BIOMARIN®

The burden of phenylketonuria (PKU)

EUCAN-PKU-00070 April 2024
For Healthcare Professionals only.
Developed and funded by BioMarin International Ltd.

The burden of phenylketonuria (PKU)

The **historical** burden

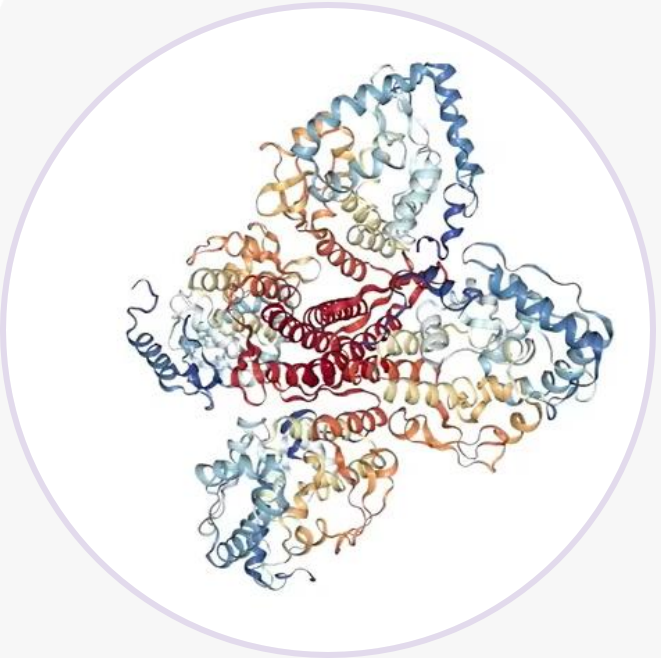
The **personal** burden

The **health** burden

The **lifelong** burden

What is phenylketonuria (PKU)?

- **Phenylalanine hydroxylase deficiency[1–3]**
- Incidence of 1 in 10,000 live births in Caucasians[1,2]
- Prevalence of 1 in 10,000 new-borns in Europe, although there is considerable geographic variation[3,4]
- >1,200 *PAH* gene mutations have been identified[5]

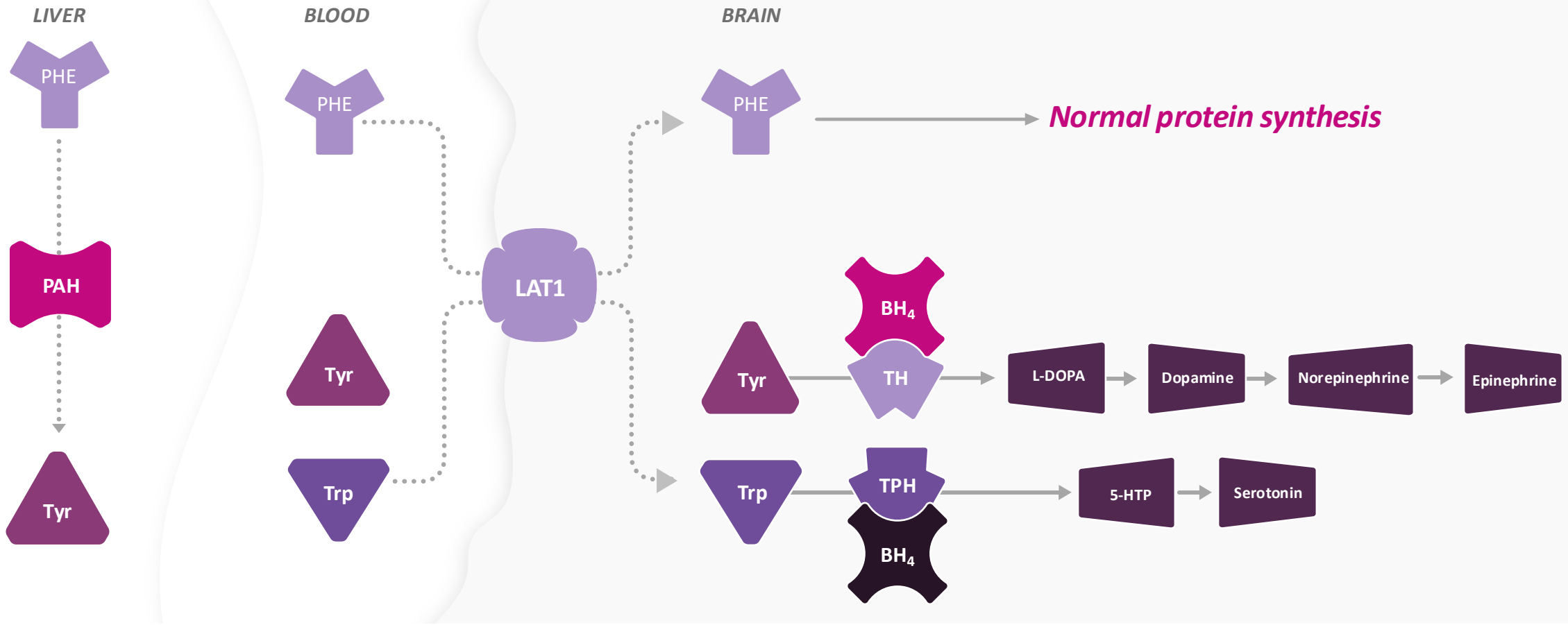


https://www.rcsb.org/pdb/ngl/ngl.do?pdbid=2PAH&bionumber=1

PAH, phenylalanine hydroxylase; PKU, phenylketonuria.

References: 1. Vockley J, *et al. Genet Med*. 2014;16(2):188–200. **2.** Waisbren SE, *et al. Mol Genet Metab*. 2007;92(1-2):63–70. **3.** van Wegberg AMJ, *et al. Orphanet J Rare Dis*. 2017;12:162. **4.** van Spronsen FJ, *et al. Lancet Diabetes Endocrinol*. 2017;5:743–756. **5.** BIOPKU. PAHvdb: Phenylalanine Hydroxylase Gene Locus-Specific Database. Available at: http://www.biopku.org/home/pah.asp (accessed January 2022).

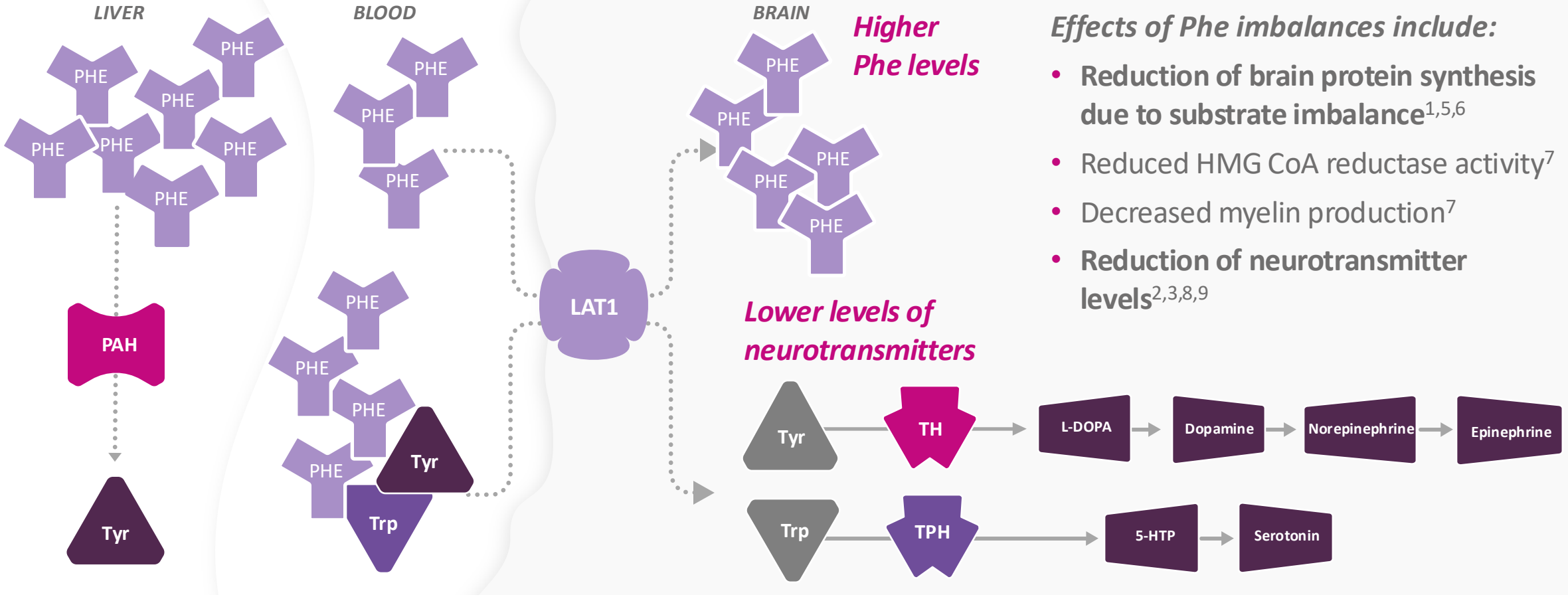
Normal and healthy person[1–3]



5-HTP, 5-hydroxytryptophan; BH_4, tetrahydrobiopterin; LAT-1, L-type amino acid transporter 1; L-DOPA, 3,4-dihydroxy-L-phenylalanine; PAH, phenylalanine hydroxylase; Phe, phenylalanine; TH, tyrosine-3-mono-oxygenase; TPH, tryptophan-5'-mono-oxygenase; Trp, tryptophan; Tyr, tyrosine.

References: 1. Surtees R, *et al. Eur J Pediatr.* 2000;159(Suppl 2):S109–S113. **2.** Blau N, *et al. Lancet*. 2010;376(9750):1417–1427. **3.** Fernstrom JD, Fernstrom MH. *J Nutr*. 2007;137(6 Suppl 1):1539S–1547S;. doi: 10.1093/jn/137.6.1539S.

Proposed pathophysiology in person with PKU[1–4]



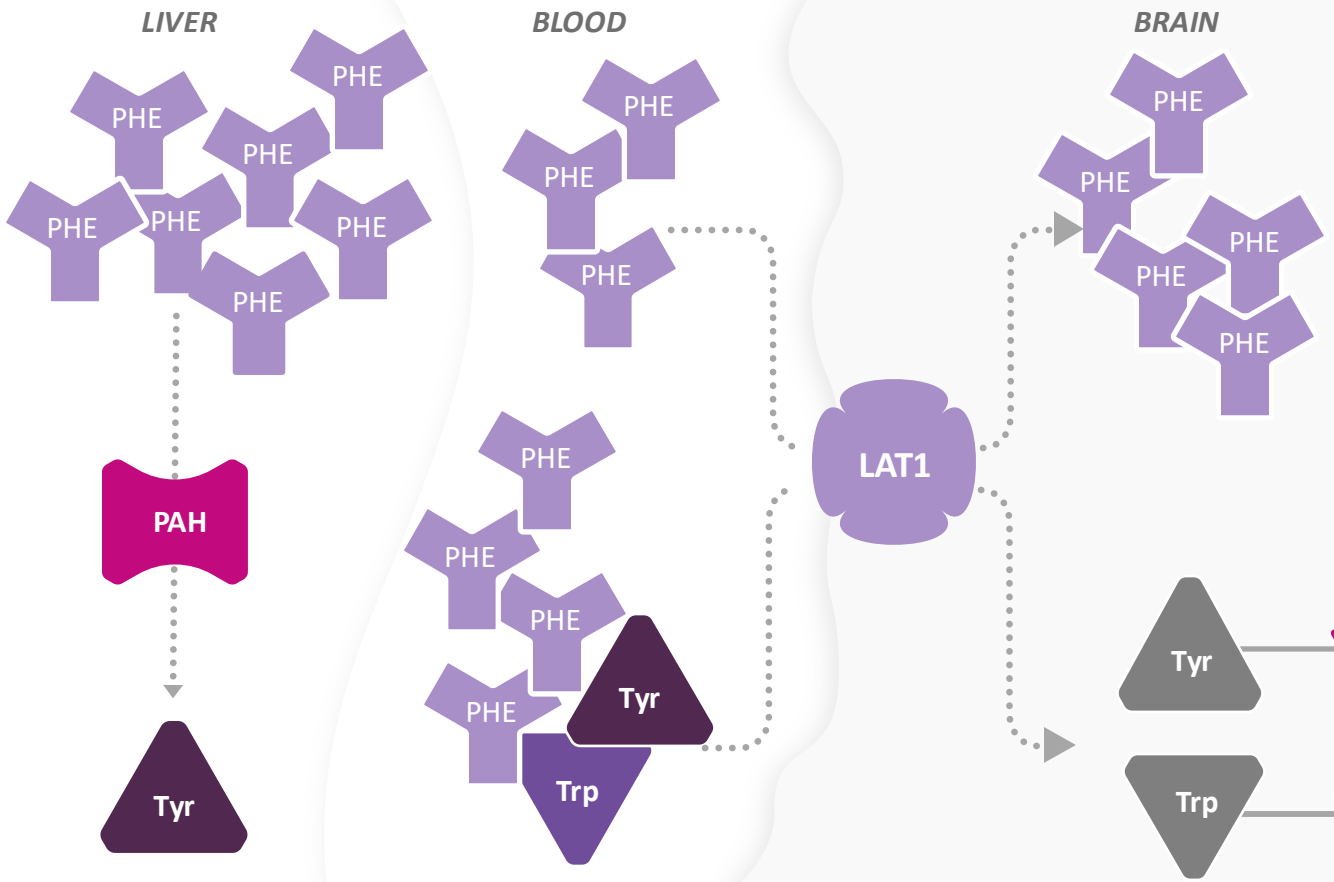
Effects of Phe imbalances include:

- **Reduction of brain protein synthesis due to substrate imbalance**[1,5,6]
- Reduced HMG CoA reductase activity[7]
- Decreased myelin production[7]
- **Reduction of neurotransmitter levels**[2,3,8,9]

5-HTP, 5-hydroxytryptophan; HMG CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LAT-1, L-type amino acid transporter 1; L-DOPA, 3,4-dihydroxy-L-phenylalanine; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; TH, tyrosine-3-mono-oxygenase; TPH, tryptophan-5'-mono-oxygenase; Trp, tryptophan; Tyr, tyrosine.

References: 1. Surtees R, *et al. Eur J Pediatr*. 2000;159(Suppl 2):S109–S113. **2.** Blau N, *et al. Lancet*. 2010;376(9750):1417–1427. **3.** van Spronsen FJ, *et al. J Inherit Metab Dis*. 2009;32(1):46–51. **4.** van Wegberg AMJ, *et al. Orphanet J Rare Dis* 2017;12:162. **5.** Hoeksma M, *et al. Mol Genet Metab*. 2009;96(4):177–182. **6.** de Groot MJ, *et al. Orphanet J Rare Dis*. 2013;8:133. **7.** Shefer S, *et al. J Neurosci Res*. 2000;61:549–563. **8.** Burlina AB, *et al. J Inherit Metab Dis*. 2000;23(4): 313–316. **9.** Ribas GS, *et al. Cell Mol Neurobiol*. 2011;31(5):653–662.

