Pathways to wasting and stunting

Research concept to fill a remaining gap in evidence and understanding

AIM OF THIS DOCUMENT

This research concept contains a description of a research gap that has been identified through the work of the Wasting and Stunting Technical Interest Group (WaSt TIG) as having broad implications for nutrition policy and programming, and what may be needed to fill it. We hope the detail presented here will support development of a funding proposal to seek resources to conduct specific research to fill the gaps described. The funding proposal may be developed by ENN and the WaSt TIG as part of the next phase of their work. The concept will also be made available on ENN's website as a resource for other researchers who may want to explore this topic. The resulting research could adopt approaches that utilise existing data and/or incorporate questions into the design of new research.

BACKGROUND

Within the work of the WaSt TIG, the need for greater clarity on the pathways that lead to wasting, stunting and concurrent wasting and stunting have been identified as a research gap with critical relevance for nutrition policy and programming[1, 2]. A better understanding of the risk factors driving these interlinking processes will help identify underlying mechanisms that can be targeted through public health and clinical interventions to prevent these forms of undernutrition. There is now considerable evidence that these risk factors and causes of wasting and stunting often overlap[3] and this presents an opportunity for programming to consider the prevention of wasting and stunting together. This is likely to improve efficiency and effectiveness of programmes that have often focussed on one in isolation of the other[4].

As a starting point for this work, the WaSt TIG prioritised the development of a research concept note. The intention was that investment in such a concept note would catalyse evidence generation to increase the understanding of the relationship between wasting and stunting and what this tells us about their aetiology, consequences, treatment and prevention. It was hoped that the concept note would also highlight the relevance of better risk identification in advancing prevention focussed efforts.

This work aims to build on the evidence and hypotheses on linear and ponderal growth (referred to below as 'growth') already generated on this subject by the WaSt TIG and others[5-11]. For example, the Knowledge Integration (Ki) research group have analysed data from 43 cohorts comprising ~86,000 children from 35 countries, resulting in three key pre-prints to date on infant and child growth trajectories[3, 12, 13]. The authors looked at data from the pooled longitudinal datasets to explore the causes and consequences of child growth failure in low- and middle-income countries and found that prenatal maternal health and nutrition characteristics, in addition to infant characteristics at birth, accounted for the largest attributable differences in later growth, including a large proportion of growth failure (*circa* 30%)[3]. These papers also provided valuable insights as to why many nutrition prevention strategies assessed to date demonstrate disappointingly small effect sizes, likely in part due to not considering and targeting the context-specific pathways to growth failure such as women's nutrition or *in utero* development. Furthermore, preventative strategies, where they exist, often fail to adopt an approach that screens and identifies children at the highest risk of growth failure who may benefit the most from preventative interventions. Lack of data on these vulnerable infants and children may mean we are underestimating the magnitude of impacts on growth failure among those most vulnerable to it. Despite the wealth of information provided by these Ki studies, the authors noted that several key exposures, such as pathogen-specific infections, sub-clinical inflammation and intestinal dysfunction, were only measured in a few cohorts and were therefore not included in analyses. The authors concluded that the

absence of data and analyses on these exposures may limit understanding of some potentially very important causes of growth failure[3].

Whilst a lack of data on mechanistic pathways precluded their exploration in the Ki papers, several studies are exploring mechanisms underpinning growth trajectories. These studies include multiple cohorts in different countries within the Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health (MAL-ED) Study[14]. Data from the MAL-ED cohorts to date have shown subclinical enteropathogen infection and the complementary feeding diet are influential factors affecting growth velocity and the development of stunting. Investigators have also found that enteric dysfunction is associated with reduced stature, weight-for-height and BMI at five years of age[15, 16]. A second example is The Hormonal and Epigenetic Regulators of Growth (HERO-G) study, currently ongoing, analysing data from 251 mother-infant pairs in rural Gambia who were followed for two years to explore epigenetic and hormonal drivers of growth failure[17]. It is hoped that the results of this study will shed further light on important risk factors and potential pathways leading to undernutrition. Furthermore, several papers have summarised the potential role that the maternal and infant microbiome could play in determining early life growth trajectories[8, 11, 18], as well as the importance of considering how metabolomic markers in infants may be associated with their growth[7, 10, 19].

THE PROPOSITION

A rapid review of the existing literature discussed above and discussion with members of the WaSt TIG has highlighted two pathways of interest which could be important for improving the effectiveness of programming that aims to address undernutrition and for which there are currently considerable knowledge gaps. These pathways include:

1. The association between a child's inflammatory, metabolic, and/or microbiome profile and his/her growth trajectory
2. Maternal determinants as drivers of infant and child growth trajectories

The focus of the analyses will be on exploring associations between risk factors and growth trajectory before a child is classified as stunted and/or wasted. The purpose will be to guide public health and clinical interventions to focus on the links in pathways to growth failure that can be impacted through programme design and that may create potential efficiencies for impacting multiple forms of undernutrition simultaneously.

