The double burden of malnutrition: etiological pathways and consequences for health

Jonathan C Wells PhD [$] [1], Ana Lydia Sawaya PhD [$] [2], Rasmus Wibaek MSc [3,4], Martha Mwangome PhD [5], Marios S Poullas MRes [1], Chittaranjan Yajnik PhD [$*] [6], Alessandro Demaio PhD* [7-9]

* Joint senior author

$ Full Professor

1. Childhood Nutrition Research Centre, UCL Great Ormond Street Institute of Child Health, 30 Guilford Street, London WC1N 1EH, UK
2. Department of Physiology, Federal University of São Paulo, Rua Botucatu, 862, Edifício de Ciências Biomédicas, 2° andar, 04023-060 São Paulo, SP, Brazil
3. Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark
4. Clinical Epidemiology, Steno Diabetes Center Copenhagen, Denmark
5. Kenya Medical Research Institute (KEMRI)/Wellcome Trust Research Program, Kilifi, Kenya
6. Diabetes Unit, KEM Hospital, Pune, India
7. EAT Foundation, Oslo, Norway
8. Melbourne School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia
9. School of Global Health, Department of Public Health, University of Copenhagen, Copenhagen, Denmark

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Key messages

- Malnutrition has long been researched and addressed in two distinct silos, focusing either on chronic or acute undernutrition, energy inadequacy and micronutrient deficiencies, or on overweight, obesity and dietary excess. The contemporary reality of the double burden of malnutrition is different, making it impossible to separate these issues, but also indicating shared opportunities to address them.
- Malnutrition harms health throughout the life-course, but its emergence early in life has particularly pernicious consequences. A variety of physiological mechanisms propagate effects of early-life malnutrition across the life-course, while adolescent and adult malnutrition can transmit effects to the next generation.
- Different forms of malnutrition can interact through the life-course and across generations. In some settings, early stunting may predispose to a more central distribution of adiposity at later ages, while the extent to which maternal obesity adversely affects early growth and development of the offspring may be exacerbated if the mother herself was under-nourished in early life.
- Life-course exposure to the double burden of malnutrition (early undernutrition followed by later overweight) increases the risk of non-communicable disease, by imposing a high metabolic load on a depleted capacity for homeostasis. The health costs of adult obesity are therefore exacerbated among those who previously experienced undernutrition. In women, life-course exposure to the double burden of malnutrition increases the risk of childbirth complications.
- Exclusive and appropriate breast-feeding protects infants against all forms of malnutrition, and protects mothers against diabetes and breast cancer, in part through healthy-weight benefits. However, maternal obesity, diabetes and micronutrient deficiencies alter the biology of lactation, and should be addressed to maximise the success of breast-feeding.
- Exposure to the double burden of malnutrition can only be fully understood in the context of broader societal drivers acting across culture, behaviour and technology. Various groups are at high risk of the double burden through elevated exposure to these drivers, often exacerbated by biological susceptibility.
- Developmental responses to malnutrition in early life are shaped by ecological factors, such as pathogen burden and extrinsic mortality risk. An evolutionary perspective, focusing on how our biological plasticity was shaped in ancestral environments to promote survival and reproduction, may help design interventions that promote linear growth and lean tissue accretion rather than excess adiposity.
- Inter-generational cycles of malnutrition have proven difficult to disrupt through public health interventions. Major societal shifts are required regarding nutrition and public health, in order to implement comprehensive change that is sustained over decades, and scaled up into the entire global food system.

Abstract

Until recently, undernutrition and overweight were considered separate public health problems affecting distinct populations, and with contrasting risk factors. However, it is increasingly recognised that these two extremes of malnutrition are connected in complex ways. Numerous physiological mechanisms contribute to long-lasting effects of malnutrition early in the life-course, while malnutrition in adolescents and adults can propagate adverse effects to the next generation. Moreover, different forms of malnutrition can interact through the life-course and across generations. Fetal undernutrition and early stunting may predispose to a more central distribution of adiposity at later ages, while the impact of maternal obesity on the offspring may be exacerbated if the mother herself was under-nourished in early life. Life-course exposure to early undernutrition followed by later overweight increases the risk of non-communicable disease, by imposing a high metabolic load on a depleted capacity for homeostasis, and in women increases the risk of childbirth complications. These life-course trajectories are shaped both by societal driving factors, that are rapidly changing diets, norms of eating and physical activity patterns, and by broader ecological factors such as pathogen burden and extrinsic mortality risk. Mitigation of the double burden of malnutrition will require major societal shifts regarding nutrition and public health, in order to implement comprehensive change that is sustained over decades, and scaled up into the entire global food system.

Keywords: Stunting; overweight; obesity; double burden; breastfeeding; non-communicable disease

Abbreviations

BMI – Body mass index

DBM – Double burden of malnutrition

DHS – Demographic and Health Survey

HIC – High-income country

LBW – low birthweight

LMIC – Low-/middle-income country

NCD – Non-communicable disease

Introduction

Undernutrition and overweight have long been considered separate challenges affecting distinct populations, and with contrasting risk factors. Undernutrition was linked with poverty, food insecurity and infection, whereas obesity was linked with affluence, dietary richness and sedentary behaviour. Increasingly, the two forms of malnutrition co-occur within communities, families and even individuals, such as those both stunted and overweight.[1] The current manifestation of this global 'double burden' of malnutrition (DBM) is summarised by Popkin and colleagues.[2] Obesogenic environments are expanding, while the causes of undernutrition persist,[2] and an increasing proportion of those currently overweight were under-nourished earlier in life.[3] To understand the implications of the DBM for health at the individual level, the explanatory framework must shift from descriptive epidemiology to biology.

Recently, Swinburn and colleagues reconceptualised the two extremes of malnutrition within a single over-arching framework, relating them to common drivers that also underlie climate breakdown.[4] Here, we develop this perspective, focusing on the biological interconnections between undernutrition and overweight. First, we describe the aetiology of malnutrition across life-courses and generations. Both undernutrition and overweight can propagate long-term effects, especially if they develop early in life, and each form may increase risk of the other occurring. Second, we show that individuals who experience the DBM through the life-course have increased risk of diverse forms of ill-health. Third, we examine why the DBM is affecting growing numbers worldwide, and highlight populations with high susceptibility. We provide an evolutionary perspective that can help understand these biological interactions and their health consequences in different settings. Our framework may help identify effective strategies for double-duty actions that address both forms of malnutrition, as addressed in subsequent papers in this series.[5,6]

Life-course manifestation of malnutrition

Malnutrition is a complex phenotype that manifests across the life-course in different ways (Appendix 1), yet its categorisation remains unsophisticated. Regarding undernutrition, simple anthropometry is used to categorise low birthweight (LBW), stunting (low height-for-age) or wasting (low weight-for-age) during infancy/childhood, and short stature or low body mass index (BMI) in adulthood. Assessed thus, undernutrition is most prevalent among younger age-groups. Undernutrition can also be assessed in terms of depleted stores or circulating levels of nutrients, reflecting dietary inadequacy. Micronutrient deficiencies remain prevalent in adults, and are of particular concern among women of reproductive age.[7]

Excess weight can likewise emerge in late fetal life (macrosomia), but usually develops from early childhood through cumulative exposure to obesogenic factors acting on both individuals and societies.[4] Many studies link elevated adiposity, especially abdominal fat, with ill-health, yet despite correlating poorly with adiposity among individuals, the simple anthropometric index BMI provides a useful metabolic risk-marker for populations.[8] Its main limitation is its inconsistent association with NCD risk across populations.[9] As with undernutrition, indices of 'nutritional excess' extend beyond the body to traits such as diet composition and physical inactivity, both of which can perturb metabolism.

