

NEUROBIOLOGY RELATIONSHIP BETWEEN STUNTING AND THE RISK OF SPEECH DELAY: A NARRATIVE REVIEW

Nurussyariah Hammado, Herman, Yade Kurnia Yasin, Nurul Ichsaniah

Program Studi Gizi, Fakultas Ilmu Keolahragaan, Universitas Negeri Makassar
Departemen Neurologi, Fakultas Kedokteran Universitas Hasanuddin, Makassar
Pendidikan Anak Usia Dini, Fakultas Ilmu Pendidikan, Universitas Negeri Makassar
Email: nurussyariah@unm.ac.id

Informasi Artikel:

Dikirim: (diisi editor) ; **Direvisi:** (diisi editor); **Diterima:** (diisi editor)
DOI: (diisi editor)



RETORIKA: Jurnal Bahasa, Sastra dan Pengajarannya berada di bawah lisensi
Creative Commons Attribution-NonCommercial 4.0 International License.

ISSN: 2614-2716 (cetak), ISSN: 2301-4768 (daring)
<http://ojs.unm.ac.id/retorika>

Abstract: Stunting is a disorder of growth and development of children due to chronic malnutrition and recurrent infections, especially in the first 1000 days of life. The negative impact of stunting on children, especially on the development of fine motor skills and cognitive abilities, including speech delays, but how stunting is related to speech delay in children has yet to be clearly understood due to restricted existing research and studies. This narrative review explains possible biomechanisms on how stunting causes speech delays in children.

Kata kunci: stunting, speech delay, children

Stunting remains a global issue, especially in developing countries (Prendergast & Humphrey, 2014), including Indonesia (Mustakim et al., 2022). Stunting is impaired linear height growth for ages below -2 WHO standards due to chronic malnutrition and recurrent infections. A high prevalence of stunting was found in children aged 8-16 months causing short and long-term adverse effects such as delays in aspects of gross and fine motor skills, language and speech (Fadila, 2017). As a long-term result of undernutrition and chronic infection in stunting increase the risk of morbidity and mortality, poor child development and learning capacity, increased risk of opportunistic infections and non-communicable diseases, increased susceptibility to child obesity, lower fat oxidation, lower energy expenditure, insulin

resistance and a higher risk of developing diabetes, hypertension, dyslipidaemia, lower working capacity and unfavourable maternal reproductive outcomes in later life (Soliman et al., 2021).

Speech and language abilities construct the noble function of humans. Speech ability is reflected by an individual's ability to produce sound by the speech organs accompanied by body movements and facial expressions to produce words needed in verbal communication. Speech and word production require complex coordination and temporospatial rhythms of speech subsystems such as respiratory, phonatory, resonators and articulatory, and prosodic components (rate, stress and intonation). (Liégeois & Morgan, 2012). The acquisition of mature speech production skills results from a

complex process involving anatomical growth, refinement of motor control of speech, and cognitive and language development. A study explains that the peak of word production in humans occurs with average speech production in the first 30-110 months of life. It is affected by children's anatomical and physiological growth (Liégeois & Morgan, 2012).

A neuroscience study on speech delay explains that the left perisylvian cortex, the primary and pre-motor cortex, the basal ganglia, and the cerebellum carry the typical speech production model in adults. Disruption of this pathway during the acquisition of speech production skills can cause speech delays in children.

Delayed speech at an early age of a child is linked to several factors, including birth order, premature delivery, birth weight, parental education, gender of the child, environmental factors, and family history of delayed language development (Sabra M, Ahmed, M.D., Hala H, Aboufaddan, 2018) while poor birth weight is also linked as a risk factor for stunting (Prendergast & Humphrey, 2014).

Understanding the neurobiological mechanisms that link stunting and the risk of speech delay in children will support understanding stunting treatment plans and targets to minimize its long-term impacts. Unfortunately, this mechanism has yet to be clearly understood due to insufficient scientific studies supporting this. This paper tries to explain the potential neurobiological mechanisms of stunting and the risk of speech development disorders in children using the narrative review method from existing research.

