Infant infection and nutrient deficiency predict impaired growth at five years: Pakistan

This is a summary of the following paper: *González-Fernández D, Cousens S, Rizvi A et al. (2023) Infections and nutrient deficiencies during infancy predict impaired growth at 5 years: Findings from the MAL-ED study in Pakistan. Frontiers in Nutrition, 10, 1104654.* **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9982131/**

This paper is a secondary data analysis of the MAL-ED[1] cohort. A subgroup of 277 healthy newborns from Sindh province, Pakistan, was selected between January 2010 and February 2012 for study. The group was followed up to age 66 months, with 14% of the group lost to follow-up.

The 237 children were from low-income families. Overcrowding (>3 people per room) was present in 75% of homes, 15% did not have access to sanitation, and 81.5% of the study group lived with food insecurity. Stunting, underweight, and wasting prevalence were high (Figure 1).

Various regression models were used to predict the impact of assorted variables (at enrolment and during the study period) on future growth failure (at the end of the study period, e.g., 54– 66 months), using anthropometry, health records, questionnaire data, and biomarkers (faecal and blood).

Stunting

Multivariate Poisson regression highlighted that acute lower respiratory infection, during the first year, at an average duration of ≥2 days per month was associated with increased stunting aged five years.

Underweight

Higher weight in the first days of life, receiving formula in the first six months, and commercial baby food feeding between 6-11 months were associated with decreased risk of underweight aged five years. Higher serum transferrin receptor concentration (indicative of intracellular iron deficiency) – but, importantly, below pathological levels – was associated with decreased underweight aged five years. No other iron status indicators were associated with child growth at five years. High neopterin levels (indicative of an immune response) in the first year and Campylobacter infection in the first six months were both associated with increased underweight aged five years.

Underweight + stunting

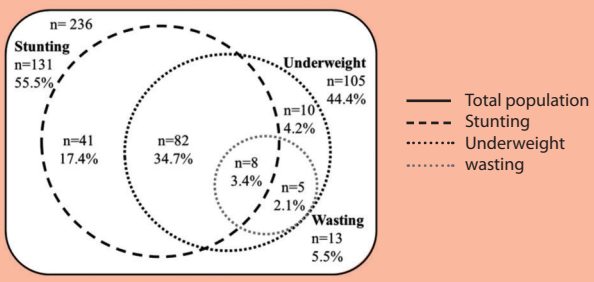
Lower weight in the first days of life, lower quantile family income, greater duration (days per month) of acute lower respiratory infection, and elevated neopterin (>6.8nmol/L) in the first year were each associated with concurrent underweight + stunting aged five years.

This study employed a robust methodology with detailed data cleaning and statistical controls. The sample size, although small for some variables (e.g., length and height data aged 0–35 months), was sufficient to answer the study objective. Various observations of variables with weaker correlations were found, but are beyond the scope of this summary.

Infant enteropathy and respiratory infection appear to predict future malnutrition and the targeting of Campylobacter and broader vaccination coverage may reduce child malnutrition in this population. The relationship between serum transferrin receptor concentration (anaemia), neopterin (inflammation), and malnutrition is complex, but these findings may also indicate that early malnutrition is the pathway for these associations aged five years. Efforts should focus on reinforcing exclusive breastfeeding under six months and supporting nutritious, diverse diets for children over six months, in addition to infectious disease prevention.

[1] https://academic.oup.com/cid/article/59/suppl_4/S193/281312

Figure 1 Prevalence and overlap of stunting, underweight, and wasting in children aged 54–66 months



Mitochondrial homeostasis and severe malnutrition

This is a summary of the following paper: *Ling C, Versloot C, Kvissberg M et al. (2023) Rebalancing of mitochondrial homeostasis through an NAD+ -SIRT1 pathway preserves intestinal barrier function in severe malnutrition. eBioMedicine, 96.* **https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10520344/**

Among other symptoms, children with severe malnutrition may develop intestinal dysfunction. This in turn limits nutrient absorption and weakens immunity, resulting in a complicated downward spiral of their condition.

"A growing body of evidence suggests that impaired mitochondrial function in epithelial cells can disrupt intestinal barrier integrity."

– Ling et al., 2023

This study randomised eight mice to a low protein diet and eight mice to a normal protein diet to simulate severe malnutrition. Another group (n=8) were fed a low protein diet then given oral nicotinamide (water-soluble vitamin B3) supplementation from mid-way through the study. Diets were controlled for vitamin B3 to increase the validity of the study.

Additional experiments were conducted on low protein diet mice using injected resveratrol[1] (n=6), injected EX-527[2] plus nicotinamide (n=6), placebo injection (n=6), and nicotinamide-only (control) (n=6). Another study investigated normal protein diet mice (control) (n=6), low protein diet mice with injected rapamycin[3] (n=8), and low protein diet mice plus placebo injection (n=6). For each mouse, multiple immunological, histological, and broader physiological tests were conducted.

Predictably, the low protein diet led to villus atrophy (reduced gut surface area), nutrient malabsorption, mitochondrial abnormalities, and intestinal barrier dysfunction. In these malnourished mice, nicotinamide supplementation increased mitophagy[4] and improved intestinal barrier function. Rapamycin supplementation reduced intestinal barrier dysfunction and nutrient malabsorption.

Oral nicotinamide supplementation may be a more promising treatment for children with severe malnutrition as it is well tolerated and does not affect immune function – severe malnutrition often occurs in high infectious burden areas. By contrast, as an immunosuppressant, rapamycin may be less applicable for this population.

A note from the editors

This paper is highly technical, and the experiment was conducted on mice in a lab setting. The exact findings and methods used are therefore less relevant for practitioners working in the field. Although a full breakdown of pathways, mechanisms, timelines, and treatment protocols is beyond the scope of this summary, these details can be found in the original study. What this paper does highlight is that this specific intervention may offer an additional therapeutic target for children with severe malnutrition. No treatments currently target the intestinal barrier, so this regimen may provide another tool to increase child survival. As this was an animal study, which are inherently limited, more research is needed in humans. However, these compounds have been shown to be safe, readily available, and inexpensive. These findings are exploratory, yet promising.

[1] Resveratrol is a readily available polyphenol supplement, often extracted from the skins of grapes and berries.
[2] EX-527 is a selective sirtuin inhibitor drug.
[3] Rapamycin is an immunosuppressant drug, commonly used to prevent organ transplant rejection. Recently, many researchers have focused on Rapamycin as a treatment to increase mitochondrial efficiency, which may exhibit numerous benefits for health and disease prevention.
[4] Mitophagy is the removal of damaged mitochondria, increasing mitochondrial efficiency.