REVIEW

Nutrition Bulletin

The double burden of malnutrition in individuals: Identifying key challenges and re-thinking research focus

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Abstract

The 'double burden of malnutrition' is a global health challenge that increasingly affects populations in both low- and middle-income countries (LMICs). This phenomenon refers to the coexistence of undernutrition and overweight or obesity, as well as other diet-related non-communicable diseases, in the same population, household or even individual. While noteworthy progress has been made in reducing undernutrition in some parts of the world, in many of these areas, the prevalence of overweight and obesity is increasing, particularly in urban areas, resulting in greater numbers of people who were undernourished in childhood and have overweight or obesity in adulthood. This creates a complex and challenging situation for research experts and policymakers who must simultaneously address the public health burdens of undernutrition and overweight/obesity. This review identifies key challenges and limitations in the current research on the double burden of malnutrition in individuals, including the need for a more comprehensive and nuanced understanding of the drivers of malnutrition, the importance of context-specific interventions and the need for greater attention to the food environment and food systems. We advocate for the re-evaluation

of research strategies and focus, with a greater emphasis on multidisciplinary and systems approaches and greater attention to the synergistic relationship between the biological, environmental, commercial and socio-economic determinants of malnutrition. Addressing these key challenges can enable us to better comprehend and tackle the multifaceted and dynamic issues of the double burden of malnutrition, particularly in individuals and work towards more effective and sustainable solutions.

BACKGROUND

Eradicating all forms of malnutrition has been a long-standing and ongoing endeavour of health organisations across the globe ('About | UN Decade of Action on Nutrition'). Malnutrition can present as undernutrition, which includes wasting (low weight-for-height), stunting (low height-for-age) and micronutrient deficiencies. Malnutrition can also present as overnutrition, which includes overweight and obesity (body mass index [BMI], calculated as weight in kilograms divided by height squared in metres and defined in adults as over $25\,kg/m^2$ and $30\,kg/m^2$, respectively). Undernutrition and overnutrition have been viewed and approached as two distinctive phenomena that require separate strategic interventions (Kerac et al., 2020). However, the recognition that both forms of malnutrition can coexist within the same community, household or even the same individual and can be driven by similar underlying factors, has led to the emergence of the 'double burden of malnutrition' (DBM) concept. This review focuses on the double burden of malnutrition in individuals.

PURPOSE OF THIS REVIEW

Recent data suggest that physiological changes induced by severe acute malnutrition (SAM) in childhood are persistent and may underpin long-term outcomes including readmission to hospitals, relapse to undernutrition and death, despite the initial nutritional rehabilitation (Gonzales et al., 2020; Kebede, 2022). Also, as many low- to middle-income countries' (LMIC) economies improve, obesity is becoming a major health problem for these populations. Children who have had periods of severe undernutrition in earlier life seem to be more vulnerable to an energy-rich environment and are at greater risk of obesity, type 2 diabetes and cardiovascular disease in later life. This has been termed the Triple Hit hypothesis (undernutrition, overnutrition and low micronutrient status occurring in the same community). However, there is very little understanding or debate on how to protect these populations from this major health problem (Blankenship et al., 2020).

There is emerging evidence that the gut microbiome and physiology may be permanently affected by SAM which will have consequences for energy and glucose homeostasis (Pai et al., 2022).

To highlight these long-term consequences of undernutrition and how they should shape the interventions and management around malnutrition we brought together leading scientists in a workshop to develop new insights into the relationship between gut function in severe undernutrition and how to improve long-term outcomes through nutritional support. This meeting (Rank Prize Forum on Malnutrition) took place at the Wellcome Collection in London on the 5–6 January 2023 (Appendix). The workshop aimed to explore the long-term consequences of severe undernutrition including the Triple Hit hypothesis and identify the research needed to improve long-term outcomes. It also delved into the current knowledge of the long-term consequences on gastrointestinal physiology, microbiome and nutritional management over the life course of children exposed to severe undernutrition with the overarching goal to identify gaps in knowledge and develop new strategies to address them.

As a result, this review paper takes on a dual role – serving as a concise introduction to DBM in individuals along with identifying the key challenges and limitations within the current research landscape that derived from the workshop. Beyond this, the review aims to provide current perspectives, guiding the research community in redirecting their focus to effectively address these identified gaps in knowledge.

DOUBLE BURDEN OF MALNUTRITION IN INDIVIDUALS

DBM, affecting the same individuals in a continuum from childhood to adulthood, poses an increasing public health concern in LMICs, despite some progress being made to address the issue (Popkin et al., 2020; Seferidi et al., 2022). Childhood undernutrition, which is a leading cause of morbidity and mortality, along with compromised cognitive and physical development (Matrins et al., 2011), runs in parallel with the increasing

trend of overweight and obesity in the same individuals during adulthood. This phenomenon, which is predominantly observed in urban areas of LMICs, contributes to a growing burden of diet-related non-communicable diseases, including diabetes, heart disease and stroke (Matrins et al., 2011).

