

3. Cognitive, Psychological and Behavioral Assessment Based Evidence for Altered Brain Function in PKU

Summary

- Some researchers gather physical evidence using sophisticated brain imaging machines. There are also other researchers such as psychologists, psychiatrists, and sociologists gathering psychological evidence to determine whether the current PKU standard therapy involving a Phe-restricted diet and meeting blood Phe targets can still lead to changes in the brain.
 - In fact, psychological evidence in the form of IQ testing was the main evidence to show the dramatic improvements in PKU patients who were treated with the Phe-restricted diet shortly after birth. Prior to current standard PKU therapy, IQ in PKU was dramatically lower in untreated individuals.
 - Although a recent study suggests that short-term spikes in blood Phe levels can cause lower IQ, the vast majority of studies indicate that maintaining a Phe-restricted diet and blood Phe levels within range result in normal IQ.
 - The research focus has shifted away from IQ to determining if more subtle psychological/emotional changes occur in PKU patients adhering to diet therapy.
 - One area of research involves something called **executive function** (EF) which is deliberate, conscious control over your own thoughts, actions and emotions. Some of the many characteristics of people with EF difficulties include disorganization, being easily frustrated, and poor judgment. The evidence for EF problems in diet-controlled PKU is a mixed bag, with some studies finding problems and some finding none. Researchers are looking to do a large-scale long-term study on EF in PKU in hope of getting a more accurate picture of what is going on.
 - Another area of research is how quickly you can react to incoming information, process it, understand it and use it. This is known as **information processing speed** and can be measured by a variety of tasks with time limits. People who suffer from problems in information processing speed might take longer to start/complete complex tasks and appear to struggle. More evidence is required to determine if information processing is affected in diet controlled PKU. However, one strong piece of evidence suggests that if one stays within the current blood Phe range for their age group then information processing will not be affected.
 - The chemical brain imbalances found in PKU are similar to those found in children with **attention deficit hyperactivity disorder** (ADHD). For this reason researchers are interested in knowing if ADHD or ADHD symptoms are more common in people with PKU. Symptoms of ADHD fall into one of three large categories: inattention (inability to concentrate), hyperactivity and impulsivity. Using standardized criteria for diagnosing ADHD, researchers have found that people with PKU are more likely to have ADHD or symptoms of ADHD. Surprisingly, only a handful of studies have been done and more research is required to strengthen the possible link between PKU and ADHD.
 - Researchers have also looked for **learning disabilities** and problems in **academic performance** in people with PKU. Of the studies done to date, it appears that math skills may be affected in some individuals with PKU. These are small studies and not conclusive by any means.

- Studies looking at whether **psychiatric disorders** occur more frequently in PKU showed no significantly different overall rate than the general population. However, psychiatric symptoms have been uncovered in some PKU patients that include, but are not limited to, anxiety, depressed moods and phobias. Most convincingly was a recent study done in adults that showed that higher blood Phe levels were associated with increased self-reported incidences of depression and fatigue.
- More psychological evidence is needed to determine the nature and frequency of any problems that may be occurring at higher rates in PKU individuals who adhere to their recommended blood Phe targets. However, it is clear that higher blood Phe levels do strongly correlate with many of the psychological and behavioral symptoms observed.

Executive function

What is executive function (EF)? One of the most studied cognitive abilities in PKU is known as **executive function** (EF).¹⁰ EF is a complex concept. Scientists and psychologists have defined EF as “*the higher-order cognitive abilities that facilitate the flexible modification of thought and behavior in response to changing cognitive or environmental demands.*”¹¹ **In basic terms EF can be thought of as deliberate, conscious control over your own thoughts, actions and emotions.**¹⁰

There is no clear-cut agreement among experts on exactly what factors make up EF, but many experts include the following “higher-order cognitive abilities” or “domains” under the umbrella of EF:^{11,12}

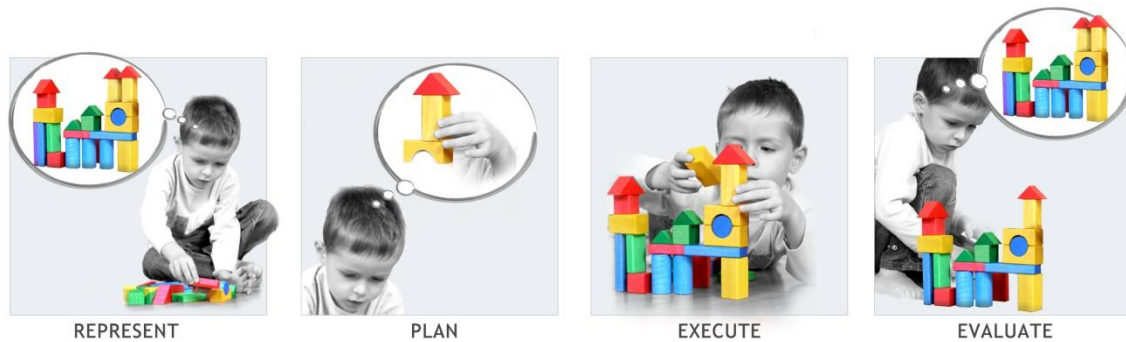
- planning
- organization
- **conceptual reasoning**
- **mental/cognitive flexibility**
- **impulse/inhibitory control**
- **selective and sustained attention**
- **working memory**

It is important to know that problems with EF have been found in many different developmental disorders (such as autism and attention deficit/hyperactivity disorder). However, EF is an umbrella of many “cognitive domains.” Because of this, different development disorders may share common EF impairments but may also have unique EF impairments. This complexity has made it difficult for experts to define and come up with a single statement to describe EF disorders. Some impairments in EF may result in obvious behavioral or learning disorders, while some will result in behaviors that are subtle in nature and not easily caught by the untrained observer.

