Clinical assessment for diet prescription

AYSHA KARIM KIANI1, MARIA CHIARA MEDORI2, KRYSTIANA DHULF2, KEVIN DONATO1, PAOLA CARUSO3, FRANCESCO FIORETTI4, MARCO ALFONSO PERRONE1, MARIA RACHELE CECCARINI6, PAOLO MANGANOTTI1, SAVINA NODARI5, MICHELA CODINI6, TOMMASO BECCARI6, MATTEO BERTELLI1,2,7
1 MAGI EUREGIO, Bolzano, Italy; 2 MAGI’S LAB, Rovereto (TN), Italy; 3 Clinical Unit of Neurology, Department of Medicine, Surgery and Health Sciences, Catania University Hospital ASUO, University of Trieste, Trieste, Italy; 4 Department of Cardiology, University of Brescia and ASST “Spedali Civili” Hospital, Brescia, Italy; 5 Department of Cardiology and CardioLab, University of Rome Tor Vergata, Rome, Italy; 6 Department of Pharmaceutical Sciences; University of Perugia, Perugia, Italy; 7 MAGISNAT, Peachtree Corners (GA), USA

Keywords
Nutritional Assessment • Micronutrients deficiency • Malnutrition • Dietary Intake Assessment • Physical Activity Assessment

Summary
Accurate nutritional assessment based on dietary intake, physical activity, genetic makeup, and metabolites is required to prevent from developing and/or to treat people suffering from malnutrition as well as other nutrition related health issues. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare setups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected. In this review we have explored different techniques used for nutritional and physical activity assessment. Dietary Intake (DI) assessment is a multidimensional and complex process. Traditionally, dietary intake is assessed through self-report techniques, but due to limitations like biases, random errors, miscategorizations, and nutrient databases-linked errors, questions arise about the adequacy of self-reporting dietary intake procedures. Despite the limitations in assessing dietary intake (DI) and physical activity (PA), new methods and improved technologies such as biomarkers analysis, blood tests, genetic assessments, metabolomic analysis, DEXA (Dual-energy X-ray absorptiometry), MRI (Magnetic resonance imaging), and CT (computed tomography) scanning procedures have made much progress in the improvement of these measures. Genes also play a crucial role in dietary intake and physical activity. Similarly, metabolites are also involved in different nutritional pathways. This is why integrating knowledge about the genetic and metabolic markers along with the latest technologies for dietary intake (DI) and physical activity (PA) assessment holds the key for accurately assessing one’s nutritional status and prevent malnutrition and its related complications.

Introduction

In the present advanced world, nutritional research mainly focuses on improving individual as well as population health through diet management. Health- and Nutrition-linked researcher have established that, along with their essential functions, both the nutrients and the non-nutrient food components interact with various metabolic pathways, thus influencing health and increasing or decreasing the risk of various diseases [1]. The precise assessment of the dietary intake (DI) as well as of physical activity (PA) is crucial for quality research in the areas of nutrition, public health, and exercise science [2]. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare setups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected. However, the differentiation between such procedures is quite subtle, especially because of the identification of significant prognostic clinical processes that are interlinked both with each other as well as to the nutritional status, like sarcopenia and frailty [3]. Several nutritional assessment and screening tools have been proposed, but none of them are truly comprehensive. However, among those assessment tools, the multidimensional ones seem to be more informative. Some of these tools are age-specific; like certain assessment tools that have been tailored specifically for older people. Moreover, in certain cases applying biochemical parameters (i.e. blood tests, genetic assessments and metabolomic analysis) might be considered significant and their extra costs should be compensated by the useful information they provide as nutrition marker for different perspectives, like nutritional status assessment, malnutrition grading, prognosis and refeeding effectiveness (Tab. I) [4].

Dietary Intake (DI) assessment in healthy adult population is a multidimensional and complex process that makes an accurate quantification somewhat challenging. Traditionally, DI is assessed via self-report techniques including diet records, FFQs (food frequency questionnaires), and recalls [5]. These self-assessment or self-reporting techniques have been known to underestimate the caloric intake by almost 11 to 35% (mostly in obese people) as compared to direct measuring techniques, such as doubly labeled water [6]. Reporting er-
errors including biases (also called “systematic errors”), random errors, mis-estimations, and nutrient databases-linked errors are the source of some of the current criticisms, which leads to questioning the adequacy of self-reporting dietary intake procedures for scientific conclusions about the relationship between dietary intake and health [7]. Additionally, the Malnutrition Universal Screening Tool (MUST) (Tab. IIa, IIb) was developed to identify malnourished individuals within all care settings (like nursing homes, hospitals, home care, etc.). MUST was the basis of the NRS-2002; however, since it did not include the last food intake, the weight loss percentage calculations might be tedious and create an obstacle for the busy staff of healthcare wards [8]. The most recent studies have thus suggested that dietary intake should be assessed using novel and improved methods, suitable to apply in independently living individuals (like biomarkers, digital photography, or remote sensing devices), instead of solely relying on self-reporting methods [2].

| Biochemical values       | Nutrition Independent Factors                                                                 | Half-Life | Appropriateness to Detect Malnutrition                                                                 |
|--------------------------|-----------------------------------------------------------------------------------------------|-----------|--------------------------------------------------------------------------------------------------------|
| Albumin                  | Increased dehydration, Decreased inflammation, Infections, Trauma, Heart Failure, Edema, Liver dysfunction, Nephrotic syndrome | 20 d      | +/-++ Not appropriate in case of anorexia and acute illness                                             |
| Transferrin              | Increased renal failure, Iron status, Acute hepatitis, Hypoxia                                | 10 d      | +                                                                                                     |
| Prealbumin/Transthyretin (TTR) | Increased renal dysfunction, Dehydration, Corticosteroid therapy Decreased inflammation, Hyperthyreosis, Liver disease, Overhydration | 2 d       | Not appropriate to detect anorexia Subnormal values within one week when fasting                      |
| Retinol bindingprotein (RBP) | Increased kidney failure, Alcohol abuse, Decreased hyperthyreosis, Chronic liver diseases, Vitamin A deficiency, Selenium deficiency | 12 h      | Idem prealbumin                                                                                        |
| Insulin-like growth factor 1 (IGF-1) | Increased kidney failure, Decreased liver diseases, Severe catabolic status, Age | 24 h      | ++ Rapid decrease in fasting periods                                                                  |
| Urinary creatinine       | Increased collection time > 24h, Infection, Trauma, Decreased and insufficient collection time, Acute kidney failure | -         | 1 mmol of creatinine is derived from 1.9 kg of skeletal muscle mass                                     |
| Lymphocytes              | Increased healing phase after infection, Hematologic diseases, Decreased sepsis, Immune suppressants, Steroids | -         | + Very unspecific                                                                                     |
Additionally, the availability of various diagnostic tools is another important issue or limiting factor to overcome in clinical practice. Particularly for muscle mass assessment, in spite of the precise result of DEXA (Dual-energy X-ray absorptiometry), MRI (Magnetic resonance imaging), and CT (computed tomography) scanning procedures, noninvasive, bedside and low-cost techniques like BIA (bioelectric impedance analysis) are still considered as an ideal solution for the routine usage and extensively used. Besides, in the absence of these instrumental methods, anthropometric measurements like calf or mid upper-arm circumference could be adequate substitutes [9].

Moreover, many subjective as well as objective methods of dietary intake (DI) and physical activity (PA) assessment exist, each of which has its own biases and limitations (Fig. 1) [2]. Besides, even though nutritional assessment and screening should be easy and quick procedures, increasing evidences are suggesting that more time should be devoted to them [3].

Assessment of nutritional status by dietary intake

Dietary intake assessment has been performed using several objective as well as subjective tools, each having its own inherent limitations and strengths. Hence, the selection of the appropriate tool for the research mostly depends upon nutrients of interest, study design, target population, availability of time and economic resources. Some limitations hinder the capability of self-report dietary intake (DI) measures to reach scientific conclusions about the relationship between dietary intake (DI) and the health outcomes. However, the traditional DI assessment methods like diet records, FFQs and recalls remain the main choice because of their familiarity, cost efficiency and the lack of consensus upon other objective methods that are capable of producing the complex required outcomes [10].

Latest advancements in technology have resulted in the development of many automated tools for dietary assessment that can overcome some of the limitations of traditional subjective tools, in addition to strive for time and cost efficiency. Such advanced assessment methods include automated self-administered 24-hour dietary assessment tool (ASA24) and food records [11], photo-assisted dietary assessments (PADAs) [12], image-based dietary assessments (IBDAs), and graphic and automated food frequency questionnaires (FFQs) [2, 13].

**Automated Self-Administered 24-hour (ASA24)**

The National Cancer Institute (NCI) introduced an upgraded version of the USDA’s (U.S. Department of Agriculture) Multiple-Pass 24-Hour Recall Method that enables automated self-administered 24-hour recalls (ASA24) by the respondent and could be used for several days to maintain food record. Automated self-administered 24-hour recalls (ASA24) overcome the limitations of traditional 24-hour recalls like reduced time, independence from trained interviewers, reduced respondent burden and reduced economic burden for researchers. In order to automate the ASA24 tool, several novel self-administered web-based food frequency questionnaires (FFQs) have been developed, like Nutrition Quest’s NCIB lock questionnaire, Fred Hutchinson Cancer Research Center FFQs, and NCI’s Diet History Questionnaire (DHQ) III. All of these are web-based
Nutritional assessment questionnaires and comprise over 100 questions concerning food items and their purchasing and preparation, with different layout designs and analytical techniques. Some of these, like NCI’s Diet History Questionnaire (DHQ) III, are also freely available for researchers. Another novel alternative, VioScreen, provides a graphical FFQ option, hence addressing the limitations of the traditional FFQs [2, 14, 15].

**Nutritional risk screening (NRS 2002)**

Globally, one of the most commonly used nutritional risk screening and evaluating tools for hospitals is the NRS-2002 (Tab. III), developed by Kondrup et al. as a generic tool for the hospital setup to be used for detecting patients who could benefit from nutritional therapy [16]. Recently, NRS-2002 was presented in large multi-centric randomized controlled study involving medical in-patient population; the results of the study established a decrease of significant clinical outcomes like mortality in patients that were evaluated by NRS-2002 and found to be at malnutrition risk. NRS-2002 is a well-validated and simple tool, incorporating the preliminary screening via four questions. If the answer to any of these questions is positive, the patient will undergo a complete screening that includes alternate measures of their nutritional status, with static as well as dynamic parameters along with data about the severity of the disease [8].

**Mini Nutritional Assessment (MNA)**

For other care settings – such as outpatient, community, institutions, rehabilitation and subacute – their evaluation should be carried out using Mini Nutritional Assessment (MNA), on the bases of the amount of data collected. Even the short-version MNA has been validated and optimized as full-assessment procedures, that identifies three categories of nutritional status even in patients without possibility of BMI measurement (measuring circumference of calf as an alternative) (Tab. IV). Hence, this nutritional assessment tool is designed to be faster and easier to complete, minimizing the requirement of patient’s participation as well as the quantity of unanswered questions, also enabling a wider distribution between healthcare professionals. Thus, all at-risk patients must undergo a complete nutritional assessment to evaluate the presence of any malnutrition [3, 17].

