) 0.000170 0.000381 -21.239 0.000 276 Wdarmedi N, 2017 (7) 0.000161 0.000279 0.000159 -25.873 0.000 276 Wdarmedi N, 2017 (7) 0.000161 0.000281 -18.314 0.000 244 Wdarmedi N, 2017 (10) 0.000129 0.000321 -30.485 0.000 249 Wdarmedi N, 2017 (10) 0.000184 0.000278 -0.000 297 30.485 0.000 297 Nasiri Sh, 2013 0.000284 0.000778 -49.923 0.000 297 33.781 0.000 244 Saadatinasab Z, 2015 0.000100 </td <td>Abbaskhanian A, 2017 (10)</td> <td>0.000063</td> <td>0.000020</td> <td>0.000196</td> <td>-16.746</td> <td>0.000</td> <td></td> <td></td> <td>2.16</td>	Abbaskhanian A, 2017 (10)	0.000063	0.000020	0.000196	-16.746	0.000			2.16
Wotamedi N, 2017 (1) 0.000120 0.000045 0.000320 -18.052 0.000 244 Wotamedi N, 2017 (2) 0.000148 0.000054 -19.724 0.000 256 Wotamedi N, 2017 (3) 0.000206 0.000334 -19.857 0.000 256 Wotamedi N, 2017 (5) 0.000171 0.000270 0.000354 -21.239 0.000 311 Wotamedi N, 2017 (6) 0.000150 0.000354 -21.385 0.000 311 Wotamedi N, 2017 (7) 0.000161 0.000279 0.000354 -21.385 0.000 311 Wotamedi N, 2017 (7) 0.000161 0.000230 0.000321 -21.385 0.000 244 Wotamedi N, 2017 (10) 0.000130 0.000230 -20.014 0.000 246 Wotamedi N, 2017 (10) 0.000191 0.000041 -22.649 0.000 256 Wotamedi N, 2017 (11) 0.000191 0.000058 -37.761 0.000 37 Wotamedi N, 2017 (11) 0.000196 0.00078 -37.81 0.000 37 Wotamedi N, 2017 (11) 0.000584 0.00078 -37.81 <td>Ordooei M, 2015</td> <td>0.000181</td> <td>0.000068</td> <td>0.000481</td> <td>-17.235</td> <td>0.000</td> <td></td> <td></td> <td>2.44</td>	Ordooei M, 2015	0.000181	0.000068	0.000481	-17.235	0.000			2.44
Motamedi N, 2017 (2) 0.000148 0.000061 0.000354 -19.724 0.000 2.64 Motamedi N, 2017 (3) 0.000206 0.000388 0.000341 -22.458 0.000 2.64 Motamedi N, 2017 (4) 0.000179 0.000370 0.000384 -19.857 0.000 2.77 Motamedi N, 2017 (5) 0.000171 0.000279 0.000359 -21.335 0.000 2.77 Motamedi N, 2017 (6) 0.000160 0.000239 -21.385 0.000 2.77 Motamedi N, 2017 (10) 0.000105 0.000281 -18.314 0.000 2.44 Motamedi N, 2017 (10) 0.000130 0.000281 -30.485 0.000 2.64 Motamedi N, 2017 (10) 0.000191 0.000281 -20.49 0.000 2.64 Motamedi N, 2017 (10) 0.000194 0.000381 -20.014 0.000 2.64 Motamedi N, 2017 (10) 0.000194 0.000381 -20.014 0.000 2.64 Motamedi N, 2013 0.000284 0.000783 -49.923 0.000 2.64 Motamedi N, 2013 0.000284 0.00154 -19	Motamedi N, 2017 (1)	0.000120	0.000045	0.000320	-18.052	0.000			2.44
Watamedi N, 2017 (\$) 0.000206 0.000098 0.000431 -22.458 0.000 2.99 Watamedi N, 2017 (4) 0.000171 0.000381 -21.239 0.000 2.64 Watamedi N, 2017 (5) 0.000171 0.000377 0.000381 -21.239 0.000 2.75 Watamedi N, 2017 (7) 0.000161 0.000270 0.000359 -21.385 0.000 2.76 Watamedi N, 2017 (8) 0.000105 0.000202 0.000381 -20.1385 0.000 2.76 Watamedi N, 2017 (9) 0.000381 0.000220 0.000220 -21.385 0.000 2.76 Watamedi N, 2017 (10) 0.000130 0.000230 0.000320 -20.014 0.000 2.66 Watamedi N, 2017 (11) 0.000191 0.000091 0.000411 -22.649 0.000 2.99 Ayairi Sh, 2013 0.000584 0.000783 -49.923 0.000 3.72 Mataresb Sadrani N, 2013 0.000284 0.00171 0.000586 -29.316 0.000 3.30 Mataresb Z, 2015 0.000100 0.000232 0.000234 -26.414 0.000 3.42	Motamedi N, 2017 (2)	0.000148	0.000061	0.000354	-19.724	0.000	I		2.64
Wotamedi N, 2017 (4) 0.000139 0.000038 0.000334 -19.857 0.000 264 Motamedi N, 2017 (5) 0.000110 0.000519 -25.873 0.000 277 Wotamedi N, 2017 (6) 0.000150 0.000519 -25.873 0.000 277 Wotamedi N, 2017 (7) 0.000150 0.000529 -21.855 0.000 277 Wotamedi N, 2017 (9) 0.000381 0.000230 0.000632 -30.485 0.000 278 Wotamedi N, 2017 (10) 0.000105 0.000054 0.000311 -20.014 0.000 264 Wotamedi N, 2017 (10) 0.000171 0.000578 0.01308 -33.781 0.000 264 Votamedi N, 2013 0.000294 0.000174 -99.2316 0.000 33 Wotamedi N, 2013 0.000058 0.000323 -20.0154 -19.520 0.000 34 Saadatinasab Z, 2015 0.000100 0.000058 -29.316 0.000 24 246 Sadatinasab Z, 2016 0.0000277 0.000258 -25.540 0.000 24 266 Sadatinasab Z, 2016 0.0000	Motamedi N. 2017 (3)	0.000206	0.000098	0.000431	-22,458	0.000			2.91
