Measuring growth and medium and longer-term outcomes in malnourished children.

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Abstract

Severe and moderate acute malnutrition are among the leading causes of mortality among children in low- and middle-income countries. There is strong evidence that growth assessed anthropometrically from conception to 2 years of age marks later risk of ill-health. This is central to the concept of the developmental origins of adult disease and is presumed to be related to modification of developmental processes during critical "window(s)" of vulnerability. Interventions to treat acute malnutrition have resulted in dramatic increase in the number of affected children surviving. Ensuring that these children thrive to fulfil their full physical and cognitive potential is a new challenge. Integral to this challenge is the need to be able to measure how earlier insults relate to the ability to survive and thrive to productive adulthood. Despite its obvious value, routine anthropometry does not adequately indicate how earlier adverse exposures affect more refined aspects of growth. Anthropometry is inadequate for predicting how disruption of healthy growth might modulate risk of disease, or any subsequent interventions correct this risk. A clear characterisation of healthy child growth is needed for determining which component best predicts later outcomes. The extent to which postnatal acute malnutrition is a consequence of maternal factors acting pre-conception or in-utero and their relationship to postnatal health and long-term risk of non-communicable diseases is not clear. Body composition measurement has significant untapped potential allowing us to translate and better understand the relationship between early insults and interventions on early growth in the short-term and long-term health outcomes.

Key Words: Growth, Acute malnutrition, DoHaD, Body composition, Assessment of Nutritional Status, Chronic Disease

Key messages

- The extent to which postnatal acute malnutrition reflects maternal risk factors operating pre-conception or in-utero and their relationship to long-term disease risk needs to be determined.
- Currently used anthropometric indicators do not adequately reflect how early adverse exposures affect short term health and are poor at predicting how disruptions and interventions to correct it affects later disease risk.
- Body composition represents the convergence of pre-conceptional, in-utero, post-natal and childhood insults, growth and long-term disease risks.
- Measurement of body composition using valid and reliable techniques will improve understanding of how early life insults interact with acute malnutrition, growth and later-life disease risk.

Introduction

Nutrition is rising to the top of the global policy agenda. Malnutrition is associated with impaired cognitive development, education performance and adult productivity, undermining the development of nations (Baye, 2017; Black et al, 2013; Global Nutrition Report, 2017). During infancy and early childhood, inappropriate feeding practices, nutrient deficiencies, frequent infections and intestinal dysfunction are among the many factors resulting in deficits of the three major anthropometric indicators of growth: wasting, underweight and stunting among children in low and middle-income countries (LMICs) (World Health Organization and United Nations Children's Fund, 2003). Stunting and underweight are associated with increased morbidity and mortality and impaired child development (World Health Organization, 2017).

In 2017, 151 million children under five years were stunted, defined as low height-for-age. 51 million children under five of age were wasted, defined as low weight-for-length (WLZ) in children under 2 years of age and as low weight-for-height (WHZ) in older children. The presence of bilateral oedema is used as an additional criterion to either WLZ or WHZ in identifying children with severe wasting which significantly increases the risk of mortality (World Health Organization, 2017). Of the wasted children, 16.4 million were severely wasted (United Nations Children's Fund, World Health Organization, World Bank Group, 2018). This is a conservative estimate of those with Severe Acute Malnutrition (SAM) since the full case definition of SAM includes not just wasting but those with oedematous malnutrition (kwashiorkor), as well as those with low mid-upper arm circumference (MUAC) (Briend et al 2016; Frison et al 2015). Moderate acute malnutrition (MAM) and SAM – (defined by low WHZ/WLZ and/or low MUAC) are among the leading causes of mortality in children in LMICs (Collins, 2007; Lenters et al 2016; World Health Organization, 2016),

predominantly by potentiating the effects of common infectious diseases. At the same time 38 million children under five years of age were overweight in 2017 (United Nations Children's Fund, World Health Organization, World Bank Group, 2018). Childhood overweight and obesity have increased 10-fold in 40 years from 1975 to 2016 (NCD Risk Factors Collaboration, 2017).

