Early life origins of the epidemic of the double burden of malnutrition: life can only be understood backwards

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The Lancet report on the double burden of malnutrition (DBM) in the Global Burden of Disease (GBD) series[1] was timed to be published in the week of World Obesity Day (4th March, 2024). The paper's message is that the world over, obesity is increasing while undernutrition is decreasing (though still substantial in many parts of the world including India and SE Asia). The report can be looked at as a world audit on inequity. My commitment and research in the 'Developmental Origins of Health and Disease' (DOHaD) phenomenon reminded me of two other closely juxtaposed days that happen to be relevant to the topic but appear to be forgotten: International Women's Day (8th March, 2024) and Mothering Sunday (10th March 2024). The DOHaD paradigm tells us that mother's health plays a central role in determining the health of her offspring, not only in the womb but throughout its life.[2] Fetal under-, as well as over-nutrition may 'program' risk of future diabetes and obesity. Exploiting DOHaD science will undoubtedly help reduce the DBM and inequity in future generations.

History is full of lessons in this context: 1) Exposure to the 'Hunger Winter' while in the mother's womb during the Second World War aggravated the risk of obesity and related diseases in the Dutch army conscripts,[3] 2) Exposure to maternal diabetes ('overnutrition') in the womb increased rates of obesity and diabetes in Pima Indians,[4,5] and 3) People born with a lower birth weight (fetal undernutrition) had a higher risk of diabetes and cardiovascular disease in the UK.[6] The power of intrauterine nutrition to influence gene expression and phenotype of the offspring ('epigenetics') was brilliantly demonstrated in Agouti mice. Feeding pregnant mice with methyl-donor nutrients (vitamins B12, folate, choline, and betaine) reduced obesity and diabetes in the offspring, despite inheriting the Agouti mutation.[7] On the other hand, 'normal' feeding for two generations to the 50-generation undernourished rat model rapidly led to obesity,[8] suggesting that multi-generational undernutrition increases susceptibility to obesity even at 'normal' nutrition levels.

The origins of present-day ill health in past nutritional exposures are well encapsulated in the 'thrifty' hypotheses. Neel's 'Thrifty genotype' hypothesis proposes that evolutionary selection of genes promoting fat (energy) deposition during food availability helps tide through subsequent famines.[9] Hales and Barker's 'Thrifty phenotype' hypothesis proposes that epigenetic adaptations help conserve nutrients and energy for survival of the undernourished fetus at the cost of growth (low birth weight).[10] A thrifty metabolism, of either genetic or epigenetic origin, predisposes to obesity during times of relative excess. The mechanisms are multiple, including altered function of neurons regulating appetite and satiety in the brain, and altered development of organs and systems influencing body composition and metabolic–endocrine pathways.

Undernourished and thin Indian newborn babies have less lean tissue, but higher adipose tissue compared to better-nourished English babies and are a prime example of the 'thrifty phenotype'.[11,12] Indian cord blood chemistry (higher insulin and leptin but lower adiponectin concentrations) suggests higher susceptibility to diabetes and adiposity. Rapid catch-up in growth during the post-natal period puts them on a fast trajectory to obesity and diabetes.[13] This data illustrates that undernutrition in early life and relative overnutrition later (i.e. a life course of DBM) is a potent risk factor for obesity and diabetes (Fig. 1).

The body mass index (BMI, weight/height^2, kg/m^2) is the most popular index for nutritional assessment in adults, but only a few appreciate the role of a smaller denominator in increasing BMI. Height is an integrated index of nutrition during growth and shorter people have higher cardiometabolic risk at a given BMI. Risk is even higher in those with shorter legs (reflecting early life growth failure).[14] BMI can thus be interpreted as a composite index of undernutrition and overnutrition. It is revealing that in the last two centuries (1830–1980) Europeans gained up to 15 cm in height while Indians and SE Asians did not gain at all or lost height.[15] This has been partly ascribed to colonial occupation and famines which were a result of exploitative policies. These have contributed to the evolution of the thin-fat phenotype,[16] which has a lower threshold for cardiometabolic disease. No wonder then, that India and SE Asia are the hotspots of the modern-day diabesity epidemic, despite persistent undernutrition, as highlighted in the Lancet DBM report.

The hope of shooing away the diabesity pandemic by controlling the lifestyle of adults and using biologics is

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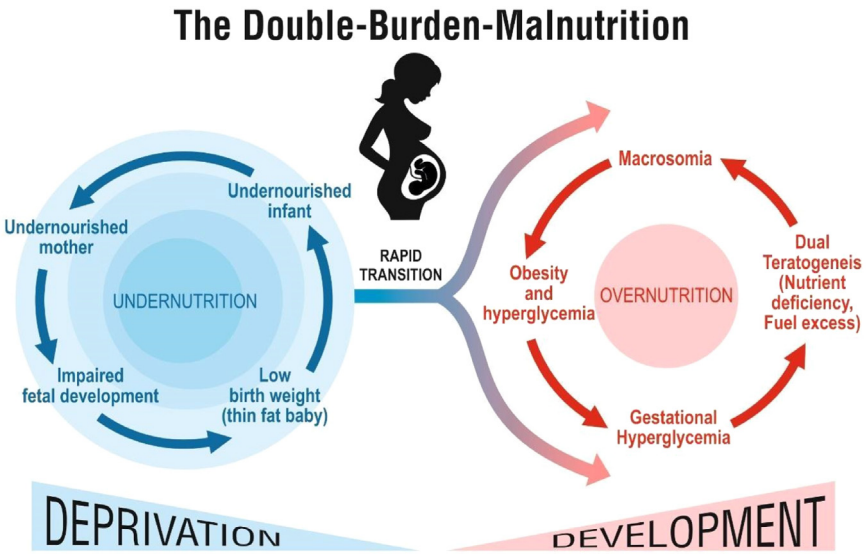

Fig. 1: **The double burden of malnutrition**. The figure shows that in the modern world, the two cycles of undernutrition and overnutrition in early life are rapidly merging into one another and contributing to the Double Burden of Malnutrition across the life course. Deprivation refers to the lack of nutritional, social, and economic availability. Development encompasses social, structural, and economic improvement. The biological unit that transmits the DBM across generations is the mother-baby dyad. Improving health of mothers and babies will improve the health of the society.

tantamount to closing the door after the horse has bolted. Only promoting adolescent and female health in the reproductive years will help primordial and primary prevention in future generations. Maternal-fetal undernutrition has seen a resurgence in the modern world due to increasing food insecurity caused by climate change, agricultural failures, wars, migration, and other catastrophes. The accumulation of diabetes risk factors ascribable to multigenerational deprivation of these mothers (low birthweight, stunting, micronutrient deficiencies, etc.) exposes the fetus also to 'gestational diabetes' and thus to DBM *in utero*.

Readers familiar with the Indian epic Mahabharata will know that Abhimanyu learned how to enter the *Chakravyuh* (a labyrinthine war formation) while in his mother's womb but did not have the opportunity to learn how to leave it, a fact which ultimately cost him his life in the war.[17] Governments and policymakers need to prioritize young women's health to equip modern Abhimanyus to conquer the *Chakravyuh* of the DBM. A 'double-duty' approach to prevent tipping into obesity while treating undernutrition is crucial. We need to learn from history. Soren Kirkegaard said it well:

"Life can only be understood backwards but has to be lived forwards."

Contributors
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Declaration of interests
The author declares no conflict of interest.

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