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ASSESSMENT OF EXECUTIVE FUNCTIONS, ADAPTIVE SKILLS, EMOTIONAL AND BEHAVIORAL OUTCOMES FROM PEDIATRIC AGE TO ADULTHOOD IN PATIENTS WITH PKU: A SYSTEMATIC REVIEW

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***ABSTRACT* – Objective:** This systematic review aims to analyze the assessment tools used to evaluate executive functions, adaptive skills, and emotional and behavioral outcomes in pediatric and adult patients with phenylketonuria (PKU). Given the impact of elevated phenylalanine (Phe) levels on cognitive and psychological development, this review seeks to provide a comprehensive overview of validated instruments employed in the literature to assess neurocognitive and psychosocial functioning.

Materials and Methods: A systematic literature search was conducted according to the PRISMA guidelines. Studies published between 2020 and 2025 were identified through PubMed using keywords related to PKU, executive functions, and cognitive functions. Inclusion criteria encompassed studies focusing on pediatric (0-18 years) and adult PKU patients and using standardized neuropsychological, behavioral, and emotional assessment tools. Studies that did not use standardized tools, as well as reviews, meta-analyses, case reports, and expert opinions, were excluded. Data extraction was performed independently by two reviewers, with discrepancies resolved by consensus.

Results: A total of 168 studies were initially identified. After removing duplicates and applying inclusion criteria, 35 studies were included: 11 studies assessed pediatric patients, 22 focused on adults, and two examined both populations. The most frequently used tools for executive function assessment included the Behavior Rating Inventory of Executive Function, The Developmental Neuropsychological Assessment - II (NEPSY-II), Trail Making Test, and Wechsler Intelligence Scale subtests. Behavioral and emotional functioning were primarily assessed using the Child Behavior Checklist and the Hospital Anxiety and Depression Scale. The review highlighted variability in assessment methodologies, with a lack of standardized protocols across studies.

Conclusions: The findings underscore the need for a standardized, comprehensive battery of neurocognitive and behavioral assessments tailored to PKU patients across different age groups. Consistent evaluation tools are crucial for monitoring disease progression and treatment outcomes, especially with emerging therapeutic options. Future research should focus on validating existing instruments and developing sensitive measures to assess the quality of life and psychosocial functioning in PKU patients.

Keywords: Phenylketonuria, Executive functions, Behavioral outcomes, Emotional outcomes.

INTRODUCTION

Phenylketonuria (PKU) is an autosomal recessive metabolic disorder caused by a deficiency of phenylalanine hydroxylase (PAH), leading to impaired conversion of phenylalanine (Phe) to tyrosine and resulting in hyperphenylalaninemia (HPA)[1]. The condition encompasses a spectrum ranging from mild HPA (120-600

µmol/L) to classic PKU (>1,200 µmol/L), and, if untreated, can lead to neurotoxic Phe accumulation and reduced tyrosine levels[2]. The most serious consequence is damage to the central nervous system, causing intellectual disability along with motor and psychiatric symptoms, aberrant behaviors, and epilepsy[3,4].

The global prevalence of PKU is about 1:20,000 newborns, with variability depending on region and ethnicity[1]; in Italy, it is estimated at 1:4,500[5]. Widespread neonatal screening enables early detection and treatment, preventing severe neurocognitive deficits[6]. The dietary therapy introduced in the 1950s consists of a low-Phe diet and amino acid supplementation. However, long-term adherence remains challenging[7], particularly in adolescence and adulthood, often impairing social participation and reducing perceived quality of life[8,9].

Cognitive and behavioral issues are attributed to multiple pathophysiological factors, including tyrosine deficiency and disrupted monoaminergic neurotransmission[6]. Deficits in executive functions – such as processing speed, planning, and inhibition – are especially common during adolescence and adulthood[10-17]. Neurological signs, including tremors, hyperreflexia and white matter changes, have been associated with poor metabolic control[18,19].

Beyond cognitive symptoms, patients may experience anxiety, depression, hyperactivity, low self-esteem, social withdrawal, and reduced autonomy[10]. Despite average IQs often being within normal ranges, they tend to be lower than in non-PKU individuals[20-22], and specific executive deficits are frequent[11-17]. These functions are crucial for behavioral adaptability, decision-making, impulse regulation, and emotional control[23-25].

Cognitive outcomes are closely linked to both Phe levels and their fluctuations over time[14,26-32]. Assessing these domains also contributes to understanding patients' quality of life[33,34]. Given the heterogeneity in assessment tools, this review aims to examine recent studies that employ standardized measures to evaluate executive, emotional, and behavioral outcomes in pediatric and adult populations with PKU.

MATERIALS AND METHODS

The authors conducted a systematic review of the literature, according to the PRISMA guidelines[35], to investigate the instruments used to assess executive function and emotional and behavioral outcomes in pediatric and adult patients with PKU.

A study protocol was developed at the outset and is available upon request. The literature search aimed to identify quantitative studies consistent with predefined inclusion criteria. One researcher conducted an electronic keyword search on PubMed, supported by the Rayyan software (Cambridge, MA, USA) for screening. To maximize retrieval due to the limited literature on this population, the search strategy included the keyword "phenylketonuria". The database search was completed on 9 January 2025.

Study Selection

The search focused on recent publications from 2020 to 2025, and the following search terms were used: "*phenylketonuria,*" AND "*executive functions*," OR "*cognitive functions*".

All articles were screened based on title and abstract.

The inclusion criteria were:

1. Studies that focused on children (aged 0-18 years) and adults diagnosed with PKU.
2. Use of standardized cognitive, neuropsychological, or behavioral assessment tools.
3. Research that provided insights into the effectiveness, reliability, and validity of the tools used.

The exclusion criteria included:

1. Reviews or meta-analyses.
2. Case studies or reports.
3. Expert opinions or recommendations.

Data Extraction and Collection

The data extracted from each study included authors and year, key findings, patient ages, and instruments to assess executive functions and behavioral or emotional functioning.

Data were extracted independently by two reviewers; disagreements were resolved by discussion between the authors.

Outcome Measures

The main outcome measures were the type and the characteristics of instruments used to assess executive function and emotional and behavioral outcomes in pediatric and adult patients with PKU.

Risk of Bias of the Studies

Given the aim of our review, the authors agreed that the risk of bias was not significant.

RESULTS

Study Selection

A total of 168 studies were identified. After the automatic removal of duplicates, the 121 remaining articles were screened by title and abstract. Among these, 23 were reviews or meta-analyses, five were case studies, and four consisted of recommendations or clinical guidelines for PKU management. In total, 53 articles were excluded for not meeting the inclusion criteria. Additionally, one study[36] was excluded due to its primary focus on neurodevelopmental disorders, without relevant analysis of executive, emotional, or behavioral functioning.

The final selection included 35 full-text articles[22,31,37-69]: 11 focused on pediatric populations, 22 on adults, and two on both. The PRISMA flow diagram summarizing the selection process is shown in Figure 1.

The selected articles were analyzed to extract data on standardized tools used to assess executive functions and emotional or behavioral outcomes, in line with the objectives of this review.

To provide readers with an immediate overview of the tools identified in the literature, we have summarized the main characteristics of the instruments assessing executive functions in pediatric and adult patients with PKU in Table 1. The list and the main results of the selected papers are available in Supplementary Table 1.

Instruments for Executive Functions

Pediatric Patients

Systematic analysis of the included articles identified 13 works[37-49] discussing neuropsychological screening tools to assess specific cognitive aspects of pediatric PKU patients, including executive function and attention span. All these studies used standardized instruments. These tools have proven essential in identifying deficits that may not be evident through IQ testing alone[10].

Specifically, to assess executive functions in PKU children, the most commonly used standardized questionnaires were the Behavior Rating Inventory of Executive Function (BRIEF)[37-43] (7/13, 53.8%) and The Developmental Neuropsychological Assessment - II (NEPSY-II)[41,44] (2/13, 15.4%).

Many studies[41,43-47] (n=6) used batteries of neuropsychological tests or scales with different subtests for assessing executive functions in children. These test batteries comprise a well-defined set of tasks designed to assess various aspects of child development and evaluate multiple executive functions. The use of defined batteries is valuable as it provides a comprehensive assessment by covering multiple domains of executive functions, ensuring greater sensitivity and specificity in detecting developmental and cognitive deficits. The different batteries identified in our review to assess executive functions in pediatric patients with PKU were NEPSY-II, Test Battery for Attentional Performance (TAP) and Test Battery for Attentional Performance for Kids (KiTAP), Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III), National Institutes of Health Toolbox (NIH Toolbox), Cambridge Neuropsychological Test Automated Battery (CANTAB), and Denver Developmental Screening Test-II (DDST-II).

Almost all studies[37-45,48,49] (n=11) used single tests, alone or in combination with standardized batteries, to assess executive functions in PKU children or adolescents. The use of single tests can be extremely valuable, particularly when the goal is to focus on specific aspects of executive functions. Single tests enable a more in-depth assessment of specific abilities, such as working memory, inhibitory control, or

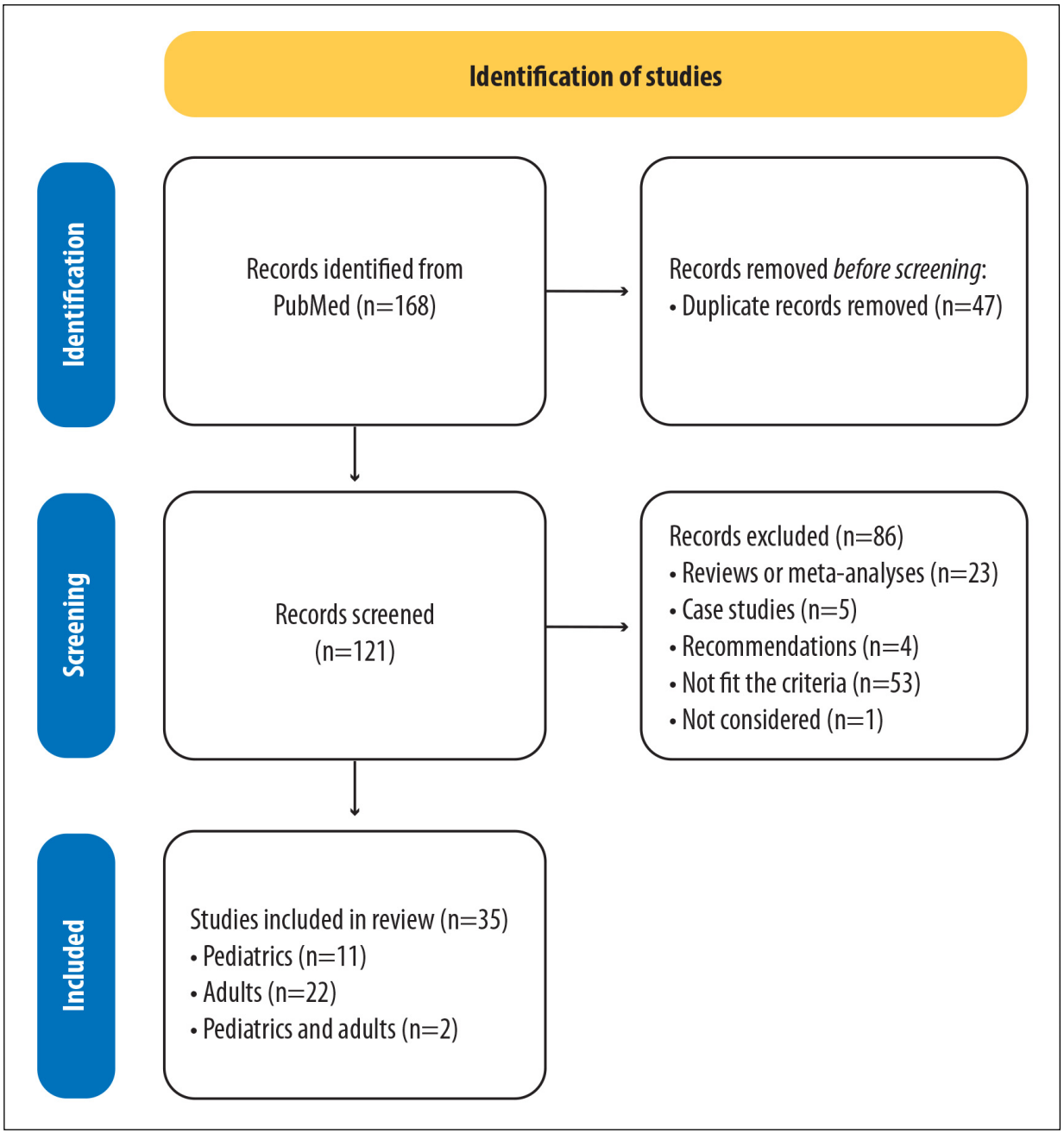

Figure 1. PRISMA diagram.