Emerging evidence indicates undernutrition as a leading cause of death in children age 5 to 14 years. For example, between 2008 and 2013, acute undernutrition contributed to 34% of deaths in this age group in Ethiopia (Dedefo et al, 2016). Among adults, non-communicable diseases (NDCs) are emerging as public health problem in LMIC. It is estimated that in 2010 they accounted for half of Disability Adjusted Life Years (DALYs) lost and for 58% of all deaths in these countries and that 70% of all deaths will be caused by NDCs in these countries (World Health Organization, 2010). The associated economic loss is estimated to be US$ 7 trillion in the period 2011-2025 (World Health Organization, 2014). There is strong evidence that growth from conception to 2 years of age reflects the effects of adverse exposures during a critical "window" which also drive later risk of ill-health. This complex chain of events is central to the concept of the developmental origins of adult disease (Cameron and Demerath, 2002). Routine post-natal growth monitoring using WHO reference growth curves is recommended practice worldwide (WHO, 2017). In the short-term 'growth trajectory' for weight-for-age is considered to indicate health and likelihood of attaining full human potential (Ashworth et al 2008). However, height is not normally assessed in routine growth monitoring in LMIC (WHO, 2017).

A big step forward in nutrition over the last two decades has involved expanded programme efforts in the treatment of acute malnutrition. The use of ready to use therapeutic foods

(RUTFs) in the context of community-based management of severe acute malnutrition (CMAM) has resulted in dramatic increase in the number of affected children being treated and thus surviving. Interventions targeting mothers during gestation such as iron/folic acid, multiple micronutrient supplements (MMN), and MMN-containing lipid based nutritional supplements (LNS) have had positive effect on in-utero fetal development (Hambidge and Krebs, 2018) and are likely to translate to better post-natal child survival. Enabling these children to thrive and fulfil their full physical and cognitive potential is the new challenge. An associated challenge is how to measure the full extent of any early nutritional/health/environmental insults and link those with future potential to not just survive but to also thrive. Weight-for-height and mid-upper arm circumferences (MUAC) are the main indicators used to admit and discharge children from SAM treatment, while body mass index (BMI) is used as a screening tool for obesity (World Health Organization, 2017). However, these anthropometric indicators do not fully reflect the impact of early adverse exposures on health and, much more importantly, are poor at predicting how disruptions and interventions to correct it affects later risk of health and disease. The following questions remain to be addressed.

Firstly, how can healthy child growth be best characterised and defined, what are its components and which of these components best predicts what will happen later? This relates to the question on which anthropometric measures should be used in primary health care to assess nutritional status in light of the double burden of malnutrition (World Health Organization, 2017). Secondly, to what extent is SAM/MAM a consequence of maternal risk factors operating before birth either pre-conception or in-utero? Thirdly, to what extent does an episode of SAM/MAM and its treatment modulate the long-term risk of non-communicable diseases and which pathways are involved? Fourthly, can body composition

measurement enable more effective translation of a better understanding of the relationships between early insults and interventions on early growth in the short-term and long-term health outcomes? Specifically, what is the body composition pre-SAM and in the stunted-obese or stunted-wasted child? A better understanding of body composition at birth, in early life and during and after the months and years following treatment for SAM and MAM potentially carries the key to predicting longer term risks and improved assessment of the effectiveness of early interventions.

It is desirable that we have the ability to co-currently identify children at risk of acute malnutrition on the one hand and those at risk of overweight and obesity on the other as per the updated Integrated Management of Childhood Illnesses (IMCI) guideline (World Health Organization, 2017). Is there single 'stone that we may use to kill two birds' at the once? In this review we posit that while routine anthropometry (weight, height and mid upper arm circumference) and associated derived indicators such as BMI are useful for programmatic purposes, body composition may be the 'Rosetta Stone' (Schoville, 2001) that allows us to translate the relationship between early growth and long-term health outcomes. (Figure 1) (Wootton and Jackson, 1996).