Our concept of malnutrition should also incorporate the gut microbiome, representing millions of genes from micro-organisms. These generate a collective metabolic activity that impacts and responds to the human host. Diverse forms of malnutrition are associated with dysbiosis, propagating adverse metabolic consequences (Appendix 2), though findings for obesity are heterogeneous. The microbiome demonstrates resilience within individuals, with implications for health maintenance and disease risk,[10] but can also respond to interventions (Appendix 2).[11]

Malnutrition harms health throughout life, but its early emergence has particularly pernicious consequences. Development is characterised by a succession of sensitive periods or 'critical windows', when phenotype is particularly responsive to nutritional influences. Physiological mechanisms characterising these periods include the differential growth of organs and tissues, establishment of hormonal set-points and epigenetic variability, telomere attrition and microbiome maturation (**Panel 1**). Crucially, these mechanisms respond to both undernutrition and over-nutrition in early life. Such physiological sensitivity explains why early nutrition and growth have major implications for both immediate survival, and long-term health and human capital.[12,13]

Many 'critical windows' close early during development, reducing the sensitivity of specific traits to environmental influences. For example, some epigenetic effects are restricted to the peri-conceptional period,[23] others to early infancy.[18] Likewise, from late infancy linear growth becomes less sensitive to nutritional intake,[24] hence short adult stature is primarily attributable to early stunting. However, other traits subsequently become plastic, and adolescence represents a key period of sensitivity to nutritional factors, especially relating to reproductive biology.[25]

At the individual level, the DBM can thus be assessed through diverse somatic, dietary and behavioural traits, as well as the microbiome, all of which may be targeted by appropriate interventions. Through the mechanisms of plasticity highlighted above, different forms of malnutrition interact through the life-course and across generations.

Inter-generational emergence of the DBM

While malnutrition manifests within life-courses, its aetiology spans generations. For example, early sensitive periods fall within pregnancy and lactation, making maternal phenotype the key nutritional factor shaping early development.[21,23,26] Through nutrition transition, increasing numbers in low-/middle-income countries (LMICs) are exposed to both nutritional deficiencies and fuel-excess at different ages, a scenario termed 'double teratogenesis'.[27]

Many LMIC populations have experienced chronic undernutrition, characterised by inter-generational 'cycles of disadvantage'. Maternal undernutrition compromises fetal growth and increases the risk of childhood underweight, stunting and micronutrient deficiency (**Figure 1** and Appendix 4). Stunting is a cumulative process, often apparent by birth but worsening until ~2 years when growth becomes canalized.[28] Linear growth faltering during infancy is exacerbated by episodes of wasting,[29] which helps explain why stunting is associated with elevated mortality risk. Such inter-generational cycles have proven difficult to disrupt through interventions: maternal supplementation from mid-pregnancy to term with macro-/micro-nutrients has modest effects on birthweight, but does not benefit growth in the longer-term.[30-32]

Inter-generational effects are equally relevant to mothers with obesity or perturbed metabolism. Maternal obesity is associated with elevated fetal adiposity, especially when compounded by gestational diabetes (**Figure 1** and Appendix 4). More generally, a high plane of nutrition in early life (greater gestational weight gain, higher birthweight, faster post-natal weight gain) is associated with greater risk of obesity, abdominal adiposity and insulin resistance in adulthood.

Increasingly, however, changes in food systems are breaking down the separation between these inter-generational cycles of nutritional deficiency and excess, hence **Figure 1** and Appendix 4 also summarise evidence for their interactions. Early undernutrition may predispose to later central adiposity and NCDs, while the offspring of obese mothers may show poor growth and development in early life;[33] though in each case there is substantial heterogeneity.

Whether early undernutrition predisposes to later adiposity depends on post-natal patterns of growth and nutrition, including complementary feeding patterns. Growth faltering in early pregnancy may induce 'catch-up' in fat mass before birth,[34] while those born small often undergo accelerated weight gain in infancy or childhood.[35] This catch-up may likewise induce elevated adiposity, and in high-income countries (HICs), rapid infant weight gain is associated with later obesity.[36] However, LMIC studies

typically associate faster infant weight gain with greater adult height and lean mass,[37] and in these settings it is broadly after two years that rapid weight gain promotes adiposity,[13] though the situation may change in concert with nutrition transition.

Associations between stunting and body composition are likewise complex. Compensatory weight gain following undernutrition typically prioritises accretion of fat over lean, through mechanisms of 'energy-sparing'.[38] In some South American studies, for example, early stunting predicts excess abdominal adiposity, mediated by changes in fuel metabolism (**Panel 2**).[39] However, stunting was not associated with impaired fat oxidation in young children from Cameroon,[40] while in Peru, children's height was positively associated with adiposity at low altitude, but inversely associated at high altitude.[41] In malnourished young children from Burkino Faso, 93.5% of weight gained during a food supplementation programme comprised lean tissue.[42] These findings indicate complex developmental links between growth patterns and adiposity, where growth may either be accelerated across all traits, or characterised by trade-offs between traits. Regardless of whether early stunting elevates abdominal adiposity, a consistent finding is that early undernutrition permanently reduces lean mass and its functional correlates such as grip strength.[43-45]

Although maternal obesity correlates with higher birthweight, it is also associated with micronutrient deficiencies that may impair offspring development, while maternal hypertension is associated with increased risk of LBW offspring, a scenario exacerbated by anti-hypertensive pharmaceutical agents.[49] Obesity is generically associated with poorer micronutrient status,[50] mediated by chronic inflammation and nutrient-poor diets, while maternal obesity may also contribute to dysbiosis in the offspring.[51]

Using Demographic and Health Survey (DHS) data from 12 LMICs, we analysed how markers of maternal malnutrition (short stature, overweight/obesity) interact in association with the risk of stunting in the offspring. While short maternal stature increases the risk of stunting, maternal overweight/obesity typically reduce this risk relative to normal BMI, providing the mother is of normal height. However, this protective effect disappears if the overweight mother is also short (**Figure 2a**). The consequences of maternal obesity for the next generation therefore depend on the mother's own developmental experience. In a Swedish study, the inter-generational transmission of obesity was threefold greater among obese mothers born small-for-gestational-age, compared to mothers of normal birthweight.[52]

Though evidence remains scarce, paternal metabolic phenotype can also impact offspring development. For example, paternal smoking and dietary intake during adolescence have been associated with offspring BMI,[53] mediated by imprinting of the sperm.[54] Paternal genes may be especially relevant in

early life as they contribute to placental function. Bariatric surgery in men has been associated with remodelling of sperm DNA methylation, in particular of genes associated with appetite control.[54] However, beyond father-child correlations in height and BMI,[55] there is currently minimal understanding of paternal biological contributions to the DBM in LMICs.