Consequences of neurotransmitter imbalance[1–4]



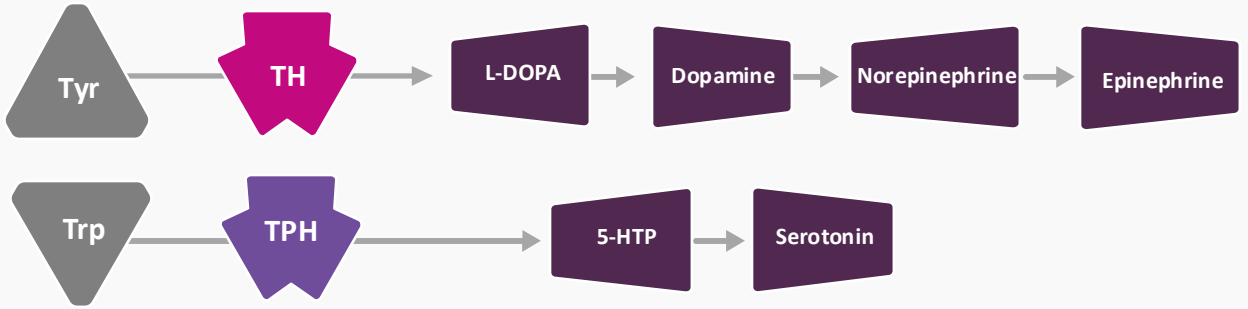
Neurotransmitter imbalance

Dopamine is important for:

- **Reward/motivation**[1]
- **Learning and cognition**[2]
- Motor activity[2]
- Action selection[3]

Serotonin deficits associated with:

- **Depression**[4]
- **Anxiety**[4]



5-HTP, 5-hydroxytryptophan; LAT-1, L-type amino acid transporter 1; L-DOPA, 3,4-dihydroxy-L-phenylalanine; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; TH, tyrosine-3-mono-oxygenase; TPH, tryptophan-5'-mono-oxygenase; Trp, tryptophan; Tyr, tyrosine.

References: 1. Arias-Carrión O, *et al. Int Arch Med.* 2010;3:24. **2.** Rioult Pedotti MS, *et al. PloS One.*DOI:10.1371/journal.pone.0124986. **3.** Howard CD, *et al. Neuron.* 2017;93:1436–1450. **4.** Albert PR, *et al. Front Behav Neurosci.* 2014;8:199.

Signs and symptoms associated with untreated PKU[1–3]

- Some patients are born developmentally normal[1,2]
- **Develop vomiting, 'musty odour', fair complexion[2]**
- **Microcephaly[2]**
- **Severe intellectual disability, IQ <50[1,2]**
- Eczema[2]
- **Autistic-like behaviour, irritability[3]**
- Aggression[3]
- Psychotic-like symptoms[3]
- Depression[3]
- **Social withdrawal[3]**
- **Seizures[1,2]**

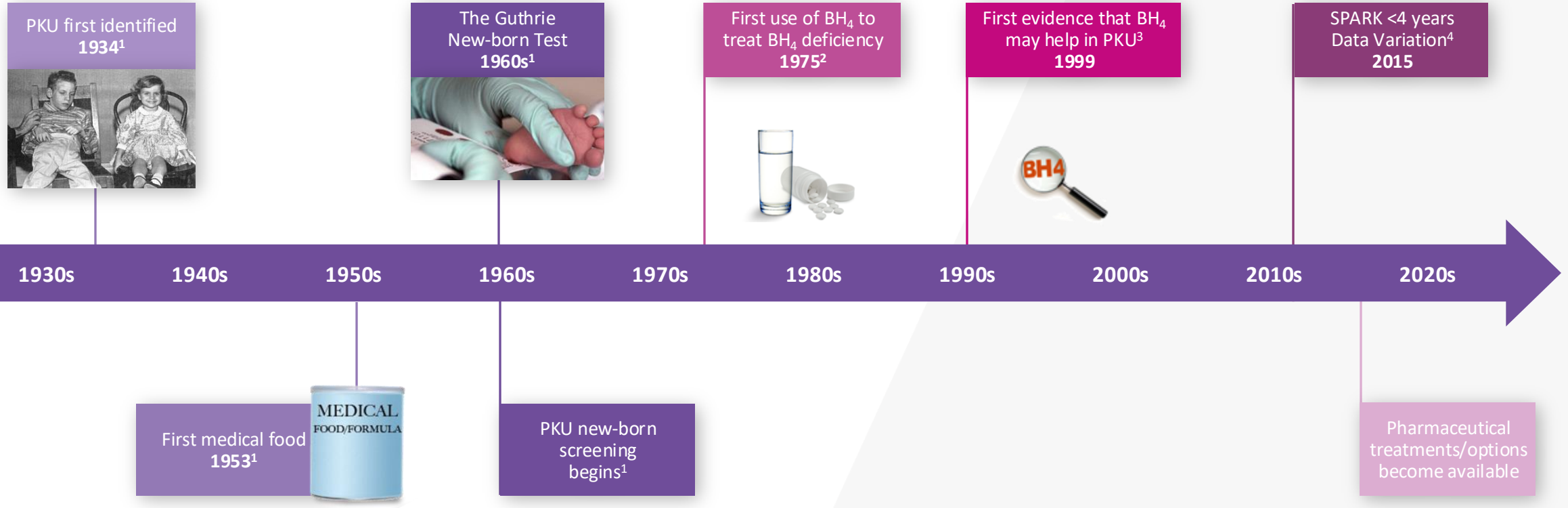
Sheila Jones with and without dietary treatment

Credits: newenglandconsortinum YouTube Channel
https://www.youtube.com/watch?v=-rs0iZW0Lb0

IQ, intelligence quotient; PKU, phenylketonuria.

References: 1. Huttenlocher PR. *Eur J Pediatr*. 2000;159(Suppl 2):S102–S106. **2.** Rezvani and Ficicioglu. Nelson Textbook of Pediatrics. 2016:636–640. **3.** Brumm VL, *et al. Mol Genet Metab*. 2010;99:S59–S63.

The history of PKU[1–7]



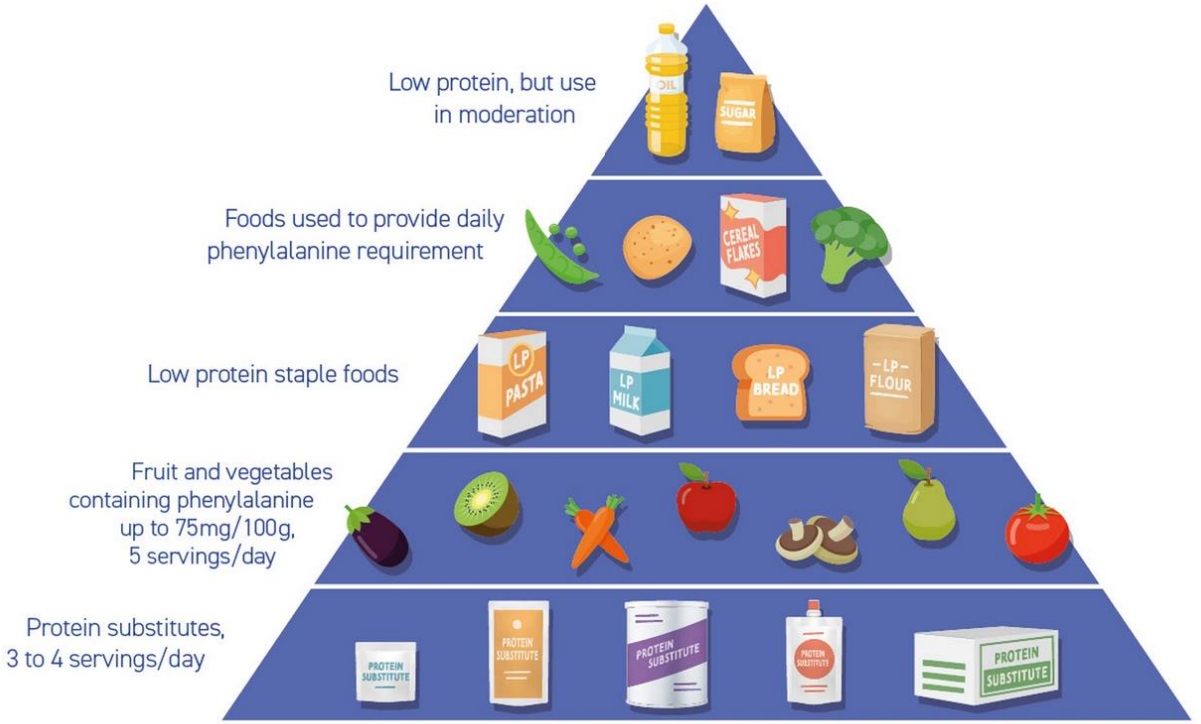
BH_4, tetrahydrobiopterin; PKU, phenylketonuria.

References: 1. Berry SA, *et al. Genet Med*. 2013;15(8):591–599. doi: 10.1038/gim.2013.10. Epub 2013 Mar 7. **2.** Blau N. *Hum Mutat*. 2016 Jun;37(6):508–515. **3.** Hanley WB. In: *Latest Findings in Intellectual and Developmental Disabilities Research*. 2012; DOI: 10.5772/29008. **4.** European Medicines Agency. Assessment report EMA/CHMP/329625/2015. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000943/WC500191479.pdf (accessed November 2021).

Historical mainstay of treatment: the PKU diet[1–3]

- **Exclusion of foods high in natural protein**
  e.g. meat, fish, eggs, nuts and seeds[1-3]
- **Restrictions on…**[1,2]
  - **Grains** e.g. bread, cereals
  - **Some vegetables** e.g. sweetcorn, peas
  - **Potatoes** and potato products e.g. chips
- **Most protein obtained from Phe-free substitutes**[1]

A Phe-restricted diet becomes increasingly difficult to adhere to and maintain throughout life[1]



Adapted from MacDonald A, *et al.*[3]

Phe, phenylalanine; PKU, phenylketonuria

References: 1. Blau N, *et al. Lancet*. 2010;376:1417–1427. **2.** Blau N. Phenylketonuria and BH4 deficiencies. 3rd Edition; Bremen:UNI-MED, 2016. **3.** MacDonald A, *et al. Orphanet J Rare Dis.* 2020;15:171 https://doi.org/10.1186/s13023-020-01391-y.

The burden of following a PKU diet for life[1–3]

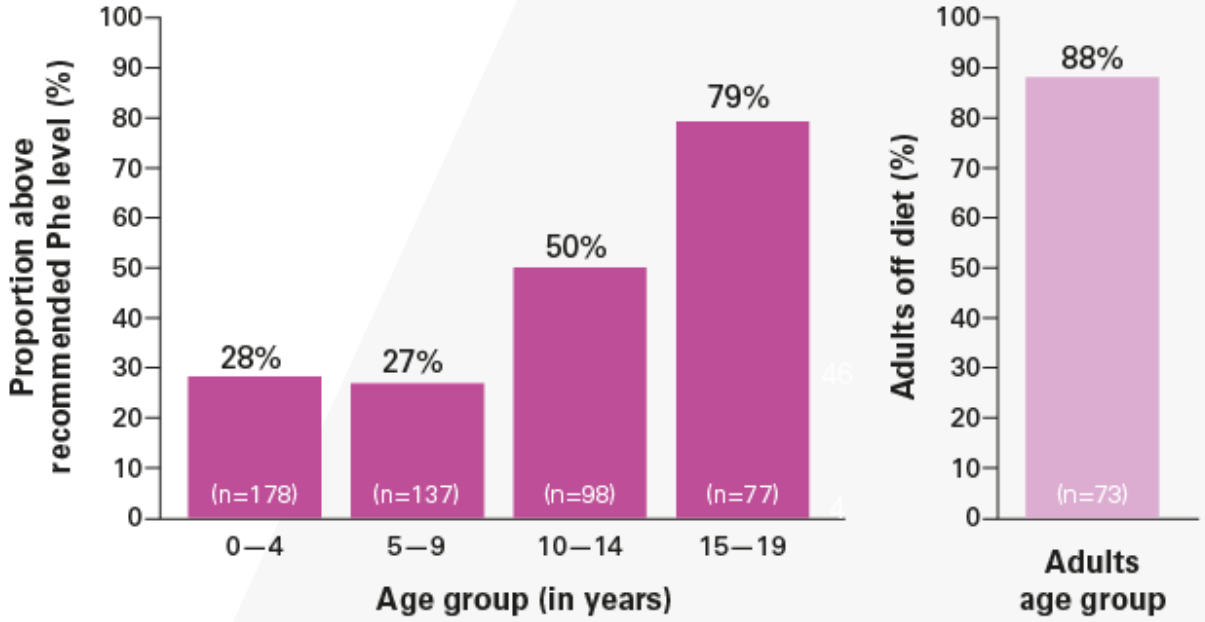
- **Planning and preparing meals is time-consuming[1]**
- Protein substitutes can be unpalatable[2]
- Hard for young families – diet requires commitment from parents[3]
- **Meals need to be rigorously planned and children can't consume the same food as their peers[3]**
- Compliance is often poor in adolescence[3]
- **Diet especially difficult to maintain in adults, leading to discontinuation[3]**

PKU, phenylketonuria.

References: 1. Blau N. Phenylketonuria and BH4 deficiencies. 3rd Edition; Bremen:UNI-MED, 2016. **2.** MacDonald *A, et al*. *Arch Dis Child.* 2003;88:327–329. **3.** Blau N, *et al. Lancet*. 2010;376:1417–1427.

Poor dietary adherence leads to poor Phe control[1–3]

- **PKU patients can find adherence difficult at any age[1]**
- In adolescence there is:
  - **Reduced adherence** due to desire for independence and peer pressure[2]
  - **High risk of being lost to follow-up** when transitioning from paediatric to adult care[2]
- **Those with elevated Phe may find adherence difficult due to cognitive impairment[3]**



Adapted from Enns GM, *et al.*[1]

Phe, phenylalanine; PKU, phenylketonuria.

References 1. Enns GM, *et al. Mol Genet Metab*. 2010;101:99–109. **2.** Vockley J, *et al. Genet Med*. 2014;16(2):188–200. **3.** Jurecki ER, *et al. Mol Genet Metab*. 2017;120(3):190–197.