RESEARCH QUESTIONS

Research area 1: The association between a child's inflammatory, metabolic and/or microbiome profile and his/her growth trajectory.

This research area aims to provide plausible hypotheses as to what biological processes and mechanisms may underpin different negative patterns of growth.

Specific questions:

- Do certain inflammatory, metabolic and/or microbiome profiles of children predict later episodes of i) stunting, ii) wasting and iii) being concurrently wasted and stunted?
- Do certain inflammatory, metabolic and/or microbiome profiles predict episodes of linear or ponderal growth faltering?
    - Note metabolic profiles could include biomarkers of nutrient status, functional markers, or markers of other metabolic pathways we are interested in (e.g. iron metabolism).

    - The samples would need to be collected before the episode of growth faltering, as we know episodes of wasting lead to disturbed metabolic and inflammatory states.
    - Inflammatory markers would include both acute phase proteins and markers of gut inflammation ideally.
- Is there a difference in the metabolic profile of those born low birthweight, versus preterm, versus SGA, versus normal birthweight?

Research area 2: Maternal determinants as drivers of infant and child growth trajectory

- Are maternal characteristics (to include pre-pregnancy and pregnancy stages) associated with birth outcomes and later growth trajectories?
    - Are maternal determinants, particularly non-anthropometric variables including socio-demographic factors, nutrition status, breastmilk quality (e.g., human milk oligosaccharides, and bioactive proteins), placental function etc. associated with a child being wasted, stunted or concurrently WaSt at birth, and in the first two years of life?
    - Is the child's inflammatory, metabolic or microbiome profile on the causal pathway between maternal characteristics and later growth trajectories?

POTENTIAL APPROACHES

There are two main approaches for this research to choose from:

1. Conduct further analyses of existing cohort data. This may include applying for funds for a dedicated researcher (preferably with experience of metabolomics) to further analyse existing cohort data, where relevant data already exists but has not been interrogated (such as within the HERO-G Study)
2. Explore these research questions in a new cohort.

An additional related activity that could be considered regardless of the chosen approach is a cohort mapping exercise that aims to summarise existing and, where possible, planned cohorts that show the potential to investigate these research questions.

Potential variables of interest to consider, suggested by existing evidence, could include:

- In the infant/child:
    - birth outcome (LBW/SGA/preterm/WFA/HFA etc.), anthropometry, measures of body composition[3, 12]
    - child feeding practices, dietary intake, antibiotic use[20]
    - blood, urine, and stool samples to investigate non-diarrheal enteropathogens, micronutrients, microbiome, metabolomics, gut inflammation and permeability, sub-clinical and systemic inflammation[5, 6, 10, 19, 21-28].
- In the mother (ideally from pre-pregnancy):
    - health and nutrition status including BMI, MUAC, sub-clinical inflammation status and self-reported illnesses[24, 29],
    - blood, urine, and stool samples to investigate micronutrient status, metabolomics, microbiome[8, 10, 18]
    - other socio-demographic factors linked to birth outcomes (e.g., maternal age at marriage/pregnancy)[29-33],
    - breastmilk characteristics[34]

Methodological considerations

Methods will vary by the specific study design, exposures and outcomes of interest. Many of the previous studies included in the reference section have used longitudinal data following a cohort of infants (often with their caregivers) over time. Such panel data often require different types of mixed-effects regression models that interrogate the association between exposures and outcomes, accounting for repeated measures of each study participant at different time-points[7, 12, 19, 28]. Very often preliminary work is needed before the regression modelling can take place to further characterise the relevant exposures, or combination of exposures, especially when considering the complex co-variation between variables that may be at play. For example, data reduction techniques such as principal components analysis and methods of hierarchical clustering can be useful when needing to identify the fewest number of exposure variables that capture the greatest variation in the data[10, 20]. Some researchers are using other methods taken from econometrics to better capture such interrelatedness between exposure variables[19].

ENN, with guidance from members of the WaSt-TIG, recently published a technical briefing paper outlining general considerations on research methods for studies looking at the relationship between wasting and stunting[35]. This included key considerations regarding characteristics of longitudinal data, the choice of outcome and exposure variables, seasonality, frequency of data collection, pooling datasets and data cleaning.

COLLABORATION

If you are interested in exploring this topic further and would like to discuss a potential collaboration with ENN and the 'WaSt TIG' please be in touch with ENN's coordinator of the WaSt TIG, Tanya Khara (tanya@ennonline.net).

For more information on research collaborations with ENN see:
https://www.ennonline.net/attachments/4251/ENN_research_partners_brief_FINAL.pdf

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