**Photo-Assisted Dietary Assessments (PADAs)**

Photo-Assisted Dietary Assessments (PADAs) involve images of the food selections and any remaining food after the meal for dietary intake estimation and might be an efficient and unobtrusive method of DI assessment among large groups of independent individuals. Mostly, they have been used to assess the DI of military recruits during their basic training, younger adults, disabled individuals, and overweight or obese females.
PADAs methods include both the traditional methods as well as advanced technologies of digital photography and remote food photography plus recalls, both of which validate direct energy measurement in different population and environment extremities. Their major limitations include lack of the fully automated nutrient analysis after capturing the photo as well as the nutrient database quality used for analysis [2, 18, 19].

Image-based dietary assessment (IBDA)

Image-based dietary assessment (IBDA) is a technique that uses images of the food selections as well as any remaining food after the meal to estimate the patient’s dietary intake (DI) but, unlike PADAs, IBDA captures the image passively (i.e., the images, automatically captured by the device, are the main information source the user provides for verification). IBDA’s updated versions have combined the automated food identification, a software for portion size estimation, and user prompts for accurate DI assessment. Some examples of these assessment techniques include the Technology-Assisted Dietary Assessment system, the Nutricam Dietary Assessment Method, and the eButton [13, 20].

**Sensors and informatics research tools**

Early studies have observed the use of smart kitchen equipment, like tables, plates, and bowls that can measure and record the weight of the food (either with or without the plates) before as well as after the consumption of the meal. Similarly, wearable sensors provide an automated record of food consumption by hand-to-mouth gestures or chewing modality (like microphones that detect the crushing of food), electro-myographic sensors for the detection of muscle activation or acceleration, and strain sensors to

---

**Tab. III. Nutritional Risk Screening (NRS-2002).**

| Sr. No | Preliminary Screening | Yes | No |
|--------|-----------------------|-----|----|
| 1      | Is the BMI of the patient < 20.5 kg/m² | -   | -  |
| 2      | Did the patient lose weight in the past 3 months? | -   | -  |
| 3      | Was the patient’s food intake reduced in the past week? | -   | -  |
| 4      | Is the patient critically ill? | -   | -  |

If yes to one of those questions, proceed to screening. If no for all answers, the patient should be re-screened weekly.

| Impaired nutritional status | Score | Severity of the disease | Score |
|-----------------------------|-------|-------------------------|-------|
| Normal nutritional status   | Absent 0 | Normal nutritional requirements | Absent 0 |
| Weight loss > 5% in 3 months OR 50-75% of the normal food intake in the last week | Mild 1 | Patient is mobile increased protein requirement can be covered with oral nutrition Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*, chronic hemodialysis, diabetes, oncology | Mild 1 |
| Weight loss > 5% in 2 months OR BMI 18.5-20.5 kg/m² AND reduced general condition OR 25-50% of the normal food intake in the last week | Moderate 2 | Patient is bedridden due to illness Highly increased protein requirement may be covered with ONS Major abdominal surgery* Stroke* Severe pneumonia Hematologic malignancy | Moderate 2 |
| Weight loss > 5% in 1 month OR BMI < 18.5 kg/m² AND reduced general condition OR 0-25% of the normal food intake in the last week | Severe 3 | Patient is critically ill (intensive care unit) Very strongly increased protein requirement can only be achieved with (par)enteral nutrition Head injury* Bone marrow transplantation* Intensive care patients (APACHE > 10) | Severe 3 |

Total A -

Total B

Age: < 70 years: 0 pt; ≥ 70 years: 1 pt

Grand Total = (A) + (B) + Age

≥ 3 points: patient is at nutritional risk, a nutritional care plan should be set up.
< 3 points: repeat screening weekly.

NRS-2002 is based on an interpretation of available randomized clinical trials.
* indicates that a trial directly supports the categorization of patients with that diagnosis.
detect the chewing motion or the frequency of swallowing [21, 22]. Chewing monitors are considered as reliable ingestion indicators for people that live in the community. Interestingly, chew counts present a significant correlation with ingested food mass. Still, these chewing monitors might also lead to false detections, for example due to gum-chewing movements, or they might be unable to detect liquids consumption, even though the intake of some liquids also cause jaw motions that are similar to chewing movements (like sucking through a straw) and therefore they might possibly be detected. On the other hand, swallowing is considered a reliable DI indicator, as all food needs swallowing to be a part of nutrition. Moreover, the intake of solid as well as liquid food could be detected as an increased swallowing frequency over spontaneous non-nutritive swallowing. Swallowing sensors are made up of microphones, motion and electrical sensors. [23]

Other informatics- and sensor-based assessment tools have been developed to determine the food type as well as its nutritional composition, such as food classification based on acoustic sensors, miniaturized portable (near infrared) spectrometers that can scan food items and determine their matrix characteristics, miniaturized tooth mounted sensor that can detect nutrients as well as wirelessly communicate to the user’s mobile. Research and developmental studies are still going on these technologies and devices, several of these require comprehensive nutrient databases to support their mechanism and technology to assess accurately the portion size [24].

**Nutrition-focused physical assessment (NFPA)**

The application and utility of the nutrition-focused physical assessment (NFPA) could cover various settings for supporting the best practice in patient care. Moreover, NFPA is a part of the nutrition care process and model (NCPM), which is a framework of the nutritional care planning in four distinct and consecutive steps, including nutrition assessment, diagnosis, intervention, as well as monitoring and evaluation. Nutrition-focused physical assessment (NFPA) is considered as an essential part of nutritional assessment, as it could be used to identify the physical outcomes linked to micronutrient deficiencies. Historically, interest in using physical assessment skills within clinical settings is higher when an increased morbidity as well as mortality rate is reported in the hospitalized patients of surgical and medical intensive care units (ICUs), linked with poor nutritional status either prior to or during hospitalization [25].

**Subjective Global Assessment (SGA)**

The awareness of the harmful effects of “malnutrition” led to the requirement of assessment and screening tools in order to identify patients at risk or suffering from malnutrition. Thus, this medical challenge brought to the development of the bedside nutrition assessment tool, the Subjective Global Assessment (SGA), which was among the first assessment tools that included a patient-generated subjective scoring system, calculating the nutrition status on the basis of physical examination as well as patient history. Unlike other traditional assessment techniques that are solely based on anthropometric and biochemical markers, SGA outlines a rating scale that is based upon the variations in dietary intake (DI), in gastrointestinal signs linked with nutrition, weight, functional capacity, subcutaneous fat loss assessment, disease severity, edema, and muscle wasting. SGA has

---

**Tab. IV. The Mini Nutritional Assessment (MNA) Screening Short-Form.**

|   |   |   |
|---|---|---|
| A | Has food intake declined over the past 3 months due to loss of appetite, digestive problems, or chewing or swallowing difficulties? | 0 = severe loss of appetite 1 = moderate loss of appetite 2 = no loss of appetite |
| B | Weight loss during the last 3 months | 0 = weight loss over 3 kg 1 = does not know 2 = weight loss between 1 and 3 kg 3 = no weight loss |
| C | Mobility | 0 = bedridden or chairbound 1 = able to get out of bed/chair but does not go out 2 = goes out |
| D | Has the patient suffered psychological stress or acute disease in the past 3 months? | 0 = yes 2 = no |
| E | Neuropsychological problems | 0 = severe dementia or depression 1 = mild dementia 2 = no psychological problems |
| F1 | Body mass index (BMI) | 0 = BMI under 19 1 = BMI 19 to under 21 2 = BMI 21 to under 23 3 = BMI 23 or higher |
| F2 | Calf circumference (CC) in cm | 0 = CC less than 31 3 = CC 31 or greater |

12-14 points: normal nutritional status. 8-11 points: at risk of malnutrition. 0-7 points: malnourished
been endorsed in several diseases due to its sensitivity and specificity in detecting nutrient deficiencies as well as malnutrition risk [25, 26].

**System-Based Examination**

Surrogate biochemical markers, formerly used for nutrition status assessment, are found to be unreliable nutrition markers; however, they indicate disease severity, inflammation, morbidity as well as mortality risks (this is the case of serum albumin, prealbumin, and transferrin, for example). Besides, according to the latest etiology-based definition of malnutrition, physical parameters depicting changes in body composition – like subcutaneous fat loss, fluid accumulation, and muscle mass wasting – are included in the six malnutrition characteristics. Clinicians are therefore required to do a brief physical examination of their patients to identify body regions that are linked to macronutrient deficiencies; the findings should be rated as normal, mild to moderate depletion, or severe depletion. These physical indicators could be integrated into the nutrition-focused physical assessment (NFPA) by performing the full head-to-toe assessment by the clinicians, along with the thorough evaluation and examination of all body systems for those physical findings associated with nutrition-linked problems. Moreover, micronutrient deficiencies could have a multifactorial etiology, including inadequate intake, enhanced nutrient requirement, malabsorption, disease processes, natural disasters (e.g. famine), or drug interaction/shortage [25, 27, 28].

According to the Academy of Nutrition and Dietetics, nutrition assessment requires critical observational and analytical skills to identify physical indications through system-based examination. The main constituents of system-based examination and evaluation of the whole body involve the general inspection of vitals, nails, skin, eyes, nose, head, hair, neck, chest, mouth, musculoskeletal, and abdomen. Different inspection techniques are used to carry out the basic examination, involving both critical eye – to observe the shape, color, texture, size of the individual – as well as palpation – that requires touching with the pads and fingertips for the evaluation and assessment of texture, tenderness, size, temperature and mobility. Consequently, data obtained from all these examinations along with other parameters could be used for nutrition assessment as well as for critical interpretation and identification of nutrition-related problems [25].

**Micronutrient Deficiencies and Analysis**

Often micronutrients deficiencies are stated as a single nutrient or multiple nutrients deficiency, on the bases of the region, phase of life cycle, or disease state. Micronutrient deficiencies universally affect over 2 million people worldwide; the predominant single-nutrient deficiencies include iodine, iron, and vitamin A. Vitamins are the essential organic micronutrient and only a small amount is required in the diet for them to play their role in many specific chemical reactions, such as growth, metabolism, and the preservation of cellular integrity [29]. Moreover, micronutrient deficiencies could also play a significant role in the development and progression of certain acute and chronic disorders, and they also could be linked to harmful changes in overall health [30]. Today the percentage of elderly individuals is much higher than in the past, thanks to the advancement in medical technology (like organ transplantation, noninvasive surgeries, obesity treatments, cancer treatment options, nutrition support modalities, etc.) and to the wider possibilities to have access to it [31]. However in spite of all these medical advances, micronutrient deficiencies are still predominant, even in the absence of malnutrition and insufficient caloric intake. Biochemical lab tests could be used to assess micronutrient status through the evaluation of metabolites or nutrient levels in urine, blood, or body tissues. However, biochemical lab tests only provides a quantitative and qualitative measurement of the micronutrient in a specific tissue or in some fluid sample like blood, urine, or plasma, but these results might fail to reveal the overall storage of that micronutrient in the body in terms of deficiency or excess [25].