cognitive flexibility, making them useful for targeted assessments or detailed investigations in clinical or research settings. Additionally, they may be preferable in situations in which time constraints or the need for a quick screening make the use of a full battery impractical. The single tests identified in our review were: BRIEF, Trail Making Test (TMT) for children, Oral Fluency, Contingency Naming Test (CNT), Digit and Spatial Span, Letters-Number Sequencing, Tonic Alertness, Corsi Test, Flanker test, Tower of London (ToL) Test, Stroop Test, Hand Game, Dimensional Change Card Sort (DCCS), Brixton Test, Children's Gambling Task (CGT), and PKU Symptom Severity and Impacts Scale (PKU-SSIS), and the Conners Continuous Performance Test – Third Edition (CPT-3).

The tools identified in our review for assessing executive functions in pediatric patients with PKU will be briefly described below.

Table 1. Summary of assessment tools used to evaluate executive, behavioral, and emotional functioning in pediatric and adult patients with PKU.

Instrument	Primary Objective/Domain	Main Features
EXECUTIVE FUNCTION ASSESSMENT TOOLS		
Pediatric patients		
NEPSY-II[41,44]	Cognitive flexibility, attention, inhibition, working memory	Neuropsychological battery (3-16 yrs); includes Animal Sorting, Auditory Attention, Inhibition, Digit Span, Corsi Block; modular and cross-linguistically adaptable.
TAP / KiTAP[45]	Attention, impulse control, flexibility, working memory	Computerized tests (TAP: ≥10 yrs; KiTAP: child-friendly); includes Go/No-Go, n-back, set-shifting, and distractibility.
Bayley-III[43]	Cognitive development, early executive skills	For ages 16 days-3.5 yrs; assesses cognition, language, motor function; includes growth scores; indirect executive assessment.
NIH Toolbox[43]	Executive function, PSI, working memory	Computerized battery (≥3 yrs); includes Flanker, DCCS, List Sorting; yields Fluid/Crystallized Cognition scores.
CANTAB[43]	Attention, flexibility, executive control	Touchscreen tasks (≥8 yrs); includes RVP, Reaction Time, Feature/Conjunction Search; measures attention under distraction.
DDST-II[46,47]	Developmental screening	For ages 0-6 yrs; assesses personal-social, motor, and language domains; identifies early delays.
BRIEF (BRIEF-P, BRIED-2)[37-43]	Behavioral manifestations of EF	Questionnaire for parents/adolescents (ages 3-17); measures inhibition, working memory, planning, and emotional control.
TMT (Switch Task)[38]	PSI, cognitive flexibility	Classic TMT and child-friendly version (4-7 yrs) using playful stimuli; assesses task-switching.
Oral Fluency Test[38]	Verbal fluency, PSI	Semantic and phonemic fluency; timed word generation by category/letter; age-normed z-scores.
Contingency Naming Test (CNT)[38]	Flexibility, response inhibition	Color-shape stimuli with rule shifts; measures accuracy, speed, and efficiency.
Digit and Spatial Span[44]	Auditory & visuospatial WM	Forward/backward recall tasks; part of Wechsler scales; assess memory span and manipulation.
Letter-Number Sequencing (LNS)[44]	Sequencing, verbal WM	Recall and reorder number-letter sequences; assesses working memory load.
Tonic Alertness[48]	Sustained attention	3-min task detecting stimuli (e.g., rabbit image); measures RT, omissions, impulsivity.

Continued

Table 1. Summary of assessment tools used to evaluate executive, behavioral, and emotional functioning in pediatric and adult patients with PKU.

Instrument	Primary Objective/Domain	Main Features
Corsi Block Tapping[48]	Visuospatial WM	Reproduction of tapped block sequences; digital version uses animated characters.
Flanker Task[48]	Inhibitory control	Visual distractors; compares accuracy/speed in congruent *vs.* incongruent conditions.
Tower of London (ToL)[45]	Planning, problem-solving	Strategic bead-moving task; involves sub-goals and working memory.
Stroop Test (Sun-Moon variant)[40]	Verbal inhibition	Reverse naming task using sun/moon stimuli; interference and error scores.
Hand Game Test[40]	Non-verbal inhibition	Gesture-based mimic *vs.* counter-mimic task; includes feedback and self-corrections.
DCCS[40]	Cognitive flexibility	Card sorting task with rule-switching and dynamic border condition.
Brixton (Preschool version)[40]	Rule deduction, set-shifting	"Mouse in a pot" pattern task; assesses implicit rule learning with rule shifts.
Children's Gambling Task (CGT)[40]	Decision-making, risk-taking	Choice task with advantageous/disadvantageous decks; reward/loss-based learning.
PKU-SSIS[49]	Executive and psychosocial symptoms	Interview for children and caregivers; explores mood, EF, physical, and social domains.
CPT-3[43]	Sustained attention, vigilance, impulsivity	14-min computerized task with letter stimuli; reports hit rate, RT, omissions, commissions.
Adult patients		
PICO Protocol[50-54]	Attention, inhibition, WM, PSI, flexibility	Composite framework using TAP, D-KEFS, WAIS-IV; standardizes cognitive assessment in PKU.
WAIS-IV Subtests[31,57-61,63]	Working memory, PSI, reasoning	Includes Digit Span Backward, Symbol Search, Coding, Matrix Reasoning; detects subtle executive deficits.
NIH Toolbox[59-65]	Executive control, WM, PSI, flexibility	Modular battery with Flanker, List Sorting, Spatial WM, DCCS, Pattern Comparison, Oral Symbol Digit; demographically normed.
CANTAB[60,62]	Attention, flexibility, executive control	Automated battery with RVP, Reaction Time tasks, Feature/Conjunction Search; validated in cognitive disorders.

Continued

Table 1. Summary of assessment tools used to evaluate executive, behavioral, and emotional functioning in pediatric and adult patients with PKU.

Instrument	Primary Objective/Domain	Main Features
D-KEFS[50-54,61]	Flexibility, inhibition, planning	Includes Phonemic Fluency, Card Sorting, Stroop, TMT A/B; comprehensive EF profiling.
TAP[50-54,64]	Attention, shifting, alertness	Computerized subtests for selective/sustained attention; used standalone or in PICO.
SAD[67]	Sustained attention, impulse regulation	Measures attentional stability and inhibitory control over time.
CPT[59]	Vigilance, inattention, impulsivity	Go/no-go task assessing sustained attention and inhibitory response patterns.
Memory Search 2 Dimensions[67]	Visual WM, multidimensional memory	Identifies features across shape/size dimensions; assesses dual-feature tracking.
Trail Making Test (TMT)[58,62,68,69]	Flexibility, PSI	Part A: speed; Part B: task-switching; sensitive to Phe-related cognitive change.
SDMT (Symbol Digit Modalities Test)[57,61,62,69]	PSI, attention, associative learning	Symbol-digit matching task; widely used in metabolic and neurodegenerative research.
PASAT[69]	WM, PSI, attention	Auditory serial addition task; sensitive to processing efficiency and Phe-level variation.
Digit Span Backward[69]	Working memory, manipulation	Reverse digit recall; used standalone or in WAIS to assess auditory WM.
COWAT (Controlled Oral Word Association Test)[57]	Verbal fluency, retrieval	Timed letter-based word generation; evaluates initiation and executive access.
Phonemic Fluency Tasks[58,62,69]	Language fluency, flexibility	COWAT variants focused on verbal flexibility and memory access.
Stroop Color-Word Test[57,69]	Inhibition, cognitive control	Color naming under interference; measures executive suppression.
Hayling Sentence Completion Test[69]	Response initiation, inhibition	Sentence completion with logical and unrelated responses; assesses response suppression.
Tower of London (ToL)[69]	Planning, problem-solving	Strategic bead placement task evaluating working memory and goal planning.
WCST (Wisconsin Card Sorting Test)[69]	Set-shifting, flexibility	Rule-based card sorting; assesses abstraction and adaptive strategy switching.
BRIEF-A[42]	Executive behavior in daily life	Self-report on inhibition, organization, emotional regulation; reflects functional EF impact.
PKU-SSIS[49]	Executive symptoms, quality of life	PKU-specific interview assessing cognitive, emotional, social, and physical domains.

Continued

Table 1. Summary of assessment tools used to evaluate executive, behavioral, and emotional functioning in pediatric and adult patients with PKU.