Watamedi N, 2017 (5) 0.000171 0.000371 0.21239 0.000 277 Watamedi N, 2017 (6) 0.000170 0.000359 -21.239 0.000 3.15 Watamedi N, 2017 (7) 0.000116 0.000073 0.000359 -21.385 0.000 277 Watamedi N, 2017 (8) 0.000105 0.000281 -18.314 0.000 24 Watamedi N, 2017 (10) 0.000331 0.000282 -30.485 0.000 24 Watamedi N, 2017 (10) 0.000184 0.000041 -22.649 0.000 26 Watamedi N, 2017 (11) 0.000184 0.000783 -49.923 0.000 26 Vasiri Sh, 2013 0.000284 0.000174 -19.520 0.000 3.37 Vasiri Sh, 2013 0.000028 0.000124 -19.520 0.000 3.3 VaramiKar H, 2010 0.0000140 0.000282 -25.440 0.000 3.4 Sadeie M, 2014 0.00143 0.000282 -29.316 0.000 3.4 3.4 Sadeie M, 2014 0.000140 0.000282 -25.440 0.000 4 3.4 <t< td=""><td>Motamedi N. 2017 (4)</td><td>0.000139</td><td>0.000058</td><td>0.000334</td><td>-19.857</td><td>0.000</td><td>E I</td><td></td><td>2.64</td></t<>	Motamedi N. 2017 (4)	0.000139	0.000058	0.000334	-19.857	0.000	E I		2.64
Watamedi N, 2017 (6) 0.000279 0.000150 0.000219 -25.873 0.000 3.15 Motamedi N, 2017 (7) 0.000161 0.000073 0.000359 -21.385 0.000 2.75 Motamedi N, 2017 (8) 0.000130 0.000201 -18.314 0.000 2.44 Motamedi N, 2017 (9) 0.000381 0.000230 0.000632 -30.485 0.000 3.35 Motamedi N, 2017 (10) 0.000130 0.000054 0.00011 -22.649 0.000 2.64 Motamedi N, 2013 0.000584 0.000130 0.000073 -49.923 0.000 3.37 Vasiri Sh, 2013 0.000584 0.000171 0.00006 -29.316 0.000 3.37 Vocarediari N, 2015 0.000058 0.00022 0.00154 -19.520 0.000 3.32 Vocarediari N, 2015 0.000058 0.000233 -28.141 0.000 3.42 4.44 Saadatinasab Z, 2015 0.000100 0.000233 -25.940 0.000 3.45 Saadie R, 2014 0.000077 0.000213 0.000265 -149.734 0.000 3.45	Motamedi N, 2017 (5)	0.000171	0.000077	0.000381	-21,239	0.000			2.79
Mathematin, 2017 (7) 0.000161 0.000033 0.000359 -21.385 0.000 2.73 Motamedi N, 2017 (8) 0.000105 0.000031 0.000281 -18.314 0.000 2.44 Motamedi N, 2017 (9) 0.000381 0.000230 0.00032 -30.485 0.000 3.33 Motamedi N, 2017 (10) 0.000130 0.000401 -22.649 0.000 2.96 Motamedi N, 2017 (11) 0.0001580 0.000783 -49.923 0.000 3.73 Maini A, 2013 0.000584 0.000780 -3.3781 0.000 3.74 Motares Sadrani N, 2013 0.000580 0.000171 0.000566 -29.316 0.000 3.33 Motares Sadrani N, 2015 0.000184 0.000237 -26.93 0.000 3.34 Motares Sadrani N, 2015 0.000144 0.000245 -19.520 0.000 3.34 Sadadatinasab Z, 2015 0.000104 0.000252 -20.928 -25.940 0.000 3.44 Sadrifi H, 2010 0.000144 0.000265 -149.734 0.000 Sanji F, 2018 (1) 0.0002	Motamedi N, 2017 (6)	0.000279	0.000150	0.000519	-25 873	0.000			3 15
Alternative (1) 2017 (8) 0.000105 0.0000281 -18.314 0.000 2.44 Motamedi N, 2017 (9) 0.000381 0.000230 0.000632 -30.485 0.000 3.33 Motamedi N, 2017 (10) 0.000191 0.000054 0.000111 -20.014 0.000 2.64 Motamedi N, 2017 (11) 0.000191 0.000058 0.00078 -49.923 0.000 2.64 Nami A, 2013 0.000584 0.000170 0.0001308 -33.781 0.000 3.54 Motares Sadrani N, 2013 0.000294 0.000171 0.000566 -29.316 0.000 3.30 Motares Sadrani N, 2013 0.000208 0.000120 -15.958 0.000 2.16 Sadiee M, 2014 0.001443 0.000258 -000208 -25.940 0.000 3.40 Sori M, 2018 0.000027 0.000208 -14.9734 0.000 3.40 3.40 Sanji F, 2018 (1) 0.000277 0.000245 -14.9734 0.000 2.14 3.40 3.40 Sanji F, 2018 (2) 0.000144 0.000445 -15.325 0.000 2.16	Motamedi N 2017 (7)	0.000161	0.000073	0.000359	-21.385	0.000			2 79
Maramedi N, 2017 (9) 0.000381 0.000230 0.000281 -0.000 3.33 Maramedi N, 2017 (10) 0.000130 0.000054 0.000131 -20.014 0.000 2.64 Maramedi N, 2017 (11) 0.000191 0.000091 0.000783 -49.923 0.000 2.93 Maramedi N, 2013 0.000584 0.000783 -49.923 0.000 3.77 Maramedi N, 2013 0.000058 0.000178 -49.923 0.000 3.54 Moramedi N, 2013 0.000058 0.000078 -49.923 0.000 3.54 Moramedi N, 2013 0.000058 0.000022 0.000164 -19.520 0.000 3.33 Moravatdar N, 2015 0.000100 0.000022 0.000154 -19.520 0.000 3.44 Saadatinasab Z, 2015 0.000100 0.00022 0.00028 -25.940 0.000 3.00 Saori M, 2018 0.00027 0.00025 0.00028 -25.940 0.000 3.64 Sanji F, 2018 (1) 0.000277 0.000265 -449.734 0.000 3.64 3.66 Sanji F, 2018 (2) 0.000204<	Motamedi N, 2017 (8)	0.000105	0.000040	0.000281	-18 314	0.000	T I		2.44
