Early life nutritional supplements and later metabolic disease

The theory of the Developmental Origins of Health and Disease is supported by many association studies showing that people who had a nutritionally adverse start in life, assessed with proxies of low birthweight or slow postnatal growth, have an increased risk for a range of metabolic diseases. The depth of evidence is substantial, but the breadth and diversity is poor. Numerous prospective studies have been done in short-lived small animals, usually with a low-protein diet as the model for nutritional adversity; such experiments tend to support data from observational studies in humans. A key feature of these studies is that metabolic vulnerability, which is programmed during crucial windows of development, is exposed by later weight gain and obesity. Metabolic adaptation to a poor nutrient supply in early life is hypothesised to create an adaptive state of the thrifty phenotype that becomes maladaptive when a later obesogenic diet and lifestyle change the nutritional circumstances. These circumstances commonly occur in low-income countries as they progress through economic transition.

In the August issue of The Lancet Global Health, Ford and colleagues add an important new piece to the puzzle by reporting the later-life metabolic and health outcomes of an early-life protein-energy supplementation trial done in Guatemala in 1969–77. Unfortunately, the results show beneficial and detrimental outcomes that create as many questions as answers, and do not clearly inform future public health interventions.

The Institute of Nutrition of Central America and Panama developed a protein-energy supplement (Atole) and a protein-free control supplement (Fresco), which were offered to pregnant women and young children in four villages; two matched villages each. The investigators followed up 1139 (69%) of 1661 traceable participants from an original cohort of 2392 children enrolled in 1969–77. This high level of attrition raises the possibility of loss-to-follow-up bias; however, with the exception of sex (ie, more men migrated out of the study area than women), the authors provide adequate assurance that such bias is unlikely. Nonetheless, the analysis is based on only 139 women and 86 men who received Atole and were available for follow-up.

A second statistical challenge is the inherent weakness of cluster randomisation to two versus two villages; essentially, randomisation to Atole versus Fresco is the same as randomisation to villages 1 and 2 versus 3 and 4. Therefore, chance differences could exist between the villages, especially over such long periods of follow-up. In a best effort to overcome this limitation, the authors used a difference-of-differences approach in which, in addition to studying the differences between supplements (villages), they also compared the outcomes for children within each village who were enrolled before the study versus those enrolled during the study.

Participants receiving Atole from conception to age 2 years had a significantly higher body-mass index (1.29 kg/m², 95% CI 0.08–2.50), body fat (1.73%, 0.20–3.26), and odds ratio for obesity (1.94, 1.11–3.40) and central obesity (2.53, 1.18–5.43). Participants also had a more atherogenic lipid profile (total cholesterol and non-HDL cholesterol) that remained significant after adjusting for the probable mediators of body-mass index and waist-to-height ratio. A tendency towards increased diastolic blood pressure was reported, which was initially significant in men, but not after adjustment for body composition. By contrast, exposure to Atole offered strong protection against diabetes defined as raised fasting or 2-h post-challenge glucose or use of diabetes medication, or both (OR 0.46, 95% CI 0.21–0.97).

Follow-up of the Institute of Nutrition of Central America and Panama study has shown that Atole improved child survival, improved growth, and enhanced human capital assessed by educational attainment and income; these benefits can be added to the apparent protection against diabetes. However, despite these benefits, the adverse atherogenic findings forced the authors to a final unsatisfactory conclusion that nutritional supplementation programmes should consider the potential mixed consequences for adult cardiometabolic health.

Where do we go from here? A first step would be to avoid the use of epidemiological simplifications when trying to interpret physiological or metabolic outcomes and define crucial windows of exposure. The authors repeatedly state that supplementation
was from conception to age 2 years and refer to the first 1000 days. The first 1000 days is an advocacy tool and confuses interpretation, particularly because the parental methylation marks inherited from ovum and sperm are erased and re-established in the first 10 days after conception, and emerging research shows that these essential processes are sensitive to parents’ nutrient status, which depends on their diet before conception. Atole supplementation started in early pregnancy and not, as stated, at conception, thus missing these early programming events.

Second, additional metabolic studies can enhance understanding of epidemiology and thus help address factors that might explain the surprising mismatch between the diabetic and atherogenic findings. This recommendation touches on an outstanding challenge in the field of cardiometabolic disease—namely, what mechanisms exist linking excess adiposity to adverse metabolic outcomes? The role of inflammation, including gut-derived inflammation, might be key in low-income settings and could be studied prospectively in this valuable cohort.

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I declare no competing interests.

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1. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: Physiology or pathophysiology? *Physiol Rev* 2014; 94: 1027–76.