Session name: Oral presentation 3
Session theme: PKU 1

Neuropsychiatric comorbidities in adults with PKU in Sweden

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COI Disclosure

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Introduction

The objective of this study was to investigate the **prevalence of neuropsychiatric comorbidities** in **adults with PKU** (the PKU cohort) compared with matched **non-PKU controls** in Sweden

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)** and results in **elevated levels of Phe** in the blood[1]

High Phe levels during early childhood can lead to profound **neurocognitive and developmental defects** in adulthood[1,2]

The mainstay of treatment for PKU in Sweden is a **consistent dietary restriction of Phe**,[2] but management with dietary intervention alone may result in sub-optimal outcomes, including neurocognitive and psychosocial impairment[3]

To date, the **burden** of **neuropsychiatric comorbidities** in **adults** with **PKU** has not been well described

PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria.

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. Enns GM, et al. *Mol Genet Metab.* 2010;101:99–109.

Methods

Study design

This was a national record-linkage observational study that used national registers (Total Population Register [TPR] and Swedish National Patient Register [PAR]) in Sweden

Eligibility criteria

Aged **≥18 years** and **residing in Sweden** between Jan 1, 2019 to Dec 31, 2020

PKU cohort

≥1 ICD code for PKU*

Non-PKU controls

No ICD code for PKU*

Cohorts matched 1:20, based on age, sex, and healthcare region

Analysis

- **Prevalence** and **prevalence ratio** of individual neuropsychiatric comorbidities†
- **Frequency of neuropsychiatric comorbidities**† per individual (0 to ≥5)
- **Cumulative lifetime prevalence** of neuropsychiatric comorbidities† by age up to the year 2020

*Between Jan 1, 1965 and Dec, 31, 2020 in PAR (ICD codes: E70.0 [ICD-10], 270B [ICD-9], or 270.0 [ICD-8]); †Defined using ICD codes, as described by Bilder et al.[1]
ICD, International Classification of Diseases; PAR, Swedish National Patient Register; PKU, phenylketonuria; TPR, Total Population Register.

