Lifetime monitoring of Phe levels in PKU from birth to adulthood in the Swedish Registry for Inherited Metabolic Diseases

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Introduction

- PKU is a rare genetic disorder caused by deficiency of the PAH enzyme, which prevents the body from breaking down the amino acid phenylalanine (Phe). This PAH deficiency results in elevated levels of Phe in the blood[1]
- The primary goal of treatment for individuals with PKU is normal neurocognitive and psychosocial functioning[2]
- Blood Phe levels are the best surrogate measure for the assessment of metabolic control. They should be routinely monitored, with the goal of keeping levels within an age-dependent target treatment range[2]
- European guideline-recommended target Phe levels are:[2]
  - Aged <12 years and during pregnancy: 120–360 µmol/L
  - Aged ≥12 years: 120–600 µmol/L
- In Sweden, the cornerstone of treatment for PKU is medical nutrition therapy with a low-Phe diet.[2] Target blood Phe ranges are aligned with European guidelines[2,3]
- However, Phe levels fluctuate throughout an individual's lifetime, and sustaining a Phe-restricted diet to maintain target Phe levels is particularly challenging for adolescents as they transition from pediatric/supervised care to greater independence[4]

Objective

- To describe Phe levels from infancy through adulthood in individuals diagnosed with PKU in Sweden

Methods

Study design

- This was a retrospective observational cohort study of individuals with PKU in Sweden enrolled in the Swedish Registry for Inherited Metabolic Diseases (RMMS)

Data source

- RMMS is a national quality register that monitors rare congenital metabolic diseases, including PKU. The first individual was enrolled into RMMS in 2013
- RMMS includes 81% of patients with PKU in Sweden[3]
- RMMS aims to ensure access to care, evaluate the quality of care provided, and improve care
- Five regional metabolic treatment centers in Sweden have specialized treatment teams with expertise in metabolic diseases, and these centers are connected to RMMS
- Both individuals with, and parents/guardians of children with, a congenital metabolic disease are eligible to enroll in RMMS (participation is voluntary)
- Demographic, diagnosis, laboratory (e.g. Phe level), treatment, and outcome data are collected[3]
- Retrospective data from the date of PKU diagnosis to the date of RMMS consent are manually inputted into RMMS, where possible, and prospective data from the date of consent are collected thereafter. Since 2017, automatic extraction and upload of laboratory data into RMMS has been implemented to ensure more systematic data collection

Data availability

- RMMS launched in 2013 and data for Phe levels dating back to 1994 are available
- Phe levels were retrospectively collected following enrollment, with data from 1994 to Jul 15, 2024 included in the current analysis

Eligibility

- Individuals of any age with PKU who were enrolled in RMMS and had recorded Phe measurements

Statistical analysis

- For each participant, the mean of all their Phe measurements at each age was calculated (e.g. if a participant had three Phe measurements while they were 17 years of age, the mean was calculated using those three values)
- All mean Phe levels for each age were then averaged to give an overall mean Phe level for that age
- The overall mean Phe levels were plotted for the total population and separated by sex
- The proportion of participants achieving mean Phe level ranges was also calculated by age group

Results

Demographics of individuals

- Of the 339 participants with PKU enrolled in RMMS in Sweden (**Table 1**):
  - Most were male (54.6%)
  - Enrollment was highest in Southern Sweden (46.3%) and lowest in Northern Sweden (9.7%)

Table 1. Demographics of individuals

Demographic	Individuals with PKU enrolled in RMMS (N=339)
Sex, n	
Female	154 (45.4)
Male	185 (54.6)
Swedish region of residence, n (%)	
Central	149 (44.0)
Northern	33 (9.7)
Southern	157 (46.3)

Conclusions

- This cohort study investigated Phe levels in individuals with PKU in Sweden, where dietary intervention is the cornerstone of treatment
- Phe levels varied across the lifespan. There was a significant rise in the proportion of individuals exhibiting uncontrolled levels during adolescence, which continued to increase into adulthood
- Results suggest that achieving guideline target Phe levels is less likely after childhood (aged ≥12 years)
- Given that uncontrolled Phe levels are associated with neurocognitive impairment,[2,4] alternative options to medical nutrition therapy should be considered for improved Phe control

