PHYSICAL EXERCISE AND NUTRITION IN PHENYLKETONURIA

Physical fitness, physical exercise prescription and nutritional guidelines

José A. Casajús • Germán Vicente-Rodríguez
Domingo González-Lamuño • Carmen Melina Morencos Pinedo

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Introduction

Daily **physical activity** is one of the most important tools for maintaining a good state of health, both among the general population and in people with phenylketonuria (PKU). One of the many benefits of physical activity and planned **physical exercise** for people with PKU, as for the rest of the population, is the prevention of overweight and obesity. As occurs in the general population, the prevalence of overweight and obesity in people with PKU is high but extremely variable. Obesity is present in 4.5% to 72% of people with PKU, depending on different populations, and several studies have observed a greater prevalence of obesity in those women with PKU with poor blood phenylalanine (Phe) control[1,2].

It is therefore advisable that individuals with PKU are physically active[3]. Given their special condition, which probably affects their **physical and functional condition**, physical exercise is not only not contraindicated in people with PKU, but rather an appropriate prescription could enhance their functional state and health. Indeed, there is no formal condition that prevents people with PKU from engaging in any kind of physical activity, including competitive sports.

Blood Phe levels in people with PKU frequently fall outside the optimal range, especially in adolescents and adults, indicating insufficient adherence to dietary recommendations for PKU management. This factor is particularly important when exercise programmes are incorporated, as this will also require dietary control and adjustments so that energy demands are met in line with the type and intensity of exercise performed. Few rigorous studies have been conducted to measure adherence to nutritional treatment in individuals with PKU and it is usually estimated based on the results of blood Phe concentration measurements. However, there is no overall agreement on the number of measurements of Phe concentrations that should be within the target range, or on the frequency or timing of such measurements. Although no strategy has been acknowledged as universally effective

in improving these patients' adherence to dietary-nutritional treatment, we suggest an individualised approach based on prescribing physical exercise together with dietary supplements.

Phenylketonuria (PKU): General characteristics of the disorder

PKU is a rare inherited disorder that causes a build-up of the amino acid Phe in the body. PKU is caused by pathogenic changes in the two copies (alleles) of the phenylalanine hydroxylase (PAH) gene. This gene encodes the enzyme needed to break down Phe into another amino acid (tyrosine).

The absence or malfunctioning of this enzyme, which is supposed to break down Phe causes a dangerous build-up of Phe when an individual with PKU eats protein-rich foods. Over time, this can lead to serious health problems.

The most severe form of the disorder is called **classical PKU**, in which the enzyme required to break down Phe is either missing or shows reduced activity. As a result, high Phe levels can lead to severe brain damage. In mild or moderate forms, the enzyme still functions to some extent, meaning Phe levels are not as high, resulting in a lower risk of significant brain damage.

Regardless of its form, most infants, children and adults with the disorder require a special PKU diet to prevent intellectual disability and other complications. Throughout their lives, people with PKU (infants, children and adults) should follow a low-Phe diet, which is mainly found in protein foods, and take protein substitutes which are free of this amino acid and enriched in tyrosine.

Certain drugs may allow some people with PKU to eat a diet with a higher amount of Phe. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved the drug sapropterin dihydrochloride for treating PKU in people with responsive forms of this BH4-like co-factor. In 2018, the FDA approved the first enzyme replacement, pegvaliase (Palynziq) to reduce Phe levels in adults

with PKU with uncontrolled Phe levels in excess of 600 µmol/L. To date, this treatment is not funded in Spain.

In the western world, this metabolic disorder is detected shortly after birth by the heel prick test. While there is currently no cure for PKU, detecting it and commencing treatment immediately can help prevent any limitations with regard to cognition, understanding and communication (intellectual disability) and more serious health problems.

Newborns with PKU initially have no symptoms; however, without treatment, babies often show signs of PKU within a few months.

The signs and symptoms of untreated PKU may be mild or severe, and include the following:

- Musty odour on the breath, skin or urine, caused by excess Phe in the body.
- Neurological problems, which may include seizures.
- Skin rashes, such as eczema.
- Lighter skin, hair and eyes than other family members, because Phe cannot be converted into melanin (the pigment responsible for skin and hair colour).
- Unusually small head size (microcephaly).
- Hyperactivity.
- Intellectual disability.
- Delayed development.
- Behavioural, emotional and social problems.
- Mental health disorders.

Diet and physical activity in PKU

INTAKE AND PROTEIN SUBSTITUTES

No cure exists for PKU, though proper treatment can prevent both intellectual disability together with many of the health problems associated with the disorder. People with PKU should be treated and monitored in a centre specialising in inherited metabolic disorders.

Treatment for PKU requires a lifelong limited protein diet and the intake of special protein substitutes to ensure a sufficient supply of essential protein (without Phe). Providing an adequate dose of protein substitute, usually based on Phe-free amino acid substitutes, is key to promoting normal growth, preventing protein deficiency, providing a source of tyrosine and helping to optimise blood Phe management. In addition to amino acid substitutes, other types of protein substitutes have recently been developed in the form of casein glycomacropeptide (CGMP), which is a peptide with low Phe content. It is a by-product of cheese whey and, while theoretically free of Phe, a minimal amount of residual Phe persists in the manufactured product due to its extraction process. Despite this minimal amount of Phe, CGMP-based protein substitutes have proved to be safe and effective in treating PKU and may be useful in those individuals with poor adherence to amino acid protein substitutes[4,5]. Protein substitutes are available in powder, capsule, tablet, bar and liquid form and may contain added carbohydrates, fats, vitamins, micronutrients and minerals.

A newborn who is diagnosed with PKU should receive specialised infant formula. This formula can be mixed with a small amount of breast milk or infant formula to ensure that the child receives enough Phe for normal development but not in excess to cause harm. In older children and adults, it is advisable to administer the protein substitute in small, frequent doses, 3-4 times evenly spread throughout the day,

rather than once or twice a day. Protein subsititutes for PKU should be consumed every day throughout the life of an individual with PKU. It should be taken alongside a natural protein source, as well as a source of carbohydrates. In addition to protein substitutes, health professionals may also recommend other nutritional supplements such as fish oil to aid fine motor coordination and other developmental aspects.

The amount of Phe tolerated will depend on the individual with PKU and may also vary over time. The recommended intake is the amount of Phe necessary for growth, development and activity level, which requires an individualised approach to the dietary prescription. Frequent blood tests and medical visits are needed to help determine whether the diet is optimal or requires any adjustments. Phe levels are determined at regular intervals and frequently in infants, and less frequently in older children and adults. Ideally, Phe levels should be kept in the range of 120-360 µmol/L, which is that set by the European Guidelines[6], in young children and pregnant women, and within higher, but controlled ranges in young people and adults. Although the diet may be more relaxed as the child grows older, studies have shown that high blood Phe can have detrimental effects in adults with PKU, and that some adults with untreated PKU who are cognitively impaired may show improved behaviour and physical manifestations when treated with a Phe-restricted diet.

Increased physical activity is associated with increased energy and nutritional requirements in the general population, including those with PKU. The nutritional prescription for people with PKU needs adapting to these increased energy demands, so it does not negatively impact blood Phe control.

Several studies show that acute physical exercise does not have a negative impact on blood Phe concentration, which supports the fact that people with PKU can participate in physical activity with no loss of metabolic control[7,8]. However, physical exercise has a significant impact on protein metabolism, so ensuring an adequate intake of essential amino acids is key to ensuring protein synthesis and muscle repair[9]. The concentration of branched-chain amino acids (BCAAs) in plasma can help identify whether catabolic states occur in both the general population and in PKU patients when they increase their exercise activity. Furthermore, changes in Phe levels may prove useful when investigating the chronic impact of physical exercise in people with PKU and its effects on Phe metabolism[10].

Taking into account that the treatment of PKU patients is based on dietary and nutritional recommendations, the most important aspects of diet in those people with PKU who exercise regularly, and especially in relation to the specific exercise programme proposed later in this chapter are:

I. Increased energy needs – ensuring sufficient carbohydrate intake to cover energy requirements.

II. Planning the intake of protein substitute doses for PKU (after consulting with their doctor and dietitian-nutritionist) immediately after training in the recovery phase; of particular importance in **strength training sessions**.

III. An adequate state of hydration.

IV. Any dietary adjustments for a individual with PKU intended to optimise physiology and exercise performance should be agreed upon with their physician and dietitian-nutritionist.

The aim of this chapter is to describe the general recommendations for the physically active PKU population and related to the proposed training programme according to the previously assessed fitness level.

People with PKU should avoid a number of protein-rich foods, including dairy, eggs, nuts, soy, legumes, meat and fish. They should also avoid the sweetener aspartame which is present in some foods, drinks and medicines as it releases Phe when digested.

People with PKU often have to limit their intake of some foods which, although lower in protein than those mentioned above are still sources of Phe such as cereals and certain fruits and vegetables. However, a PKU-friendly diet can include low-protein foods such as certain types of pasta, cereals and egg substitute and other special products. These products can be consumed freely as long as all the ingredients are Phe-free (e.g. composed of starches and oils). If they have ingredients containing protein and over 25 mg Phe per 100 g, this Phe content must be taken into account in the diet.

For individuals with classical PKU, a protein substitute is likely to provide at least 75% of the daily nitrogen requirement. PKU patients who are engaged in intense physical training may require a greater amount of protein substitute due to increased protein requirements.

ENERGY REQUIREMENTS

The body needs a constant supply of energy for walking, muscle recovery and brain function. An adequate energy supply makes it possible to plan and perform intense physical exercise and delays the feeling of fatigue. At the same time, energy is also needed to maintain an adequate body temperature.

The measure of energy supplied is the kilocalorie (kcal) and its main source is macronutrients, i.e. carbohydrates, fats and proteins. One gram of carbohydrate or protein provides 4 kcal and 1 g of fat provides 9 kcal.

Energy requirements vary between people, depending on several factors such as age, gender, weight, muscle mass, amount and type of physical activity performed throughout the day, etc. Adjusting the nutritional intake to individual needs (particularly in the case of young athletes) protects against the negative health impact that an insufficient intake would have (such as fatigue, growth disorders or inadequate pubertal development). Carbohydrates are the main source of energy used during exercise and it is therefore important to consume carbohydrate-rich foods before and after physical exercise sessions: beforehand, to obtain the necessary energy when the duration of the effort requires it (generally more than 1 hour of high intensity), and afterwards to ensure recovery from the effort and for adequate metabolic and muscular adaptation. Protein intake is also essential for proper regeneration of muscle tissues damaged during physical exercise, particularly in the case of strength training. In order to maintain safe blood Phe concentrations in individuals with PKU, it is important to ensure adequate protein intake, both through low Phe protein substitutes and food. Macronutrients are discussed in more detail in the next section.

The **basal metabolic rate (BMR)** is the number of calories the body needs for basic life functions, such as breathing, eye movement and bowel movement, assuming no additional physical activity. There are several ways to measure energy expenditure, such as the double-labelled water method and indirect calorimetry commonly used in research. In everyday practice, formulas for estimating BMR such as the Harris-Benedict are used[11]:

- Men:
  BMR = 66 + (13.8 × weight in kilograms) + (5 × height in cm) − (6.8 × age in years)
- Women:
  BMR = 655 + (9.5 × weight in kilograms) + (1.9 × height in cm) − (4.7 × age in years)

To calculate the total energy expenditure (TEE) of an individual, the BMR should be multiplied by the individual's physical activity coefficient, as shown in **table 1**.

According to the World Health Organisation's definition, **moderate physical activity** is that which requires medium effort and significantly increases the heart rate, such as brisk walking, slow dancing, vacuuming, etc. **Intense physical activity** requires a great deal of effort, leading to a significant acceleration in the breathing and heart rate, such as skipping, playing football, running fast…

TABLE 1. Physical Activity Level (PAL) based on total weekly duration[12,13]

Physical activity level (PAL)	Active time per week	Example
1.2	No physical activity	Lying in bed
1.24	Moderate activity, up to 140 minutes. Intense, up to 100 minutes	Office worker, activity related to domestic work only
1.5	Moderate activity, up to 280 minutes. Intense, up to 200 minutes	An office worker who trains intensively 2-3 times per week for at least one hour
1.75	Moderate activity, up to 420 minutes. Intense, up to 300 minutes	An office worker who trains intensively 3-4 times per week for at least one hour
2.0	Moderate activity, up to 560 minutes. Intense, up to 400 minutes	A professional athlete who trains at least 6 hours per week or a person who works hard physically

Example: a 22-year-old man, body weight 71 kg, height 184 cm, student, trains at the gym three times a week for 1.5-2 hours (CrossFit and cardio exercises).

Men: TMB = 66 + (13.8 × 71 kg) + (5 × 184 cm) − (6.8 × 22 yr) = 1,816.2 kcal
GEE = 1,816.2 × 1.5 = 2.724

The total energy requirement per day would be approx. 2.725 kcal.

NUTRIENTS AND HYDRATION IN THE PHYSICALLY ACTIVE PKU PATIENT

1. Carbohydrates

Carbohydrates are the most important source of energy for muscles, where they are stored as well as in the liver in the form of glycogen. During exercise, through **glycogenolysis**, muscle and liver glycogen are broken down to release glucose molecules, which the muscle use as "fuel".