The nature of growth in childhood

Good health during childhood consists of timely development and maturation of physiological, physical, neurocognitive, emotional and social functions (Cameron, 2008). The achievement of health at all ages is characterized by an ability to cope with environmental challenges, which include physical, chemical, microbiological, behavioural, emotional and social insults that also determine the timing, magnitude and duration of growth (Cameron ,2007; Cameroon, 2008; Hochberg, 2011). When the sum total of the challenges

(allostatic load) exceeds the ability of the individual to cope (allostatic capacity), ill health or pathology supervenes and becomes increasing evident as clinical disease including greater NCD risk (Wells, 2018). For example, stunting and wasting in early childhood may deplete metabolic capacity thereby increasing the risk of NCDs (Wells, 2018; Ferraro and Bechere, 2013; Jackson 1996; Wootton and Jackson, 1996). Growth is a regulated process by which the organism increases in mass, size and physical and metabolic complexity. During growth, there are substantial changes in the distribution, architecture and relative masses of body tissues. The pattern of growth and development between conception and adulthood is absolutely dependent on adequate provision of energy and nutrients interacting with genetic, hormonal and environmental influences (Jackson & Wootton, 1989; Jackson, 1990; Hochberg, 2011).

Thus, normal growth is an ordered process, but its progressive nature means that all later stages are built on the amount and quality of growth in earlier stages. This cumulative process leads to the structural and functional phenotype of the adult, thereby giving a life-course reflection of healthy lifetime opportunities (Wootton & Jackson, 1996; Hochberg, 2011). The processes of normal growth can be disrupted at any of the four stages (fetal, infancy, childhood and adolescence) by inadequate nutrition and/or environmental challenge, potentially limiting opportunities for health at all later ages (Gluckman et al 2005; Prado and Dewey, 2014). High growth and developmental velocity during fetal and early postnatal life (before the age of about 2 years) implies that restriction of nutrient supply and other insults will have greatest effect when experienced at these stages of life (Hochberg, 2011; Prado and Dewey, 2014; Victora et al 2010).

Inadequate intake of energy and nutrients during development can result in irreversible alteration of organ and tissue architecture and function (Wootton and Jackson, 1996; Jackson et al, 1996). The consequence of such insults is "programming" of an individual's phenotype, evident as alteration of body structure, composition and metabolic function resulting in heightened risk for non-communicable diseases in adulthood (Ross and Beall, 2008).

Experimental studies in animals have demonstrated the existence of "critical periods" (Cameron and Demerath, 2002) in early development during which alteration of nutrient supply may alter structure and function irreversibly. This phenomenon has been labelled "nutritional programming" (Langley-Evans, 2015; Vaiserman, 2014). A recent review demonstrated how events in the periconceptional period may contribute to developmental programming (Fleming et al 2018). It offers time-limited opportunities for intervention, which may reduce the risk of NCDs in later life.

Upon provision of adequate nutritional intake following growth restriction there is a tendency for growth to be accelerated (Wootton & Jackson, 1989; Jackson 1990). This is known as "catch-up" or "compensatory" growth (Adair, 1999; Zhang et al 2016). There is some evidence that this phenomenon is positively correlated with maternal height (Desmond and Casale, 2017) and the intra-uterine growth environment (Cho and Suh, 2016; Dunlop et al, 2015; Morrison et al 2010). Adolescent catch up growth has also been described and is thought to represent previous insults (Prentice et al. 2013). Catch-up growth may also occur due to improvements in living and psychological conditions, freedom from infections and via nutrient supplementation (Martorell et al, 1994). During this catch-up growth, the normal proportionate distribution and relative weight of tissues and organ systems may be disrupted. Consequent alterations in body composition may be mirrored in altered metabolic function

and chronic disease risk (Cho and Suh, 2016). The tendency for "catch-up" to occur makes independent effects of pre- and postnatal nutrient supply on chronic disease risk hard to separate. Post-natal growth occurs in three phases of infancy, childhood and adolescence which are easily influenced by environmental factors (Cameron, 2007; Prentice et al 2013) in ways that may result in individual patterns deviating from generally acceptable patterns.

