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Report of a Meeting

Paving the way for improved action: how nuclear techniques can advance the assessment of malnutrition

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ABSTRACT

Malnutrition in all its forms—including undernutrition, micronutrient deficiencies, and overnutrition—continues to rise globally, driven by complex structural and biological factors that contribute to an increased risk of noncommunicable diseases (NCDs). Addressing this multifaceted challenge requires precise assessment tools. To advance this effort, the International Atomic Energy Agency held a technical meeting of global experts to explore how nuclear techniques, specifically stable isotope tracers and imaging methods, and emerging technologies can enhance nutrition assessments to better address malnutrition. On the basis of the meeting's discussions, this report highlights the application of nuclear techniques to improve the measurement of body composition across life stages and disease states, assess nutrient bioavailability more holistically, elucidate nutrient flux under conditions of malnutrition, trace metabolic processes linked to NCDs, and refine nutrient requirements to better reflect diverse populations. The integration of nuclear techniques with emerging tools such as artificial intelligence and model-based compartmental analysis was emphasized as a key strategy to enhance their utility. This report also highlights the important role of nuclear techniques in addressing malnutrition and calls for interdisciplinary collaboration and reduced research silos to fully leverage these techniques to combat this condition more effectively.

Keywords: double burden of malnutrition, stable isotope techniques, body composition, nutrient bioavailability, nutrient flux, nutrient requirements, artificial intelligence, model-based compartmental analysis, breaking research silos

Abbreviations used: CT, computed tomography; DBM, double burden of malnutrition; DLW, doubly labeled water; DXA, dual-energy X-ray absorptiometry; IAEA, International Atomic Energy Agency; LMICs, low- and middle-income countries; MBCA, model-based compartmental analysis; NAFLD, nonalcoholic fatty liver disease; NCD, noncommunicable disease; TEE, total energy expenditure.

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Summary of meeting

The global prevalence of malnutrition, in all its forms, continues to rise [1]. Efforts to address this public health problem are challenged by the complexity of malnutrition itself, as well as the reliance on simple and often non-specific assessment tools to help understand this condition. However, the application and broader dissemination of nuclear techniques offers promise in helping to mitigate some of these challenges. This report highlights areas where nuclear and imaging techniques, along with emerging technologies, can advance our understanding and assessment of malnutrition to better address this multifaceted issue. The topics and examples presented are drawn from discussions at a technical meeting hosted by the International Atomic Energy Agency (IAEA).

The authors met in person, or virtually, at the IAEA Headquarters in Vienna, Austria from October 10–13, 2023, following the agenda available at https://www.iaea.org/events/evt2103664. This meeting titled 'The Role of Nuclear Techniques to Tackle Nutritional Challenges in the 21st Century,' brought together global experts in the use of nuclear techniques in nutrition research with the aim to review developments in this field and explore how these techniques can be better leveraged to address current nutritional challenges. The overarching goals were to share insights on the use of nuclear techniques in nutrition, reflect on progress made across distinct areas, and guide future directions to strengthen their application for improved nutritional outcomes in both public health and clinical settings. Secondary objectives included expanding professional networks, fostering greater collaboration among diverse researchers, and generating recommendations to help the IAEA more effectively support Member States in translating scientific advancements into practice.

Introduction

The double burden of malnutrition (DBM) refers to "malnutrition in all its forms," which includes the coexistence of undernutrition—wasting, stunting, underweight, or micronutrient deficiencies—and overnutrition, characterized by overweight and obesity, in communities, households, or even individuals across their life course [2]. The prevalence of the DBM varies greatly within and across countries [3], yet the global prevalence is increasing. The etiology of the DBM is influenced by many structural and behavioral factors that make up the nutrition transition, a decrease in healthy diets along with low physical activity patterns [4]. This shift has also led to the increased prevalence of micronutrient deficiencies in individuals with overweight or obesity, a phenomenon known as "hidden hunger" due to its lack of physically apparent symptoms [5]. Some have advocated for the term the "triple burden of malnutrition" to highlight the co-occurrence of undernutrition, overnutrition, and micronutrient deficiencies [6]. The confluence of biological and environmental factors that support the development of noncommunicable disease (NCDs), low physical activity, and excess adiposity as well as those limiting growth or promoting micronutrient deficiencies, illustrates the complexity of stemming the rise of malnutrition, especially in low- and middle-income countries (LMICs) that are undergoing the nutrition transition.

