GLOBAL TECHNICAL MEETING

LONG-TERM CONSEQUENCES OF CHRONIC UNDERNUTRITION IN EARLY LIFE

BACKGROUND NOTE

15th AUGUST 2012

UNICEF HEADQUARTERS

NEW YORK
The long-term consequences of chronic undernutrition in early life and its implications for future health and development

The Millennium Development Goals (MDGs) set out to promote development by improving social and economic conditions in the world’s poorest countries. The first of these goals was to eradicate extreme poverty and hunger. It has been reported that the first part of MDG 1 has been achieved ahead of time – the World Bank reports that the number of people in extreme poverty had fallen to half of its 1990 level by 2010. But the second part of MDG 1, which relates to hunger and child nutrition, remains far from being reached.1

Over 180 million children under 5 years of age in low- and middle-income countries are failing to attain their development potential because of chronic undernutrition. A further 20 million children suffer from severe acute malnutrition and its adverse consequences.2 These nutritional deficiencies, which include micronutrient deficiencies such as iodine and iron, are key modifiable risk factors affecting child development.3

While it is accepted that chronic undernutrition during the intrauterine period and first two years of life leads to decreased physical growth and increased child morbidity and mortality,4 it is less well understood how chronic undernutrition in early life affects brain development, and how systemic growth failure impacts early child development. It is also not clear how chronic undernutrition can lead to changes in health and disease in adulthood, and affect the health of subsequent generations.

**Early life undernutrition and neurodevelopment:** Nutrients play a key role in brain development, both in the formation of structural components and regulation of metabolic pathways. During the critical window between pregnancy and the first two years of life, the developing brain has a rapid “growth spurt.”5 During the development of the nervous system, complex and overlapping processes, regulated by genetic programming, determine the proliferation, migration, differentiation, and pathfinding of 10 billion to 1 trillion neurons, resulting in complex organized neuronal networks.6

More than 60% of resources delivered by the placenta to support the fetus are used for neurodevelopment.6 In the first 8 weeks of gestation, more than 70% of brain cells that last into adulthood develop.7 By around 25 weeks gestation, cell numbers in most regions of the brain reach their maximum.5 However, cell growth continues, with an increase in the size of neuronal cell bodies and the genesis of supporting tissues to facilitate the formation of neural networks.5,8

Given the varied role of different nutrients at different times in brain development, disentangling the effects of nutrient deficiencies in neurodevelopment is challenging. However, since as early as the 1960s, animal

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2 State of the World’s Children, UNICEF
4 Lancet Nutrition Series, 2008
studies showed that even mild undernutrition affects brain development, with differential impacts on the structure and function of the developing brain. Subsequent animal and human studies indicate that the effect of nutritional depletion on neurodevelopment depends on type and severity of deficiency (some nutrients may have greater impact), the timing (more impact in rapidly developing brain areas), brain area (some areas such as the cerebellum are more vulnerable), the nutrient’s role in metabolic pathways and neural structures, and the duration of deficit.

In general, nutrient deficits early in gestation affect cell numbers, whereas later deficits affect migration, proliferation, formation of synapses and neural networks. Between 24 and 42 weeks gestation the brain is particularly vulnerable to nutrient deficits because this is when synapses are formed and myelin formation occurs. Studies of malnourished infants show such structural neurological changes, as nerve cells have fewer, shorter, abnormal branches that form smaller and less complex neural networks. Gross anatomical changes in brain structure have also been detected on radiological imaging.

While the developing brain has some ability to repair itself after nutritional insults, the processes determining this capacity to repair itself (plasticity) are not well understood. It appears that during late gestation and the early postnatal period, susceptibility to nutrient depletion may outweigh such plasticity, with permanent deficits even after nutrient repletion.

**Consequences of early life undernutrition:** Early life undernutrition, and the resultant growth failure, has major consequences for human capital formation. A substantial literature describes the impact of growth failure, often captured by the variable of short adult height, on future educational, income and productivity outcomes. Stunting is associated with poor school attainment, poor school performance, and higher drop-out rates. Studies have shown that stunting is associated with 2.91 deficit in school grades (even higher in the context of poverty), which translates to a 22.2% loss of yearly income in adulthood. Recent studies emphasize the importance of timing of nutrient deficits and growth failure. While a follow-up cross-sectional study from Thailand showed that prenatal (size at birth) and early infancy (birth to 4 months) growth was associated with increased IQ at age 9 years, a follow-up of Nepalese children who had previously participated in a randomized controlled of micronutrient supplementation age 12-35 months (after the period of rapid neurodevelopment), showed no long-term benefits of iron or zinc supplementation at age 7 to 9 years on intellectual, motor, and executive function. These studies emphasize the importance of the early critical window of opportunity for neurodevelopment.