As already stated, EF is a complex topic. An expert in the field, Dr. Philip David Zelazo, has written a series of comprehensive and easy-to-understand articles that make EF easier to understand.¹⁰ In his articles, he refers to the analogy of a business executive to describe EF. “An executive is someone *who decides upon a course of action, issues commands by*

virtue of rank in a hierarchy, and ensures that the commands are implemented. Executive function, therefore, refers to the business of making decisions and carrying them out, as when one is deliberately trying to solve a problem.” He further explains that, in the context of problem solving, EF can be broken down into subfunctions. In order to deliberately solve a problem, it is necessary to do several smaller things, in a specific sequence:^{10,13}

1. Identify the goal and the barriers to achieving it: **Represent** the problem by asking, “What do I need to accomplish? What is preventing me from accomplishing it?”
2. Create an action plan: Come up with a **plan** for a solving the problem.
3. Take action: Actually **execute** or carry out that plan.
4. See if the goal was reached: **Evaluate** the adequacy of the attempted solution.



Individuals with difficulties in EF may present some of the following characteristics¹⁴:

- **poor frustration tolerance:** not persisting in completing a task that is the least bit difficult. This can result in angry outbursts, including yelling and throwing things.
- **disorganization:** not being able to obtain necessary information, make it accessible, and then use it for decision making. A disorganized person may lose things frequently, be messy, and have difficulty in putting their thoughts together in writing.
- **difficulty coping with change:** not liking their daily routine altered. This may manifest in anxiety when their daily routine is altered.
- **poor judgment:** frequently choosing courses of action that have negative consequences either to themselves or to others.
- **emotional instability:** having frequent mood swings.
- **disinhibition:** being impulsive and appearing to lack control of their own behavior. This may manifest as interrupting others in a conversation, talking out of turn, or laughing or crying too easily.
- **forgetfulness:** making mental errors or getting distracted when performing a task.
- **apathy:** lacking motivation. They may start something but fail to finish it.
- **not following rules in spite of knowing the rules:** not following authority.
- **difficulty in understanding consequences and cause-and-effect relationships:** see poor judgment.
- **inefficiency:** taking longer to complete tasks (e.g., homework) than warranted under the circumstances.
- **difficulties learning from past experience:** see poor judgment.

Why people with PKU may have EF difficulties:^{11,15} There are two main reasons why psychologists and researchers have focused on EF as a potential problem area in people with PKU.

1. EF has been linked to the frontal lobes of the brain, specifically an area of the frontal lobe called the *prefrontal cortex*, which is one of the very last regions of the brain to fully mature (typically in early adulthood). There is strong evidence that the **neurotransmitter dopamine** (one of several chemical messengers in the brain) is involved with normal functioning of the prefrontal cortex, and there is evidence that dopamine levels may be lower in individuals with PKU.
2. Clinicians have noticed that diet-treated PKU patients have certain behavioral, learning and cognitive problems despite having normal-range intelligence. Many of these behavioral problems appear to fall under the big umbrella of EF.

How EF is measured: Researchers have devised “tasks” or “tests” that measure different aspects (domains) of EF. Extensive research and testing have helped them understand what the “normal range” is for each test/task for healthy individuals at different ages. Scores below the normal range may indicate a potential problem in EF. This is similar to IQ testing, where scores below the normal range indicate a deficit in intelligence. However, it is important to remember that IQ testing and EF testing do not measure the same abilities. An individual can have normal or high-range IQ and still have EF difficulties.

If a clinician thinks a person may have problems with EF, they might refer that person to a psychologist. The psychologist will conduct an interview and may decide to administer a “battery” of EF tests, which simply means a bunch of tests that measure many “domains” of EF. One example of a “battery” EF test for children aged 5–18 years is called the Behavior Rating Inventory of Executive Function (BRIEF).^{16,17} This 10- to 15-minute test measures 8 domains of executive function.

Alternatively, the psychologist may have an idea of what EF domain(s) are affected after conducting the initial interview and decide on administering EF domain-focused tasks/tests. One such test is called the Go-NoGo Task. For this task, children are required to respond to one cue, called the “Go stimulus,” while refraining from responding to another stimulus, called the “NoGo stimulus.” This task provides a measure of the EF domains of mental flexibility, selective and sustained attention and inhibitory control.¹⁰

Evidence of EF difficulties in people with PKU: Recently, a group of experts published a review of studies done on EF in people with PKU. The authors concluded that there are mixed results from studies of EF in diet-treated PKU.¹¹ Some studies found EF deficits in diet-treated PKU patients and some did not; some studies found a relationship between blood phenylalanine (Phe) levels and difficulties in EF and some did not. The authors found that the domains most commonly associated with EF deficits in diet-treated PKU were working memory and inhibitory control. The authors concluded that it was hard to compare different studies because they used different measures of EF. Another criticism