When intense training is performed for longer than 60-90 minutes, especially cardiorespiratory endurance exercise, muscle glycogen stores are significantly depleted and muscle protein may be used to meet energy requirements, which in people with PKU may raise blood Phe levels. An adequate supply of carbohydrates through food

is therefore essential in PKU patients who perform regular, intense physical activity, in addition to enhancing performance, preventing muscle protein catabolism and maintaining Phe concentrations in range.

Whereas in the past it was recommended that 60-70% of the total energy in the diet should come from carbohydrates[14] the IOC (International Olympic Committee), ACSM (American College of Sports Medicine), ADA (American Dietetic Association) and DC (Dietitians of Canada) guidelines now recommend calculating carbohydrate requirements from body weight and training volume, as glycogen storage capacity is proportional to muscle mass and body weight, i.e. under normal conditions, the greater the body weight, the greater the muscle mass and the greater the glycogen storage capacity. The larger the training volume, the more carbohydrate will be needed to fuel the muscles. **Table 2** summarises the carbohydrate requirements.

TABLE 2. Carbohydrate requirements according to the volume of training performed

Activity level	Recommended intake of carbohydrates
Very light training (low intensity or activity based on the technique)	3-5 g daily/kg body weight
Moderate intensity training (approx. 1 h daily)	5-7 g daily/kg body weight
Moderate-high intensity training (1-3 h weight per day)	6-10 g daily/kg body weight
Very high intensity training (> 4 h daily)	8-12 g daily/kg body weight

Foods high in carbohydrates should be consumed both before and after exercise. If the exercise lasts longer than 1 hour, these should be consumed during exercise, preferably in the form of drinks. The diet of PKU patients is usually rich in carbohydrates, so problems in meeting the demand for this macronutrient are rarely observed. Sources of carbohydrate in low Phe diets are special low-protein foods (bread, pasta, rice substitutes, flour products, breakfast cereals, sweets) as well as fruits, vegetables and juices made from them, sugary drinks, and sweeteners such as sugar and honey. However, it should be noted that some special protein substitutes for PKU provide significant amounts of simple sugars. It is always advisable to check the composition first.

2. Protein/Protein equivalent

Proteins are part of the basic structure of tissues, and have key metabolic and regulatory functions. The European PKU guidelines recommend that total protein intake in PKU patients should be 40% higher than the FAO/WHO/UNU[6] recommended intake for the general population. This intake represents both natural protein intake and protein equivalent from **protein substitutes** and would compensate for inefficient absorption of natural/intact protein (mainly of plant origin), poor utilisation of L-amino acids and sometimes sub-optimal energy intake. Phe-free liquid nutritional preparations fall into the category of foods for special medical purposes and should only be used under medical supervision. Depending on the type and severity of the disorder, protein substitutes provide 52-80% of the daily protein requirement, the rest being obtained through dietary food, based on the individual's tolerance to Phe. Protein substitutes should be consumed regularly, spread throughout the day, ideally in a minimum of 3-5 portions.

Physical exercise has a significant impact on the body's use of protein. As the level of physical activity increases, especially when strength training is also practiced, the amount and timing of the protein substitute intake must be adjusted to compensate for the increased muscle breakdown that occurs during and after intense exercise, as well as to build new muscle cells. Due to the lack of official recommendations regarding protein requirements for physically active people with PKU, this requirement is determined based on recommendations for the general population but, considering the European guidelines previously mentioned by van Wegberg[6], it should be assessed whether an increase is necessary. Below, we discuss recommendations for protein intake in the general athletic population and mention some key aspects to be taken into account for individuals with PKU.

According to ACSM recommendations, protein requirements range from 1.2-2 g/kg body weight/day, depending on the type and intensity of the training.

2.1. Aerobic endurance training

People who perform intense, prolonged aerobic endurance training have increased protein requirements compared to the non-active population. When intense endurance training exceeds 60-90 minutes, muscle glycogen stores are significantly depleted, causing the body to use certain amino acids as a source of energy. Therefore, in people with PKU, in addition to ensuring adequate carbohydrate intake to maintain muscle glycogen stores, protein intake must be sufficient to avoid muscle catabolism and elevated blood Phe. The ACSM recommends an intake of 1.2-1.4 g/kg protein per day for this type of exercise.

2.2. Strength training

Strength training stimulates muscle synthesis and recommendations for protein requirements range from 1.2-1.7 g/kg body weight/day[15], rising to 2 g/kg/day or more for in certain cases of heavy training volume or periods of weight loss, in order to preserve muscle mass[16,17]. In addition to attaching importance to the quantity and quality of protein intake, the latest ACSM recommendations emphasise the timing of intakes. Protein intake should be divided into 3-4 portions per day, with one taken immediately after physical exercise. This is because muscle protein synthesis after strength training is optimised by consuming high biological value proteins that provide around 10 g of essential amino acids in the 0-2 hours after exercise[18,19]. This translates into 15-25 g net protein (0.25-0.3 g/kg) in most of the active population. In individuals with PKU this 15-25 g of protein will have to come from an amino acid or glycomacropeptide based protein substitute.

TABLE 3. Protein requirements in the athletic population[20]

Daily protein requirement	Type of activity	Example
1.2-1.4 g/kg	Cardiorespiratory endurance	Running, cycling, swimming
1.2-1.7 g/kg	Strength and endurance	Weightlifting, combat sports
1.6-2.2 g/kg	Training focused on building muscle mass	Bodybuilding training

Determining the protein requirements in physically active individuals with PKU should be individualised and should take into account the frequency, intensity and type of physical activity being performed. Excessive protein intake in relation to caloric intake may be unsuitable as it cannot be used by the body for muscle regeneration. In addition, consuming too much protein can compromise carbohydrate intake and thus affect physical performance.

Protein intake together with carbohydrates promotes muscle anabolism because, in addition to stimulating glucose uptake in the muscles, insulin inhibits protein catabolism and thus assists metabolic balance. For this reason, it is advisable to ingest the protein substitute after training together with a carbohydrate rich food, such as fruit, potato starch, maize starch or rice starch. Low-protein pasta, maize or rice is

another option. Another alternative would be a protein substitute based on amino acids or glycomacropeptides containing carbohydrates. Other protein substitutes should be taken with other meals during the day.

3. Fats

Fats are another important source of energy during exercise. While carbohydrates are the main source of energy for muscles and are primarily used as "fuel", the fat oxidation process also plays an important role in supplying energy during exercise. In general, fats provide approximately 20-35% of the total energy in a diet. For better cardiovascular health, most of the fat in the diet should come from vegetable sources such as olive oil, nut oils and avocado, while minimising the consumption of hydrogenated and trans fats. Unfortunately, many ultra-processed foods and some low-protein foods contain them, so it is advisable to check their nutritional labelling and choose those with as little as possible.

Since digesting and absorbing fats is slower than that of carbohydrates and protein, high-fat foods should be avoided immediately before, during and immediately after exercise. Some sources of healthy fats for the general population, such as nuts, are not a suitable choice for people with PKU, so caution should be exercised with food choices. In the practical examples we will look at which sources of fats are the best and when and how to take them around physical training sessions.

4. Vitamins and minerals

In addition to carbohydrates and fats, most PKU protein substitutes also contain vitamins and minerals which minimises the risk of deficiency. However, not all protein substitutes contain all vitamins or minerals and selecting the appropriate protein substitute for PKU should be discussed with a physician and health professionals specialising in nutrition for inborn metabolic errors.

5. Hydration

Losing over 2% of body weight during exercise indicates dehydration and can be a major cause of fatigue and reduced physical, mental and cognitive performance. In individuals with PKU it is important to be aware of the degree of hydration, especially when physical activity is accompanied by an increased intake of protein substitutes. Among others, the symptoms of dehydration include: irritability, dizziness, headaches and muscle cramps.

It is advisable to communicate to patients that they should not wait to feel thirsty to detect the need for replacing fluids as when this occurs the loss of fluids in the body is too much. The colour of urine is another indicator of hydration; a darker colour indicates dehydration, while a pale-yellow colour indicates an adequate supply of fluids in the body. On average, an adult should drink 2 to 2.5 litres of fluids per day, most of which should be water. Greater physical activity increases water requirements by 0.4 to 0.8 litres per hour of exercise. In addition, once the physical exercise has finished, 1.25-1.5 litres of fluid should be taken for every kilogram of body weight lost during the following hours.

Isotonic drinks are suitable for fluid replacement during prolonged physical exercise, but they also supply a significant number of calories that should be considered part of the caloric intake of the diet. It is vital to note that some commercially available products contain aspartame and should be avoided by PKU patients. Table 4 shows some of the beverages available on the market that that are aspartame-free as of review date 19 February 2024. An isotonic drink can also be prepared as follows:

- 1 litre of water.
- 1 dessert spoon of sodium bicarbonate.
- 1 dessert spoon iodised sea salt.
- 2 tablespoons honey or sugar.
- The juice of 2 lemons.

TABLE 4. Some of the aspartame-free isotonic drinks available as of 19/2/2024

As the composition of the products may change, we should always check in the list of ingredients that they are aspartame-free	
Maurten Drink Mix 320	https://maurten.es/productos/22-drink-mix-320.html
Victory Endurance	https://victoryendurance.com/producto/bebida-isotonica/
Isodrink Orange	https://dextro-energy.com/products/iso-drink-orange?_pos=1&_sid=78973d3c3&_ss=r
Isotonic +	https://keepgoing.es/hidratacion/698-11456-isotonic-plus.html

ADDITIONAL SPORTS SUPPLEMENTS

Protein supplements available to the general sports population often **contain a high amount of Phe, may be a source of aspartame and are should therefore never be used by people with PKU**. In addition, some bars and gels that are primarily car-

bohydrate-oriented also include aspartame and Phe, so it is essential to check the labelling of any product before consumption, and when in doubt, consult a medical professional. The topic of sports supplements in physically active people with PKU is a subject of constant interest and numerous discussions, so here is some important information on the composition of selected supplements: BCAAS, creatine and caffeine.

Sports supplementation should always be discussed first with your doctor and/or dietitian/nutritionist.

1. Branched-chain amino acids (BCAAs)

People who train intensively (especially aerobic endurance training) often look for supplements containing branched-chain amino acids (leucine, isoleucine, valine) known as BCAAs. However, the suitability of using solely BCAA supplements for muscle building is questionable. This process is most effective when, in addition to leucine, isoleucine and valine, the body receives a large amount of other amino acids that it cannot produce on its own[21,22]. Therefore, in the general population who do frequent and intense physical exercise, an increased protein intake is advisable, either in the form of the natural protein found in food or in the form of food and protein supplements[23].

For physically active people with PKU, the intake of most of the essential amino acids can be increased by appropriately adjusting the dosage of protein substitutes for PKU, as their composition includes them. Phenylalanine, which is also an essential amino acid, should be consumed in specific, limited amounts to keep its blood concentration within safe limits. The main nutritional goal in physically active individuals with PKU is to meet protein requirements and only under certain circumstances would the use of BCAAs be justified, provided it is prescribed by a healthcare professional specialised in inborn metabolic disorders (IMDs).

2. Creatine

Available data show that creatine is one of the few substances that increase the ergogenic effects, i.e. the exercise capacity of the body. Creatine is an organic compound that contains no Phe and is used particularly in power and strength sports to improve strength and muscle mass. At the same time, it allows you to increase the load during exercise and increase the number of repetitions. In addition, by improving muscle hydration, creatine helps to shape the figure. To date, the evidence for the use of creatine in an individual with PKU is limited[3]. In the context of a general sports population, creatine supplements in the form of creatine monohydrate, in the amount of 3-5 g/day, are known to be safe, even if consumed on a long-term

basis. As with BCAA supplements, if you are considering taking creatine, talk to your doctor and IMD nutritionist, as the primary nutritional goal in physically active people with PKU is to meet protein requirements, while extra supplements would only be justified under certain circumstances.

3. Caffeine

Caffeine is another substance with a recognised ergogenic effect and is commonly used in many aspects of life, not only in sport. Many energy drinks contain caffeine. Here we must emphasise that consuming any drinks containing aspartame is totally forbidden for people with PKU.

Drinking coffee is the most common way it is consumed. People who like coffee and drink it in moderate amounts, such as espresso or Americano, can obtain health benefits due to the presence of many bioactive substances it contains. The dose of caffeine commonly considered safe for your health is up to 400 mg/day. Consuming over 1,200 mg/day of caffeine is toxic. A 240 ml cup of coffee contains on average 80-100 mg of caffeine. It is important to note that physical exercise has the effect of raising blood pressure and drinking caffeine may unnecessarily boost this effect.

ALCOHOL CONSUMPTION, PKU AND SPORT

Drinking alcohol is harmful to your health. For people involved in professional sports, alcohol consumption should be kept to a minimum or eliminated altogether, especially when seeking to get into better shape and achieving results in competitions.

In addition to having a negative effect on concentration, alcohol interferes with metabolic changes, thermoregulation and the body's recovery rate. One gram of pure alcohol provides 7 kcal, and alcohol also triggers uncontrolled food consumption, so frequent alcohol can significantly increase the amount of energy consumed and negatively affect body composition. A glass of beer (approx. 250 ml), a small glass of wine (100 ml) or half a glass (approx. 30 ml) of vodka provides 10 g of pure alcohol.