MATERIALS AND METHODS

This narrative review was intended to seek the neurobiological mechanisms of speech delay in children with stunting. For this narrative review, the Pubmed database has been used to search articles about stunting and speech development problems in children. The search was narrowed to articles between 2012 and 2022. The search terms were “stunting”, “Developmental” “cognitive”, “speech delay and “mechanisms”. There was A total of 165 materials were initially identified to be potentially relevant for the review. When the

search was limited to the word "stunting" and "speech delay" A total of 16 articles were included, and they were found to match the inclusion criteria. Questions included research problems, literature review research design, study sample, data collection, results, and limitations. The review aimed to find answers to the following questions. How does stunting put the risks of speech delay in children? Moreover, what is the potential biomechanism?

FINDINGS AND DISCUSSION

The average growth rate is below -2 standard deviations of the WHO age group growth rate (HAZ score) caused by chronic nutritional deficiencies and recurrent infections since conception, neonates and the first two years of life (Prendergast & Humphrey, 2014). The conditions that trigger stunting and stunting themselves contribute to impaired motor and cognitive development in children.

In the brain, Speech skills are generally regulated by three different brain areas: Wernicke's, Broadman's and Broca's. Wernicke's and Broadman's areas acquire receptive skills, while Broca's areas promote the expressive function of speech.

Speech delay occurs due to disturbances in receiving stimuli (sensory disorder) and expressive disorder (Ali et al., 2021).

The neurobiological mechanisms of stunting and the risk of speech delay in children converge on the microbiota-gut-brain axis. There are at least 3 phases that may link stunting in children and speech delay through this axis: the undernutrition phase during the conception period, the dysbiosis gut microbiota phase and the brain development disorder phase. The description of this mechanism will be explained below.

A. Stunting and Delayed Speech

Table 1 presents the results of a literature review from several studies linking stunting and delayed speech in children. Searches were conducted on the Pubmed and Google Scholar databases by entering the keywords "stunting", "speech problem", and "speech delay" and limited to publications within the last ten years from 2013-2023. The search yielded 165 articles, but when the selection was made based on inclusion

criteria, namely articles that explicitly used the words "stunting" and "speech delay" in the title and the research variables used, the articles that met the requirements were reduced to 7 articles.

B. Gut Microbiota Dysbiosis and Stunting

The etiology of stunting ranges from inadequate food, an unbalanced diet, and insufficient vitamin/micronutrient intake to poor hygiene and repeated infections (Vonaesch, Randremanana, et al., 2018). The neurobiological mechanisms of stunting and speech delay converge in gut microbiota dysbiosis, causing dysregulation of 2 pathways, namely the microbiota-gut-brain (MGB) axis and the Hypothalamic-Pituitary-Adrenal (HPA) axis. On the MGB Axis pathway, existing studies describe microbiota dysbiosis due to undernutrition and chronic reinfection (Hennessey et al., 2021) in stunting (Dinh et al., 2016; Suroño, Widiyanti, et al., 2021) interferes with two main physiological barriers, i.e. the blood-brain barrier (BBB) and the enteric barrier (Keunen et al., 2015; Sarubbo et al., 2022) thus opening wide the passage of noxious substance to brain tissue (Liu et al., 2022) dan disrupts the action of messenger-RNA BDNF (protein precursor neurogenesis) (Agnihotri & Mohajeri, 2022). Meanwhile, The microbiome may significantly limit children's growth as the increasing intestinal permeability, and infections exposure disturb intestinal functioning and expected growth (Jahnke et al., 2021). Moreover, microbiome-induced gut barrier function changes may influence micronutrient bioavailability and metabolic processes (Hoffman et al., 2017).