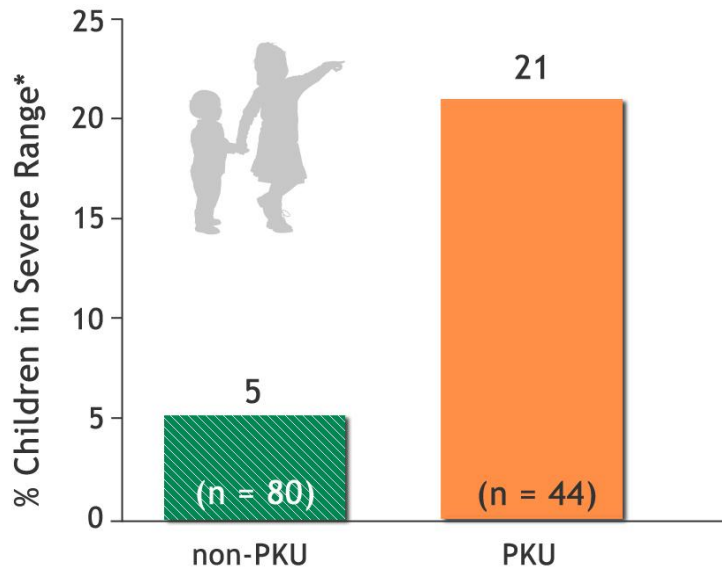
they made was that it was not known how EF scores relate to “day-to-day” functioning (i.e., classroom, home, social and work environments).

The authors call for large-scale and long-term studies of the EF of people with PKU using standardized measures of EF (i.e., everyone uses the same tests to evaluate EF) and assessing if these EF scores are related to day-to-day functioning in different environments. One such tool that should be considered is the BRIEF questionnaire for parents and teachers of school-age children, which provides a profile of behaviors associated with EF at home and in school.¹⁶

One recent study that used the BRIEF questionnaire and showed day-to-day EF deficits in children with PKU is shown below.¹⁷ Clinicians administered the BRIEF questionnaire to 189 children aged 5–18 years, who were divided into 4 groups:

- 44 with early-treated PKU (treatment started in the first month of life, no elevated Phe levels reported)
- 45 with early-treated hydrocephalus (a condition where treatment involves inserting a shunt in the first 12 months of life to relieve “water on the brain”); these subjects were included because “water on the brain” can affect EF functioning
- 20 with focal frontal-lobe lesions (documented with MRI scan); these subjects were included because many EF attributes exist in the frontal lobe of the brain and damage (i.e. lesions) in the frontal lobe can affect EF
- 80 unaffected controls (healthy siblings of other group members or recruited from local schools); these were included as “normal controls”

The overall scores of the BRIEF questionnaire showed a significant difference in the percentage of children with severe EF deficits in the hydrocephalus, frontal-lobe lesion and PKU groups compared to the “normal controls.” In the frontal-lobe lesions group, 55% had severe EF deficits. In the PKU group, 21% had severe EF deficits. In the hydrocephalus group, 18% had severe EF deficits. Only 5% of the normal control group had severe EF deficits.



*Based on Behavior Rating Inventory of EF (BRIEF) global executive composite score

Information processing speed

What is information processing speed? Your **information processing speed** is how quickly you can react to incoming information, process it, understand it and use it.¹⁸ This is not the same as intelligence. Someone can have high intelligence but process information more slowly.

Speed of information processing is influenced by a variety of factors, including:¹⁸

- the balance of **neurotransmitters** in the brain
- the amount of electrical insulation on the nerves, which is called myelin or “white matter”^{18,19}
- the organization of the networks in the brain that allow communication and information flow
- the size of synaptic spaces in the brain, which is the distance between the nerves.
- the efficiency of the frontal lobes (the front part of the brain) in organizing and directing the flow of information
- knowledge and experience (e.g., the more a person knows about a topic, the quicker it is for the person to process new information about that topic)

Individuals with slow information processing speed may be affected throughout life in varied settings such as school, home or work. Some of the following characteristics have been observed in people with slow information processing speeds in terms of thinking:¹⁹

- struggling with complex tasks or tasks that require multiple steps
- taking more time to do complex tasks
- taking longer to begin tasks
- working less efficiently under time constraints than their peers

Why people with PKU may have slow information processing difficulties:^{19,20,21}

There are 3 main reasons why psychologists and researchers have focused on information processing as a potential problem area in people with PKU:

1. Information processing speed has been linked to neurotransmitter levels and there is evidence suggesting that the levels of the neurotransmitter called dopamine may be lower in individuals with PKU.
2. Information processing speed has been linked to the amount and integrity of the insulation (myelin or “white matter”) on nerves. There is evidence showing that there are abnormalities in this insulation in some diet-treated individuals with PKU.
3. Clinicians have noticed that diet-treated PKU patients may have certain behavioral and learning problems despite having normal range intelligence. Studies have shown that many of these behavioral problems may be associated with slow information processing speed.