The life-course and inter-generational physiological pathways that we have summarized above underlie associations of the DBM with several forms of ill-health, as we discuss next.

The DBM and NCD risk

Associations of adult obesity and unhealthy lifestyle with NCDs are well-recognised,[56] but there is compelling evidence that exposure to undernutrition in early life exacerbates these relationships. To elucidate this, we present a 'capacity-load' conceptual model.[57,58]

Initially, associations of NCD risk with birthweight were attributed to long-term consequences of fetal undernutrition. The 'thrifty phenotype' hypothesis proposed that inadequate fetal nutrition reduced growth of some organs (eg pancreas, liver, kidney) to protect the brain. Later, such individuals would have lower tolerance of obesity and energy-dense diets, elevating NCD risk.[46] However, birthweight demonstrates inverse dose-response with NCD risk across most of its range,[59,60] while macrosomic infants have increased NCD risk.[61] This variability refutes the notion that fetal undernutrition is the primary developmental mechanism.

The capacity-load model addresses continuous associations of both developmental and adult traits with NCD risk, and can be applied to diverse traits through the life-course and to various NCD outcomes (Appendix 7). 'Metabolic capacity' refers to traits, strongly contingent on growth and metabolic exposures during early life, that have life-long implications for the capacity for homeostasis.[57] Relevant traits include pancreatic beta cell mass/function, nephron number, organ/tissue mass, airway and blood vessel diameter, and cardiac structure. All of these scale with the magnitude of growth during the period of hyperplasic growth. Environmentally-induced epigenetic variability and microbiome development can be considered within the same conceptual framework,[62,63] though the extent to which early variability in these traits persists long-term remains uncertain.[64] Size at birth and early post-natal growth patterns act as useful, though imperfect, composite markers of metabolic capacity.

'Metabolic load' refers to traits that challenge homeostasis, including excess adiposity, physical inactivity, lipogenic diet, smoking, infection and psychosocial stress.[57,58] These traits broadly show dose-response associations with NCD risk, and are all associated with increased oxidative damage. Metabolic

load can increase early in life in association with catch-up growth, which elevates not only adiposity but also molecular markers of NCD risk (epigenetic effects, telomere attrition).[65] Macrosomic infants already have elevated adiposity (high load), and potentially also low capacity, by birth.

According to this conceptual model, NCD risk decreases in association with metabolic capacity, and increases in association with metabolic load. Substantial evidence supports the model,[59,60] but the majority is from studies in HICs. Evidence from Asian and sub-Saharan African populations is summarised in Appendix 8. One caveat is that the specific role of linear growth in this model varies by outcome. For cardiovascular disease, diabetes and hypertension, linear growth promotes metabolic capacity, indicated by elevated NCD risk among those with poor early growth or short adult stature (Appendix 9a). This is likely because height is a good proxy for organ growth and development through the life-course. However, for many forms of cancer, linear growth may better be considered a component of metabolic load, as faster growth and taller height are associated with elevated risk (Appendix 9b).[66,67] These associations indicate that efforts to reduce LBW and stunting in LMICs may increase future cancer incidences.

This conceptual model helps explain why the DBM is strongly associated with NCD risk. LBW, child stunting and wasting all deplete components of metabolic capacity, while overweight and unhealthy environmental exposures exacerbate metabolic load. Importantly, the extent to which early undernutrition leads to overt NCDs depends strongly on subsequent nutritional status. For example, survivors of severe malnutrition during early life in Malawi had long-term deficits in height, lean mass and grip strength, however NCD risk was negligibly affected, most likely because these children remained relatively thin and had low metabolic load.[45] It is the combination of poor early growth and subsequent elevated BMI that appears key to adult NCD risk.[68]

Figure 3 illustrates how nutrition transition is driving the NCD epidemic in Pune, India, combining data from three cohorts at different stages of economic development. Following multi-generational exposure to energy-scarcity and micronutrient deficiencies, the rural cohort has experienced a modest secular increase in adult size, but a quarter of young adults have developed pre-diabetes, and 12% of the young mothers have gestational diabetes. These trends are more extreme in a matching urban cohort, with some of the offspring developing child obesity, and higher rates of gestational diabetes among young overweight mothers. Finally, among an urban cohort born to diabetic mothers, 40% have themselves developed pre-diabetes at 15 years, while 15% of the young mothers have produced large-for-gestational-age neonates.

That the 'toxicity' of obesity is exacerbated among those initially under-nourished has been shown in diverse populations (Appendix 8).[59,69] Studies in Brazil have revealed some of the physiological mechanisms through which childhood stunting may predispose to central fat deposition and NCD risk (**Panel 2**). Notably, however, a combination of better diet quality and prevention of infections appears able to reverse these effects.[47]

Likewise, nutritional supplementation in early life may potentially promote metabolic capacity and thus reduce NCD risk. Supplementation during pregnancy reduces the risk of LBW[30,70] but propagates few beneficial effects into childhood,[32,71] whereas a community food supplementation programme provided to both pregnant women and their offspring in early childhood improved childhood growth and was associated with greater height and lean mass but not adiposity in early adulthood.[72] However, the longer-term consequences of this intervention for NCD risk were mixed,[73] possibly because the intervention spanned several different developmental stages and may have impacted both metabolic capacity and load.

The optimal timing for interventions to prevent the DBM therefore remains in need of further research. We suggest that alongside the pre-conception period and pregnancy,[23] early infancy may be another crucial window of opportunity.[5] For example, the period of exclusive breast-feeding is simultaneously a developmental period when many mechanisms of plasticity respond to nutritional influences (Appendix 10), an important period for the development of metabolic capacity, and a period when metabolic load can be suppressed.[58] However, the success of breast-feeding is itself threatened by maternal malnutrition (**Panel 3**), indicating that interventions targeting breast-feeding mothers may simultaneously improve maternal health while also mitigating the DBM in the next generation.

While malnutrition damages health in all populations, its manifestation and physiological consequences also vary. First, the two sexes often differ in the prevalence and consequences of malnutrition. Low adult BMI and childhood stunting tend to be slightly more common in males than females in LMICs,[80,81] whereas adult women show higher prevalences than men of obesity and anaemia.[82,83] Moreover, the life-course development of NCD risk also differs by sex.[84]

Second, ethnicity contributes to variability in the health consequences of the DBM. Human morphology and physiology vary with geography, in ways that also change through the life-course.[85] For example, South Asian populations demonstrate high rates of LBW and stunting and relatively short adult stature, all indicative of reduced metabolic capacity, but also a high fat-lean ratio and abdominal adiposity, indicative of elevated metabolic load for a given BMI value.[86,87] These traits are strongly implicated in

the elevated NCD susceptibility of South Asian populations, however, they are overlaid by economic and cultural factors, including diet preferences, migration patterns and social inequality.