Table 2 shows the studies conducted in the last ten years regarding gut microbiota dysbiosis in stunted children. Tropical enteropathy was proposed as an essential factor in undernutrition. This small intestinal pathology called environmental enteric dysfunction (EED) causes linear growth faltering. EED is characterized by reduced villus height, increased crypt depth, lymphocytic infiltration, impaired absorption and increased small intestinal permeability. Loss of intestinal barrier function enables microbial translocation resulting in systemic inflammation. Raised proinflammatory cytokines suppress insulin-like growth factor 1 (IGF-1) plasma concentrations, thereby restraining linear growth. EED is acquired early in life among children living in impoverished conditions. Chronic

exposure to enteric pathogens is likely the primary cause of EED, although nutrient deficiencies and fungal toxin exposure are also potential causative or predisposing factors (Mutasa et al., 2021). Chronic disruption of the enteric barrier will allow the passage of noxious stimulus to cross the blood-brain barrier, elicit the inflammation cascade in brain tissue, and subsequently interfere with brain metabolism and neuronal dan glial growth.

C. Stunting, disruption of the Gut-brain axis and the risk of speech delay

Most existing gut-brain axis (GBA) studies remain limited in neuropsychiatric disorders such as anxiety, autism spectrum disorder and multiple sclerotic (Maiuolo et al., 2021) and yet lack of study in specifically language developmental disorder. It has been hypothesized that microbiota and the brain communicate through the microbiota-gut-brain axis. This communication occurs via various pathways, including the immune and enteric nervous systems, involving microbial metabolites such as short-chain fatty acids, branched-chain amino acids, and peptidoglycans. Many factors can influence microbiota composition in early life, including chronic undernutrition and infection, which can alter the axis pathway.

Table 3 shows the existing studies of stunting and dysbiosis, Gut microbiota-gut-brain axis, and developmental brain disorder.

Chronic undernutrition causes macronutrient deficiencies and changes in the type and function of the gut microbiota. These changes cause an increase in energy loss.

The intestine can interact with the brain through microbiota-brain co-metabolism reciprocal communication (Carabotti et al., 2015), which includes three main signalling pathways: 1) the enteric nervous system, involving the enteroendocrine cells (EECs) and neurotransmitter of the gut; 2) the hypothalamic pituitary adrenal axis; and 3) the neurogenesis of the brain (Maiuolo et al., 2021).

The enteric nervous system

Gut microbiota can influence the onset and modulation of neurogenesis by modulating

Table 1. A study reviews the risk of speech delay in stunted children

No	Title	Authors	Research Setting	Year	Method Used	Issue addressed	Statistical consideration
1	Risk Factors of Delayed Language Development among children attending Assiut University Hospitals	(Sabra M, Ahmed, M.D., Hala H, Aboufaddan, 2018)	Assiut University Children/s Hospital Egypt	2018	Case control with purposive sampling with inclusion/exclusion criteria	Risk Factors of Delayed Language Development among children	Of 300 participants aged 3-5 yrs, the history of perinatal events is a significant risk factor for delayed Language development
2	Association of Malnutrition with Delayed Speech among Children 2-6 Years Undergoing Speech Therapy at Rehabilitation Center	(Ali et al., 2021)	National Institute of Rehab Medicine Islamabad	2021	Descriptive cross-sectional study with non-probability consecutive sampling	Association of Malnutrition with Delayed Speech among Children	Of 138 children aged 2-6 yrs, No significant relationship between malnutrition and delayed speech level
3	Exploring swallowing, feeding and communication characteristic of toddlers with severe acute malnutrition	(Eslick et al., 2022)		2022	An exploratory, prospective, collective case study	Swallowing, feeding and communication characteristics of hospitalized toddlers with SAM	sensorimotor dysfunction and disruptive feeding behaviours were identified. Risk for oropharyngeal and speech problems
4	Association between stunting and early childhood development among children aged 36-59 months in South Asia	(Kang et al., 2018)	Multiple Indicator Cluster Surveys in Bangladesh (n = 8,659), Bhutan (n = 2,038), Nepal (n = 2,253), and Pakistan (Punjab n = 11,369 and Sindh n = 6,718)	2018	Survey study	Examined associations between z scores (i.e., height for age [HAZ], weight for age [WAZ], and weight for height [WHZ]) and undernutrition (i.e., stunting [HAZ < -2], wasting [WHZ < -2], and underweight [WAZ < -2]) with learning/cognition and social-emotional development among children 36-59 months of age.	In a pooled sample, on-track learning/cognition development was positively associated with HAZ (OR = 1.17, 95% CI [1.07, 1.27]) and WAZ (OR = 1.18, 95% CI [1.07, 1.31]) and negatively associated with stunting (OR = 0.72, 95% CI [0.60, 0.86]) and underweight (OR = 0.75, 95% CI [0.66, 0.86]) but not associated with WHZ or wasting