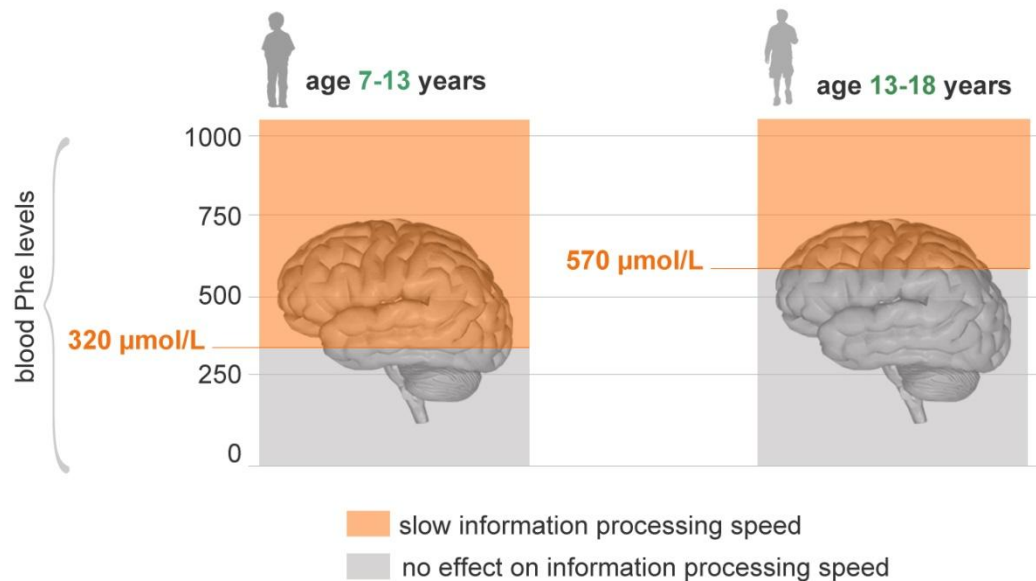
How information processing speed is measured: Researchers have devised “timed tasks” to measure information processing speed. Extensive research and testing have helped establish what the “normal-range time” is for each task for healthy individuals at different ages. Times above the normal range may indicate slow information processing speeds.

One test that measures speed of processing is called choice reaction time.^{19,20,21,22} In the choice reaction time test, a person might be asked to sit in front of a computer monitor where an arrow (the stimulus) is displayed on either the left or the right side of the screen.²² The subject must press the left hand button on the press pad if the stimulus is displayed on the left side of the screen, and the right hand button on the press pad if the stimulus is displayed on the right side of the screen. This task will go on for several minutes. At the end of the test, researchers assess the number of correct and incorrect responses, the number of late or early responses, and the average response speed. The scores are compared against those of a “normal range.”

Evidence of slow information processing speed in people with PKU: A number of studies using a variety of different tests and parameters have found that people with PKU tended to have slower information processing than “control” (non-PKU) subjects.^{19,20,21} One “study of studies” (known as a meta-analysis – looking at a variety of results from multiple PKU studies) examined many different outcomes including information processing speed.²⁰ Using sophisticated math techniques, the authors concluded that of all the different cognitive difficulties found in people with PKU, slow information processing was the most likely to be present compared to impairments in other cognitive domains.

Another research group came along after that to try to determine if slow information processing speed observed in PKU was related to blood phenylalanine (Phe) levels.²¹ They did their own meta-analysis on information processing speed PKU studies that reported blood Phe levels and age of their participants. Using sophisticated math to analyze the data, these authors then suggested that information processing speed is

affected by blood Phe levels depending on age. Their results recommend upper thresholds (the maximum level before there is an effect on information processing speed) for blood Phe concentrations of about 320 $\mu\text{mol/L}$ (5.3 mg/dL) for children between 7 and 13 years of age and about 570 $\mu\text{mol/L}$ (9.5 mg/dL) for adolescents between 13 and 18 years of age. Adults showed no blood Phe concentration effect on information processing speed; the authors suggested that there still might be an effect, but more studies need to be done to determine the effect.



Attention deficit hyperactivity disorder (ADHD)

What is attention deficit hyper activity disorder (ADHD)?²³ Attention deficit hyperactivity disorder (ADHD) is a disorder that may be characterized by a pattern of inattention (inability to concentrate) sometimes combined with hyperactivity and impulsivity. This pattern is persistent and developmentally inappropriate, and occurs in at least two different contexts.

Many people think ADHD and ADD (attention deficit disorder) are two different conditions, but they are in fact two names for the same condition. Other names no longer in use are minimal brain dysfunction (MBD) and hyperactivity.

ADHD affects 5–15% of school-aged children, occurring more frequently in boys than girls. ADHD may persist into adulthood in many cases. An inability to integrate in social, academic, or work-related settings is a pattern seen in people with a history of ADHD. In childhood, a person with ADHD may have academic problems, as the condition affects a person's ability to concentrate and focus on tasks. Because they are unable to organize their work or pay attention to their studies, children with ADHD may try to distract other children in class.

People with ADHD are especially sensitive to sensory stimuli such as noise, touch and visual cues. They can easily be overstimulated, leading to changes in behavior that may include aggressiveness.

Symptoms of a child with ADHD fall into three large categories: inattention, hyperactivity, and impulsivity. They may include:

- fidgeting or squirming excessively
- having difficulty remaining seated
- being easily distracted
- not paying attention to details
- having difficulty organizing tasks
- being forgetful
- having difficulty awaiting their turn in games
- blurting out answers to questions
- having difficulty following instructions
- having difficulty sustaining attention
- shifting from one activity to another
- having difficulty playing quietly
- often talking excessively
- often interrupting
- often not listening to what is said
- often losing things
- often engaging in dangerous activities

There's no official symptom list for adults, but symptoms are similar to those listed above.

Why people with PKU may have ADHD:^{23,8} There are two main reasons why psychologists and researchers have focused on ADHD as a potential problem area in people with PKU:

1. ADHD has been linked to lower levels of the neurotransmitter dopamine, and there is evidence suggesting that dopamine levels may be lower in individuals with PKU.
2. Clinicians have noticed that there are certain behavioral and learning problems in diet-treated PKU patients despite having normal-range intelligence. Studies have shown that many of these symptoms are similar to those found in individuals diagnosed with ADHD.

