Intelligence quotient scores among phenylketonuria patients receiving early dietary management: Results from a systematic literature review

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1. Background:

- In phenylketonuria (PKU), high phenylalanine (Phe) is associated with lower cognitive abilities.[1-2]
  - Two meta-analyses on intelligence quotient (IQ) in PKU showed lower IQ in PKU patients.[3,4]
  - A higher impact of PKU on health-related quality-of-life (HRQoL) has been reported among those with lower IQ scores.[5]
- Adhering to dietary management is challenging but is needed to preserve neurocognition.[1,6-8]
- While development will be within normal limits, the exact impact of early continuous dietary management on cognition is not well known.[9] Data on cognitive abilities of this group compared to controls are needed.
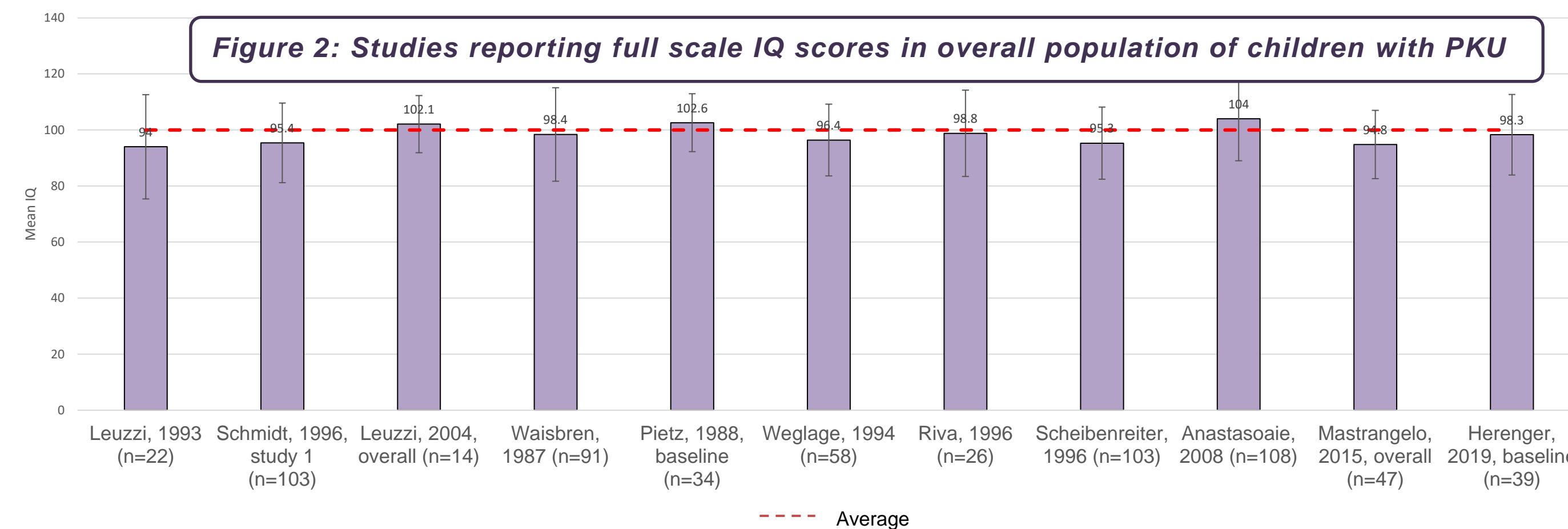
2. Objective:

- To synthesize published data on the cognitive impact of PKU measured by IQ scores, among patients receiving early dietary management.
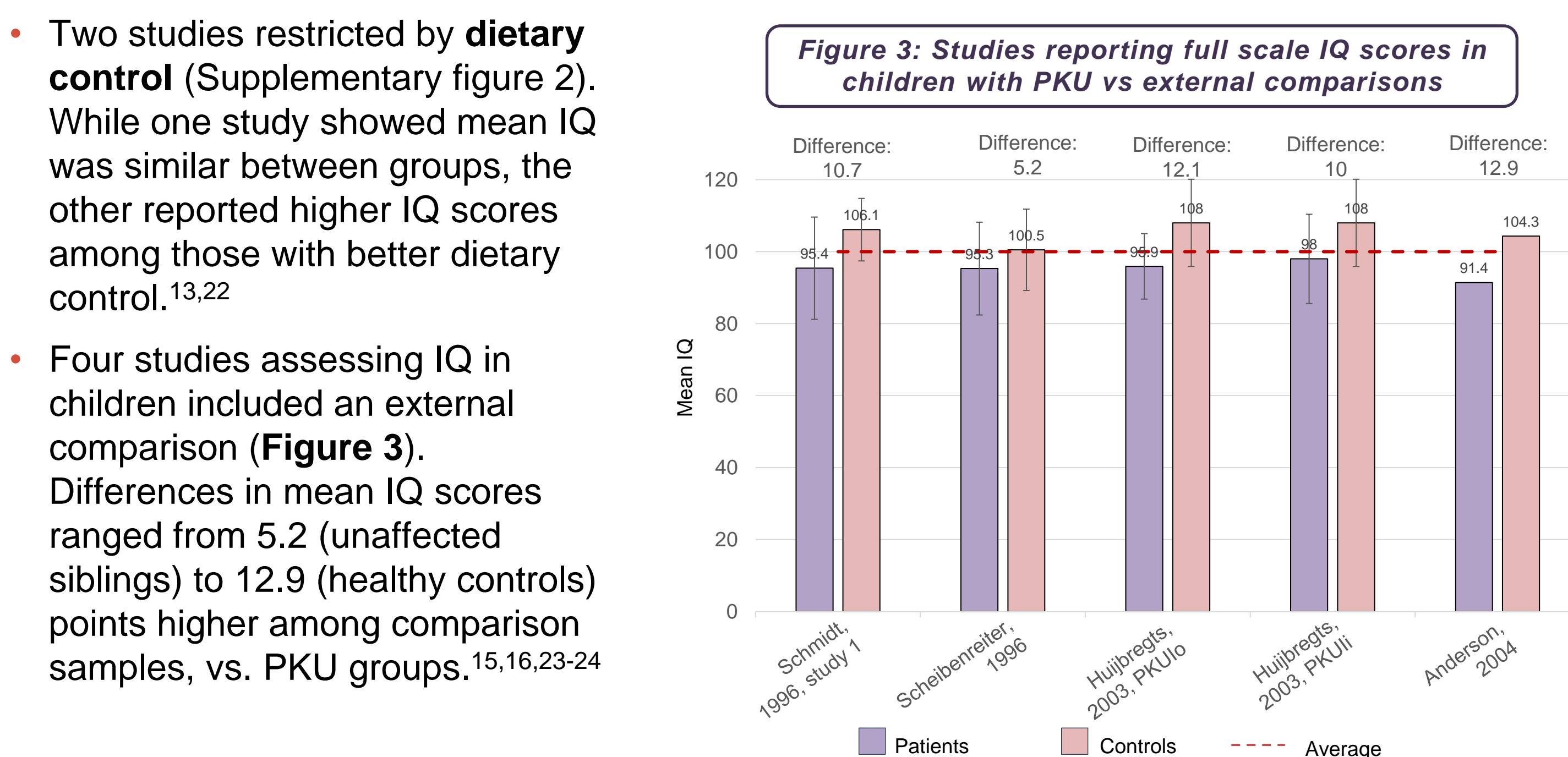
3. Methods:

Overview

- A systematic literature review was conducted following PRISMA guidelines in March 2023, using MEDLINE, EMBASE and Northern Lights databases.
- Two researchers (MV, LH) independently reviewed all identified records against the PICOS criteria: Observational studies assessing IQ among early-diagnosed and treated PKU patients [blood Phe level >600 µmol/L at screening] in English.