5	The associations between stunting and wasting at 12 months of age and developmental milestones delays in a cohort of Cambodian children	(Van Beekum et al., 2022)	Cambodia	2022	Longitudinal/Cohort study in children aged 0 to 24 months were recruited from three provinces in Cambodia and followed up seven times from March 2016 to June 2019 until their five years	Assessing acquisition of motor and cognitive developmental milestones in early childhood and their associations with stunting and wasting	Data were available for 7394 children. At 12 months, the prevalence of stunting and wasting were 23.7% and 9.6%, respectively. Stunting was strongly associated with delays in gross motor milestones (HR < 0.85; p < 0.001). Wasting was more strongly associated with delays in fine motor development and most cognitive milestones (HR < 0.75; p < 0.001)
6	Malnutrition matters: Association of stunting and underweight with early childhood development indicators in Nepal.	(Shrestha et al., 2022)	Nepal	2022	An adjusted logistic regression using Nepal's national household Multiple Indicator Cluster Survey (MICS) 2019 datasets	To assess the association of stunting, wasting and being underweight with the four domains of the ECD index (literacy-numeracy, physical, social-emotional and learning development) among children 36-59 mo	Stunting was associated with lower odds of not being developmentally on track according to the ECD index and the literacy-numeracy, physical and learning domains of the ECD index.

Table 2. Study review of microbiota changes in stunted children

No	Title	Authors	Research Setting	Year	Method Used	Issue addressed	Statistical consideration
1	Linear growth faltering in infants is associated with <i>Acidaminococcus</i> sp. and community-level changes in the gut microbiota.	(Gough et al., 2015)	Malawi and Bangladesh	2015	Cohort Studies.	The specific changes in the gut microbiota that contribute to growth remain unknown, and no studies have investigated the gut microbiota as a determinant of chronic malnutrition.	Children's growth length is associated with community-wide changes in the gut microbiota and with the abundance of the bacterial genus, <i>Acidaminococcus</i> .
2	Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa.	(Vonaesch, Morien, et al., 2018)	Sub Saharan Africa	2018	A cross-sectional study in duodenal, gastric and fecal samples of 406 children was then sequenced using 16S Illumina Amplicon sequencing.	Challenging the current view of stunting arising solely as a consequence of small intestine overstimulation through recurrent infections by enteric pathogens	There was an overrepresentation of oral bacteria in fecal samples of stunted children. In addition, <i>E coli/Shigella</i> sp. and <i>Campylobacter</i> sp. were found to be more prevalent in stunted children, while <i>Clostridia</i> , were reduced. The study further showed stunting is associated with a microbiome "decompartmentalization" of the gastrointestinal tract characterized by increased, oropharyngeal bacteria from the stomach to the colon.
3	High prevalence of small intestine bacteria overgrowth and asymptomatic carriage of enteric pathogens in stunted children in Antananarivo, Madagascar	(Collard et al., 2022)	Antananarivo Madagascar	2022	A cross-sectional study from 464 children (96 severely stunted, 104 moderately stunted, and 264 non-stunted) and the prevalence of SIBO in 109 duodenal aspirates from stunted children (61 from severely stunted and 48 from moderately stunted children)	Bacterial pathogen exposure in stunted and non-stunted children in Antananarivo, Madagascar	Feces screening by qPCR showed a high prevalence of bacterial enteropathogens, especially those categorized as being enteroinvasive or causing mucosal disruption, such as <i>Shigella</i> spp., enterotoxigenic <i>Escherichia coli</i> , enteropathogenic <i>E. coli</i> and enteroaggregative <i>E. coli</i> . These pathogens were detected at a similar rate in stunted children and controls