Changes in skin color are mostly related to deficiencies of iron or B-complex vitamins or both, as these micronutrients are involved in several hematologic processes. Vitamin A deficiency (VAD) causes impairment of cell differentiation and maturation, leading to changes in the mucosal membranes and skin. Furthermore, protein and/or iron deficiencies could result in pallor, spoon-shape, clubbing, transverse banding, or ridging of nails. Where-as vitamin C deficiency leads to coiled and corkscrew hair, vitamin A deficiency affects the vision and can cause night blindness. The depletion of iodine, protein, and energy causes thyroid enlargement as well as fat and muscle wasting, with noticeably bony chest [25].

Nutrition-Focused Physical Assessment (NFPA) techniques analyze the obvious physical signs to assess macronutrients deficiencies during a head-to-toe physical examination and assessment. Thus, identifying the physical and clinical changes in different regions of the body caused by the unavailability of nutrient could be a cost-effective alternative approach to recognize micronutrient deficiencies (Tab. V) [25].

**Nutritional Assessment in Older People**

In older people, another significant aspect to be considered is the functional status impairment, evaluated by analyzing muscle strength and physical performance. Various factors are involved in functional status evaluation via screening procedures in older people; specifically, the relationship between muscle atrophy and decreased physical functioning acts as an independent diagnostic factor. Certainly, impaired functioning mostly results from muscle loss that is linked to disease-related malnutrition or immobility [32]. To maximize general health with aging, older individuals should undergo a complete geriatric assessment, including multidisciplinary diagnostics as well as treatment processes that identify medical, functional, and psychosocial capabilities. Similarly, nutrition status is mostly assessed due to its associations with functional status and disabilities. Therefore, the evaluation of
### Clinical Signs and Symptoms of Micronutrient Deficiencies

| Affected Organs | Symptoms | Micronutrient deficiencies |
|-----------------|----------|---------------------------|
| Skin            | Petechiae, Purpura, Pigmentation, Decubitus, Seborrhelic dermatitis, Unhealed wounds | Vitamins A and C, Vitamins C and K, Niacin, Folic acid, iron, biotin, vitamins B12 and B6, Protein, energy, Vitamin B6, biotin, zinc, essential fatty acids, Vitamin C, protein, zinc |
| Nails           | Pallor or white coloring, Clubbing, Spoon-shape, Transverse ridging/banding, Excessive dryness, Darkness in nails, Curved ends | Iron, protein, vitamin B12 |
| Head/Hair       | Dull/lackluster, Banding/sparse, Alopecia, Hair depigmentation, Scaly/flaky scalp | Protein and energy, biotin, copper, essential fatty acids |
| Eyes            | Pallor conjunctiva, Night vision impairment, Photophobia | Vitamin B12, folic acid, iron, Vitamin A, Zinc |
| Oral cavity     | Glossitis, Gingivitis, Fissures, stomatitis, Cheilosis, Pale tongue, Atrophied papillae | Vitamins B2, B6, B12, niacin, iron, folic acid, Vitamin C, Vitamin B2, iron, protein, Niacin, vitamins B2 and B6, protein, Iron, vitamin B12, Vitamin B2, niacin, iron |
| Nervous system  | Mental confusion, Depression, lethargy, Weakness, leg paralysis, Peripheral neuropathy, Ataxia, Hyporeflexia, Muscle cramps, Fatigue | Vitamins B1, B2 and B12, water, Biotin, folic acid, vitamin C, Vitamins B1, B6 and B12, pantothenic acid, Vitamins B2, B6 and B12, Vitamin B12, Vitamin B1, Vitamin B6, calcium, magnesium, Energy, biotin, magnesium, iron |

Assessment of nutritional status by physical activity

Physical activity (PA) can be defined as the bodily movements that are produced by the skeletal muscles and results in caloric expenditure. According to this comprehensive concept, the amount of energy expenditure (EE) is directly proportional to the size of the muscle mass involved. In the last few decades, technology usage for the personalized dietary intake (DI) assessment along with PA has been expanding rapidly. Typically, both self-report techniques and mechanical devices are used for PA assessment. Self-report measures for PA assessment include usage of questionnaires and completion of comprehensive diaries and logs. On the other hand, device-based techniques include motion sensors like accelerometers, heart rate monitors, pedometers, and other multisensory devices. Although these novel technologies have exhibited some advantages in the methodology of dietary intake and physical activity assessment, there are still many challenges and limitations [2, 38].
PA-related energy expenditure of an individual is affected by their body weight as well as their movement efficiency. Evidently, activity energy expenditure (AEE) involves a broad range of activities, including physical activity during leisure time, occupation, sports, household activities, transportation, home and personal care. In 1992, the American Heart Association published a report identifying physical inactivity as the fourth most significant and treatable risk factor of coronary heart disease (CHD) [39, 40].

Therefore, an accurate quantification of PA becomes essential in determining how much PA is of importance for a specific health outcome, in monitoring temporal events of PA, in evaluating the effectiveness of intervention programs, and in studying dose-response relationships. There are three main types of physical activity assessment methods/techniques, namely criterion, objective, and subjective [39].

**Criterion techniques**

Calorimetry

Physical activity is defined as the body movement that results in the expenditure of energy. The so-called “direct calorimetry”, which measures energy expenditure (EE) by quantifying the heat production or heat loss, is considered as the gold standard of the physical activity measurement and other methods should be validated against it. However, its feasibility is not likely because of practical reasons. Hence, the mostly used criterion for assessment validation is by indirect calorimetric method, which involves the quantification of energy expenditure or heat production by calculating oxygen consumption or carbon dioxide production [39].

Direct behavioral observation

The initial methods for physical activity assessment include direct behavioral observation of motor activities by some skilled observers. Although now there are many assessment techniques to evaluate different physical activity (PA) settings, like sport classes, physical education, or independent living conditions, the main goal is to classify PA behaviors into separate categories that can be analyzed and quantified using different codes. However, the strength of this technique mostly relies on its access to contextual information.

Another important factor that influences physical activity is environmental conditions. This relationship is very significant for cognitive behavior research, as it could suggest change in sedentary behavior. The direct behavioral observation method is mostly used to assess children’s physical activity patterns, while other assessment techniques like questionnaires or pedometers are not useful for them. Unfortunately, this method is a very time-consuming and tiresome method and therefore it is not suitable for larger studies [39, 41].

Doubly labelled water method (DLW)

The doubly labelled water method (DLW) is an isotope-based technique for the assessment of daily energy expenditure and average daily metabolic rate of an organism over a period of time and could be used for both field and lab studies. DLW measures metabolic processes that are directly linked to physical activity. The DLW principle involves the ingestion of two stable isotopes, i.e., 2H and 18O, in the form of water (2H2O18O) in standard amount. These isotopes are then evenly distributed in the body water, as observed from urine samples. Elimination of Deuterium (2H) from the body takes place in the form of water (2H2O), whereas 18O is removed from the body in the form of water (H218O) as well as carbon dioxide (C18O2). The elimination rates difference (over 5 to 14 days) between isotopes presents the quantity of CO2 produced, which leads to the assessment of energy expenditure (EE) [42]. In adults, the accuracy of this method is almost 3-10% of the calorimeter values and the variation of DLW within a subject is 8%; moreover, DLW is also applicable in children and provides precise measurements for free living conditions because it does not influence PA patterns [43]. Still, DLW also has some limitations. The production as well as the analysis of isotopes is quite expensive, which is why this method is not suitable for larger studies; also, it could only calculate the TEE, therefore not distinguishing between physical activity energy expenditure (AEE), diet-induced energy expenditure (DEE), and basal metabolic rate (BMR) [39, 44].

**Objective techniques**

Pedometers

Motion sensors can register body motion. Pedometers are small electromechanical devices that have a spring mechanism to register the vertical movements and are generally worn on the waist. They are used for counting steps during a certain time period, mostly from morning to night. Then, these steps are converted into distance by entering the individual’s average stride length. As a result, pedometers can only register physical activities related to running or walking, but it cannot monitor correctly movements of the upper body, cycling, carrying a load, swimming, or even movements on land or soft surfaces. Yet, as walking and running is a major part of our physical activity pattern, pedometer use remains highly valuable for estimating total daily movements. Hence, pedometers are considered as very helpful instruments for various health campaigns, such as “10,000 steps a day”. In his study, Crouter et al. assessed the validity of 10 different pedometers and found out that the accuracy of pedometers is excellent for step counts, whereas they are less accurate for the assessment of distance and the accuracy of kilocalories assessment is even less [39, 45].

Accelerometers

An accelerometer is a sophisticated monitor that records the person’s movements on several different planes. Instead of through a mechanical lever, as in pedometers, accelerometers function with piezoelectric transducers, along with microprocessors for the quantification of the magnitude as well as the direction of acceleration, which
is also considered as the dimensionless “counts”. Tri-axial accelerometers are considered the best available accelerometer to date because, theoretically, they have the ability to record all movements; however, like pedometers, they still have some limitations in recognizing complex movements, such as upper body movements, cycling, graded terrain, etc. Also, studies have showed that there is a linear relationship between accelerometer counts and energy expenditure (EE). Subsequently, the EE of physical activities could be estimated by using linear regression equations along with body weight, height, gender, and age as co-variables. However, most studies have revealed that accelerometers provide a sufficiently accurate estimation of the overall PA, but its accuracy level for EE is relatively low, specifically for the point estimation of specific activities. Still, accelerometry is one of the most popular techniques used in PA research [46, 47].

**Heart Rate monitoring (HR)**
Another objective PA assessment method is the heart rate monitoring (HR). The heart rate indicates the intensity of the relative stress applied to the cardio-respiratory system by the movement, therefore indirectly measuring physical activity. This method basically relies upon the linear relationship of heart rate with oxygen consumption during moderate to intense PA range. While in resting state or during low-intensity physical activities, this heart rate/oxygen consumption relationship might not be linear and it is also affected by many other factors in addition to energy demands, like smoking, stress, caffeine, and body position. After establishing this relationship, the heart rate calculation could lead to the estimation of oxygen consumption, which in turn helps estimating energy expenditure in free living conditions. The heart rate records are usually maintained minute-by-minute and can be stored for many hours or even for days, hence providing information about the frequency, duration, and intensity of certain activity in addition to total energy expenditure (TEE). For the estimation of energy expenditure (EE) from the heart rate values, the FLEX HR methodology is a comprehensively examined approach. The HR data can show a great variability because of many confounding factors, thus making the EE estimation quite unreliable at individual level; still, this method shows significant epidemiological validity [39, 48, 49]. The next generation assessment PA in free-living conditions combines both HR monitoring and movement sensor, which might improve the precision an accuracy of activity energy expenditure (AEE) assessment [50].