Suboptimal outcomes can exist in all age groups[1]

- A growing body of evidence suggests that **neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology and maternal PKU outcomes are suboptimal** in PKU patients treated early with diet alone.[1]

Infants	Children/adolescents*	Adults*	Seniors
• Reduction in LC-PUFA status[2]	• White matter abnormalities and decrease in brain volume[4]	• White and grey matter abnormalities[11]	• Patients diagnosed at birth are now 50-60s years old[16]
• Deficits in cognitive functioning/abilities[2,3]†	• Deficits in cognitive functioning/abilities[5]†	• Deficits in cognitive functioning/abilities[12]†	• Long-term repercussions of dietary management under debate[16]
	• Linear growth impairment[6] /overweight[7]	• Increased BMI/overweight[13]	
	• High rates of internalising problems[8]	• Behavioural problems[14]	
	• Learning difficulties and reduced academic achievement[9,10]	• Anxiety/depressiveness[15]	

Adapted from Enns GM, *et al.*[1]

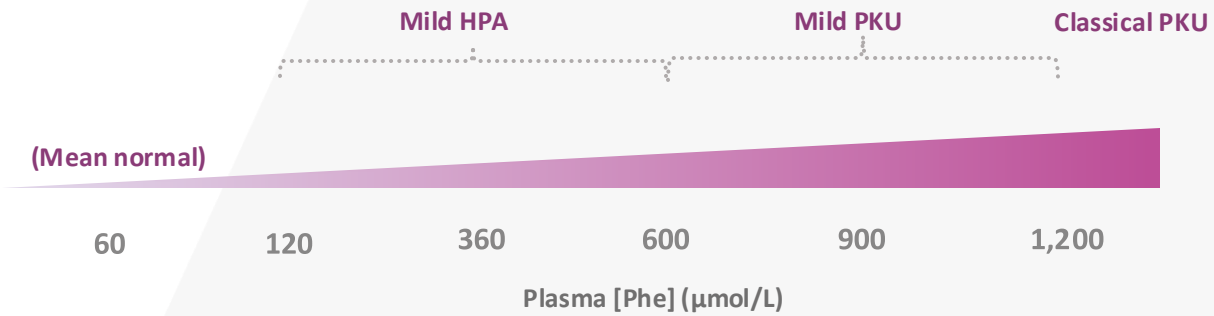
*Includes early-treated PKU patients who may or may not be adhering to dietary treatment.
†Measures of deficit in cognitive functioning/abilities in PKU were too many to list in entirety.
BMI. Body mass index; LC-PUFA, long-chain polyunsaturated fatty acids; PKU, phenylketonuria.

References 1. Enns GM, *et al. Mol Genet Metab*. 2010;101:99–109. **2.** Agostoni C, *et al. Dev Med Child Neurol*. 2003;45:257–261. **3.** Malloy-Diniz LF, *et al. Arq Neuropsiquiatr* 2004;62:473–479. **4.** White DA, *et al. Mol Genet Metab.* 2010;99(01):S41–S46. **5.** Janos AL, *et al. Neuropsychol*. 2012;26(6):735–743. **6.** Arnold G,L *et al. Pediatr.* 2002;141:243–246. **7.** Acosta PB, *et al. J Am Diet Assoc.* 2003;103:1167–1173. **8.** Weglage J, *et al. J Inherit Metab Dis.* 2000;23:487–496. **9.** Chang PN, et al. Eur J Pediatr 2000;159 (Suppl 2):S96–S99. **10.** Gassio R, *et al. Pediatr Neurol* 2005;33:267–271. **11.** Ding XQ, *et al. J Magn Reason Imag*. 2008;27:998–1004. **12.** Moyle JJ, *et al. Neuropsychol Rev*. 2007;17:91–101. **13.** Macleod EL, *et al. Mol Genet Metab.* 2009;98:331–337. **14.** Smith I, *et al. Eur J Pediatr.* 2000;159:S89–S93. **15.** Bik-Multanowski M, *et al. J Inherit Metab Dis.* 2009;32:126. **16.** Vardy ERLC, *et al. J Inherit Metab Dis.* 2020;43:167–178.

A wide spectrum of disease based on residual enzyme activity and blood Phe level[1–4]

- Allelic variation leads to…[2,3]
  - **Heterogeneous disease severity**
  - **Heterogeneous response to therapy**
- **Patients have varying degrees of dietary and treatment adherence[3]**
- Evolving standards of care are not uniform between regions[3]

- **No global consensus on classification system**
  - **European guidelines.** Patients with PAH deficiency classified as either: a) Not requiring treatment or b) Requiring diet, BH4 or both[3]
  - **ACMG guidelines.** HyperPhe defined as any blood Phe > normal range, but allow for ‘classic’ PKU (>1200 µmol/L)[2]
  - Most literature is based on following categorisation:[4]



ACMG, American College of Medical Genetics; BH_4, tetrahydrobiopterin; HPA, hyperphenylalaninemia; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

References: 1. Trefz KF, *et al. Orphanet J Rare Dis*. 2019;14:181. **2.** Vockley J, *et al. Genet Med*. 2014;16(2):188–200. **3.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162. **4.** Blau N, van Spronsen FJ, Levy HL. *Lancet.* 2010;376:1417–1427.

Different cohorts have different phenotypes[1–3]

Toxic effects of high Phe are dependent on many factors[1]

- Age at diagnosis
- Historical Phe variability
- Average Phe level
- Genetic factors

Early-treated (ETPKU)[2]

Treatment initiated before the age of 3 months

Subcategories

- Early and continuously treated
- Early treated but relaxed/ discontinued

Late-treated PKU[2]

Treatment begun between 3 months and 7 years of age

Untreated PKU[2]

Untreated at age 7 or older

Increasing severity of disease

Lost to follow-up ('LTFU')

??

Approx. one third of PKU patients of all ages are LTFU[3]

LTFU, lost to follow-up; Phe, phenylalanine; PKU, phenylketonuria.

References: 1. Blau N, van Spronsen FJ, Levy HL. *Lancet.* 2010;376:1417–1427. **2.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162. **3.** Jurecki ER, *et al. Mol Genet Metab.* 2017;120(3):190–197.

Understanding of PKU has evolved[1–3]

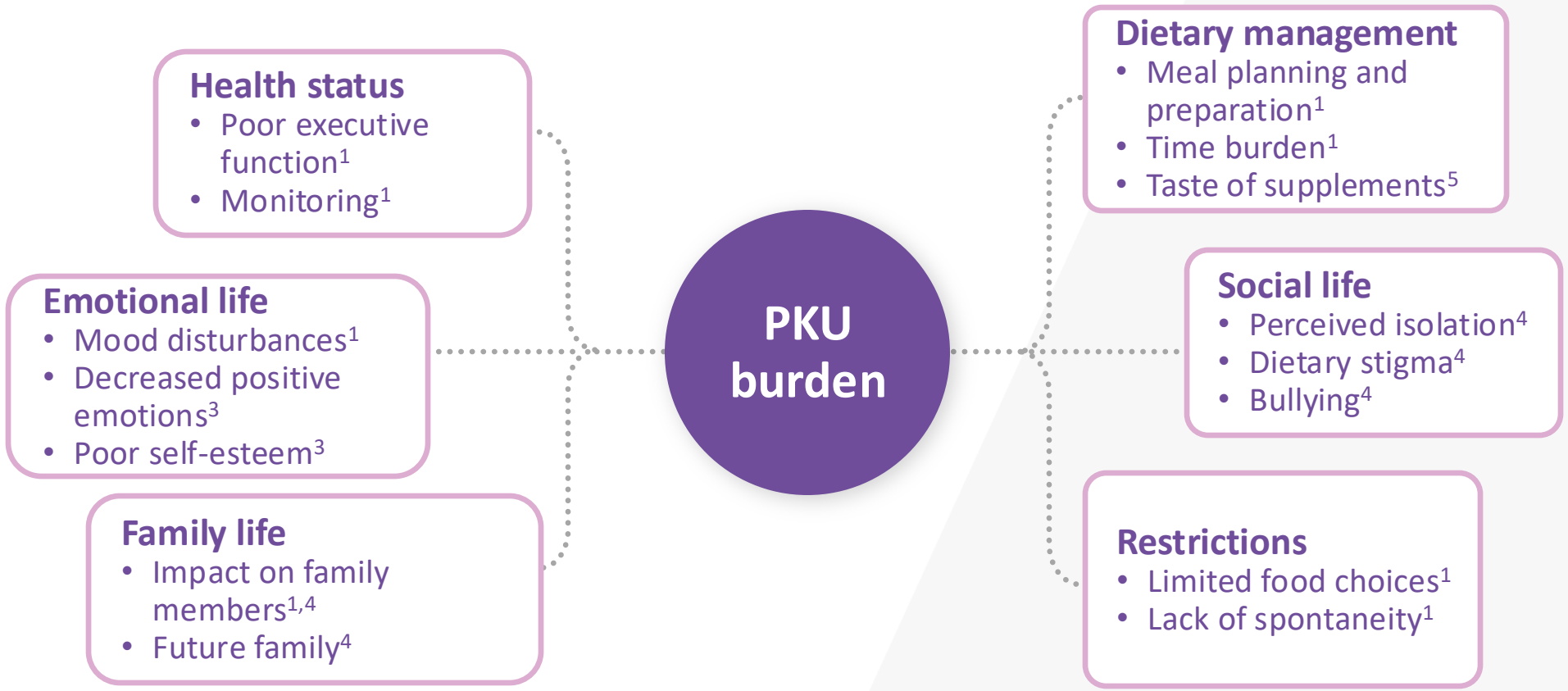
But suboptimal outcomes remain[2] › PKU should be treated for life[2,3] ›

- **These measures have prevented intellectual disability** previously associated with PKU[1–3]
- However, **patient outcomes are still not comparable to their unaffected siblings**[2]
- International consensus is that **PKU should be treated for life**[2,3]

  EU: Phe target, 120-600 µmol/L[2*]
  US: Phe target, 120-360 µmol/L[3]

*Patients > 12 years old.
Phe, phenylalanine; PKU, phenylketonuria.
References: 1. Burton BK, *et al. Mol Genet Metab*. 2010;101:110–114. **2.** van Spronsen FJ, *et al. Lancet Diabetes Endocrinol*. 2017;5:743–756. **3.** Vockley J, *et al. Genet Med*. 2014;16:188–200.

PKU places a personal burden on people with PKU and their caregivers[1,2]



PKU, phenylketonuria.

References: 1. Eijgelshoven I. *et al. Mol Genet Metab.* 2013; 109: 237–242. **2.** MacDonald A. *et al. Mol Genet Metab Rep.* 2016; 9: 1–5. **3.** Brumm VL, *et al. Mol Genet Metab.* 2010;99(Suppl 1):S59–S63. **4.** Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63. **5.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162.

PKU patients may lack self-awareness[1]

A survey of 111 adult PKU patients in Italy found that:

40% did not consider PKU to be a disease[1]

A study of adherent (n=12) and non-adherent (n=9) young adults with PKU in Italy found that:

Non-adherent patients

- Were aware of consequences of non-adherence in children, but not adults[2]
- **Did not fully accept their disease**[2]
- **Failed to recognise PKU symptoms**[2]
- Reported **more emotional issues** related to PKU[2*]
- Seemed to be **lacking organisational/planning ability**[2*]

*versus adherent patients

Phe, phenylalanine; PKU, phenylketonuria.

References 1. Cazzorla C, *et al. Mol Genet Metab Rep.* 2018;16:39–45. **2.** Borghi L, *et al. Mol Genet Metab Rep.* 2020;100585.

PKU patient stories

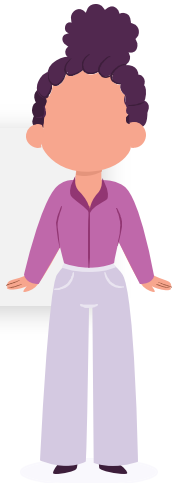
Kevin
Lost to follow up

Cindi
Diagnosed age 12

Practical, social and psychological issues of people living with PKU[1]

- **One of the largest surveys of people living with PKU (n=631)**[1]
- Participants from the UK identified **significant neurocognitive, mental health and general health issues**[1]

Problems experienced by adults with PKU:[1]



Problems experienced by children with PKU:[1†]

Limits on socialisation, perception of social isolation and dietary stigma are major obstacles which are difficult to overcome with conventional dietary management.[1]

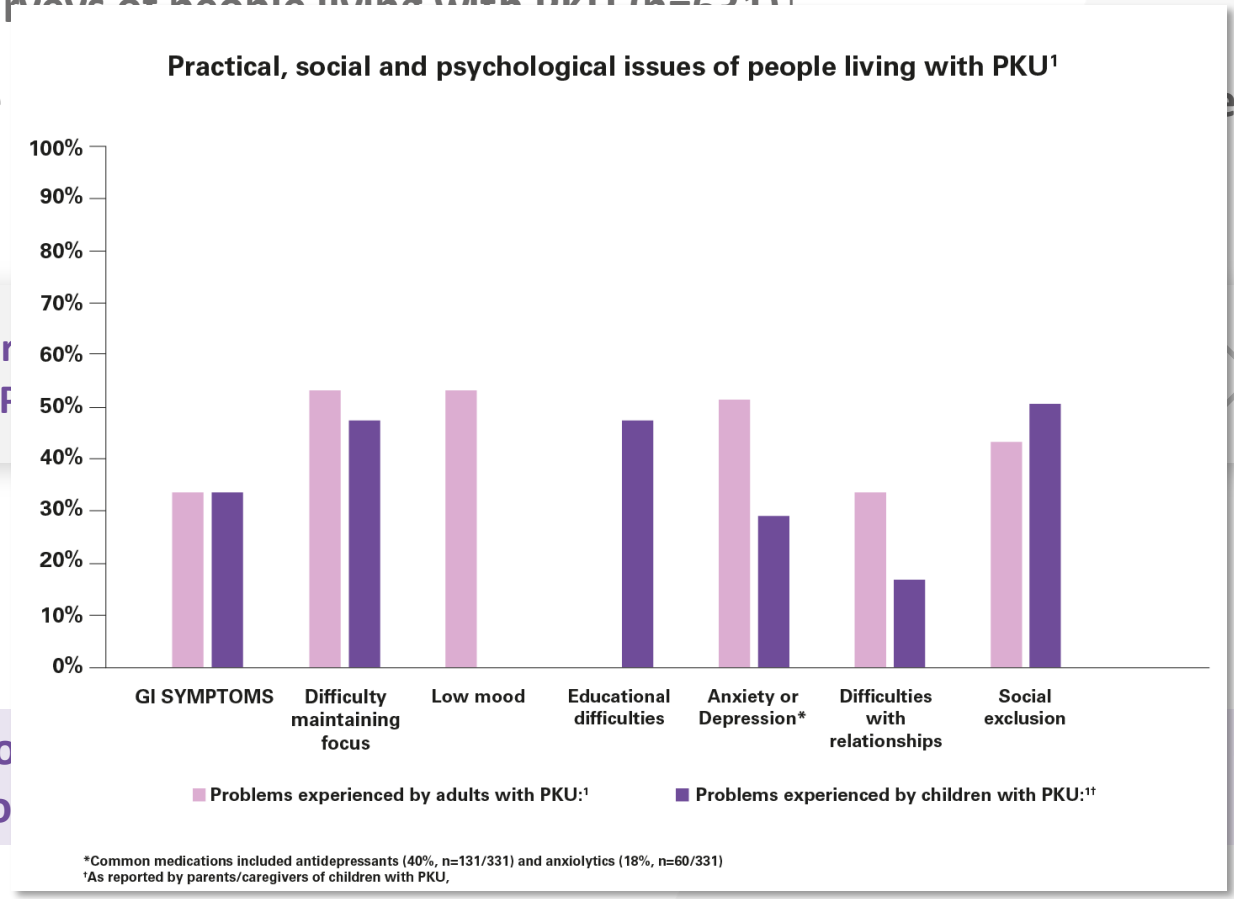
PKU, phenylketonuria.