It is important to note that some alcoholic beverages are not Phe-free. Patients with PKU should not consume alcoholic beverages containing milk, cream or eggs (orujo cream, eggnog). As regards beer, it should also be remembered in mind that 100 ml of beer contains 15 mg of Phe (considering that the size of a normal beer is usually between 200 and 500 ml, so adding Phe to the diet, if consumed) while wine and vodka would be 0 mg.

DIET FOR A INDIVIDUAL WITH PKU ON A PHYSICAL EXERCISE PROGRAMME

1. Number and frequency of meals

Meal times may vary from day to day depending, among other things, on whether they are adapted to physical activity and training sessions. During the day, it is advisable to plan for 3 main meals and 1-2 supplementary meals, so that the protein substitute is consumed in at least 3 portions and the breaks between meals are no longer than 3-4 hours. The number of meals on training days need not differ from those on non-training days, but the amount, composition and timing of them should be adjusted in line with the intensity and duration of the training, especially in the case of high-performance athletes.

2. Pre-training meal

The main meal, together with the protein substitute for PKU, should be taken 3-4 hours before training. Large meals just before exercise should be avoided; instead, it is advisable to consume a small carbohydrate-containing snack about an hour beforehand to ensure the "fuel" required during exercise. This minimises both the risk of feeling hungry and the sensation of heaviness from overeating and ensures that protein is not degraded as a source of energy. The best snack for physically active people with a delicate stomach is liquid and semi-liquid foods (mixed drinks, jellies, puddings).

An example of a pre-workout snack (about 1 hour before starting):

- Fruit smoothie or fruit salad.
- Low protein bread jam sandwich with milk substitute (vegetable drink).
- Low protein bread with fruit juice.

It is important to drink 1-2 glasses of water before training. Furthermore, it is important to note that high-fibre (a large portion of fruit or vegetables) and/or high fat meals when consumed shortly before physical activity, can cause discomfort and negatively affect the quality of the exercise or participating in competitions, and should therefore be avoided.

3. During training

When performing physical exercise for over one hour, it is advisable to add a portion of 30-60 g of carbohydrates[15]. Furthermore, consuming an isotonic drink that contains 6-9% of different types of sugars (without aspartame) is recommended every 15-20 min.

4. Post-training meal

After exercise, the body needs to replenish fluids, replenish muscle glycogen stores and provide a dose of protein for muscle protein synthesis. It is advisable to consume 15-25 g of protein in the form of a PKU-specific protein substitute, with a carbohydrate-rich food or a protein substitute that is also carbohydrate-rich. This amount can be higher (up to 40 g protein equivalent), when carrying out high intensity strength training, especially that focused on building muscle mass.

In practice, this would mean having a small snack immediately after exercise, followed by a full, healthy meal, including a portion of protein substitute for PKU, within one hour after ending the exercise session. Providing an adequate post-exercise meal replenishes carbohydrate loss and makes for swifter recovery in preparation for subsequent activities.

An example of a snack immediately after training:

1) Post-aerobic training:
    - Fresh fruit.
    - Natural fruit juice.
    - Aspartame-free isotonic drink.
2) Post strength training (up to 1 hour after finishing) and depending on each patient's requirements (taking into consideration body composition and volume of strength exercise performed):
    - Shake with fresh fruit or natural fruit juice + protein substitute of 20 g PE or 10 g PE.
    - Protein substitute of 20 g PE or 10 g PE containing carbohydrates.
    - Aspartame-free isotonic drink + 20 g PE or 10 g PE protein substitute.

Table 5 below shows an example of a post-workout meal (up to one hour after the end of training) for both aerobic and strength training.

TABLE 5. Example of post-workout meal

	Completed with PKU-specific protein substitute*	
Meal idea	**Post-aerobic workout**	**Post-strength workout**
Salad and baked potato with vegetable skewer	Protein substitute specific for PKU of 20 g PE	a) A PKU specific protein substitute of 20 g PE + one of 10 g PE (30 g PE) b) Two PKU specific protein substitutes of 20 g PE (40 g PE)
Sautéed vegetables and rice	Protein substitute specific for PKU of 20 g PE	a) A PKU specific protein substitute of 20 g PE + one of 10 g PE (30 g PE) b) Two PKU specific protein substitutes of 20 g PE (40 g PE)
Low-protein pasta salad and vegetables with herb dressing	Protein substitute specific for PKU of 20 g PE	a) A PKU specific protein substitute of 20 g PE + one of 10 g PE (30 g PE) b) Two PKU specific protein substitutes of 20 g PE (40 g PE)
Vegetable cream with croutons, rice, pasta and potato within Phe-tolerance or using low-protein products	Protein substitute specific for PKU of 20 g PE	a) A PKU specific protein substitute of 20 g PE + one of 10 g PE (30 g PE) b) Two PKU specific protein substitutes of 20 g PE (40 g PE)

**Quantity depending on each patient's requirements, taking into consideration body composition and volume of strength exercise performed.*

5. Helpful tips

- Plan and prepare meals in advance, e.g. the day before. This will save time, ensure that the nutritional requirements are met swiftly, during and after training, and avoid macro- and micronutrient deficiencies.
- A well-nourished and hydrated body performs better physically. To achieve this, it is a good idea to write down a daily schedule, taking into account the training time and the distribution of the individual meals and protein substitute portions.

- Fresh meals can be stored in the refrigerator for two to three days. There are also certain foods that can be frozen, such as low-protein bread, and even some that can be bought already frozen, such as vegetables.
- Full meals can be prepared using fresh food and stored in the refrigerator for two or three days, or they can be frozen. One tip is to attach a label describing the contents of each container when freezing meals. It is advisable to include the estimated amount of protein or Phe content on the label.
- Certain foods, such as low-protein pasta, low-protein rice substitute or vegetables, can be baked or boiled and used throughout the week.

Characteristics of exercise prescription in PKU

PHYSICAL ACTIVITY IN PKU

In 21st century society, physical activity and physical exercise have become an essential health tool for every type of population. Sedentary lifestyles and physical inactivity underlie the most prevalent pathologies in developed societies.

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles that requires energy consumption[24]. The energy consumption associated with each PA will depend mainly on the type of activity, its duration, and its intensity. We generally distinguish between four areas: occupational, domestic, transport and recreational.

The World Health Organisation[25] regularly establishes a series of recommendations on physical activity and the fight against sedentary lifestyles. The current WHO recommendations as of December 2020 can be found in **figure 1**. The PKU population should, at a minimum, reach these targets. For the adult population, moderate-to-vigorous physical activity lasting 150 min/week results in a significant reduction of the risk of such diseases as diabetes, cancer, dementia, cardiovascular disease and osteoporosis.

Based on whether or not a person complies with WHO PA recommendations, we can differentiate between people who are active from those who are inactive. Any level of PA is beneficial to health and the subjects who are more active will gain greater benefits than those who do not reach the recommended level of PA.

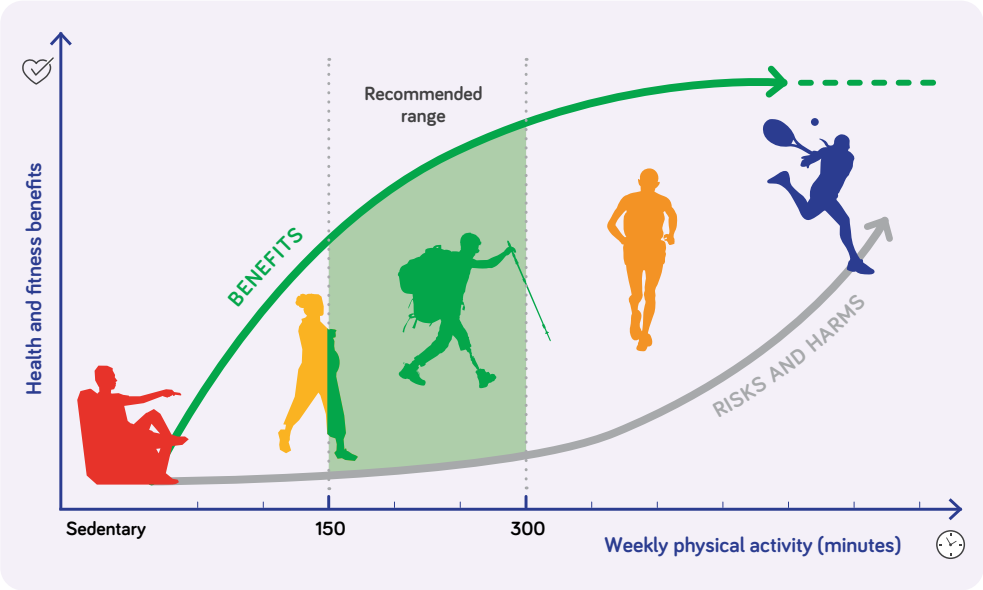


FIGURE 1. WHO recommendations for physical activity and combating sedentary lifestyles (2020)[25].

There is also scientific evidence that regular physical exercise, defined as planned, structured, repetitive and purposeful PA[24], is effective in preventing and treating up to 26 non-communicable diseases, including depression, anxiety, dementia, obesity, diabetes, metabolic syndrome, hypertension, osteoarthritis, osteoporosis and cancer[26].

Until the late 20th century, physical fitness was considered a marker of physical performance solely within the field of sports and high-performance sport. Physical fitness, defined as "the ability to carry out daily tasks with vigour and thoroughness, without undue fatigue, and with ample energy remaining to enjoy leisure-time pursuits and to meet unforeseen emergencies"[24] is one of the most important markers of health in the populations of developed countries. Both the level of cardiorespiratory fitness and muscle strength and power have been shown to be determining markers of the present and future health of any type of population[27,28] (**figure 2**).

Physical activity and interventions with exercise **training programmes** and nutrition have been shown to be highly effective in delaying functional losses due to sedentary lifestyles and ageing[29].

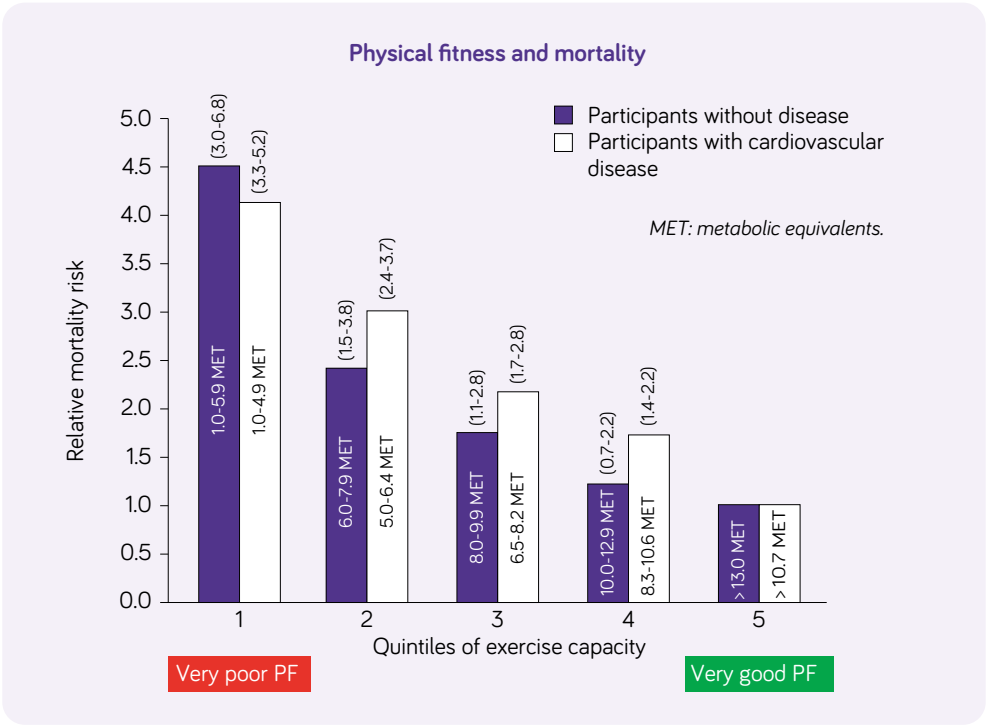


FIGURE 2. Physical fitness (PF) and mortality. *Adapted from Myers et al. 2002*[28].

In the **proposal for physical exercise in individuals with PKU** it should be noted that:

- PKU does not imply any limitation on physical training or sports practice.
- The sooner the physical exercise programme starts, the greater the chances of success.
- The physical exercise programme is safe, even for those who have no experience with physical exercise programmes and have a very low functional capacity.
- It is necessary to work with their environment to get them to exercise. Their doubts need to be cleared up and their confidence gained. Lack of adherence to the programme is a risk that must be addressed.
- Each subject must start from his or her initial condition and make gradual progress. Start off slowly, there will be time to improve!
- The exercise programme will be implemented for those subjects who have been assessed and evaluated by specialists and nutritionists.

- Take into account the interaction between any pharmacological treatment they may be receiving and the physical exercise itself.
- Assess the overall situation of the subjects and not only their PKU diagnosis.
- Approach the intervention from a multidisciplinary perspective throughout the functional conditioning process.

Precautions and limitations:

- Good interdisciplinary coordination (especially with nutritionists) and with the environment when managing subjects with PKU.
- Should any of these symptoms arise during the physical exercise programme, they must halt immediately and consult a specialised physician:
  - Increased shortness of breath.
  - Chest pain appears or increases.
  - Palpitations or sudden changes in heart rhythm appear.
  - Dizziness.
  - Reduced ability to exercise.
  - Sudden changes in vision.
- Whenever in doubt, stop and consult.