How ADHD is diagnosed:^{24,25} Psychologists use a comprehensive manual to diagnose mental disorders, called the Diagnostic and Statistical Manual for Mental Disorders (DSM), which includes criteria for diagnosing ADHD. The following simplified diagnostic information should only be used by a trained health care provider to accurately diagnose or treat ADHD. This information is taken from the most recent version of the DSM, known as DSM-IV.

Based on the criteria below, three types of ADHD are identified:

Type of ADHD	Presence of Criteria IA for the past 6 months	Presence of Criteria IB for the past 6 months	Presence of Criteria II, III, IV and V
Combined	Yes	Yes	Yes
Predominantly inattentive	Yes	No	Yes
Predominantly hyperactive-impulsive	No	Yes	Yes

- IA** Six or more of the following symptoms of inattention have been present for at least 6 months to a point that is disruptive and inappropriate for developmental level:
1. Often does not give close attention to details or makes careless mistakes in schoolwork, work, or other activities.
 2. Often has trouble keeping attention on tasks or play activities.
 3. Often does not seem to listen when spoken to directly.
 4. Often does not follow instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions).
 5. Often has trouble organizing activities.
 6. Often avoids, dislikes, or doesn't want to do things that take a lot of mental effort for a long period of time (such as schoolwork or homework).
 7. Often loses things needed for tasks and activities (e.g. toys, school assignments, pencils, books, or tools).
 8. Is often easily distracted.
 9. Is often forgetful in daily activities.

OR

- IB** Six or more of the following symptoms of hyperactivity-impulsivity have been present for at least 6 months to an extent that is disruptive and inappropriate for developmental level:
- Hyperactivity**
1. Often fidgets with hands or feet or squirms in seat.
 2. Often gets up from seat when remaining in seat is expected.
 3. Often runs about or climbs when and where it is not appropriate (adolescents or adults may feel very restless).
 4. Often has trouble playing or enjoying leisure activities quietly.
 5. Is often "on the go" or often acts as if "driven by a motor."
 6. Often talks excessively.
- Impulsivity**
1. Often blurts out answers before questions have been finished.
 2. Often has trouble waiting one's turn.
 3. Often interrupts or intrudes on others e.g., butts into conversations or games.

+

II Some symptoms that cause impairment were present before age 7 years.

+

III Some impairment from the symptoms is present in two or more settings (e.g. at school/work and at home).

+

IV There must be clear evidence of significant impairment in social, school, or work functioning.

+

V The symptoms do not happen only during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder. The symptoms are not better accounted for by another mental disorder (e.g. Mood Disorder, Anxiety Disorder, Dissociative Disorder, or a Personality Disorder).

Evidence of ADHD in people with PKU:⁸ The author of a recent review found it surprising that there are only a handful of studies investigating the correlation of ADHD with PKU, given the fact that ADHD and PKU have similar underlying potentials for neurotransmitter deficiencies in the brain. However, of the studies performed to date, it is not surprising that the authors found that people with PKU are more likely to have ADHD.

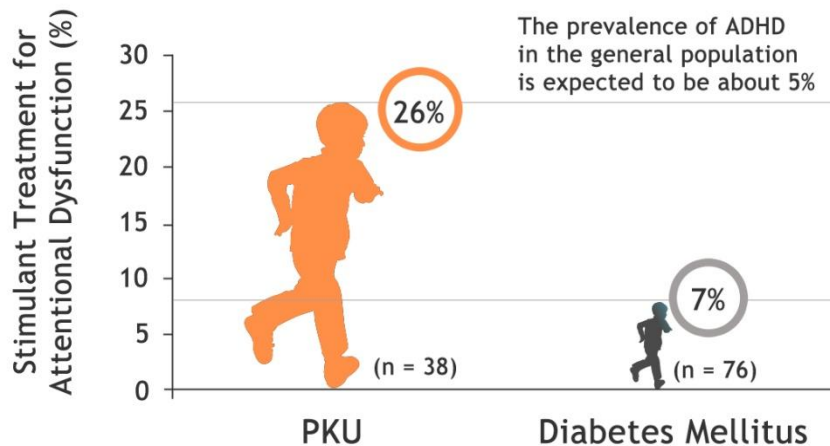
One study using the DSM-IV diagnostic criteria of ADHD found that children with PKU who were on diet treatment were 2.5 times as likely to have ADHD as those without PKU. The same authors also found that many children did not meet the full DSM-IV criteria of ADHD diagnosis but still shared many of the inattentive symptoms (but few of the impulsive or hyperactive symptoms). Thus, it appears that PKU children may be at risk for the predominantly inattentive type of ADHD. The author also stated that there seems to be a relationship between ADHD symptoms and blood Phe levels: higher levels of Phe were associated with a greater number of ADHD symptoms.

In the same review, the author described what would be considered “circumstantial” but strong evidence for ADHD in PKU from another study. This was based on the discovery that stimulant medications used to treat ADHD were also being prescribed at a high level to kids with PKU (26% of PKU children in this study were prescribed stimulant medication compared to only 5% in the general population of non-PKU children).²⁶

This study examined how often stimulant medications were prescribed to 38 youths with diet-treated PKU (23 males, 15 females; age range 5–20 years). There was a “control” group of 76 youths with type 1 diabetes (46 males, 30 females; age range 5–20 years). Children with type 1 diabetes were chosen as the control group since diabetes and PKU have some things in common, such as diet alteration and the requirement for family support to help maintain metabolic control.