Reference: 1. Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63.

Practical, social and psychological issues of people living with PKU[1]

- One of the largest surveys of people living with PKU (n=631)[1]
- Participants from the [illegible] eneral health issues[1]

Problems exper[illegible]
by adults with P[illegible]



Limits on socialisatio[illegible] obstacles which are difficult
to overcome with co[illegible]

GI, gastrointestinal; PKU, phenylketonuria.

Reference: 1. Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63.

Living with PKU: low Phe diet and protein supplements[1]

Low Phe diet

Sticking to the diet all the time requires a tremendous amount of discipline and self-control.[1]
– Adult patient

My daughter, as a teenager, does not stick to the diet. She is often grumpy and resents having a disorder that other people do not understand… much of her life is restricted particularly in social situations.[1]
– Caregiver

If Phe levels are raised, then your ability to stick to the diet is diminished leading to a vicious circle scenario.[1]
– Adult patient

As you get older you learn more and at least you start to understand the importance of it, but by this point you've gotten so used to fighting against it, it is hard to get back to a proper PKU diet.[1]
– Adult patient

Protein supplements

Our greatest struggle is getting our son taking his supplements. He refuses to take it and it can take up to 45 min for him to finish one with a lot of upsets.[1]
– Caregiver

Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63.

Living with PKU: eating and social isolation[1]

Eating

I am a foodie and eat everything I want. I have no self-control for the PKU diet and have never been back on it since my teens.[1]
– Adult patient

I also have a horrible relationship with food but no counselling is available to me… It's also extremely restrictive and I get stressed, fed up and upset about food very easily.[1]
– Adult patient

Social isolation

My daughter gets extremely upset in social situations. She gets very panicky about the food and what she can and cannot have. I still haven't been able to leave her at a party.[1]
– Caregiver

I do find it difficult having PKU. I would love to just say 'Let's go out for dinner!' and not have to sit there thinking of where to go that will cater for me well. It makes me feel like a burden within my friendship group.[1]
– Adult patient

Phe, phenylalanine; PKU, phenylketonuria.
References: 1. Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63.

Living with PKU: quality of life affects patients and caregivers[1]

Adult patients

I feel that I am not able to realise my potential at work and in relationships with friends and family.[1]
– Adult patient

I conform to the diet.
I take all my medication.
I maneuver my whole life around it.
I STILL SUFFER.[1]
– Adult patient

Parent / Caregivers

There's never a break - home, school, social events it's a cloud that hangs over her.[1]
– Parent / Caregiver

When you can cause irreversible brain damage to your child, it causes a lot of worry, stress and even panic.[1]
– Parent / Caregiver

...having a child with PKU has been the most difficult thing I have experienced in my life because of my child's continual rebellion against the condition...the fact that it will never go away has had a massive detrimental impact on my mental health and wellbeing.[1]
– Parent / Caregiver

Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Ford S, O'Driscoll M, MacDonald A. *Mol Genet Metab Rep.* 2018; 17: 57–63.

Personal time and cost burden of living with PKU[1]

A **systematic literature review** identified PKU management factors that potentially cause a **time or financial burden**[1]

- Findings were confirmed by PKU experts and patients/ caregivers and a questionnaire was developed[1]
- **22 adult patients and 24 caregivers from 7 metabolic centers in the Netherlands** were surveyed on personal impact of the factors[1]

Median time burden of managing PKU[1]

527 hours/year – **caregivers**[1]

175 hours/year – **adult patients**[1]

46% of time is spent cooking/preparing meals for a Phe-restricted diet[1]

11% of time is spent monitoring protein/ Phe intake[1]

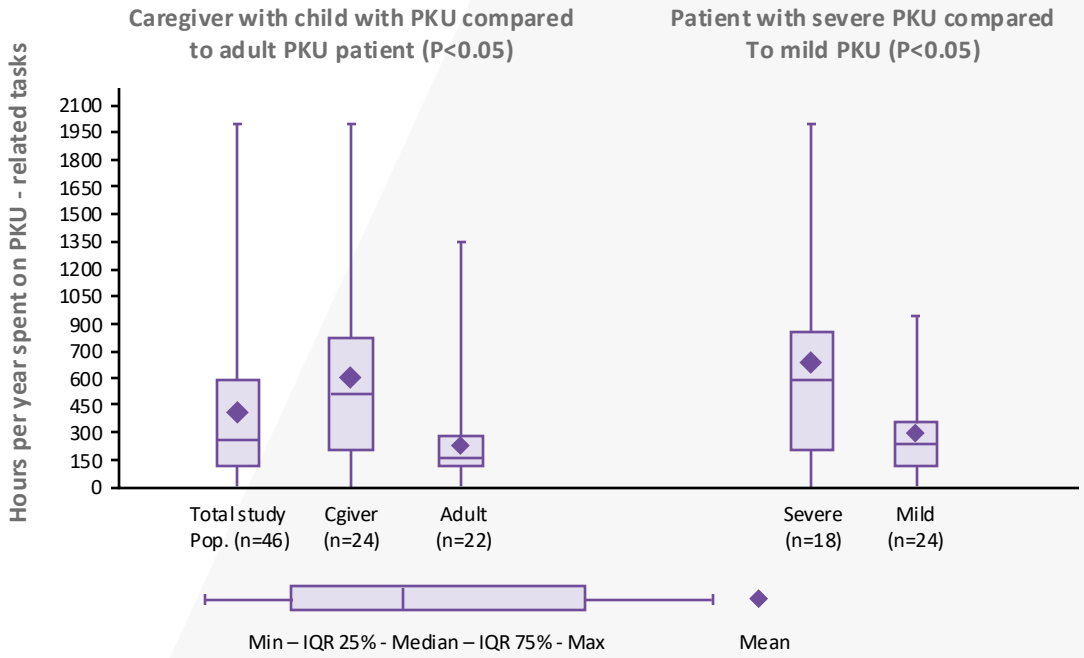
Managing a Phe-restricted diet imposed a daily time burden of 1 h and 24 mins for caregivers and 30 mins for adults.[1]

H, hour; IQR, interquartile range; Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Eijgelshoven I, *et al. Mol Genet Metab.* 2013; 109: 237–242.

Personal time and cost burden of managing PKU[1]

- **Caregivers spent significantly more time managing PKU than adult patients** (*P*<0.05)[1]
- 'Severe' PKU patients spent significantly more time on PKU-related tasks than 'mild' patients (*P*<0.05)[1]
- **The main cost burden was expenditure on low protein food**[1]



Adapted from Eijgelshoven I, *et al.*[1]

The most important outcome of the study was the considerable time burden PKU places on patients and families.[1]

Cgiver, caregiver; IQR, interquartile range; Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Eijgelshoven I, *et al. Mol Genet Metab.* 2013; 109: 237–242.

Relationships between childhood experiences and adulthood outcomes in women with PKU[1]

- **Study to explore how key childhood experiences shape the adult experience of PKU**[1]
- **Eight women with PKU from Australia** underwent semi-structured interviews which were evaluated using thematic analysis[1]
- Interviews revealed **these childhood factors had a combined long-term impact**:[1]

Feelings of difference to peers due to eating behaviour	Parental and extended family support	Increased difficulty with dietary compliance during adolescence	Perception of PKU as a burden

These findings suggest early psychosocial intervention relating to these childhood experiences has the potential to enhance positive outcomes for adults with PKU.[1]

PKU, phenylketonuria.

Reference: 1. Roberts RM, *et al. JIMD Rep.* 2016; 17: DOI 10.1007/8904_2016_567.

Adult outcomes in PKU may be related to childhood experiences[1]

Negative experiences in childhood tended to turn into **negative** experiences in adulthood, whereas **positive** experiences in childhood tended to turn into **positive** experiences in adulthood[1]

Negative experiences[1]

Participant 1 reported poor mental health and was not on diet.

She discussed feeling socially excluded as a child.

She reported less support than many other participants from her parents and extended family, as well as perceiving PKU as a burden.

Positive experiences[1]

Participant 5 reported good mental health and was on diet (strict).

She described extensive parental and extended family support as a child.

She did not report feeling socially excluded as a child and did not perceive PKU as a burden.[1]

PKU, phenylketonuria.

Reference: 1. Roberts RM, *et al. JIMD Rep.* 2016; 17: DOI 10.1007/8904_2016_567.

Relationships between childhood experiences and adulthood outcomes in women with PKU – childhood themes[1]

Feeling different to peers

...you see all your friends eating this and then you're like, well I can't have that and they're all buying their lunch and you can't buy nothing cos you know, it's pies and pasties and everything else.[1]

Parental support
(positive and negative)

…extremely thankful to my parents for sticking to the diet so umm, so greatly and so accurately, because you know, here I am…a graduate student, I've got a profession...[1]

…mum never experimented with me, like with the drinks and food and stuff.[1]

Extended family support

…if there was a big party or something, they'd ring mum and say, you know, what can she have. Or we've made her this, so she can have that as well…always made sure I had something so yeah, it was good.[1]

Managing PKU during adolescence

…a teenager's brain would not care at all about what happens in the future.[1]

Perception of PKU as a burden

Having to eat all my low protein foods and do all that type of thing and have my supplements, take them to friends' places. Or even something as simple as going on camps and stuff like that…That would probably be the hardest thing.[1]

PKU, phenylketonuria.

Reference: 1. Roberts RM, *et al. JIMD Rep.* 2016; 17: DOI 10.1007/8904_2016_567.

Relationships between childhood experiences and adulthood outcomes in women with PKU – adult themes[1]

Eating out socially

. . .so really socially, it's probably been an impact and going to parties and things like that. Having functions on where umm. . . I almost have to eat before I go, I can't eat there..[1]

Attitude towards PKU

(negative and positive)

…oh my god, this is so hard, I've gotta weigh everything, I can't go out, I can't do this, I have to take my own food with me, so it is a big, it is a big stress…[1]

I don't really worry about it, I don't think about it. . .I've had it my whole life, it's who I am, you know.[1]

Psychological wellbeing

…my eating was umm…a problem for me…so I think it [PKU] might have been a part of it. Like it was all, like cuz I wasn't allowed. I didn't have a choice, I wasn't allowed to…[1]

(Participant with previous eating disorder).

Effects of dietary compliance

I can feel it. I just go, oh I feel like my brain's all fuzzy and I can't think straight…[1]

Management of PKU

I like the liberty of having a normal cookie or biscuit every now and again.[1]

PKU, phenylketonuria.

Reference: 1. Roberts RM, *et al. JIMD Rep.* 2016; 17: DOI 10.1007/8904_2016_567.

PKU patients with high Phe levels risk serious neurological and neuropsychological complications[1–3]

- **Poor neurocognitive outcomes such as impaired executive functioning can have a profound effect on day-to-day life**[4,5]
- This can add to **poor dietary adherence** and **initiates a cycle of decline**[4,6]
- Poor adherence particularly **impacts young adults who may be transitioning to self-management**[6]
- European guidelines set out clear goals for adult treatment, one of which is **to achieve normal neurocognitive and psychosocial functioning**[7]

The key to reducing health risks associated with PKU is metabolic control throughout life.[6]

Phe, phenylalanine; PKU, phenylketonuria.

References: **1.** Bilder DA *et al. Dev Neuropsychol.* 2016;41(4):245–260. **2.** Bilder DA *et al. Mol Genet Metab.* 2017;121(1):1–8. **3.** Jahja R *et al. Neuropsychology.* 2017;31(4):437–447. **4.** Enns GM, *et al. Mol Genet Metab.* 2010;101:99–109. **5.** Brumm VL, *et al. Mol Genet Metab.* 2010;99(Suppl 1):S59–S63. **6.** Gentile JK, Ten Hoedt AE, Bosch AM. *Mol Genet Metab.* 2010;99:S64–S67. **7.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162.

Blood Phe vs IQ[1]

Observation period	Range of blood Phe (µmol/L)	Lifetime IQ loss for each 100 µmol/L increase in blood Phe
Critical period (0–12 years old)	423–750	1.3–3.1
Lifetime (all ages)	394–666	1.9–4.1

A 100 µmol/L increase in lifetime Phe

Results in a 1.9–4.1-point reduction in IQ

IQ, intelligence quotient; Phe, phenylalanine.

Reference: 1. Waisbren SE, *et al. Mol Genet Metab*. 2007;92(1-2):63–70.

Blood Phe vs IQ[1]

- Variability in blood Phe levels is a better predictor of IQ in ETPKU than mean blood Phe[1,2]
- **In a study of 47 school-age children with early-treated and continuously treated PKU, Phe variability was the strongest predictor of cognitive performance**[1]
- In a retrospective chart review of 46 early-treated and continuously treated children, **FSIQ decreased 4.3 points with every 1-point increase in standard deviation of blood Phe**[2]
  - The correlation between the SD of blood Phe levels and most recent FSIQ was -0.36 (P=0.06)[2]

ETPKU, early treated PKU; FSIQ, full-scale intelligence quotient; Phe, phenylalanine; PKU, phenylketonuria, SD, standard deviation, IQ, intelligence quotient;

References: 1. Hood A, *et al. Mol Genet Metab*. 2014;111(4):445–451. **2.** Anastasoaie V, *et al. Mol Genet Metab*. 2008;95(1-2):17–20.

Patients with PKU may have subtle neurocognitive and neuropsychiatric deficits despite early treatment[1,2]

Early-treated children and adolescents

- Attention problems[1,2]
- School problems[1,2]
- Less achievement motivation[2]
- Decreased social competence[1,2]
- Decreased autonomy[1,2]
- Low self-esteem[1,2]

Early-treated adults

- Depressed mood[1,2]
- Generalised anxiety[1,2]
- Phobias[1,2]
- Decreased positive emotions[1,2]
- Low self-esteem[1,2]
- Social maturity deficits[1,2]
- Social isolation/ withdrawal[1,2]
- Lack of autonomy[1,2]

PKU, phenylketonuria.

References: 1. Enns GM, *et al. Mol Genet Metab.* 2010;101:99–109. **2.** Brumm VL, *et al. Mol Genet Metab.* 2010;99(Suppl 1):S59–S63.