Removal of the risk of environment hazards by ensuring high standards of hygiene and sanitation is crucial, but alone may not influence growth positively, as demonstrated by the results of one (Arnold et al, 2018; Null et al, 2018) of the largest randomised studies addressing this theme. Environmental challenges embrace a range of stresses or stressors, notably those associated with infection, neglect or the range of challenges imposed by poverty or social disruption. A good example is the environmental enteric dysfunction (EED) phenomenon that is believed to affect linear growth in yet to be defined ways (Keusch et al, 2013; Owino et al, 2016). Environmental hazards with endocrine disrupting properties and microbial toxins such as mycotoxins, are also thought to be involved in fetal programming and post-natal growth disruption (Gong et al, 2016; Owino et al, 2018, Zheng et al 2016). The effects of stressors on growth are determined by their timing, character and the duration of the adverse experiences. Milder insults of relatively short duration are potentially reversible (Lundeen et al, 2014, Martorell et al, 1994; Singh et al, 2017) but more severe insults of longer duration or insufficient recovery time can have lasting impact. The specific effect of any particular stressor on the body will be determined by the timing of the insult in relation to the timing of development of particular organs, tissues or function. Individual organs are most vulnerable to insults during their period of most rapid differentiation and growth and the effects may be irreversible. Within this complexity of developmental changes, any disruptions to normal growth in either the short or longer term, are most simply marked by

inadequate growth in height, weight, MUAC or abnormalities in their relative proportions, yet these are relatively indirect measures of specific tissues and processes.

Interventions to address acute malnutrition

Since the Millennium there have been extensive programmatic efforts to address acute malnutrition in many countries. These programmes often neglect the fact that many acutely malnourished children are concurrently stunted, with wasting increasing the risk of stunting and vice versa – the exact relationship being complex and likely setting-specific (Angood, 2014; Briend et al 2015). Standardisation of treatment protocols including development of specific therapeutic products and scale up of the integrated management of acute malnutrition (IMAM) approach has resulted in a significant reduction in SAM case fatality while allowing rapid scale up and significant increase in programme and geographical coverage. The high short-term benefit of the treatment has been confirmed by reduced post-discharge mortality among those who completed the treatment when compared to those who defaulted (Bahwere et al, 2012). Although, results on relapse rates are contrasting, several studies have shown that relapse rates after an episode of SAM can be low in some settings (Bahwere et al, 2008; Burza et al, 2016; Khanum et al, 1998; Pecoul et al, 1992; Somasse et al, 2015). There is a strong body of epidemiological evidence that the co-occurrence of undernutrition and infectious diseases increases the risk of death in children suffering from common childhood infectious diseases such as diarrhoea and pneumonia (Jones and Berkley, 2014; Rodriguez et al, 2011; World Health Organization, 2010b). Thus, treating acute malnutrition contributes to preventing death from these diseases. In contrast to short term benefits, the medium and long-term benefits of treating acute undernutrition are less well described and less well understood. The main reasons for this are that longer-term patient follow-up is often difficult in the resource-poor settings where SAM and MAM are common and until recently the main focus

of nutrition programmes has been on short term survival. This is however changing, with longer term perspectives becoming increasingly important.