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

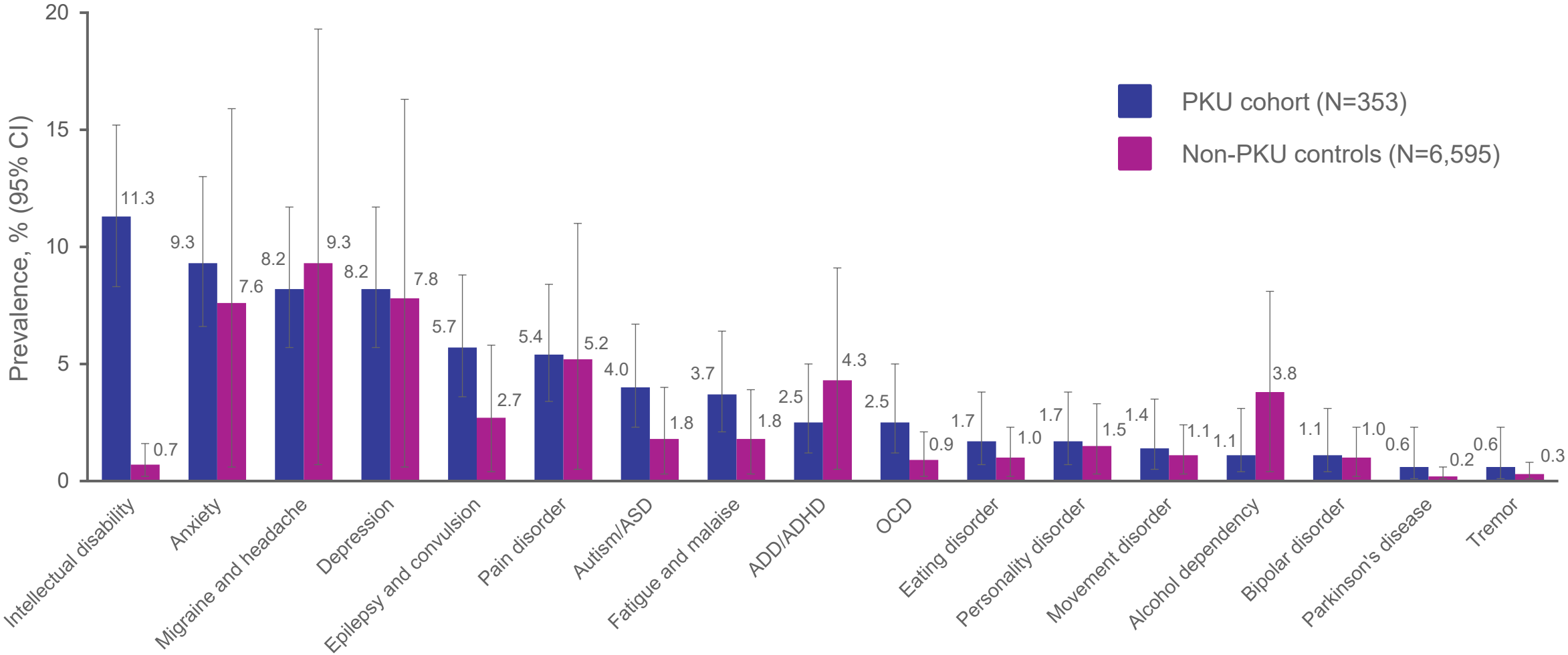
Characteristics of individuals

- A total of **353 adults with PKU** and **6,595 non-PKU controls** matched 1:20 based on age, sex, and healthcare region, were analyzed
- **Median age** was **40 years**; 51.8% were male
- Most individuals were **born in Sweden,** and 82% lived in Central or Southern Sweden
- **Median follow-up** from PKU diagnosis to the year 2020 was **25.2 years**
- A small proportion (6.2%; n=22) of individuals with PKU had a history of treatment with sapropterin dihydrochloride

Demographic/characteristic	PKU cohort (N=353)	Non-PKU controls (N=6,595)
Age in 2020, years		
Mean (SD)	43.5 (17.6)	42.7 (17.0)
Median (IQR)	40 (28–55)	40 (28–55)
Range	20–91	20–91
<65, n (%)	305 (86.4)	5,801 (88.0)
≥65, n (%)	48 (13.6)	794 (12.0)
Sex, n (%)		
Female	170 (48.2)	3,200 (48.5)
Male	183 (51.8)	3,395 (51.5)
Birth country, n (%)		
Sweden	310 (87.8)	6,095 (92.4)
Other (including missing)	43 (12.2)	500 (7.6)
Swedish region of residence,* n (%)		
Central	148 (41.9)	2,762 (41.9)
Northern	41 (11.6)	764 (11.6)
Southern	141 (39.9)	2,630 (39.9)
Missing	23 (6.5)	439 (6.7)
Follow-up from time of PKU diagnosis to 2020, years		
Mean (SD)	26.5 (14.1)	N/A
Median (IQR)	25.2 (16.7–38.4)	N/A
Range	0.1–65.5	N/A
History of sapropterin dihydrochloride, n (%)	22 (6.2)	N/A

Percentages may not total 100% due to rounding.
*Swedish regions of residence represent groups of healthcare regions.
IQR, interquartile range; N/A, not applicable; PKU, phenylketonuria; SD, standard deviation.