Malnutrition and inflammation

The life-course manifestation of malnutrition varies markedly across ecological settings. In HICs, the obesity epidemic developed in the context of low burdens of communicable disease and child undernutrition. In LMICs, however, both extremes of malnutrition co-exist with persistent burdens of infections. Both undernutrition and overweight are associated with inflammation,[88,89] effectively generating a triple challenge to metabolic health with major implications for NCD risk.

Poor nutrition in early life (fetal growth faltering, post-natal stunting, sub-optimal breast-feeding) has been associated with elevated markers of inflammation in childhood and young adulthood, while obesity is also a chronic inflammatory condition.[88,90-92] Although research from LMICs is lacking, studies from HICs indicate that the inflammatory load of obesity may be exacerbated by early-life undernutrition.[93,94]

An unfavourable gut microbiome may contribute to these associations (Appendix 2). Microbiota immaturity, increased enteropathogen burden and gut barrier dysfunction are interrelated factors associated with inflammation in early life.[95] The microbiota of stunted Indian children was depleted in probiotic species and enriched in inflammogenic taxa, relative to control children.[96] At later ages, dysbiosis contributes to associations of obesity with insulin resistance and systemic inflammation.[97,98] Among obese adults with similar BMI, those with greater dysbiosis have higher NCD risk,[99] while dysbiosis also contributes to inflammatory process associated with sarcopenia.[100]

Manipulation of the microbiome, for example by providing probiotics or fecal transplantation, might beneficially modify NCD risk markers (Appendix 2), but further research is needed to understand how this could achieve long-lasting effects mitigating both forms of malnutrition.

The DBM and childbirth complications

While much emphasis has been placed on the implications of the DBM for NCD risk, both short stature and overweight are also independent risk factors for obstructed labour, related to maternal mortality.[101] The DBM may therefore impact health outcomes of mothers and offspring related to childbirth. For short women, the primary underlying mechanism is likely to be reduced pelvic dimensions while, for overweight women, a key mechanism is perturbed fuel metabolism, increasing birthweight.[101] Globally, many mothers stunted in early life become overweight before reproducing, while overweight women

are also more likely to develop gestational diabetes if previously stunted.[101] The combined effect is predicted to increase the risk of obstructed labour.

We analysed DHS surveys from 11 LMICs, demonstrating that while both maternal stunting and overweight each increase risk of caesarean delivery (a correlate of obstructed labour), the risk tends to be further amplified among stunted-overweight and stunted-obese women (**Figure 2b**). While increases in caesareans have been linked with indices of wealth, the financial incentives of health care providers, and defensive medicine to minimise litigation,[102,103] the emerging DBM may therefore be an additional factor.[3]

Given the profound health penalties of the DBM in individuals, we need to understand what is driving the global epidemic. We show below that biological susceptibility interacts with societal factors, and provide an evolutionary perspective to help understand how we might combat the DBM most effectively.

Societal driving factors

The biological inter-linkages described above can only be fully understood in the context of broader societal drivers, which mediate differential exposure to the causes of malnutrition. The global DBM is closely associated with rapid economic development and increases in *per capita* income,[2] but also incorporates a constellation of societal trends acting across culture, behaviour and technology.[4] Many of those most exposed to these trends are not the wealthiest, but rather those least empowered to resist adverse societal and corporate influences.[5,58] The metabolic consequences of unhealthy diets that are both energy-dense and micronutrient-poor[104] are exacerbated by increases in sedentary behaviour,[105] while exposure to psychosocial stress has been associated with unhealthy food choices and eating patterns, and with perturbed appetite, weight gain and central adiposity.[106,107]

At a societal level, gender inequality exacerbates female exposure to the DBM.[108,109] From a political perspective, governments struggle to restrain commercial activities in the interests of population health, but may also contribute to the DBM through the promotion of international trade and national economic development, and the opening of domestic markets to multi-national corporations. Policy-makers are increasingly exploring strategies to reduce malnutrition that place less emphasis on economic growth, by addressing issues as food sovereignty, gender equality, education and healthy food systems.[108,110-112] Nevertheless, the emerging DBM is a stark indication of how a large proportion of the global population, especially in LMICs, is poorly protected from multiple factors driving malnutrition in all its forms.

High-risk groups

While the DBM affects many countries,[2,4] various groups are at high risk and merit particular attention. This susceptibility relates to diverse factors spanning both biology and environmental stressors.

In HICs such as Canada, Australia and the UK, for example, first-nation, aboriginal and ethnic minority populations typically show higher levels of LBW and child undernutrition compared to the general population, but also increased risk of obesity and NCDs in later life (Appendix 12). Similarly, African Americans show persisting deficits in birthweight relative to those of European ancestry, while Hispanic and African Americans have greater prevalence of adult obesity than Europeans.[113] Similar patterns increasingly apply to minority groups within LMICs, such as tribal populations in India.[114]

To track such population-specific susceptibility, ethnic differences in physique and metabolism should be addressed. In the UK, for example, adjusting for ethnic differences in the BMI-adiposity relationship reveals that obesity is most prevalent and increasing fastest in south Asian children compared to other groups.[115] Moreover, body fat is 'more toxic' in south Asian than European children, having a stronger association with insulin resistance.[116] These patterns help explain why some groups show high susceptibility to NCDs in early adulthood, even at relatively low BMI thresholds.

As noted by Popkin et al.,[2] within LMICs, rural-urban migration exposes increasing numbers to drastic changes in diet, physical activity and living conditions. Rural populations demonstrate high rates of childhood stunting,[117] while migration to cities is typically associated with rapid increases in BMI and abdominal fat. This adiposity elevates NCD risk in comparison to the rural population, but typically to lower levels compared to established urban populations.[118] These health penalties may increase through lengthier urban residence and at older ages, however research on malnutrition in the elderly in LMICs remains very scarce.[119,120]

Because of their imminent reproduction, adolescents are another particularly important group. Surveys indicate high prevalences of underweight, overweight and anaemia in adolescents, though varying by country.[121,122] Adolescents are also among the first groups to adopt new diets and lifestyles, in part through their tendency to migrate in search of new economic opportunities. The combination of overweight and anaemia in adolescent women is difficult to address, as obesity-mediated inflammation may impede iron absorption and reduce the efficacy of supplementation programmes.[121] Finally, infants are susceptible to complementary foods that are fattening while also micro-nutrient deficient.[123]