The study found that 26% of the PKU patients (7 boys and 3 girls) had been prescribed a stimulant medication because of inattentive problems, while only 6.5% (4 boys and 1 girl) of the diabetes control group were prescribed a stimulant medication. Additionally, the stimulant prescriptions were higher in the PKU group than for the general population (5%).

Of particular interest was the mean blood Phe level for the past year in the stimulant-using group: it was 792 $\mu\text{mol/L}$ (13.2 mg/dL), compared to 486 $\mu\text{mol/L}$ (8.1 mg/dL) in the non-stimulant-using PKU group. The author suggests the possibility of stimulant medications being used to manage cases where dietary Phe intake is less well controlled. Future research should investigate if stricter dietary management improves the inattentive symptoms. It might be that there is no need for the stimulant medication, just better Phe control. The author also notes that, in spite of better Phe control, it is possible the ADHD inattentive symptoms may persist, since Phe levels in individuals with well-treated PKU are still 2–10 times as high as in the general population.



Learning disabilities and academic performance

What do learning disabilities and academic performance mean?⁸ Academic performance is how well a person performs in school. It is based on scholastic outcomes, such as educational level obtained. Learning disability is a clinical diagnosis made by a trained professional. Learning disabilities include a number of disorders that may affect acquiring, organizing, retaining, understanding or using of information. These disorders affect learning in individuals who otherwise have normal intellectual abilities for thinking and/or reasoning. Thus, a person can have poor academic performance with no learning disability.

Why people with PKU may have learning and academic performance difficulties:⁸ There are many reasons why psychologists and researchers have focused on academic performance issues and learning disabilities as potential problem areas in people with diet-treated PKU:

1. The potentially lower levels of the neurotransmitter dopamine and the observed white matter abnormalities seen in PKU patients provide physical evidence for altered brain function, suggesting that individuals with PKU may be at risk for learning disabilities and lower academic performance.
2. Clinicians, teachers and parents have observed lower academic performance and learning disabilities in diet-treated PKU patients despite their having normal-range intelligence.
3. The potential for people with PKU to have learning disabilities and academic performance difficulties is also supported by the evidence of cognitive deficits in executive function (EF) and speed of processing. Problems in these domains can lead to learning and academic difficulties.
4. The knowledge that people with PKU may be more likely than normal to have inattentive symptoms of ADHD is also an important consideration, because it is well-known that ADHD can lead to learning disabilities and lower academic performance.

How learning disabilities are diagnosed and academic performance is measured:^{8,27}

Psychologists use a comprehensive manual to diagnose learning disabilities, called the Diagnostic and Statistical Manual for Mental Disorders (DSM), which provides criteria for diagnoses. This is the same manual used for diagnosing other disorders that affect the mind, such as ADHD. The latest version of the DSM, known as the DSM-IV, uses the following criteria to diagnose learning disabilities:

- An individual's achievement on standardized measures of academic attainment is substantially below expectations for age, schooling, and level of intelligence.
- To diagnose a learning disability, it is not enough for academic achievement to be substantially below what would be expected on the basis of intelligence. It must be accompanied by significant interference with academic achievement or activities of daily living that require an academic skill. For example, someone who has a relatively high IQ but has just average academic performance wouldn't likely be diagnosed with a learning disability.

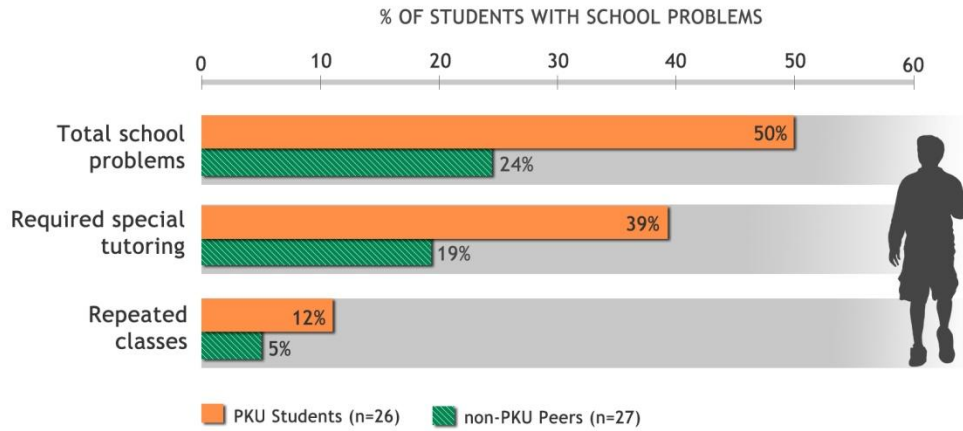
Academic performance is mainly an observation made by teacher and parents. These include grades, repeated years, the need for specialized help, and the education level obtained. However, there are standardized psychological tests that are used by clinicians to evaluate academic achievement. One such commonly used test is called the Wide Range Achievement Test (WRAT), which can assess an individual's achievement in academic domains such as reading, spelling and math.