Executive function: a set of cognitive abilities critical to perform everyday life activities[1–5]

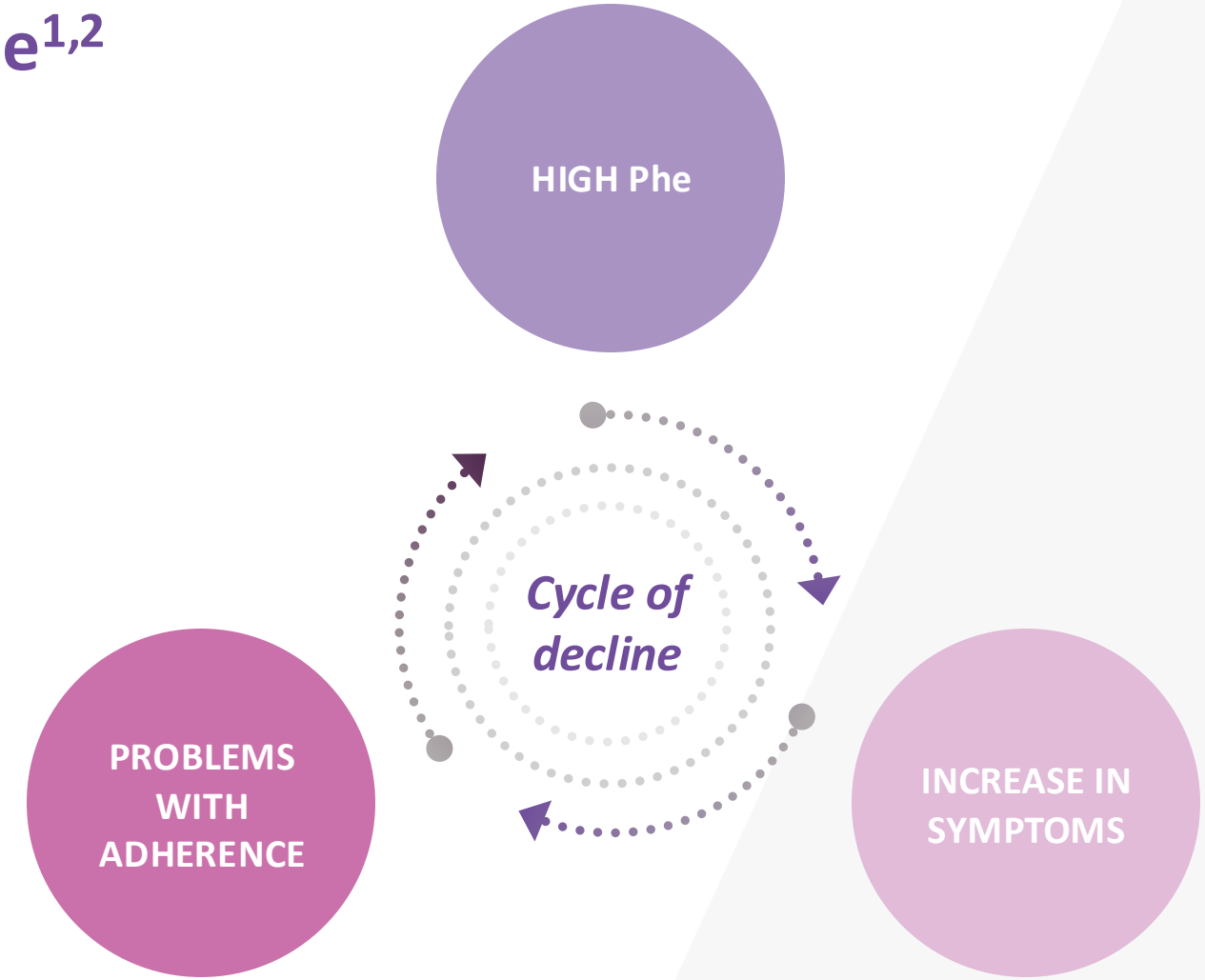
- **A collection of cognitive skills that are required to self-regulate and organise mental efforts in order to achieve goals**[1,2]
- Measured by neuropsychological tests like CANTAB and BRIEF-A[3,4]
- **Executive function is believed to be particularly affected in PKU**[1]

Executive function area	Day-to-day impact
Processing speed	Comprehension, ability to complete tasks, and school or work performance[5]
Working memory	The ability to hold information in mind that will be used to guide one's actions, whether now, or at a later time[1]
Attention	Ability to sustain attention or persistence of effort to tasks[2]
Impulse control	Self-control to avoid 'off limit' foods, refraining from outbursts[2,5]
Planning & organising	Thinking out acts and purposes in advance – meal planning, task planning, thought organisation[5]

BRIEF-A, Behaviour Rating Inventory of Executive Function–Adult Version; CANTAB, Cambridge Neuropsychological Test Automated Battery; PKU, phenylketonuria.

References: 1. Christ SE, *et al. Mol Genet Metab.* 2010;99(3):S22–S32. **2.** Karbach J, Unger K. *Front Psychol*. 2014;5:390. **3.** Waisbren S, White DA. *Mol Genet Metab.* 2010;99(S1):S96–S99. **4.** Bik-Multanowski M, Pietrzyk JJ, Mozrzymas R. *Mol Genet Metab.* 2011;102(2):210–213. **5.** Gentile JK, Ten Hoedt AE, Bosch AM. *Mol Genet Metab.* 2010;99:S64–S67.

Cycle of decline[1,2]



Phe, phenylalanine.

References: 1. Enns GM, *et al. Mol Genet Metab.* 2010;101(2–3):99–109. **2.** Gentile JK, *et al. Mol Genet Metab.* 2010;99(Suppl 1):S64–S67.

PKU patient case vignettes – neurocognitive and psychosocial effects of low Phe[1]

Ms T a 43-year-old single woman[1]

- Diagnosed after 12 m
- Dietary treatment from 18 m to 9 years
- Resumed diet aged 30

Mr C a 47-year-old engineer, father of two[1]

- Diagnosed at birth
- Dietary control was “strict” until age 13, “relaxed” until age 17, then ceased

Ms N a 36-year-old married lady[1]

- Diagnosed at birth
- Adhered to a low Phe diet until 7 years old then ceased
- Recommenced on diet at age 35 due to symptomatic PKU

Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Ashe K, *et al. Front Psychiatry*. 2019;10:561.

PKU patient case vignettes – neurocognitive and psychosocial effects of low Phe[1]

Ms T a 43-year-old single woman[1]

- Ms T presented with attentional deficits, hyperactivity and social cognition issues throughout childhood
- She developed a psychotic illness in her late teens. This was largely treatment refractory. During periods of poor dietary control (Phe >1,500 µmol/L), she suffered from poor frustration tolerance and impulse control, anxiety and worsened chronic hallucinations
- When dietary control was good (Phe 400–600 µmol/L), psychotic symptoms were significantly attenuated, anxiety was minimal, and impulse control returned to normal

Mr C a 47-year-old engineer, father of two[1]

- Diagnosed at birth
- Dietary control was “strict” until age 13, “relaxed” until age 17, then ceased

Ms N a 36-year-old married lady[1]

- Diagnosed at birth
- Adhered to a low Phe diet until 7 years old then ceased
- Recommenced on diet at age 35 due to symptomatic PKU

Phe, phenylalanine; PKU, phenylketonuria; SSRI, selective serotonin reuptake inhibitor.

Reference: 1. Ashe K, *et al. Front Psychiatry*. 2019;10:561.

PKU patient case vignettes – neurocognitive and psychosocial effects of low Phe[1]

Ms T a 43-year-

- Ms T presented with
hyperactivity and so
throughout childhoo
- She developed a psy
teens. This was large
During periods of po
>1,500 µmol/L), she
frustration tolerance
anxiety and worsene
- When dietary contro
µmol/L), psychotic s
significantly attenua
and impulse control

Ms N a 36-year-old married lady[1]

- Ms N had a long history of mental health difficulties starting in childhood. She had difficulties regulating her mood and had episodes of depression
- Had her first panic attack in her mid-teens, along with generalized anxiety symptoms and infrequent self-harming behaviours. She had been under psychiatric care since her teenage years and had several psychiatric admissions
- Saw a psychologist on a regular basis and had been on SSRIs since her early 30s, with some improvement
- She reported significant cognitive limitations, including difficulties with attention and concentration, memory, planning, and organisation and slowed mental processing
- These difficulties had affected her ability to maintain productive employment, leading to feelings of inferiority and low self-esteem
- After 12 months of good dietary control (reducing Phe from ~700 to <300 µmol/L), she made statistically significant improvements on tasks of psychomotor speed (from 9 percentile at baseline to 63 percentile on diet), planning and organization (from <0.1 percentile at baseline to 77 percentile on diet), divided attention (from 9 percentile at baseline to 50 percentile on diet), and self-monitoring (from 1 percentile on diet to 37 percentile on diet)

Phe, phenylalanine; PKU, phenylketonuria; SSRI, selective serotonin reuptake inhibitor.

Reference: 1. Ashe K, *et al. Front Psychiatry*. 2019;10:561.

PKU publications: burden of illness studies

Data	Topic	Reference
Systematic review and meta-analysis	**Neuropsychiatric symptoms in executive functioning in adults with PKU**	Bilder DA, *et al. Dev Neuropsychol.* 2016;41(4):245–260.
Retrospective cohort study	**Neuropsychiatric comorbidities in PKU**	Bilder DA, *et al. Mol Genet Metab.* 2017;121(1):1–8.
Retrospective, case-controlled study	**Prevalence of comorbid conditions among adults diagnosed with PKU**	Burton BK, *et al. Mol Genet Metab.* 2018;125:228–234.
Retrospective study	**Burden of illness in adults with PKU and associated comorbidities**	Trefz KF, *et al. Orphanet J Rare Dis.* 2019;14:181.

PKU, phenylketonuria.

Systematic Review and Meta-Analysis of Neuropsychiatric Symptoms and Executive Functioning in Adults With Phenylketonuria

Deborah A. Bilder [a], J. Kay Noel [b], Erin R. Baker [b], William Irish [b], Yinpu Chen [c], Markus J. Merilainen [c], Suyash Prasad [d], and Barbara J. Winslow [c]

[a]Department of Psychiatry, University of Utah, Salt Lake City, Utah; [b]CTI Clinical Trial and Consulting Services Inc., Cincinnati, Ohio; [c]BioMarin Pharmaceutical Inc., Novato, California; [d]Audentes Therapeutics, San Francisco, California

Reference: 1. Bilder DA, *et al. Dev Neuropsychol*. 2016;41(4):245–260.

Systematic review[1]

Neuropsychiatric symptoms

- **8 out of 10 interventional studies**, comprising 253 patients, **reported neuropsychiatric improvements associated with lower Phe levels**
- The 2 out of 10 studies which showed no effect were performed in late-treated or untreated adults
- **13 out of 20 case reports showed improvements in late-onset neurologic/neuropsychiatric symptoms upon treatment**
- An additional 7 out of 8 case reports showed marked reduction of disruptive behaviours on introduction of a Phe-restricted diet

Executive function

- **5 studies comparing cohorts with low vs high blood Phe found that having low Phe improved measures of attention** (4 studies), **working memory** (2 studies), and **psychomotor speed/reaction time** (3 studies)
- 4 single-cohort intervention studies found that reducing Phe resulted in improvements in reaction time (1 study), attention (3 studies), and cognitive flexibility (1 study)
- One study with 50 classical PKU patients without intellectual disability found visual trends of worsening executive function with increasing blood Phe levels

Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Bilder DA, *et al. Dev Neuropsychol*. 2016;41(4):245–260.

Meta-analysis: executive function[1]

Executive function domain	Number of study arms	Number of PKU subjects	Effect size: standardised mean difference (95% CI) [P-value]
Attention	11	252	0.74 (0.55 to 0.93) [*P*<0.0001]
Working memory	5	112	0.08 (−0.45 to +0.61) [P=0.77]
Cognitive flexibility	7	157	0.43 (0.12 to 0.74) [*P*=0.006]
Inhibitory control	6	119	0.41 (0.005 to 0.81) [*P*=0.047]

An effect size of 0.4 means:[1]

- the score is 0.4 standard deviation below that for an average person in the control group
- the score is 66% of that of the control group

- **Executive function was significantly worse for early-treated adults when compared with matched controls in the domains of attention, inhibitory control, and cognitive flexibility[1]**
- The only EF domain that failed to show a difference between these two groups was working memory[1]
- Other work suggests that **working memory impairments may emerge as individuals with early-treated PKU age[2]**

CI, confidence interval; EF, executive function; PKU, phenylketonuria.

References: 1. Bilder DA, *et al. Dev Neuropsychol*. 2016;41(4):245–260. **2.** Christ SE, *et al. Mol Genet Metab.* 2010;99:S22–S32.

Meta-analysis: neuropsychiatric symptoms[1]

Psychiatric symptoms	Number of study arms	Number of PKU participants tested	Symptom prevalence (95% CI)
Inattention			
Overall	5	805	49% (26%–73%)
Early-treated PKU	2	586	20% (17%–23%)
Late/untreated PKU	3	219	68% (54%–81%)
Hyperactivity			
Overall	8	945	20% (14%–28%)
Early-treated PKU	6	745	16% (12%–22%)
Late/untreated PKU	2	200	34% (20%–51%)
Anxiety			
Overall	8	889	22% (11%–36%)
Early-treated PKU	5	670	8% (6%–11%)
Late/untreated PKU	3	219	49% (26%–72%)
Depression			
Overall	8	889	18% (8%–31%)
Early-treated PKU	6	689	12% (5%–22%)
Late/untreated PKU	2	200	35% (16%–58%)

- **High prevalence of neuropsychiatric symptoms in adults with PKU**
- Lower in adults with early-treated compared with late/untreated PKU

CI, confidence interval; PKU, phenylketonuria.

Reference: 1. Bilder DA, *et al. Dev Neuropsychol*. 2016;41(4):245–260.

Meta-analysis: neuropsychiatric symptoms[1]

	Number of study arms	Number of PKU participants tested	
			Symptom prevalence (95% CI)
Epilepsy/seizures			
Overall	14	1,028	10% (5%–17%)
Early-treated PKU	7	745	3% (1%–5%)
Late/untreated PKU	7	283	21% (17%–26%)
Tremors			
Overall	14	1,028	29% (16%–44%)
Early-treated PKU	7	745	18% (9%–29%)
Late/untreated PKU	7	283	40% (17%–65%)

CI, confidence interval; PKU, phenylketonuria.

Reference: 1. Bilder DA, *et al. Dev Neuropsychol*. 2016;41(4):245–260.