An evolutionary perspective

The profound health risks associated with life-course exposure to the DBM may seem puzzling. First, why does nutrition transition not resolve the effects of multi-generational undernutrition? Why do stunted children often remain short in adulthood and become overweight, rather than growing tall and remaining lean? Second, why is the combination of early stunting and later overweight so detrimental to health? An evolutionary perspective may help explain why different forms of malnutrition interact and shape NCD risk. Evolutionary life history theory assumes that every organism allocates energy between four competing functions: maintenance, growth, reproduction and defence, resulting in 'trade-offs' between these functions.[124] The optimal allocation strategy for maximising reproductive fitness is expected to vary in association with developmental trajectory and ecological conditions.[125]

A key factor influencing these 'allocation decisions' comprises extrinsic mortality risk. In high-risk environments, selection favours 'discounting the future', diverting energy away from maintenance and growth towards defence (short-term survival) and reproduction. This insight helps understand the combination of high fertility and lower birthweights in chronically undernourished populations with high infectious burdens: fitness is maximised by producing more offspring, but investing less in each. Sub-optimal fetal nutrition not only constrains the development of metabolic capacity, but is also associated with long-term central adiposity and inflammation, promoting immune function through the life-course.[58,92]

Economic development increases dietary energy availability and alters life history strategy, however the nature of this change depends on both extrinsic mortality risk and diet composition. In high-pathogen food-insecure environments, if energy supply increases during childhood it is too late to allocate it to 'maintenance' as the physiological critical windows already closed. Instead, the surplus is primarily diverted to survival (pro-inflammatory state, energy stores) and reproduction (gaining weight during adolescence). This helps understand why those initially under-nourished do not entirely resolve their growth deficit, and are prone to central adiposity and elevated inflammation.[93,94,126] Reduced fertility among obese women[127] suggest that these trade-offs evolved in ancestral environments characterised by energy scarcity, and in contemporary settings they may be exacerbated through exposure to processed foods high in energy but low in protein/micronutrients. Inflammation disrupts many components of homeostasis relevant to NCD risk, such as appetite, sleep, insulin metabolism, arterial health and oxidative balance.[128] The result is a high metabolic load superimposed on a depleted capacity, provoking NCDs at relatively low thresholds of age/overweight.

In food-secure low-pathogen settings, conversely, lower infant mortality means that mothers can maximise fitness by producing fewer offspring, and investing more in each during early life. This allows each offspring to divert more energy to maintenance and early growth, promoting life-long homeostasis and health, and a likely lengthier reproductive career.

This perspective helps explain why in HICs with long-term efforts to reduce infectious disease, economic development has induced prolonged secular increases in height and lifespan,[129] whereas in many LMICs where poor quality diets and high infectious burdens persist, economic development is more strongly associated with trends in BMI,[82] and an escalating NCD burden. Secular trends in stature in LMICs remain weak,[130,131] instead a secular decline in menarchal age has occurred, especially in urban settings (Appendix 13).[58] The mechanisms of developmental plasticity described in **Panel 1** may play a key role orchestrating such life history trade-offs in association with ecological conditions.

Trade-offs between biological functions may prove especially rewarding targets for interventions aiming to reduce malnutrition and its adverse health effects. In particular, whether efforts to reduce adult NCD risks in LMICs are successful may be contingent on reducing both early undernutrition and the burden of infection. This proposition is supported by evidence that, independent of nutritional supply, childhood vaccination benefits linear growth.[132]

Conclusion

Examining the DBM from the perspective of individual health is very different from approaching it at the population level. Beyond their common driving factors,[4] undernutrition and overweight show multiple physiological connections and interactions. As LMICs undergo economic development and nutrition transition, the resulting DBM is exposing growing numbers of individuals to various forms of ill-health, including growth retardation, dysbiosis, inflammation, obesity, NCDs and childbirth complications. Recognising these inter-connections may open up new, shared opportunities to improve metabolic health.

Our evolutionary perspective helps understand why the DBM is so harmful to health. Exposure to malnutrition during early 'critical periods' results in the body reducing its valuation of the future, diverting energy from growth and health to survival and potential reproduction. If the only significant environmental change through the life-course comprises increased dietary energy, these trade-offs may simply intensify. This could explain why some programmes aiming to prevent undernutrition have inadvertently increased obesity and NCD risk.[73] High-energy diets that are low in protein and micronutrients may drive over-consumption of fat and carbohydrate.[133] High burdens of infectious

disease also constrain linear growth and favour inflammation, which is further exacerbated by overweight.

The programme of treatment for child malnutrition in Brazil (**Panel 2**) highlights where efforts should be directed to break this cycle.[47] The programme improves dietary quality while also cutting the burden of infection. This composite improvement makes the long-term future more attainable, and the body responds by promoting linear growth rather than adiposity, whilst restoring metabolism to lower levels of NCD risk.

To be effective, the double-duty actions proposed in this series by Hawkes et al.[5] should achieve two goals. First, they need to impact each generation early in life, so that the trajectory of development can be shifted beneficially through the physiological mechanisms listed in **Panel 1**. This highlights the importance of optimising nutrition among adolescents, whose metabolism constitutes the developmental niche for the next generation. Secondly, interventions need to be sufficiently comprehensive to impact the functional trade-offs outlined above. Successful interventions may need to begin before conception and continue through pregnancy and lactation. A cautionary note is that these interventions still need to balance health benefits and costs. For example, research is required to optimise the balance between promoting fetal growth and maintaining maternal metabolic health during pregnancy. Such interventions should be supported by the sustained provision of healthy complementary foods, and effective reductions in the burden of infection during childhood.

No single intervention can solve the DBM, and efforts must also be sustained over decades to realise their full benefits. Even if stunting is reduced, adults already overweight will bear additional health penalties if they were under-nourished during development. On the positive side, effective double-duty actions[5,6] may benefit health across the lifespan and into the next generation. To achieve these goals, major societal shifts are required regarding nutrition and public health. Ultimately, the global DBM reflects many adverse trends through which individuals are disempowered and their nutritional status and health undermined. Paper 4 in this series shows that specific interventions to reduce the DBM can be cost-effective,[6] but significant progress requires that this approach be scaled up into the entire global food system, while also meeting the need for human food systems to maintain planetary health.[134]

Contributors

The paper was conceptualised by AD, JW and CY, and its development steered by JW, CY, AS and AD. Literature reviews were conducted by JW, RW and MM. Data extraction and coding was undertaken by MP. Statistical analysis was conducted by RW and JW. Summaries of research in India and Brazil were prepared by CY and AS respectively. The conceptual diagram was developed by JW and RW. JW wrote

the first draft of the manuscript, and all authors contributed to revising it and approved the final version.

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Conflict of interest statement

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Panel 1. Physiological mechanisms through which nutrition during early life is associated with long-term phenotypic variability

• Early nutrition generates long-term effects on organ size, structure and function. Mammalian growth in fetal life and early infancy comprises hyperplasia (cell proliferation), crucial for the development of organ structure, whereas from late infancy, growth comprises hypertrophy (increases in cell size).[14] Early growth variability has long-term effects, for example, LBW infants have altered cardiac structure and small liver, kidneys and spleen,[15,16] while macrosomic infants may demonstrate organomegaly.