Instrument	Primary Objective/Domain	Main Features
BEHAVIORAL AND EMOTIONAL FUNCTION ASSESSMENT TOOLS		
Pediatric patients		
ADHD Rating Scale-IV (ADHD RS-IV)[37]	Inattention, hyperactivity, impulsivity	Parent-rated; 18 items on a 4-point scale; two 9-item subscales; max score = 54.
Conners Comprehensive Behavior Rating Scale (Conners CBRS)[38]	Behavioral and emotional problems, academic performance	Multi-informant (ages 6-18); assesses emotional/behavioral issues and academics; includes 25-item Clinical Index and validity checks.
Child Behavior Checklist (CBCL)[39,41,44]	Broad emotional and behavioral problems	Parent-report for ages 6-18; covers aggression, anxiety, depression, hyperactivity, and socialization; provides T-scores for clinical use.
PROMIS[43]	Mental health and psychosocial well-being	Self- and parent-report (ages 5-17); assesses anxiety, depression, fatigue, pain, peer relations; T-scores enable cross-study comparison.
Social Skills Rating System (SSRS)[39]	Social skills, problem behaviors, academic competence	Multi-rater tool with forms for teachers, parents, and students; evaluates key social and behavior domains; yields standard scores.
Adaptive Behavior Assessment System - Second Edition (ABAS-II)[44]	Daily living skills, adaptive functioning	Parent form (ages 5-21); 211 items; provides Conceptual, Social, and Practical domain scores plus General Adaptive Composite.
Adult patients		
Conners' Adult ADHD Rating Scales (CAARS)[59]	Inattention, hyperactivity, impulsivity, emotional regulation	Self-report for adults; assesses ADHD symptoms and their impact on emotional regulation and daily life; yields severity scores and indexes.
Behavioural and Emotional Disturbance (ASR 18-59)[57]	Broad behavioral and emotional disturbances	Part of Achenbach System; self-report for ages 18-59; evaluates mood, anxiety, aggression; includes syndrome and DSM-oriented scales.
Beck Anxiety Inventory (BAI)[59,57]	Anxiety symptoms	21-item self-report; assesses somatic and cognitive symptoms of anxiety; uses 4-point scale; sensitive to symptom severity.
Beck Depression Inventory (BDI)[59,57]	Depressive symptoms	21-item questionnaire measuring mood, pessimism, fatigue; widely used to assess depression severity.
Hospital Anxiety and Depression Scale (HADS)[61]	Anxiety and depression in medical settings	14 items (7 per subscale); excludes somatic symptoms; indicates severity from normal to abnormal.

Continued

Table 1. Summary of assessment tools used to evaluate executive, behavioral, and emotional functioning in pediatric and adult patients with PKU.

Instrument	Primary Objective/Domain	Main Features
Perceived Stress Scale (PSS)[61]	Subjective stress perception	10-item self-report; measures perceived stress and loss of control; uses a 5-point Likert scale.
Neuropsychiatric Inventory (NPI)[15]	Psychiatric and neurobehavioral symptoms	Caregiver-reported; assesses delusions, hallucinations, apathy, depression, irritability, and sleep disturbances.
Relationship Scale Questionnaire (RSQ)[61]	Attachment styles and relational patterns	Assesses trust, intimacy, avoidance in relationships; identifies interpersonal difficulties.
Family Adaptability and Cohesion Evaluation Scale (FACES)[61]	Family functioning and dynamics	Measures family cohesion and adaptability; provides insight into relational and psychosocial support.

2D = Two-Dimensional; ABAS-II = Adaptive Behavior Assessment System, Second Edition; ADHD RS-IV = Attention Deficit Hyperactivity Disorder Rating Scale–Fourth Edition; ASR = Adult Self-Report; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; BRIEF = Behavior Rating Inventory of Executive Function; BRIEF-A = Behavior Rating Inventory of Executive Function – Adult Version; CAARS = Conners' Adult ADHD Rating Scales; CBCL = Child Behavior Checklist; CANTAB = Cambridge Neuropsychological Test Automated Battery; CGT = Children's Gambling Task; CNT = Contingency Naming Test; Conners CBRS = Conners Comprehensive Behavior Rating Scales; COWAT = Controlled Oral Word Association Test; CPT = Continuous Performance Test; CPT-3 = Conners' Continuous Performance Test, Third Edition; D-KEFS = Delis-Kaplan Executive Function System; DCCS = Dimensional Change Card Sort; DDST-II = Denver Developmental Screening Test, Second Edition; FACES = Family Adaptability and Cohesion Evaluation Scale; HADS = Hospital Anxiety and Depression Scale; KiTAP = Child version of the Test of Attentional Performance; LNS = Letter–Number Sequencing; NEPSY-II = Developmental Neuropsychological Assessment, Second Edition; NIH = National Institutes of Health; NPI = Neuropsychiatric Inventory; PASAT = Paced Auditory Serial Addition Test; PICO = Phenylketonuria-specific Integrated Cognitive Outcome protocol; PKU-SSIS = PKU Symptom Severity and Impacts Scale; PROMIS = Patient-Reported Outcomes Measurement Information System; PSI = Processing Speed Index; PSS = Perceived Stress Scale; RSQ = Relationship Scale Questionnaire; RT = Reaction Time; RVP = Rapid Visual Information Processing; SAD = Sustained Attention and Distractibility test; SDMT = Symbol Digit Modalities Test; SSRS = Social Skills Rating System; TAP = Test of Attentional Performance; TMT = Trail Making Test; ToL = Tower of London; WAIS-IV = Wechsler Adult Intelligence Scale, Fourth Edition; WCST = Wisconsin Card Sorting Test; WM = Working Memory.

NEPSY-II

The NEPSY-II was used in two studies[41,44]. It is a developmental neuropsychological battery designed to assess executive functions and social cognition in children aged 3-16 years. Widely used in clinical and research settings, particularly in the treatment of neurodevelopmental disorders, it has demonstrated high reliability. NEPSY-II evaluates multiple cognitive domains, with emphasis on executive function and attention.

Key subtests include Animal Sorting (cognitive flexibility), Auditory Attention (selective attention), response set (vigilance), and inhibition (task-switching and inhibitory control). It also incorporates standard working memory tasks, such as Digit Span and the Corsi Block-Tapping Test, as well as verbal and semantic fluency assessments. Its modular format allows for targeted or comprehensive use, and its validated scoring and cross-linguistic adaptability support both diagnostic and research purposes in pediatric populations.

Test Battery for Attentional Performance (TAP) and Test Battery for Attentional Performance for Kids (KiTAP)

The TAP was used by Tomm et al[45] to assess attention functions in individuals aged 10 years and above. This computer-based tool includes reaction tasks using language-free stimuli, with performance measured *via* response time, errors, and omissions. It is well-validated and offers age-normed data.

Subtests administered included working memory (n-back), flexibility (set-shifting), divided attention (dual tasking), impulse control (Go/NoGo), and incompatibility (stimulus-response conflict). The KiTAP, a child-friendly version, preserves subtests on flexibility, divided attention, and impulse control and adapts tasks for sustained attention and distractibility, where no direct TAP equivalents exist.

Bayley Scales of Infant and Toddler Development – Third Edition (Bayley-III)

The Bayley-III scales were used by Christ et al[43] to assess developmental progress in children aged 16 days to 3.5 years. These individually administered tools help identify developmental delays and inform early intervention. The battery covers five domains: cognitive, language, motor, socio-emotional, and adaptive behavior.

The cognitive scale examines early abilities such as sensory-motor skills, memory, and concept formation. The language scale includes receptive (e.g., vocabulary, comprehension) and expressive (e.g., language production) components. The motor domain assesses both fine motor skills (manipulation, coordination) and gross motor skills (balance, movement).

Socio-emotional and adaptive behavior are assessed through parent reports, providing insight into emotional regulation and functional independence. The Bayley-III's age-appropriate materials, clear instructions, and modular format support both full and domain-specific use. Growth scores facilitate tracking over time, making the tool valuable for clinical and research purposes.

National Institutes of Health Toolbox (NIH Toolbox)

The NIH Toolbox was used by Christ et al[43] and administered to participants aged 3 years and older. Developed under the NIH Blueprint for Neuroscience Research, this computer-based battery assesses cognitive, executive, emotional, sensory, and motor functions. It is designed to be used across age groups and research settings, enabling standardized comparisons.

The Cognition Battery comprises 3-7-minute subtests and yields two composite scores: crystallized cognition (verbal abilities) and fluid cognition (executive function, processing speed, and memory). Fluid cognition scores are not calculated for children under 6 years due to subtest constraints.

A major advantage is the use of normative scores adjusted for age, sex, ethnicity, and education, allowing culturally appropriate interpretation across populations.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

CANTAB was used by Christ et al[43] for pediatric and adult participants aged over 8 years. This automated neuropsychological battery is widely used in clinical and research settings to assess attention, memory, processing speed (PSI), executive control, and cognitive flexibility.

Key subtests include Rapid Visual Information Processing (RVP) for sustained attention, Simple Detection and Detection with Distractors for reaction time and attentional control, and Choice Reaction Time for decision speed. Feature and Conjunction Search tasks assess visual search and target recognition in complex stimuli, reflecting PSI and flexibility.

Denver Developmental Screening Test-II (DDST-II)

The DDST-II was used in two studies[46,47] to assess global development in children from birth to 6 years. It evaluates four domains: personal-social, fine motor-adaptive, language, and gross motor. The test includes 125 items and applies corrected age for children under 2 years to adjust for prematurity. It is administered at specific ages to monitor developmental milestones. Scoring follows age-specific criteria, with items rated as pass (1) or fail (0). Since no total score is provided, raw scores are derived by summing passed items in the current and earlier developmental windows, enabling consistent cross-administration analysis. The DDST-II's structured format and clear classification system make it a reliable tool for identifying developmental delays and guiding early interventions.

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Scoring uses age-specific criteria, with items marked as pass (1) or fail (0). Although no total score is provided, raw scores are calculated by summing passed items within and below the child's developmental level, allowing for consistent analysis. The DDST-II's structured design facilitates the early identification of developmental delays and effective intervention planning.

Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF was the most frequently used tool, appearing in seven studies[37-43]. It is a standardized questionnaire assessing executive functions in children and adolescents, including inhibition, flexibility, emotional control, initiation, working memory, planning, organization, and self-monitoring.

Versions include the BRIEF-P (ages 3-5 years, parent report), BRIEF-2 (ages 6-17 years, parent report), and BRIEF-2 self-report (ages 11-17 years). Respondents rate the frequency of behavior (e.g., difficulty waiting for a turn) as "never," "sometimes," or "often" a problem. Scores generate clinical scales and indices, including the Global Executive Composite, reflecting everyday executive challenges.

Trail Making Test (TMT)

The TMT was used by Randell et al[38] in a child-specific version and by Hanusch et al[48] through a digital adaptation called The Switch Task. It assesses processing speed (PSI), visual scanning, psychomotor coordination, working memory, and executive functions, including cognitive flexibility and task switching.

Part A involves connecting numbers in order; Part B alternates numbers and letters (e.g., 1-A-2-B). Timed performance reflects executive efficiency. The Switch Task, adapted for children aged 4-7, uses visual stimuli (e.g., rabbits and carrots) and records reaction time and switch costs to assess early cognitive flexibility.

Oral Fluency Test

This test was used in one study[38]. The Oral Fluency Test is a brief neuropsychological tool assessing verbal ability, executive functioning, and processing speed (PSI). It includes semantic fluency (e.g., naming animals) and phonemic fluency (e.g., words starting with F, A, or S), typically within a 60-second limit. Performance is scored using Z-scores based on age-normed data.

Contingency Naming Test (CNT)

The Contingency Naming Test (CNT) was used by Randell et al[38] to assess executive functions, including processing speed (PSI), cognitive flexibility, working memory, and response inhibition. It features four trials of increasing complexity using colored shapes, internal figures, and backward arrows.

The first two trials involve simple naming, while the latter ones require rule-switching based on shape-color rules. Sensitive to frontal lobe function, the CNT helps detect executive deficits from neurodevelopmental issues or injury. Performance is evaluated based on errors, completion time, and efficiency, with Z-scores used for standardized analysis.

Digit and Spatial Span Tests

These assessments were used in two studies: Trimarco et al[44] used Digit Span alone, while Parmentier et al[40] applied both Digit Span and Spatial Span.