Neuropsychiatric comorbidities in adults with phenylketonuria: A retrospective cohort study

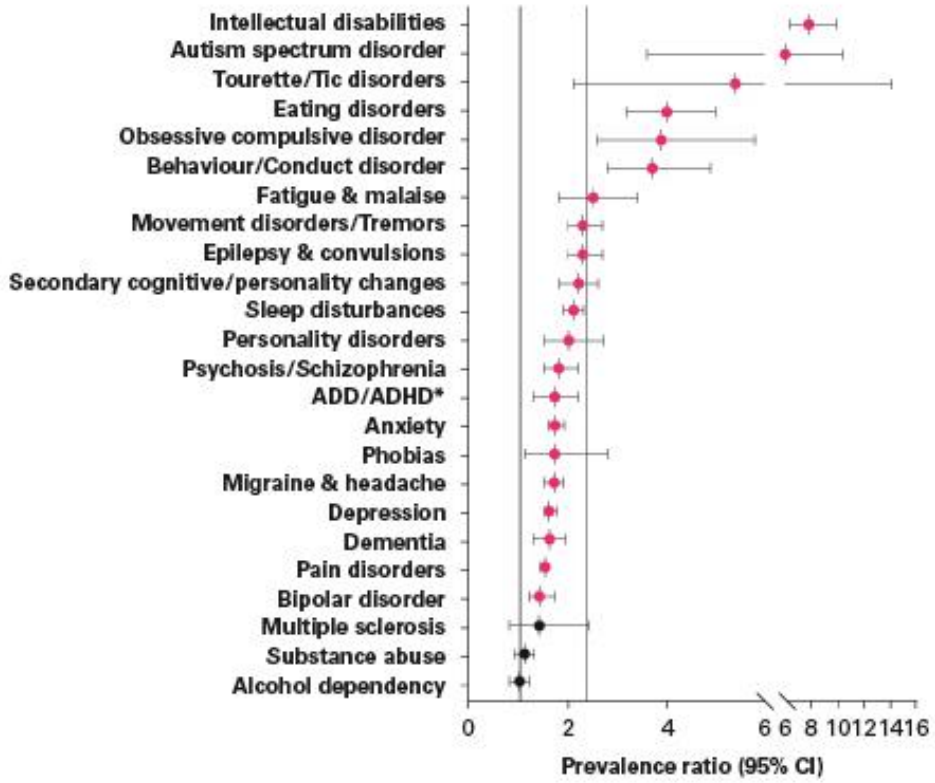
Deborah A. Bilder [a,*], Joyce A. Kobori [b], Jessica L. Cohen-Pfeffer [c], Erin M. Johnson [c], Elaina R. Jurecki [c], Mitzie L. Grant [d,e]

[a] *Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, USA*
[b] *Department of Genetics, Kaiser Permanente, San Jose, CA, USA*
[c] *Medical Affairs, BioMarin Pharmaceutical Inc., Novato, CA, USA*
[d] *Department of Psychiatry, Drexel University, College of Medicine, Philadelphia, PA, USA*
[e] *Department of Pediatrics, Drexel University, College of Medicine, Philadelphia, PA, USA*

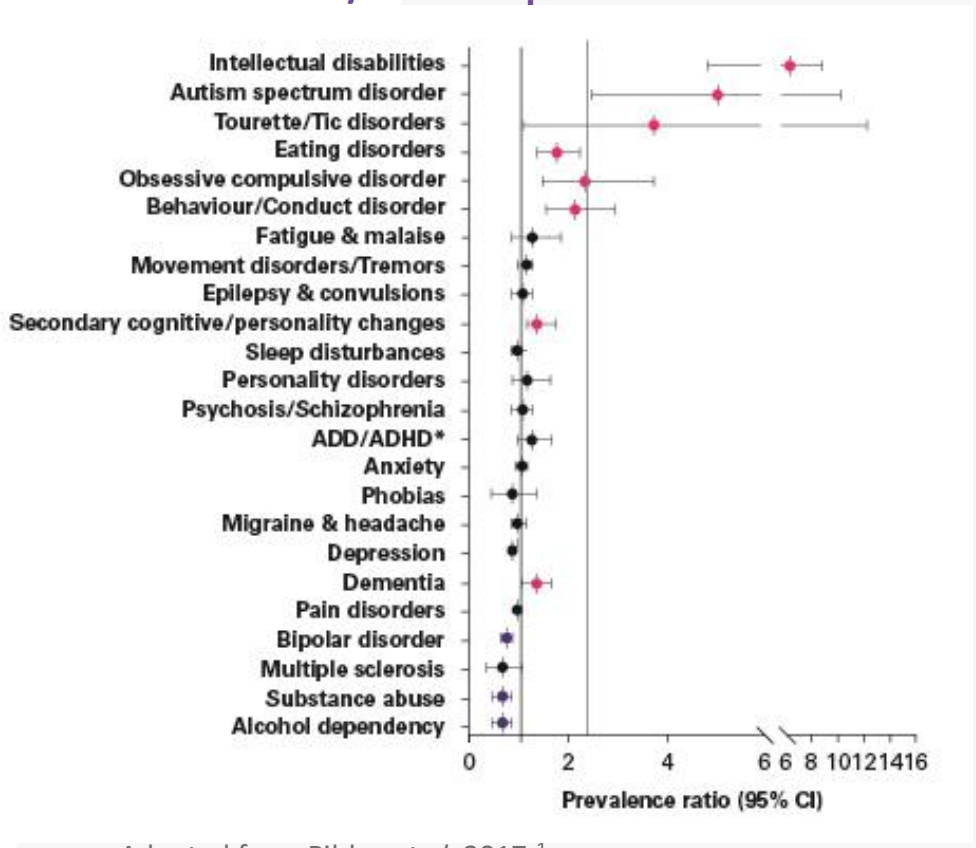
Reference: 1. Bilder DA, *et al. Mol Genet Metab*. 2017;121(1):1–8.

Adjusted prevalence ratio of comorbid neurocognitive conditions in PKU[1]

PKU/general population prevalence ratio



PKU/diabetes prevalence ratio



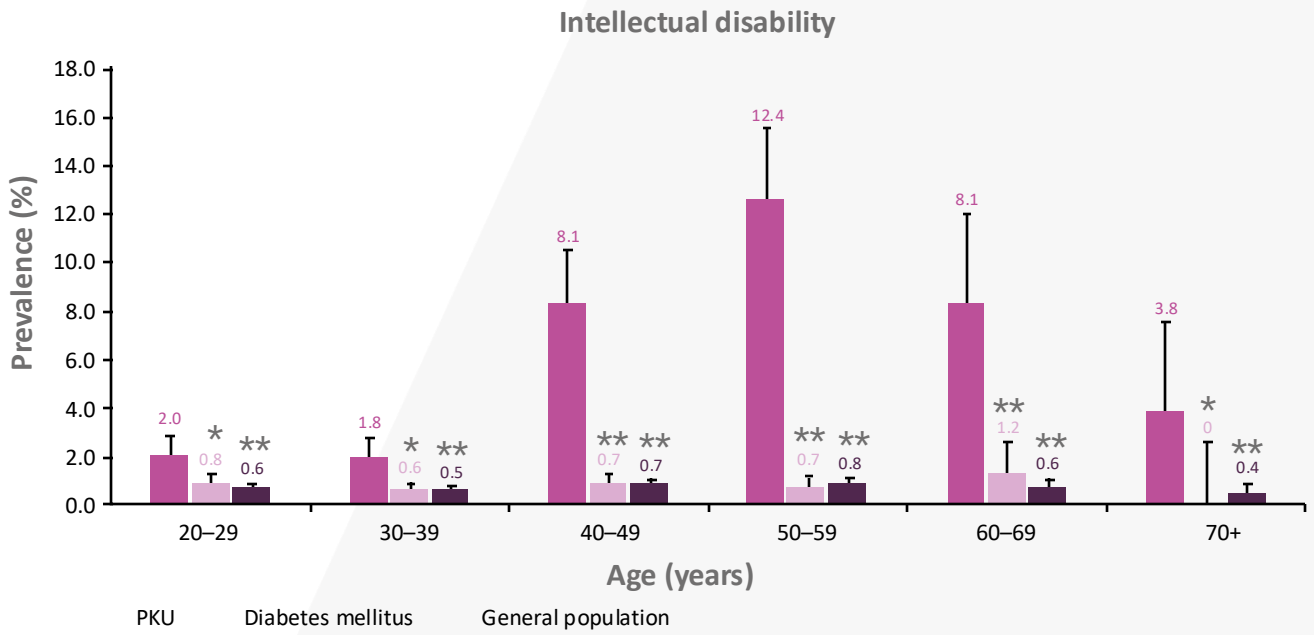
ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; CI, confidence interval; PKU, phenylketonuria; PR, prevalence ratio.

Reference: 1. Bilder DA, *et al. Mol Genet Metab*. 2017;121(1):1–8.

Adapted from Bilder *et al*. 2017.[1]
PKU n=3,714, Diabetes mellitus n=7,060, General population n=22,726.

Intellectual disability by age group[1]

- **Intellectual disability peaked strongly in middle age** and was **more common for PKU vs**:[1]
  - **General population** overall (4.8% vs 0.6%, *P*<0.0001) and for all age groups (*P*<0.0001)
  - **Diabetes mellitus population** overall (4.8% vs 0.7%) and for all age groups (*P*=0.002 to *P*<0.0001)
- No significant difference between the diabetes and general population cohorts[1]



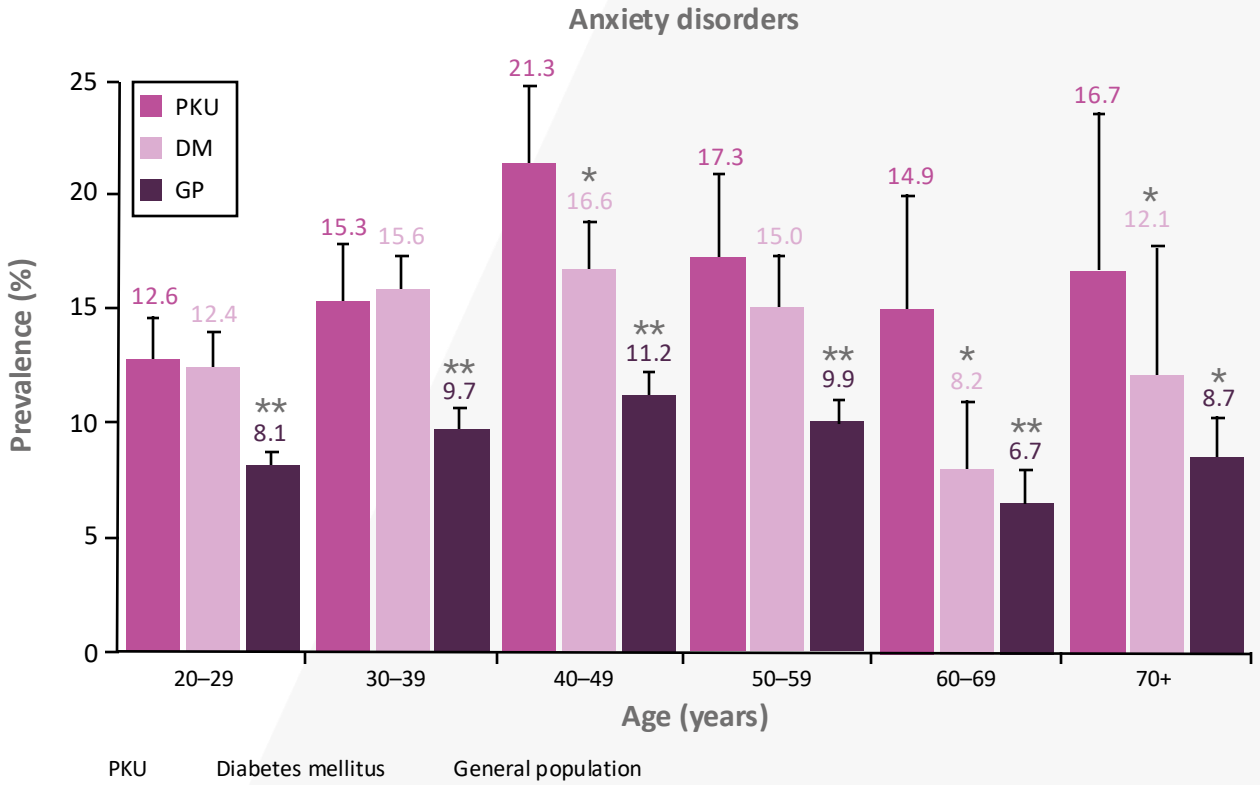
Adapted from Bilder *et al*. 2017.[1]
**P*=0.002; ***P*<0.0001.

PKU, phenylketonuria

Reference: 1. Bilder DA, *et al. Mol Genet Metab*. 2017;121(1):1–8.

Anxiety disorders by age group[1]

- **Anxiety disorders were more common for PKU vs**:[1]
  - **General population** overall (15.6% vs 9.2%, *P*=0.0001) for all age groups below 70 (*P*<0.0001) and over 70 (*P*=0.003).
  - **Diabetes mellitus population** overall (15.6% vs 14.1%, *P*=0.03), and for age groups 40–49 y (*P*=0.017), and 60–69 y (*P*=0.009)



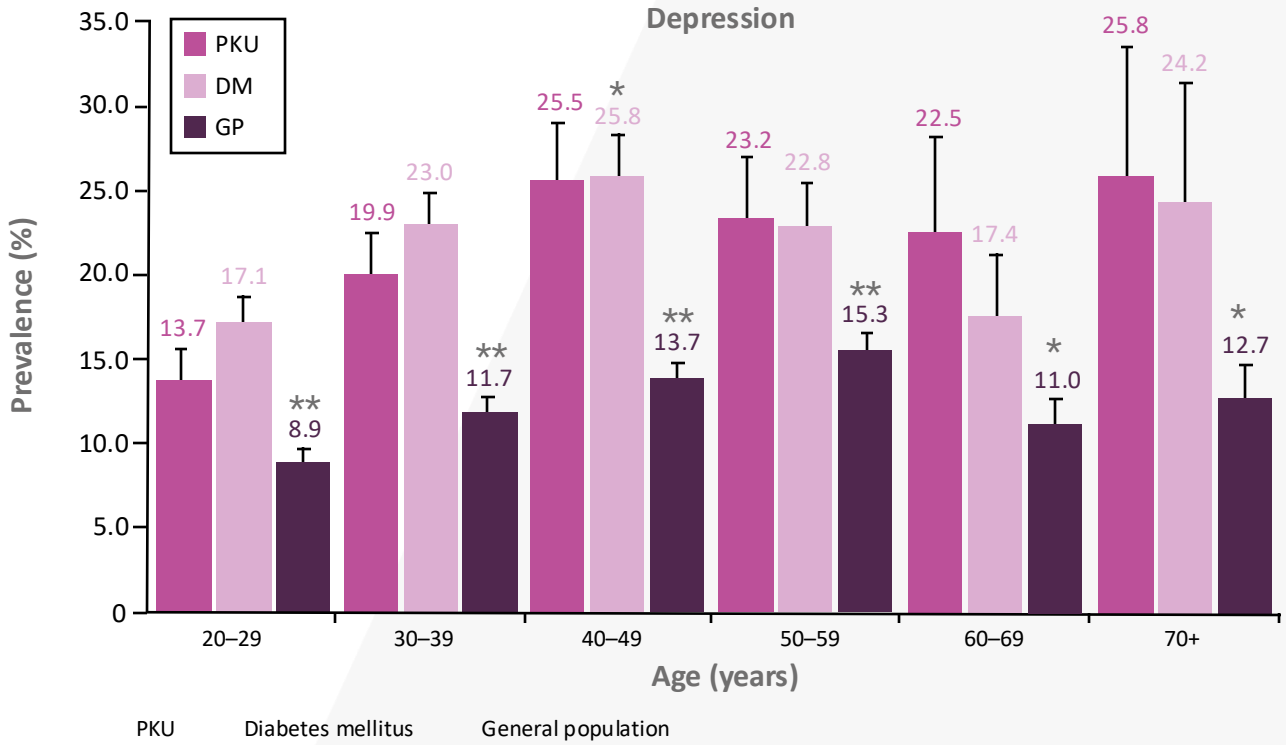
Adapted from Bilder *et al*. 2017.[1]
**P*<0.05; ***P*<0.0001.