World-wide reduction in under-5 child mortality has made it important for the global community moves beyond the "survive" agenda alone and enables children to also "thrive", fulfilling their full physical and cognitive potential. For this to happen, systems and approaches to problems must be "transformed"; hence the "Survive, Thrive and Transform" call of the Global Strategy for Women's, Children's and Adolescent's Health (2016-2030) (World Health Organization, 2015). There is growing interest in how the "Developmental Origins of Health and Disease (DOHaD) theory (Barker, 1995; Barker, 2007) applies to acute malnutrition in early childhood. Most focus however has been on in-utero exposures to malnutrition, with clear evidence arising that timing of insults and rate of subsequent catch-up growth are key determinants of long term effects. Given the severity of an episode of acute malnutrition, it is plausible that this too would have an independent effect on long term risk - but data showing this is limited. In particular, it has not yet been possible to distinguish to what extent SAM/MAM and treatment interventions are on the causal pathway to long term NCD-related risk and to what extent they reflect and are symptoms of earlier in-utero and maternal risk factors. For example, one recent study followed up children 7 years post-SAM and found both functional and structural impairments including reduced linear growth and a body composition profile (waist-hip ratio) consistent with future NCD risk. Critically however, this study did not have details of children's birth weights (nor data on whether or not they were preterm at birth) or their detailed clinical/growth histories prior to the episode of SAM (Lelijveld et al, 2016). It did however document the fact that most children were concurrently stunted, and that there was some catch-up of height after the age of 2 years since the original episode of SAM in some of the survivors.

It is important to understand the limits of the window of plasticity under DOHaD and the factors which most strongly influence long term outcomes. In practice, current treatment and prevention programmes focus on short term cure. As understanding of long term outcomes improves, the details of treatments may change (e.g. composition of therapeutic/supplementary foods; target weight gains in programme). It is also possible that post-treatment interventions may develop as a way of reducing adverse long-term outcomes (e.g. social support or longer-term antibiotic prophylaxis). Lastly, policy makers and funders seeking to address the global epidemic of adult NCDs should be aware that since the major antecedents are in childhood, appropriate investment in child health is a key way to tackle adult problems.

During the treatment of SAM and MAM the primary objective of treatment is correction of specific nutrient deficits and is measured by correction of deficits in weight. Over the longer-term improvement in wider functional deficits is a preferred objective, which may be better indicated by the correction of height deficits. There is variation in the response of individual children to different aspects of the correction of weight deficits, height deficits or functional deficits which may be determined by a range of factors related to prior experience and wider environmental constraints. Enabling correction of height deficits may be achievable in contexts where the wider environmental stressors have been adequately addressed, but this remains to be determined in clinical trials. The outstanding question is whether improving lean mass without excessive deposition of fat mass during treatment of SAM and MAM will lead ultimately to improved functional capability and increased resilience to environmental challenge, thereby mitigating vulnerability to NCD in later life.

Body composition in relation to growth and long-term health

Body size, shape and composition affect health and disease risk (Baumgartner et al 1995). At attended delivery, birth weight, length and head circumference might be measured as major indicators of pregnancy outcome and growth during infancy and childhood, comparing measurements against the recently launched WHO Growth Standards (World Health Organization, 2007). Body composition connotes the components that comprise an individual's body weight such as water, lean and fat mass (Jackson 1990; Wells and Fewtrell 2006). Most commonly, a two-compartment model is used that assumes that the body is composed of fat and fat-free mass. Body composition is influenced by many factors including age, sex, race, genes and dietary and lifestyle behaviours (Baumgartner et al 1995). Appropriate balance between fat mas and fat-free-mass is necessary for good health but changes with age. Excess body fat is associated with physiological changes that can lead to non-communicable diseases, such as diabetes, CVD and some cancers. Abnormal regional distribution of body fat, especially visceral and liver fat accumulation is linked to increased risk of CVD (Despére 2012; Well sand Fewtrell, 2006). On the other hand, inadequate food intake or increased demand for certain amino acids caused by chronic inflammation can result in muscle wasting and ultimately death (International Atomic Energy Agency, 2009; Owino et al, 2017).