Some of these symptoms often occur during the physical exercise programme:

- Delayed Onset Muscle Soreness (DOM). When beginning, it is normal for some minor discomfort to appear, especially muscular discomfort. It will disappear as the subject adapts to the exercise.
- Shortness of breath. This is a normal response when starting moderately intense exercise. It is advsable to start at a lower intensity so this is less of an issue.
- Fatigue will be felt after the sessions. This is normal.

The patient's functional capacity, ability to understand, development of concomitant illnesses, communication skills, comfortable surroundings and other medical considerations should be individualised.

The **goal is to achieve the greatest functionality** possible[25]:

- Prevent PKU subjects from developing or worsening their sarcopenia.
- Achieve a sound functional balance.
- Improve muscular **strength and power**, especially of the lower limbs.

- Increase self-confidence for daily activities which will result in increased physical activity.
- Achieve the highest possible adherence to the physical exercise program.
- Implement a physical exercise programme in their daily activities.
- Secure improvements in all health-related aspects of physical fitness.
- Ensure that patients carry out their daily activities without fear and without undue fatigue, maintaining and improving their functional capacity and independence.

PHYSICAL FITNESS ASSESSMENT

Insofar as possible, the exercise programme should be adapted to the characteristics, needs and objectives of each individual. It is important to try to form a preliminary assessment of their initial functional status using simple tests that can be carried out in the consultation room or wherever the intervention is to be performed.

- Assess weight and **body composition**. **Electrical bioimpedance** may be an appropriate method to assess progress.
- Assessment of **cardiorespiratory capacity**: Astrand bench test.
- **Isometric strength** of upper limbs: manual dynamometry (handgrip).
- **Strength** of lower limbs:
  - Under 18 years old: long jump with feet together
  - Adults: Chair stand test: 5 repetitions.

Periodic checks will be carried out (3 months, 6 months or a year) to assess the response to the programme and to reschedule the workloads.

1. Cardiorespiratory assessment: Astrand step test

The Astrand test[30] indirectly determines the **maximal oxygen consumption** (maximal aerobic power or VO_2max).

- **Equipment needed:**
  - 33 cm bench or step for women and 40 cm for men.
  - Metronome.
  - Band and watch to measure heart rate.
  - Chronometer.

- **Procedure:**
  - The subject must stand in front of the step.
  - The participant must step onto and off a 33 cm for women and 40 cm for men in four steps; this consists of raising one foot/raising the other foot/ lowering one foot and lowering the other foot.
  - The pace is set for 5 minutes at 22.5 complete cycles/min; measured by a metronome at 90 beats/min, and each metronome beat corresponds to one movement.
  - As soon as the test ends, the heart rate is measured with the band placed around the subject's chest or by measuring the HR in the radial pulse, to calculate the VO_2max using the Astrand Nomogram (figure 3).
  - It is performed in one go.
  - Environmental parameters such as the temperature should be monitored as they may influence the results. The test shall be performed in a comfortable, quiet environment, with a temperature between 18-23 °C.

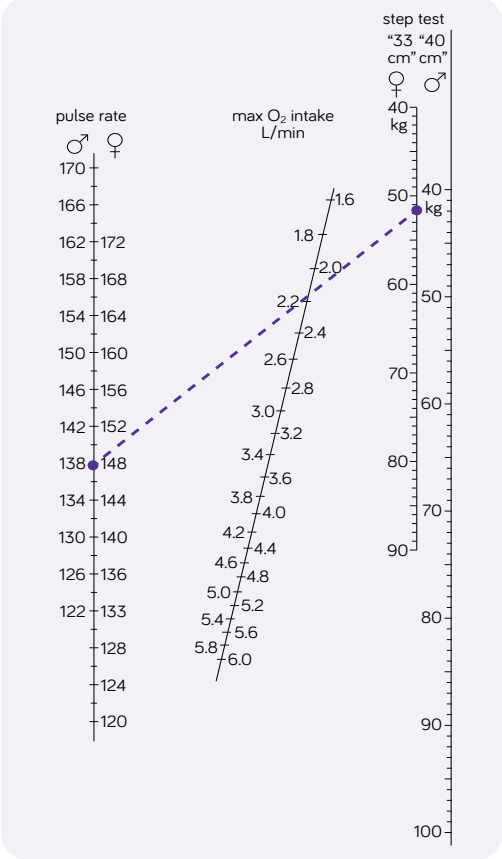


FIGURE 3. Astrand Nomogram.

The value marked on the oblique line of the Nomogram represents the absolute value of the subject's maximal oxygen consumption at maximum effort. To obtain the relative value of VO_2max (L/min), the absolute VO_2 figure is divided by the weight of the subject. The age of the participant must be taken into account to make the corrections shown in **table 6**.

TABLE 6. Correction factor based on age

Age	Factor
15	1.10
25	1.00
35	0.87
40	0.83
45	0.78
50	0.75
55	0.71
60	0.68
65	0.65

Example. *A 15-year-old girl weighing 52 kg and with a heart rate of 148 bpm at the 5th minute of the test, what is her VO_2max?*

- *At the cut-off with the oblique line it is 2.2 L/min. If the age is 15, it should be multiplied by 1.10 (which corresponds to the age correction factor, **table 6**), so the age-corrected VO_2max estimate would be:*

$$2.2\ L/min \times 1.10 = 2.42\ L/min$$

- *The value shown on the Astrand Nomogram (**figure 3**) is in L/min and, as shown in the table of reference values, the units in which it is expressed are in mL/kg/min, so we should change from L/min to mL/min and, depending on the weight, it would be:*

$$(2.41\ L/min \times 1.000\ ml)/52\ kg = 46.5\ mL/kg/min$$

There are formulas in the literature that allow us to calculate VO_2max using the results of the Astrand test. Song et al.[31] propose the following:

- Men: VO_2max (L/min): $3.744 \times [(PC + 5)/(HR - 62)]$
- Women: VO_2max (L/min): $3.750 \times [(PC - 3)/(HR - 65)]$

In the example above:

$$VO_2max\ (L/min): 3{,}750 \times [(52 - 3)/(148 - 65)] = 2{,}21$$

The age correction factor must be applied to this result. As can be seen, the results are similar (2.2 vs. 2.21 L/min).

The results obtained are contrasted with the reference values (table 7). In this case, the subject evaluated would have a very good cardiorespiratory condition.

TABLE 7. Reference values. VO_2max classification by age group and gender

	Men VO_2max (mL/kg/min)					Women VO_2max (mL/kg/min)				
Age (years)	Low	Very low	Medium	Good	Very good	Low	Very low	Medium	Good	Very good
< 20	< 39	40-43	44-46	47-49	> 50	< 34	35-37	38-40	41-44	> 44
20-29	< 37	38-41	42-44	45-48	> 49	< 31	32-34	35-37	38-41	> 42
30-39	< 35	36-39	40-42	43-47	> 48	< 29	30-32	33-35	36-39	> 40
40-49	< 33	34-37	38-40	41-44	> 45	< 27	28-30	31-32	33-36	> 37
50-59	< 30	31-34	35-37	38-41	> 42	< 24	25-27	28-29	30-32	> 33
> 60	< 26	27-30	31-34	35-38	> 39	< 23	24-25	26-27	28-31	> 32

2. Isometric strength of upper limbs: manual dynamometry (handgrip)

Manual dynamometry is a method of assessing isometric handgrip strength. It is a commonly used method in daily clinical practice as validated and standardised reference values exist for all populations (table 8) and it is very easy to perform in a short time.

- **Material:** dynamometer (figure 4).
- **Procedure:**
  - Stand upright and extend the arm holding the dynamometer.
  - The arm is held slightly away from the body with the screen of the device facing the examiner.
  - The handgrip of the device will be adjusted to the hand of the subject, so that the second phalanx of the middle finger is approximately at a right angle.
  - The examiner performs a prior demonstration.
  - Before the test is carried out, time shall be allowed for the participant to familiarise himself with the dynamometer.

- No exertional movements (such as tugging with the arm or body) are permitted.
- The subject shall press firmly and progressively, finally squeezing the grip of the dynamometer with all their strength for 3-5 seconds.
- Three attempts shall be made alternately with each hand, allowing one minute's rest between each hand.

TABLE 8. Reference values for manual dynamometry (right + left)

Age ranges (years)	15-19		20-29		30-39	
Sex	M	W	M	W	M	W
Good	103-112	64-70	113-123	65-70	113-122	66-72
Average	95-102	59-63	106-112	61-64	105-112	61-65
Below average	84-94	54-58	97-105	55-60	97-104	56-60
Very low	≤ 83	≤ 53	≤ 96	≤ 54	≤ 96	≤ 55
Age ranges (years)	**40-49**		**50-59**		**60-69**	
Sex	**M**	**W**	**M**	**W**	**M**	**W**
Good	110-118	65-72	102-109	59-64	98-101	54-59
Average	102-109	59-64	96-101	55-58	86-92	51-53
Below average	94-101	55-58	87-95	51-54	79-85	48-50
Very low	≤ 93	≤ 54	≤ 86	≤ 50	≤ 78	≤ 47

**Values used by the Canadian Society for Exercise Physiology and the American College of Sports Medicine. Sum of right + left values. M: man; W: woman.*

FIGURE 4. Dynamometry.

3. Lower limb strength

For under 18 years: long jump, feet together, and for adults: chair stand-up test, 5 repetitions.

3.1. Long jump feet together. Children under 18 years (figure 5)

- **Material:**
  - Line on the floor.
  - Tape measure.
- **Procedure:**
  - Starting position: the subject stands upright with feet slightly apart and toes behind the starting line.
  - Performance: the subject must take gain momentum by bending their legs and pushing forward with their arms from behind. They jump by quickly extending the legs and stretching their arms forward.
  - Finish: at the moment of falling, the subject must keep their feet in the same place where they made contact with the ground without losing balance.

Assessment of the test: the distance in centimetres is recorded. The better of the 2 results must be recorded.

FIGURE 5. Long jump feet together.

TABLE 9. Reference values for long jump (cm)

Girls	P10	P20	P30	P40	P50	P60	P70	P80	P90	P100
13 yr	116.0	125.2	132.0	137.7	143.2	143.2	148.6	154.4	161.3	170.9
14 yr	117.5	127.1	134.2	140.3	146.1	146.1	152.0	158.3	165.8	176.4
15 yr	122.1	131.7	138.8	144.9	150.8	150.8	156.8	163.3	171.1	182.1
16 yr	124.9	134.0	140.8	146.7	152.3	152.3	158.0	164.3	171.7	182.3
17-18,5 yr	121.8	130.5	136.9	142.5	147.8	147.8	153.2	159.0	166.0	175.8
Boys	**P10**	**P20**	**P30**	**P40**	**P50**	**P60**	**P70**	**P80**	**P90**	**P100**
13 yr	134.3	146.6	155.2	162.4	168.9	168.9	175.3	182.1	189.8	200.3
14 yr	146.3	159.3	168.3	175.8	182.6	182.6	189.2	196.2	204.2	215.0
15 yr	158.3	171.6	180.7	188.2	195.0	195.0	201.7	208.6	216.5	227.2
16 yr	168.0	180.7	189.4	196.5	202.9	202.9	209.2	215.6	223.0	232.9
17-18,5 yr	171.2	182.9	190.9	197.5	203.4	203.4	209.1	215.0	221.8	230.8

yr: years.
Interpretación: values < 40th percentile are considered low, 40-60 average and > 60 high.
Adapted from: Ortega et al (2005)[32].

3.2. Chair stand test: 5 repetitions. Subjects over 18 years (figure 6)

- **Material:**
  - Chair of known height (generally 40-50 cm).
  - Chronometer.
  - There is an APP (Powerfrail) application for Android/iOS that performs the calculations automatically by filming the test with the smartphone camera or by entering the data manually.

- **Procedure:**
  1. The subject is seated with arms crossed over the chest (this is how they should remain for the duration of the test).
  2. Perform 5 repetitions (stand up and sit down on the chair) as fast as they can, but make sure they fully straighten their knees when standing up and at least touching the chair with the buttocks when sitting down.
  3. Record the time taken in tenths of a second. If filming with the camera, record from the "read" signal until 5 repetitions have been completed.
  4. Verbally encourage the subject during the performance of the test.
  5. It is advisable to do two repetitions and stay with the best result.