National N, 2017 (10) 0.000130 0.000054 0.000311 -22.649 0.000 2.66 Ajami A, 2013 0.000584 0.000130 0.0000578 0.00130 -22.649 0.000 3.72 Ajami A, 2013 0.000584 0.000178 -49.923 0.000 3.74 3.72 Ajami A, 2013 0.000294 0.000171 0.000566 -29.316 0.000 3.54 Modares Sadrani N, 2013 0.000020 0.000154 -19.520 0.000 3.33 Saadatinasab Z, 2015 0.000100 0.00022 0.000154 -19.520 0.000 2.14 Saadatinasab Z, 2015 0.000104 0.00022 0.00028 -25.940 0.000 3.40 Karamifar H, 2010 0.000140 0.000252 0.00028 -25.940 0.000 3.40 Sadiee M, 2018 0.000027 0.00028 -25.940 0.000 3.40 Garaji F, 2018 (1) 0.000077 0.00024 -149.734 0.000 4.44 Sanji F, 2018 (2) 0.000049 0.000471 -15.228 0.000 4.44 Sanji F, 2018 (3)	Motamedi N, 2017 (9)	0.000381	0.000230	0.000632	-30 485	0.000			3 37
Notamed N, 2017 (10) 0.000191 0.000091 0.000411 -22.649 0.000 Ajami A, 2013 0.000584 0.000783 -49.923 0.000 3.72 Nasiri Sh, 2013 0.000294 0.000171 0.000506 -29.316 0.000 3.37 Viodares Sadrani N, 2013 0.000294 0.000171 0.000506 -29.316 0.000 3.33 Viodares Sadrani N, 2015 0.000022 0.000154 -19.520 0.000 3.30 Sadiee M, 2014 0.001443 0.000884 0.002353 -26.141 0.000 3.00 Badiee M, 2018 0.000020 0.000140 0.00052 0.000208 -25.940 0.000 3.00 Sorid M, 2018 0.000237 0.000213 0.000254 -149.734 0.000 3.86 Gaiji F, 2018 (1) 0.000044 0.000454 -15.325 0.000 4.244 Sanji F, 2018 (2) 0.000144 0.000445 -15.325 0.000 4.244 Sanji F, 2018 (4) 0.000144 0.000454 -15.325 0.000 4.244 Sanji F, 2018 (4) 0.000144 0.	Motamedi N, 2017 (10)	0.000130	0.0000200	0.000311	-20.014	0.000	. .		2.64
Ajami A, 2013 0.000584 0.000436 0.000783 -49.923 0.000 3.72 Ajami A, 2013 0.000584 0.000783 -49.923 0.000 3.72 Nasiri Sh, 2013 0.000588 0.000171 0.000506 -22.9316 0.000 3.52 Modares Sadrani N, 2013 0.000058 0.000022 0.000154 -19.520 0.000 3.33 Saadatinasab Z, 2015 0.000100 0.000032 0.000039 -15.958 0.000 2.16 Saadatinasab Z, 2015 0.000104 0.000052 0.000208 -25.940 0.000 3.00 Saraifar H, 2010 0.000144 0.000052 0.000208 -25.940 0.000 3.00 Soori M, 2018 0.000237 0.000213 0.000265 -149.734 0.000 3.66 Sanji F, 2018 (1) 0.000277 0.000110 0.000455 -9.474 0.000 2.16 Sanji F, 2018 (2) 0.000152 0.00049 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (3) 0.000140 0.00045 -15.325 0.000 2.16 <td< td=""><td>Motamedi N, 2017 (10)</td><td>0.000190</td><td>0.0000004</td><td>0.000311</td><td>-20.014</td><td>0.000</td><td></td><td></td><td>2.04</td></td<>	Motamedi N, 2017 (10)	0.000190	0.0000004	0.000311	-20.014	0.000			2.04
Stanti A, 2013 0.000869 0.00078 0.00130 4.0.000 3.74 Nasiri Sh, 2013 0.000869 0.000171 0.000578 0.001308 -33.781 0.000 3.54 Wodares Sadrani N, 2013 0.000224 0.000154 -19.520 0.000 3.64 Saadatinasab Z, 2015 0.00100 0.00032 0.000309 -15.958 0.000 2.16 Saadatinasab Z, 2015 0.001144 0.00052 0.00208 -25.940 0.000 3.64 Saadiee M, 2014 0.00104 0.000052 0.00208 -25.940 0.000 3.64 Sori M, 2018 0.0000237 0.000213 0.00265 -149.734 0.000 3.64 Ganji F, 2018 (1) 0.000277 0.000213 0.000245 -9.474 0.000 2.16 Sanji F, 2018 (2) 0.000172 0.000477 0.000545 -9.474 0.000 2.16 Sanji F, 2018 (3) 0.000120 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000445 -15.325 0.000 2.16 Wahmoodi M, 2013		0.000191	0.000031	0.000401	-22.043	0.000			3.72
Watam Shi, 2013 0.000294 0.000171 0.000506 -29.316 0.000 3.30 Worovatdar N, 2015 0.000188 0.000022 0.000154 -19.520 0.000 2.44 Saadatinasab Z, 2015 0.000100 0.00032 0.000309 -15.958 0.000 2.16 Saadiee M, 2014 0.001443 0.00022 0.000208 -25.940 0.000 3.40 Karamifar H, 2010 0.000014 0.00027 0.00028 -25.940 0.000 3.40 Soori M, 2018 0.000088 0.000265 -149.734 0.000 3.60 3.60 Heydari A, 2016 0.000277 0.000245 -9.474 0.000 3.86 Ganji F, 2018 (1) 0.000077 0.000543 -16.993 0.000 1.14 Ganji F, 2018 (2) 0.000144 0.000471 -15.228 0.000 2.16 Ganji F, 2018 (4) 0.000152 0.000144 -19.650 0.000 2.16 Ganji F, 2018 (4) 0.000174 0.000214 -19.650 0.000 2.16 Ganji F, 2018 (0, 000194 0.000177 0.000212	Naciri Sh. 2013	0.000004	0.000430	0.000700	-33 781	0.000			3.72