**Subjective techniques**

**Questionnaires/Surveys**
Traditionally, physical activity questionnaires and surveys are an inexpensive tool of PA assessment that can be used efficiently for larger populations. However, this technique mostly depends on subjective analysis of the questions as well as observation related to the PA behavior of the individual. When dealing with very young or elderly people, extra care and attention should be taken, because their memory could be compromised [51]. Over- or under-estimation of the physical activity could be influenced by various factors like age, social desirability, questionnaire complexity, seasonal variation, as well as the span of the surveyed period [52]. Surveying techniques can be divided into four categories: interviewer-assisted questionnaires, self-report questionnaires, diaries, and proxy-report questionnaires. All of these questionnaires must undergo validation against the criterion methods (direct observation, DLW, or indirect calorimetry) or against objective techniques (HR, pedometers, or accelerometers). During their research, Philippaerts et al. evaluated the reliability as well as the validity of the three most frequently used PA questionnaires against doubly labelled water method (DLW) [53] and established that the Baecke Questionnaire [54], the Tecumseh Community Health Study Questionnaire [55], and the Five City Project Questionnaire [56] provided the most valid as well as reliable physical activity data. Whereas, Racette and colleagues [57] made the comparison of seven-day physical activity recall questionnaire for obese women against DLW, as well as two other physical activity questionnaires, like PA scale for elderly and Zutphen physical activity questionnaire, and their results validated that method against DLW in elderly people. Also, the results of these validation studies have shown that in general questionnaires classify the population into various distinctive categories of physical activity behavior such as low, moderate or highly active categories, but they are still not suitable for EE assessment at individual level [39, 58].

The latest developments in information technology (IT) – like computer networking, internet, and multimedia software – leads to the development of electronic surveys that are useful for PA research. Information technology facilitates the researcher in simultaneously administering the questionnaires to a great number of people. In addition, in electronic surveys the subjects directly enter their answers or response on the computer, eliminating all the coding errors that could occur in interviews or traditional paper-pencil surveys. Moreover, in electronic surveys the subjects could not omit any question. Additionally, depending upon the subject’s answers, the computer program could skip the unnecessary questions, which results in brief administration time. Lastly, certain studies have also indicated that people might be relatively more honest about any objectionable behavior to a computer rather than a researcher or paper-pencil questionnaires [39, 59].

**Assessment of nutritional status by metabolomics**
To overcome the limitations of self-reporting dietary assessment methods, nutritional epidemiologists have started to examine the biomarkers as measures of the nutritional status and dietary intake. Dietary biomarkers
were proven to be a more accurate and objective measure for DI in comparison with traditional questionnaires because they also consider the nutrient bioavailability as well as its metabolism [1]. The human genome initiative has introduced new visions for biological research as well as its translation into human health [1], and metabolomics is one of the most significant tools for its implementation [60]. Metabolomics uses different approaches than analytical chemistry and provides a comprehensive picture of all the metabolites that are present in the bio-fluids at a certain time [61]. The analysis of metabolites in blood – like glucose, cholesterol, and triglycerides – is already employed to diagnose monitor diabetes risk and heart diseases. Metabolomics provides the potential to magnify the intrinsic capability of urine and plasma metabolites to evaluate the human health status (Tab. VI) [60]. Researchers strongly believe that metabolites are highly sensitive to dietary exposure because diet is not only a significant source of the variation in metabolites, but it also induces metabolic responses. The two major approaches applied in metabolomics are MS (mass spectroscopy) and NMR (nuclear magnetic resonance) spectroscopy. The use of metabolomics in characterizing habitual dietary exposure as well as in identifying nutritypes have proven it to be a very exciting and emerging field that has many potential applications in the field of nutrition epidemiology [61].

The mechanisms that drive these metabolic and nutritional pathways are intricate and multi-factorial. The latest advancements of the large-scale metabolite profiling for larger epidemiological studies not only provide insights of molecular mechanisms causing age-linked diseases, but they also help in the assessment of metabolites that could predict the risk factors for cardio-metabolic disorders [61]. Metabolite profiling might identify and estimate such metabolites, like acylcarnitines, sphingolipids, and glycerophospholipids, that could not be estimated by the HDI (Healthy Diet Indicator) score. Moreover, these metabolites are known to be associated with greater risks of insulin resistance, fatty acid oxidation, cardiovascular diseases (CVD), and type 2 diabetes (T2D) [31, 32]. Several metabolites, like phosphatidylcholine and acylcarnitines, are associated with gut microbial-dependent pathways that are involved in the hepatic production of TMAO (trimethylamine-N-oxide) from choline; TMAO is subsequently converted into trimethylamine (TMA) within the microbiota, which might increase atherosclerosis risk [37] as well as glucose metabolism [36, 38]. TMAO plays a role in cardiovascular disease, as it promotes accumulation of macrophage foam cells that lead to reverse cholesterol transport inhibition and affect bile as well as sterol metabolism, which subsequently enhances the hyperactivity of platelets along with the initiation of atherosclerotic plaque formation [39, 40] (M2).

Several studies have investigated the association of overall diet with metabolites and mostly these investigations have evaluated the metabolites through mass spectrometry. For instance, in a large prospective cohort study like The European Prospective Investigation into Cancer and Nutrition (EPIC-Potsdam), which included 2,380 adults, the dietary intake patterns were analyzed by the methods of reduced rank regression, and the results showed maximum metabolites variations as well as the weak association of habitual diet with serum metabolites [62]. Similarly, in the ARIC (Atherosclerosis Risk in Communities) study, 1,977 participants samples were assessed for 336 metabolites; the results have revealed an association between a high-sugar (both in food and beverages) dietary pattern and seven long-chain unsaturated fatty acids, two sex steroids, five 2-hydroxybutyrate-linked metabolites, five γ-glutamyl dipeptides, as well as 4 metabolites involved in other pathways [63]. Likewise, the Women’s Health Initiative study exhibited the association of Prudent dietary pattern with 85 metabolites (most of them are lipids). Another study examined 502 participants from a Lung, Prostate, Ovarian and Colorectal Cancer Screening Trial and established the correlation of 412 metabolites with food groups as well as the Healthy Eating Index score [64]. The researchers established the association of 39 metabolites with 13 different dietary groups, thus confirming the usefulness of metabolomics in identifying biomarkers and thus endorsing the nutritional intake effects on human metabolic system [61].

Identifying the strong associations of dietary habits with metabolites might thus provide a better prospect to understand the pathways through which nutritional intake mediates the protection against various chronic diseases, like CVDs [61].

Tab. VI. Metabolites, their Function and associated Disease Condition.

| Disease Condition | Metabolites | Sample type | Function | Analyzing Technique |
|-------------------|-------------|-------------|----------|--------------------|
| Dysbiosis         | Skatole     | Urine Plasma| Pulmonary toxin that induces the expression of AhR regulated genes | HPLC |
|                   | Indican     | Urine       | Stimulated vascular smooth muscle cell proliferation in vitro | Liquid chromatography/electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS) |
|                   | Propionate  | Serum       | Lower lipogenesis, serum cholesterol levels, and carcinogenesis | HPLC |
| Disease Condition | Metabolites        | Sample type | Function                                                                 | Analyzing Technique                                      |
|------------------|-------------------|-------------|--------------------------------------------------------------------------|----------------------------------------------------------|
| Oxidative stress | Homocysteine      | Blood       | Lipid peroxidation, free radical formation, inflammation, and endothelial dysfunction | HPLC                                                     |
|                  | Vitamin D         | Blood       | Promotes calcium absorption in the gut                                   | Liquid chromatography (LC), Liquid chromatography-mass spectrometry (LC-MS), Tandem mass spectrometry, Radioimmunoassays (RIA), Chemiluminescence immunoassays (CLIA) |
|                  | Thioglycolic acid | Urine       | Present as cysteine-thioglycolic acid                                   | HPLC, Gas chromatography                                 |
| Amino acid profile | Histidine         | Serum, Urine | Associated with both lower AHEI score and increased incident CVDs risk  | Mass spectrometry                                        |
|                  | Isoleucine        | Plasma, Urine | Protein synthesis stimulation and reduction of muscle protein breakdown after a physical trauma | Mass spectrometry                                        |
|                  | Leucine           | Plasma, Urine | Calcium absorption and collagen formation                               | Mass spectrometry                                        |
|                  | Methionine        | Plasma      | Angiogenesis, overconsumption is related to cancer growth               | High performance liquid chromatography                   |
|                  | Cysteine          | Plasma, Urine | Antioxidant                                                             | Mass spectrometry                                        |
|                  | Phenylalanine     | Blood, Plasma, Urine | Gluconeogenesis, lower chronic inflammation                           | HPL, Tandem mass spectrometry                           |
|                  | Tyrosine          | Urine, Plasma | Production of neurotransmitters                                          | Mass spectrometry                                        |
|                  | Threonine         | Serum, Plasma | Keeping connective tissues and muscles throughout the body strong and elastic | Peptide microarray technology                            |
|                  | Tryptophan        | Urine, Serum | Part of melatonin and serotonin production                               | HPLC, Liquid chromatography-tandem mass spectrometry     |
|                  | Valine            | Plasma       | Muscle growth and tissue repair                                           | NMR spectroscopy, Mass spectrometry                     |
|                  | Alanine           | Plasma, Urine | Source of energy for muscles and central nervous system                  | NMR spectroscopy                                         |
|                  | Aspartic acid     | Urine, Plasma | Fatigue, athletic performance, and muscle strength                       | Mass spectrometry                                        |
|                  | Glutamic acid     | Urine, Plasma | Sugars and fats metabolism, neurotransmitter                            | Mass spectrometry                                        |
|                  | Glycine           | Urine, Plasma | Acts as neurotransmitter, proteins production                           | NMR spectroscopy                                         |
|                  | Asparagine        | Urine, Plasma | Production of body's proteins, enzymes and muscle tissue                | Mass spectrometry                                        |
|                  | Proline           | Urine, Plasma | Role in protein synthesis, metabolism, nutrition, wound healing, antioxidative reactions, and immune responses | NMR spectroscopy                                         |
|                  | Glutamine         | Urine, Plasma | Substrate for protein synthesis, anabolic precursor for muscle growth, acid-base balance in the kidneys | Mass spectrometry                                        |
|                  | Arginine          | Urine, Plasma | Important role in cell division, wound healing, removing ammonia from the body, immune function, and hormone release | Mass spectrometry                                        |
|                  | Serine            | Urine, Plasma | Biosynthesis of proteins, purines, pyrimidines, enzymes, and muscle tissue | Mass spectrometry                                        |
### Non-protein amino acid

| Metabolites     | Sample type | Function                                                                 | Analyzing Technique                        |
|-----------------|-------------|--------------------------------------------------------------------------|--------------------------------------------|
| Carnitine       | Urine       | Energy production support, general brain function maintenance           | NMR spectroscopy                           |
| Taurine         | Urine/Plasma| Nerve growth support, blood pressure lowering, calming the nervous system| Mass spectrometry                          |
| Glutathione     | Urine/Plasma| Antioxidant, involved in nutrient metabolism, cellular events regulation | Mass spectrometry, NMR spectroscopy        |