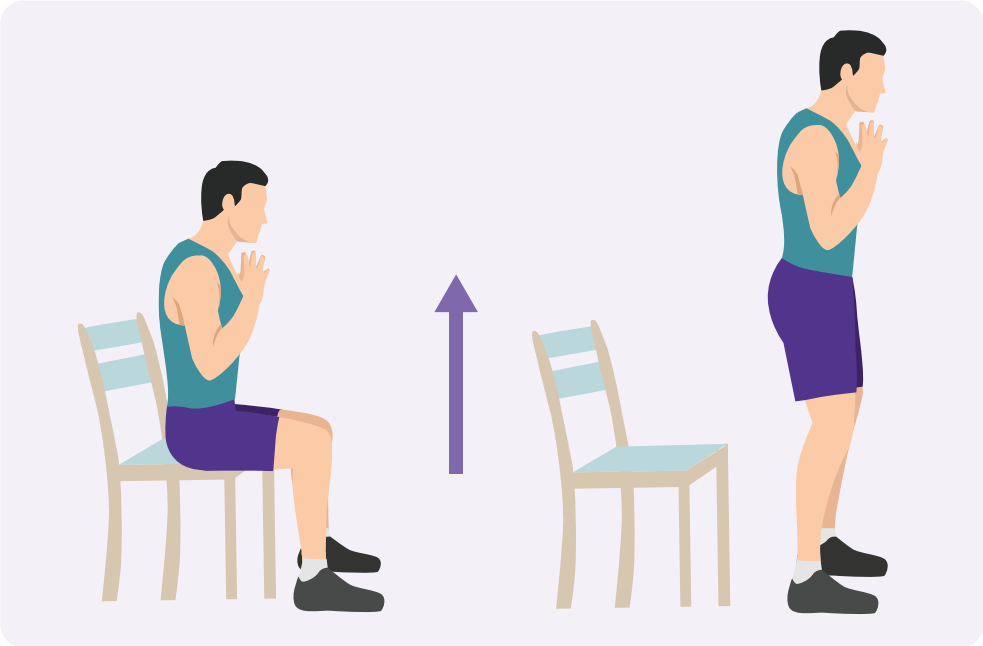


FIGURE 6. Chair stand test, 5 times.

TABLE 10. Reference values of 5 repetitions (s). Chair height 48 cm

	20-39 years		40-59 years		> 60 years	
	Man	Woman	Man	Woman	Man	Woman
Good	< 4,44	< 4,44	< 5,98	< 5,98	< 8,23	< 9,00
Medium	4,45-5,98	4,45-5,60	5,98-7,52	5,98-7,03	8,23-10,46	9,00-10,98
Low	5,99-8,7	5,61-9,30	7,53-9,06	7,04-9,31	10,47-11,85	10,99-13,36
Very low	> 8,8	> 9,31	> 9,07	> 9,31	> 11,85	> 13,36

Adapted from: Klukowska AM et al.[33].

Once the tests have been assessed, the subjects can be classified as follows:

a) Low functional ability or with significant limitations.
b) Average functional capacity or with slight limitations.
c) High functional capacity and no limitations.

GENERAL ISSUES TO BE CONSIDERED WHEN PRESCRIBING PHYSICAL EXERCISE

Physical training programmes that take place outside the home require facilities, specific equipment and a two- or three-day-week trip to the facility. This model can be chosen If the circumstances are favourable, but in other cases it is difficult to achieve good adherence to a physical exercise programme. Therefore, a guided home-based physical exercise programme is proposed based on the physical fitness tests performed. If the subjects have a sports facility available they can perform a mixed programme (at home and at the facility).

A physical exercise programme with strength and power training, cardio-respiratory fitness, **neuromotor exercise** (**balance, coordination, posture and proprioception**) and **flexibility** would be most appropriate, adapted to each subject's age and characteristics.

All training components (strength, power…) will increase in volume and intensity depending on individual responses and adaptations. Preference will be placed on work on the lower limbs. The full range of movement is worked on with no pain.

- **Frequency:**
  - Muscle strength and power: 3 sessions per week on alternate days.
  - Neuromotor and flexibility: 2 to 4 days.
  - Cardiorespiratory (C-R): carry out in all sessions for 10-20 min. Try to increase the actions in day-to-day life and where possible use an exercise bike, pedals or similar.
- **Type:** Multicomponent and cardiorespiratory exercise.
- **Intensity:** Light, moderate, intense depending on the results of their functional capacity (low, medium, high). As a general rule, start with low intensity training adapted to the patient's condition.
- **Strength:** Start with workloads that the subject can perform for 20 repetitions correctly and without interruption, noting that they are making an effort towards the end. The **Rate of Perceived Exertion** (RPE) or Borg scale 1-10 can be used (2-3 light-easy, 4-5 moderate-somewhat hard, 6-7 intense-hard) (see **table 15**). Progressively increase the load.
- **Neuromotor:** Gradually increase the difficulty with unstable bases, proprioception, dual tasks, etc.
- **Cardiorespiratory (aerobic):** Start at 35-40% of reserve heart rate (3-4 on the **Borg scale**, 3 METs), increase to 60-70% of reserve heart rate (6-7 on the Borg scale, 5-6 METs). Include coordination and mobility work. Also consider **interval training**.

- **Duration:** Physical exercise sessions will last between 20 and 60 minutes. More complicated patients or those with a greater functional deficit will start with 10-15 minutes and gradually increase the duration of the sessions.
- **Volume:**
  - **Strength:** 1-3 sets of 10-15 repetitions. All muscle groups, and the lower limbs in particular.
  - **Cardiorespiratory (aerobic):** 10-30 min per session. Start with 5-10 min at your normal walking pace, rest 30-60 seconds and walk a further 5-10 minutes. Gradually increase the walking time. The objective would be to reach 3 sessions of 30 minutes' moderate-intense intensity and/or to exceed 150 minutes per week.
  - **Neuromotor and flexibility:** 1-2 sets of 4-10 different exercises with a progressive increase in difficulty.
- **Supervision:** during the checks carried out during the doctor's and/or nutritionist's visits.

TABLE 11. General exercise prescription

	Cardiorespiratory	Strength	Neuromotor	Flexibility
Frequency	3-5 days/week	2-3 days/ week	2-3 days/ week	2-3 days/week
Intensity	– Light: RHR: 35-40%; RPE 3-4. METs: 3 – Moderate: RHR: 50%; RPE: 5-6. METs: 4-5 – Intense: RHR 60%; RPE 7. METs: 6-7	Start below 30% 1RM, and slowly progress. RPE 2-3	Not established	Movements throughout entire joint range
Time	20-30 min/session 150 min/week if moderate or 75 min/ week if intense	At least one sets of 10-15 repetitions	20-30 min	10-30 s static stretching of the main muscle groups
Type	Prolonged and rhythmic activities (walking, exercise bike, pedalling…)	Free weights or functional exercises	Balance, coordination, posture, agility and proprioception activities	Stretching of all muscle groups, according to individual limitations

RHR: reserve heart rate; 1RM: 1 maximum repetition; RPE: rate of perceived exertion or Borg scale (1-10).

I. Cardiorespiratory (CR). Light-moderate-vigorous

The following guidelines can be used as a reference:

Percentage of reserve heart rate (Karvonen).

- Light training HR (40%) = [(Theoretical HR max − resting HR) × 0.4] + resting HR.
  For a 30-year-old person and RHR 60 bpm:
  [(220−30) − 60) × 0.4] + 60 = 112 ppm; Borg-RPE: 3-4; 3 METs
- HR moderate training (50%) = [(Theoretical HR max − resting HR) × 0.5] + resting HR.
  For a 30-year-old person and RHR 60bpm:
  [(220−30) − 60) × 0.5] + 60 = 125 ppm; Borg-RPE: 6-7; 4-5 METs
- HR vigorous training (60%) = [(Theoretical HR max − resting HR) × 0.6] + resting HR.
  For a 30-year-old person and RHR 60 bpm:
  [(220−30) − 60) × 0.6] + 60 = 138 ppm; Borg-RPE 8; 6-7 METs

Let us remember that there are other methods to obtain the Theoretical HR max, such as Tanaka's formula [208 − (0.7 × age)].

Example for a 14-year-old boy with a resting HR of 55 bpm, who has to train at 60% RHR = [([208 − (0.7× 14)] − 55) × 0.6] + 55; which would be 141 bpm.

II. Strength training

The usual method of choice for overloaded work would be to program the intensities as a percentage of 1MR (light 30% 1MR; moderate 40% 1MR; vigorous 50% 1MR).

When it is not possible or appropriate to calculate 1MR, it may be useful to use the number of repetitions, so you can check the load with which you can do 30 repetitions. With this load, light intensity sessions would be performed. The load with which they can perform 20 repetitions would be appropriate for moderate and vigorous intensities. Currently, another way of indicating the intensity of the effort which is somewhat more precise is in relation to the repetitions in reserve (RIR), which has to do with the capacity we have remaining until we can no longer carry out more repetitions. This therefore allows a high degree of individualisation at any stage. Lastly, probably the simplest, but also the least accurate way is the use of the Borg-RPE (1-10) subjective effort scale using graphical scales. (Omni-Scale).

To facilitate making the prescription, the following chapter sets out a schedule according to gender, age and fitness level.

Specific training planning for PKU children, adolescents and adults

A specific training programme is proposed for children, adolescents and adults on the assumption that they are individuals with low levels of physical activity and physical fitness, and that they are not involved in any regular sports practice.

The main recommendation, especially during childhood and adolescence, would be for them to adopt some form of sport, or even combining several (team or individual sports), in which case with 3-4 days a week practice, many of these desired exercise requirements in this programme would already be met.

With this planning we seek to propose a generic programme as a progression guide, in which some parameters afford us a certain range of individualisation, but more specific results can always be obtained by having a professional attending to an individualised progression for each patient.

The training focuses on cardiovascular endurance and strength, the most complex parameters to work on and those that currently show the greatest link with health.

Should the maximum levels of training load proposed here in this programme result in low perceived effort, other types and levels of training should be adopted, and again, bespoke guidance by professionals ensures that the training is appropriately adapted.

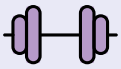
SPECIFIC PRESCRIPTION BY THE HEALTH PROFESSIONAL

Depending on the level of cardiorespiratory fitness and muscular strength, 3 levels are established according to the assessment obtained during the evaluation. Remember that the percentiles proposed are those generally used in health care, based on the reference values for adolescents[30] or adults[32] (see **tables 7** and **9**):

- Low (percentile ≤ 40)
- Medium (percentile 40 ≤ 60)
- High (percentile > 60).

The individual's level sets the prescription guideline, which is summarised in **table 12**. Here we see how for each level of cardiorespiratory fitness or strength the patient is assigned a starting level, and according to each level, progression options (A, B or C) are established depending on how close or far the patient is from that 40th percentile. If, for example, the level estimated with the tests carried out is low, i.e. it is below the 40th percentile, but the patient is very sedentary and far from the target, they will start at the low level and progression A; when the person presents a perception of exertion for that level between 1 and 4, they can progress to level low-B, and so on progressively from subjective effort between 1 and 4 at low-C level, or after having repeated the assessment tests is above the 40th percentile, they will progress to the medium level and so on.

TABLE 12. Prescription algorithm for cardiorespiratory and strength training

Physical fitness component	Level	Progression	Progression criteria
Cardiorespiratory 	Low (Percentile ≤ 40)	A	RPE 1-2 ☺
		B	RPE < 2 ☺
		C	RPE < 2 ☺ or exceed percentile 40
	Medium (Percentile 40 ≤ 60)	A	RPE < 4 ☺
		B	RPE < 4 ☺ or exceed percentile 60
	High (Percentile > 60)	A	RPE < 6 ☺
		B	RPE < 6 ☺ or exceed percentile 85
Strength 	Low (Percentile ≤ 40)	A	RPE < 2 ☺
		B	RPE < 4 ☺
		C	RPE < 8 ☺ or exceed percentile 40
	Medium (Percentile 40 ≤ 60)	A	RPE < 2 ☺
		B	RPE < 4 ☺
		C	RPE < 8 ☺ or exceed percentile 60
	High (Percentile > 60)	A	RPE < 2 ☺
		B	RPE < 4 ☺
		C	RPE < 8 ☺ or exceed percentile 85

Cardiorespiratory fitness or strength level (low, medium or high) according to the established percentiles (see Tables 7 and 9); proposed progression (A, B or C) within each level and criteria for progression or level progression. RPE: rate of perceived exertion.

The following describes how to organise training, an exercise pattern that aims for specific results, is more complex than a mere activity-related advice and therefore requires proper planning and progression according to the individual. We will explain step by step what, how many days, when and at what intensity we should exercise according to age and gender, and how to progress in our training as we improve. To stay on track during this process and to make proper use of all the resources contained in this guide, we can use this algorithm (figure 7).