• Early nutrition impacts hormonal axes regulating growth and appetite. For example, both under- and excess nutrition in the perinatal period affect insulin metabolism and hypothalamic circuits regulating food intake.[17] LBW infants may be insulin-sensitive at birth, but are susceptible to insulin-resistance in association with faster childhood weight gain.

• Both inter-uterine growth retardation and maternal diabetes expose the fetus to oxidative stress, impacting cardiac and vascular structure, haemodynamics and endothelial function.

• Offspring gene expression is shaped by maternal nutrition in pregnancy and by nutritional experience after birth. For example, peri-conceptional exposure to maternal famine has been associated with epigenetic changes in IGF1 expression that persisted into early old-age,[18] while season of conception in rural Africa was associated with diverse epigenetic effects in infancy.[19] Gestational diabetes is associated with epigenetic effects on genes associated with metabolic disease. Some epigenetic changes may have adverse long-term health effects.

• Early exposure or lack of exposure to different tastes may shape food preferences and diet choices at later ages.

• Telomere length provides a marker of cellular aging that is sensitive to early nutritional experience. For example, placental and/or neonatal telomere length is associated with some components of maternal nutritional status, and predicts post-natal body composition,[20] while exclusive breast-feeding may reduce telomere attrition.[21]

• The gut microbiome rapidly matures in early life, and early malnutrition can disrupt this process. For example, among twins discordant for kwashiorkor, the affected sibling developed narrower gut microbiome diversity, and transplanting this biota to germ-free mice induced weight loss de novo.[22]

• Collectively, these mechanisms contribute to a profound imprint of early malnutrition on later phenotype, impacting both the risk and the metabolic effects of subsequent overweight.

An expanded, fully referenced version of this panel is available in Appendix 3

Panel 2: Developmental links between stunting, obesity and cardio-metabolic risk in Brazil

• Undernutrition in early life promotes survival by energy-sparing, selectively preserving some tissues and organs over others.[38,46] This adaptation is achieved by endocrine changes impacting growth, energy expenditure and body composition, which then interact with the composition and energy content of the diet.

• Among children from Brazilian shanty-towns, stunting is associated with reduced lean mass but greater adiposity, especially central abdominal fat. These physical traits are associated with increased insulin sensitivity, reduced insulin production, higher cortisol, and a reduced capacity for fat oxidation.[47]

• By adulthood, the adverse effects of overweight on cardio-metabolic traits are exacerbated among those also stunted. Stunting is associated with lower T3, higher insulin resistance, and higher glycated haemoglobin. In women, stunting is also associated with dyslipidaemia and higher blood pressure.[48]

• Adequate treatment of undernutrition during childhood with recovery in height and weight leads to normalization of insulin activity, leptin, cortisol stress response, body composition and bone mineral density.[47]

An expanded, fully referenced version of this panel is available in Appendix 5

Panel 3: The pivotal role of breast-feeding in mitigating the DBM

• Breast-feeding highlights the potential of maternal phenotype to reduce the risk of both components of malnutrition in the offspring, whilst also promoting maternal health. First, breast-feeding is strongly protective against diarrhoea and infections in the offspring, and therefore reduces the risk of mortality, stunting and wasting in early life.[74] Second, breast-feeding constrains excess BMI in the offspring during early sensitive periods, and there is suggestive evidence that it protects against later obesity, as well as NCDs such as diabetes, though it is not associated with all NCD risk markers.[74] Third, breast-feeding may be considered to mitigate some of the maternal metabolic stresses induced by pregnancy. For example, prolonged breast-feeding is associated with increased insulin sensitivity that persists at least two years post-weaning, and reduces long-term diabetes risk of mothers as well as the risk of breast cancer.[75] Given these beneficial effects, breast-feeding represents an ideal target for interventions, as explored in Paper 3 in this series.[5]

• However, successful breast-feeding is challenged not only by societal constraints on women's autonomy and employment, but also by both forms of maternal malnutrition. Among severely under-nourished mothers, low breast-milk volume and micronutrient status may affect growth and micronutrient status of the offspring.[76] Poor maternal diet reduces the diversity of the maternal microbiome, which is then transmitted to the offspring where it is associated with increased risk of severe malnutrition. Human milk oligosaccharides, unique to our species, play a key role in the establishment of a healthy gut microbiome. Animal studies have already demonstrated that promoting certain types of oligosaccharides increases lean tissue accretion in early life.[77]

• At the other extreme, maternal obesity has been associated with lower likelihood of breast-feeding, as well as reduced duration of any/exclusive breast-feeding. At the level of physiology, glucose intolerance during pregnancy may impede milk synthesis and contribute to delayed lactogenesis, while excessive gestational weight gain is associated with raised inflammatory markers in breast-milk.[78] Recent studies of diabetic women show that a longer duration of breastfeeding is necessary, compared to non-diabetic women, to achieve the beneficial protective effects against childhood obesity (Appendix 11).[79]

• Both social support and metabolic health of the mother are therefore crucial to maximising the success of breast-feeding, and capturing the health benefits to both mother and offspring. Maternal dietary intake, NCD status and the composition of the maternal microbiome are all potential targets for interventions, but further work is required to better understand the mechanisms and to develop effective solutions.

Legends for illustrations

Figure 1. Complex inter-connections between inter-generational cycles of undernutrition and nutritional excess and the impact of nutrition transition. The inter-generational cycle of undernutrition (blue) associated with energy-inadequate diets and micro-nutrient deficiencies constrains growth and reduces the metabolic capacity for homeostasis, while the inter-generational cycle of over-nutrition (red) associated with energy-dense diets is characterized by excess metabolic fuel and elevated adiposity, each of which challenges homeostasis. Both cycles of malnutrition contribute to a wide range of adverse health outcomes (grey), while specific diseases also increase the risk of malnutrition (black). Through nutrition transition, individuals shift between these cycles within the life-course, both increasing the risk and exacerbating the magnitude of health penalties. This framework helps identify connections between many different forms of ill-health – eg LBW, stunting, central obesity, diabetes, and caesarean delivery.

Figure 2. (a) Associations of stunting in 12 populations with maternal nutritional phenotype. Maternal short stature elevates the risk of stunting, whereas maternal overweight or obesity tend to reduce the risk. However, these protective effects vanish if overweight/obese mothers are also short. (b) Associations of caesarean section risk in 11 populations with maternal nutritional phenotype. Maternal short stature and overweight/obesity both tend to elevate the risk, and more so when they occur in combination. Based on DHS survey data. All models adjust for wealth, parity and offspring sex, full details are given in Appendix 6.