Evidence for learning disabilities and academic performance difficulties in people with PKU:⁸ The author of a recent review looked at academic performance and learning disability studies published on individuals with early-and-continuously-treated PKU. In terms of academic performance, it appears that in the academic realms of reading and spelling, people with PKU are on par with the average population. However, two large studies have found a significant trend of below-average performance in math compared to the general population and the individual's non-affected siblings. Math difficulties in PKU were not unexpected, given that math skills require a high degree of abstract reasoning and problem-solving ability. These cognitive abilities involve executive functions (EF), which may be compromised in some individuals with controlled PKU.

In terms of blood Phe levels and academic performance, studies show that individuals with PKU who maintained a strict diet had significantly higher scores in all academic realms (spelling, reading, and math) in late childhood and early adolescence compared to those who did not stick to a strict diet. These studies were all based on the scores of the WRAT standardized academic achievement test performed in clinical settings.

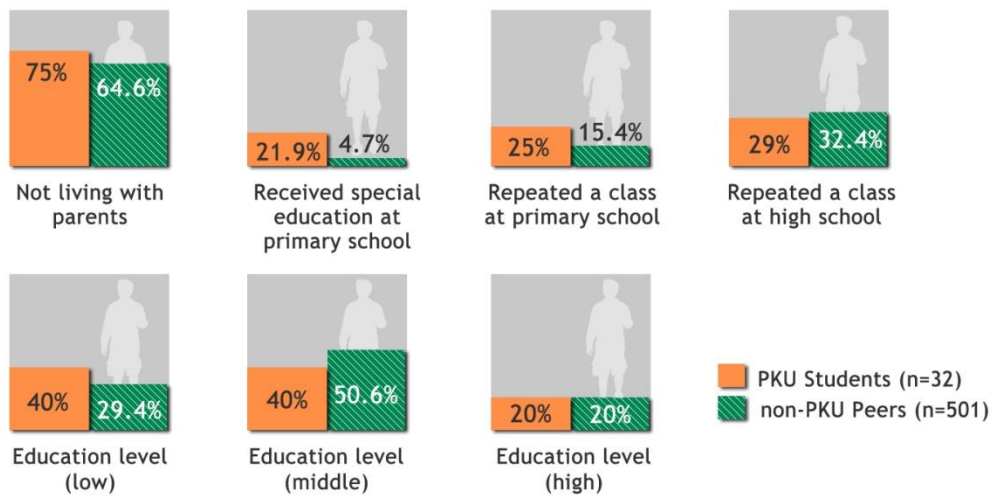
Other studies have looked at real-world academic performance by assessing each individual's day-to-day classroom performance as reported by their teachers. In one such study the authors followed 26 youths (14 males, 12 females; average age of 12.3 years) with early-and-continuously-treated PKU.²⁷ The study also used 21 classmates who didn't have PKU, matched by age and sex, for "controls" for comparison. The average intelligence levels of the two groups were the same. The study found that 50% (13/26) of the youths with PKU had school difficulties, 38.5% (10/26) required special tutoring and

11.5% (3/26) had to repeat a year. All percentages were higher than those of the control classmate participants (23.8%, 19% and 4.8%, respectively, for school problems, special tutoring and repeated classes; see figure below).



The results from these small studies are not conclusive evidence by any means. Other studies have looked at larger groups of people and found that although children with PKU did receive significantly more special tutoring in school, they did not have significantly more repeated years, and many went on to obtain high education levels at a rate similar to the large non-PKU control population (see figure below).²⁸ Additionally, there are no studies reporting a higher-than-average frequency of clinically diagnosed learning disabilities in the PKU population compared to the general population.⁸

PKU PATIENTS HAVE SIMILAR LIVING CONDITIONS, EDUCATION, AND EMPLOYMENT TO NON-PKU PEERS



Psychiatric symptoms and disorders in PKU

What is a psychiatric disorder?^{29,30,25} A **psychiatric disorder** is a clinical diagnosis based on a set of criteria that only a trained expert such as a psychiatrist or psychologist can assess. Psychiatric disorders may be characterized by behavioral and/or psychological abnormalities, often accompanied by physical symptoms. The psychiatric symptoms may significantly affect many aspects of a person's day-to-day life, causing significant distress or impairment in social and work settings.

In all, there are more than 300 different types of psychiatric disorders that have their own criteria for diagnosis. The disorders are typically categorized into larger disorder families based on the predominant psychiatric symptom. For example, Anxiety Disorders include disorders in which anxiety is the main symptom, such as phobias, social anxiety and post-traumatic stress disorders.

Why people with PKU may have psychiatric symptoms and disorders:^{31,12,32} There are 3 main reasons why psychologists and psychiatrists have focused on the potential for psychiatric symptoms and disorders in people with diet-treated PKU.

1. The strict PKU diet can be stressful to maintain over the long term, and psychosocial stressors such as this or others (e.g., unemployment, loss of a loved one) are known to play an important part in mental health and contribute to psychiatric symptoms and disorders. In terms of PKU and other chronic diseases, this psychosocial stressor is generally referred to as “the burden of chronic disease” or “treatment fatigue.”
2. Many psychiatric disorders are rooted in altered brain chemistry and function. The potentially lower levels of the neurotransmitter dopamine and the observed white matter abnormalities seen in people with diet-treated PKU provide physical evidence of altered brain function and a basis for investigating the presence of psychiatric disorders in PKU.
3. Deficits in cognitive abilities, such as executive function (EF) and speed of information processing, in people with diet-treated PKU may play an important role in some aspects of mental health.