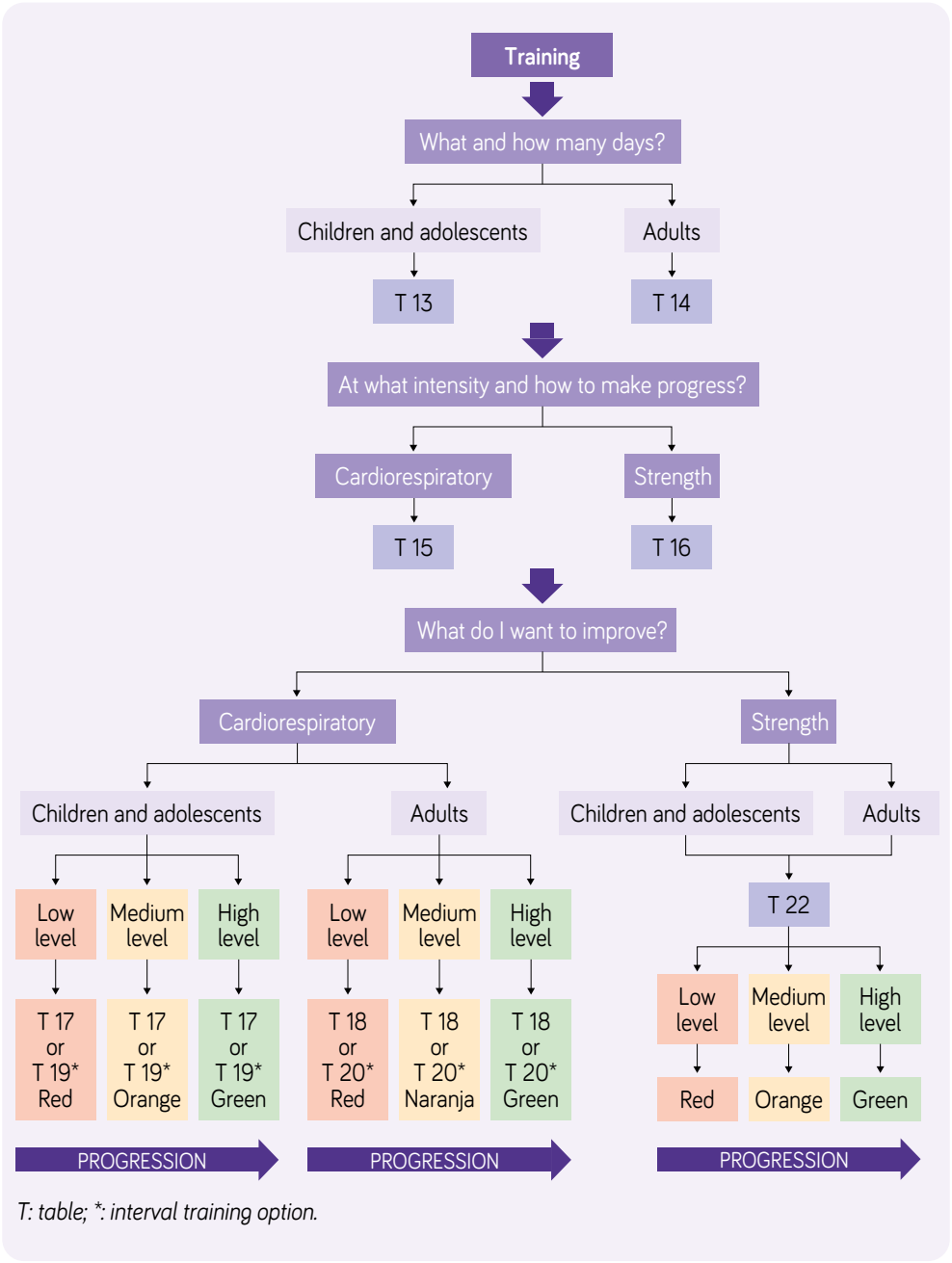


FIGURE 7. Algorithm of resource use to organise training according to age, gender and fitness level.

WHAT AND HOW MANY DAYS TO TRAIN?

The distribution of the type of training to be done and the days of the week on which they are done are specified for children and adolescents in **table 13**, and for adults in **table 14**.

TABLE 13. Weekly training table for children and adolescents

Weekly training for children and adolescents					
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday/Sunday**
CR	Interval CR	CR	Interval CR	CR	Leisure activities involving physical activity are recommended. Matches and competitions are also often hosted on these days. One of the strength sessions could be moved to the weekend.
S		S		S	
Other complementary daily recommendations					
Maintain low levels of sedentary time					
Maintain active travel habits					
Engaging in sports activity is recommended					

CR: cardiorespiratory; S: strength.

For the child and youth population group the aim is to be at least moderately active **1 hour a day including at least 3 days focusing on muscle and bone strengthening**[23]; this can be achieved in many ways. Here we propose specific training for 5 days, 3 of which should combine cardiorespiratory and strength training, 2 days dedicated to cardiorespiratory interval training (by sets) seeking out different stimuli, higher intensity and shorter duration of training, and the other two to other recreational physical-sports activities.

Similarly, training for adults is organised in **table 14**, which in their case requires at least 2 days combining cardio-respiratory and strength training, two additional days of cardio-respiratory only and the rest leisure activities totalling at least 30 minutes of moderate/vigorous intensity each day.

TABLE 14. Weekly training for adults

Weekly training for adults					
Monday	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday/Sunday**
CR	Interval CR		CR	CR	Recreational activities involving physical activities are recommended. The Thursday strength training could be moved to the weekend.
	S		S		
Other complementary daily recommendations					
Maintain low levels of sedentary time					
Maintain active travel habits					
Engaging in sporting activity is recommended					

CR: cardiorespiratory; S: strength.

HOW IS THE INTENSITY LEVEL SET?

All exercise load/dosage values are adjusted according to the reference values for adolescents[30] or adults[32].

There are numerous ways of assessing both the effort involved in an exercise load and of proposing the dose (intensity of the load that a given effort must have) for the specific target as designed.

These forms of assessment may vary in simplicity or sophistication, thus providing greater or lesser precision in the prescription; and some of them are also specific to cardiorespiratory training (table 15) or strength training (table 16). Several of these equivalent ways of identifying intensity are included in the tables below, so that the user can choose from among the different options that which best suits their needs, knowledge or technical equipment.

However, for monitoring by the patient we could consider that the rate of perceived exertion (RPE) is the simplest and most useful for both training (cardiorespiratory or strength). In any event, other specific variables that may be useful for professionals are also presented.

Intensity and progression in cardiorespiratory endurance training programme

TABLE 15. Equivalent forms of intensity assessment or indication for cardiorespiratory training

	Intensity	RPE (1-10)	% HRmax	% RHR	METs	Equivalence progression level CRF	When progress?
Mild ☺	Very light	1-2	< 57%	< 30%	< 3	A	2 weeks
	Light	3-4	57-64%	30-39%	3-4,9	A	RPE 1-2
Moderate-hard 😐	Moderate	5-6	64-75%	40-59%	5-5,9	A-B	RPE < 4
	Vigorous	7-8	76-95%	60-89%	6-7	B-C	RPE < 6
Very hard ☹	Very vigorous	9-10	≥ 96%	≥ 90%	> 7	C	RPE < 8

CRF: cardiorespiratory fitness; RPE: rate of perceived exertion; % HRmax: maximum heart rate percentage; % RHR: reserve heart rate percentage; METs: metabolic equivalent.

See page 35 for information on calculating % RHR.

Note: all of them are equivalent and you can choose the one that best suits your needs, knowledge or technical equipment

Intensity and progression in the strength training programme

Intensity is mainly based on the rate of perceived exertion (RPE) and the repetitions in reserve (RIR) which is related to our remaining capacity until we can no longer do any more repetitions. This therefore allows for a high degree of individualisation at any stage. Although it is common to see strength training in which the intensity is calculated in relation to the 1RM, in this case it is not suitable because we do not work with external overloads, but with body weight, the % of RM requires measuring or calculating the 1RM for each exercise, which also renders it difficult to apply in unsupervised programmes. If the target RPE is not reached when performing the given number of repetitions, the patient should then increase or progress (increase resistance or number of repetitions) until the target RPE is attained for each strength and progression level. If necessary, especially in people with a high level of strength, some type of overload can be added to increase the resistance, either with weighted garments, elastics, dumbbells, kettlebells, etc.); again, in these cases, the supervision or direct programming by a professional will provide fuller guarantees.

Progression between training levels occurs when the load of the last sets is mild (going from A to B or from B to C) for our assessed level of strength. If, on the other hand, the work could not be completed or results in a very hard RPE, we should reduce the intensity (going from C to B or from B to A), until we reach the appropriate level of effort. Table 16 shows the progression.

TABLE 16. Different equivalent methods of assessing the intensity for strength training and indications for making progress

Mild	Moderate-hard	Very hard
☺	😐	☹
RPE 1-3	RPE 4-7	RPE 8-10
RIR 6	RIR 4	RIR 2
Increase	Maintain	Reduce

RPE: rate of perceived exertion; RIR: repetitions left in reserve.

Note: All of them are equivalent and you can choose the one that best suits your needs and knowledge.

CARDIORESPIRATORY TRAINING

Three levels are established according to the assessment of the cardiorespiratory fitness previously evaluated.

Planning considerations

- Cardiorespiratory exercise will be performed according to the FITT-VP parameters (frequency, intensity, type of activity and time of exercise, total exercise volume and progression) outlined below in tables 17 and 18. Additionally, interval training is provided in tables 19 and 20, for a more varied training.
- To estimate the intensity, the rate of perceived exertion (RPE), the percentage of the maximum or reserve frequency (HR) or metabolic equivalents (METs) will be used as explained above. When prescribed to the patient, the simplest way perhaps is to use RPE or percentage of maximum HR (if a heart rate monitor or similar is available).
- There is a wide range of types of activity for exercising to choose from, in accordance with ability and preference: walking, running, conventional or static cycling, swimming, etc. Especially during childhood and adolescence, it is advisable to adopt some form of sport, even combining several types (team or individual sports).

- If you have a heart rate monitor or a smart watch with a heart rate reader, you can adjust the intensity of your exercise using your maximum or reserve heart rate percentages. (see **table 15**).
- The type of activity can be varied even within the same week, but it is very important to achieve the target intensities and times.
- You can choose to incorporate cardiorespiratory interval training (**tables 19** and **20** for young people or adults, respectively).

TABLE 17. Cardiorespiratory fitness training in children and adolescents

CF level	Progression level	Activity	Sets	Rep	Option to choose	Intensity	Duration	Recovery
Low	A	Running, cycling, swimming, etc.	1	10		Light RPE 3-4 40% RHR	1 min	30" active Very light between rep
	B		1	20		Light RPE 3-4 40% RHR	1 min	30" active Very light between rep
	C		1	10		Moderate RPE 5-6 50% RHR	2 min	30" light (RPE 3-4) between rep
Medium	A	Running, cycling, swimming, etc.	2	6		Moderate RPE 5-6 50% RHR	2 min	30" light (RPE 3-4) between rep/ 3 min between sets
	B		2	5	Op A	Moderate RPE 5-6 50% RHR	3 min	15" light (RPE 3-4) between rep/ 2 min between sets
			2	5	Op B	Vigorous RPE 7-8 60% RHR	4 min	Active 2 min at light intensity (RPE 3-4)

(Continues)

TABLE 17 *(Cont.)*. Cardiorespiratory fitness training in children and adolescent

CF level	Progression level	Activity	Sets	Rep	Option to choose	Intensity	Duration	Recovery
High	A	Running, cycling, swimming, etc.	3	5	Op A	Moderate RPE 5-6 50% RHR	4 min	15" light (PES 3-4) between rep/ Active 2 min at light intensity (RPE 3-4)
			2	5	Op B	Moderate-Vigorous RPE 6-7 60% RHR	5 min	Active 2 min at light intensity (RPE 3-4)
	B		3	6	Op A	Moderate-Vigorous RPE 5-7 50% RHR	4 min	15" light (RPE 3-4) between rep/ Active 2 min at light intensity (RPE 3-4)
			2	6	Op B	Vigorous RPE 7-8 70% RHR	5 min	Active 2 min at light intensity (RPE 3-4)

CF: cardiorespiratory fitness; RPE: rate of perceived exertion; % RHR: reserve heart rate percentage; rep: repetitions.

TABLE 18. Cardiorespiratory fitness training for adults

CF level	Progression	Activity	Sets	Option to choose	Intensity	Duration	Recovery
Low	A	Walking, cycling, swimming, etc.	1		Light 3-4 RPE 40% RHR	10 min	
	B		2		Light 3-4 RPE 40% RHR	10 min	3 min
	C		2		Moderate 5-6 RPE 50% RHR	10 min	3 min
Medium	A	Running, cycling, swimming, etc.	2		Moderate 5-6 RPE 50% RHR	12 min	3 min
	B		2	Op A	Moderate 5-6 RPE 50% RHR	15 min	2 min
			2	Op B	Moderate-Vigorous 7-8 RPE 60% RHR	12 min	Active 2 min at light intensity (RPE 3-4)
High	A	Running, cycling, swimming, etc.	2	Op A	Moderate 5-6 RPE 50% RHR	20 min	Active 2 min at light intensity (RPE 3-4)
			3	Op B	Moderate-Vigorous 7-8 RPE 60% RHR	10 min	Active 2 min at light intensity (RPE 3-4)
	B		2	Op A	Moderate 5-6 RPE 50% RHR	25 min	Active 2 min at light intensity (RPE 3-4)
			3	Op B	Moderate-Vigorous 7-8 RPE 70% RHR	15 min	Active 2 min at light intensity (RPE 3-4)

CF: cardiorespiratory fitness; RPE: rate of perceived exertion; % RHR: reserve heart rate percentage;

Cardiorespiratory interval training option

This is a short, high-intensity workout, so the speed to cover that distance in that time is equivalent to an intensity of 90-100% of the maximum heart rate calibrated in accordance with the cardiorespiratory fitness percentiles of the Spanish population.

This type of training should start with a general **warm-up** including joint mobility and light aerobic exercise for 5-10 minutes.