Birth height and weight, childhood growth and adiposity, adult attained height and adult obesity have been linked to increased risk of developing NCD (Li et al, 2015), such as cardiovascular disease (Berenson et al, 2016; Ohlsson et al, 2017), non-alcoholic fatty liver disease (Ayonrinde, et al, 2017; Yan et al, 2017), some cancers (Brown et al, 2018; Hendriks et al, 2018), chronic kidney disease (Erickson, et al, 2018) and dementia (Russ et al, 2014). The double burden of malnutrition where stunting, wasting and micronutrient deficiencies

occur alongside overweight and obesity seems to drive the risk of NCD in ways that are yet to be fully comprehended.

Structural measures of growth such as weight and height do not fully reflect how early adverse exposures affect health and, much more importantly, are poor at predicting how any disruption and any intervention to correct it affects later risk of disease. It is also apparent that body composition seems to be the convergence point between what happens early in life and both short and long-term metabolic response (Jackson, 1996; Jackson and Wootton, 1996). Figure 1 presents the pathways underpinning the relationship between early nutritional insults and later outcomes including risk for metabolic dysfunction.

Intra-uterine exposures that influence growth also act through body composition. For example, it has been shown that cord blood adiponectin affects infant size via altered adiposity in African-American children (Schneider et al, 2018). Cord blood leptin has been linked to smaller birth size and rapid weight gain in the first 6 months of life, while cord blood adiponectin directly predicted increased central adiposity at 3 years of age (Mantzoros et al, 2009). Fat-free mass and not fat-mass accretion in infancy is related to linear growth in childhood according to a study from Ethiopia (Admassu et al 2018). A study from Burkina Faso showed that children treated for MAM using lipid based nutritional supplement (LNS) put on more lean mass than fat mass post-discharge (Fabiansen et al, 2017), contrary to the wide held concern that weight gain in such interventions is mainly due to increased body fat. Short children in the same study had slower gain of both fat free mas and fat mass (Fabiansen et al 2018). More research is needed to build stronger evidence in this area. Body composition and not body weight has been found to correlate to CVD risk (Segal et al 1997). Body fat has been shown to be positively correlated with CVD and metabolic syndrome risks in both women and men (Chuang et al 2012).

The validity of anthropometric measures of body composition has been questioned (Henricksson et al 2017; Jensen et al, 2015; Brambilia et al, 2000). Yet, over the decades BMI has been used as the main indicator to estimate unhealthily low (or high) body fat. This is because BMI is a quick, field-applicable and useful screening tool (Buss, 2014) for identifying high risk individuals. However, a major limitation is that BMI represents inadequate or excess weight for height and does not distinguish between fat and fat-free mass. The relationship between BMI and body fat is also affected by factors such as hydration, maturation, and ethnicity, making BMI a poor indicator of adiposity. It has been demonstrated that people of Asian ethnicities have lower BMI but higher body fat than Caucasians of European descent do (Wang et al, 1994). The accuracy of BMI to predict body fat has also been found to be lower compared to densitometry (Okorodudu, 2010).

Infants of similar birth weight, weight, height or even weight for height can vary substantially in body composition. A study from Ethiopia found that newborn fat mass was determined by sex and birth order and that fat mass was positively associated with birth weight in both boys and girls (Andersen et al 2011). For example, babies born to optimally healthy mothers in rural India have been characterised as having the thin-fat phenotype because although small and thin at birth they have proportionally more body fat and centrally deposited fat than European newborns (Yajnik, 2003). This difference in body composition phenotype appears to be related to birth size and marks a fundamental metabolic difference and greater risk of later non-communicable diseases during adult life (Kensara et al, 2006). These observations emphasise the importance of more detailed characterisation of body structure and composition to identify high risk of poor health at an early age (Corvalan et al, 2009). Accurate, sensitive, simple and non-invasive techniques of body composition are needed to fully understand the effect of interventions. Techniques to assess body composition include