Digit Span, part of the Wechsler Scales, evaluates working memory, auditory attention, and executive function. It includes Forward (repeat in order) and Backward (repeat in reverse) tasks, with the latter requiring more cognitive flexibility. Scoring is based on the longest correctly recalled sequence.

Spatial Span assesses visuospatial working memory using a 10-cube board. Children reproduce sequences in forward or backward order, with the longest accurately repeated sequence scored. Together, these tests provide a detailed view of auditory-verbal and visuospatial memory, aiding in the detection of domain-specific deficits.

Letter-Number Sequencing (LNS)

The Letter-Number Sequencing (LNS) subtest, part of the Wechsler Scales, was used in one study[44]. It assesses working memory, attention, and executive functioning by requiring participants to reorder mixed sequences of digits and letters, repeating numbers in ascending order and letters alphabetically. Administered orally, the LNS measures cognitive flexibility, sequencing, and manipulation of information, with performance scored by the number of correctly recalled sequences.

Tonic Alertness Test

The Tonic Alertness Test, used by Hanusch et al[48], assessed sustained attention and the ability to maintain alertness over time. Children tapped the screen when a black fixation circle changed into a colorful rabbit across 50 trials over 3 minutes. Outcome measures included mean reaction time, missed responses (no response within 1,500 ms), and commission errors (responses during the fixation phase).

Corsi Block Tapping Task

The Corsi Test is a standard measure of visuospatial short-term memory, assessing the ability to retain and manipulate spatial sequences. It typically uses a board with nine cubes tapped in sequences of increasing length (2-10 items), with participants reproducing the order. Progression requires at least two correct trials out of three, and span is defined by the longest accurately recalled sequence.

Hanusch et al[48] created a digital, child-friendly version using animated animals appearing in sequence. Children tap screen locations across 12 sequences (1-4 items, repeated three times). This adaptation maintains reliability and is effective for evaluating visuospatial working memory in young children.

Flanker Task

The Flanker Task assesses inhibitory control by testing the ability to suppress responses to distracting stimuli. Participants indicate the direction of a central target while ignoring flankers that may be congruent, incongruent, or neutral, measuring interference and cognitive flexibility.

Hanusch et al[48] used a child-friendly computerized version with orange fish as targets and distractor fish as flankers. Children tapped the square, matching the direction of the target fish. Reaction time and accuracy in congruent *vs.* incongruent trials were used to assess inhibitory control.

Tower of London (ToL) Test

The Tower of London (ToL) test was used in one study[45] to assess executive functions, particularly planning, problem-solving, and strategic decision-making. Participants move three colored balls across vertical pegs of varying height to match a target arrangement in as few moves as possible, with peg capacity limiting placement.

Performance requires working memory, sub-goal sequencing, and strategic planning guided by the supervisory attentional system of the prefrontal cortex. The ToL is widely used to evaluate how individuals coordinate complex, interdependent actions.

Stroop Test

The Stroop Test assesses selective attention, cognitive flexibility, and inhibitory control – core components of executive functioning. The classic version includes reading color names in black ink (baseline), naming colored squares (control), and naming the ink color of incongruent color words (inhibition). The final phase requires suppressing automatic reading, with performance assessed *via* reaction time, errors, and interference scores.

Paermentier et al[40] used a Sun-Moon variant to measure verbal inhibition. In the control phase, children named the image; in the inhibition phase, they gave the opposite response. Interference and error scores were used to evaluate inhibitory control.

Hand Game Test

The Hand Game, used in one study[40], assesses non-verbal inhibitory control. In the control phase, children mimic the examiner's hand gesture (fist or pointing finger); in the interference phase, they perform the opposite gesture, testing the ability to suppress automatic responses.

The adapted version included six control and fifteen interference trials in random order. Feedback was provided after each response, with scoring based on accuracy, errors, and self-corrections. Unlike the adult version, which ends after six correct responses, the child version administered all interference trials.

Dimensional Change Card Sort (DCCS)

The Dimensional Change Card Sort (DCCS), used by Paermentier et al[40], assesses cognitive flexibility – the ability to shift attention and adjust to new rules. Children first sort cards by one criterion (e.g., color or shape), then switch to the other if they correctly sort at least five out of six cards.

In the advanced "border" phase, sorting depends on border presence: cards with a black border are sorted by color, others by shape. Scoring ranges from 0 to 3, with one point awarded for each completed phase.

Brixton Test

The Brixton Test for preschoolers, used in one study[40], assesses cognitive flexibility, rule deduction, and set-shifting. In this adapted version, children guess which of 30 clay pots hides a mouse. To reduce the working memory load, the examiner reminds them of the last correct location.

The rule changes three times, each over eight trials. After each guess, the correct pot is shown, allowing the child to infer the pattern. The total score reflects correct guesses, capturing set-shifting and implicit rule learning.

Children's Gambling Task (CGT)

The Children's Gambling Task (CGT), used by Parmentier et al[40], evaluates decision-making and risk-taking in children. Participants select cards from two decks: one offering small, consistent gains (advantageous) and another with larger gains but higher, more frequent losses (disadvantageous). Sweets are used as incentives to maintain engagement. After a practice phase, children complete test trials. A proportion score reflects the preference for advantageous choices, with higher scores indicating better risk evaluation and decision-making.

PKU Symptom Severity and Impacts Scale (PKU-SSIS)

The PKU Symptom Severity and Impacts Scale (PKU-SSIS) is a structured patient-reported interview designed to assess the impact of PKU on cognitive, social, and academic functioning in early-treated children. Described by Quinn et al[49], it captures how PKU and its dietary treatment influence neuropsychological performance and daily life.

The 22-item tool includes input from children and caregivers, covering three symptom domains (emotional/psychological, neurocognitive/executive, physical health) and four impact areas (social relationships, independence, well-being, self-care), offering a detailed view of disease burden.

Conners Continuous Performance Test – Third Edition (CPT-3)

The CPT-3 was administered by Christ et al[43] to participants aged 8 years and older. This 14-minute computerized task assesses sustained attention, inattention, impulsivity, and vigilance. Participants respond to a sequence of letters by pressing a button for all except the non-target letter "X". Scoring includes age-normed metrics such as discriminability, hit reaction time, and response time variability, offering a detailed profile of attentional performance.

Adult Patients

A systematic analysis of the included articles identified 24 studies[22,31,42,49-69] discussing neuropsychological screening tools to assess specific cognitive aspects in adults with PKU. All of these studies used standardized instruments. As with children, these tools have proven essential in identifying deficits that may not be evident through IQ testing alone.

Standardized tests were predominantly used to assess executive functions in adult PKU patients, including both batteries and single tests. The use of questionnaires was less frequent. Many studies did not employ entirely standardized batteries but rather selected specific tools to assess particular executive functions. These tools included subtests from the Wechsler Adult Intelligence Scale (WAIS), TAP, CANTAB, NIH Toolbox for the Assessment of Neurological and Behavioral Function, Delis-Kaplan Executive Function System (D-KEFS), Sustained Attention and Inhibitory Control (SAD), and CPT. Additionally, individual standardized tests such as Memory Search 2 Dimensions, TMT, Symbol Digit Modalities Test (SDMT), Paced Auditory Serial Addition Test (PASAT), Digit Span Backward, Controlled Oral Word Association Test (COWAT), Verbal Fluency, Stroop-Color Word Test, Hyling Sentences Completion Test, ToL, and Wisconsin Card Sorting Test (WCST) were employed.

Two questionnaires were used to evaluate executive functions: the BRIEF-Adult Version (BRIEF-A) and the PKU-SSIS. Some studies have adopted the Phenylalanine and its Impact on Cognition (PICO) protocol, which is specifically designed for studying executive functions in adults with PKU and incorporates carefully selected subtests from standardized batteries. Of the 24 studies analyzed, seven[50-56] (7/24) employed the PICO protocol, three[22,68,69] (3/24) utilized only individual tests, eight[31,57,58,61-64,66] (8/18) combined individual tests with subtests from standardized batteries, three[59,60,67] (3/24) combined only subtests from standardized batteries, one[65] (1/24) exclusively used subtests from a single tool (NIH), and two[42,49] (2/24) relied solely on questionnaires. All the selected tools were aimed at a detailed assessment of specific executive functions rather than serving as screening instruments. The individual tools will be described in detail in the following paragraphs.

Phenylalanine and Its Impact on Cognition (PICO) protocol

A group of studies[50-56] used the PICO protocol, a standardized framework for assessing cognitive functions in adult PKU patients. It targets attention, executive function, and general intelligence, enabling reliable cross-study comparisons.

Key tools include the TAP (attention, working memory), D-KEFS (inhibition, flexibility), and WAIS-IV, which measures intellectual ability through subtests such as Symbol Search and Visual Matrices, both indirectly reflecting executive function. Reported deficits include inhibition, sustained attention[52,53], working memory, cognitive flexibility, and processing speed[51]. PKU patients also showed lower average IQ scores compared to controls[50].

Wechsler Adult Intelligence Scale IV (WAIS-IV)

WAIS subtests have been widely used in PKU research, both within the PICO protocol[50-56] and in 8 of 24 reviewed studies[31,57-63]. The WAIS evaluates domains like working memory, verbal comprehension, reasoning, and processing speed (PSI). Common subtests include Digit Span Backward (working memory), Matrix Reasoning (fluid intelligence), Digit Symbol (Coding), and Symbol Search (PSI, visual accuracy). Deficits in PSI – especially in visual search[58-60,62] – and working memory impairments in Digit Span Backward[61] were frequently reported.

National Institutes of Health Toolbox (NIH Toolbox)

Two studies[59,65] used the NIH Toolbox to assess cognitive, motor, and emotional functioning in adults with PKU. Designed for both clinical and research use, the battery provides a rapid, standardized evaluation of domains, including attention, memory, and executive control.

Tests included the Flanker Inhibitory Control task (inhibition, sustained attention), List Sorting and Spatial Working Memory (working memory), and the Dimensional Change Card Sort (DCCS) for cognitive flexibility. Additional tasks assessed processing speed (Pattern Comparison) and symbol-number matching (Oral Symbol Digit). These contribute to the Fluid Cognition Composite Score, a measure of executive and reasoning ability.

Both Clocksin et al[59] and Christ et al[65] reported deficits in executive functioning, particularly in the Fluid Cognition Composite.

Cambridge Neuropsychological Test Automated Battery (CANTAB)

CANTAB was used by Manti et al[31], Schoen et al[60] and Romani et al[64] to evaluate cognitive function in adult PKU patients. This automated battery is widely used in clinical and research settings to assess attention, memory, processing speed (PSI), executive control, and cognitive flexibility.

Subtests included Rapid Visual Processing (sustained attention), Simple Detection and Detection with Distractors (reaction time and attentional control), and Choice Reaction Time (decision speed). Feature Search and Conjunction Search assessed visual search and flexibility. These studies reported impairments in working memory[60] and sustained attention[64].

Delis-Kaplan Executive Function System (D-KEFS)

This tool is included in the PICO protocol[50-56] and was also used in other studies[61]. It assesses executive functions such as cognitive flexibility, planning, inhibitory control, and problem-solving and is especially useful in individuals with executive impairments.