Interpreting IQ scores

- IQ assessments by Wechsler Intelligence Scale (WIS) were included.
- IQ scores of 100 represent 'average intelligence'.
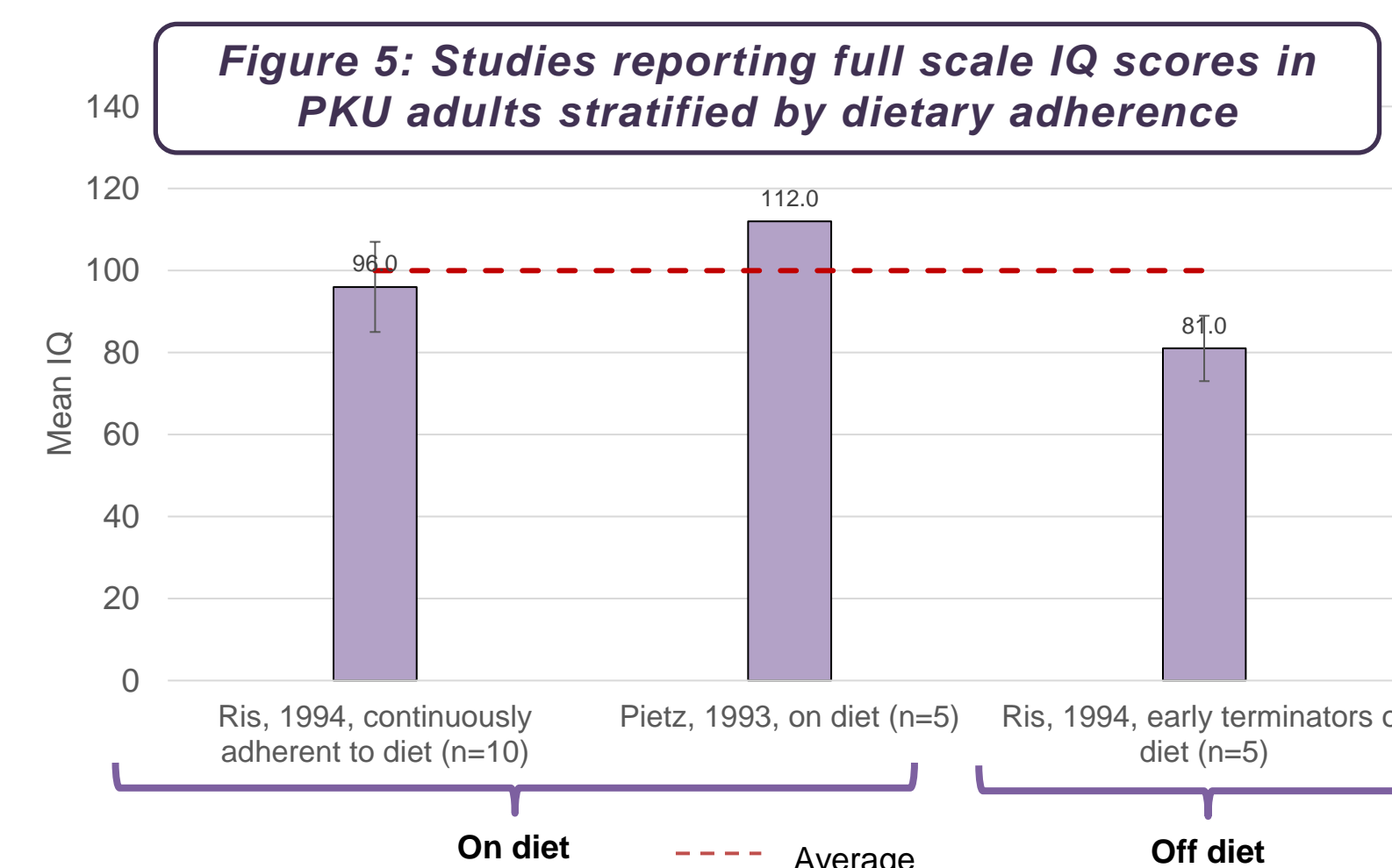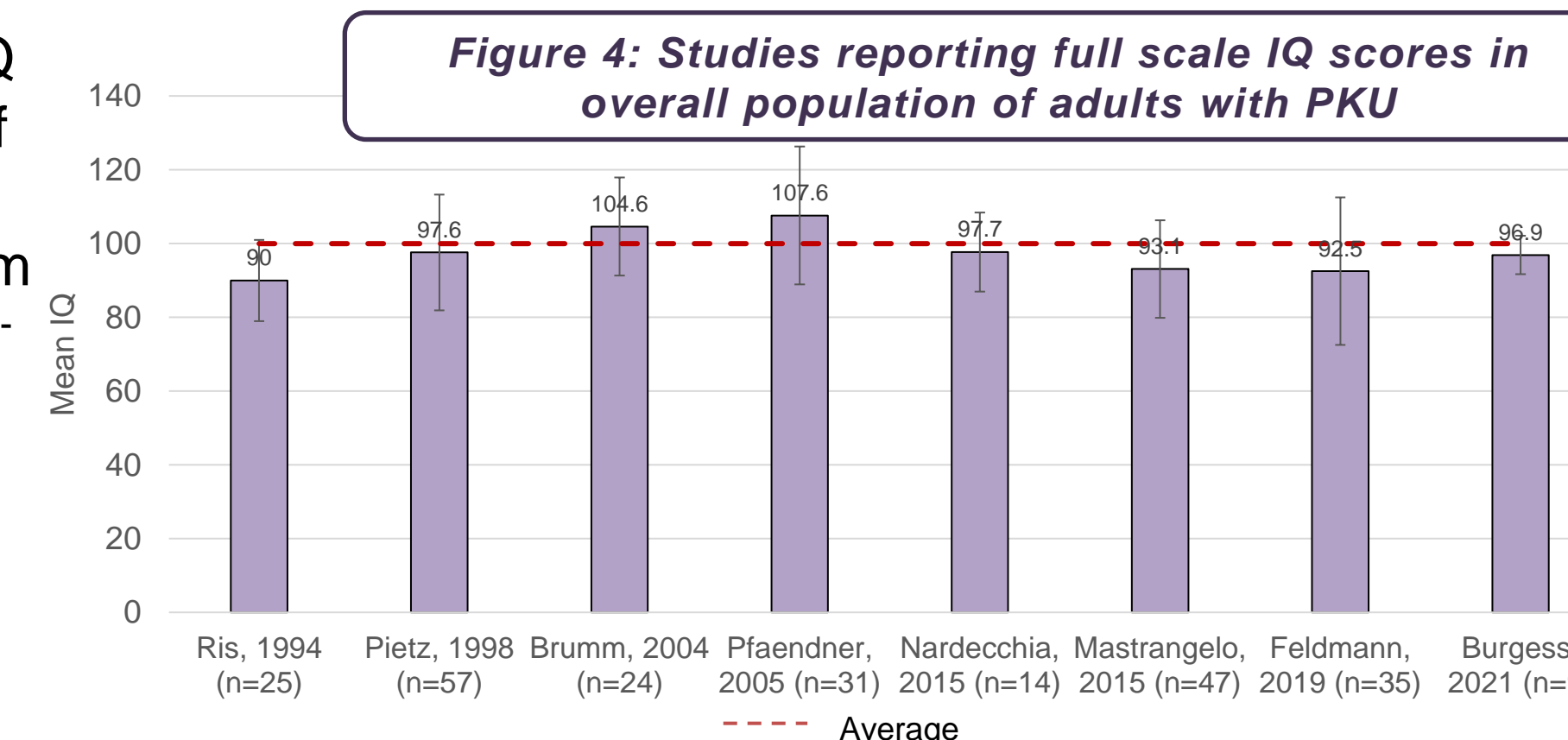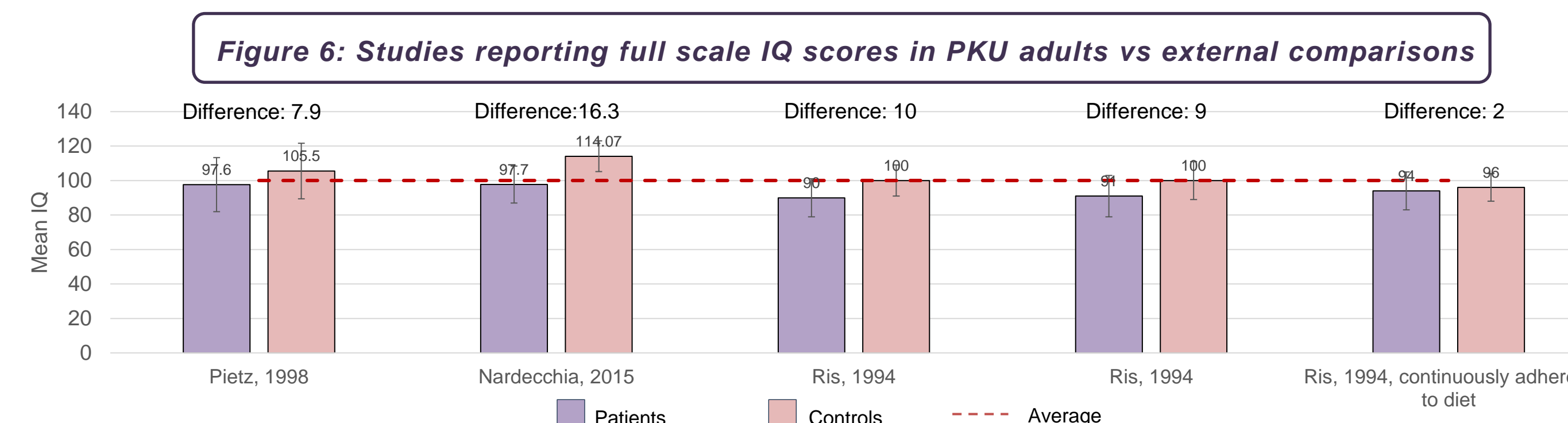- 'Intellectual disability' is classified as an IQ<70.