TABLE 19A. Interval cardiorespiratory training in children and adolescents

CF level	Age (years)	Activity	Sets	Rep	Distance	Duration	Rec rep	Rec sets
Women								
Low	≤ 15	Running	4	10	50 m	20”	20”	2 min
	> 15	Running	4	10	55 m	20”	20”	2 min
Medium	≤ 15	Running	4	10	55 m	20”	20”	2 min
	> 15	Running	4	10	55 m	20”	20”	2 min
High	≤ 15	Running	4	10	60 m	20”	20”	2 min
	> 15	Running	4	10	60 m	20”	20”	2 min
Men								
Low	≤ 15	Running	4	10	55 m	20”	20”	2 min
	> 15	Running	4	10	60 m	20”	20”	2 min
Medium	≤ 15	Running	4	10	60 m	20”	20”	2 min
	> 15	Running	4	10	65 m	20”	20”	2 min
High	≤ 15	Running	4	10	65 m	20”	20”	2 min
	> 15	Running	4	10	70 m	20”	20”	2 min

CF: cardiorespiratory fitness; Rep: repetitions; Rec: recovery.

Option B with further progression

TABLE 19B. Interval cardiorespiratory training in children and adolescents

CF level	Age (years)	Activity	Sets	Rep	Distance	Duration	Rec rep	Rec sets
Women								
Low	≤ 15	Running	4	10	40 m	15”	20”	2 min
	> 15	Running	4	10	40 m	15”	20”	2 min
Medium	≤ 15	Running	4	10	55 m	20”	20”	2 min
	> 15	Running	4	10	55 m	20”	20”	2 min
High	≤ 15	Running	4	10	70 m	25”	20”	2 min
	> 15	Running	4	10	75 m	25”	20”	2 min
Men								
Low	≤ 15	Running	4	10	45 m	15”	20”	2 min
	> 15	Running	4	10	50 m	15”	20”	2 min
Medium	≤ 15	Running	4	10	60 m	20”	20”	2 min
	> 15	Running	4	10	65 m	20”	20”	2 min
High	≤ 15	Running	4	10	80 m	25”	20”	2 min
	> 15	Running	4	10	85 m	25”	20”	2 min

CF: cardiorespiratory fitness; Rep: repetitions; Rec: recovery.

For adults, we propose that this training be done at maximum work power (interval) for two fundamental reasons: 1) cardiorespiratory adaptations are achieved with short training sessions, and, 2) this allows us to optimise the training day to incorporate the strength programme while maintaining the beneficial effects of concurrent training. For this reason, the speed to cover that distance in that time is equivalent to an intensity of 90% of the maximum aerobic power/maximum heart rate according to the reference values for cardiorespiratory fitness of the adult population.

This training could be adapted to cycling by maintaining the work times and the intensity of the effort at 90% of the maximum power in the interval.

This type of training should start with a general warm-up including joint mobility and light aerobic exercise for 5-10 minutes. If the effort load drops, it is probably due to training adaptations that result in cardiorespiratory improvements, which, once confirmed, allow us to progress to higher levels of training.

TABLE 20. Interval cardiorespiratory training in adults

CF level	Age (years)	Sets	Rep	Distance	Duration	Rec rep	Rec sets
Women							
Low	Up to 30	3	10	36 m	15”	20”	2 min
	30-40	3	10	34 m	15”	20”	2 min
	40-50	3	10	33 m	15”	20”	2 min
	50-60	3	10	28 m	15”	20”	2 min
Medium	Up to 30	4	10	54 m	20”	20”	2 min
	30-40	4	10	50 m	20”	20”	2 min
	40-50	4	10	48 m	20”	20”	2 min
	50-60	3	10	42 m	20”	20”	2 min
High	Up to 30	4	10	60 m	20”	20”	2 min
	30-40	4	10	57 m	20”	20”	2 min
	40-50	4	10	53 m	20”	20”	2 min
	50-60	3	10	48 m	20”	20”	2 min
Men							
Low	Up to 30	3	10	57 m	20”	20”	2 min
	30-40	3	10	56 m	20”	20”	2 min
	40-50	3	10	51 m	20”	20”	2 min
	50-60	3	10	47 m	20”	20”	2 min
Medium	Up to 30	4	10	63 m	20”	20”	2 min
	30-40	4	10	60 m	20”	20”	2 min
	40-50	4	10	57 m	20”	20”	2 min
	50-60	3	10	53 m	20”	20”	2 min
High	Up to 30	4	10	71 m	20”	20”	2 min
	30-40	4	10	66 m	20”	20”	2 min
	40-50	4	10	63 m	20”	20”	2 min
	50-60	3	10	59 m	20”	20”	2 min

CF: cardiorespiratory fitness; Rep: repetitions; Rec: recovery.

STRENGTH TRAINING

Planning considerations

- Musculoskeletal strength training, as well as muscle conditioning and maintaining muscle mass throughout life is essential; and in particular during stages of growth and this should be calibrated in relation to the type of cardiorespiratory activities that are performed to be complementary. For example, if sports activities with osteogenic characteristics, such as football, basketball, handball, volleyball, tennis, etc., are performed at least three times a week, the subject's osteogenic exercise needs are probably covered. However, supplementing these practices with the proposed strength training can enhance muscular capacity and also help to prevent injuries, if the sports programme itself does not incorporate it.
- If sports activities are carried out with high musculoskeletal demands such as sports gymnastics, the strength and osteo-skeletal stimulus requirements are probably covered.
- Exercises with body weight are proposed, but where the level of muscular condition requires, the intensity of the exercises can be increased with some type of overload; this situation can occur more easily in adults, but if this is the case while growing, strict control of the technical execution will be required.
- This proposal includes exercises as examples; any of the exercises can be replaced by others of a similar character and muscularity.
- It is assumed that the programme will be carried out in circuit format, in the order show in **table 21**.
- The planning of the strength training and its progression is set out in **table 22**, as the intensity of the load is adjusted individually, the table is valid for all ages. Progress to the next level (e.g. from B to C) when the subjective effort perception for the repetitions required at that level (RPE at B) drops to a lower level (RPE at A).

TABLE 21. Strength exercises

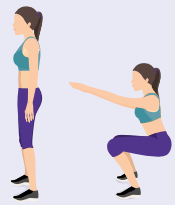
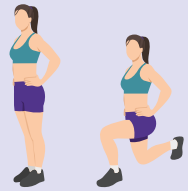
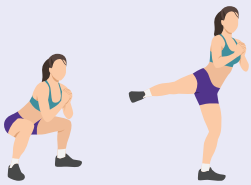
Squats	1. Stand with your feet shoulder width apart and your arms relaxed at your sides. 2. Maintain an upright posture and tight in the abdomen. 3. Raise your arms straight up to parallel to the floor while bending both knees and hips keeping your back straight and your knees at 90°. 4. Then return to the starting position to continue with the next repetition.	
Lunges	1. Stand with your feet shoulder-width apart and your arms on your hips. 2. Maintain an upright posture and tight in the abdomen. 3. Step forward with one leg and bend both knees and hips keeping your back straight until your knees reach 90°. 4. Then return to the starting position to continue with the next repetition, alternating legs.	
Overhead reach	1. Stand with your feet shoulder width apart and your arms relaxed at your sides. 2. Maintain an upright posture and tight in the abdomen. 3. Raise one arm straight up and over your head, turning your torso slightly to the opposite side, while bringing the raised arm leg back and slightly bending the forward leg to begin the change of side. 4. Then slowly lower your arm and repeat the movement with the other arm, turning to the opposite side.	
Rise and plie	This exercise is an evolution of the squat. Perform a squat but with your hands on your hips and bending your knees a little more (120°), and when you return to the starting position, complete the movement by standing on your tiptoes.	
Squat and kick	This exercise is an evolution of the squat. 1. Perform a squat but with your legs wider than shoulder width apart and your elbows bent so that your hands are at face level. 2. When you return to the starting position, complete the movement by putting your weight on one leg and lifting the other leg sideways for a slight kick. 3. Repeat alternately.	

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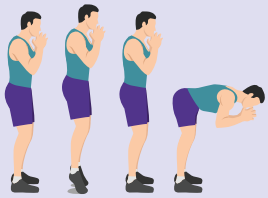
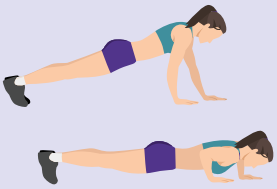
TABLE 21 *(Cont.)*. Strength exercises

Forward calf raises	1. Stand with your feet shoulder-width apart, arms bent at the elbows and hands at face level. 2. Maintain an upright posture and tight in the abdomen. 3. Lift your body by extending your ankles (stand on tiptoe). 4. Return to the starting position and begin to bend at the hips, bringing your body forward until it is parallel to the floor while keeping your legs straight. 5. Return to the starting position to continue with the next repetition. 
Donkey kicks right	1. Get into a dog position with your hands and knees on the floor. 2. Keep one leg bent as you lift it backwards and upwards, keeping the other knee on the floor. 3. Return to the starting position and continue with the rest of the repetitions. 
Donkey kicks left	Same as above, but with the other leg.
Knee push ups	1. Rest your hands and knees on the floor while keeping your hips and elbows extended. 2. Bend your elbows until your chest is on the floor. 3. Push down hard on the floor to extend your arms and return to the starting position. 4. Repeat the entire movement. 
Push ups	1. Rest your hands and feet on the floor while keeping your knees, hips, and elbows extended. 2. Bend your elbows until your chest is on the floor. 3. Push down hard on the floor to extend your arms to regain the initial position. 4. Repeat the entire movement. 

(Continues)

TABLE 21 *(Cont.)*. Strength exercises

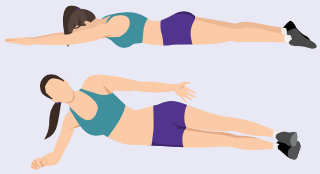
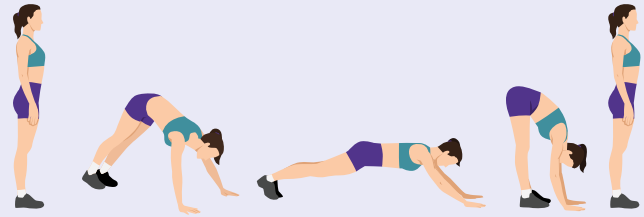
Swing backs	1. Lie down on the mat looking down and arms extended forward. 2. Alternatively extend your hips raising your back upwards as you rotate your torso and bring your arm backwards to touch your thigh with your hand. 3. Return to the starting position to repeat the movement alternately with each arm. 
Burpees	1. Stand with your feet shoulder width apart and your arms relaxed at your sides. 2. Bend at the hips, bringing the trunk forward and down while extending your arms to rest on the floor. 3. Without moving your toes, walk with your hands until you fully extend your hips and stand on your hands with your elbows extended.. 4. Do a push-up (like the push-up exercise).  5. Without lifting your hands off the ground, bring your feet close to your hands and jump up. 6. Repeat the sequence of the movement.
Walk downs	1. Stand with feet shoulder width apart and arms at your sides. 2. Bend at the hips, bringing your torso forward and down while extending your arms to rest on the floor. 3. Without moving your toes, walk with your hands until you fully extend your hips and stand on your hands with your elbows extended. 4. Then, walk your hands backwards, undoing the movement until you stand up and return to the starting position and repeat the movement. 

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TABLE 21 *(Cont.)*. Strength exercises

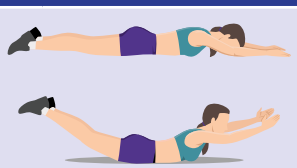
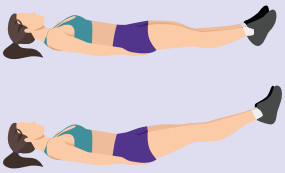
Superman	1. Lie face down on the mat and arms stretched out in front of you. 2. Hyperextend your hips slightly, lifting your legs and arms off the floor. 3. Return to the starting position to repeat the movement.	
Isometric plank	1. Rest your forearms and feet on the mat with your knees, hips and elbows extended. 2. Tighten your abdomen trying to bring your pelvis forward. 3. Maintain this position by tensing and straining your abdomen for the set time.	
Face up leg lift	1. Lie down on the mat with your legs extended and arms alongside the body. 2. Tighten your abdomen, trying to pull your pelvis forwards. 3. Lift your legs outstretched and hold them out in front of you slightly off the ground and performing repeated lifting motions, with force and tension in the abdomen for the set number of repetitions.	