Global estimates highlight that 22.3% of children under 5 years around the world (149 million children) are stunted and 6.7% (13.7 million children) are wasted as of 2022 (Joint child Malnutrition Estimates (JME) (UNICEF-WHO-WB), 2022). Most of the affected population is in Asia and Africa and consequently, it has been estimated that 32% and 27.4% of children under 5 years in Africa and Asia are stunted respectively. Thirteen nations have prevalences of wasting above 10%, including five Asian and eight African countries. Moreover, Western Africa is the region with the highest levels of wasting in children under 5 years globally. The prevalence of undernutrition in Asia and Africa is more than 10 times that of Europe and between 2 and 4 times higher than that of the Americas and Oceania (Ssentongo et al., 2021). In addition to undernutrition, obesity and overweight are also an issue in these regions, although rates are not as high as in the developed world. Around 1 in 20 children in Sub-Saharan Africa is estimated to be obese or overweight (Ayele et al., 2022). Together, under- and overnutrition can pose serious long-term consequences for public health, development and productivity of LMICs (Sustainable Development Goals [SDGs], n.d.).

RISK FACTORS FOR THE DOUBLE BURDEN OF MALNUTRITION IN INDIVIDUALS

The contributing factors to DBM in LMICs are complex and multifaceted, predominantly driven by a combination of socio-economic and environmental factors including poverty, food insecurity, urbanisation, globalisation and lifestyle changes (Otten & Seferidi, 2022). The rise of obesity in parallel to undernutrition is seen particularly in urban areas, where changes in lifestyle, economic status, commercial determinants and diets are more prominent and exposure to an obesogenic environment is higher. Studies investigating the risk factors for DBM in individuals have identified associations with a number of factors. These include infant feeding practices, both affluence and poverty (Alaba et al., 2023), advanced maternal age, abdominal obesity in women and larger household sizes (Sunuwar et al., 2020). The interplay between nutritional deprivation and early-life infections contributes to metabolic changes, which we discuss in more detail later in this review, increasing susceptibility to obesity in adulthood (Leocádio et al., 2021). Consequently, the combination of inflammation and food insecurity coupled with the

ready availability of energy-dense foods, presents a substantial risk in the development of DBM, creating a threefold challenge to metabolic health and significantly impacting the risk of non-communicable diseases.

THE ROLE OF DIET IN THE DOUBLE BURDEN OF MALNUTRITION

There has been a rapid transition in LMIC communities, from traditional diets which included fresh, minimally processed ingredients to 'modern westernised' diets containing highly processed foods and meals (Roberts et al., 2018). This transition leads to a change from high-fibre, low-energy-density, micronutrient-rich diets to a low-fibre, high-energy-density, micronutrient-poor dietary intake (Otten & Seferidi, 2022; Wells et al., 2020). Diet plays a central role in shaping the intricate trajectory of childhood undernutrition and the subsequent emergence of obesity in later stages of life (Bentham et al., 2017; Popkin et al., 2012). Lack of access to nutritionally dense foods increases the risk of undernutrition, while, at the same time, the growing availability in LMICs of cheap and energy-dense foods that are low in dietary fibre and low in intact food structures contributes to the rise of obesity but at the same time can impair micronutrient status (Little et al., 2020; Popkin & Ng, 2022). There is also growing evidence that undernutrition in early life is a risk factor for NCDs in later life (Grey et al., 2021). Mechanisms underlying this are poorly understood but might include epigenetics and reduced 'capacity-load' whereby slow initial growth reduces the metabolic capacity to deal with later-life stressors (Wells, 2018).

Dietary fibre can have a protective role against obesity partly owing to its low energy density and its role in stimulating appetite-reducing (satiety) hormone release through bacterial fermentation (Akhlaghi, 2022). Bacterial fermentation of specific carbohydrates (fibre including resistant starch) results in the production of short-chain fatty acids (SCFAs) which are known stimulants for the release of appetite-reducing hormones, for example glucagon-like peptide 1 (GLP-1) and peptide tyrosine tyrosine (PYY), both of which have been shown to impact energy intake and bodyweight (Cani & Delzenne, 2009; Covasa et al., 2019). Typically, highly processed, convenience foods are low in fibre but high in energy density. One recent study highlighted that more *ad libitum* energy was consumed from processed foods compared to an energy, macronutrient and energy density-matched diet of minimally processed foods (Hall et al., 2019). In this randomised, cross-over trial, participants consumed around 500 kcal more daily and weighed 1.5 kg more on the minimally processed diet than on the processed diet at the end of the 14-day intervention period. It was highlighted that the increased