Figure 3. Rapid transition and evolution of the DBM in India over the last 40 years, based on data from rural and urban cohorts in Pune. Rural mothers (F0 generation) show the legacy of multigenerational undernutrition (stunting and underweight during reproductive years, low energy intake and excess physical activity from subsistence farming, multiple micronutrient deficiencies and low rates of gestational diabetes). The contemporary urban cohort shows improved nutrition, lower physical activity and moderate rates of gestational diabetes (GDM). The urban cohort of GDM women are overweight/obese and have diets providing excessive energy though inadequate micronutrients, coupled with very low physical activity. Babies born to rural mothers had low average weight and a characteristic 'thin-fat' composition (low lean mass but high fat mass compared to European babies). Babies in the urban cohort had somewhat higher birthweight but were still 'thin-fat'. Though the babies born in GDM pregnancies were the heaviest, a fourth were still SGA and 11% LGA by INTERGROWTH criteria.[135] The rural F1 young adults were still thin though adipose, and 25% have prediabetes and 15% GDM, representing a DBM within one lifetime. Their babies were 200g heavier at birth than their mothers, highlighting an intergenerational effect of the DBM. The urban and GDM cohorts highlight the progressively increasing burden of adiposity and glucose intolerance at younger age.

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Figure 1

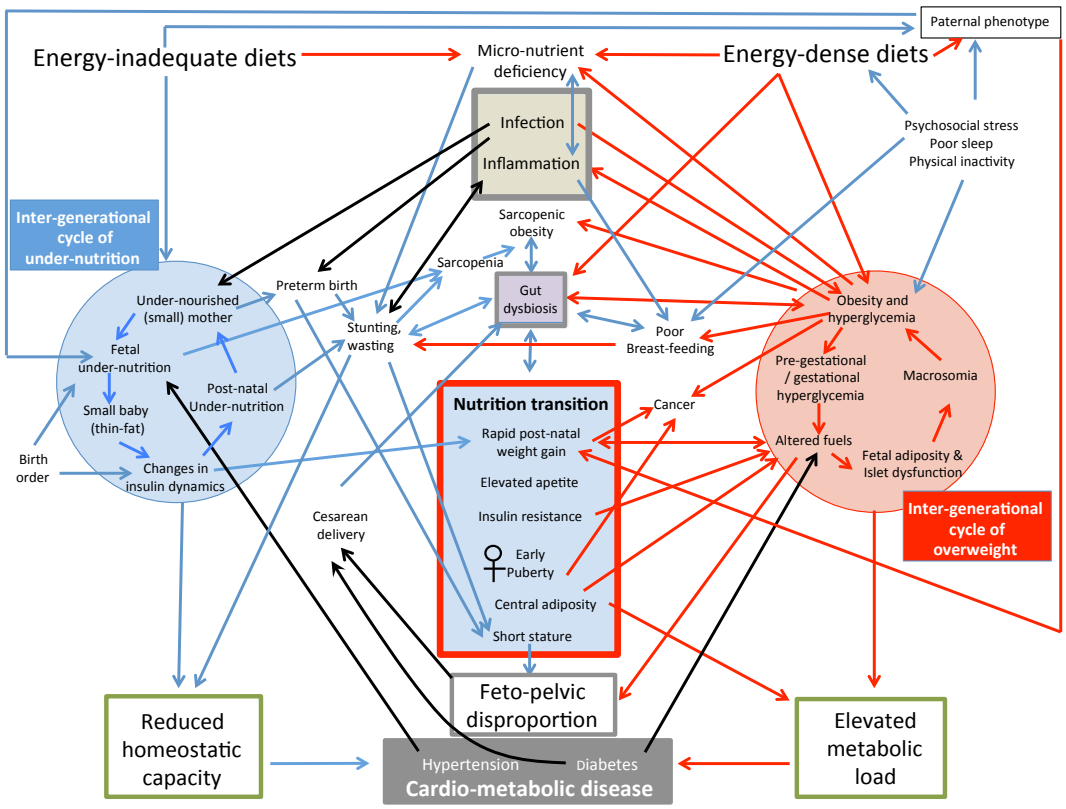
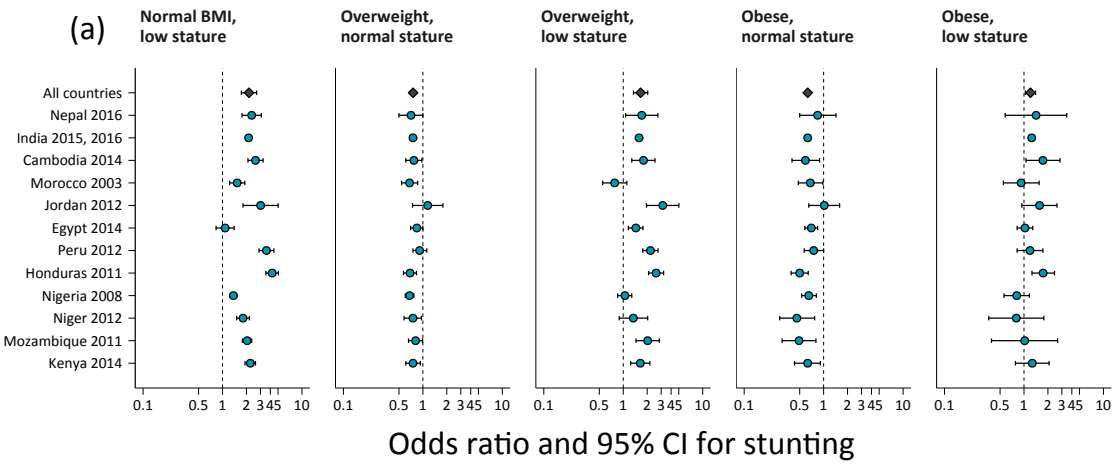

Paternal phenotype
Energy-inadequate diets
Micro-nutrient deficiency
Energy-dense diets
Infection
Inflammation
Psychosocial stress
Poor sleep
Physical inactivity
Inter-generational cycle of under-nutrition
Sarcopenic obesity
Sarcopenia
Gut dysbiosis
Under-nourished (small) mother
Preterm birth
Stunting, wasting
Poor Breast-feeding
Obesity and hyperglycemia
Fetal under-nutrition
Post-natal Under-nutrition
Pre-gestational / gestational hyperglycemia
Macrosomia
Small baby (thin-fat)
Nutrition transition
Cancer
Birth order
Changes in insulin dynamics
Rapid post-natal weight gain
Altered fuels
Fetal adiposity & Islet dysfunction
Elevated apetite
Insulin resistance
Inter-generational cycle of overweight
Cesarean delivery
Early Puberty
Central adiposity
Short stature
Feto-pelvic disproportion
Reduced homeostatic capacity
Elevated metabolic load
Hypertension
Diabetes
Cardio-metabolic disease

Figure 2


(a)
Normal BMI, low stature
Overweight, normal stature
Overweight, low stature
Obese, normal stature
Obese, low stature
All countries
Nepal 2016
India 2015, 2016
Cambodia 2014
Morocco 2003
Jordan 2012
Egypt 2014
Peru 2012
Honduras 2011
Nigeria 2008
Niger 2012
Mozambique 2011
Kenya 2014
0.1 0.5 1 2 3 4 5 10
Odds ratio and 95% CI for stunting

