# Birth prevalence of phenylalanine hydroxylase deficiency: A systematic literature review and meta-analysis

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## Background & Objectives

- Phenylalanine hydroxylase (PAH) deficiency is an autosomal recessive disorder that results in abnormally high concentrations of phenylalanine (Phe) in the blood from the typical mean of 60 µmol/L. If left untreated, the accumulation of Phe in tissues can result in profound neurocognitive disability and psychological problems[1]
- Newborn screening (NBS) for PAH deficiency began in North America and the UK in the early 1960s and became widespread in the rest of the developed world by the early 1970s[1]
- The objective of this systematic literature review and meta-analysis was to estimate the global birth prevalence of PAH deficiency from NBS studies and to evaluate regional differences, overall and for various clinically relevant Phe cutoff values used in confirmatory testing

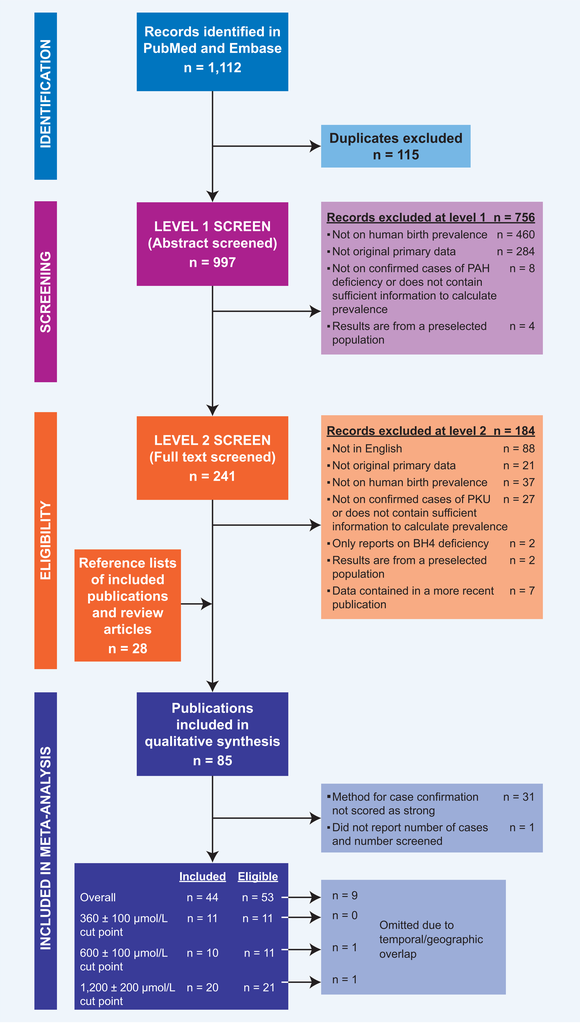
## Methods

- The protocol for this literature review was registered with PROSPERO (international prospective register of systematic reviews)
- Studies with numeric birth prevalence reports of confirmed PAH deficiency were included and classified as strong, moderate, or weak in a quality assessment tool across five domains: case definition, study setting/source population, statistical methods, precision of prevalence estimate, and diagnostic method. Only estimates derived from confirmatory diagnostic assays that were assessed as strong in the quality assessment tool were eligible for meta-analysis
- Meta-analyses were performed to determine aggregated regional birth prevalence (Europe, North America, Middle East/North Africa, Latin America, South Pacific, and West Pacific) and a global birth prevalence
- A regionally-weighted global prevalence was calculated by weighting results from each region by the region's relative contribution to the total population of all the regions included in the analysis
- For both regional and global birth prevalence determinations, birth prevalence was calculated stratified by three confirmatory Phe concentration cutoff values used for case confirmation (360 ± 100 µmol/L, 600 ± 100 µmol/L, 1,200 ± 200 µmol/L) as well as an unstratified estimation

## Results

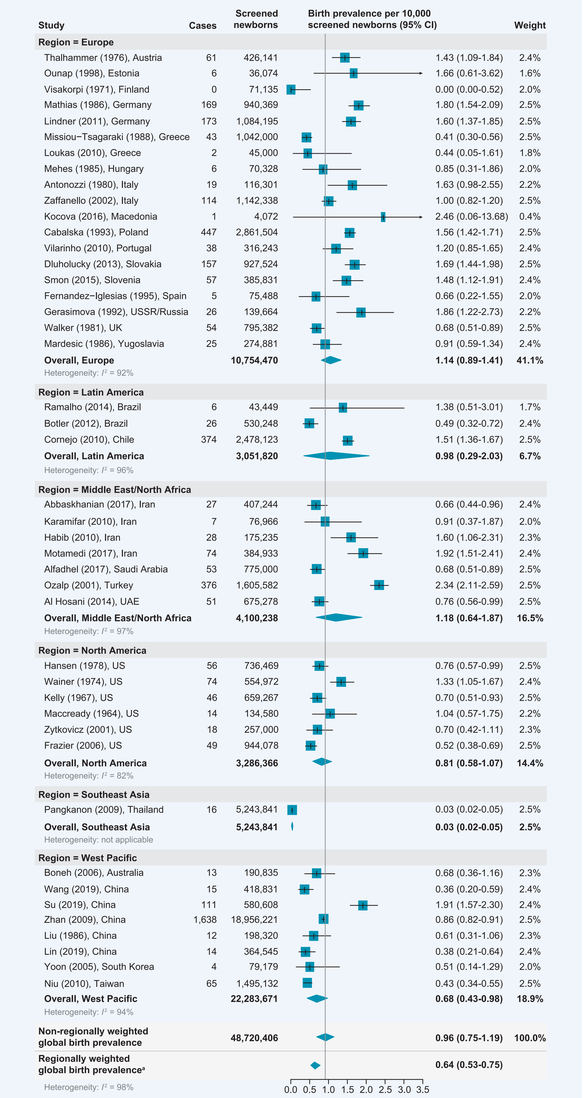
- From an initial 1,112 entries identified and screened, 85 publications met eligibility criteria for inclusion in this review **(Figure 1)**
- After excluding prevalence estimates that did not meet quality assessment criteria or because of temporal and regional overlap, estimates from 45 publications were included in at least one meta-analysis