energy intake was possibly due to higher eating rates and lower stimulation of homeostatic satiety signals. Combined with a more sedentary lifestyle and reduced energy expenditure, the higher energy intakes caused by highly processed foods can lead to body-weight gain and ultimately obesity over time. This can in part explain the positive association seen between energy-dense, processed food consumption and obesity in the world, including LMICs (Poti et al., 2017; Reardon et al., 2021). The switch from undernutrition during early life and exposure to excess energy during later life can also increase the risk of obesity and cardiovascular disease in adulthood in LMICs. In addition to the diet, other factors such as neuroendocrine dysregulation, gut microbiota dysregulation and genetic/epigenetic mechanisms are all implicated in the development of obesity in these countries, all of which are comprehensively reviewed elsewhere (Poti et al., 2017; Reardon et al., 2021) and some of these will be further discussed in the following paragraphs.

The role of nutrition during the critical first 1000 days in the development of DBM in individuals

Despite the DBM phenomenon arising from socio-economic and environmental factors, it is important to also recognise individual-level factors, such as genetic predisposition, particularly through human single nucleotide polymorphisms (SNPs) that alter host genes, affecting nutrient absorption and metabolism (Ahmed et al., 2009) and biological drivers that contribute to DBM onset (Wells et al., 2020). The underlying biological mechanisms are complex, varied and, to date, not comprehensively understood. Numerous non-communicable diseases are thought to occur due to multiple underlying factors (such as epigenetic modification) that are related to disruptions in nutritional supply believed to occur as early as the foetal stage (Cuevas-Sierra et al., 2019; World Health Organization, n.d.).

The nutrition environment experienced in utero can have significant and long-lasting effects on health (Scientific Advisory Committee on Nutrition, 2011). Nutrition quantity and quality during those critical stages can affect immune function, cognitive development and energy storage and expenditure, including fat stores. The relationship between maternal nutritional status, birthweight and intrauterine growth restriction (IUGR) is well-established (Schellong et al., 2012; Turnbaugh et al., 2006). Numerous studies have shown that insufficient micronutrients such as iron, vitamin B_{12} and vitamin D intake during pregnancy can lead to the disruption of intrauterine hormones and growth factors, ultimately resulting in low birthweight (Black et al., 2013; Bruce & Hanson, 2010). In turn, this can contribute to the child's undernourished status and increase the

risk of mortality (Turnbaugh et al., 2006). In addition, a metagenomic study in Mexican populations reported a causal relationship between low weight at birth, with lower concentrations of insulin and adiponectin, leading to adipose tissue accumulation in childhood (Ahmed et al., 2009).

Furthermore, poor maternal nutrition before and during pregnancy can significantly increase the risk of maternal anaemia, preterm birth and low infant birth-weight, increasing the risk of metabolic disease and abdominal adiposity later in life (Fleming et al., 2018) Overweight women face an elevated risk of developing gestational diabetes and delivering offspring with larger birthweights, which was shown to increase the likelihood of childhood obesity (Cuevas-Sierra et al., 2019; Ford et al., 2017; World Health Organization, n.d.). Furthermore, it has been demonstrated that accelerated weight gain, often as 'catch-up growth' in response to a period of impaired growth during early childhood is positively associated with the development of a higher BMI and a heightened risk of type 2 diabetes (T2DM) in adulthood (Ford et al., 2017).

In addition to inadequate maternal nutrition during the critical *1000-day period*, which starts with conception, poor post-natal feeding practices and early introduction of complementary foods before 6 months of age have also been linked to both overweight/obesity and undernutrition (Corvalán et al., 2007). When inadequate maternal nutrition is coupled with poor preventive health care and high rates of infectious disease, there is evidence of adverse effects on growth (Adair, 2007). These findings underscore the significant role that inadequate maternal nutrition and suboptimal infant feeding practices can play in the development of malnutrition and poor growth outcomes among infants.