4 Duodenal Microbiota in Stunted Undernourished Children with Enteropathy	(Chen et al., 2020)	Urban slum in Dhaka, Bangladesh	2020	They perform endoscopy and quantification of plasma protein level and duodenal biopsy in 80 children with biopsy-confirmed EED and available plasma and duodenal samples.	Environmental enteric dysfunction (EED) is postulated to play a role in childhood undernutrition. The pathophysiological features of EED and its contribution to impaired linear and growth have been hampered by the difficulty in directly sampling the small intestinal mucosa and microbial community (microbiota)	These results support a causal relationship between growth stunting and components of the small intestinal microbiota and enteropathy and offer a rationale for developing therapies that target these microbial contributions to EED
5 Growth and the Microbiome - Integrating Global Health with Basic Science	(Xavier, 2020)	Two African Countries	2020	A cross-sectional study in two African countries and 1,000 children aged 2 to 5 years assessed the microbiota in the stomach, duodenum, and feces. Upper gastrointestinal samples were obtained from stunted children and stratified according to stunting severity. Fecal samples were collected. Investigation in the role of clinical isolates in EED pathophysiology using tissue culture and animal models	Assessing the changes in the proximal and distal intestinal microbiota in the context of stunting and EED and testing for a causal role of these bacterial isolates in the underlying pathophysiology	Small intestinal bacterial overgrowth (SIBO) is prevalent (>80%) in stunted children. SIBO is frequently characterized by an overgrowth of oral bacteria, leading to increased permeability, inflammation, and replacement of classical minor intestinal strains. These duodenal bacterial isolates decrease lipid absorption in cultured enterocytes and mice, providing a mechanism by which they may exacerbate EED and stunting. Further, we find a specific fecal signature associated with the EED markers fecal calprotectin and alpha-antitrypsin.

- | | | | | | | | |
|---|----------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------|------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6 | Longitudinal Analysis of the Intestinal Microbiota in Persistently Stunted Young Children in South India | (Dinh et al., 2016) | A slum community in south India | 2016 | Clinical Trial | Lack of primary longitudinal studies comparing the intestinal microbiota of persistently stunted children to that of non-stunted children in the same community | The microbiota of control children was enriched in probiotic species <i>Bifidobacterium longum</i> and <i>Lactobacillus mucosae</i> , whereas that of stunted children was enriched in inflammogenic taxa, including those in the <i>Desulfovibrio</i> genus and <i>Campylobacteriales</i> order |
| 7 | Gut microbiota profile of Indonesian stunted children and children with normal nutritional status | (Surono, Widiyanti, et al., 2021) | Two regions in Banten and West Java provinces: Pandeglang and Sumedang, Indonesia | 2021 | Fecal samples, anthropometric measurements, and economic and hygiene status were collected from 78 stunted children and 53 children with normal nutritional status. Sequencing amplicons of the V3-V4 region of the 16S rRNA gene determined the gut microbiota composition. | Examine the difference in gut microbiota composition of stunted Indonesian children and children of normal nutritional status between 3 and 5 years. | <i>Prevotella 9</i> , the most abundant genus in children, was significantly lower in stunted children. The abundance of <i>Prevotella</i> has been correlated with dietary fibre intake, which was lower in these stunted children. Since the gut microbiota ferments fibres into SCFA, and these SCFA are a source of energy for the host, increasing the proportion of <i>Prevotella</i> in stunted children may be of benefit |

8	Differences in immune status and fecal SCFA between Indonesian stunted children and children with normal nutritional status	(Surono, Jalal, et al., 2021)	Indonesia	2021	Cross-sectional study	They compared immune status and fecal microbial metabolite concentrations between stunted and normal children.	Macronutrient intake was lower in stunted children for all components, but after correction for multiple comparisons significant only for energy and fat. Only TGF- β significantly differed between stunted children and children of normal nutritional status after correction for multiple comparisons. TNF-alpha, IL-10, lipopolysaccharide-binding protein in serum and secretory IgA in feces were not significantly different. Strikingly, all the individual short-chain and branched-chain fatty acids were higher in fecal samples of stunted children (significant for acetate, valerate and total SCFA); different microbial taxa but did not show a specific pattern.
---	-----------------------------------------------------------------------------------------------------------------------------	-------------------------------	-----------	------	-----------------------	----------------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