### Figure 1. Study selection process




- The regionally-weighted global birth prevalence of PAH deficiency was 0.64 (95% CI, 0.53-0.75) per 10,000 births and ranged from 0.03 per 10,000 births (95% CI, 0.02-0.05) in Southeast Asia to 1.18 per 10,000 births (95% CI, 0.64-1.87) in the Middle East/ North Africa **(Figure 2)**

### Figure 2. Meta-analysis results by region: Overall analysis




[a]The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to the figure to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.

### Table 1. Meta-analysis[a] of birth prevalence estimates stratified by confirmatory Phe cutoff values and region

| Confirmatory test Phe cutoff value | Region | Birth prevalence per 10,000 screened newborns (95% CI) | $I^2$ | Number of studies |
|---|---|---|---|---|
| 360 ± 100 µmol/L | Europe | 0.97 (0.52; 1.53) | 93.8 | 4 |
| | Latin America | 1.38 (0.51; 3.01) | NA | 1 |
| | Middle East/North Africa | 1.60 (1.06; 2.31) | NA | 1 |
| | North America | 0.49 (0.38; 0.61) | 0.0 | 2 |
| | West Pacific | 0.63 (0.03; 1.75) | 96.5 | 3 |
| | *Non-regionally weighted global birth prevalence* | *0.85 (0.51; 1.26)* | *95.9* | *11* |
| | *Regionally weighted global birth prevalence[a]* | *0.96 (0.50; 1.42)* | *NA* | *11* |
| 600 ± 100 µmol/L | Europe | 1.18 (0.75; 1.69) | 85.8 | 4 |
| | Latin America | 0.65 (0.14; 1.46) | 64.2 | 2 |
| | Middle East/North Africa | 0.37 (0.21; 0.61) | NA | 1 |
| | West Pacific | 0.23 (0.12; 0.36) | 55.9 | 3 |
| | *Non-regionally weighted global birth prevalence* | *0.66 (0.38; 1.02)* | *94.1* | *10* |
| | *Regionally weighted global birth prevalence[a]* | *0.50 (0.37; 0.64)* | *NA* | *10* |
| 1200 ± 200 µmol/L | Europe | 0.78 (0.40; 1.30) | 96.9 | 7 |
| | Latin America | 0.58 (0.30; 0.94) | 29.2 | 2 |
| | Middle East/North Africa | 0.36 (0.04; 0.94) | 91.2 | 3 |
| | North America | 0.53 (0.38; 0.72) | NA | 1 |
| | Southeast Asia | 0.03 (0.02; 0.05) | NA | 1 |
| | West Pacific | 0.22 (0.03; 0.56) | 94.6 | 6 |
| | *Non-regionally weighted global birth prevalence* | *0.47 (0.26; 0.74)* | *98.0* | *20* |
| | *Regionally weighted global birth prevalence[a]* | *0.30 (0.20; 0.40)* | *NA* | *20* |

[a]The regionally weighted global prevalence was not produced directly as part of the meta-analysis but was calculated by taking a weighted average of the meta-analysis results for each of the regions, weighting them by the relative population size of each of these regions. We have added this prevalence estimate to facilitate comparison with the non-regionally weighted overall estimate from the meta-analysis.

- Regionally-weighted global birth prevalence estimates per 10,000 births by confirmatory test Phe cutoff values were 0.96 (95% CI, 0.50-1.42) for the Phe cutoff value of 360 ± 100 µmol/L, 0.50 (95% CI, 0.37-0.64) for the Phe cutoff value of 600 ± 100 µmol/L, and 0.30 (95% CI, 0.20-0.40) for the Phe cutoff value of 1,200 ± 200 µmol/L **(Table 1)**

## Conclusions

- Substantial regional variation in the birth prevalence of PAH deficiency was observed in this systematic literature review and meta-analysis of published evidence from newborn screening
- Although current findings confirm that regional differences exist in the birth prevalence of PAH deficiency, data elements key to understanding the reported birth prevalence estimates were often missing
- In addition, the precision of the reported prevalence was low for most of the included estimates due to small sample sizes, despite widespread and longstanding newborn screening in much of the world
- These observations highlight the need for more comprehensive and systematic data collection as well as improved standards for reporting results of newborn screening programs

### References

**1.** Vockley J et al. *Genet Med.* 2014;16(2):188-200.

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