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10 “Protein, iron, since, selenium, iodine, folate, vitamin A, choline and long-chain polyunsaturated fatty acids” [Ref 7: Georgieff MK]
11 A Synapse is the space between neurons where nerves signals pass
12 Myelin insulates nerve axons ensuring rapid transmission of nerve signals
The consequences of early life undernutrition in infancy persist, even with subsequent improvements in nutrition and environment. Studies of malnourished Korean orphans adopted into American families showed residual poor performance in cognitive test scores based on nutritional status at the time of adoption. Furthermore, early adoption (before age two) was associated with significantly higher cognitive test scores, compared to those adopted later.\(^\text{19}\) Another series of follow-up studies from Cape Town, South Africa assessed the impact of severe malnutrition before the age of 2 years, on later physical growth and intellectual functioning in adolescence 15 years later. Even after improvements in environment and catch-up growth, there was \textit{irreversible} intellectual impairment (motor-visual perception, disturbed body concept, abnormal electrical activity) among children who had experienced chronic undernutrition in early infancy.\(^\text{20}\) Similarly, a small study from India demonstrated that chronic protein energy malnutrition was associated with poor attention, memory impairment and impaired learning and memory in children between 5-7 and 8-10 years of age. Moreover, the results showed that stunting was associated with impaired higher cognitive functioning, and with a slowing in the \textit{rate} of cognitive development.\(^\text{21}\)

Consequences of early life undernutrition for adulthood and subsequent generations: The impact of undernutrition early in life may affect health later in adulthood, and be further transmitted across generations. The “Developmental Origin of Health and Disease [DOHaD]” hypothesis suggests that exposures experienced by one generation can result in changes for the next generation. Maternal nutrition and the uterine environment is critical, as early life undernutrition may impact future growth, and body composition, and predispose to non-communicable diseases such as cardiovascular disease and diabetes.\(^\text{22}\) For example, nutrient depletion early in the first trimester has been associated with increased risk of hypertension, whereas nutrient depletion in the second trimester has been associated with increased risk of glucose intolerance in adult life.\(^\text{23}\) The mechanisms underlying this phenomenon are not fully understood, ranging from sociocultural factors to changes in the patterns of gene expression. Improving our understanding of this has important implications – stunted children may be at even greater risk of developing obesity and other chronic diseases in adulthood – and this may compound the growing epidemic of chronic disease in many low and middle-income countries.\(^\text{20}\) Many of these countries are also progressing through the nutrition transition, where shifts in diet and lifestyle with increasing urbanization are resulting in the rapid development of obesity and other nutrition-related chronic diseases.

The mechanisms by which stunting is transmitted across generations is an exciting area of research. “Metabolic programming,” “metabolic imprinting” or “developmental plasticity” describe the possible processes where certain exposures, such as nutrient depletion, can lead to changes in gene expression.\(^\text{24}\) This is important as gene expression regulates all metabolic pathways, and controls cell growth and function. The mechanisms may occur through epigenetic modifications\(^\text{25}\) of genes, and consequently the result of early

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\(^{19}\) Lien NM, Meyer KK, Winick M. Early malnutrition and “late” adoption: a study of their effects on the development of Korean orphans adopted into American families. American Journal of Clinical Nutrition, 1977

\(^{20}\) Stoch MB, Smythe PM. 15-year developmental study on effects of severe undernutrition during infancy on subsequent physical growth and intellectual functioning. Archives of Disease in Childhood, 1976


\(^{23}\) Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. In press


\(^{25}\) Epigenetic modifications include changes in DNA methylation, modification of histone and chromatin structures, and modification of RNA; these can be transmitted genetically
exposure to nutrient depletion and other stresses can be transmitted across generations. As our understanding of the intergenerational effects of stunting increases, it may be possible to accurately identify when sensitivity to epigenetic changes by nutrient depletion is greatest, and thus identify the critical time for intervention.²²,²⁶