Malnutrition is a complex condition, yet it is often assessed through simple and nonspecific anthropometric markers such as low birth weight, wasting, stunting, BMI, and body circumferences [7]. Although anthropometric indices have widespread utility as they are convenient, efficient, and have minimal costs [8], their main limitation is their capacity to capture only one aspect of nutritional imbalance with limited capacity to differentiate between lean and fat masses [9]. This is concerning in both pediatric [10,11] and older adult [12] populations, whose body composition and energy expenditure are changing rapidly (e.g., growth compared with sarcopenia, lean gain compared with lean loss, etc.) with wholly different outcomes. Biochemical indicators can also be used to assess malnutrition and commonly used indicators for protein-energy and micronutrient malnutrition include serum albumin, prealbumin, transferrin, retinol binding protein, among others [13,14]. Their effectiveness as sensitive indicators for malnutrition, however, is severely limited by the presence of concurrent conditions that can affect their specificity (e.g., inflammation, infection, or diseases of the liver, kidney, or thyroid) [13,15]. Measures of nutritional inadequacy, excess, and imbalance are also influenced by diet quality (optimal micronutrient composition of diets) and physical activity, both of which have marked influences on metabolism and nutrient flux [7] yet are not fully captured by these indices.

Nuclear approaches, including stable isotope tracer methods and imaging techniques, have been instrumental in bridging the gaps between conventional anthropometric and biochemical methods [16] as they can safely [17] assess a diverse array of outcomes related to human health and nutrition with a high degree of accuracy and precision (Table 1) [18–33]. Several nuclear and imaging techniques have been used to discern the differences between fat and lean masses [34,35], determine energy expended for physical activity levels [36–38], and the bioavailability and storage of micronutrients that are used for physiologic function [39,40], all of which are ways to assess the etiology of malnutrition. Among these, assessing body composition across the life course is a particularly important application for understanding malnutrition. These assessments are critical in evaluating NCD risk and monitoring its progression, by identifying high adiposity (an index of metabolic load) or low lean mass (a composite index of homeostatic metabolic capacity), or their combination as in sarcopenic obesity [41,42]. This issue is important with reference to the life-course exposure to the DBM, whereby wasting and stunting in early life deplete mass and homeostatic function, whereas subsequent obesity further perturbs homeostasis and drives the emergence of overt NCDs [7,43]. In addition, as the use of nuclear techniques becomes more widespread, the integration with new tools, such as artificial intelligence and novel analysis methods, will greatly enhance our ability to understand and assess malnutrition.

Given the complexities of malnutrition, effective strategies to address this condition must prioritize both prevention and treatment efforts. Prevention programs are especially critical in LMICs, where access to services often requires a focus on reducing the future development of NCDs. Addressing the DBM requires coordinated action across multiple levels. Nuclear techniques can serve as valuable tools to assess the effectiveness of interventions and to strengthen programs that target the DBM.

This report summarizes how nuclear techniques have advanced the understanding of malnutrition and how new technologies can be harnessed to improve the assessment of energy expenditure, body composition, nutrient flux, nutrient bioavailability, and requirements. As well, a brief discussion is provided on the importance of strengthening collaboration among groups to better integrate new and diverse methods for assessing malnutrition that will maximize the efficiency and productivity of research and intervention programs while minimizing funding needs.

TABLE 1
Comparison of techniques used to measure nutrition-related outcomes and the advantages of using nuclear techniques.