Early life malnutrition: Impacts on metabolism and its long-term relevance to DBM

During the crucial *'first 1000 days'* of life, insufficient energy intake can result in wasting, the body's adaptive response to starvation, typically observed in severely undernourished individuals. This can lead to growth impairment and loss of fat, muscle and visceral mass, which results in a corresponding reduction in basal metabolic rate and total energy expenditure. Consequently, hormonal counter-mechanisms, including secretion of thyroid, insulin and growth hormones, as well as metabolic and glucose-regulating pathways, are instigated (Bhargava et al., 2004; Corvalán et al., 2007; Kaldenbach et al., 2022). Undernutrition during infancy has been shown to lead to adverse alterations in glucose metabolism in children (Bhargava et al., 2004; Bhutta et al., 2017; Kaldenbach et al., 2022). A study investigating the

effects of undernutrition during the first year of life on glucose tolerance and plasma insulin levels revealed that undernutrition during infancy was associated with chronic hyperinsulinemia and reduced insulin sensitivity in adults which was exacerbated by a higher BMI even within a healthy BMI range (González-Barranco et al., 2003). This was also supported by other studies conducted on this topic (Emery, 2005). The risk of type 2 diabetes is strengthened with increasing BMI in adulthood (Mahant et al., 2021). Additionally, high cortisol and growth hormone levels antagonise insulin and prevent hypoglycaemia during malnutrition (Bréant et al., 2006; Kajubi, 1972). Narayan and colleagues investigated the pathophysiology of type 2 diabetes in South Asian communities that experience a much higher risk of type 2 diabetes despite a lower bodyweight (Narayan & Kanaya, 2020). This increased susceptibility is underscored by evidence suggesting that South Asians, in diaspora and in South Asian countries, exhibit greater insulin resistance than Caucasians, even when BMI and total body fat percentages are comparable. Additionally, South Asians display early impairments in β-cell function, a tendency towards visceral fat deposition from infancy and altered levels of circulating plasma adiponectin and leptin. The difference in the risk is particularly evident at lower BMIs, indicating the role of factors other than just obesity (Gujral et al., 2013). This is also true in African countries, particularly when undernutrition is coupled with infectious disease. Evidence highlights that generations of undernutrition and malnutrition in these communities may have impacted their metabolic health and capacity leading to reduced lean muscle mass, compromised organ development and therefore increased diabetes susceptibility (Hardikar et al., 2015; Pomeroy et al., 2019). Diabetes in these communities is typically characterised by a reduced number of beta cells and beta cell dysfunction resulting in reduced insulin secretion, rather than the insulin resistance, that is prevalent in people with diabetes from Western communities (Filteau et al., 2021). Being adversely affected by undernutrition during pregnancy, or the first 3 years of life, had the highest impact on an individual's metabolic capacity and diabetes risk, highlighting the role of malnutrition in driving the observed risk patterns (Filteau et al., 2021; Wells, 2018).

Research has also shed light on the role of amino acid deficiencies in the pathogenesis of severe undernutrition. Inadequate consumption of high-quality, protein-rich foods can lead to insufficient bioavailability of indispensable amino acids (IAAs), which can have a detrimental effect on a child's physiological development since amino acids play a crucial role in a variety of biological functions as well as acting as the building blocks for body proteins and related molecules (Matrins et al., 2011). Furthermore, a lack of bioavailable IAAs

can lead to the inhibition of growth regulatory pathways, such as the master growth regulatory pathway (mTORC1), which are associated with musculoskeletal development. Insufficiency of IAAs can also hinder the general control nonderepressible 2 (GCN2) kinase pathway, a nutrient-sensing pathway which plays a role in modulating amino acid metabolism in response to nutrient deprivations. Together, these effects result in reduced capacity for protein synthesis and protein breakdown along with hindered bone growth (Matrins et al., 2011).

The potential long-term implications of these metabolic alterations into adulthood are further reinforced by long-term, prospective studies investigating the aftermath of famine, exemplified by the Chinese and Dutch famines. Data stemming from those events demonstrated that women who experienced the 1959 Chinese famine aged 3 years or less at the time, were 1.5 times more prone to overweight or obesity as adults compared to those born after the famine (Wang et al., 2010). Additionally, an examination of the medical records from male cohorts whose mothers were exposed to hunger in early pregnancy during the Dutch famine demonstrated that they were 30% more prone to being overweight, with a BMI of 25 or higher, by the age of 19 years, compared to a comparable group that was not exposed to famine in utero (Lumey et al., 2021).

Effect of malnutrition on the gut microbiota

The establishment and maturation of the gut microbiota in early life are dynamic and influenced by environmental factors including delivery method (caesarean or vaginal), hygiene practices, antibiotic usage and diet (Sommer et al., 2017). The complex and interrelated nature of undernutrition and infection is well established (Bhargava et al., 2004). This bi-directional relationship may result in various adverse outcomes, including the loss of integrity of the gut barrier function, disruption of the normal gut microbiota, impaired mucosal immunity, increased risk of gram-negative bacteraemia (Semba et al., 2016) and the malabsorption of nutrients. There is significant microbiota immaturity in undernourished children, characterised by decreased bacterial diversity and depletion of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, with increased levels of pathogenic species such as *Escherichia coli, Staphylococcus aureus, Streptococcus* spp. and *Fusobacterium mortiferum*, suggesting a direct link between undernutrition and intestinal dysbiosis (Bejon et al., 2005; Velly et al., 2017). There is increasing evidence to suggest that recurrent intestinal dysfunction, particularly during critical periods of development and growth, may result from complex interactions between