Several D-KEFS subtests were applied in adult PKU studies: the Phonemic Fluency Task (word generation by letter), the Card Sorting Subtest (flexibility in adapting to shifting rules), Trail Making Test (Parts A and B for processing speed and strategy shifts), and the Stroop Color-Word Test (response inhibition *via* color-word conflict naming).

Test of Attentional Performance (TAP)

The TAP is a neuropsychological tool designed to assess various aspects of attention and executive function. It includes a series of subtests that evaluate different attention-related processes, such as selective attention, sustained attention, and shifting of attention. The TAP is part of the PICO protocol[50-56] but was also included by Scala et al[66].

Sustained Attention and Inhibitory Control (SAD)

This tool was selected in the work of van Wegberg et al[67]. It is a task that evaluates the subject's ability to maintain focus over an extended period while also controlling impulsive responses. This test is important for assessing attention and inhibitory control, which are crucial for performing tasks that require concentration and the suppression of distractions or automatic reactions. Significant differences in reaction times were found in the study by van Wegberg et al[67].

Continuous Performance Tests (CPT)

The CPT has been used to assess attention, vigilance, and response inhibition. PKU patients typically show deficits in these areas, which are related to executive functioning and PSI[59]. These tests help clinicians identify early cognitive dysfunction, especially in areas requiring sustained attention.

Memory Search 2 Dimensions

The Memory Search 2-Dimensional task evaluates the subject's ability to search and retrieve information from memory across two dimensions (e.g., size and shape). This test involves presenting the subject with a set of stimuli and requiring them to identify specific features, assessing their ability to process and retrieve information based on multiple characteristics. This tool was used by van Wegberg et al[67].

Trail Making Test (TMT)

The TMT, a common neuropsychological tool, was used in many studies[22,58,63,64,68,69] to assess executive functions, such as cognitive flexibility and PSI in PKU patients. Lower performance compared with the control group was found by Romani et al[64] and Brachet et al[58]. According to Costa-Lathan et al[68], patients with poorer time-based performance on TMT Form A and Form B had higher ranges and maximum Phe levels.

Rapid Visual Information Processing

Used by Thomas et al[62] and Manti et al[31], assesses sustained attention and working memory by requiring participants to detect target sequences of digits presented rapidly on a screen. It measures reaction time, accuracy, and sensitivity, providing indices of cognitive vigilance.

Symbol Digit Modalities Test (SDMT)

The SDMT is a cognitive assessment that measures PSI, attention, and the ability to associate symbols with numbers. This tool has been used in many studies[57,61,64,69]. The subject uses a key that pairs symbols with digits and must quickly match each symbol to its corresponding number. It is particularly helpful in assessing cognitive function in individuals with conditions affecting PSI. Performance on the SDMT is lower in PKU patients, according to Luna et al[57] and Aitkenhead et al[61].

Paced Auditory Serial Addition Test (PASAT)

The PASAT is a neuropsychological assessment that measures cognitive functions such as attention, working memory, and PSI. This tool was used exclusively in the work by Burlina et al[69]. According to the results, the PASAT is a valuable tool for assessing cognitive efficiency in PKU patients and monitoring changes associated with Phe management.

Digit Span Backward

This tool was used as a single test by Burlina et al[69]. In other studies, it is a subtest of the WAIS. It is used to assess working memory and cognitive flexibility. In this task, participants are asked to repeat a sequence of digits in reverse order, testing their ability to temporarily hold and manipulate information.

Controlled Oral Word Association Test (COWAT)

The COWAT assesses verbal fluency by asking the subject to generate as many words as possible within a set time limit that begins with a specific letter (e.g., “F” or “A”). It measures the subject’s ability to retrieve words from memory under time constraints, indicating executive function and lexical access. This tool was used by Luna et al[57], and Thomas et al[62].

Verbal Fluency – Phonemic Fluency Task

Verbal Fluency and Phonemic Fluency are assessed through a cognitive task in which a person is asked to generate as many words as possible, starting with a specific letter, within a set time. This tool has been used by Pilotto et al[22], Manti et al[31], Brachet et al[58], Burlina et al[69] and Romani et al[64]. It measures verbal fluency, language retrieval, and cognitive flexibility, reflecting executive function and memory efficiency. PKU patients have lower performance in fluency tasks, according to Romani et al[64] and Brachet et al[58].

Stroop Color-Word Test

The Stroop Color-Word Test is designed to assess cognitive control, particularly the ability to inhibit automatic responses. In this test, subjects are asked to name the color of a word, while the word itself may refer to a different color (e.g., the word “red” written in blue). The Stroop Test was used as a single test by Thomas et al[62] and Burlina et al[69], while it was part of a battery of tests in the study by Luna et al[57], where alterations were found.

Hayling Sentence Completion Test

The Hayling Test is a neuropsychological assessment designed to evaluate executive functions, particularly response initiation and suppression. It consists of two sections: one test response initiation by completing sentences with fitting words, and the other assesses response suppression using unrelated words. This tool was used in Manti et al[31], Thomas et al[62] and Burlina et al’s[69] work.

Tower of London (ToL) Test

The ToL is a neuropsychological instrument used to assess executive functions. It requires participants to rearrange beads on pegs to match a target, assessing planning and problem-solving skills while following specific rules. This tool was used in Pilotto et al[22] and Burlina’s work[69].

Wisconsin Card Sorting Test (WCST)

The WCST is a neuropsychological assessment commonly used to evaluate executive functions, particularly cognitive flexibility, problem-solving, and set-shifting abilities. It involves sorting cards according to different rules (such as color, shape, or number), with the rule changing periodically without the participant's knowledge. Participants must adapt their strategy to the new rule, testing their ability to shift cognitive strategies and solve problems. This tool was used by Thomas et al[62], Romani et al[64] and Scala et al[66] to evaluate executive function in adult PKU patients.

Behavior Rating Inventory of Executive Function – Adult Version (BRIEF-A)

The Behavior Rating Inventory of Executive Function–Adult Version (BRIEF-A), used by Christ et al[42], is a standardized questionnaire-based tool for evaluating executive functions in adults. It assesses real-world behaviors related to inhibition, emotional regulation, working memory, and organization, making it particularly useful for identifying cognitive impairments and tracking changes over time in clinical populations, including adults with PKU.

PKU Symptom Severity and Impacts Scale (PKU-SSIS)

The PKU Symptom Severity and Impacts Scale (PKU-SSIS)[49] is a patient-reported outcome tool developed to assess the neuropsychological symptoms and daily life impact of phenylketonuria (PKU). Based on patient interviews and expert input, it offers insight into the disease burden beyond biochemical data.

The 22-item scale evaluates symptoms across emotional (e.g., anxiety, depression), cognitive (e.g., attention, memory, executive function), and physical (e.g., headaches, fatigue, sleep) domains. It also measures the broader impact of PKU on social relationships, independence, overall well-being, and the management of dietary and treatment needs.

Behavioral and Emotional Functioning

Pediatric patients

The analysis identified six studies[37-39,41,43,44] reporting standardized tools used to assess behavioral and/or emotional functioning in children with PKU.

Specifically, to evaluate executive functions in PKU children, the most commonly used standardized questionnaire was the Child Behavior Checklist (CBCL, 3/6, 50%), used in three studies[39,41,44].

The tests identified in our review were: Inattention or Hyperactivity/Impulsivity Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD RS-IV), The Conners Comprehensive Behavior Rating Scale (Conners CBRS), Patient-Reported Outcomes Measurement Information System (PROMIS), Social Skills Rating System (SSRS), and Adaptive Behavior Assessment System, Second Edition (ABAS-II).

Below, we describe the instruments identified to assess the behavioral and emotional functioning of pediatric patients with PKU.

Inattention or Hyperactivity/Impulsivity Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD RS-IV)

The ADHD Rating Scale-IV (ADHD RS-IV), used in one study[37], is a validated parent-reported questionnaire designed to assess inattention, hyperactivity, and impulsivity in children. It comprises 18 items rated on a 4-point Likert scale, divided into two nine-item subscales – one for inattention and one for hyperactivity/impulsivity. Each subscale yields a maximum score of 27, with a total score up to 54; higher scores indicate greater symptom severity.

The Conners Comprehensive Behavior Rating Scale (Conners CBRS)

The Conners Comprehensive Behavior Rating Scales (Conners CBRS), used in one study[38], assess emotional, behavioral, and academic functioning in children and adolescents. Forms are available for parents and teachers (ages 6-18 years) and self-report (ages 8-18 years), enabling a multi-informant view.

The CBRS evaluates issues such as emotional distress, aggression, hyperactivity, social difficulties, compulsive behavior, and academic problems. It includes validity checks and a 25-item Clinical Index to aid diagnosis and track treatment progress.

Child Behavior Checklist (CBCL)

The Child Behavior Checklist (CBCL), used in three studies[39,41,44], is a widely used parent-report tool for assessing emotional and behavioral problems in children aged 6-18 years. It is applied in both clinical and research settings to identify issues such as aggression, anxiety, depression, hyperactivity, social difficulties, and problem-solving deficits.

The CBCL includes three parts: a main questionnaire covering behavioral domains, an Adaptive Functioning Scale for daily skills, and a School Problem Scale for attention and academic concerns. Results are reported as T-scores, with values above 70 indicating clinically relevant problems. It is often combined with other tools for a full behavioral assessment.

Patient-Reported Outcomes Measurement Information System (PROMIS)

The Patient-Reported Outcomes Measurement Information System (PROMIS), used by Christ et al[43], is a person-centered tool designed to assess physical, mental, and social health across ages. In this study, two pediatric modules were used: the Parent-Proxy-49 Profile (ages 5-17 years) and the Self-Report Pediatric-49 Profile (ages 8-17 years).

These profiles assess domains such as anxiety, depression, physical function, pain interference, fatigue, and peer relationships. Each yields a T-score, with higher values indicating more of the trait measured (e.g., greater anxiety or better physical function).

Social Skills Rating System (SSRS)

The Social Skills Rating System (SSRS), used in one study[39], is a multi-informant tool for assessing social skills, problem behaviors, and academic competence in children from preschool through grade 12. It includes forms for teachers, parents, and students.

The SSRS evaluates five social domains (cooperation, assertion, responsibility, empathy, self-control) and three behavioral domains (externalizing, internalizing, hyperactivity). Items are rated on a 3-point scale for frequency and importance. It yields standard scores and percentiles and is widely used in educational and clinical settings to support behavioral interventions.

Adaptive Behavior Assessment System, Second Edition (ABAS-II)

The Adaptive Behavior Assessment System, Second Edition (ABAS-II) is a standardized scale for evaluating daily living skills and independent functioning across the lifespan, especially in individuals with developmental or neuropsychological disorders. Trimarco et al[44] used the Parent Rating Form for children aged 5-21 years, which includes 211 items.

It provides composite scores in three domains – conceptual, social, and practical – and a general adaptive composite for overall functioning. The ABAS-II is widely applied to assess real-world skills and inform individualized interventions.

Adult patients

The analysis identified three studies[57,59,61] that reported the use of standardized tools for investigating behavioral and/or emotional functioning in adult patients with PKU.