**Interventions to address early life undernutrition and programmatic experiences:** While observational studies have demonstrated the adverse outcomes associated with stunting, interventional studies have examined the impact of nutrition interventions to address stunting, on health, educational and cognitive outcomes. For example, a follow up study from a large cluster randomized trial of breastfeeding, demonstrated that exclusive and prolonged breastfeeding in infancy was significantly associated with increased cognitive performance (IQ testing and teachers’ academic ratings) assessed at age 6.5 years.²⁷

We have also amassed considerable programmatic experiences in different contexts.²⁸ Importantly, we have evidence of the intergenerational effects of nutrition interventions: the INCAP Longitudinal Study and its follow-up studies conducted in Guatemala provided opportunity to evaluate the impact of improved early nutrition on various outcomes and on subsequent generations.²⁹ The studies demonstrate that improved nutrition was associated with increased cognitive, schooling and work capacity outcomes and that improved nutrient intake up to age 2 years translated to a 46% increase in wages.³⁰ Follow-up studies examining intergenerational effects show the transmission of benefits to the offspring of mothers who had received nutrition interventions: for mothers who had received nutritional supplementation in childhood, their offspring had improved anthropometric measures, including significantly increased head circumference (0.6cm),³¹ and improved cognitive outcomes.³²

**Addressing the global crisis of stunting - from evidence to action:** Given the extent of the global crisis of stunting, it is crucial that we better understand how growth failure early in life impacts child development. Enormous human potential is being lost because of undernutrition early in life - but it is also important to recognize stunting as a marker for chronic systemic failure at a critical time in the life cycle, representing the broader biological and social determinants of chronic disadvantage. We need to think about how best to use the knowledge we have, how to address gaps in that knowledge, and what are the research priorities that will best guide our programmatic response. To address early child development holistically, we also need to further assess how programming to address undernutrition early in life should be integrated and synergized with other sectors, such as water and sanitation and education. Building our knowledge base, designing optimal interventions to address child stunting and strengthening our advocacy efforts will help to break the intergenerational cycle of poor health, poverty and inequity.

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²⁸ World Bank. What can we learn from Nutrition Impact Evaluations? World Bank, 2010
³¹ Martorell R, Zongrone A. Intergenerational influences on child growth and undernutrition. In press
Goals of the Global Technical Meeting

This technical meeting will review existing knowledge about the lasting impact of nutritional deficiencies during pregnancy and early childhood on i) brain development, ii) other genetically regulated metabolic processes in relation to child development, and iii) consequences for adulthood and the next generation. Existing policies and programme strategies aimed at dealing with undernutrition will be reviewed in this context. Specifically, we will look at:

- How nutritional deficiencies during pregnancy and early infancy influence brain development, and the consequences for brain structure and functioning later in life.
- How early nutritional deficiencies influence health, cognitive function and education later in life.
- How undernutrition in early life can lead to the development of disease later in adulthood, such as cardiovascular disease.
- How undernutrition in early life may lead to changes in gene expression and have intergenerational consequences.
- What we know about the positive impacts of interventions to prevent stunting on improving health, education and cognitive outcomes, and the next generation.
- How programmatic interventions for stunting should be integrated with other strategies, such as water and sanitation, health and early childhood development.
- How programmatic interventions for stunting can address the needs of young, new and early mothers as well as their children’s needs.
- Whether current programming strategies and approaches adequately address stunting and its consequences, what should be done moving forward.

Global Technical Meeting Format and Broadcast

This one-day technical meeting will be held on Wednesday 15th August 2012 in New York in the 22nd Floor Conference Room, UNICEF, 633 3rd Avenue New York, NY.

The opening introductory session will set the context for the discussion and explain the need to expand our knowledge in this area. Then experts will present on the state-of the-art knowledge in the topics outlined above, with particular reference to the goals of the meeting. Each presenter will speak for 20 minutes. There will be a closing panel discussion to discuss the implications of the technical findings for programming.

In an effort to secure the maximum audience for this seminar globally, the event will use web-based and videoconferencing technologies to give us the broadest possible reach. Although the technical meeting will be held in New York, participants from Europe, Africa and Asia will be able to join from their desktop computers. Participants at the meeting (n=50) and those watching the meeting online can ask questions through a moderator, who will field the questions, summarize, and encapsulate them for the presenters. There will be further opportunity at the close of the seminar for more general comments and discussion, again fielded through the moderator.