the diet and gut microbiota. A study by Subramanian et al. (2014) revealed persistent immaturity of the gut microbiota in malnourished Bangladeshi children in the first 2 years of life. The researchers found that despite nutritional interventions, the microbiota of malnourished children remained underdeveloped, highlighting the long-term effect of malnutrition on the gut microbiota (Subramanian et al., 2014). This can create long-term implications for the programming of immune and metabolic functions, as well as increasing the risk of developing various metabolic diseases over the lifespan (Boulangé et al., 2016; Dinh et al., 2016; Velly et al., 2017).

In summary, undernutrition particularly during early childhood, which is a crucial period of rapid growth and development, has detrimental effects on the development of multiple physiological systems, predisposing such children to the adverse effects of overnutrition in later life. Children experiencing undernutrition in early life coupled with previously highlighted socio-economic risk factors, may later adopt a Westernised diet, abundant in heavily processed foods – often high in sugar and fat, while lacking dietary fibre. This, combined with a more sedentary lifestyle, results in a positive energy balance and the accumulation of excessive fat in relation to their body size (Calcaterra et al., 2023). This phenomenon illustrates the interrelationship between undernutrition, obesity and diabetes with a negative impact on the quality of life (Calcaterra et al., 2023; Nakphong & Beltrán-Sánchez, 2021).

RESEARCH GAPS AND CHALLENGES IN IMPROVING THE DOUBLE BURDEN OF MALNUTRITION IN LMICs

Despite the increased attention to the DBM issue in the same individual, there are still multiple unanswered research questions that hinder our understanding of this complex phenomenon.

Socio-economic challenges

The main challenge is the lack of access to affordable and nutritious food, as a direct result of poverty, low agricultural productivity, limited access to food markets and weak food supply chains, leading to inadequate supplies of fresh, nutritious food and high food prices (Moisi et al., 2011; Nakphong & Beltrán-Sánchez, 2021). On the other hand, a growing trend is observed, particularly in urban settings, for an increased availability of high energy-dense foods, which often provide a cheaper option compared to their healthier and in some cases, more traditional, counterparts (Roberts et al., 2018). This underscores the multidimensional nature of DBM, encompassing a network of interconnected risk factors, as also outlined in UNICEF's conceptual framework ('UNICEF Conceptual Framework | UNICEF', 2020), contributing to the complexity of this challenge.

Healthcare challenges

In the face of changing societies that are becoming more urbanised and more overweight, it is also important to address the obesity side of the malnutrition burden. Obesity is still an emerging health issue in the LMICs which have health systems that are focused on tackling undernutrition and infectious disease. Poverty and other factors that limit access to healthcare and healthy foods further limit the management of obesity in these countries. The double burden of malnutrition presents a complex challenge as interventions have historically tended to focus on either undernutrition or overnutrition, but not both simultaneously. This has resulted in a fragmented approach that fails to address the root causes of malnutrition and may even exacerbate the problem. It should be noted that policies and strategies that target obesity have had limited success not only in LMICs but also in higher-income countries. Therefore, an improved approach is needed globally, which the World Health Organization (WHO) aims to target with its recent Health Service framework (World Health Organisation, 2022).

Research gaps

Despite the significant efforts made towards elucidating the complex underlying biological and social mechanisms contributing to DBM in individuals, significant gaps remain in our understanding of the key metabolic and inflammatory pathways. These pathways may be fundamental in deciphering the mechanisms driving this phenomenon.

The implementation of WHO nutritional and integrated management guidelines has contributed to the improvement of malnutrition outcomes over the past decades. While the global prevalence of stunted growth remains alarmingly high, there has been a gradual reduction in cases since 1990 ('Reduce stunting | UNICEF Eastern and Southern Africa,', n.d.). However, the same cannot be said for wasting and its severe forms, since instances of these conditions have persisted without substantial improvement, particularly in children hospitalised with SAM presenting with complications, where even with strict adherence to guidelines, mortality rates continue to exceed the recommended <5% indicated by the WHO protocols (Grimbeek & Saloojee, 2022; Karunaratne et al., 2020; Tickell & Denno, 2016). Within this latter group of malnourished children are those