- | | | | | | | | |
|----|---------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------|------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9 | Immunoglobulin recognition of fecal bacteria in stunted and non-stunted children: findings from the Afribiota study | (Huus et al., 2020) | Sub Saharan African | 2020 | Fecal bacteria from 200 children between 2 and 5 years old in Antananarivo, Madagascar, and Bangui, Central African Republic (CAR), were sorted into IgA-positive (IgA+) and IgA-negative (IgA-) populations by flow cytometry and subsequently characterized by 16S rRNA gene sequencing to determine IgA-bacterial targeting. We additionally measured IgG+ fecal bacteria by flow cytometry in a subset of 75 children. | Determine whether chronic undernutrition (stunting) or intestinal inflammation was associated with antibody recognition of the microbiota. | Stunted children (height-for-age z-score ≤ -2) had a more significant proportion of IgA+ bacteria in the fecal microbiota than non-stunted controls. Two of the most highly IgA-recognized bacteria, regardless of nutritional status, were <i>Campylobacter</i> (in CAR) and <i>Haemophilus</i> (in both countries), both of which were previously shown to be more abundant in stunted children; however, there was no association between IgA-targeting of these bacteria and either stunting or inflammatory markers. IgG-bound intestinal bacteria were rare in both stunted and non-stunted children, similar to levels observed in healthy populations. |
| 10 | Nutrition and the Gut Microbiota in 10- to 18-Month-Old Children Living in Urban Slums of Mumbai, India | (Huey et al., 2020) | Urban slums of Mumbai, India, | 2020 | The collection of rectal swabs from children aged 10 to 18 months in urban slums of Mumbai participated in a randomized controlled feeding trial and conducted 16S rRNA sequencing to determine the composition of the gut microbiota. | How nutritional status, including anthropometric measurements, dietary intakes from complementary foods, feeding practices, and micronutrient concentrations, are associated with their gut microbiota | Among undernourished children living in urban slums of Mumbai, India, a high relative abundance of Proteobacteria, a phylum including many potentially pathogenic species similar to the composition in preterm infants, suggesting immaturity of the gut, or potentially a high inflammatory burden. Also, the head circumference, fat and iron intake, and current breastfeeding were positively associated with microbial diversity, while hemoglobin and weight for length were associated with lower diversity |

11 Stunting among children aged 24-59 months and associations with sanitation, enteric infections, and environmental enteric dysfunction in rural northwest Ethiopia	(Gizaw et al., 2022)	Rural northwest Ethiopia	2022 A community-based cross-sectional study was conducted among 224 randomly selected children aged 24-59 months in rural areas of the east Dembiya district.	They assess the associations of stunting with sanitation, enteric infections, and EED in early childhood.	Of the 224 children, 33% (95% CI 27, 39%) were stunted. Stunting in children was significantly associated with poor dietary intake (AOR 3.0, 95% CI 1.2, 7.3), open defecation practice (AOR 3.0, 95% CI 1.2, 7.9), presence of animal excreta in the living environment (AOR 3.4, 95% CI 1.2, 9.9), E. coli contamination of drinking water (AOR 4.2, 95% CI 1.1, 15.3), diarrheal disease incidence (AOR 3.4, 95% CI 1.5, 7.7), intestinal parasites in children (AOR 3.3, 95% CI 1.3, 8.8), and higher EED disease activity scores (AOR 2.9, 95% CI 1.2, 6.7)
----------------------------------------------------------------------------------------------------------------------------------------------------------------------	----------------------	--------------------------	----------------------------------------------------------------------------------------------------------------------------------------------------------------	-----------------------------------------------------------------------------------------------------------	------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

microglia function (Liu et al., 2022). Germ-free (GF) animal studies have shown that bacterial colonization of the gut suppressed the development of the brain hippocampus in GF rats compared to that in its counterpart. This is central to the development and maturation of both ENS and CNS (Carabotti et al., 2015). Gut microbiota modulates the action of microglia by facilitating neuroinflammation, releasing microbial-derived metabolites and altering neurotrophins and brain neurotransmitters.