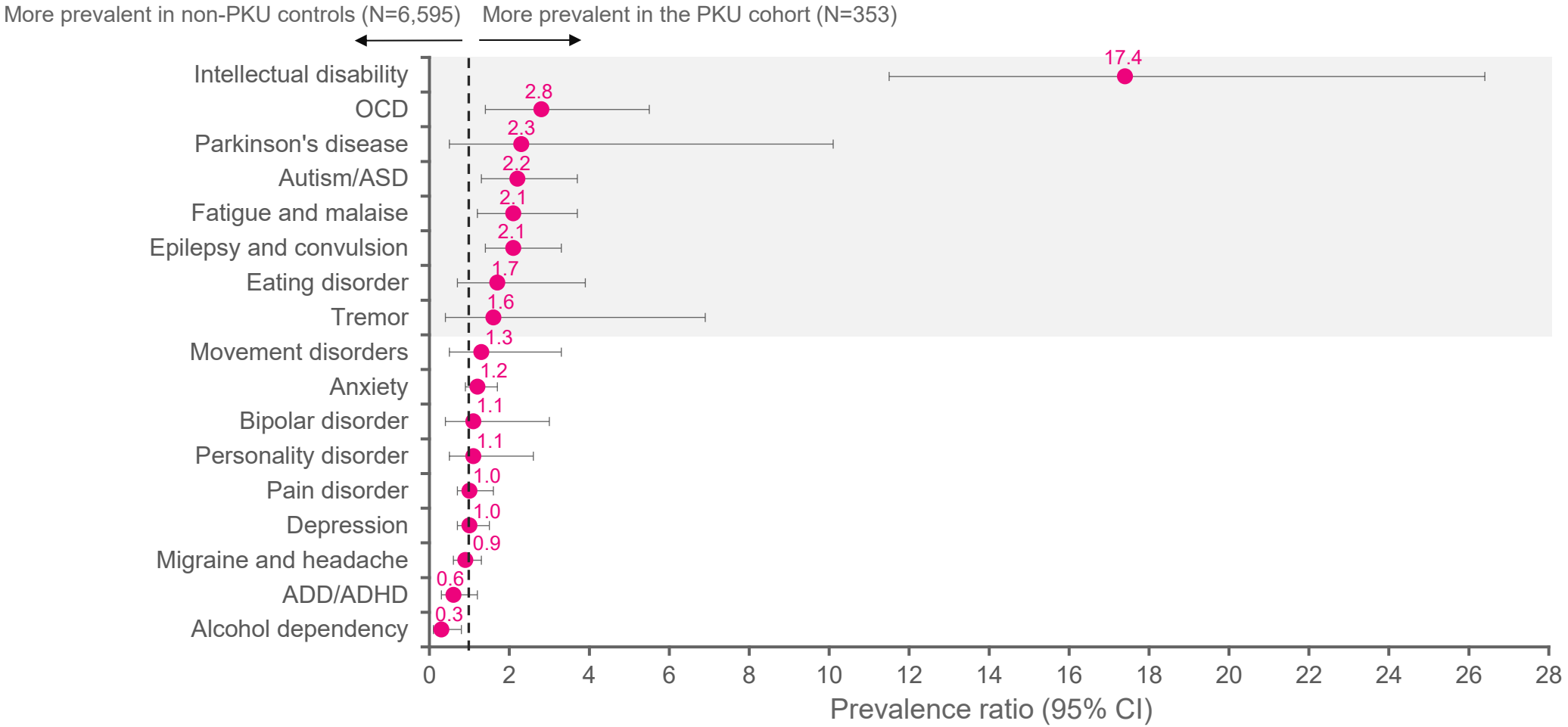
Prevalence of neuropsychiatric comorbidities



Many neuropsychiatric comorbidities were **more prevalent in the PKU cohort** compared to non-PKU controls

ADD, attention deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; OCD, obsessive compulsive disorder; PKU, phenylketonuria.