Outcome	Nuclear technique(s)	Other method(s)	Advantages of nuclear technique(s) in vivo
Energy expenditure [18–20]	Doubly labeled water (DLW)	Direct or indirect calorimetry Predictive equations Activity trackers: Physical activity questionnaires Heart-rate monitors Accelerometers Pedometers	Ability to measure habitual energy expenditure in free-living individuals Relatively simple, noninvasive and safe Can be used in many populations, including infants and children, older adults, those with acute or chronic conditions, or those who are pregnant and/or lactating Long-term measurement (provides an assessment of average energy expended over a 14-d period) High degree of accuracy Can be used to estimate activity energy expenditure when combined with measurement of basic/resting metabolic rate Can be used to validate more subjective estimates of energy expenditure
Body composition [21–23]	Deuterium dilution Dual-energy X-ray absorptiometry (DXA) Computed tomography (CT) Whole-body potassium counting (WBKC)	Air-displacement plethysmography Hydrostatic/underwater weighing Bioelectrical impedance (BIA) Anthropometry Weight and height Body/waist circumferences Skinfold thickness Derived indices (for example, BMI, waist-to-hip ratio, waist-to-height ratio, fat mass index, fat-free mass index)	Accurately and precisely quantifies and differentiates between fat-free and fat masses For deuterium dilution, relatively simple, noninvasive and safe For DXA and CT, they are quick and considered noninvasive, but individuals are exposed to a low dose of radiation For CT, it provides a detailed visualization and quantification of tissues, organs, and constituents such as muscle and adipose tissue For WBKC, it is the reference standard to measure the metabolically active tissue, the body cell mass which is useful in conditions of changed hydration status Can be used in many populations, as described for the DLW technique Can be used to validate simpler techniques such as BIA and anthropometry
Nutrient flux [24, 25]	Stable isotopically labeling substrates with ^{13}C or ^{15}N, either coupled with deuterium oxide ($^{2}H_2O$) or alone, and tracing their fate in vivo Substrates used in metabolic flux studies include glucose, fructose, pyruvate, glutamine, aspartate, arginine, acetate, lactate, alanine, glycerol, propionate, among others	In vitro metabolic flux methods	Ability to precisely capture the physiology of a biological process (for example, gluconeogenesis) or a disease state (for example, NAFLD) more thoroughly than with in vitro studies alone Stable isotope labels provide analytical, logistic, and safety advantages
Nutrient bioavailability[1] [26–33]	All in vivo methods:[2] Iron: erythrocyte iron incorporation technique, iron isotope dilution technique Zinc: dual isotope tracer ratio absorption technique Calcium: dual stable isotope technique Vitamin A: retinol isotope dilution technique Vitamin B_{12}: [^{13}C]-cyanocobalamin as a tracer Folate (vitamin B_9): dual-labeled stable isotope technique	All in vivo methods: Iron: blood markers (for example, hemoglobin, ferritin, soluble transferrin receptor); oral iron absorption test Zinc: serum or plasma zinc concentration Calcium: balance studies, urinary calcium excretion Vitamin A: serum retinol concentration, relative dose–response (RDR) and modified RDR tests Vitamin B_{12}: Schilling's test (not in use due to radioactive cobalt use); qualitative CobaSorb test folate (vitamin B_9): plasma, serum or urinary folate	For all nutrients: stable isotope techniques to measure nutrient bioavailability offer a high degree of accuracy, are noninvasive, and safe to use in many populations, including infants, children, pregnant and lactating individuals as well as older adults. They can be used to validate prediction equations and in vitro models. For iron, using the iron isotope dilution technique: ability to accurately quantify long-term body iron balance (for example, absorption and loss); direct quantification of iron from dietary sources or supplementation. For vitamin A: provides an accurate quantitative assessment of total body stores of vitamin A (from deficiency to excess) in comparison to methods that only provide information on deficiency alone and/or are semiquantitative screening tests.

Abbreviations: IAEA, International Atomic Energy Agency; NAFLD, nonalcoholic fatty liver disease.

[1] Only a select number of nutrients are described in this table and paper. The nutrients described here were part of presentations and discussions that comprised a technical meeting, hosted by the IAEA, which discussed current nutritional challenges and how nuclear techniques could address them.

[2] In vitro methods and prediction equations do exist to assess the bioavailability of the nutrients listed; however, for simplicity, the comparisons presented here focus on nuclear techniques used in vivo to measure nutrient bioavailability compared with nonnuclear techniques used in vivo.