Word as Satural N, 2013 0.00024 0.000171 0.00000 19.520 0.000 2.44 Saadatinasab Z, 2015 0.000100 0.000032 0.000309 -15.958 0.000 2.16 Saadatinasab Z, 2015 0.000144 0.000250 0.000233 -26.141 0.000 3.40 Karamifar H, 2010 0.000144 0.000250 0.000285 -25.940 0.000 3.00 Soori M, 2018 0.000237 0.000213 0.000265 -149.734 0.000 0.66 Sanji F, 2018 (1) 0.000077 0.000545 -9.474 0.000 1.14 Ganji F, 2018 (2) 0.000049 0.000471 -15.228 0.000 2.16 Ganji F, 2018 (3) 0.000152 0.000471 -15.228 0.000 2.16 Ganji F, 2018 (4) 0.000144 0.00045 -15.325 0.000 2.16 Sahine M, 2015 0.000313 0.00020 0.00144 -19.650 0.000 2.16 Sahine M, 2015 0.000194 0.000177 0.000212 -68.581 0.000 2.16 Sahine M, 2015 0.000194	Madaras Sadrani N. 2013	0.000808	0.000378	0.001308	-33.701	0.000			3.54
Saadatinasab Z, 2015 0.000036 0.000022 0.000134 -15.950 0.000 2.14 Saadatinasab Z, 2015 0.000100 0.000032 0.000399 -15.958 0.000 2.16 Saadatinasab Z, 2015 0.000144 0.000384 0.002353 -26.141 0.000 3.40 Saadatinasab Z, 2016 0.000140 0.000052 0.000208 -25.940 0.000 3.00 Saaji F, 2018 0.000027 0.000213 0.000265 -149.734 0.000 4.14 Sanji F, 2018 0.000027 0.000077 0.000545 -9.474 0.000 4.14 Sanji F, 2018 0.0000152 0.000047 1.000545 -9.474 0.000 1.14 Sanji F, 2018 (2) 0.000077 0.000543 -16.993 0.000 2.16 Sanji F, 2018 (3) 0.000152 0.000445 -15.325 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000174 -15.228 0.000 2.16 Sanji F, 2018 (3) 0.00020 0.00144 -19.650 0.000 2.16	Viouares Saurani N, 2015	0.000294	0.000171	0.000300	-29.310	0.000			3.30
Saadial 1143a3 D2, 2015 0.000100 0.000032 0.000303 -26.141 0.000 3.40 Sadiee M, 2014 0.001443 0.0000884 0.002353 -26.141 0.000 3.40 Karamifar H, 2010 0.000104 0.000052 0.000208 -25.940 0.000 3.60 Soori M, 2018 0.000027 0.000213 0.000265 -149.734 0.000 3.66 Heydari A, 2016 0.000277 0.000245 -9.474 0.000 4 3.40 Sanji F, 2018 (1) 0.000077 0.000045 -9.474 0.000 4 3.42 Ganji F, 2018 (2) 0.000077 0.000543 -16.993 0.000 2.44 Sanji F, 2018 (3) 0.000144 0.000471 -15.228 0.000 2.16 Ganji F, 2018 (4) 0.000144 0.000144 -19.650 0.000 2.16 Shineh M, 2015 0.000194 0.000177 0.00021 -33.108 0.000 2.44 Behineh M, 2015 0.000194 0.000117 0.000321 -33.108 0.000 3.37 Rezabigidavarani E, 2018 0.	Rodotinasch Z. 2015	0.000000	0.000022	0.000104	15 050	0.000			2.44
Sadie W, 2014 0.00144.3 0.000844 0.002353 -25.940 0.000 3.44 Karamifar H, 2010 0.000052 0.000208 -25.940 0.000 3.00 Soori M, 2018 0.000237 0.000213 0.000265 -149.734 0.000 0.67 Jeydari A, 2016 0.000277 0.000213 0.000265 -9.474 0.000 1.14 Sanji F, 2018 (1) 0.000077 0.000545 -9.474 0.000 1.14 Sanji F, 2018 (2) 0.000152 0.000477 0.000543 -16.993 0.000 2.16 Sanji F, 2018 (3) 0.000152 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (4) 0.000054 0.000144 -19.650 0.000 2.16 Mahmoodi M, 2013 0.000078 0.00129 -11.412 0.000 2.16 Rezabigidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 3.37 Heterogeneity: I ² = 82.56; P<0.001	Dadualinasab Z , 2013	0.000100	0.000032	0.000308	-13.836	0.000			2.10
Variaminar H, 2010 0.000104 0.0000052 0.000205 -25.940 0.000 3.00 Soori M, 2018 0.000088 0.000005 0.001400 -6.606 0.000 0.67 Heydari A, 2016 0.000237 0.000265 -149.734 0.000 3.86 Sanji F, 2018 (1) 0.000077 0.000545 -9.474 0.000 1.14 Sanji F, 2018 (2) 0.000152 0.000471 -15.228 0.000 2.44 Sanji F, 2018 (3) 0.000144 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000445 -15.325 0.000 2.14 Shineh M, 2015 0.000313 0.000179 0.00129 -11.412 0.000 2.44 Sehineh M, 2015 0.000194 0.000117 0.00021 -33.108 0.000 3.37 Rezabigidavarani E, 2018 0.000194 0.000117 0.000212 -68.581 0.000 3.37 Heterogeneity: I ² = 82.56; P<0.001	Sadiee IVI, 2014	0.001443	0.000884	0.002353	-20.141	0.000	I		3.40