DM, diabetes mellitus; GP, general population; PKU, phenylketonuria.

Reference: 1. Bilder DA, *et al. Mol Genet Metab*. 2017;121(1):1–8.

Depression by age group[1]

- **Depression was more common for PKU vs**:[1]
  - **General population** overall (19.5% vs 11.8%, *P*<0.0001) and for all age groups (*P*=0.0004 to *P*<0.0001)
- **Lower prevalence of depression for PKU vs diabetes** overall (19.5% vs 21.1%, *P*=0.046)[1]
  - Also lower in PKU vs diabetes for age 20–29 y (*P*=0.008), but not for other age groups



Adapted from Bilder *et al*. 2017.[1]
*P<0.05; **P<0.0001.

DM, diabetes mellitus; GP, general population; PKU, phenylketonuria.

Reference: 1. Bilder DA, *et al. Mol Genet Metab*. 2017;121(1):1–8.

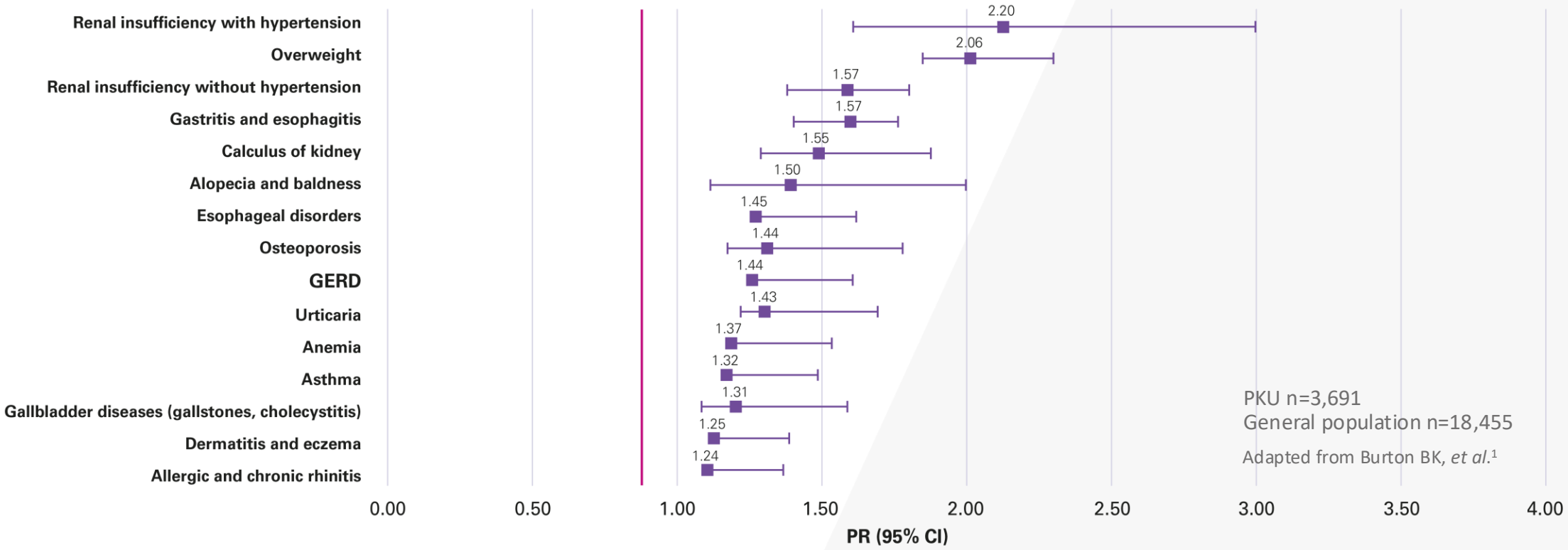
Prevalence of comorbid conditions among adult patients diagnosed with phenylketonuria

Barbara K. Burton[a], Kyle Bradford Jones[b], Stephen Cederbaum[c], Fran Rohr[d], Susan Waisbren[e], Debra E. Irwin[f], Gilwan Kim[f], Joshua Lilienstein[g], Ignacio Alvarez[g], Elaina Jurecki[g,*], Harvey Levy[d]

[a] *Ann & Robert Lurie Children's Hospital, 225 E. Chicago Ave., Chicago, IL 60611, United States*
[b] *University of Utah School of Medicine, Department of Family and Preventive Medicine, 375 Chipeta Way Ste A., Salt Lake City, UT 84108, United States*
[c] *University of California, Los Angeles, 635 Charles E Young Dr Los Angeles, CA 90095-7332, United States*
[d] *Boston Children's Hospital and Harvard Medical School, 1 Autumn St., Rm #526, Boston, MA 02115, United States*
[e] *Boston Children's Hospital and Harvard Medical School, 1 Autumn Street, #525, Boston, MA 02115, United States*
[f] *Truven Health Analytics, An IBM Watson Health Company, 7700 Old Georgetown Rd, 6th Floor, Bethesda, MD 20814, United States*
[g] *BioMarin Pharmaceutical Inc., 105 Digital Drive, Novato, CA 94949, United States*

Reference: 1. Burton BK, *et al. Mol Genet Metab*. 2018;125:228–234.

US ICD-9 codes database: adjusted prevalence ratio of selected comorbid conditions in PKU patients compared with control subjects from the general population[1]



CI, confidence interval; GERD, gastroesophageal reflux disease; ICD-9, International Classification of Diseases, Ninth Revision; PKU, phenylketonuria; PR, prevalence ratio.

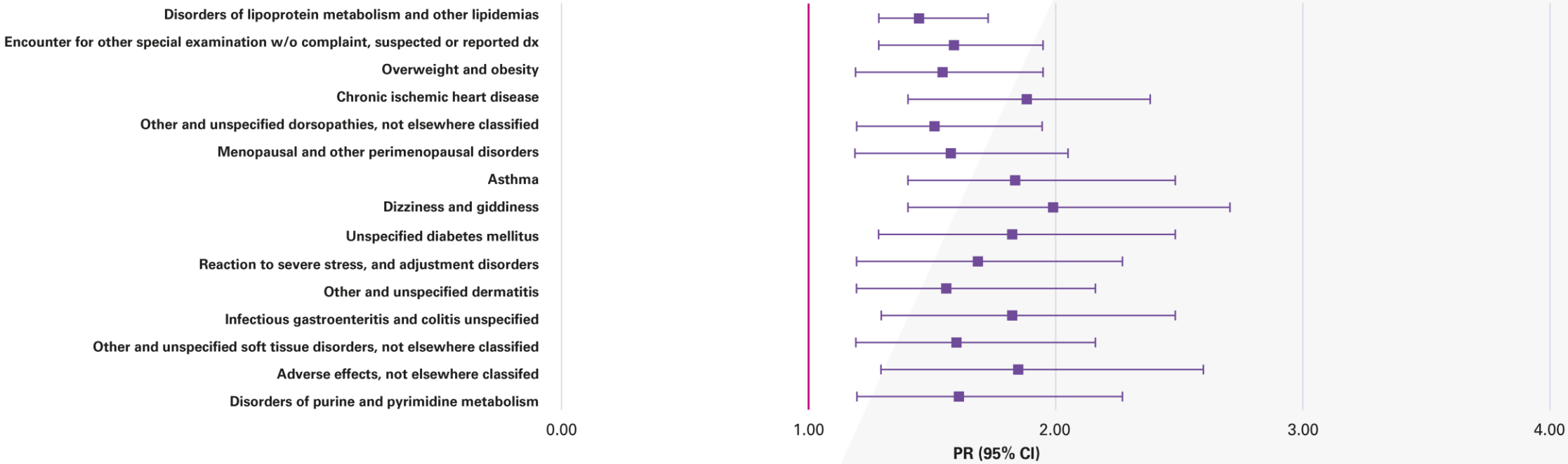
Reference: 1. Burton BK, *et al. Mol Genet Metab*. 2018;125:228–234

Clinical burden of illness in patients with phenylketonuria (PKU) and associated comorbidities - a retrospective study of German health insurance claims data

K. F. Trefz[1], A. C. Muntau[2], K. M. Kohlscheen[3], J. Altevers[3], C. Jacob[3], S. Braun[3], W. Greiner[4], A. Jha[5], M. Jain[5], I. Alvarez[5], P. Lane[5], C. Schröder[6] and F. Rutsch[7*]

Reference: 1. Trefz KF, *et al. Orphanet J Rare Dis*. 2019;14:181.

German ICD-10 codes database: prevalence ratio of top 50 comorbid conditions in PKU patients compared with control subjects from the general population[1]

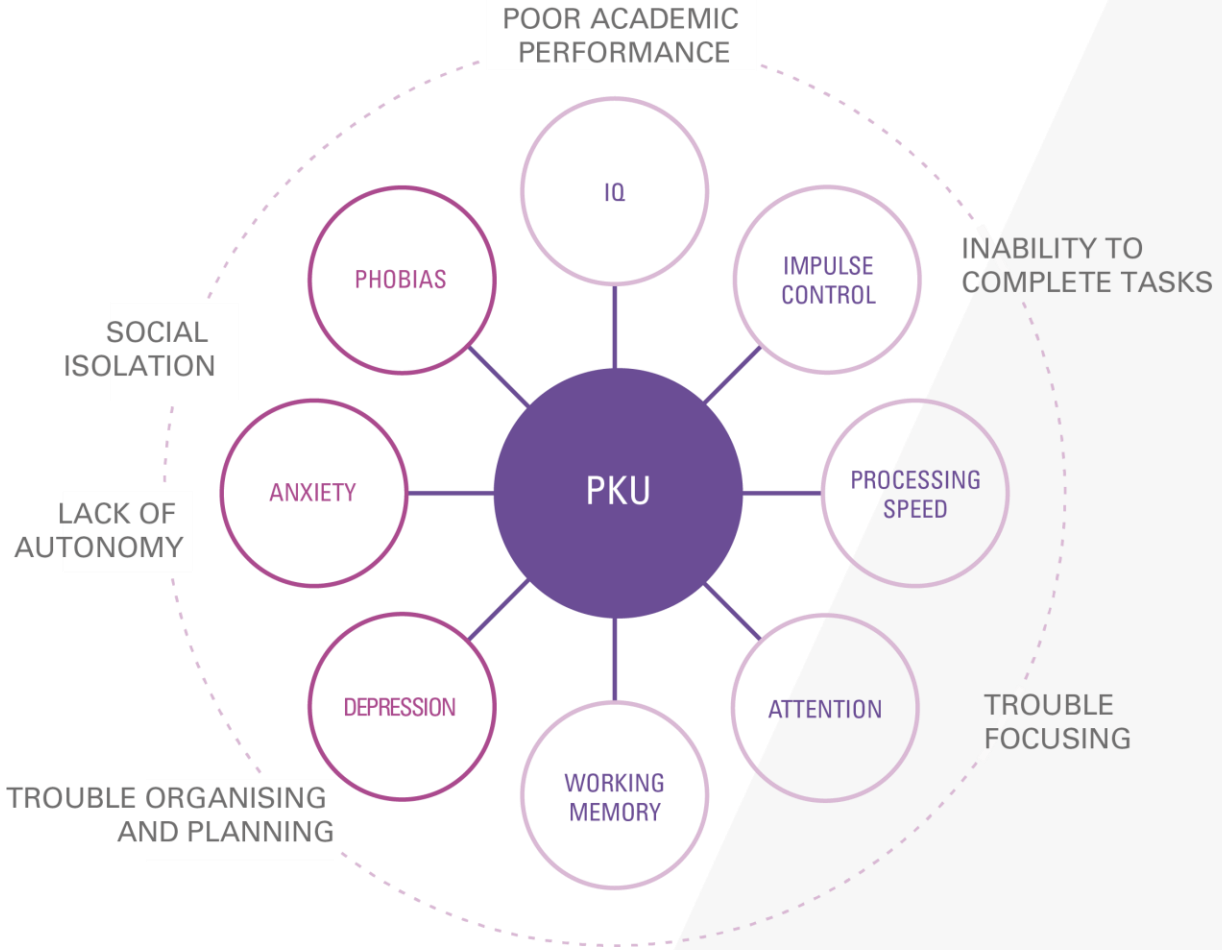


PKU n=377
Control n=3,770
Adapted from Trefz KF *et al.* 2019.[1]

CI, confidence interval; ICD-10, International Statistical Classification of Diseases and Related Health Problems, 10th revision; PKU, phenylketonuria; PR, prevalence ratio.

Reference: 1. Trefz KF, *et al. Orphanet J Rare Dis*. 2019;14:181.

PKU can cause neurocognitive and psychiatric symptoms[1–7]



IQ, intelligence quotient; PKU, phenylketonuria.

References: 1. Enns GM, *et al. Mol Genet Metab.* 2010;101(2–3):99–109. **2.** Pietz J, *et al. Pediatrics*. 1997;99(3):345–350. **3.** Waisbren SE, *et al. Mol Genet Metab.* 2007;92(1–2):63–70. **4.** Gassio R, et al. *Pediatr Neurol*. 2005;33(4):267–271. **5.** Christ SE, *et al. Mol Genet Metab.* 2010;99:S22–S32. **6.** White DA, *et al. J Int Neuropsychol Soc*. 2002;8(1):1–11. **7.** Bilder DA, *et al. Mol Genet Metab.* 2017;121(1):1–8.