Some tools are primarily designed to assess the presence of anxiety and depressive symptoms, such as the Hospital Anxiety and Depression Scale (HADS) and Beck Anxiety and Depression Inventory, which were used in the studies by Clocksin et al[59] and Luna et al[57]. Other tools aim to assess symptoms typical of patients with ADHD, such as the Conners' Adult ADHD Rating Scale, used by Clocksin et al[59]. The Behavioral and Emotional Disturbance Adult Self-Report (ASR) 18-59, used by Luna et al[57], provides a general evaluation of cognitive and behavioral alterations. At the same time, the Perceived Stress Scale (PSS) focuses on perceived stress. Finally, Aitkenhead et al[61] utilized questionnaires designed to evaluate relationships in social and family contexts.

Connors' Adult ADHD Rating Scales

This tool was used by Clocksin et al[59] to assess ADHD symptoms in adults, focusing on inattention, hyperactivity, impulsivity, and emotional regulation in adult PKU patients. It provides valuable insights into the severity of symptoms and their impact on daily functioning.

Behavioral and Emotional Disturbance Adult Self-Report (ASR) 18-59

The ASR is a standardized assessment used to identify behavioral and emotional disturbances in adults aged 18-59 years. It includes a series of questions that focus on various aspects of mental health, including mood, anxiety, depression, and behavioral issues. The ASR provides a self-reported measure of how individuals perceive their emotional and behavioral functioning. It was used by Luna et al[57] to assess behavioral and emotional alterations in adult PKU patients.

Beck Anxiety and Depression Inventory

The Beck Anxiety and Depression Inventory includes two widely used tools designed to measure the severity of anxiety and depressive symptoms. The Beck Anxiety Inventory evaluates anxiety through 21 items focusing on somatic and subjective experiences, while the Beck Depression Inventory assesses depressive symptoms with 21 items addressing mood, interest, and energy levels. Pilotto et al[22], Clockisin et al[59] and Luna et al[57] used this tool to investigate the presence of anxiety and depressive symptoms in adult PKU patients.

Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-report tool consisting of 14 items divided into two subscales for anxiety and depression. It is designed to assess psychological symptoms without including physical symptoms linked to medical conditions, making it useful in non-psychiatric settings. The HADS is commonly used in clinical and research settings to evaluate anxiety and depression. It was chosen in the work of Aitkenhead et al[61] to assess anxiety and depressive symptoms in adult PKU patients.

Perceived Stress Scale (PSS)

The PSS is a tool used to measure an individual's perception of stress, focusing on how unpredictable, uncontrollable, and overwhelming life feels. It includes 10 items rated on a 5-point scale. The PSS is widely used in research, including studies on adult PKU patients[61], to assess the impact of perceived stress on emotional and psychological well-being.

Neuropsychiatric Inventory

The Neuropsychiatric Inventory was used by Pilotto et al[22] to assess behavioral and psychological symptoms in individuals with neurological disorders, particularly dementia. It evaluates various domains such as delusions, hallucinations, depression, anxiety, apathy, irritability, and sleep disturbances, providing insights into a patient's mental health and behavioral challenges.

Relationship Scale Questionnaire (RSQ)

The RSQ is a tool designed to assess individuals' perceptions of their interpersonal relationships, particularly in the context of attachment styles. It evaluates dimensions such as intimacy, trust, and communication, aiming to identify patterns in how people relate to others. This tool has been used in studies[61] involving adult PKU patients to assess social and family relationships.

Family Adaptability and Cohesion Scale (FACES)

The FACES is used to assess family dynamics, focusing on adaptability and emotional closeness among family members. It helps identify strengths and challenges within family relationships and is commonly used in clinical and research settings, including studies[61] on adult PKU patients, to understand the impact of family dynamics on health and well-being.

DISCUSSION

The neurocognitive profile of early-treated PKU (ETPKU) patients is typically marked by slightly reduced intellectual ability compared to healthy peers, along with deficits in executive function, PSI, attention, and motor control[70-72]. Executive dysfunction, inattention, hyperactivity, impulsivity, and neuropsychiatric symptoms are commonly reported in both children and adults with ETPKU[10,18,19], and these issues are often linked to elevated blood Phe levels. Higher Phe exposure is associated with greater symptom severity[20]. While many ETPKU patients attain comparable academic and occupational outcomes to peers, impairments in social functioning and emotional well-being are still frequently observed[1,73]. A recent systematic review by De Giorgi et al[74] highlighted the importance of maintaining metabolic control during adolescence, emphasizing that consistently low Phe levels and reduced fluctuations are critical across the lifespan.

European guidelines[1] offer clear recommendations on the timing of neuropsychological evaluations in all PKU patients. They also advise the use of supplementary tools when metabolic control is suboptimal, academic or work challenges arise, or when emotional, behavioral, or cognitive concerns are raised by the patient, family, or care team.

The extent of neurobehavioral abnormalities in ETPKU, especially among adults, remains debated, and identifying tests sensitive to high Phe levels remains challenging. Test selection often reflects clinician preference or center-specific protocols. To date, no standardized and comprehensive set of tools exists for evaluating executive, behavioral, and emotional functioning in PKU patients across age groups.

An Italian multidisciplinary expert group[33] convened to develop a more comprehensive approach to neurocognitive, psychopathological, and neurological assessment in PKU patients, drawing from both literature and clinical practice. Age-specific tests were selected based on their diagnostic sensitivity, applicability across patient populations (e.g., those with limited Italian proficiency), and ease of use.

While there is broad consensus on the tools used to assess IQ or developmental quotient[75], no standardized approach exists for evaluating executive functions. In this review, we aimed to explore not only the use of standardized tools for executive function but also instruments assessing emotional and behavioral domains.

Emotional and behavioral aspects are closely linked to executive functions and can significantly influence functioning in social, academic, and work environments[25]. Executive dysfunction may impair

emotional regulation, stress management, and social responsiveness, leading to impulsivity, emotional outbursts, or poor interpersonal interactions that impact mental health and relationships.

In clinical contexts like PKU, it is crucial to assess executive and emotional/behavioral domains together, as cognitive deficits can worsen emotional challenges and trigger behavioral issues. Comprehensive tools should evaluate both areas to guide targeted interventions that support cognitive control, emotional regulation, and adaptive functioning.

Executive functions are high-level cognitive processes that enable individuals to regulate thoughts and actions to achieve goals[76]. They underpin complex skills such as reasoning, theory of mind, arithmetic, decision-making, and creativity and develop progressively with age, influenced by both genetic and environmental factors[77-79].

A recent brain imaging study[80] supports this developmental trajectory, showing that increased segregation of structural brain network modules with age mediates improvements in executive functions.

Executive functions begin to develop in infancy, with foundational skills emerging before age 3 years and more refined abilities developing through early childhood[76]. Their developmental trajectory varies by domain: working memory peaks around age 30 years and declines thereafter[81-83], while inhibitory control is weakest in early childhood, improves in adulthood, and decreases in older age[84].

Given this variability, selecting age-appropriate tools to assess executive functions is essential.

This review examined instruments used to assess executive functions and behavioral and emotional outcomes in pediatric and adult PKU patients. EF, behavioral, and emotional aspects were evaluated in 13 pediatric[37-49] (<18 years) and 24 adult studies[22,31,42,49-69].

Most studies used standardized tools to ensure reliable, comparable results. For pediatric PKU patients, the tools identified provide important insights into cognitive and behavioral challenges. However, their sensitivity to subtle deficits can vary. Moreover, fluctuating Phe levels and dietary adherence complicate assessment, highlighting the need for longitudinal studies to better understand these outcomes.

To assess cognition in younger children, tools such as the Wechsler Preschool and Primary Scale of Intelligence (WPPSI, for children aged 3-7 years) and the Wechsler Intelligence Scale for Children (WISC, for children aged 6-16 years) are widely used. These tests evaluate domains such as working memory, verbal comprehension, visual perception, and problem-solving, supporting longitudinal monitoring of intellectual development.

However, they do not provide detailed insight into executive functions or behavioral and emotional outcomes.

In pediatric patients, the WPPSI-IV and WISC-IV are commonly used, while the LEITER-3 is preferred in cases of language difficulties. For executive function, the BRIEF-P is widely applied. Neurocognitive tools include the WCST and ToL (planning/problem-solving), ROCF, Grooved Pegboard Test (GPT), and Digit Span (visual-spatial memory, coordination, and short-term memory). Other measures assess PSI, sustained attention (Bells Test), verbal fluency (Semantic Fluency), and memory (RAVLT)[33].

In adolescents, the WAIS-IV is used to assess intelligence, and the BRIEF-2 is used to evaluate executive functions. Neurocognitive tools include the WCST, TMT, and ToL, targeting visual-spatial memory, inhibition, PSI, and sustained attention[33]. However, inconsistency in tools across studies limits comparability. Standardized protocols are needed to improve reliability and clinical relevance.

Studies on adult PKU patients show an increasing use of specific cognitive tools rather than general IQ tests, such as the WAIS, which often yield normal-range scores. These targeted instruments have revealed notable differences in executive function compared to controls, particularly in processing speed (e.g., SDMT, PASAT), inhibition (e.g., Stroop, Hayling), attention (e.g., SAD, TAP), and working memory.

Importantly, these impairments do not suggest intellectual disability.

When interpreting these findings, it is important to consider the combined effects of Phe levels, their variability, and neuroimaging abnormalities (e.g., white matter changes) on cognition. These factors influence the PKU cognitive profile, underscoring the need for targeted assessments using tools with high sensitivity and specificity. Attention should also be paid to low-normal or low-average scores, which may reflect atypical patterns. Neuropsychological evaluations in PKU require tailored approaches distinct from those used in focal or degenerative conditions, as deficits are typically subtle. For both pediatric and adult patients, assessments must incorporate these considerations to ensure accurate profiling and guide personalized interventions.

CONCLUSIONS

An evaluation of the available tools for assessing executive functions and emotional and behavioral aspects is useful for monitoring their progression over time, especially in light of new therapeutic options for patients with PKU. There is a need for standardized, comprehensive assessment tools that address

the full spectrum of cognitive, neuropsychological, behavioral and emotional issues in pediatric PKU patients. Future research should focus on validating existing tools and developing new, more sensitive instruments to evaluate the impact of PKU on quality of life and psychosocial functioning.