with multiple comorbidities, which adds to the complexity of care and increases the risk of poor outcomes (Munthali et al., 2015). These include mortality (~20%) and relapse/readmission (~10%) rates over the following 6 months which remain stubbornly high despite advances in nutritional and medical support and treatment. For comorbidities, SAM children with pneumonia have a 15-fold increase in mortality compared to their well-nourished counterparts with pneumonia (Ginsburg et al., 2015; Walson & Berkley, 2018) and SAM children are at significantly higher risk of mortality due to diarrhoea, with estimates indicating a three-fold increase compared to children with diarrhoea associated with adequate nutritional status. It is estimated that more than 200 000 deaths resulting from diarrhoea are directly attributed to acute malnutrition on an annual basis (Tickell et al., 2020; Walson & Berkley, 2018). Aside from the high mortality rates of those presenting with SAM, a study comparing the metabolic profiles of adults that survived SAM versus controls of matched community participants, showed that SAM survivors had distinctive metabolic characteristics, with suggestive metabolic variables associated with diabetes, reduced hepatic fatty acid oxidation and hypertension (Thompson et al., 2020). These findings further support the hypothesis that SAM exposure in the first critical years of life can have long-term metabolic consequences, increasing the risk of NCDs.

Moreover, the failure of broad-spectrum antibiotics to address the mortality risk due to concurrent infections, associated with severe undernutrition, remains an unresolved piece of the puzzle. The degree to which the use of antibiotics may significantly impact the gut microbiota of an undernourished child, who is already lacking microbial diversity and their role in long-term recovery, has not been studied extensively. The potential negative consequences of these microbial disruptions are speculated to have a negative impact on morbidity and mortality, as it creates a favourable environment for opportunistic pathogenic organisms (Amadi et al., 2017; Trehan et al., 2010, 2016). In addition, a widely acknowledged obstacle is the dearth of research in defining the parameters that describe a healthy gut microbiota (McBurney et al., 2021). This makes the comparison between healthy individuals and individuals with compromised gut function difficult. This is further exacerbated by the fact that gut microbiota is susceptible to environmental factors which can vary across geographical regions, households and individuals.

NEW PERSPECTIVES IN ADDRESSING THE DOUBLE BURDEN OF MALNUTRITION IN LMICs

To address the complex challenge of the double burden of malnutrition in individuals, a holistic and inclusive approach is crucial, recognising the intricate interplay between socio-economic determinants and physiological factors. This is detailed in the following sections.

Holistic approach to tackling the double burden of malnutrition

There is an increased need for research focussing on identifying key biological derangements occurring during the critical first 1000 days of a child's life, along with key socio-economic and environmental factors, within the same window, which can offer new insights into the gaps in the transition from undernutrition to obesity later in life. A comprehensive exploration of the diverse pathophysiological and phenotypic manifestations associated with type 2 diabetes, spanning both population-level and individual-level analyses has been widely endorsed ('LSHTM Data Compass'; Lelijveld et al., 2023). This growing recognition emphasises the significance of understanding the inherent biological dysfunction in insulin secretion, paving the way for personalised prevention and treatment initiatives.

Malnutrition markers

A major challenge at present is the lack of a robust methodology to predict recovery from complex and severe malnutrition, both in the short term (morbidity and mortality) and long term (non-communicable disease). Traditional anthropometric measures, although good at monitoring nutritional recovery, have poor predictive capacity. Recent evidence suggests that inflammatory and metabolic markers may be a more effective method of evaluating systemic physiological recovery and resilience to environmental insults (Njunge et al., 2020; Wen et al., 2022).

Examples of such biomarkers, particularly, for SAM, include C-reactive protein (CRP), where elevated levels are observed in SAM children, interleukin06 (IL-6) and TNF-alpha which are pro-inflammatory cytokines, which levels are elevated in children with SAM indicating systematic inflammation (Sturgeon et al., 2023), Moreover, studies, such as those by Njunge et al. (2020) (Wen et al., 2022), have shown that malnourished children often exhibit alterations in these metabolic markers, including reduced levels of IGF-1 and adiponectin and elevated levels of leptin (Sturgeon et al., 2023).

In addition, metabolic alterations in SAM include disruptions in amino acid metabolism, TCA cycle dysfunction, increased ketone body production and enhanced gluconeogenesis. SAM leads to dysregulation in amino acid levels, particularly branched-chain amino acids (BCAAs), reflecting altered protein synthesis and breakdown. Furthermore, impairments in the TCA cycle manifest as changes in metabolic intermediates like

citrate and succinate, indicating compromised energy metabolism. Elevated ketone body production, such as beta-hydroxybutyrate (BHB), signifies increased lipid catabolism and ketosis in response to decreased glucose availability. Moreover, SAM induces gluconeogenesis, evidenced by altered markers like lactate and pyruvate, to maintain blood glucose levels (Mayneris-Perxachs & Swann, 2019).