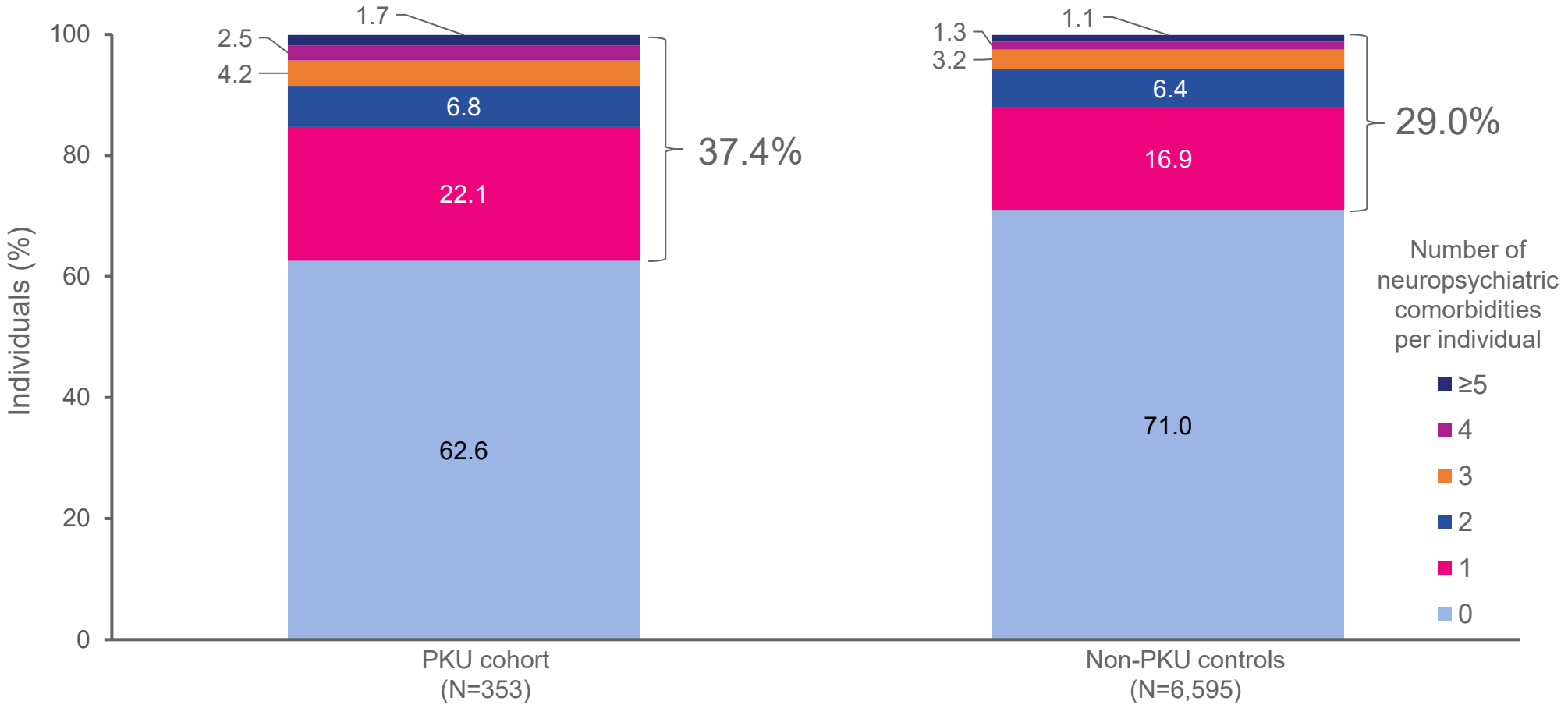
Prevalence ratio of neuropsychiatric comorbidities



Neuropsychiatric comorbidities for which the prevalence ratio was >1.5 were intellectual disability, OCD, Parkinson's disease, autism/ASD, fatigue and malaise, epilepsy and convulsion, eating disorder, and tremor

Gray shading indicates neuropsychiatric comorbidities for which the prevalence ratio was >1.5.
ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; CI, confidence interval; OCD, obsessive-compulsive disorder; PKU, phenylketonuria.