### Inflammation and lipidomics

| Metabolites                  | Sample type | Function                                                                 | Analyzing Technique                        |
|------------------------------|-------------|--------------------------------------------------------------------------|--------------------------------------------|
| Fatty acid amides            | Urine/Plasma| Signaling lipids, modulation of neurobehavioral processes in mammals, including pain, sleep, feeding, and locomotor activity | Gas chromatography, Mass spectrometry      |
| Leukotrienes                 | Urine/Plasma| Potent inflammatory mediator                                             | Liquid chromatography, Mass spectrometry   |
| Prostaglandin                | Blood/Urine| Regulation of smooth muscle tissue contraction and relaxation           | Liquid chromatography, Mass spectrometry   |
| Thromboxane                  | Blood       | Blood clotting and constriction of blood vessels                         | Liquid chromatography, Mass spectrometry, Thin layer radio-chromatography |

### Steroids

| Metabolites                  | Sample type | Function                                                                 | Analyzing Technique                        |
|------------------------------|-------------|--------------------------------------------------------------------------|--------------------------------------------|
| Aldosterone                  | Serum/Urine | Increased sodium and water retention, increased potassium excretion, blood pressure regulation | Liquid chromatography/tandem mass spectrometry |
| Cortisol                     | Blood/Urine/Saliva | Metabolism and immune response regulation | Liquid chromatography/tandem mass spectrometry |
| Corticosterone               | Blood       | Involved in metabolism, energy balance, stress and adaptation           | Mass spectrometry, HPLC, ELISA, Radioimmunoassays |
| Dehydroepiandrosterone sulfate | Blood/Plasma | Involved in the development of male sexual characteristics at puberty | Liquid chromatography/tandem mass spectrometry |
| 11-Deoxycortisol             | Serum/Plasma | Metabolic intermediate within the glucocorticoid pathway                 | Mass spectrometry                          |
| 21-Deoxycortisol             | Blood/Plasma/Urine | Marker of congenital adrenal hyperplasia due to 21-hydroxylase deficiency | Liquid chromatography/tandem mass spectrometry, HPLC |
| Androstenedione              | Serum/Urine | Increasing the production of the hormone testosterone to enhance athletic performance, build muscle, reduce body fat, increase energy | Liquid chromatography/tandem mass spectrometry |
| Testosterone                 | Blood       | Sexual development regulation, muscle mass, and red blood cells production | Liquid chromatography/tandem mass spectrometry |
| 17-OH-Progesterone           | Blood       | Marker for congenital adrenal hyperplasia (CAH)                         | Liquid chromatography/tandem mass spectrometry |
| Dehydroepiandrosterone       | Blood       | Endothelial function modulation, inflammation reduction, improvement of insulin sensitivity, blood flow, cellular immunity, body composition, bone metabolism... | Gas chromatography-mass spectrometry (GC-MS), Liquid chromatography-mass spectrometry (LC-MS) |
| Progesterone                 | Serum/Urinary | Menstruation regulation and pregnancy support                           | Liquid chromatography-mass spectrometry (LC-MS) |
| Estradiol                    | Blood/Urinary | Development and maintenance of female reproductive system              | HPLC, Liquid chromatography-mass spectrometry (LC-MS) |
| Estrone                      | Serum/Urine | Involved in female sexual development and function                      | Gas chromatography-mass spectrometry (GC-MS), Liquid chromatography-mass spectrometry (LC-MS) |

### Toxoma

| Metabolites | Sample type | Function | Analyzing Technique |
|-------------|-------------|----------|---------------------|
| More than 5,000 toxins | -         | -        | -                   |
Assessment of nutritional status by genetic biomarkers

Genetic biomarkers play a crucial role in determining the association between intermediate biomarkers like fasting glucose, inflammation markers, plasma lipids, oxidative markers, etc. and the occurrence of diseases like type 2 diabetes, cardiovascular diseases, neurodegenerative diseases, cancer, etc. Currently, hundreds of SNPs are known to be persistently associated with various phenotypes of nutrition-linked diseases (Tab. VII); hence, nutritional epidemiological studies require the knowledge of most of the genetic polymorphisms that are linked to the phenotypes of interest to establish reliable associations between the diet and the disease. This phenomenon is especially relevant to understand individual variations associated with certain gene variants that might influence the correct evaluation of the nutritional status [65].

Lactase 13910C>T polymorphism /rs4988235 located on MCM6 gene is one example of the effect of genetic polymorphism on nutritional status, as it affects the lactase gene (LCT). It strongly affects the persistence of lactase synthesis, which in turn influences the individual’s intolerance or tolerance to lactose [66]. Usually, those who have a CC genotype exhibit a physiological decrease of lactase activity within the intestinal cells because of the difficulty in lactose metabolism. Therefore, CC genotype variant of Lactase 13910C>T polymorphism has been proposed to act as proxy for the low consumption of milk [67]. Similarly, genetic variants also affect the intake biomarkers concentration, like phylloquinone/vitamin K1, which is the major circulating vitamin K form and reflects the intake of vitamin from plants. Circulating phylloquinone acts as a biomarker associated with a healthy lifestyle, while its lower concentrations are considered to be associated with an enhanced risk of different chronic diseases. Thus, understanding the gene variants that might affect phylloquinone concentration might explain the individual variability in the response of phylloquinone intake from the diet or supplements [68].

Additionally, genetic variability also plays significant role in accurately assessing the micronutrient status, which might have a small safety range between the toxic and safe dosage, as well as regulate the bioavailability of these micronutrients. For instance, zinc homeostasis is usually regulated by the zinc transporter genes, and the zinc transporter SLC30A8 polymorphism is found to be associated with an increased risk of type 2 diabetes, as zinc is required for insulin metabolism within the pancreatic beta-cells. Empirically, the total zinc intake is inversely related with the level of fasting plasma glucose in people having the glucose increasing A allele. Moreover, many studies have evidently proposed that zinc levels might be considered at individual basis [65, 69]. In addition to dietary intake (DI), genes also affect physical activity (PA). Since physical activity is one of the major factors contributing to the total energy expenditure (TEE), it plays a vital role in regulating energy balance. It is commonly established that the training-associated metabolic changes are mostly influenced by the individual’s genetic background. Moreover, identifying the genetic markers that enhance the beneficial effects of training might be helpful in assessing various training programs that, along with dietary intervention, could improve the body weight reduction among obese individuals. Therefore, personalized interventions for obesity reduction would be significant in the clinical management of obesity and obesity-related diseases, such as lymphedema [70-73].

In the last two decades, genome-wide association studies (GWAS) and the development of new technologies in the fields of molecular biology and human genetics have enabled scientists to easily perform hundreds of genomic analyses, as well as high throughput DNA sequencing techniques. Such broad-range techniques have facilitated the identification of novel genes and established the correlations between different SNPs related with training capabilities (collectively, such genetic factors are known as performance-enhancing gene polymorphisms, or PEPs) [74]. Recently, a scientific review has identified the association of 5,147 genes with training and physical activity (PA). However, 51% of these genes have up-regulatory effect by training and PA, while 42% of the genes have shown down-regulatory effects by PA [74,75]. For instance, MYBPH gene encodes the structural component of the muscle sarcomeres, which is a myosin-binding protein that might be involved in myosin interaction with the thick A-band myofilaments [76]. Similarly, PDK4 gene encodes the protein kinase (PTK) enzymes, which are located in the mitochondrial matrix and are involved in the inhibition of pyruvate dehydrogenase complex (PDC), which reduces glucose usage and increases free fatty acid (FFA) catabolism [77]. Likewise, ACE (angiotensin-converting enzyme) gene is a reliable candidate for the genetic predisposition to athletic physical activity. Several studies have shown that insertion (allele I) or deletion (allele D) polymorphism of 287bp Alu repetitive sequence located in intron 16 have an association with increased performance as well as duration of exercise in many subjects [78]. A common single nucleotide polymorphism (SNP) rs1801282 C>G (Pro12Ala) in PPARG ( Peroxisome Proliferator Acti-vated Receptor Gamma) gene is known to be associated with various muscle changes linked with exercise. Also, the Ala variant of the SNP rs1801282 could enhance the positive effects on increased muscle mass related with training resistance [70, 79].