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REFERENCES

1. van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, van Rijn M, Trefz F, Walter JH, van Spronsen FJ. The complete European guidelines on phenylketonuria: diagnosis and treatment. Orphanet J Rare Dis 2017; 12: 162.
2. van Spronsen FJ, Blau N, Harding C, Burlina A, Longo N, Bosch AM. Phenylketonuria. Nat Rev Dis Primers 2021; 7: 36.
3. Blau N, Hennermann JB, Langenbeck U, Lichter-Konecki U. Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies. Mol Genet Metab 2011; 104 Suppl: S2-S9.
4. van Spronsen FJ, van Wegberg AMJ, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, Burlina A, Campistol J, Feillet F, Giżewska M, Huijbregts SC, Kearney S, Leuzzi V, Maillot F, Muntau AC, Trefz FK, van Rijn M, Walter JH, MacDonald A. Key European guidelines for the diagnosis and management of patients with phenylketonuria. Lancet Diabetes Endocrinol 2017; 5: 743-756.
5. Hillert A, Anikster Y, Belanger-Quintana A, Burlina A, Burton BK, Carducci C, Chiesa AE, Christodoulou J, Đorđević M, Desviat LR, Eliyahu A, Evers RAF, Fajkusova L, Feillet F, Bonfim-Freitas PE, Giżewska M, Gundorova P, Karall D, Kneller K, Kutsev SI, Leuzzi V, Levy HL, Lichter-Konecki U, Muntau AC, Namour F, Oltarzewski M, Paras A, Perez B, Polak E, Polyakov AV, Porta F, Rohrbach M, Scholl-Bürgi S, Spécola N, Stojiljković M, Shen N, Santana-da Silva LC, Skouma A, van Spronsen F, Stoppioni V, Thöny B, Trefz FK, Vockley J, Yu Y, Zschocke J, Hoffmann GF, Garbade SF, Blau N. The genetic landscape and epidemiology of phenylketonuria. Am J Hum Genet 2020; 107: 234-250.
6. Blau N, Van Spronsen FJ, Levy HL. Phenylketonuria. Lancet 2010; 376: 1417-1427.
7. Burlina A, Biasucci G, Carbone MT, Cazzorla C, Paci S, Pochiero F, Spada M, Tummolo A, Zuvadelli J, Leuzzi V. Italian national consensus statement on management and pharmacological treatment of phenylketonuria. Orphanet J Rare Dis 2021; 16: 476.
8. MacDonald A, van Wegberg AMJ, Ahring K, Beblo S, Bélanger-Quintana A, Burlina A, Campistol J, Coşkun T, Feillet F, Giżewska M, Huijbregts SC, Leuzzi V, Maillot F, Muntau AC, Rocha JC, Romani C, Trefz F, van Spronsen FJ. PKU dietary handbook to accompany PKU guidelines. Orphanet J Rare Dis 2020; 15: 171.

9. Cazzorla C, Bensi G, Biasucci G, Leuzzi V, Manti F, Musumeci A, Papadia F, Stoppioni V, Tummolo A, Vendemiale M, Polo G, Burlina A. Living with phenylketonuria in adulthood: The PKU ATTITUDE study. Mol Genet Metab Rep 2018; 16: 39-45.
10. Bilder DA, Arnold GL, Dimmock D, Grant ML, Janzen D, Longo N, Nguyen-Driver M, Jurecki E, Merilainen M, Amato G, Waisbren S. Improved attention linked to sustained phenylalanine reduction in adults with early-treated phenylketonuria. Am J Med Genet A 2022; 188: 768-778.
11. Welsh MC, Pennington BF, Ozonoff S, Rouse B, McCabe ER. Neuropsychology of early-treated phenylketonuria: specific executive function deficits. Child Dev 1990; 61: 1697-1713.
12. Weglage J, Pietsch M, Funders B, Koch HG, Ullrich K. Deficits in selective and sustained attention processes in early treated children with phenylketonuria--result of impaired frontal lobe functions? Eur J Pediatr 1996; 155: 200-204.
13. Brumm VL, Azen C, Moats RA, Stern AM, Broomand C, Nelson MD, Koch R. Neuropsychological outcome of subjects participating in the PKU adult collaborative study: a preliminary review. J Inherit Metab Dis 2004; 27: 549-566.
14. Leuzzi V, Pansini M, Sechi E, Chiarotti F, Carducci C, Levi G, Antonozzi I. Executive function impairment in early-treated PKU subjects with normal mental development. J Inherit Metab Dis 2004; 27: 115-125.
15. VanZutphen K, Packman W, Sporri L, Needham M, Morgan C, Weisiger K, Packman S. Executive functioning in children and adolescents with phenylketonuria. Clin Genet 2007; 72: 13-18.
16. Palermo L, Geberhiwot T, MacDonald A, Limback E, Hall SK, Romani C. Cognitive outcomes in early-treated adults with phenylketonuria (PKU): A comprehensive picture across domains. Neuropsychology 2017; 31: 255-267.
17. De Felice S, Romani C, Geberhiwot T, MacDonald A, Palermo L. Language processing and executive functions in early treated adults with phenylketonuria (PKU). Cogn Neuropsychol 2018; 35: 148-170.
18. Burlina AP, Lachmann RH, Manara R, Cazzorla C, Celato A, van Spronsen FJ, Burlina A. The neurological and psychological phenotype of adult patients with early-treated phenylketonuria: A systematic review. J Inherit Metab Dis 2019; 42: 209-219.
19. Merkel M, Berg D, Brüggemann N, Classen J, Mainka T, Zittel S, Muntau AC. Characterisation and differential diagnosis of neurological complications in adults with phenylketonuria: literature review and expert opinion. J Neurol 2023; 270: 3675-3687.
20. Waisbren SE, Noel K, Fahrbach K, Cella C, Frame D, Dorenbaum A, Levy H. Phenylalanine blood levels and clinical outcomes in phenylketonuria: a systematic literature review and meta-analysis. Mol Genet Metab 2007; 92: 63-70.
21. Mitchell JJ, Trakadis YJ, Scriver CR. Phenylalanine hydroxylase deficiency. Genet Med 2011; 13: 697-707.
22. Pilotto A, Zipser CM, Leks E, Haas D, Gramer G, Freisinger P, Schaeffer E, Liepelt-Scarfone I, Brockmann K, Maetzler W, Schulte C, Deuschle C, Hauser AK, Hoffmann GF, Scheffler K, van Spronsen FJ, Padovani A, Trefz F, Berg D. Phenylalanine effects on brain function in adult phenylketonuria. Neurology 2021; 96: e399-e411.
23. Cristofori I, Cohen-Zimerman S, Grafman J. Executive functions. Handb Clin Neurol 2019; 163: 197-219.
24. Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol 2003; 85: 348-362.
25. Rodas JA, Leon-Rojas J, Rooney B. Mind over mood: exploring the executive function's role in downregulation. Front Psychol 2024; 15: 1322055.
26. Smith M, Klim P, Hanley WJ. Executive function in school-aged children with phenylketonuria. Dev Phys Disabil 2000; 12: 317-332.
27. Antshel SE, Waisbren S. Timing is everything: executive functions in children exposed to elevated levels of phenylalanine. Neuropsychology 2003; 17: 458-468.
28. Manti F, Nardecchia F, Paci S, Chiarotti F, Carducci C, Dalmazzone S, Cefalo G, Salvatici E, Banderali G, Leuzzi V. Predictability and inconsistencies in the cognitive outcome of early treated PKU patients. J Inherit Metab Dis 2017; 40: 793-799.
29. Romani C, MacDonald A, De Felice S, Palermo L. Speed of processing and executive functions in adults with phenylketonuria: Quick in finding the word, but not the ladybird. Cogn Neuropsychol 2018; 35: 171-198.
30. Huijbregts SC, de Sonneville LM, Licht R, Sergeant JA, van Spronsen FJ. Inhibition of prepotent responding and attentional flexibility in treated phenylketonuria. Dev Neuropsychol 2002; 22: 481-499.
31. Manti F, Nardecchia F, De Leo S, Carducci C, Romani C, Palermo L, Angeloni A, Leuzzi V. Towards precision medicine for phenylketonuria: The effect of restoring a strict metabolic control in adult patients with early-treated phenylketonuria. Mol Genet Metab 2023; 140: 107666.
32. Cleary M, Trefz F, Muntau AC, Feillet F, van Spronsen FJ, Burlina A, Bélanger-Quintana A, Giżewska M, Gasteyger C, Bettiol E, Blau N, MacDonald A. Fluctuations in phenylalanine concentrations in phenylketonuria: a review of possible relationships with outcomes. Mol Genet Metab 2013; 110: 418-423.
33. Manti F, Caviglia S, Cazzorla C, Dicintio A, Pilotto A, Burlina AP. Expert opinion of an Italian working group on the assessment of cognitive, psychological, and neurological outcomes in pediatric, adolescent, and adult patients with phenylketonuria. Orphanet J Rare Dis 2022; 17: 443.
34. Maissen-Abgottspon S, Muri R, Hochuli M, Reismann P, Barta AG, Alptekin IM, Hermida-Ameijeiras Á, Burlina AP, Burlina AB, Cazzorla C, Carretta J, Trepp R, Everts R. Health-related quality of life in a European sample of adults with early-treated classical PKU. Orphanet J Rare Dis 2023; 18: 300.
35. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Moher D. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021; 372: n71.
36. Azevedo Soares C, Ferreira Almeida M, Soares G, Tkachenko N, Fortuna AM, Carmona C. Predicting factors of neurodevelopmental performance in children with phenylketonuria. Am J Med Genet A 2023; 191: 1525-1529.
37. Grant ML, Jurecki ER, McCandless SE, Stahl SM, Bilder DA, Sanchez-Valle A, Dimmock D. Neuropsychiatric function improvement in pediatric patients with phenylketonuria. J Pediatr 2023; 260: 113526.
38. Randell NJS, Barker-Collo SL, Murrell K, Wilson C. Outcomes in mild hyperphenylalaninemia: a comparison with PKU and healthy controls across cognition, behaviour, and quality of life. N Z Med J 2022; 135: 31-42.
39. van Vliet K, van Ginkel WG, Jahja R, Daly A, MacDonald A, Santra S, De Laet C, Goyens PJ, Vara R, Rahman Y, Cassiman D, Eyskens F, Timmer C, Mumford N, Gissen P, Bierau J, van Hasselt PM, Wilcox G, Morris AAM, Jameson EA, de la Parra A, Arias C, Garcia MI, Cornejo V, Bosch AM, Hollak CEM, Rubio-Gozalbo ME, Brouwers MCGJ, Hofstede FC, de Vries MC, Janssen MCH, van der Ploeg AT, Langendonk JG, Huijbregts SCJ, van Spronsen FJ. Neurocognitive outcome and mental health in children with tyrosinemia type 1 and phenylketonuria: A comparison between two genetic disorders affecting the same metabolic pathway. J Inherit Metab Dis 2022; 45: 952-962.