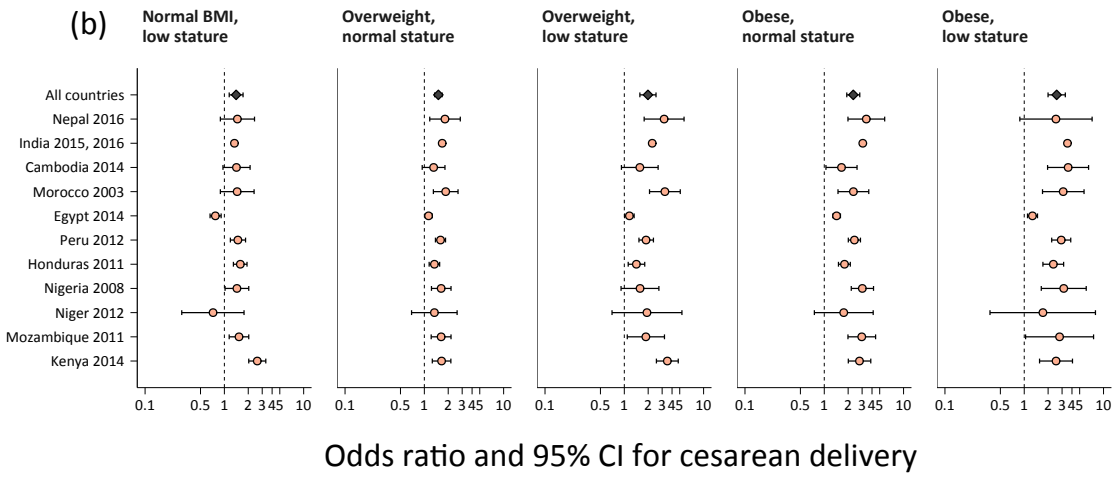
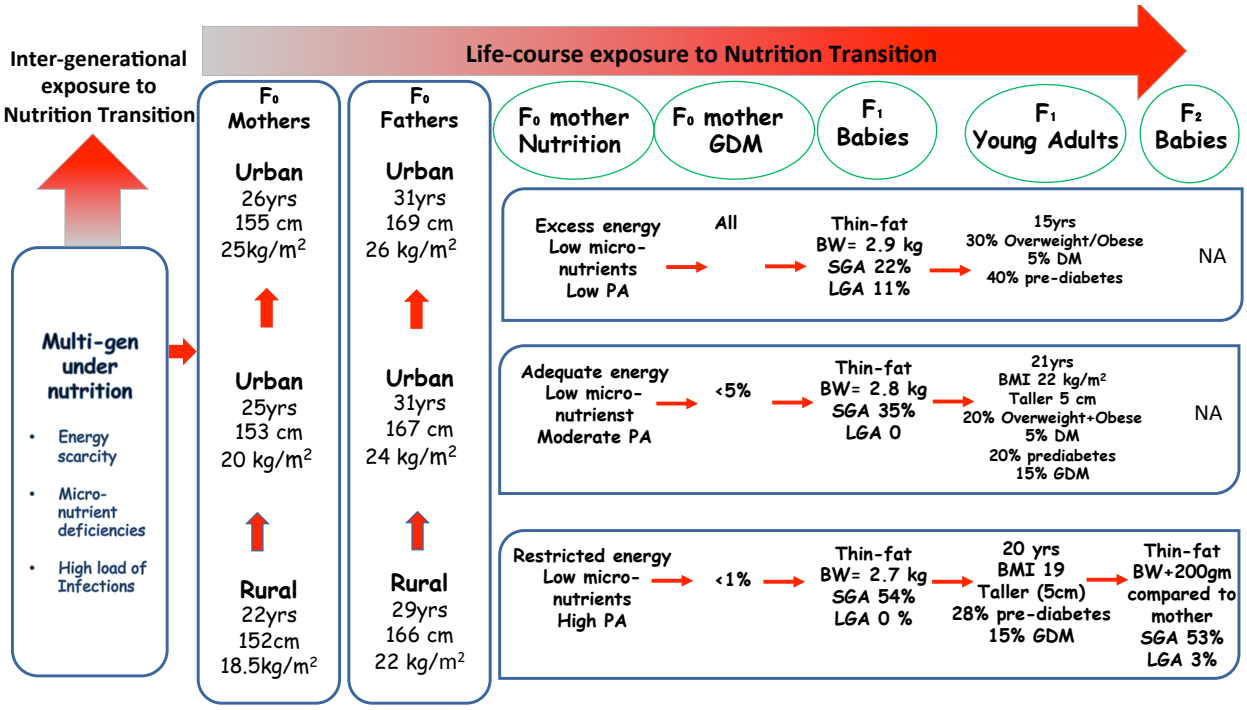

(b)
Normal BMI, low stature
Overweight, normal stature
Overweight, low stature
Obese, normal stature
Obese, low stature
All countries
Nepal 2016
India 2015, 2016
Cambodia 2014
Morocco 2003
Egypt 2014
Peru 2012
Honduras 2011
Nigeria 2008
Niger 2012
Mozambique 2011
Kenya 2014
0.1 0.5 1 2 3 4 5 10
Odds ratio and 95% CI for cesarean delivery

Figure 3


Inter-generational exposure to Nutrition Transition
Life-course exposure to Nutrition Transition
Multi-gen under nutrition
Energy scarcity
Micro-nutrient deficiencies
High load of Infections
F0 Mothers
Urban
26yrs
155 cm
25kg/m2
Urban
25yrs
153 cm
20 kg/m2
Rural
22yrs
152cm
18.5kg/m2
F0 Fathers
Urban
31yrs
169 cm
26 kg/m2
Urban
31yrs
167 cm
24 kg/m2
Rural
29yrs
166 cm
22 kg/m2
F0 mother Nutrition
F0 mother GDM
F1 Babies
F1 Young Adults
F2 Babies
Excess energy
Low micro-nutrients
Low PA
All
Thin-fat
BW= 2.9 kg
SGA 22%
LGA 11%
15yrs
30% Overweight/Obese
5% DM
40% pre-diabetes
NA
Adequate energy
Low micro-nutrienst
Moderate PA
<5%
Thin-fat
BW= 2.8 kg
SGA 35%
LGA 0
21yrs
BMI 22 kg/m2
Taller 5 cm
20% Overweight+Obese
5% DM
20% prediabetes
15% GDM
NA
Restricted energy
Low micro-nutrients
High PA
<1%
Thin-fat
BW= 2.7 kg
SGA 54%
LGA 0 %
20 yrs
BMI 19
Taller (5cm)
28% pre-diabetes
15% GDM
Thin-fat
BW+200gm compared to mother
SGA 53%
LGA 3%