Conclusion

Food is required to maintain activities of life. The nutrients and the non-nutrient food components interact with various metabolic pathways, thus influencing health. Nutrient deficiencies could play a significant role in the development and progression of several acute and chronic disorders, and they also could be linked to harmful changes in overall health. For nutritional assessment or screen-
| Sr. No. | Gene     | SNP               | Alleles       | Gene function                                                                                                                                 |
|--------|----------|-------------------|---------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| 1      | LTB4R2   | rs1950504         | A/G           | Chemotaxis mediation of granulocytes and macrophages                                                                                         |
|        |          | rs4987105         | C/T           | Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes                                               |
|        | AOX5     | rs59459148        | del(GGGGCC)4/3/2 | Epoxyde hydrolase that catalyzes the final step in the biosynthesis of leukotriene B4                                                        |
|        |          | rs4769874         | G/A           | Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes                                               |
| 3      | LTA4H    | rs17525495        | C/T           | Epoxide hydrolase that catalyzes the final step in the biosynthesis of leukotriene B4                                                        |
|        |          | rs1978331         | C/T           | Metalloproteinase involved in vasculature remodeling, angiogenesis, tissue repair, and inflammation                                           |
| 4      | MMP2     | rs1030868         | G/A           | Cell-cell adhesion molecule with roles in angiogenesis and immune response modulation, reduction of inflammasome activity, blood vessel remodeling through endothelial cell differentiation and migration, vascular permeability regulation |
|        |          | rs2241145         | G/C           | Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes                                               |
| 5      | CEACAM1  | rs8110904         | G/A           | Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes                                               |
|        |          | rs8111171         | G/T           | Catalyzes the first step in leukotriene biosynthesis and has a role in inflammatory processes                                               |
| 6      | FOXC2    | rs199772307       | G/A           | Transcriptional activator. Involved in mesenchymal tissue formation                                                                          |
|        |          | rs34221221        | A/G           | Transcriptional activator. Involved in mesenchymal tissue formation                                                                          |
| 7      | TNF      | rs1800629         | G/A           | Cellular responses to cytokines and stress, regulates the immunological response to infections                                               |
| 8      | TLR2     | rs121917864       | C/T           | Key role in the innate immune system. It is expressed in macrophages, B lymphocytes, mast cells                                               |
| 9      | TLR4     | rs4986791         | C/T           | Key role in the innate immune system. It is expressed in macrophages, B lymphocytes, mast cells                                               |
| 10     | VEGFA    | rs699947          | C/A           | Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization |
|        |          | -1154             | G>A           | Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization |
|        |          | -460              | C>T           | Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization |
|        |          | +405              | G>C           | Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization |
|        |          | +936              | C>T           | Growth factor active in angiogenesis, vasculogenesis, and endothelial cell growth. induces endothelial cell proliferation, promotes cell migration, inhibits apoptosis and induces blood vessels permeabilization |
| 11     | HGF      | rs5745652         | C/T           | Role in angiogenesis, tumorogenesis, tissue regeneration                                                                                   |
|        |          | rs2074725         | C/A           | Role in angiogenesis, tumorogenesis, tissue regeneration                                                                                   |
| 12     | CYP26B1  | rs2241057         | A/G           | Involved in the retinoid acid metabolism                                                                                                   |
| 13     | PROX1    | rs340874          | T/C           | Critical role in neurogenesis and in the development of the heart, eye lens, liver, pancreas, and lymphatic system                            |
| 14     | RORC     | rs11801866        | A/T           | Essential for lymphoid organogenesis                                                                                                        |
|        |          | rs12120871        | G/A           | Essential for lymphoid organogenesis                                                                                                        |
|        |          | rs12045886        | A/G           | Essential for lymphoid organogenesis                                                                                                        |
| 15     | LCP2     | rs572192          | C/T           | T-cell antigen receptor-mediated signaling                                                                                                  |
|        |          | rs6866753         | C/T,G         | T-cell antigen receptor-mediated signaling                                                                                                  |
|        |          | rs315721          | A/G           | T-cell antigen receptor-mediated signaling                                                                                                  |
|        | NRP2     | rs849530          | G/T           | Interaction with vascular endothelial growth factor (VEGF)                                                                                 |
|        |          | rs849563          | T/A,G         | Interaction with vascular endothelial growth factor (VEGF)                                                                                 |
|        |          | rs16837641        | G/A,C,T       | Interaction with vascular endothelial growth factor (VEGF)                                                                                 |
| 17     | SYK      | rs158689          | T/A           | Regulation of innate and adaptive immunity, vascular development. Crucial role in the innate immune response to fungal, bacterial and viral pathogens. Activates the inflammasome and NF-kappa-B-mediated transcription of chemokines and cytokines in presence of pathogens. Involved in vascular development, where it may regulate blood and lymphatic vascular separation |
| 18     | VCAM1    | rs3176861         | C/T           | Pathophysiological role in immune responses and leukocyte emigration to inflammation sites                                                 |
| Sr. No. | Gene       | SNP          | Alleles | Gene function                                                                                                                                                                                                 |
|--------|------------|--------------|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 19     | miR499     | rs3746444    | A/C,G   | miR-499 gene targets are involved in remodeling and inflammation-related signaling pathways, including fibrogenic and immune-modulator pathways. |
| 20     | CDKN2B-AS1 | rs1335048    | A/C,G   | Interacts with polycomb repressive complex-1 and -2, leading to epigenetic silencing.                                                                                                                      |
| 21     | CALCRL     | rs185008808  | C/T     | Receptor for calcitonin-gene-related peptide together with RAMP1 and receptor for adrenomedullin together with RAMP3 and RAMP2.                                                                             |
|        |            | rs61759309   | A/G     |                                                                                                                                                                                                             |
|        |            | rs10177093   | C/C,T   |                                                                                                                                                                                                             |
| 22     | VEGFC      | rs2333496    | C/T     | Growth factor active in angiogenesis of veins and lymphatic vessels, and in endothelial cell growth, stimulating their proliferation and migration, and permeability of blood vessels. |
|        |            | rs7664413    | C/T     |                                                                                                                                                                                                             |
| 23     | EPHB4      | rs314313     | T/A,C,G | Cell adhesion and migration regulation, angiogenesis, blood vessel remodeling and permeability.                                                                                                          |
|        |            | rs314311     | T/G     |                                                                                                                                                                                                             |
| 24     | PLAZG4A    | rs10798069   | G/T     | Hydrolyzes arachidonyl phospholipids for releasing arachidonic acid. Implicated in the initiation of the inflammatory response.                                                                           |
| 25     | IL1R1      | rs949963     | C/T     | Mediator involved in cytokine-induced immune and inflammatory responses.                                                                                                                                 |
| 26     | IL4        | rs2227284    | T/C,G   | B-cell activation, DNA synthesis stimulation, expression induction of MHC-II on resting B-cells, secretion enhancement and cell surface expression of IgE and IgG, expression regulation of CD23 IgE receptor on lymphocytes and monocytes, expression induction of IL31RA in macrophages, autophagy stimulation in dendritic cells |
| 27     | IL6        | rs2066992    | G/A,C,T | Inducer of the acute phase response, final differentiation of B cells into Ig-secreting cells, lymphocyte and monocyte differentiation, generation of Th17 cells, myokine, increased fats breakdown, improved insulin resistance |
| 28     | IL10       | rs1518111    | T/C     | Cytokine produced by monocytes, lymphocytes, pleiotropic effects in immunoregulation, inflammation, down-regulation of Th1 cytokines expression, MHC-II, macrophages stimulator, B cell survival enhancement, proliferation, antibody production |
|        |            | rs1518110    | A/C,G,T |                                                                                                                                                                                                             |
| 29     | NFKB2      | rs1056890    | G/A,C   | Pleiotropic transcription factor ubiquitously expressed involved in inflammation, immunity, differentiation, cell growth, tumorigenesis, apoptosis.                                                      |
| 30     | ANGPT2     | rs6990020    | C/A,T   | Endothelial cell migration and proliferation.                                                                                                                                                              |
| 31     | SOX17      | rs12541742   | C/G,T   | Embryonic vascular development, postnatal angiogenesis.                                                                                                                                                     |
| 32     | FLT4       | rs75614493   | C/T     | Lymphangiogenesis and lymphatic endothelium maintenance.                                                                                                                                                     |
|        |            | rs10464065   | A/G     |                                                                                                                                                                                                             |
|        |            | rs307814     | G/A     |                                                                                                                                                                                                             |
|        |            | rs307811     | C/T     |                                                                                                                                                                                                             |
|        |            | rs11960352   | C/T     |                                                                                                                                                                                                             |
|        |            | rs1739214    | G/C     |                                                                                                                                                                                                             |
| 33     | KDR        | rs2239702    | G/A     | Endothelial proliferation, survival, migration, tubular morphogenesis, sprouting.                                                                                                                                |
|        |            | rs4576072    | A/G     |                                                                                                                                                                                                             |
|        |            | rs10020464   | C/A,T   |                                                                                                                                                                                                             |
|        |            | rs11153560   | C/T     |                                                                                                                                                                                                             |
| 34     | CYP2A6     | rs1801272    | T/A     | High coumarin 7-hydroxylase activity.                                                                                                                                                                        |
| Sr. No. | Gene | SNP | Alleles | Gene function |
|--------|------|-----|---------|---------------|
| 35     | PLIN1 | rs228948 | A>G/A>T | Modulators of lipolysis and triglyceride levels; protection of lipid storage droplets from hormone-sensitive lipases |
|        |       | rs894160 | C>T     |               |
|        |       | rs250479 | A>C     |               |
|        |       | rs105270 | -       |               |
|        |       | rs2304794 | T>A    |               |
| 36     | ADRB2 | rs1042713 | G>A     | Induction of thermogenesis in response to cold and diet, lipolysis induction |
|        |       | rs1042714 | G>A     |               |
| 37     | ADRB3 | rs4994 | A>G     | Induction of thermogenesis in response to cold and diet; induction of lipolysis |
| 38     | PPARC1A | rs8192678 | C>T     | Transcriptional regulation of white adipocyte differentiation, insulin, and adipokine pathways |
| 39     | TFAM  | rs1937 | G>C     | Maintenance of normal levels of mitochondrial DNA |
| 40     | PPARA | rs4253778 | G>C     | Stimulating the expression of genes required for fatty acid oxidation in mitochondria |
| 41     | PPARD | rs2016520 | C>A/T   | Regulation of the peroxisomal beta-oxidation pathway of fatty acids in mitochondria |
| 42     | GABPB1 | rs7181866 | A>G     | Activation of cytochrome oxidase expression and nuclear control of mitochondrial function |
|        |       | rs12594956 | C>A/G   |               |
|        |       | rs8031051 | C>T     |               |
|        |       | rs12594956 | C>A/G   |               |
| 43     | ACE   | rs4646994 | -       | Regulation of energy expenditure, lipolysis and glucose incorporation into lipids in adipocytes |
| 44     | AMPD1 | rs17602729 | -       | Critical role in energy metabolism |
| 45     | CKM   | rs8111989 | -       | Central role in energy transduction in tissues with large fluctuating energy demands (skeletal muscles, heart) |
| 46     | ADRB2 | rs1042713 | -       | Induction of thermogenesis in response to cold and diet, lipolysis induction |
| 47     | IL6   | rs1800795 | -       | Increase in fat breakdown, insulin resistance improvement |
| 48     | UCP3  | rs1800849 | -       | Uncoupling of oxidative phosphorylation, thermogenesis |
| 49     | AGT   | rs699 | -       | Activation of lipogenic enzymes, induction of lipid transport into adipocytes, increase in delivery of fatty acids to adipocytes |
| 50     | KCNJ11 | rs5219 | -       | Insulin secretion |
| 51     | COL5A1 | rs12722 | -       | Ubiquitous connective tissue component that also binds insulin |
| 52     | HIF1A | rs11549465 | -       | Activation of glucose transporter transcription under hypoxic conditions, encodes glycolytic enzymes |
| 53     | PPARC | rs1801282 | -       | Regulator of adipocyte differentiation |
| 54     | GABPB1 | rs12594956 | -       | Activation of cytochrome oxidase expression and nuclear control of mitochondrial function |
|        |       | rs7181866 | -       |               |
| 55     | SOD2  | rs4880 | -       | Destroys toxic superoxide anion radicals normally produced in cells |
| 56     | ACTN3 | rs1815739 | -       | Structural component of sarcomeric Z line in skeletal muscle |
| 57     | BDKRB2 | rs1799722 | -       | Mediators of pain and inflammation |
| 58     | AQP1  | rs1049305 | -       | Passive transport of water across osmotic gradient |
| 59     | MTHFR | rs1801131 | -       | Conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate |
| 60     | NOS3  | rs2070744 | -       | Vasodilation in response to training |
| 61     | FTO   | rs9939609 | -       | Stimulation of food consumption |
|        |       | rs1558902 | -       |               |
|        |       | rs8050156 | -       |               |
Tab. VII. Continues.