Energy Expenditure and Requirements

The two most common forms of malnutrition, undernutrition, and overnutrition, result from an imbalance between energy intake and energy expenditure. Doubly labeled water (DLW) is the reference standard method to assess total energy expenditure (TEE) in free-living individuals [44]. In this method, individuals consume water labeled with the stable isotopes of deuterium (^{2}H) and oxygen-18 (^{18}O) which equilibrates in the body water pool within 4–6 h [45]. The differential elimination of these isotopes is monitored over a 1-to-3-wk period through the collection of urine, saliva, or blood samples, which are then analyzed using mass spectrometry [45]. The relative loss of the 2 isotopes is used to calculate carbon dioxide production, a proxy for TEE. DLW is noninvasive, safe, and applicable in many populations, including children [46], older adults [47], in individuals with acute or chronic illnesses [48], and those who are hospitalized or lactating [49].

Beyond assessing energy expenditure, accurately estimating human energy requirements is essential for addressing malnutrition and informing public health initiatives, such as nutrient labeling, the formulation of food aid rations, the development of school meal programs, feeding practices for infants and toddlers, and menu planning for older adults. The DLW method plays an important role in this process by enabling precise assessments of energy expenditure under free-living conditions, thereby supporting the development of more accurate dietary guidelines to better address the DBM.

The application of DLW has expanded our understanding of energy needs in different populations and circumstances. For instance, a study of growth-restricted Brazilian children demonstrated that energy requirements, when corrected for metabolically active tissue, did not vary by growth status [50]. DLW measurements have also contributed to the development of new predictive equations for adults in LMICs [51], and validated less expensive tools, such as physical activity questionnaires for adolescents [52], which allows for improved access to affordable methods of estimating energy expenditure and needs in resource-limited settings.

The use of the International Atomic Energy Agency (IAEA) DLW database has further emphasized the value of DLW data. Pontzer et al. [53] mapped the life-course trajectory of energy metabolism, identifying distinct phases of energy expenditure across the lifespan with data from this database. Subsequent analyses indicated that age-related declines in mitochondrial efficiency contributed to the observed reductions in energy expenditure, and thereby lower requirements, among older adults [54]. These particular findings highlight the pressing need to update energy requirement guidelines to reflect regional and population-specific differences. Without diverse, context-specific normative data, the quantification of energy needs remains challenging. DLW-based studies among young adults [55] and adolescents [56] in Brazil, children in Mauritius [57], and adults in India [58] found that current dietary reference intake equations overestimated energy requirements compared with estimates based on TEE measured by DLW, further illustrating the importance of generating population-specific data. More recently, the Institute of Medicine [59] reported significant reductions in TEE between the ages of 20 and 80 y, even after adjusting for body composition, emphasizing the need for revisiting the calculation of Dietary Reference Intakes for Energy.

Taken together, these examples demonstrate the importance of using stable isotope techniques to reassess energy requirements under diverse physiological and context-specific conditions. Continued research using this method is necessary for understanding energy needs in different situations and populations to then develop targeted recommendations on energy intake to improve health and mitigate the DBM.

Body Composition

Accurately assessing body composition, which refers to the proportion of fat and lean mass, provides valuable data on an individual's nutritional status, particularly in the face of adverse conditions that may disrupt healthy growth, aging, and physiological homeostasis. There are several nuclear techniques available to monitor changes in body composition across the lifespan. The techniques range from stable isotope tracers to more advanced imaging methods. By integrating these techniques with emerging technologies, such as artificial intelligence, researchers and clinicians can enhance the accuracy of body-composition assessments, ultimately improving the diagnosis and treatment of malnutrition and related health conditions in a broad sample of ages and disease states.