Data synthesis

- Mean full scale IQ scores using the age-appropriate WIS, overall and by subgroups (e.g., children vs. adults), were extracted.
- We reported results by age and subgroup:
  - **Overall population**: Data from studies that reported IQ measures for an overall PKU population, by age.
  - **Restricted subgroups**: Data from studies that restricted to particular subgroups (e.g. patients who went on or off diet; by high/low Phe levels within age groups).
- Differences in IQ between PKU and comparison samples (siblings or healthy controls) from the same studies were explored.
- The percentage of studies where patients had mean IQ scores <100 was reported.

69	70	80	90	110	120	130
ID	Borderline ID	Low average	Average	High average	Superior	Very superior

Abbreviations: ID=intellectual disability

4. Results

OVERALL

- From 1,713 abstracts, 23 studies (27 publications)[10-32] were included (**Figure 1**).
  - 14 studies included children, 8 included adults, and 1 study included both.
- All patients were on dietary management and no other pharmacological treatments.
- Twelve of 23 studies reported IQ over time or by age.
- Sample sizes of interest ranged from 4-103.

Figure 1: PRISMA diagram of included studies that reported relevant IQ outcomes

Abstracts excluded:	1199
Population	280
Intervention/Comparator	0
Study design	220
Outcomes	0
Duplicate publication	384
Other	315

Full texts excluded:	478
Population	185
Intervention/Comparator	0
Study design	38
Outcomes	239
Duplicate publication	0
Other	16

Publications excluded:	9
Culture Fair Intelligence Test	5
Stanford-Binet Intelligence Scale	1
Raven Progressive Matrices	1
Not reporting Wechsler Intelligence Full Scale IQ scores	2

4. Results continued:

CHILDREN

- Eleven studies reported IQ in overall populations of children (**Figure 2**).[10-20]
- Mean (SD) full scale IQ scores ranged from 94.0 (18.6) to 104.0 (15).
  - Eight studies (72.7%) reported mean IQ <100.