| Sr. No. | Gene | SNP | Alleles | Gene function |
|---------|------|-----|---------|---------------|
| 62      | ADIPOQ | rs1501299 | - | Energy expenditure |
| 63      | LEP  | 164160 | - | Appetite regulation |
| 64      | LEPR  | rs1805094 | - | |
| 65      | INSC2 | rs7566605 | - | Regulation of cholesterol and fatty acid synthesis |
|         |      | rs17782515 | - | |
| 66      | MC4R  | rs1943227 | - | Energy homeostasis, appetite regulation |
|         |      | rs1943218 | - | |
|         |      | rs17066829 | - | |
|         |      | rs9966412 | - | |
|         |      | rs17066959 | - | |
|         |      | rs9965495 | - | |
|         |      | rs12970134 | - | |
|         |      | rs17706833 | - | |
|         |      | rs11873305 | - | |
|         |      | rs8091237 | - | |
|         |      | rs7240064 | - | |
| 67      | PCSK1 | rs2539118 | - | Insulin resistance |
| 68      | PPARG | rs1801282 | - | Increased BMI |
| 69      | ADBR2 | rs1042714 | - | Adaptive thermogenesis |
|         |      | rs1042713 | - | |
| 70      | ADBR3 | rs4994 | - | |
| 71      | GHRP  | rs966217 | - | Appetite regulation |
| 72      | FABP2 | Ala54Thr-polymorphism | - | Fatty acid uptake |
| 73      | APOA5 | rs964184 | - | Lipoprotein metabolism |
|         |      | rs662799 | - | |
| 74      | APOA1 | rs670 | - | |
| 75      | LPC   | rs2070895 | - | |
| 76      | CETP  | rs3764261 | - | |
| 77      | MTNR1B | rs10830963 | - | Appetite regulation |
| 78      | NPY   | rs16147 | - | |
| 79      | GIPR  | rs2287019 | - | Insulin signaling |
| 80      | IRS1  | rs1522813 | C>A/G>C | Blood glucose homeostasis |
|         |      | rs2943641 | T>A/T>C | |
| 81      | TCF7L2 | rs12255572 | G>T | Lactose intolerance, adult type (#223100) |
|         |      | rs7903146 | C>G/C>T | |
| 82      | PCSK1 | rs6232 | T>C | Energy metabolism |
|         |      | rs6234 | C>C | |
| 83      | MCM6 (*601806) | rs4988355 | C>T (C) | |
|         |      | rs182549 | G>A (G) | |
|         |      | rs145946881 | G>C (G) | |
| 84      | HLA-DQA1 (*146880) | rs2187668 | C>T (C) | Susceptibility to celiac disease 1 (#212750) |
|         |      | rs2395182 | G>T (G) | |
|         |      | rs4639334 | G>A (G) | |
|         |      | rs4715386 | A>G (G) | |
|         |      | rs7454108 | T>C (C) | |
| 85      | HLA-DQB1 (*604305) | rs7775228 | T>C (C) | |
### Tab. VII. Continues.

| Sr. No. | Gene         | SNP                  | Alleles | Gene function                              |
|---------|--------------|----------------------|---------|--------------------------------------------|
| 86      | HJV (608374) | rs74315323           | C>A     | Hemochromatosis, type 2A (#602390)         |
|         |              | rs74315324           | G>A     |                                            |
|         |              | rs74315325           | A>T     |                                            |
|         |              | rs74315326           | A>G     |                                            |
|         |              | rs28940586           | A>C,G   |                                            |
|         |              | rs74315327           | A>G     |                                            |
|         |              | rs121434574          | G>C,T   |                                            |
|         |              | rs76205063           | (GA)G>GA|                                            |
|         |              | rs121434575          | T>A     |                                            |
| 87      | SLC40A1 (OMIM 604653) | rs104893662 | T>A,G   | Hemochromatosis, type 4                    |
|         |              | rs28939076           | G>T     |                                            |
|         |              | rs878854984          | (CAA)G>(CAA)G |                                        |
|         |              | rs104893663          | T>A,C   |                                            |
|         |              | rs104893670          | C>A,T   |                                            |
|         |              | rs104893671          | C>A     |                                            |
|         |              | rs104893672          | T>A     |                                            |
|         |              | rs104893673          | C>A     |                                            |
|         |              | rs104893664          | C>T     |                                            |
| 88      | HFE (615609) | rs1800562            | G>A     | Hemochromatosis                             |
|         |              | rs1799945            | C>G,T   |                                            |
|         |              | rs1800750            | A>T     |                                            |
|         |              | rs1800758            | G>A     |                                            |
|         |              | rs28954889           | G>A     |                                            |
|         |              | rs111035557          | G>A     |                                            |
|         |              | rs28954595           | A>C     |                                            |
|         |              | rs111035558          | G>C,T   |                                            |
|         |              | rs28954596           | T>C     |                                            |
|         |              | rs28954597           | G>C     |                                            |
|         |              | rs111035653          | A>C     |                                            |
| 89      | TFR2         | rs80359880           | G>C     | Hemochromatosis, type 3                    |
|         |              | rs80359877           | (G)G>(G)G |                                        |
|         |              | rs80359879           | A>T     |                                            |
|         |              | rs41305501           | C>T     |                                            |
|         |              | rs80359889           | T>C,G   |                                            |
| 90      | FTH1         | rs387906549          | T>A     | Hemochromatosis, type 5                    |
| 91      | ADH1B (103720) | rs1229984          | A>G     | G/C, higher alcohol consumption             |
|         |              | rs2066702            | C>T     | A/T, acetaldehyde accumulation              |
| 92      | ADH1C (103730) | rs1693482          | C>T     | Type II alcoholism                          |
|         |              | rs698                | T>A,C   | (C)                                         |
| 93      | ALDH2 (100650) | rs671               | G>A     | Acute alcohol sensitivity (#610251)        |
| 94      | CYTP1A2 (+124060) | rs7625551          | C>A     | Higher risk of nonfatal myocardial infarction |
| 95      | ADORA2A (102776) | rs5751876          | T>C     | Greater caffeine sensitivity, sleep impairment, increased beta activity during non-REM sleep |
|         |              | rs35320474          | delT    | Greater caffeine-induced anxiety            |
| 96      | DRD2         | rs1110976           | T>G     | Greater caffeine-induced anxiety            |
| 97      | COMT         | rs4680              | G>A     | Higher risk of acute myocardial infarction  |
| 98      | ALDOB (6127241) | rs1800546         | C>G     | Fructose intolerance (#229600)              |
|         |              | rs76917243           | G>T     |                                            |
|         |              | rs118204425         | AAGdel  | (del)                                      |
| 99      | UGT1A1 (191740) | rs6742078          | G>T     | Bilirubin serum level (#601816)            |
| 100     | G6PD (505900) | rs1050828           | C>T     | Nonspherocytic hemolytic anemia (#300908)   |
| 101     | BCO1         | rs12954922          | A>T     | Reduced conversion of beta-carotene to retinol|
|         |              | rs7501331           | C>T     |                                            |
ing, precise evaluation of the dietary intake (DI) as well as of physical activity (PA) is crucial. Nutritional screening ought to be considered as an essential part of clinical assessment for every patient on admission to healthcare set-ups, as well as on change in clinical conditions. Therefore, a detailed nutritional assessment must be performed every time nutritional imbalances are observed or suspected.

**Dietary Intake (DI) assessment** is a multidimensional and complex process. Traditionally, DI is assessed through self-report techniques including diet records, FFQs (food frequency questionnaires), and recalls. But due to reporting errors such as biases, random errors, misestimations, and nutrient databases-linked errors, questions arise about the adequacy of self-reporting dietary intake.

Table VII: Continues.

| Sr. No. | Gene | SNP          | Alleles   | Gene function                                      |
|---------|------|--------------|-----------|----------------------------------------------------|
| 102     | GC   | rs2282679    | T>G (G)   | Lower vitamin D levels                             |
|         |      | rs4588       | G>T (T)   |                                                    |
|         |      | rs842999     | C>G (C)   |                                                    |
| 103     | SLC23A1 | rs33972513   | C>T (T)   | Reduction of circulating levels of vitamin C       |
| 104     | SLC5A6 | rs11558471   | A>G (G)   | Susceptibility to diabetes mellitus                |
| 105     | SLC5A6 | rs1395       | C>A (A)   | Reduced intestinal uptake, cellular delivery, and transplacental transport of pantothenate and biotin |
| 106     | TCN2  | rs1801198    | C>G (G)   | Decreased serum vitamin B12, increased homocysteine|
| 107     | TTPA  | rs4501570    | G>A (A)   | Vitamin E deficiency                               |
|         |      | rs4587328    | T>C (C)   |                                                    |
|         |      | rs4606052    | C>T (T)   |                                                    |
| 108     | VDR   | rs751256     | A>G (G)   | Immune weakness, increased cancer risk, early bone loss, increased cognitive decline risk, mood disorders |
| 109     | CYP2R1 | rs10741657   | A>G (G)   | Lower vitamin D levels                             |
|         |      | rs10766197   | A>G (A)   |                                                    |
| 110     | LPA   | rs10455872   | A>G (G)   | Coronary artery disease                            |
|         |      | rs3798220    | C>T (C)   | Cardiovascular events risk                         |
| 111     | CDKN2B-AS1 | rs10757274 | A>G (G)   | Heart disease risk                                 |
|         |      | rs2385207    | A>G (G)   |                                                    |
|         |      | rs235206     | A>G (G)   |                                                    |
| 112     | intergenic | rs10757278 | A>G (G)   | Heart attack risk                                  |
| 113     | MCR1  | rs17782515   | C>T (C)   | Increased BMI                                      |
| 114     | APOA2 | rs5082       | C>T (C)   | Higher total energy, fat, protein intake           |
| 115     | PCSK1 | rs6232       | A>G (G)   | Higher risk of obesity and insulin sensitivity     |
| 116     | APOA5 | rs662799     | A>G (G)   | Higher risk of early heart attack, less weight gain on high-fat diets |
| 117     | SH2B1 | rs7498665    | A>G (G)   | Obesity, type-2 diabetes                           |
| 118     | SLC2A2 | rs5400       | C>T (T)   | Higher sugar consumption                           |
| 119     | F2    | rs1799963    | A>G (A)   | Higher risk of thrombosis and cerebral stroke      |
| 120     | F5    | rs6025       | A>G (A)   | Higher risk of thrombosis                          |
| 121     | FUT2  | rs602662     | A>G (G)   | Lower vitamin B12 levels                           |
| 122     | ALPL  | rs4654748    | C>T (C)   | Lower Vitamin B6 blood concentration               |
| 123     | CYP2R1 | rs10741657  | A>G (G)   | Lower vitamin D levels                             |
|         |      | rs10766197   | A>G (A)   |                                                    |
| 124     | CC    | rs4588       | G>T (T)   |                                                    |
|         |      | rs842999     | C>G (C)   |                                                    |
| 125     | MTHFR (*607093) | rs1801153 | G>A (A)   | Homocystinuria (#236250)                           |
| 126     | CBS (*613381) | rs121964962 | C>T (T)   | Homocystinuria (#236200)                           |
| 127     | FOXO3 | rs2802292    | C>T (T)   | Longer lifespan                                     |
|         |      | rs2802288    | A>G (A)   |                                                    |
|         |      | rs2802292    | T>G (G)   |                                                    |
| 128     | SIRT1 | rs2236319    | -         | Higher basal energy expenditure                    |
|         |      | rs2227273    | -         |                                                    |
| 129     | PEMT  | rs12325817   | C>C (C)   | Low choline                                        |
| 130     | CHDH  | rs12676      | C>T (T)   |                                                    |
Acknowledgements

This research was funded by the Provincia Autonoma di Bolzano in the framework of LP 15/2020 (dgp 3174/2021).