Monitoring changes in body composition provides important data on the relative health status of an individual. One commonly used nuclear technique, deuterium dilution, involves administering a single oral dose of deuterium-labeled water, allowing 3–5 h for the deuterated water to equilibrate within the body's water pool [60]. Biological samples (saliva, urine, or blood) are collected before and after dosing to estimate total body water, which is then used to calculate fat and fat-free masses [60]. This simple, noninvasive protocol can be applied across the lifespan, from infants to older adults, and is particularly effective for tracking body compositional changes in individuals experiencing either undernutrition or overnutrition. Deuterium dilution has been used to evaluate the impact of interventions or programs intended to treat adverse body composition. For example, Plasqui et al. [61] studied changes in body composition in adults with overweight and obesity during a 6-mo dietary intervention, whereas a study in Sierra Leone assessed changes in body composition in children treated for moderate acute malnutrition after the consumption of specialized nutritious foods [62]. Similarly, a trial in Burkina Faso found that children with malnutrition fed lipid-based nutrient supplements gained more fat-free mass during rehabilitation than those fed corn-soy blends [63], whereas another study with children randomly assigned to 1 of 4 different dietary treatments reported no significant differences in body composition during malnutrition recovery [64]. Beyond interventions, deuterium dilution has also been used to monitor body composition in children undergoing chemotherapy for lymphoma or solid tumors [65]. Indeed, deuterium dilution is a safe, reliable method for accurately assessing body composition across various populations, providing valuable insights into conditions impacting nutritional status and the effectiveness of dietary interventions intended to prevent and treat malnutrition.

In terms of imaging techniques, dual-energy X-ray absorptiometry (DXA) and computed tomography (CT) provide accurate and detailed regional estimates of body-composition. DXA is a noninvasive method, emitting a low dose of radiation, with minimal participant burden that precisely quantifies body composition across 3 distinct compartments: fat, lean, and bone masses [66]. DXA was designed to measure bone mineral density [67], and it also provides detailed assessments of lean soft tissue and regional distribution of adipose tissue. Standard DXA-derived images report whole-body and regional fat and lean masses, including arms and legs, trunk, head, and abdomen [68]. Yet advancements in artificial intelligence, in particular deep learning models, have continued to improve DXA analysis. Deep learning

models have been developed to now consider all the global and localized variations of fat, lean mass, and bone in whole-body images. For instance, Glaser et al. [69] demonstrated that combining sequential raw DXA images with clinical risk factors created a more robust model for predicting adult mortality when compared with clinical risk factors alone. Similarly, Leong et al. [70] showed that deep learning models could be trained to report the distribution of body fat and muscle distribution so accurately that they could generate analyzable DXA images from 3D optical surface scans. The increasing use of deep learning not only enhances the precision of body-composition analysis using DXA but also highlights its potential in aging research and the design of therapeutic interventions for malnutrition.

CT offers a precise assessment of body composition at the tissue–organ level by generating high-resolution images [71]. In addition to quantifying muscle mass, CT also provides an assessment of muscle composition, including fat infiltration and deposition in skeletal muscle. This phenomenon may reflect age-related changes in skeletal muscle function and could serve as a potential risk factor for chronic disease, such as type II diabetes [72]. The increasing availability of CT imaging from patient medical records has made body-composition data readily accessible to researchers, further enhancing its utility in both clinical and research settings. Research using CT commonly focuses on skeletal muscle mass and adipose tissue, including subcutaneous, visceral, and intramuscular types [73,74]. However, the advent of fully automated software is ushering in a new era that allows for the inclusion of various organs and tissues in body-composition analysis, expanding the scope, practicality, and precision of these evaluations [75].

In summary, nuclear techniques have become essential tools in accurately monitoring changes in body composition over time. As advancements in technology continue to refine these tools, their ability to measure body composition across various settings and conditions will only improve and support better health outcomes for individuals and communities affected by malnutrition.

Nutrient Flux

Understanding nutrient metabolism is vital for addressing malnutrition, yet characterizing metabolic processes *in vivo* is complex. Recent advancements in physiological, analytical, and mathematical techniques have made *in vivo* nutrient flux analysis more accessible and less invasive [24]. To that end, stable isotopes allow for the study of metabolic processes (e.g., lipid and glucose flux) *in vivo* [24,25], to understand individual and community responses to different nutritional environments. This research distinguishes the metabolic effects of both excess and inadequate nutrient intake, which is crucial in the context of malnutrition where individuals can experience both under- and overnutrition throughout the life course.