Soon M, 2018 0.000088 0.000008 0.001400 -5.068 0.000 0.000 0.00 Heydari A, 2016 0.000237 0.000213 0.000265 -149.734 0.000 3.86 Ganji F, 2018 (1) 0.000277 0.00011 0.000545 -9.474 0.000 1.14 Sanji F, 2018 (2) 0.00024 0.00077 0.000543 -16.993 0.000 2.44 Sanji F, 2018 (3) 0.000144 0.000445 -15.325 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000144 -19.650 0.000 2.16 Sanji F, 2018 (2) 0.000144 0.000144 -19.650 0.000 2.16 Sanji F, 2018 (3) 0.000054 0.000129 0.001249 -11.412 0.000 2.16 Mahmoodi M, 2013 0.000078 0.001249 -11.412 0.000 0.00 2.44 Sehineh M, 2015 0.000194 0.000117 0.000321 -33.108 0.000 3.37 Rezabigidavarani E, 2018 0.000129 0.000212 -68.581 0.000 0.001 Heterogeneity: I ² = 82.56; P<0.		0.000104	0.000052	0.000208	-25.940	0.000			3.00
Heydari A, 2016 0.000237 0.000213 0.000265 -149.734 0.000 3.68 Ganji F, 2018 1 0.000077 0.000011 0.000545 -9.474 0.000 1.14 Ganji F, 2018 0.000123 0.000077 0.000543 -16.993 0.000 2.44 Ganji F, 2018 0.000152 0.00049 0.000471 -15.228 0.000 2.16 Ganji F, 2018 (3) 0.000144 0.000445 -15.325 0.000 2.16 Ganji F, 2018 (4) 0.000054 0.000144 -19.650 0.000 2.16 Sehineh M, 2013 0.000054 0.000177 0.000321 -33.108 0.000 2.44 Sehineh M, 2015 0.000194 0.000171 0.000321 -33.108 0.000 3.37 Rezabigidavarani E, 2018 0.000194 0.000212 -68.581 0.000 1.17 Heterogeneity: I ² = 82.56; P<0.001	500ri IVI, 2018	0.000088	0.000005	0.001400	-0.000	0.000			0.67
Sanji F, 2018 (1) 0.000077 0.000041 0.000445 -9.474 0.000 1.12 Sanji F, 2018 (2) 0.000204 0.000077 0.000543 -16.993 0.000 2.44 Sanji F, 2018 (3) 0.000152 0.000049 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000445 -15.325 0.000 2.16 Sahineh M, 2013 0.000020 0.00144 -11.412 0.000 2.44 Sehineh M, 2015 0.000131 0.000212 -68.581 0.000 1.77 Rezabigidavarani E, 2018 0.000194 0.000212 -68.581 0.000 3.37 Heterogeneity: 1 ² = 82.56; P<0.001	Heydari A, 2016	0.000237	0.000213	0.000265	- 149.734	0.000	T		3.89
Sanji F, 2018 (2) 0.000204 0.000077 0.000543 -16.993 0.000 2.42 Sanji F, 2018 (3) 0.000152 0.000049 0.000471 -15.228 0.000 2.16 Sanji F, 2018 (4) 0.000144 0.000046 0.000445 -15.325 0.000 2.16 Sanji F, 2018 (4) 0.000054 0.000020 0.000144 -19.650 0.000 2.16 Sahineh M, 2013 0.0000313 0.000078 0.001249 -11.412 0.000 1.77 Rezabigidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 1.77 Heterogeneity: I ² = 82.56; P<0.001	Ganji F, 2018 (1)	0.000077	0.000011	0.000545	-9.474	0.000			1.14
Sampli F, 2018 (3) 0.000192 0.000491 -15.228 0.000 2.16 Ganji F, 2018 (4) 0.000144 0.00046 0.000445 -15.325 0.000 2.16 Mahmoodi M, 2013 0.000054 0.000020 0.000144 -19.650 0.000 2.44 Sehineh M, 2015 0.000132 0.000177 0.000321 -33.108 0.000 1.77 Rezabigidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 1.77 Heterogeneity: I ² = 82.56; P<0.001	Janji F, 2018 (2)	0.000204	0.000077	0.000543	-16.993	0.000			2.44
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Janji F, 2018 (3)	0.000152	0.000049	0.0004/1	-15.228	0.000			2.16
Vianmoodi M, 2013 0.00026 0.000144 -19.650 0.000 2.44 Sehineh M, 2015 0.000313 0.000078 0.001249 -11.412 0.000 1.77 Rezabigidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 1.337 Heterogeneity: $I^2 = 82.56; P<0.001$ 0.001 0.001 0.01 0.01	∋anji F, 2018 (4)	0.000144	0.000046	0.000445	-15.325	0.000			2.16
Seninen M, 2015 0.000313 0.000078 0.001249 -11.412 0.000 1.77 Rezabigidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 1.337 0.000165 0.000129 0.000212 -68.581 0.000 1.000 0.01 0.01	vianmoodi IVI, 2013	0.000054	0.000020	0.000144	-19.650	0.000			2.44
Rezablgidavarani E, 2018 0.000194 0.000117 0.000321 -33.108 0.000 3.37 0.000165 0.000129 0.000212 -68.581 0.000 0.00 0.01 0.01 Heterogeneity: 1 ² = 82.56; P<0.001	Senineh M, 2015	0.000313	0.000078	0.001249	-11.412	0.000			1.77
0.000165 0.000129 0.000212 -68.581 0.000 Heterogeneity: I ² = 82.56; P<0.001 0.01 0.01	Rezabigidavarani E, 2018	0.000194	0.000117	0.000321	-33.108	0.000			3.37
Heterogeneity: I ² = 82.56; P<0.001 0.00 0.01 0.01		0.000165	0.000129	0.000212	-68.581	0.000			
	Heterogeneity: I ² = 82.56;	P<0.001					0.00 0.01	0.01	