Conflicts of interest statement

Authors declare no conflict of interest.

Author’s contributions

MB: study conception, editing and critical revision of the manuscript; AKK, MCM, Kristjana D, Kevin D, PC, FF, MAP, MRC, PM, SN, MC, TB: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

References

[1] O’Gorman A, Gibbons H, Brennan L. Metabolomics in the identification of biomarkers of dietary intake. Comput Struct Biotechnol J 2013;4:e201301004. https://doi.org/10.5936/csbj.201301004

[2] McClung HL, Promey LT, Shook RP, Aggarwal A, Gorczyca AM, Sazonov ES, Becofsky K, Weiss R, Das SK. Dietary intake and physical activity assessment: current tools, techniques, and technologies for use in adult populations. Am J Prev Med 2018;55:e93-e104. https://doi.org/10.1016/j.amepre.2018.06.011

[3] Cereda E, Veronese N, Caccialanza R. The final word on nutritional screening and assessment in older persons. Curr Opin Clin Nutr Metab Care 2018;21:24-29. https://doi.org/10.1097/MCO.0000000000000431

[4] Delièvre S, Cyonber L. Is transferrin a good marker of nutritional status? Clin Nutr 2017;36:364-70. https://doi.org/10.1016/j.clnu.2016.06.004

[5] Chen M, Sun Q, Giovannucci E, Mozaffarian D, Manson JE, Willett WC, Hu FB. Dairy consumption and risk of type 2 diabetes: 3 cohorts of US adults and an updated meta-analysis. BMC Med 2014;12:1-14. https://doi.org/10.1186/s12916-014-0215-1

[6] Park Y, Dough KD, Kipnis V, Thompson FE, Potischman N, Schoeller DA, Bao DJ, Midthune D, Troiano RP, Bowles H. Comparison of self-reported dietary intakes from the Automated Self-Administered 24-h recall, 4-d food records, and food-frequency questionnaires against recovery biomarkers. Am J Clin Nutr 2018;107:80-93. https://doi.org/10.1093/ajcn/nqx002

[7] Archer E. The use of implausible data without caveats is misleading. Am J Clin Nutr 2017;106:949-50. https://doi.org/10.3945/ajcn.116.150870

[8] Reber E, Gomes F, Vasiloglou MF, Schuetz PT, Stanga Z. Nutritional risk screening and assessment. J Clin Med 2019;8:1065. https://doi.org/10.3390/jcm8071065

[9] Lardies-Sánchez B, Sanz-París A, Boj-Carceller D, Cruz-Jentoft A. Systematic review: prevalence of sarcopenia in ageing people using bioelectrical impedance analysis to assess muscle mass. Eur Geriatr Med 2016;7:256-61. https://doi.org/10.1118/s40200-017-0302-x

[10] Dhurandhar NV, Schoeller D, Brown AW, Heymsfield SB, Thomas D, Sørensen TL, Speckman JR, Jeunesse M, Allison DB. Energy balance measurement: when something is not better than nothing. Int J Obes 2015;39:1109-13. https://doi.org/10.1038/ijb.2014.199

[11] Schatzkin A, Subar AF, Moore S, Park Y, Potischman N, Thompson FE, Leitzmann M, Hollenbeck A, Morrissey KG, Kipnis V. Observational epidemiologic studies of nutrition and cancer: the next generation (with better observation). Cancer Epidemiol Biomarkers Prev 2009;18:1026-32. https://doi.org/10.1158/1055-9965.EPI-08-1129

[12] McClung HL, Champagne CM, Allen HR, McGraw SM, Young AJ, Montain SJ, Crombie AP. Digital food photography technology improves efficiency and feasibility of dietary intake assessments in large populations eating ad libitum in collective dining facilities. Appetite 2011:369-89. https://doi.org/10.1016/j.appet.2011.10.017

[13] Boushey C, Spoden M, Zhu F, Delp E, Kerr D. New mobile methods for dietary assessment: review of image-assisted and image-based dietary assessment methods. Proc Nutr Soc 2017;76:283-94. https://doi.org/10.1017/S0029665416002913

[14] National Cancer Institute. Automated Self-Administered 24-Hour (ASA24) Dietary Assessment Tool. https://epi.grants.cancer.gov/asa24/. Accessed on: June 26, 2022.

[15] Kristal AR, Kolar AS, Fisher JL, Plasck J, Stumbo P, Weiss R, Paskett ED. Evaluation of web-based, self-administered, graphical food frequency questionnaire. J Acad Nutr Diet 2014;114:613-21. https://doi.org/10.1016/j.jand.2013.11.017

[16] Kondrup J, Rasmussen HH, Hamberg O, Stanga Z, Group AAHEW. Nutritional risk screening (NRS 2002): a new method based on an analysis of controlled clinical trials. Clin Nutr 2003;22:321-36. https://doi.org/10.1016/S0261-5614(03)00033-3

[17] Cereda E. Mini nutritional assessment. Curr Opin Clin Nutr Metab Care 2012;15:29-41. https://doi.org/10.1097/MCO.0b013e32834d7647

[18] Martin CK, Correa JB, Han H, Allen HR, Rood JC, Champagne CM, Gunturk BK, Bray GA. Validity of the Remote Food Photography Method (RPFM) for estimating energy and nutrient intake in near real-time. Obesity 2012;20: 891-99. https://doi.org/10.1038/oby.2011.344

[19] Promey LT, Willis EA, Horas JJ, Mayo MS, Washburn RA, Herrmann SD, Sullivan DK, Donnelly JE. Validity of energy intake estimated by digital photography plus recall in overweight and obese young adults. J Acad Nutr Diet 2015;115:1392-99. https://doi.org/10.1016/j.jand.2015.05.006

[20] Zhu F, Bosch M, Khanna N, Boushey CJ, Delp EJ. Multiple hypotheses image segmentation and classification with application to dietary assessment. IEEE J Biomed Health Inform 2014;19:377-88. https://doi.org/10.1109/JBHI.2014.2304925

[21] Dong Y, Hoover A, Scisco J, Muth E. A new method for measuring meal intake in humans via automated wrist motion tracking. Appl Psychophysiol Biofeedback 2012;37:205-15. https://doi.org/10.1007/s10484-012-9194-1
[55] Reiff GG, Montoya HJ, Remington RD, Napier JA, Metzner HL, Epstein FH. Assessment of physical activity by questionnaire and interview. J Sports Med Phys Fitness 1967;7:135-42.

[56] Kohl HW, Blair SN, PAFFENBARGER Jr RS, Macera CA, Kronenfeld JJ. A mail survey of physical activity habits as related to measured physical fitness. Am J Epidemiol 1988;127:1228-39. https://doi.org/10.1093/oxfordjournals.aje.a114915

[57] Racette SB, Schoeller DA, Kushner RF. Comparison of heart rate and physical activity recall with doubly labeled water in obese women. Med Sci Sports Exerc 1995;27:126-33.

[58] Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med 2003;37:197-206. https://doi.org/10.1136/bjsm.37.3.197

[59] Ridley K, Dollman J, Olds T. Development and validation of a computer delivered physical activity questionnaire (CDPAQ) for children. Pediatr Exerc Sci 2001;13:35-46.

[60] Zivkovic AM, German JB. Metabolomics for assessment of nutritional status. Curr Opin Clin Nutr Metab Care 2009;12:501. https://doi.org/10.1097/MOC.0b013e32832f1916

[61] Akbaraly T, Würtz P, Singh-Manoux A, Shipley MJ, Haapakoski Zivkovic AM, German JB. Metabolomics for assessment of nutrition status. Curr Opin Clin Nutr Metab Care 2009;12:501. https://doi.org/10.1097/MOC.0b013e32832f1916

[62] Cieszczyk P, Leonska-Duniec A, Jastrzebski Z, Zarebska A, Abbot EL, McCormack JG, Reynet C, Hassall DG, Buchan E, Naureen Z, Perrone M, Paolacci S, Maltese PE, Dhuli K, Kurti D, Dautaj A, Casadei A, Fioretti B. Genetic test for the personalization of sport training. Acta Biomed 2020;91. https://doi.org/10.23750/abmn.v91i13-S.10593

[63] Picó C, Serra F, Rodríguez AM, Keijer J, Palou A. Biomarkers concentrations. Am J Clin Nutr 2014;100:1462-69. https://doi.org/10.1155/2014/373782

[64] Guertin KA, Moore SC, Sampson JN, Huang W-Y, Xiao Q, Zheng Y, Yu B, Alexander D, Steffen LM, Boerwinkle E. Human genome-wide association studies for circulating phylloquinone geno.1993.1136

[65] Adamski J, Pischon T, Boeing H. Variation of serum metabolites related to habitual diet: a targeted metabolomic approach in EPIC-Potsdam. Eur J Clin Nutr 2013;67:1100-08. https://doi.org/10.1038/ejcn.2013.147

[66] Zheng Y, Yu B, Alexander D, Steffen LM, Moehrke K, Almon R, Patterson E, Nilsson T, Engfeldt P, Sjöström M. Genetics of fat deposition Eur Rev Med Pharmacol Sci 2018;25:14-22. https://doi.org/10.26355/eurrev_201812_27329

[67] Dhuli K, Ceccarini MR, Preonec V, Maltese PE, Bonetti G, Paolacci S, Dautaj A, Guerri G, Marceddu G, Beccari T, Michelinì S, Bertelli M. Improvement of quality of life by intake of hydroxytyrosol in patients with lymphedema and association of lymphedema genes with obesity Eur Rev Med Pharmacol Sci 2021;25:33-42. https://doi.org/10.26355/eurrev_202112_27331

[68] Vettori A, Pomppuci G, Paolini B, Del Ciondolo I, Bressan S, Kundrich M, Menonu A, Sillanpää M, Lehtimäki T, Mikkilä V, Karlowska A. The Pro12Ala polymorphism of the peroxisome protein 3e ketohexokinase isoform gene expression in cultured human muscle cells. FEBS J 2005;272:3004-14. https://doi.org/10.1016/j.fjes.2005.070746

[69] Vettori A, Pomppuci G, Paolini B, Del Ciondolo I, Bressan S, Kundrich M, Menonu A, Sillanpää M, Lehtimäki T, Mikkilä V, Karlowska A. The Pro12Ala polymorphism of the peroxisome protein 3e ketohexokinase isoform gene expression in cultured human muscle cells. FEBS J 2005;272:3004-14. https://doi.org/10.1016/j.fjes.2005.070746

[70] Vettori A, Pomppuci G, Paolini B, Del Ciondolo I, Bressan S, Kundrich M, Menonu A, Sillanpää M, Lehtimäki T, Mikkilä V, Karlowska A. The Pro12Ala polymorphism of the peroxisome protein 3e ketohexokinase isoform gene expression in cultured human muscle cells. FEBS J 2005;272:3004-14. https://doi.org/10.1016/j.fjes.2005.070746