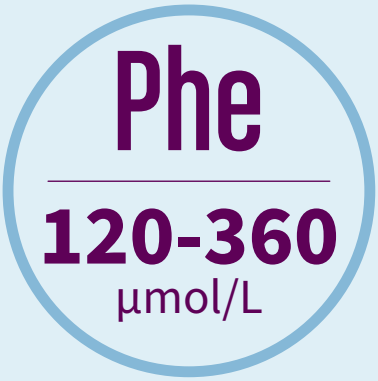
PUBLICATION SUMMARY

Relationship Between Elevated Phe and Neuropsychiatric Symptoms and Cognitive Deficits in Adults With PKU

Bilder DA, Noel JK, Baker ER, et al. Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria. *Dev Neuropsychol*. 2016;41(4):245-260.

This summary is based on the publication referenced above and is not comprehensive. This publication was supported and funded by BioMarin and should be reviewed in its entirety.

Phenylketonuria (PKU) is a rare autosomal recessive disorder characterized by complete or partial deficiency of phenylalanine hydroxylase (PAH) activity, leading to elevated levels of the essential amino acid phenylalanine (Phe) in the blood and brain.



Guideline–recommended blood Phe levels

The impact of elevated blood Phe levels

Long-term high blood Phe levels can lead to psychological and neurocognitive deficits, which can have debilitating effects on people with PKU (primarily based on pediatric studies).

Anxiety
Depression
Impaired executive function
Trouble focusing
Working memory impairment

OBJECTIVE: This systematic review (SR) and meta-analysis (MA) investigates the impact of elevated blood Phe levels on neuropsychiatric and cognitive outcomes in adults with PKU.

Methodology

1327 articles screened

82
studies included:

40 interventional
42 noninterventional

SR
Effects of change in blood Phe levels on:

Neuropsychiatric Symptoms
10 studies ≥3 weeks

- Introducing or reintroducing a Phe-restricted diet or Phe load in untreated/early treated adults
- 20 case reports after introduction of Phe-restricted diet

Executive Function
9 studies

- 4 single-cohort
- 5 comparing symptoms on-diet vs off-diet

MA
Prevalence of PKU symptoms/scores

Psychiatric Symptoms
10 studies

- Inattention
- Hyperactivity
- Anxiety
- Depression

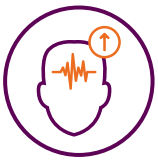
Neurologic Symptoms
10 studies

- Tremors
- Epilepsy/seizures

Executive Function Scores
13 studies

- Mean test scores with variance estimates in early treated adults

SR Findings



Reducing blood Phe levels markedly improved neurologic and/or psychiatric symptoms in:

- **13 of 20** adults with PKU with late-onset symptoms
- **7 of 8** adults with PKU with disruptive behaviors and intellectual disability on a Phe-restricted diet

Improvement in executive functioning domains, including:

- Attention
- Cognitive flexibility
- Psychomotor speed and inhibitory control
- Reaction time
- Working memory

MA Findings

Higher than expected prevalence estimates of neuropsychiatric symptoms than in the general population

Overall prevalence of neuropsychiatric complications:

49%	Inattention	**20%**	Hyperactivity
29%	Tremors	**18%**	Depression
22%	Anxiety	**10%**	Epilepsy/seizures

Positive correlation between increased blood Phe levels and pronounced deficits in executive functioning domains

- Cognitive flexibility
- Inhibitory control
- Working memory

Limitations

While the SR and MA findings provide a collective representation of reported PKU observations, the following limitations should be taken into account:

- The small size (<50 adults) of most of the published findings, which were observational studies of fair/poor quality
- The heterogeneity of symptoms and populations in most of the studies were not clearly defined
- Since a large percentage of adults with PKU are reported as lost to follow-up, we must assume some selection bias
- Blood Phe levels varied widely within studies suggesting variable metabolic control
- Considerable variability exists in the standards of care and assessment of adults with PKU, particularly in late-treated patients

Conclusions

Adults with PKU experience a broad range of neuropsychiatric and executive functioning deficits associated with long-term elevated Phe levels

Lowering Phe levels in symptomatic adults with PKU may improve neuropsychiatric symptoms and executive functioning

The heterogeneity of symptoms within this population, as well as limitations in study designs and sample sizes, highlights inherent challenges in establishing evidence-based guidelines for life-long maintenance of low blood Phe levels

Overall, findings support that lowering blood Phe levels in PKU patients correlates to improvement in neurologic and neuropsychiatric symptoms and improved executive functioning. **However, more than 70% of adults are not actively treated at a metabolic clinic**

Because there remains an unmet need in the adult PKU population, new strategies for lifelong management could help improve metabolic control and patient care

Reference: 1. Bilder DA, Noel JK, Baker ER, et al. Systematic review and meta-analysis of neuropsychiatric symptoms and executive functioning in adults with phenylketonuria. *Dev Neuropsychol*. 2016;41(4):245-260.