These metabolic shifts during SAM highlight the body's adaptive mechanisms to nutrient deficiency, emphasising the significance of these markers as indicators of inflammation and metabolic health. Monitoring these metabolic shifts provides valuable insights into SAM's metabolic status and guides interventions to restore metabolic homeostasis, complementing traditional anthropometric measures in predicting recovery and addressing SAM effectively.

The gut is a crucial organ that is particularly susceptible to the detrimental effects of undernutrition, which can impede the digestion and absorption of nutrients and undermine the immune response. Despite an abundance of research highlighting the link between malnutrition and gut function, which in turn impacts long-term recovery, recent work has demonstrated abnormalities in the mucosa and amino acid transporter systems in the gut of undernourished adults (Chama et al., 2019). There remains a significant knowledge gap regarding how the undernourished gut handles the digestion and absorption of macro- and micronutrients making this a crucial area of research (Thompson et al., 2021). Gut function significantly influences the bioavailability of proteins and carbohydrates, which are crucial macronutrients essential for growth and optimal health. The integrity of the intestinal epithelial barrier and the functionality of digestive enzymes and transporters within the gut directly impact the digestion and absorption of these nutrients. Proteins are broken down into amino acids by proteolytic enzymes, while carbohydrates are hydrolysed into simple sugars by enzymes like amylase (Goodman, 2010). Malnutrition-related gut dysfunction can impair the production of these enzymes and reduce the surface area available for absorption, limiting the bioavailability of amino acids and sugars. Additionally, disruptions in the intestinal barrier and alterations in gut microbiota composition further exacerbate these effects, leading to incomplete nutrient digestion and absorption (Chama et al., 2019). Therefore, understanding the complex interplay between gut function and nutrient bioavailability is essential for developing effective interventions to improve nutritional outcomes in malnourished individuals.

Clinical and nutritional management

With respect to clinical management of the persistent issues of SAM, the current WHO recommendation for nutritional treatment of acutely ill children hospitalised with SAM is mainly milk-based feeds (called F75 and F100 indicating their calorie content per ml) for inpatient management followed by ready-to-use therapeutic feeds (RUTF) for rehabilitation. There is substantial evidence that there is a need for a critical appraisal and development of novel strategies for the current nutritional 'feeding bundle' to try to address the poor outcomes for these children (Schoonees et al., 2019). Yet, progress around optimal nutritional feed regimens for those who have been hospitalised with SAM has been very slow and piecemeal. These include re-examining the evidence supporting the nutritional composition of milk-based feeds currently recommended by the WHO and investigating the potential benefits of altering protein and energy contents. Community-based care utilising RUTFs has been successful in improving recovery rates for SAM (Schoonees et al., 2019). However, limited research has been conducted in comparing alternative therapeutic feeds that can support gut integrity for hospitalised SAM cases with severe comorbidities, such as diarrhoea, sepsis and pneumonia. Innovative feeding strategies or therapeutic interventions that focus on gut repair and optimise the microbial environment could provide nutritional support after immediate recovery. However, further research is needed to understand if these new strategies can improve clinical outcomes compared to standard treatment and, potentially, be less costly (Kelly et al., 2019). This would be a substantive starting point from which to revise treatment guidelines.

Calder et al. (2021) conducted a proof-of-principle trial investigating the efficacy and safety of three experimental nutritional strategies in 58 Ugandan children with SAM. The study compared the use of standard feeds (F75 and F100 as controls) with feeds enriched with cowpea flour or inulin, over 28 days. They demonstrated that the cowpea and inulin-enriched feeds were safe and tolerated by the children and resulted in similar weight gains to the standard feed. They also showed a reduction in the antibiotic-mediated decrease in gut microbiota richness at day 7 with the standard feed. An increase in gut microbiome diversity was also observed (Calder et al., 2021). This and another pilot study support a need for future research examining legume-based feeds as nutritional interventions targeting growth and global improvement in gut health in children with SAM, for improving long-term clinical outcomes (Agapova et al., 2018).

Dietary changes

This section focuses on new research that aims to improve food systems to provide access to healthy, nutrient-dense food; promoting healthy eating habits

and lifestyles that address the root causes of malnutrition, such as poverty and food insecurity.

Food structure is an important determinant of nutrient bioavailability in the gut. Certain intact plant structures, such as the cell walls in legumes, protect the intracellular nutrients from digestion (Holland et al., 2020). This results in more nutrients reaching the microbiota-rich distal gut. Here, carbohydrates become available for bacterial fermentation, yielding SCFAs (Pérez-Reytor et al., 2021). Production of SCFAs can have a beneficial impact on both ends of the malnutrition spectrum. From a weight management angle, SCFAs are known stimulants to produce appetite-reducing hormones GLP-1 and PYY. Indeed, increased colonic levels of SCFAs have been shown to be protective against weight gain (Chambers et al., 2015). Accordingly, diets high in fibre that increase fermentation and SCFA production have been associated with lower bodyweights (Dagbasi et al., 2020). From the undernutrition angle, while high-fibre diets are usually lower in energy density, the inclusion of fibre in the diets can support the gut microbiome. This can improve the gut function and inflammation and be protective against some of the negative impacts of undernutrition such as impaired gut integrity and nutrient malabsorption.