Figure 2: Studies reporting full scale IQ scores in overall population of children with PKU

- Three studies described subgroups by **dietary adherence** (Supplementary figure 1); children with poorer adherence showed poorer cognitive ability.[10,12,21]
  - Mean (SD) full scale IQ scores in those "on diet" (ranging from 97.3 [10.3] to 106.5 [19.2]), were higher than among those "off diet" (ranging from 87.9 [NR] to 95.6 [15.3]).
- Two studies restricted by **dietary control** (Supplementary figure 2). While one study showed mean IQ was similar between groups, the other reported higher IQ scores among those with better dietary control.[13,22]
- Four studies assessing IQ in children included an external comparison (**Figure 3**). Differences in mean IQ scores ranged from 5.2 (unaffected siblings) to 12.9 (healthy controls) points higher among comparison samples, vs. PKU groups.[15,16,23-24]

Figure 3: Studies reporting full scale IQ scores in children with PKU vs external comparisons

ADULTS

- Eight studies reported mean IQ scores in overall populations of adults (**Figure 4**); mean (SD) full scale IQ scores ranged from 90.0 (11.0) to 107.6 (18.7).[19,25-31]
  - Six studies (75%) reported mean IQ <100.

Figure 4: Studies reporting full scale IQ scores in overall population of adults with PKU

Figure 5: Studies reporting full scale IQ scores in PKU adults stratified by dietary adherence
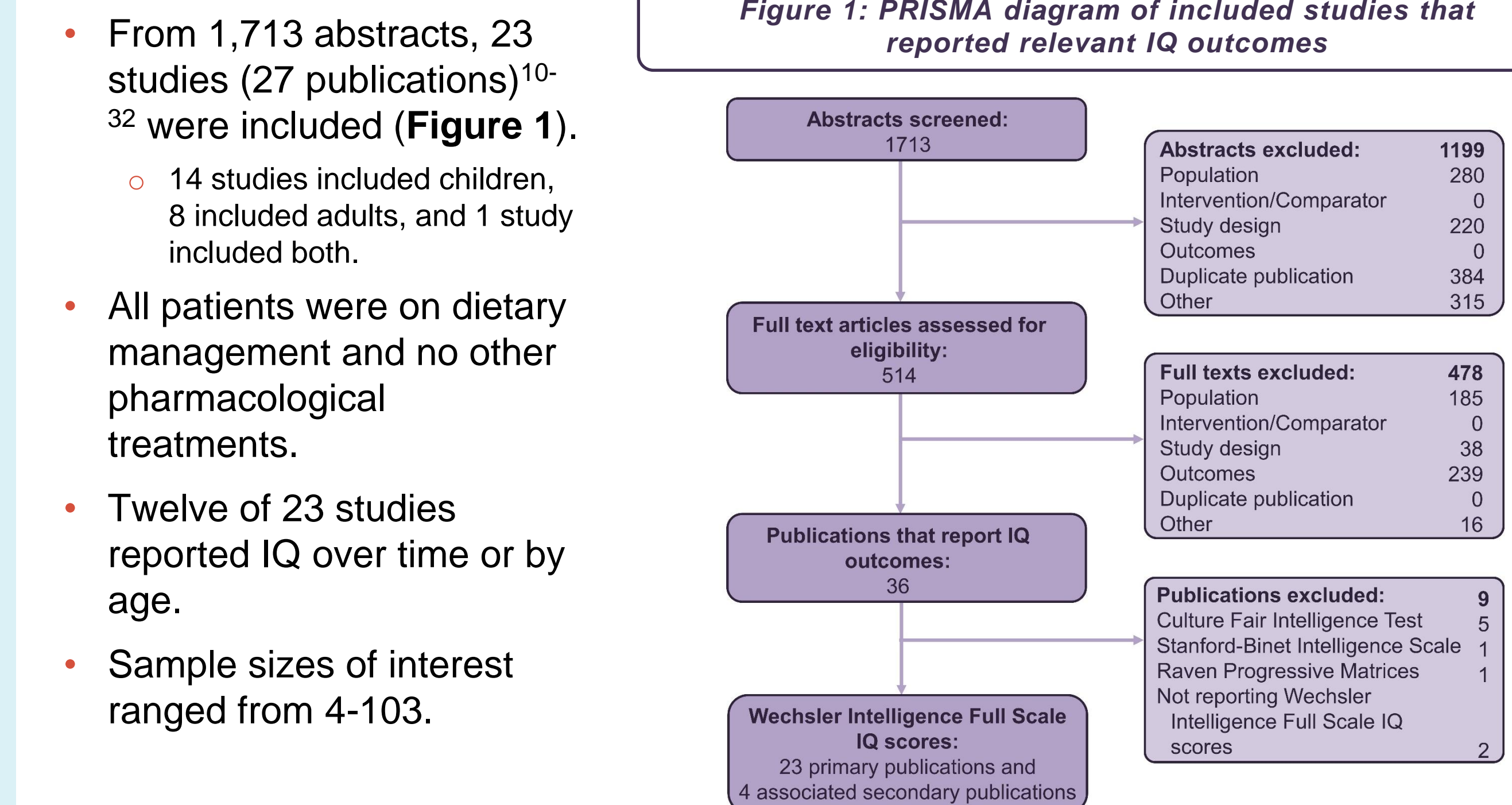
- Two studies restricted by **dietary adherence** (**Figure 5**): mean (SD) IQ scores were 81.0 (8.0, ended diet early) and 112.0 (NR; continuously on diet).[25,32]