TABLE 22. Strength training to be carried out in circuit format

	Progression								
	A			B			C		
Exercise	Sets	6 rep	rec between sets	Sets	10 rep	rec between sets	Sets	14 rep	rec between sets
LOW strength level									
Squats	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Overhead reach	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Rise and plie	–	–	–	–	–	–	–	–	–
Squat and kick	–	–	–	–	–	–	–	–	–
Forward calf raises	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Donkey kicks right	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Donkey kicks left	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Lunges									
Knee push ups	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Push ups									
Burpees	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Walk downs	2	RPE 1-3	30"	2	RPE 4-7	30"	2	RPE 8-9	30"
Swing backs	–	–	–	–	–	–	–	–	–
Superman	–	–	–	–	–	–	–	–	–
Plank	–	–	–	–	–	–	–	–	–
Face up leg lift	–	–	–	–	–	–	–	–	–

(Continues)

TABLE 22 *(Cont.)*. Strength training to be carried out in circuit format

	Progression								
	A			B			C		
Exercise	Sets	6 rep	rec between sets	Sets	10 rep	rec between sets	Sets	14 rep	rec between sets
MEDIUM strength level									
Squats	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Overhead reach	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Rise and plie	–	–	–	1	RPE 4-7	30”	1	RPE 8-9	30”
Squat and kick	–	–	–	–	–	–	–	–	–
Forward calf raises	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Donkey kicks right	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Donkey kicks left	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Lunges	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Knee push ups	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Push ups	–	–	–	–	–	–	–	–	–
Burpees	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Walk downs	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Swing backs	2	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Superman	–	–	–	–	–	–	–	–	–
Plank	2	20”	30”	2	30”	30”	2	40”	30”
Face up leg lift	–	–	–	–	–	–	–	–	–

(Continues)

TABLE 22 *(Cont.)*. Strength training to be carried out in circuit format

	Progression								
	A			B			C		
Exercise	Sets	6 rep	rec between sets	Sets	10 rep	rec between sets	Sets	14 rep	rec between sets
HIGH strength level									
Squats	–	–	–	–	–	–	–	–	–
Overhead reach	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Rise and plie	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Squat and kick	2	RPE 1-3	30”	2	RPE 4-7	30”			
Forward calf raises	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Donkey kicks right	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Donkey kicks left	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Lunges	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Knee push ups	1	RPE 1-3	30”				1	RPE 8-9	30”
Push ups	1	RPE 1-3	30”	2	RPE 4-7	30”	2	RPE 8-9	30”
Burpees	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Walk downs	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Swing backs	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Superman	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”
Plank	2	20”	30”	2	30”	30”	3	20”	30”
Face up leg lift	2	RPE 1-3	30”	2	RPE 4-7	30”	3	RPE 8-9	30”

rep: repetition; rec: recovery; RPE: rate of perceived exertion.

Key messages

- PKU is a disorder that does not restrict sports or physical training.
- All clinical aspects linked to PKU are related to the nutritional state, so nutritional assessment and treatment are essential in the follow-up of these subjects.
- Muscle mass is an important marker of nutritional condition and is a key component in maintaining the subject's health and functional capacity.
- Physical exercise programmes and increased daily physical activity are a cornerstone in maintaining a good state of health.
- Adherence to physical exercise programmes requires multidisciplinary action in conjunction with nutritionists to achieve synergy between the two actions.
- Strength and neuromotor exercises are decisive in the success of the intervention.
- Prescribing physical exercise will be carried out on an individual basis, taking into account the overall situation of each subject.

Digital tools/ useful websites

- The **American College of Medical Genetics and Genomics** has developed a guide entitled Phenylalanine Hydroxylase Deficiency: Diagnostic and Management. https://www.acmg.net/docs/PKU_guideline_ES.pdf
- **Physical exercise and health network. EXERNET,** conducts research into the effects of prescription on specific population groups. It brings together the most outstanding Spanish research groups in the field of physical exercise and health. https://redexernet.com/
- **Exercise is Medicine**. This is an initiative of the American College of Sports Medicine (ACSM) that seeks to implement the assessment of physical activity and the prescription of physical exercise in medical consultations. https://www.exerciseismedicine.org/about-eim/
- **Vivifrail.** Practical guide for the prescription of a multicomponent physical training programme for the prevention of frailty and falls in the over 70s. https://vivifrail.com/

Glossary

1RM: A maximum repetition is the greatest amount of weight that can be lifted once, for a given muscle group and technique, during a strength exercise.

Accelerometers: Small devices that act as motion sensors, usually attached to a person's waist or wrist, that enable data collection for measuring physical activity.

Adaptation: The body's ability to assimilate and integrate different training stimuli (body's response to exercise).

Agility: Ease of executing something quickly, physically or mentally.

Anaerobic threshold: Physiological parameter indicating the change in the predominance of the main metabolism that provides energy to perform an action at a given intensity. This parameter can be found by different methods.

Balance: Ability to maintain or recover body position during the execution of static or moving positions.

Basal metabolic rate (BMR): a calculation used to estimate the amount of energy the body expends to maintain such vital functions as heartbeat, breathing and brain function, without taking into account the energy expended in other activities throughout the day.

Body composition: The study of the different components that make up the human body and their proportions. It is also understood as a part of physical fitness related to maintaining healthy percentages of fat mass, muscle mass and bone mass.

Calisthenics: Exercises performed without equipment, using one's own body weight as resistance, and designed to improve muscular strength and/or flexibility.

Cardiorespiratory activities: Also referred to as cardiovascular, cardiopulmonary or aerobic activities. These are prolonged activities that require large muscle groups with increased heart rate and breathing rate in order to supply oxygen to the working muscles.

Cardiorespiratory endurance: Efficiency of the cardio-respiratory system to take in oxygen, transport it and obtain energy. Ability to perform dynamic exercise involving large muscle groups at moderate or high intensity for prolonged periods of time.

DOMS: Delayed onset muscle soreness, commonly called muscle ache.

Dynapenia: Loss of the ability to generate strength in older people, either for morphological (sarcopenia) or neural reasons and which will affect functional performance in everyday activities.

Elasticity: It is the body's ability to deform when subjected to external forces, which may cause the deformation to be irreversible, or to return to its original, natural form when the external forces cease their action or power.

External load: Indicator of the quantification of training by physical parameters that can be increased or decreased by modifying the training components (volume, intensity, frequency, etc.).

FITT principle: Frequency, Intensity, Time and Type of physical activity, components that are modified in order to vary the dose (or load) of physical exercise.

Flexibility: Ability to move a joint throughout its range of motion.

Fragility: Progressive age-related deterioration of the physiological systems resulting in diminishing reserves of intrinsic capacity, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health outcomes.

Frequency: The number of times someone takes part in physical activity (often expressed as number of times per week).

Functional capacity: The set of physical, mental and social skills that enable the subject to carry out the activities required by their environment and/or surroundings.

Glycogenolysis: The biochemical process by which glycogen, the body's form of carbohydrate storage, is broken down into a simple sugar, such as glucose. This process occurs when our body needs glucose for immediate energy. However, it ceases when there is an excess of glucose in the bloodstream.

Health: An individual's ability to successfully meet the challenges of everyday life.

Heart rate reserve: The difference between resting heart rate and maximum heart rate. It is used in the Karvonen method to calculate ideal heart rate intervals for physical activity.

Heart rate: The number of beats per minute (bpm) of the heart.

Impedance: Measurement of the total opposition to the electrical current flowing through the body. Bioimpedance (BIA) is used to assess body composition.

Inactive: Subject who does not meet the physical activity recommendations for their age group and sex.

Intensity: Level of exertion of physical activity. Often described as light, moderate or vigorous. It can also be expressed in the form of heart rate, rating of perceived exertion or MET (Metabolic Equivalent) level, among other methods. See **tables 15** and **16** of intensity equivalences with different methods.

Internal load: It is the effect that the external load has on the subject's organism, triggering certain physiological reactions associated with the training stimulus (heart rate, lactate, etc.).

Interval training: Several intermittent sets of aerobic exercise of varying intensity separated by periods of rest or rest.

Light physical activity: Activity with an intensity between 1.6 and 3 METs. Generally abbreviated as LPA.

Macrocycle: Phase of the training programme that groups together several mesocycles.

Maximal oxygen uptake: The maximum amount of oxygen (O2) that the body can absorb, transport and consume per given unit of time, i.e. the maximum volume of oxygen in the blood that our body can transport and metabolise. Also called *aerobic power or* VO_2max.

Maximum heart rate: The maximum number of beats per minute of a person's heart. This value generally decreases as a person ages. It can be assessed directly by means of a progressive exercise test until maximum effort is reached, or indirectly by using the equations.

Medical prescription: A note written by a physician indicating the medicine to be given to a patient, as well as the instructions for proper administration.

Mesocycle: Phase of the training program that groups together several microcycles.

MET: The term MET stands for Metabolic Equivalent Task. 1 METs is the rate of energy consumption when at rest. As a convention, oxygen consumption is considered to be 3.5 millilitres per kilogram of body weight per minute (or 1 kcal/kg/hour). Physical activities are often classified in terms of their intensity using METs as a point of reference.

Microcycle: A phase of a training programme that generally lasts between 1 and 4 weeks.

Moderate physical activity: Activity with an intensity between 3.1 and 6 METs. Generally abbreviated as MPA.

Muscle hypertrophy: Increase in muscle size.

Muscle resistance: Ability to maintain a given muscle action for a long time.

Overcompensation: Stimulation of anabolic processes produced as an alarm mechanism in order to protect the structure from excessive depletion of its capacity in the event of a recurrence of the stimulus that triggered the catabolic process.

Overload principle: Known as the Schultz-Arnold Law, it sets a threshold for the training stimulus. A training stimulus of a magnitude below the threshold does not induce sufficient disruption of homeostasis to elicit an adaptive response.

Overload: The load or amount of resistance of an exercise, which involves a greater stress or load on the body than the body is accustomed to in order to improve physical fitness.

Pedometers: Small devices that measure the steps taken while walking.

Periodisation: Advanced form of training with systematic modifications of exercise volume, intensity and frequency in order to achieve a specific goal.

Physical activity: Any body movement produced by skeletal muscles and resulting in energy expenditure in excess of the resting state.

Physical exercise: It is planned, structured, repetitive and intentional physical activity with the aim of improving or maintaining one or more of the components of physical fitness.

Physical fitness: The ability to carry out daily activities with energy and diligence, without undue fatigue and with sufficient energy to enjoy leisure time activities and to cope with unforeseen emergencies as they arise.

Plyometrics: A type of training that is carried out with the aim of making an athlete able to perform movements that are faster and more powerful.

Power: The amount of work done in a given unit of time, measured in Watts (W).

Principle of alternation: When planning a training session, we must alternate different types of stimuli designed to work the different physical capacities, thus respecting recovery periods in order to achieve a higher adaptation.

Principle of continuity: Training should be performed at an appropriate level of frequency. This will allow the training adaptations obtained through overcompensation to be exploited.

Principle of individuality: The same training stimulus will produce different levels of adaptation depending on various characteristics of the subject. This concept is related to that of adaptation reserve, among others.

Principle of minimum stimulus: In subjects with a low current adaptation reserve, the application of a training stimulus characterised by low volume and intensity allows an optimal adaptive response to be induced, whereas, in subjects with a current adaptive reserve close to their full reserve, a more demanding training stimulus is required. This principle is also known as the principle of progression or progressively increasing load.

Principle of reversibility: It consists of the loss of adaptations obtained through training. It is related to the principle of continuity.

Principle of specificity of adaptation: The imbalance or alteration of homeostasis caused by a given training stimulus is specific to the morphological and functional system targeted by the training stimulus, and therefore adaptation and performance enhancement is specific to these systems.

Progression: It is the way in which the overload is increased to promote continuous improvement in physical fitness. It should be a gradual increase in frequency, intensity or time, or a combination of all three components.

Protein substitutes: A source of very low or phenylalanine-free protein, which replaces the natural protein removed from the diet.

Rate of Perceived Exertion (RPE) or Borg Scale: Numerical scale that quantifies the perceived effort. It includes written verbal descriptors ranging from 0 ("no effort") to 10 ("maximum effort"). It provides a valid measure of exercise intensity. Graphical representations such as Omni-Scale are available.

Sarcopenia: A progressive, widespread musculoskeletal disorder associated with an increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality.

Sedentary activity: Activity with an intensity lower than 1.5 METs.

Sedentary: Subject who spends a lot of time performing activities in a seated position (sitting, lying down, etc.) regardless of their level of physical activity.

Sets: Number of times a specified number of repetitions of a given exercise is performed.

Sports: Physical activity, performed as a game or competition, the practice of which involves training and adherence to rules.

Strength: The ability of muscles to exert pressure against resistance. In the international system it is measured in Newtons (N).

Talk test: A simple exercise intensity verification test that rates the ease with which the person can speak while performing the exercise.

Total energy expenditure (TEE): Amount of energy the body expends per day. It includes both the energy required to maintain vital functions, such as breathing or keeping the heart beating, and the energy expended in daily activities such as work or exercise.

Training programme: Physical exercise guidelines indicated by a competent professional, as well as the rules for their correct performance. Also referred to as a physical exercise prescription.

Vigorous physical activity: Activity with an intensity greater than 6 METs. Generally abbreviated as VPA.

Waist-to-hip ratio: Waist circumference divided by hip circumference; used to measure upper body obesity.

Warm-up: A set of exercises involving all muscles and joints, arranged to gradually prepare the body for better physical performance and to avoid injury.

Work: It is the force applied to a body to produce a displacement, measured in Joules (J).

Abbreviations

- ACSM: American College of Sports Medicine
- ADA: American Dietetic Association
- BCAAs: branched-chain amino acids
- BMR: basal metabolic rate
- CD: Canada Dietitians
- CGMP: casein glycomacropeptide
- CR: cardiorespiratory
- CRF: cardiorespiratory fitness
- DOMS: delayed onset muscle soreness
- EMA: European Medicines Agency
- FAO: Food and Agriculture Organisation of the United Nations
- FDA: American Food and Drug Administration
- HR: heart rate
- IMD: inborn metabolic disorder
- IOC: International Olympic Committee
- MET: metabolic equivalent

- MR: maximum repetition
- PA: physical activity
- PAH: phenylalanine hydroxylase
- PF: physical fitness
- Phe: phenylalanine
- PKU: phenylketonuria
- REC: recovery
- REP: repetitions
- RHR: reserve heart rate
- RIR: repetitions in reserve
- RPE: rate of perceived exertion
- S: strength
- TEE: total energy expenditure
- UNU: United Nations University
- VO_2max: maximum oxygen consumption
- WHO: World Health Organisation

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