Furthermore, the microbiota can influence ENS activity by producing molecules acting as local neurotransmitters, such as GABA, serotonin, melatonin, histamine and acetylcholine and by generating a biologically active form of catecholamines in the lumen of the gut. Microbiota can interact with GBA also through the modulation of afferent sensory nerves, as reported for *Lactobacillus reuteri*, enhancing their excitability by inhibiting calcium-dependent potassium channels opening, modulates gut motility and pain perception. *Lactobacilli* also utilize nitrate and nitrite to generate nitric oxide and to produce hydrogen sulphide that modulates gut motility by interacting with the vanilloid receptor on capsaicin-sensitive nerve fibres (Carabotti et al., 2015; Sarubbo et al., 2022).

The hypothalamic pituitary adrenal (HPA) axis

Microbial colonization of the gut leads to a normalization of the axis in an age-dependent manner, with reversibility of the exaggerated stress response being observed after GF colonization only in very young mice, supporting the existence of a critical period during which the

CONCLUSION

Stunting remains a global issue. It has a negative effect on motor and cognitive development, including delays in developing speech skills. The neurobiological mechanism for how stunting is a risk factor for speech delay enters through the microbiota-gut-brain axis. Disruption of this pathway is preceded by intestinal microbiota dysbiosis characterized by changes in the dominance of pathogenic microbiota species and their function. Chronic

plasticity of neural regulation is sensitive to input from microbiota (Carabotti et al., 2015).

Studies conducted on germ-free animals have also demonstrated that microbiota influences stress reactivity and anxiety-like behaviour and regulates the set point for HPA activity. These animals generally show decreased anxiety and an increased stress response with augmented levels of Adreno Corticotrophine Hormone-ACTH and cortisol.

The neurogenesis of the brain

Brain growth and development depend on the ability of brain tissue neurogenesis. Neurogenesis refers to generating new neurons by differentiating neural stem cells and the maturation of neural progenitor cells. GBA and brain neurogenesis research are currently limited to experimental animal studies. However, the results shown by these studies are similar.

Changes in the intestinal environment by several conditions, such as changes in dietary patterns due to chronic undernutrition, administration of antibiotics, changes in homeostasis gut microbiota altered expression of synaptic plasticity-related genes, with significantly lower BDNF mRNA expression in the hippocampus, amygdala, and cingulate cortex in GF mice; of note, these areas participate in neurogenesis and are critical components of the neural circuitry underlying behaviour (Sarubbo et al., 2022).

Increased neurogenesis leads to better brain growth, including motor and sensory areas responsible for speech and language performance, while perturbation of neurogenesis contributes to neurological impairment

dysbiosis causes stunting, characterized by a non-linear physical growth rate with age, smaller head circumference and less muscle mass. In parallel, intestinal dysbiosis causes damage to the enteric barrier and blood-brain fields, opening up the passage of noxious compounds into brain tissue and disrupting the metabolism of neurons and brain glia.

Although the studies of stunting or chronic undernutrition, gut microbiome and GBA remain predominantly in animal studies, further research still needs to be done to answer these questions and fill the gap in humans. For example, is there

a direct relationship between stunting and neuronal growth factor (NGF-Nerve Growth Factor)? Are there biomarkers that can directly measure the degree of intestinal dysbiosis and impaired function of the sensory cortex in the brain? Scientific research is still needed to explain