and 10.1/100,000 (95% CI: 7.1-14.5), respectively, and the differences in subgroup analysis were significant (P = 0.002) (Fig. 6).

The prevalence of different types of phenylketonuria

The prevalence of PKU types was investigated in 16 studies with a sample size of 714,845 Iranian neonates. The prevalence of mild to moderate HPA was estimated 9.7/100,000 (95% CI: 5.1–18.4) and the prevalence of classical PKU was estimated 4.4/100,000 (95% CI: 2.5–7.8)

(Fig. 7). In other words, the prevalence of mild to moderate HPA and the prevalence of classical PKU among PKU patients were 71.15% (95% CI: 61.88–78.93) and 28.85% (95% CI: 21.07–38.12), respectively (Supplementary Figure 1).

Meta-regression

Meta-regression for the prevalence of suspected HPA, PKU, classical PKU and mild to moderate HPA based on the year of study was (meta-regression coefficient: -0.132, 95% CI -0.346 to 0.081, P = 0.226), (meta-

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study name		Statistic	cs for each	study		Eve	nt rate and 95	% CI	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
labib A, 2010	0.000172	0.000104	0.000286	-33.562	0.000			1	50.00
bbaskhanian A, 2017 (2)	0.000096	0.000024	0.000385	-13.077	0.000	+			6.67
bbaskhanian A, 2017 (3)	0.000022	0.000001	0.000355	-7.576	0.000	ł			1.67
bbaskhanian A, 2017 (4)	0.000227	0.000094	0.000545	-18.762	0.000	-			16.67
bbaskhanian A, 2017 (5)	0.000140	0.000045	0.000434	-15.370	0.000	+			10.00
bbaskhanian A, 2017 (6)	0.000047	0.000007	0.000335	-9.960	0.000	+			3.33
bbaskhanian A, 2017 (7)	0.000046	0.000006	0.000327	-9.986	0.000	+			3.33
bbaskhanian A, 2017 (8)	0.000022	0.000001	0.000351	-7.584	0.000	+			1.67
bbaskhanian A, 2017 (9)	0.000044	0.000006	0.000313	-10.029	0.000	+			3.33
bbaskhanian A, 2017 (10)	0.000043	0.000006	0.000306	-10.051	0.000	+			3.33
	0.000133	0.000093	0.000190	-48.893	0.000				
						0.00	0.01	0.01	

Heterogeneity: I²= 14.65; P=0.308

Meta Analysis

B

Study name		Statistic	s for each	study			Event rate	e and 95% (CI	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value					Relative weight
Habib A, 2010	0.000147	0.000086	0.000254	-31.804	0.000					47.27
Abbaskhanian A, 2017 (2)	0.000023	0.000001	0.000370	-7.546	0.000	Ŧ				1.82
Abbaskhanian A, 2017 (3)	0.000086	0.000022	0.000345	-13.234	0.000	- +				7.27
Abbaskhanian A, 2017 (4)	0.000085	0.000021	0.000342	-13.246	0.000	÷				7.27
Abbaskhanian A, 2017 (5)	0.000022	0.000001	0.000348	-7.591	0.000	- +				1.82
Abbaskhanian A, 2017 (6)	0.000021	0.000001	0.000342	-7.603	0.000	- +				1.82
Abbaskhanian A, 2017 (7)	0.000044	0.000006	0.000314	-10.027	0.000	+				3.64
Abbaskhanian A, 2017 (8)	0.000129	0.000042	0.000400	-15.511	0.000	• •				10.91
Abbaskhanian A, 2017 (9)	0.000122	0.000039	0.000379	-15.604	0.000					10.91
Abbaskhanian A, 2017 (10)0.000082	0.000021	0.000330	-13.298	0.000					7.27
	0.000109	0.000075	0.000158	-47.850	0.000					
Hatana zanaitan 12-0. D-0.	706					0.00	0.	01	0.01	

Heterogeneity: I²= 0; P=0.706

Meta /	Analvsis
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Meta Analysis

Fig. 5 Prevalence of phenylketonuria in girls (a) and boys (b) and girls to boys odds ratio (d) in national neonate screening program in Iran in Iran



A	A

Study name		Statis	tics for ea	ch study		Ev	ent rate and 95%	6 CI	
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Senemar S, 2009	0.000184 (0.000107	0.000318	-30.997	0.000		1	1	7.79
Abbaskhanian A, 2017 (2)	0.000024 (0.000003	0.000168	-10.653	0.000				4.65
Abbaskhanian A, 2017 (3)	0.000044 (0.000011	0.000175	-14.194	0.000	.			5.95
Abbaskhanian A, 2017 (4)	0.000132 (0.000059	0.000294	-21.878	0.000	H			7.31
Abbaskhanian A, 2017 (5)	0.000045 (0.000011	0.000180	-14.153	0.000				5.95
Abbaskhanian A, 2017 (6)	0.000023 (0.000003	0.000160	-10.700	0.000				4.65
Abbaskhanian A, 2017 (7)	0.000023 (0.000003	0.000160	-10.700	0.000				4.65
Abbaskhanian A, 2017 (8)	0.000065 (0.000021	0.000202	-16.692	0.000				6.56
Abbaskhanian A, 2017 (9)	0.000064 (0.000020	0.000197	-16.738	0.000				6.56
Abbaskhanian A, 2017 (10)	0.000042 (0.000011	0.000169	-14.247	0.000	i			5.95
Drdooei M, 2015	0.000136 (0.000044	0.000420	-15.425	0.000				6.56
ami A, 2013	0.000429 (0.000305	0.000603	-44.537	0.000				8.07
/lodares Sadrani N, 2013	0.000113 (0.000047	0.000272	-20.319	0.000				7.15
Badiee M, 2014	0.001352 (0.000816	0.002242	-25.562	0.000				7.85
Karamifar H, 2010	0.000065 (0.000027	0.000156	-21.559	0.000				7.15
Soori M, 2018	0.000088 (0.000005	0.001400	-6.606	0.000				3.23
	0.000097 0	0.000051	0.000184	-28.328	0.000				
Heterogeneity: I ² = 87.9:	P<0.001					0.00	0.01	0.01	