How psychiatric disorders are diagnosed:^{29,25} Psychologists and psychiatrists use a comprehensive manual to diagnose psychiatric disorders, called the Diagnostic and Statistical Manual for Mental Disorders (DSM; the latest version is known as DSM-IV), which provides criteria for diagnoses. The book is the “bible” for any psychologist or psychiatrist who diagnoses psychiatric disorders in the US and many other countries. It is also the same manual used to diagnose others disorders of the mind, such as learning disabilities and ADHD.

As mentioned previously, there are more than 300 different psychiatric disorders that use different diagnostic criteria. Diagnosing psychiatric disorders is mainly based on what the symptoms are, how long they last and how much they interfere with day-to-day function. However, the DSM-IV criteria also look at underlying issues such as psychosocial stressors (family problems, employment status, etc.) and the highest level of function attained in the previous year. After taking everything into consideration, the psychologist

or psychiatrist will recommend a treatment action plan to relieve symptoms and treat the underlying cause of the problem. Treatment may include a combination of medication, behavior therapy and stress-management techniques.

Evidence for psychiatric symptoms in people with PKU:^{31,12,32} In two recent reviews of studies of PKU involving psychiatric disorders and symptoms, the conclusions were similar: it appears that people with PKU do not have a significantly different overall rate of psychiatric disorders than the general population.^{31,12} However, there does seem to be a pattern of psychiatric symptoms found in PKU, including increased occurrences of depressed moods, anxiety, phobias and the feeling of social isolation, as well as decreased feelings of autonomy, positive emotions, school achievement and social competence (see Figure 3 and Table 2).

Figure 3: Psychiatric symptoms affecting people with PKU

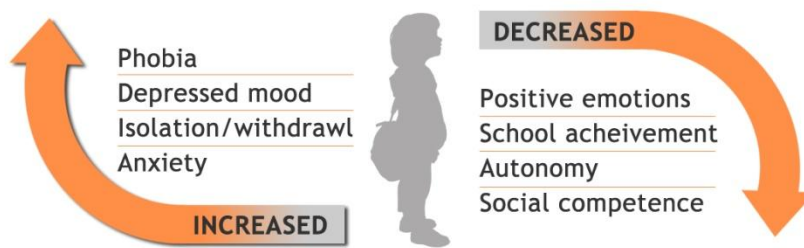


Table 2: Psychiatric, emotional and behavioral symptoms found in people with PKU¹²

Untreated individuals	Early-treated children and adolescents	Early-treated adults
<ul style="list-style-type: none"> • Psychotic symptoms • Autistic behaviors • Hyperactivity • Aggression • Anxiety • Depressed mood • Impaired social skills associated with profound intellectual disability • Social withdrawal 	<ul style="list-style-type: none"> • Attentional problems • School problems • Less achievement motivation • Decreased social competence • Decreased autonomy • Low self-esteem 	<ul style="list-style-type: none"> • Depressed mood • Generalized anxiety • Phobias • Decreased positive emotions • Low self-esteem • Social maturity deficits • Social isolation/withdrawal • Lack of autonomy

The main question is whether the psychiatric symptoms observed in people with PKU have to do with increased blood Phe levels or with "treatment fatigue" from maintaining the strict low-Phe diet. Although both are likely to be contributing factors, evidence suggests that psychiatric symptoms are more likely to be more common and severe when

blood Phe levels are high. Individuals with poor metabolic control during the critical years of brain development (childhood and adolescence) are more likely to show more symptoms that are more serious. Adults also appear to be at risk for increased psychiatric symptoms based on blood Phe levels (see Table 2).

A recent study has given us one of the most compelling pieces of evidence for the involvement of elevated blood Phe in affecting mood and behavior of people with PKU.³² This study involved a randomized double-blind placebo controlled trial – a type of trial called the “gold standard” in clinical experiments. In the study, 9 continuously-treated adults with well-controlled PKU underwent two 4-week supplementation periods: one with Phe (to increase blood Phe levels) and one with placebos (“sugar pills”). The subjects didn’t know what they were taking in either period and were randomly assigned either Phe pills or placebo in the first 4-week period. After the 4 weeks, there was a period of at least 4 weeks in which the subjects went back to their normal routine (i.e., were not taking either Phe pills or placebo). Then the second period of supplementation started and lasted 4 weeks. During the second period, if subjects were receiving placebo in the first period, then they received Phe pills in the second period, and vice versa.

In each period, the subjects were given a “mood state” questionnaire to complete to evaluate their mood, with researchers noting when they had high and low blood Phe levels. Additionally, a friend or relative of each patient completed a questionnaire about the patient’s mood.

The average blood Phe level in the placebo period was 709 $\mu\text{mol/L}$ (11.8 mg/dL), while the average blood Phe level in the Phe pill period was 1,259 $\mu\text{mol/L}$ (21 mg/dL). When blood Phe levels were higher, the patients reported a significant increase in depression symptoms and fatigue and felt less vigorous (see Figure 4). Spouses, relatives and friends also observed increased depression and fatigue when blood Phe levels were high (see Figure 4). They also reported that the patients appeared to be more angry when blood Phe levels were high (see Figure 4).

Thus, the study suggests that high blood Phe levels have a direct negative effect on mood in adult patients with PKU. Because of the effect on mood, the study supports the “diet for life” treatment recommendation. It is important to note that a similar study cannot be done ethically with PKU children because of the irreversible brain damage that high Phe levels can cause during this critical period of brain development. However, the results of this study in adults point to the potential for similar mood problems in children during periods of elevated blood Phe levels.

Figure 4: Relation of Phe levels to mood