- Three studies assessing IQ among adults included an external comparison (**Figure 6**), and mean IQ scores ranged from 2 (unaffected siblings) to 16.3 (age and sex matched healthy controls) points higher than among PKU adults.[25-26,30]
- The differences between PKU and control groups tended to be larger (except among continuously diet-adherent adults) in adults compared to children.

Figure 6: Studies reporting full scale IQ scores in PKU adults vs external comparisons

5. Discussion:

- This synthesis revealed the impact of early dietary management on IQ; approximately three quarters of studies of children and adults reported mean IQ scores <100 (i.e., below 'average intelligence').
  - Data from comparison groups from the same studies help highlight the extent of the deficit: IQ scores among PKU samples were 5 to 16.3 points lower.
  - Higher mean IQ scores were reported among those who remained on diet compared to who did not.
- Smaller and more heterogenous samples resulted in larger variance around estimates within the adult samples.
- Strengths include:
  - The rigorous systematic review methodology employed and focus on observational studies, which can have longer follow-up (compared to trials), provide real-world insights into diet adherence, and include more generalizable samples.
  - Studies were restricted to those that defined PKU or blood Phe levels >600µmol/L at diagnosis, and to those on early treatment or dietary management, to reduce heterogeneity within the samples.
  - Subgroup analyses that revealed important insights into the changing effects of PKU on cognition across different age groups and dietary management approaches.
- Limitations include small sample sizes and considerable variability in reported estimates; and the lack of individual patient data. Presenting overall (mean) values may obscure trends in IQ in PKU.[11]

6. Conclusions:

- Individual IQ scores among patients with PKU from studies included in our review were variable. However, a larger proportion of studies reported mean IQ scores <100 points. In addition, patients with poor dietary adherence showed poorer cognitive ability. Furthermore, mean IQ scores were consistently lower compared to control groups, despite all patients in this review receiving early dietary management.
- These data highlight that IQ is affected in PKU, even with early dietary management. Treatments that reduce Phe levels have an opportunity to reduce burden in PKU, brought upon by lower cognitive abilities.

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8. Abbreviations:

EMBASE, Excerpta Medica Database
HRQoL, health-related quality of life
ID, intellectual disability
IQ, intelligence quotient
MEDLINE, Medical Literature Analysis and Retrieval System Online
NR, not reported
Phe, phenylalanine
PICOS, population, intervention, comparator, outcomes and study design
PKU, phenylketonuria
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD, standard deviation
WIS, Wechsler Intelligence Scale