Assessing an individual's lipid flux using stable isotope techniques allows researchers to understand alterations in lipid metabolism across different malnutrition states and identify nuanced, individual variations in metabolic processes. For example, in severe acute malnutrition, elevated lipid flux facilitates energy production in a calorie-restricted state to conserve and redirect fuel for the maintenance of biological systems [76]. Conversely, in an obesogenic state, high lipid flux promotes fat deposition to preserve energy reservoirs, ultimately contributing to the development of obesity [77]. Stable isotope techniques also play an important role in evaluating the effects of excess or reduced lipid flux across populations and are also useful in their ability to investigate metabolic disease phenotypes in different ethnic groups and age categories. This is especially relevant among populations who are undergoing rapid social, economic and nutritional transitions and are at high genetic risk for NCDs. For instance, for adults of African descent, elevated rates of lipolysis, gluconeogenesis, and *de novo* lipogenesis are not early characteristics of diabetes, despite a high genetic predisposition to these metabolic alterations [78,79]. Continuing to leverage stable isotope techniques can help define metabolic profiles across diverse populations to then guide targeted interventions that mitigate the impacts of malnutrition at the population level.

A deeper understanding of glucose metabolism and flux is equally important in addressing malnutrition as disruptions in glucose homeostasis can contribute to undernutrition-related wasting and overnutrition-related metabolic disorders. For instance, in cachexia and metabolic disease states, such as cancer and diabetes, protein catabolism is upregulated to supply precursors for gluconeogenesis [80,81]. Stable isotope tracers, such as ^{13}C-labeled glucose precursors and deuterated water, allow researchers to quantify hepatic glucose production in healthy populations and those with metabolic disease [25,82]. Populations with varying health and nutritional statuses may also have different pathways of nutrient flux. Indeed, in healthy populations, Fromentin et al. [83] suggest that dietary protein intake only contributes minimally to postprandial glucose production, yet the effects may greatly differ for those exposed to chronic undernutrition or overnutrition. In such cases, metabolic adaptations could alter the contribution of dietary protein to gluconeogenesis, potentially affecting overall glucose homeostasis. Such evidence highlights the value of stable isotope tracers for distinguishing the varied metabolic responses to dietary exposures in individuals or communities affected by specific conditions.

Understanding nutrient flux using stable isotope techniques across populations is an important approach for addressing malnutrition. Such data can support more targeted interventions and ultimately guide efforts to alleviate the metabolic consequences of malnutrition. Future research using these techniques can address gaps in knowledge in malnutrition treatment, especially if focused on interactions between nutrient fluxes in individuals exposed to both under- and overnutrition at different life stages.

Nutrient Bioavailability and Requirements

Micronutrient deficiencies occur when dietary patterns include foods that are perhaps energetically sufficient, but limited or devoid of micronutrients. The extent to which diets provide essential nutrients for optimal health status is largely determined by diet quality and nutrient bioavailability. Nutrient bioavailability is influenced by food-related factors, such as the food matrix and meal composition, the presence of antinutritional factors (e.g., phytate), processing and preparation, as well as host-related factors, such as age, genetics, physiological stage, body composition, or the presence of deficiencies, disease (e.g., malaria), inflammation or disruptions in the microbiome [84,85]. Stable isotope techniques have become important tools in studying nutrient bioavailability in the presence of these factors, providing critical information into strategies for addressing micronutrient-related malnutrition.

Historically, nutrient bioavailability has been studied from the perspective of single foods or meals. Over time, tracer protocols were developed to quantify how different food matrices reduce the bioavailability of folate from supplements or fortified foods, and the dependence of the administered folate form [86,87]. For iron and zinc,

several studies have assessed bioavailability across the life span (e.g., infants, children, adults, etc.) and from fortified and biofortified foods (e.g., maize [26], yogurt [88], cereals [89], etc.) or meals [90–92]. Intrinsic labeling approaches have also been developed to allow an isotopic tracer to be embedded directly in the food matrix, thereby providing a more accurate assessment of nutrient bioavailability from certain foods [93,94].