Psychosocial manifestations are seen at all ages[1]

Early-treated children and adolescents:[1,2]

- **Behavioural problems and learning difficulties**

Early-treated adults:[1,2]

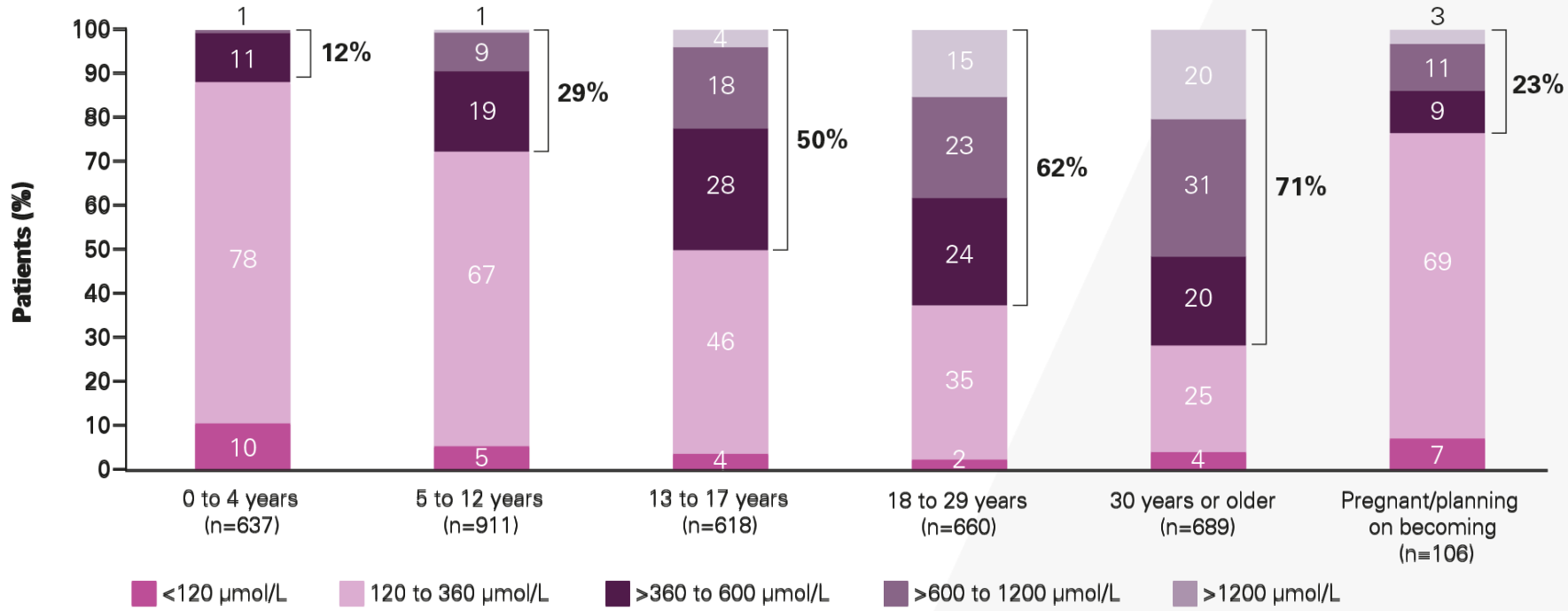
- **Reduced achievement**
- **More likely to live with parents**
- **More PKU patients were unmarried** vs controls (82% vs 55%)
  - Majority of unmarried PKU patients were not in a stable relationship (95% of males)
- **Fewer PKU patients had children** vs controls (12% vs 47%)

PKU, phenylketonuria.

References: 1. Enns GM ,*et al. Mol Genet Metab.* 2010;101(2–3):99–109. **2.** Gentile JK, *et al. Mol Genet Metab.* 2010;99(Suppl 1):S64–S67.

As patients age, fewer meet blood Phe targets[1]

Patients meeting clinic-recommended blood Phe target levels[1]



Adapted from Jurecki ER *et al.* 2017.[1] N.B. some categories do not add up to 100% due to rounding.

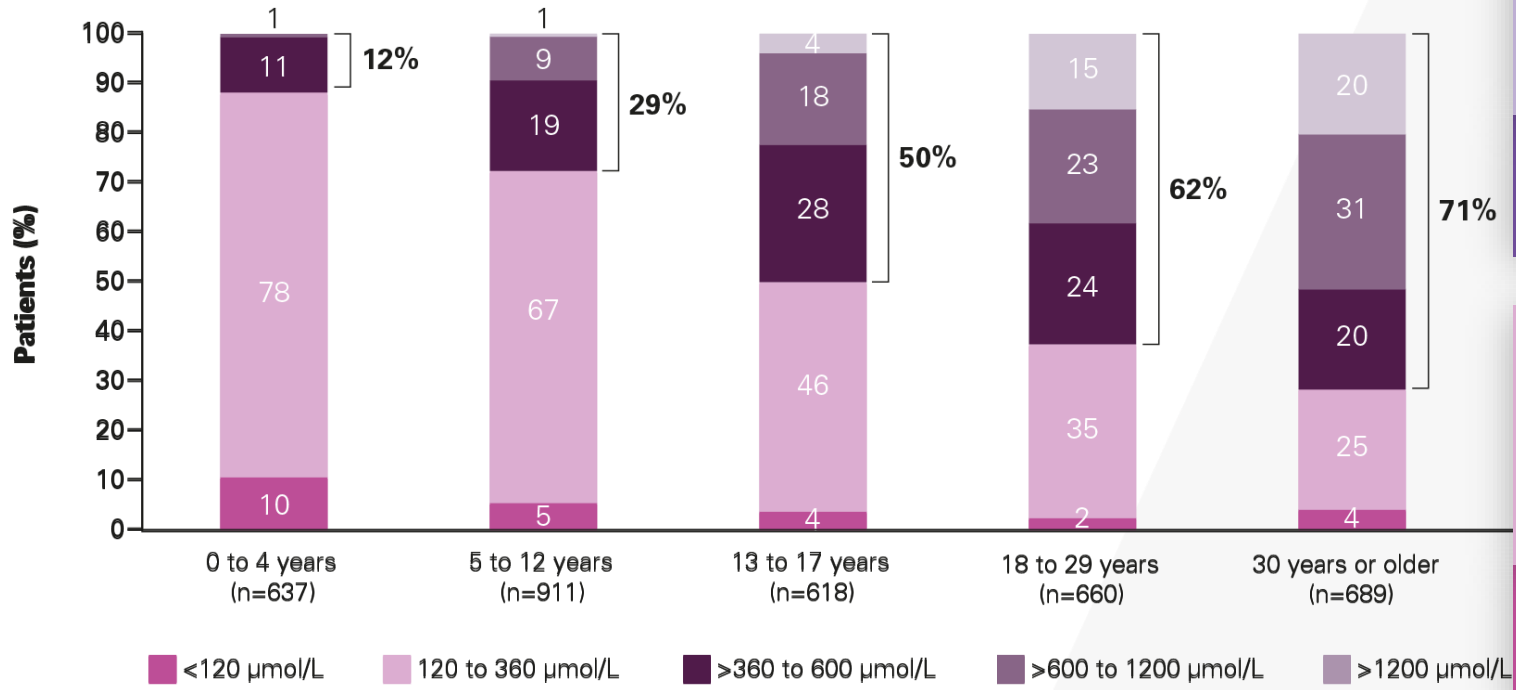
The majority of adults are above clinic-recommended Phe levels.[1]

Phe, phenylalanine.

References: 1. Jurecki ER, *et al. Mol Genet Metab*. 2017;120(3):190–197.

As patients age, fewer meet blood Phe targets[1]

Patients meeting clinic-recommended blood Phe target levels[1]



Recommended blood Phe target levels

120-600 µmol/L for patients >12 years of age[2]

European Guidelines

69

120-360 µmol/L for all patients[3]

American College of Medical Genetics and Genomics (ACMG) Guidelines

Adapted from Jurecki ER *et al.* 2017.[1] N.B. some categories do not add up to 100% due to rounding.

The majority of adults are above clinic-recommended Phe levels.[1]

Phe, phenylalanine.

References: 1. Jurecki ER, *et al. Mol Genet Metab*. 2017;120(3):190–197. **2.** van Spronsen FJ, *et al. Lancet Diabetes Endocrinol*. 2017;5:743–756. **3.** Vockley J, *et al. Genet Med*. 2014;16:188–200.

Many adults with PKU have uncontrolled Phe levels[1,2]

Among in-clinic adult PKU patients actively managed by diet across 81 PKU treaters in 24 countries in the EU, Asia and Latin America:[2]

72%

of patients were reported as having mean blood Phe levels **>600 µmol/L**[2]

18%

of patients were reported as having mean blood Phe levels **>1200 µmol/L**[2]

- **Patients find it difficult to adhere to metabolic control through diet alone**[3]
- A growing body of evidence suggests that **neurocognitive, psychosocial, quality of life, growth, nutrition, bone pathology and maternal PKU outcomes are suboptimal**[3]

As lifelong control of blood phenylalanine concentration by diet alone is difficult, substantial unmet needs remain for patients with PKU, and only limited therapeutic options exist.[4]

Phe, phenylalanine; PKU, phenylketonuria.

References: 1. Jurecki ER, *et al. Mol Genet Metab*. 2017;120(3):190–197. **2.** Trefz FK *et al. Eur J Pediatr*. 2015;174(1):119–127. **3.** Enns GM *et al. Mol Genet Metab.* 2010;101(2-3):99–109. **4.** Blau N, Longo N. *Expert Opinion Pharmacother*. 2015;16(6):791–800.

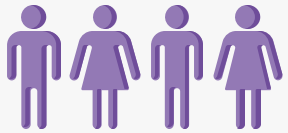
Factors affecting compliance in PKU patients[1]

A survey of 111 adult PKU patients from 5 metabolic centres in Italy found that:[1]

- **Compliance with diet among adult PKU patients was poor, with less than half (42%) claiming full adherence**[1]
- Main factors that impact on compliance:[1]
  - **Lack of awareness of disease and its consequences**
  - **Psychological difficulties in coping with dietary restriction**
  - **Negative features of AA supplements**
- However, follow-up visits and family support promote compliance[1]

Metabolic control and compliance with dietary treatment in adult PKU patients are poor.[1]

The PKU paradox



40% of patients did not consider PKU to be a disease[1]

85% said they regularly monitored their Phe levels.[1]

However…

48% reported a high Phe level over the last 6 months (> 600 µmol/L)[1]

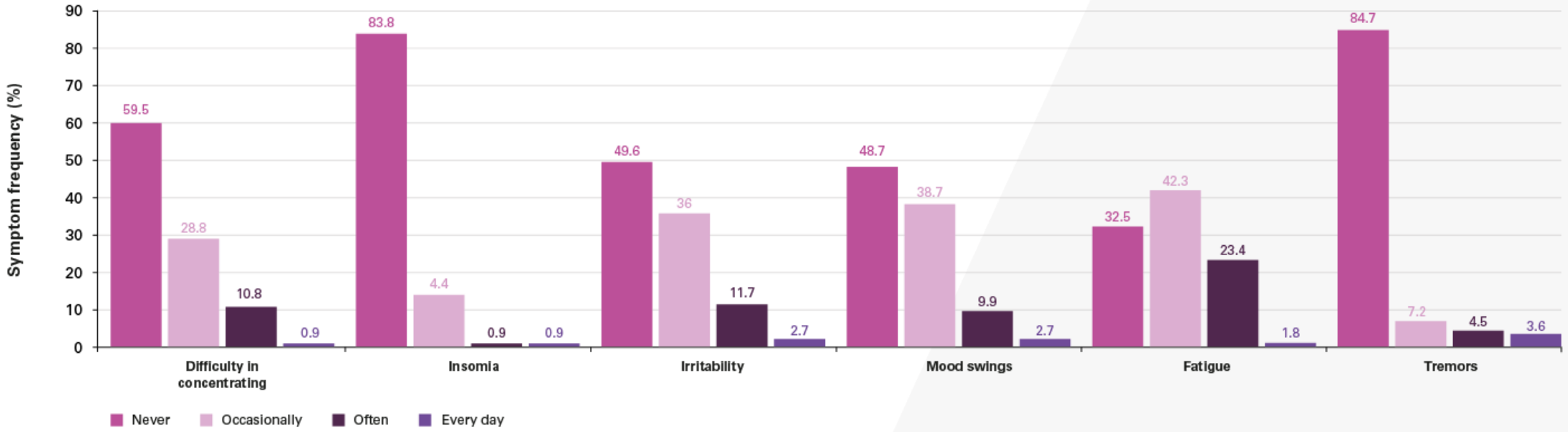
31% were unable to specify what their Phe level was[1]

AA, amino acid; Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Cazzorla C, *et al. Mol Genet Metab Rep.* 2018;16:39–45.

Factors affecting compliance in PKU patients[1]

Frequency (%) of symptoms ascribed to high plasma Phe levels (n=111)[1]



Symptoms ascribed to high plasma Phe levels were reported at least twice a week or even every day in a significant proportion of patients.[1]

Phe, phenylalanine; PKU, phenylketonuria.

Reference: 1. Cazzorla C, *et al. Mol Genet Metab Rep.* 2018;16:39–45.

Adapted from Cazzorla C, *et al.*[1]

PKU in later life[1]

- New-born screening and low Phe diets have transformed outcomes for people with PKU[1]
- **Those who have benefited from early treatment are now approaching their 5th and 6th decade**[1]
- **It is time to consider multimorbidity in PKU and effects of ageing**, in parallel with the wider **benefits of emerging treatment options** in addition to dietary relaxation[1]

There are many gaps in knowledge of the impact of PKU on co-morbidity[1]

Are people with PKU at increased risk of:

- **Frailty and sarcopenia?**
- **Renal disease?**
- **Diabetes, metabolic syndrome or CV disease?**
- **Dementia?**

Further research is required.[1]

In PKU, lifelong, systematic follow-up is recommended independent of the degree of adherence and treatment choice, to screen for long-term complications and provide appropriate patient support.[2]

CV, cardiovascular; Phe, phenylalanine; PKU, phenylketonuria.

References: 1. Vardy ERLC, *et al. J Inherit Metab Dis.* 2020;43:167–178. **2.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162.

Summary

- PKU is a serious lifelong disease which requires lifelong follow-up[1]
- Dietary management represents a significant patient burden[1,2]
- A large proportion of patients find it difficult to adhere to metabolic control through diet alone[3]
  - Evidence demonstrates that significant suboptimal outcomes exist in the PKU population treated with diet alone[1,3]
- European guidelines recommend lifelong treatment to control blood Phe levels[1*]
- Pharmaceutical therapy has a place alongside diet in appropriate patients[4]

Few individuals can maintain full dietary control lifelong, and even with good control, an elevated risk remains of— in particular— mood, anxiety, and attentional disorders across the lifespan.[5]

*Patients ≥12 years with untreated Phe levels <600 µmol/L do not require treatment.[1]
Phe, phenylalanine; PKU, phenylketonuria.
References: **1.** van Wegberg AMJ, *et al. Orphanet J Rare Dis.* 2017;12:162. **2.** Cazzorla C, *et al. Mol Genet Metab Rep.* 2018;16:39–45. **3.** Enns GM, *et al. Mol Genet Metab.* 2010;101:99–109. **4.** van Spronsen FJ, *et al. Lancet Diabetes Endocrinol.* 2017;5:743–756. **5.** Ashe K, *et al. Front Psychiatry.* 2019;10:561.