40. Paermentier L, Cano A, Chabrol B, Roy A. Executive functions in preschool children with moderate hyperphenylalaninemia and phenylketonuria: a prospective study. Orphanet J Rare Dis 2023; 18: 175.
41. de Almeida Duarte CM, Piazzon FB, Rocco IS, de Mello CB. Influence of blood phenylalanine level variations on the development of executive functions and social cognition in children with phenylketonuria. J Pediatr (Rio J) 2023; 99: 507-513.
42. Christ SE, Clocksin HE, Burton BK, Grant ML, Waisbren S, Paulin MC, Bilder DA, White DA, Saville C. Executive function in phenylketonuria (PKU): Insights from the Behavior Rating Inventory of Executive Function (BRIEF) and a large sample of individuals with PKU. Neuropsychology 2020; 34: 456-466.
43. Christ SE, Arnold G, Lichter-Konecki U, Berry GT, Grange DK, Harding CO, Jurecki E, Levy H, Longo N, Morotti H, Sacharow S, Thomas J, White DA. Initial results from the PHEFREE longitudinal natural history study: Cross-sectional observations in a cohort of individuals with phenylalanine hydroxylase (PAH) deficiency. Mol Genet Metab 2024; 143: 108541.
44. Trimarco B, Manti F, Nardecchia F, Melogno S, Testa M, Meledandri G, Carducci C, Penge R, Leuzzi V. Executive functioning, adaptive skills, emotional and behavioral profile: A comparison between autism spectrum disorder and phenylketonuria. Mol Genet Metab Rep 2020; 23: 100577.
45. Tomm A, Thiele AG, Rohde C, Kirmse S, Kiess W, Beblo S. Executive functions and metabolic control in phenylketonuria (PKU) and mild hyperphenylalaninemia (mHPA). Mol Genet Metab 2024; 143: 108544.
46. İlgüy M, Yıldırım GK, Eyüboğlu D, Çarman KB, Yarar C. The relationship between serum phenylalanine levels, genotype, and developmental assessment test results in non-phenylketonuria mild hyperphenylalaninemia patients. Eur J Pediatr 2024; 184: 99.
47. Mütze U, Garbade SF, Gramer G, Lindner M, Freisinger P, Grünert SC, Hennermann J, Ensenauer R, Thimm E, Zirnbauer J, Leichsenring M, Gleich F, Hörster F, Grohmann-Held K, Boy N, Fang-Hoffmann J, Burgard P, Walter M, Hoffmann GF, Kölker S. Long-term outcomes of individuals with metabolic diseases identified through newborn screening. Pediatrics 2020; 146: e20200444.
48. Hanusch B, Falkenstein M, Volkenstein S, Dazert S, Lücke T, Sinningen K. No impairment in bone turnover or executive functions in well-treated preschoolers with phenylketonuria—A pilot study. Nutrients 2024; 16: 2072.
49. Quinn J, Georgiadis A, Lewis HB, Jurecki E. Measuring burden of illness in phenylketonuria (PKU): Development of the PKU Symptom Severity and Impacts Scale as a robust patient-reported outcome. Adv Ther 2022; 39: 971-991.
50. Muri R, Maissen-Abgottspon S, Rummel C, Rebsamen M, Wiest R, Hochuli M, Jansma BM, Trepp R, Everts R. Cortical thickness and its relationship to cognitive performance and metabolic control in adults with phenylketonuria. J Inherit Metab Dis 2022; 45: 1082-1093.
51. Muri R, Maissen-Abgottspon S, Reed MB, Kreis R, Hoefemann M, Radojewski P, Pospieszny K, Hochuli M, Wiest R, Lanzenberger R, Trepp R, Everts R. Compromised white matter is related to lower cognitive performance in adults with phenylketonuria. Brain Commun 2023; 5: fcad155.
52. Muri R, Rummel C, McKinley R, Rebsamen M, Maissen-Abgottspon S, Kreis R, Radojewski P, Pospieszny K, Hochuli M, Wiest R, Trepp R, Everts R. Transient brain structure changes after high phenylalanine exposure in adults with phenylketonuria. Brain 2024; 147: 3863-3873.
53. Muri R, Reed MB, Maissen-Abgottspon S, Kreis R, Hochuli M, Lanzenberger R, Trepp R, Everts R. Reversible white matter changes following a 4-week high phenylalanine exposure in adults with phenylketonuria. J Inherit Metab Dis 2025; 48: e12823.
54. Steiner L, Muri R, Wijesinghe D, Jann K, Maissen-Abgottspon S, Radojewski P, Pospieszny K, Kreis R, Kiefer C, Hochuli M, Trepp R, Everts R. Cerebral blood flow and white matter alterations in adults with phenylketonuria. Neuroimage Clin 2024; 41: 103550.
55. Abgottspon S, Muri R, Christ SE, Hochuli M, Radojewski P, Trepp R, Everts R. Neural correlates of working memory and its association with metabolic parameters in early-treated adults with phenylketonuria. Neuroimage Clin 2022; 34: 102974.
56. Trepp R, Muri R, Maissen-Abgottspon S, Haynes AG, Hochuli M, Everts R. Cognition after a 4-week high phenylalanine intake in adults with phenylketonuria - a randomized controlled trial. Am J Clin Nutr 2024; 119: 908-916.
57. Luna PM, López-Paz JF, García M, Amayra I, Martínez O, Pérez M, Rodríguez AA, Pérez-Núñez P, Ceberio I, Mansilla N, Soria C. Cognitive Functioning in Adults with Phenylketonuria in a Cohort of Spanish Patients. Behav Neurol 2023; 2023: 9681740.
58. Brachet M, Charrière S, Douillard C, Feillet F, Fouilhoux A, Astudillo L, Lavigne C, Arnoux JB, Odent S, Gay C, Schiff M, Mazodier K, Kuster A, Rigalleau V, Thauvin-Robinet C, Leguy-Seguin V, Gissot V, Maillot F. Neuropsychological profile of French adults with early-treated phenylketonuria: a multicenter study. J Neurol 2024; 272: 53.
59. Clocksin HE, Abbene EE, Christ S. A comprehensive assessment of neurocognitive and psychological functioning in adults with early-treated phenylketonuria. Journal of the International Neuropsychol Soc 2023; 29: 641-650.
60. Schoen MS, Boland KM, Christ SE, Cui X, Ramakrishnan U, Ziegler TR, Alvarez JA, Singh RH. Total choline intake and working memory performance in adults with phenylketonuria. Orphanet J Rare Dis 2023; 18: 222.
61. Aitkenhead L, Krishna G, Ellerton C, Moinuddin M, Matcham J, Shiel L, Hossain S, Kiffin M, Foley J, Skeath R, Cleary M, Lachmann R, Murphy E. Long-term cognitive and psychosocial outcomes in adults with phenylketonuria. J Inherit Metab Dis 2021; 44: 1353-1368.
62. Thomas L, Aitkenhead L, Stepien KM, Woodall A, Macdonald A, Romani C. Cognition and well-being in middle-aged early treated people with phenylketonuria: Preliminary results and methodological lessons. Mol Genet Metab Rep 2024; 41: 101160.
63. Feldmann R, Leberer EP, Fromm J, Och U, Weglage J, Rutsch F. Neurocognitive functioning remained unchanged in adults with phenylketonuria: Report of a 15-year follow-up. Acta Paediatr 2025; 114: 648-653.
64. Romani C, Manti F, Nardecchia F, Valentini F, Fallarino N, Carducci C, De Leo S, MacDonald A, Palermo L, Leuzzi V. Cognitive Outcomes and Relationships with Phenylalanine in Phenylketonuria: A Comparison between Italian and English Adult Samples. Nutrients 2020; 12: 3033.
65. Christ SE, Clocksin HE, Zalik M, Goodlett BD, Sacharow SJ, Abbene EE. Neuropsychological assessment of adults with phenylketonuria using the NIH toolbox. Mol Genet Metab 2023; 139: 107579.
66. Scala I, Riccio MP, Marino M, Bravaccio C, Parenti G, Strisciuglio P. Large Neutral Amino Acids (LNAAs) Supplementation Improves Neuropsychological Performances in Adult Patients with Phenylketonuria. Nutrients 2020; 12: 1092.
67. van Wegberg AMJ, van der Weerd JC, Engelke UFH, Coene KLM, Jahja R, Bakker SJL, Huijbregts SCJ, Wevers RA, Heiner-Fokkema MR, van Spronsen FJ. The clinical relevance of novel biomarkers as outcome parameter in adults with phenylketonuria. J Inherit Metab Dis 2024; 47: 624-635.

68. Costa-Lathan C, Vazquez-Agra N, Marques-Afonso AT, Cruces-Sande A, Martinez-Olmos MA, Araujo-Vilar D, Hermida-Ameijeiras A. The role of phenylalanine levels in the neuropsychological and neuroanatomical status of adult patients with phenylketonuria: The impact of fluctuations. J Investig Med 2023; 71: 149-158.
69. Burlina AP, Manara R, Carretta J, Cazzorla C, Loro C, Gragnaniello V, Burlina AB. Effect of enzyme substitution therapy on brain magnetic resonance imaging and cognition in adults with phenylketonuria: A case series of three patients. Eur J Neurol 2024; 31: e16508.
70. Janos AL, Grange DK, Steiner RD, White DA. Processing speed and executive abilities in children with phenylketonuria. Neuropsychology 2012; 26: 735-743.
71. Moyle JJ, Fox AM, Arthur M, Bynevelt M, Burnett JR. Meta-analysis of neuropsychological symptoms of adolescents and adults with PKU. Neuropsychol Rev 2007; 17: 91-101.
72. ten Hoedt AE, de Sonneville LM, Francois B, ter Horst NM, Janssen MC, Rubio-Gozalbo ME, Wijburg FA, Hollak CE, Bosch AM. High phenylalanine levels directly affect mood and sustained attention in adults with phenylketonuria: a randomised, double-blind, placebo-controlled, crossover trial. J Inherit Metab Dis 2011; 34: 165-171.
73. Anjema K, van Rijn M, Verkerk PH, Burgerhof JG, Heiner-Fokkema MR, van Spronsen FJ. PKU: high plasma phenylalanine concentrations are associated with increased prevalence of mood swings. Mol Genet Metab 2011; 104: 231-234.
74. De Giorgi A, Nardecchia F, Manti F, Campistol J, Leuzzi V. Neuroimaging in early-treated phenylketonuria patients and clinical outcome: A systematic review. Mol Genet Metab 2023; 139: 107588.
75. Bonichini S, Mazzotti S. La valutazione dell'intelligenza. La valutazione psicologica del bambino. Carocci Faber 2010; 55-80.
76. Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A, Wager TD. The unity and diversity of executive functions and their contributions to complex "Frontal Lobe" tasks: a latent variable analysis. Cogn Psychol 2000; 41: 49-100.
77. Diamond A. Executive functions. Annu Rev Psychol 2013; 64: 135-168.
78. Friedman NP, Miyake A. Unity and diversity of executive functions: Individual differences as a window on cognitive structure. Cortex 2017; 86: 186-204.
79. Shing YL, Lindenberger U, Diamond A, Li SC, Davidson MC. Memory maintenance and inhibitory control differentiate from early childhood to adolescence. Dev Neuropsychol 2010; 35: 679-697.
80. Baum GL, Ciric R, Roalf DR, Betzel RF, Moore TM, Shinohara RT, Kahn AE, Vandekar SN, Rupert PE, Quarmley M, Cook PA, Elliott MA, Ruparel K, Gur RE, Gur RC, Bassett DS, Satterthwaite TD. Modular Segregation of Structural Brain Networks Supports the Development of Executive Function in Youth. Curr Biol 2017; 27: 1561-1572.e8.
81. Garon N, Bryson SE, Smith IM. Executive function in preschoolers: a review using an integrative framework. Psychol Bull 2008; 134: 31-60.
82. Hartshorne JK, Germine LT. When does cognitive functioning peak? The asynchronous rise and fall of different cognitive abilities across the life span. Psychol Sci 2015; 26: 433-443.
83. Johnson W, Logie RH, Brockmole JR. Working memory tasks differ in factor structure across age cohorts: Implications for dedifferentiation. Intelligence 2010; 38: 513-528.
84. Comalli PE Jr, Wapner S, Werner H. Interference effects of Stroop color-word test in childhood, adulthood, and aging. J Genet Psychol 1962; 100: 47-53.