- The mean number of Phe measurements by birth year group generally increased over time (**Table 2**)

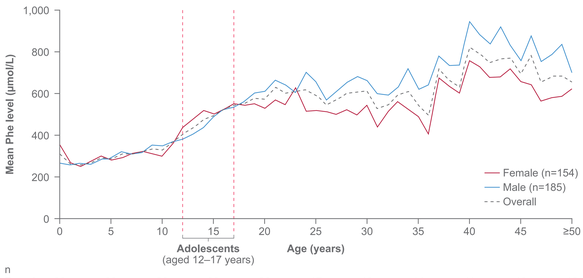
Table 2. Mean number of Phe measurements by birth year group

Birth year group	Individuals with PKU enrolled in RMMS (N=339)	Mean number of Phe measurements per participant
1955–1964	10	36.7
1965–1974	25	58.8
1975–1979	17	48.5
1980–1984	17	107.8
1985–1989	27	124.6
1990–1994	36	110.9
1995–1999	28	93.1
2000–2004	42	116.8
2005–2009	44	167.3
2010–2014	43	280.3
2015–2020	50	252.5

Lifetime Phe levels

- Phe levels were lowest before 12 years of age and increased throughout adolescence and into adulthood (**Figure 1**)
  - There was a significant difference in mean Phe level between individuals aged 12 and 18 years: median difference 57.3 µmol/L (Wilcoxon signed-rank test; p=0.007)
- Generally, Phe levels were lower in females than males, particularly during reproductive years (20–49 years) (**Figure 1**)

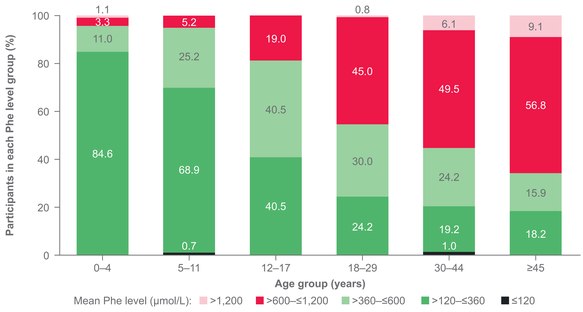
Figure 1. Overall mean Phe levels at each age, by sex



n											
Female	36	33	30	33	20	17	13	14	11	10	16
Male	40	46	48	44	25	20	18	10	6	7	12
Overall	76	79	78	77	45	37	31	24	17	17	28

- Achievement of Phe levels ≤360 µmol/L, including normal (or physiological) blood Phe, significantly decreased with increasing age (Z-test; p<0.001) (**Figure 2**)
- Across all age groups, the greatest increase in the proportion of individuals with Phe levels >600 µmol/L (i.e. outside the guideline-recommended target threshold)[2] was during the transition from adolescence (aged 12–17 years) to early adulthood (aged 18–29 years), with an increase of 26.8 percentage points (**Figure 2**)

Figure 2. Mean Phe levels by age



Participants were categorized into Phe level ranges by first calculating the mean Phe level at each age, and then taking the mean of the age-level Phe means within each age group

References

1. van Spronsen FJ, et al. *Nat Rev Dis Primers.* 2021;7:36
2. van Wegberg AMJ, et al. *Mol Genet Metab.* 2025;145:109125
3. RMMS. Annual Report. https://rmms.se/media/qnpdhwqo/%C3%A5rsrapport-2023-rmms.pdf (accessed Aug 27, 2025)
4. Vockley J, et al. *Genet Med.* 2014;16:188–200

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Abbreviations

PAH, phenylalanine hydroxylase; **Phe**, phenylalanine; **PKU**, phenylketonuria; **RMMS**, Swedish Registry for Inherited Metabolic Diseases.

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