This information indicates that feeding a diet rich in fibre and intact plant structures, such as legumes, can be beneficial from a malnutrition perspective (both under- and overnutrition). Traditional African diets are high in both fibre and legumes, a habit that is declining with the Westernisation of diets. Nutrition programmes and strategies should focus on utilising local and nutritious traditional plant-derived foods in modern African diets, such as the school feeding programmes established in Nigeria (Drake et al., 2017; Fernandes et al., 2016). However, it needs to be recognised that the perception and acceptability of foods are complex and it is influenced by social networks. For example, certain foods may be associated with wealth or poverty and this may have more impact on whether a food is bought and consumed than the health benefits. The purchase of Western-style fast food items may be seen as desirable since it is associated with wealth. To make a difference there is a need to bring nutritional and social sciences together.

CONCLUSION

The issue of DBM in LMICs not only poses significant health risks for individuals but also has profound economic and social consequences for communities and societies. Despite the long-lasting scientific contributions aimed at tackling this challenge, current strategies and interventions have fallen short of achieving the desired outcomes over the past two decades, highlighting the urgency for a thorough re-evaluation of approaches to DBM research. It is evident that addressing DBM requires a comprehensive and integrated response, necessitating multidisciplinary collaborations among researchers to improve food systems, promote healthy diets and address the biological and socio-economic determinants of malnutrition. Through the adoption of this holistic approach, there is a promising prospect of formulating more effective and targeted interventions that can lead to tangible improvements in both individual-level wellbeing and broader societal health outcomes.

CONFLICT OF INTEREST STATEMENT

Gary Frost leads the Imperial College Partnership with Nestle and Sosei Heptares. He has also received research funding from Quorn and Unilever. None of this funding overlaps with the current paper. All other authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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APPENDIX

RANK PRIZE MEETING SCHEDULE

Day 1 Severe undernutrition as a driver of excess mortality and morbidity.

Time	Topic	Speaker	Length of time
9:00	**Registration**		
9:45	Welcome and overview of the 2 days	Kath Maitland/Gary Frost	15 min
Chairing: Prof Kathryn Maitland			
Vignettes on the Major Issues in the management of SAM			
10:00	Persistent morbidity and mortality	Jay Berkley	15 min +5 discussion
10:20	Effect of concurrent disease HIV	Andy Prendergast	
10:40	Effect of concurrent disease sickle cell disease	Tom Williams	
11:00	Discussion		
11:20–11:40	**Coffee**		
11:40	What does not work-Feed	Kath Maitland	15 min +5 discussion
12:00	What does not work- Antibiotics	Jay Berkley	
12:20	Could the gut be the problem	Douglas Morrison	
12:40	Microbiota and Metabolites in severe under nutrition, can they help?	Jon Swan	
13:00–13:20	Discussion -Defining the problems		
13:20–13:50	**Lunch**		
13:50	WHO milk feeds and RUTF	Andre Briend	15 min +5 discussion
14:10	Is it possible to redesign feeds to support SAM	Kath Maitland and Kevin Walsh	
14:25	Production of local feeds for SAM	Brian Rwabwogo	
14:45	Learning from MIMBLE trials	Gary Frost	
15:00–15:30	Discussion		
15:30–16:00	**Coffee**		
16:00	Open discussion where to next		
17:00	**Close**		

Day 2 Severe undernutrition as a driver for Non-Communicable Disease.

Time	Topic	Speaker	Length of time
09:15–09:40	Setting the seen	Gary	15 min + 5 discussion
09:40–10:10	The case of obesity	Marko Kerac	
10:10–10:30	A case of impact on the gut	Stephan O'Keefe (online)	
10:30–11.00	Discussion		
11:00–11:30	**Coffee**		
11:30–12.00	The case of diabetes	Venkat Narayan (online)	
12.00–12.20	Microbiota and dietary change	Jia Li	15 min + 5 discussion
12.20–12.40	Changing Food environment	Marisa Miraldo	
12:40–13.00	Discussion		
13.00–13.30	**Lunch**		
13.30–14.10	Feeding a population to reduce risk of NCD	Lesley Drake	15 min + 5 discussion
14.10–14.50	Is dietary fibre the key	Gary Frost	
14.50–15.30	Discussion		
15.30–15.45	Next steps		