anthropometry, densitometry (air displacement plethysmography, underwater weighing), dual energy X-ray absorptiometry, isotope dilution and bioelectrical impedance analysis (Most et al, 2018, International Atomic Energy Agency, 2009). Body composition techniques rely on assumptions and each technique has its strengths and weakness in terms of accuracy, precision, and applicability to populations and settings. Available literature suggest that, compared to the the gold standard 4 compartment model, isotope dilution using deuterium oxide is more accurate compared to other single techniques in a variety of paediatric populations (Gately et al 1985; Bray et al 2002; Ramirez et al 2009; Vasquez et al 2012; Silva et al 2013; Martinez et al 2017). The current review is limited to raising the question on why it is important to consider body composition as central indicator of exposure to and recovery from acute malnutrition. Given the rapid technological advancement in this area in recent years, a separate comprehensive review updating on the various body composition measurement techniques, their applicability, limitations and feasibility for use, especially in malnourished children and pregnant and lactating mothers is recommended.

Conclusion

Acute malnutrition is likely to remain pervasive in LMICs for the foreseeable future and the intensity of interventions to address it will increase towards achieving global goals. Child growth will continue to be the key benchmark for evaluation of progress. The urgency for more accurate ways to measure *healthy* growth and to better understand the longer-term outcomes of insults and interventions cannot be belaboured, we need to look beyond growth to the composition of the body. Better understanding of body composition in the months and years following treatment for SAM and MAM is key to predicting longer term risks of adult disease. Measuring body composition should be based on valid, reliable and non-invasive approaches. An update of different techniques to measure body composition is urgently needed.

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Conflict of interest

All authors have no conflict of interest to declare

Contributor statement

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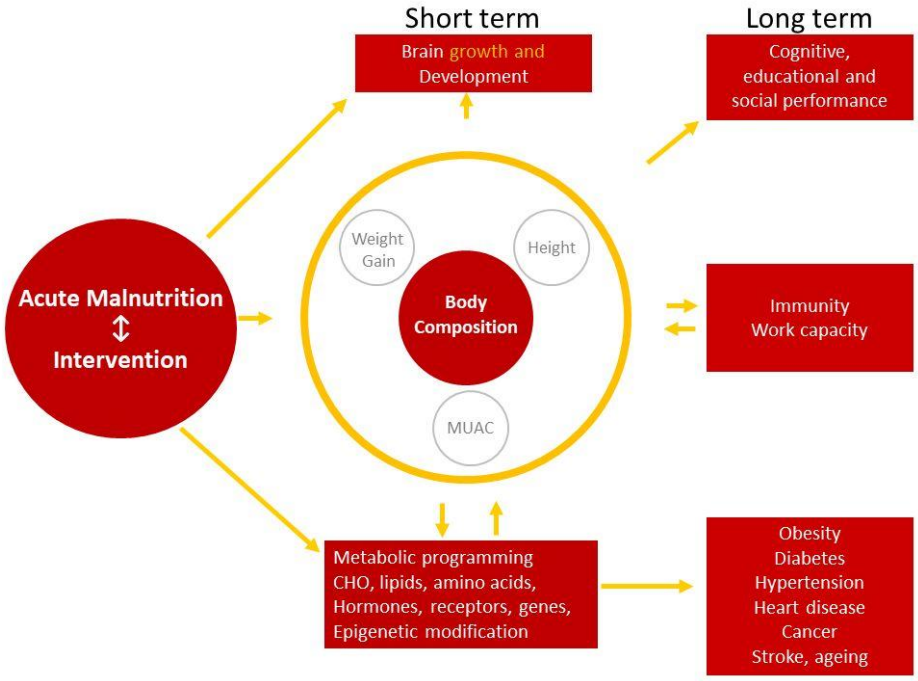

Figure 1. Conceptual framework of pathways underpinning the relationship between early nutritional insults and later outcomes including risk for metabolic dysfunction. Adapted from Jackson et al 1996 and Wootton and Jackson, 1996.