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B
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Study name	Statistics for each study			Event rate and 95% CI					
	Event rate	Lower limit	Upper limit	Z-Value	p-Value				Relative weight
Senemar S, 2009	0.000028	0.000007	0.000113	-14.806	0.000	•	1		8.02
Abbaskhanian A, 2017 (2)	0.000024	0.000003	0.000168	-10.653	0.000				5.43
Abbaskhanian A, 2017 (3)	0.000011	0.000001	0.000175	-8.077	0.000	•			3.29
Abbaskhanian A, 2017 (4)	0.000022	0.000003	0.000156	-10.724	0.000				5.43
Abbaskhanian A, 2017 (5)	0.000023	0.000003	0.000160	-10.701	0.000				5.43
Abbaskhanian A, 2017 (6)	0.000011	0.000001	0.000180	-8.056	0.000	•			3.29
Abbaskhanian A, 2017 (7)	0.000023	0.000003	0.000160	-10.700	0.000				5.43
Abbaskhanian A, 2017 (8)	0.000011	0.000001	0.000174	-8.082	0.000				3.29
Abbaskhanian A, 2017 (9)	0.000021	0.000003	0.000150	-10.762	0.000				5.43
Abbaskhanian A, 2017 (10)	0.000021	0.000003	0.000150	-10.767	0.000				5.43
Ordooei M, 2015	0.000045	0.000006	0.000321	-10.004	0.000	<u>.</u>			5.43
Ajami A, 2013	0.000156	0.000089	0.000274	-30.366	0.000				13.34
Modares Sadrani N, 2013	0.000181	0.000090	0.000362	-24.372	0.000				12.51
Badiee M, 2014	0.000090	0.000013	0.000640	-9.313	0.000	-			5.43
Karamifar H, 2010	0.000039	0.000013	0.000121	-17.584	0.000				9.54
Soori M, 2018	0.000088	0.000005	0.001400	-6.606	0.000	•			3.29
	0.000044	0.000025	0.000078	-34.643	0.000				
Heterogeneity: I ² = 50.80; P0.010					0.00	0.01	0.01		
Meta Analysis									
Fig. 7 Prevalence of mild to moderate hyperphenylalaninemia (a) classic phenylketonuria (b) in national neonate screening program in Iran									

regression coefficient: 0.008, 95% CI – 0.076 to 0.92, P = 0.851), (meta-regression coefficient: 0.101, 95% CI – 0.213 to 0.416, P = 0.528) and (meta-regression coefficient: 0.020, 95% CI – 0.212 to 0.416, P = 0.253), respectively (Supplementary Figure 2).

Sensitivity analysis and publication bias

Sensitivity analysis for prevalence of suspected HPA, PKU, classical PKU, and mild to moderate HPA with the omission of one study showed that overall estimation is still robust (Supplementary Figures 3, 4, 5). Egger's and

Begg's tests for HPA prevalence (P = 0.137 and P < 0.001, respectively), overall PKU prevalence (P = 0.005 and P = 0.009), classical PKU (P < 0.001 and P = 0.002) and mild to moderate PKU (P = 0.710 and P < 0.001) were significant (Supplementary Figure 6).

Discussion

The present study is the first comprehensive systematic review and meta-analysis on PKU screening in Iranian newborns. The prevalence of PKU in Iranian neonates was estimated to be 16.5/100,000. NBS is an important form of prevention in newborns with congenital metabolic diseases. This activity is very useful for detecting errors in many birth-related errors. It should be noted that many types of congenital disorders can be successfully treated if early diagnosis is achieved. If specific biochemical supplements are taken at an early stage, many metabolic disorders will be stopped from progressing and causing permanent damage to patients. The NBS is managed under the national public health policies. Metabolic disorders of the nervous system vary clinically and pathologically. Mental retardation and epilepsy syndrome are prominent in these disorders [42, 43].

The first pilot study to assess HPA in neonates in Iran began in 1982 [44] and the first National Neonate Screening Program (NNSP) in Iran started in Fars province in 2004 [45] and continued in Mazandaran province in 2007 [16]. Based on law, all Iranian infants should be screened for three diseases, including hypothyroidism, PKU, and glucose 6-phosphate dehydrogenase deficiency.

The published evidence confirms that the global NBS for PKU meets all accepted screening criteria and justifies the cost and infrastructure needed to collect and test dried blood spots [46]. Screening in infants is considered a national duty even in countries where there is no PKU population. Because of high migration in countries, detection of PKU has remained probable. Neonatal screening requires: 1) a solid infrastructure in which blood is collected from all neonates to ensure timely treatment; 2) a well-equipped laboratory that can effectively administer blood spot. Low-income countries may consider using NBS laboratory facilities of other countries [47, 48].

In the present study, the prevalence of suspected HPA (45.6/100,000) was much higher than the prevalence of PKU. Differential diagnosis of HPA includes high intake of natural protein, liver disease, tetrahydrobiopterin (BH4) deficiency, and being premature [49, 50].

The prevalence of PKU varies across ethnic groups and geographical regions around the world [51]. The prevalence of PKU has been reported to range from less than 1/220,000 to 1/4500. Table 2 summarizes the prevalence of PKU in different populations. In the present study, due to ethnic differences in different geographical regions of Iran, the prevalence of PKU

Table 2 Summarizes the prevalence of PKU in different populations

Regions	Countries	Incidence of PKU ^a
Asian populations	Turkey, 1986 (53)	1: 4500
	Saudi Arabia, 2017 [8]	1: 14245
	United Arab of Emirates, 2000 (54)	1: 20050
	United Arab of Emirates, 2014 (55)	1: 14544
	Iraq, 2015 (56)	1.2: 10000
	Thailand 2009 and 2015 (13, 57)	< 1: 220,000
	Mexico, 2012 (58)	1:161,748
	Japan, 2017 (59)	1:143,000
European populations	Ireland, 1978 (60)	1 in 4500
	Sweden, before and after 1990 [52]	1:18,300 to 1:14,200
	Germany, 2002 and 2014 (61)	1:10,339
	Greece, 2016 (62)	1: 10000
	Bulgaria, 2016 (62)	1: 18000
	Poland, 2016 (62)	1: 7000
	Spain, 2016 (62)	1: 7400
	Italy, 2016 (62)	1: 11500
South America	Brazil, 2014 (63)	1:8690
North America	United States (Caucasians) (64)	1 in 10,000
	Canada, 1986 (65)	1 in 22,000

^a Phenylketonuria

was significantly different in five different regions of Iran.