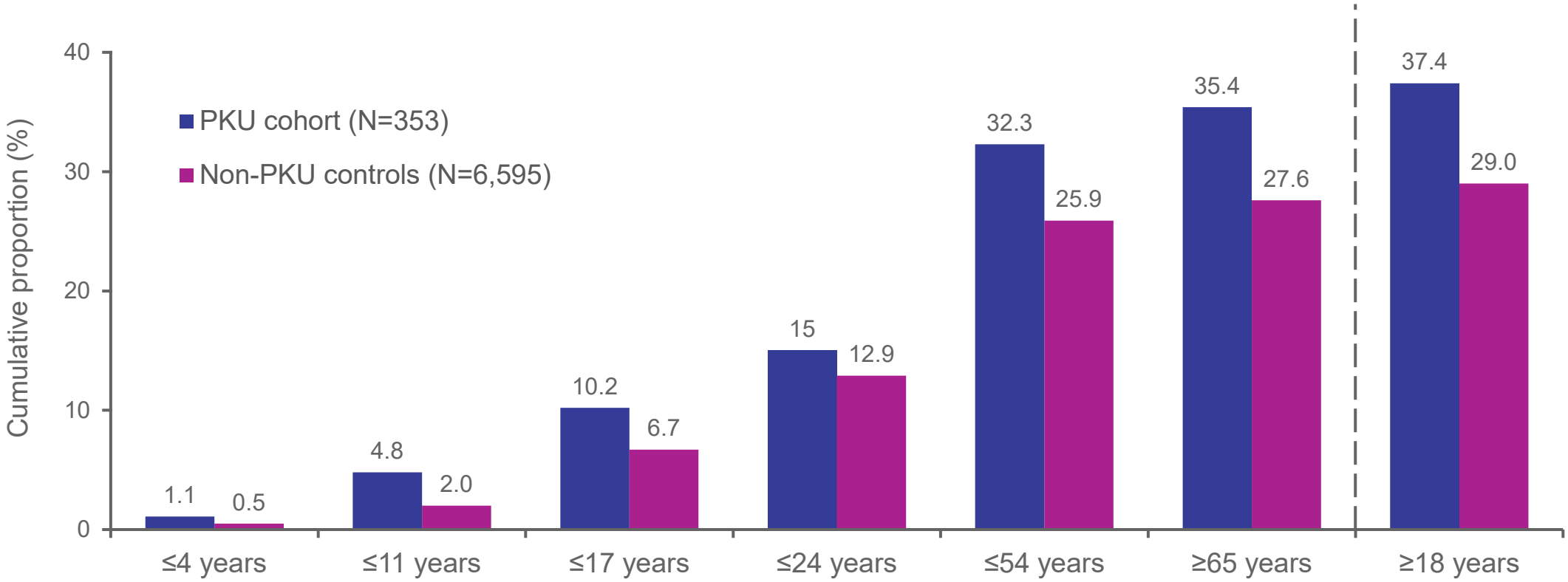
Number of neuropsychiatric comorbidities



The PKU cohort were **more likely** than non-PKU controls to have **≥1 neuropsychiatric comorbidity** (37.4% vs 29.0%)

Percentages may not total 100% due to rounding.
PKU, phenylketonuria.

Cumulative proportion of individuals with ≥1 neuropsychiatric comorbidity, by age



The cumulative percentage of individuals with ≥1 neuropsychiatric comorbidity **increased with age from infancy to adulthood** and was **higher in the PKU cohort versus non-PKU controls**

Adult age cut-offs are based on working age groups (18–24 years: early working age; 25–54 years: prime working age; 55–64 years: mature working age; ≥65 years: older working age).
Phe, phenylalanine; PKU, phenylketonuria.

Conclusions

In this Swedish cohort of **adults with PKU treated primarily with a lifelong low-Phe diet**, results are indicative of **sub-optimal outcomes**

- Many **neuropsychiatric comorbidities** were **more prevalent in the PKU cohort** compared to non-PKU controls
- The **PKU cohort were more likely to have ≥1 neuropsychiatric comorbidity** than matched non-PKU controls
- The **burden of neuropsychiatric comorbidity increased with age from infancy to adulthood**

These findings suggest that **treatment via dietary management alone may not be sufficient**

- **Early optimization of effective treatments is required** to improve outcomes for individuals with PKU and ensure **sustained therapeutic benefit over the long term**

Similar data from an adolescent US cohort are being presented at this meeting

- Poster P-595; poster session: Wed Sep 3, 18:00–19:00 (Exhibition & Poster 2 [Event Hall, KICC])

Phe, phenylalanine; PKU, phenylketonuria.

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