These studies not only inform our understanding of absorption but also have important implications for estimating nutrient requirements in specific populations. For example, a study in children from Bangladesh with evidence of environmental enteric dysfunction, a condition associated with impaired growth, demonstrated significantly lower zinc absorption using stable isotope tracers compared with healthy infants in a high-resource setting [95]. This finding suggests that dietary zinc requirements may be 2- to 3-fold higher in vulnerable populations affected by compromised gut function. Similarly, a study conducted in India explored the paradox of the low prevalence of vitamin B_{12} deficiency despite low intake estimates [96]. Using ^{13}C-cyanocobalamin as a tracer [96], researchers found significant B_{12} absorption via enterohepatic recirculation and colonic reabsorption mediated by the microbiome [97], leading to a lower daily excretion of B_{12}, and thus lower physiological requirements.

Although tracer protocols are informative at the individual level, applying a single fixed factor to assess bioavailability may not accurately account for population variability, variations in nutrient homeostasis, or differences in control mechanisms for different nutrients. To address this, researchers have formulated meal-based and diet-based prediction equations to estimate bioavailability. Typically focused on only food-related factors, prediction equations for iron [98–101], zinc [102], and calcium [103] may still reflect differences in nutrient bioavailability across divergent dietary patterns, including omnivorous, vegetarian, and vegan diets [104]. However, such prediction equations have rarely been validated, and reliable data on dietary factors such as antinutrients are oftentimes lacking, subjecting these equations to criticism with respect to their accuracy [105]. To address these limitations and generate comprehensive data beyond single food or meal studies, stable isotope techniques can be leveraged in studies of whole-diet interventions. Once validated, prediction equations could significantly enhance our ability to estimate nutrient bioavailability with a greater degree of accuracy.

Another promising method is the iron isotope dilution technique, which has gained renewed interest for estimating both iron absorption and loss [106]. This technique relies on the fact that iron, once absorbed, has a long retention time in the body as there is no active excretion route. Thus, any ingested stable iron isotope (^{57}Fe) from food or supplements is repeatedly recycled and detectable for several years. Incorporated into erythrocytes after consumption, ^{57}Fe eventually enters the circulating iron pool upon cell breakdown, reaching isotopic equilibrium in about a year in adults. Any newly consumed iron with a natural abundance (e.g., ^{56}Fe) dilutes the isotopically enriched iron pool, leading to a gradual decline in ^{57}Fe concentration. Periodic blood samples to measure changes in total body iron over months or years allow for the estimation of true dietary iron bioavailability with minimal data input [27,107]. It is worthwhile to explore if this dilution approach can be adapted for other nutrients or iron itself under various conditions, such as in the presence of inflammation, infection or states of malnutrition.

Model-based compartmental analysis (MBCA) can be a useful tool to further enhance our understanding of micronutrient metabolism in the context of malnutrition [108]. MBCA has been applied to both animal and human data to describe and quantify the metabolism of vitamins (e.g., A, D, and B_6), minerals (calcium, zinc, copper, iron), hormones, lipoproteins, and cell culture systems [109–117]. Researchers postulate a compatible compartmental model and then test and refine the model using kinetic data obtained by following either tracer responses after the administration of a stable isotope or perturbing unlabeled moieties. The data are analyzed with accessible modeling software (e.g., Windows version of the Simulation, Analysis, and Modeling software) [118] to obtain a final fit and generate kinetic parameters describing the system, as well as estimates of nutrient compartment masses and turnover rates. Once a model is developed, it can be adjusted to accommodate new information, advance knowledge, and allow for hypothesis testing. By simulating a specified change (e.g., altered vitamin A balance, lactation, inflammatory status, etc.), the impacts on nutrient kinetics can be evaluated. The use of MBCA has been important in advancing stable isotope dilution methods for assessing nutrient status and can serve as a substitute for resource- and time-intensive pilot studies [119,120].

In conclusion, there are new approaches that allow for a more holistic perspective, that is, embracing both food-based and host-related factors, when studying nutrient bioavailability in the context of malnutrition. Such approaches hold promise to better clarify and quantify differences in nutrient bioavailability between geographies and population groups. This will eventually help evaluate the nutritional quality of diets more accurately and will provide more granularity in estimating nutrient needs to help avert malnutrition.