In the present study, prevalence of mild to moderate HPA and prevalence of classical PKU among PKU patients were 71.15 and 28.85%, respectively, indicating that the majority of patients with PKU suffer from mild to moderate HPA in Iran. This can play a key role in the initiation and non-initiation of PKU treatment and management of these patients. That's because untreated Phe concentration determines the management of people with PKU. If blood Phe concentrations are below 360 µmol/l, no intervention is required. If Phe blood concentration is between 360 µmol/l and 600 µmol/l, treatment up to the age of 12 is recommended and lifelong treatment is recommended if the concentration is above 600 µmol/l. For women trying to get pregnant (maternal PKU), untreated Phe blood concentration drops to more than 360 µmol/l. On the other hand, management of PKU is associated with a severe financial burden on patients' families, which may lead to inadequate treatment or a change in blood Phe concentration [2, 3].

The trend of changes in the prevalence of suspected HPA, PKU, classical PKU and mild to moderate HPA did not change significantly over time. PKU as an autosomal-recessive disorder is not only related to consanguineous marriage and also occurs in regions with a low incidence of consanguineous marriage e.g. Europe [52]. In Iran, three main areas of prevention and control of hereditary metabolic diseases for PKU include NSB for this disease, selected one-stop clinics and premarriage screening program. Therefore, one can say that Iran's national programs regarding pre-marriage genetic counseling have not been effective in reducing PKU.

This study has several strengths: 1) A comprehensive search strategy was used in this study to maximize the possibility of identifying all relevant literature and even gray literature; 2) All research steps were conducted independently by two researchers, and disagreements were resolved by group discussion, 3) To obtain additional information and to make decisions about duplicate publication, we contacted the authors of the studies, 4) In cases where heterogeneity was significant, the random effects model was used to integrate data to provide a conservative estimate and on the other hand, subgroup analysis and meta-regression model were used to find the cause of heterogeneity and publication bias, and 5) We excluded studies on certain patients such as mentally retarded patients or studies with non-random sample and the resulting estimate can be generalized to the total population.

The limitations of the present study include the limitation of Iranian databases in combined search. In addition, there was a high heterogeneity among studies that investigated the prevalence of suspected HPA and PKU, and based on the available data, we were only able to do subgroup analysis based on geographical regions and provinces, which was significant. Therefore, the differences between studies can be attributed to these issues. However, it seems that more important issues such as differences in the percentage of consanguineous marriages and genetic differences between different populations of Iran (given that Iran includes various ethnic groups) may also be the reason for differences between studies. It was not possible to address these issues in this study. Other studies including the study of Hardelid et al. in England showed that the prevalence of PKU is lower among the Sub-Saharan Africans and South Asians who migrated to England [51]. Studies in other European countries showed that the increased incidence of PKU may be due to new mutations in this disease and migration of people of different races to their country [52].

Conclusions

The prevalence of PKU in Iran was estimated to be 16.6/ 100,000 or 1/6.024. Due to ethnic and demographic similarities in Iran, we may also expand our results and estimates to Iranians living in other countries. It should be considered that for phenylketonuria there is a highly effective dietary treatment which can prevent the clinical symptoms of phenylketonuria if initiated early after detection by newborn screening.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10. 1186/s12887-020-02230-6.

Additional file 1: Figure 1. Prevalence of mild to moderate hyperphenylalaninemia (a) and classic phenylketonuria (b) among phenylketonuria patients.

Additional file 2: Figure 2. Meta-regression model for prevalence of suspected hyperphenylalaninemia (a), phenylketonuria (b), classic phenylketonuria (c), and mild to moderate hyperphenylalaninemia (d) based on year of study.

Additional file 3: Figure 3. Sensitivity analysis for prevalence of suspected hyperphenylalaninemia in national neonate screening program in Iran.

Additional file 4: Figure 4. Sensitivity analysis for prevalence of phenylketonuria in national neonate screening program in Iran.

Additional file 5: Figure 5. Sensitivity analysis for prevalence of mild to moderate hyperphenylalaninemia (a) classic phenylketonuria (b) in national neonate screening program in Iran.

Additional file 6: Figure 6. Publication bias for prevalence of suspected hyperphenylalaninemia (a), phenylketonuria (b), classic phenylketonuria (c), and mild to moderate hyperphenylalaninemia (d) based on year of study.

Abbreviations

PKU: Phenylketonuria; PAH: Phenylalanine hydroxylase; Phe: Phenylalanine; HPA: Hyperphenylalaninemia; NBS: Newborn screening; RICST: Regional Information Center for Science and Technology; SID: Scientific Information Database; IranDoc: Iranian Research Institute for Information Science and Technology; NNSP: National Neonate Screening Program; MOOSE: Metaanalyses Of Observational Studies in Epidemiology; PRISMA: Systematic Reviews and Meta-analysis; OR: Odds ratio; CI: Confidence interval; DBS: Dried Blood Spot; HPLC: high-Performance Liquid Chromatographic; PROSPERO: International prospective register of systematic reviews; PICO: Patient, Population, or Problem; Intervention, Prognostic Factor, or Exposure; Comparison or Intervention (if appropriate); Outcome; NOS: Newcastle-Ottawa Scale; BH4: Tetrahydrobiopterin

Acknowledgements

We since rely thank llam University of Medical Sciences for helping us with this research.

Authors' contributions

MA, MS, GhB, HZ, FK and PK acquired the data. MA and MS analyzed and interpreted the data. MS drafted the manuscript; MA, MS, GhB, HZ, FK and PK critically revised the manuscript for important intellectual content. M.S. supervised the study. All Authors read and approved the manuscript.

Funding

This study was funded by the llam University of Medical sciences. The role of the funding agency was only to financial support.

Availability of data and materials

Not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

We declare no competing interests.

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Received: 8 January 2020 Accepted: 30 June 2020 Published online: 24 July 2020

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