The Way Forward

Malnutrition remains a significant global public health issue that requires interdisciplinary approaches for effective solutions. Nuclear techniques and emerging technologies offer crucial data for assessing malnutrition, but progress is hindered by a lack of collaboration across disciplines, which tend to operate in isolating “silos”. This situation is exacerbated by constraints such as excessive time spent on building expertise [121], outdated incentives [122], and rigid funding structures. In addition, effective collaboration should not involve only various academic disciplines [123] but also stakeholders from government, non-govermental organizations, and corporations, to address the complexity of malnutrition and develop tangible solutions.

Breaking down “research or disciplinary silos” to address malnutrition faces several challenges. At an implementation level, these challenges can include limitations in the techniques used, or investigators involved, due to funding stipulations, logistical complexities when multiple methods are considered, and a lack of cross-disciplinary knowledge or awareness. Moreover, investigator-centered expertise and infrastructure may lead to a loss of generational or regional expertise. However, opportunities exist to overcome these challenges. For one, protocols which utilize stable isotopes to test mechanistic hypotheses offer a framework for integrating multiple methods. As an example, zinc and B-vitamin-dependent enzymes play an important role in DNA synthesis and maintaining cellular homeostasis. Variations in zinc and/or B-vitamin intakes, whether low or high, can lead to enzyme dysfunction, dysregulation of DNA synthesis/methylation and the development of disease (e.g., certain cancers, nonalcoholic fatty liver disease, neuropathy, etc.) [124,125]. By using stable isotope tracers, researchers can trace the fate of these nutrients under highly controlled conditions (e.g., inadequate or excess dosing) to gain a better understanding of the associated metabolic ramifications in affected populations.

Combining research protocols aimed at different health and metabolic outcomes can optimize data from a single cohort. Integrating various nuclear techniques, both simple and complex, can enhance collaboration. For example, measuring whole-diet nutrient bioavailability alongside body composition can produce synergistic results. Importantly, developing best practices to combat malnutrition requires continued support to build expertise in nuclear techniques among the next generation of scientists and in strengthening analytical platforms. Adopting these strategies can foster collaboration, optimize resources, and lead to innovative solutions for more effective malnutrition treatment.

In conclusion, this report describes where nuclear techniques and emerging technologies can advance the understanding and assessment of malnutrition to effectively address this complex issue. Yet, challenges to developing coordinated and interdisciplinary approaches to combat this condition continue due to several constraints. Solutions to these challenges do exist, but they require collective action from organizations, universities, and experts. Shifting research away from a "siloed" model toward broader, coordinated research programs that bring together diverse stakeholders, allowing them to leverage expertise, logistics, and complementary nuclear techniques to pursue multiple and related objectives is vital to reducing the prevalence of the DBM. Indeed, the IAEA has proven to be an important and significant facilitator of such coordinated approaches as evidenced by its extensive track record of improving research capacity in LMICs, bridging disciplines to improve research, and hosting technical meetings and conferences that bring together a broad group of experts all focused on better understanding how to address the complexities of the DBM.

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Author contributions

The authors' responsibilities were as follows – SPS, CUL: designed the research; SPS, RP, STC, CG, DJH, KSJ, PK, NFK, AK, YL, VL-T, AM-B, FCP, CMP, SBR, JS, PW, JCKW: wrote the paper; SPS, RP: primary responsibility for the final content; and all authors: read and approved the final manuscript.

Conflict of interest

SPS, VL-T, and CUL report employment with the International Atomic Energy Agency. STC reports employment with the National Institute of Diabetes and Digestive and Kidney Diseases. CMP reports consulting or advisory roles with Abbott Nutrition, Nutricia, Nestle Health Science, and Pfizer, and has received grant funding from Almased. NFK and AK are associate editors of AJCN. VL-T contributed to this manuscript while at Universidad de Sonora and is now employed by the IAEA. She declares no other conflicts. All other authors declare no known competing interests.

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