DAFTAR PUSTAKA

- Agnihotri, N., & Mohajeri, M. H. (2022). Involvement of Intestinal Microbiota in Adult Neurogenesis and the Expression of Brain-Derived Neurotrophic Factor. *International Journal of Molecular Sciences*, 23(24). <https://doi.org/10.3390/ijms232415934>
- Ali, M., Khan, E., Khan, M. N., & Khan, A. U. (2021). Association of Malnutrition with Delayed Speech among Children 2-6 Years Undergoing Speech Therapy at Rehabilitation Center. *Journal of the Liaquat University of Medical and Health Sciences*, 20(5), 324–328. <https://doi.org/10.22442/JLUMHS.2021.00834>
- Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology*, 28(2), 203. [/pmc/articles/PMC4367209/](https://pubmed.ncbi.nlm.nih.gov/27209/)
- Chen, R. Y., Kung, V. L., Das, S., Hossain, M. S., Hibberd, M. C., Guruge, J., Mahfuz, M., Begum, S. M. K. N., Rahman, M. M., Fahim, S. M., Gazi, M. A., Haque, R., Sarker, S. A., Mazumder, R. N., Di Luccia, B., Ahsan, K., Kennedy, E., Santiago-Borges, J., Rodionov, D. A., ... Gordon, J. I. (2020). Duodenal Microbiota in Stunted Undernourished Children with Enteropathy. *The New England Journal of Medicine*, 383(4), 321–333. <https://doi.org/10.1056/NEJMOA1916004>
- Collard, J. M., Andrianonimiadana, L., Habib, A., Rakotondrainipiana, M., Andriantsalama, P., Randriamparany, R., Rabenandrasana, M. A. N., Weill, F. X., Sauvonnet, N., Randremanana, R. V., Guillemot, V., Vonaesch, P., & Sansonetti, P. J. (2022). High prevalence of small intestine bacteria overgrowth and asymptomatic carriage of enteric pathogens in stunted children in Antananarivo, Madagascar. *PLoS Neglected Tropical Diseases*, 16(5). <https://doi.org/10.1371/JOURNAL.PNTD.0009849>
- Dinh, D. M., Ramadass, B., Kattula, D., Sarkar, R., Braunstein, P., Tai, A., Wanke, C. A., Hassoun, S., Kane, A. V., Naumova, E. N., Kang, G., & Ward, H. D. (2016). Longitudinal analysis of the intestinal microbiota in persistently stunted young children in south India. *PLoS ONE*, 11(5). <https://doi.org/10.1371/JOURNAL.PONE.0155405>
- Eslick, C. J., Krüger, E., & Kritzing, A. (2022). Exploring swallowing, feeding and communication characteristics of toddlers with severe acute malnutrition. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif Vir Kommunikasieafwykings*, 69(1), e1–e10. <https://doi.org/10.4102/SAJCD.V69I1.874>
- Fadila, S. (2017). *Correlation of Stunting With Developmental Delays on Children Age Under 24 Months in Growth and Development Division of Dr. Soetomo General Hospital Surabaya 2018 (Analytical Observational Research)* [Airlangga]. <https://repository.unair.ac.id/107530/2/ABSTRAK.pdf>
- Gizaw, Z., Yalew, A. W., Bitew, B. D., Lee, J., & Bisesi, M. (2022). Stunting among children aged 24-59 months and associations with sanitation, enteric infections, and environmental enteric dysfunction in rural northwest Ethiopia. *Scientific Reports*, 12(1). <https://doi.org/10.1038/S41598-022-23981-5>
- Gough, E. K., Stephens, D. A., Moodie, E. E. M., Prendergast, A. J., Stoltzfus, R. J., Humphrey, J. H., & Manges, A. R. (2015). Linear growth faltering in infants is associated with *Acidaminococcus* sp. and community-level changes in the gut microbiota. *Microbiome*, 3(1). <https://doi.org/10.1186/S40168-015-0089-2>
- Hennessey, C., Keogh, C. E., Barboza, M., Brust-Mascher, I., Knotts, T. A., Sladek, J. A., Pusceddu, M. M., Stokes, P., Rabasa, G., Honeycutt, M., Walsh, O., Nichols, R., Reardon, C., & Gareau, M. G. (2021). Neonatal Enteropathogenic *Escherichia coli* Infection Disrupts Microbiota-Gut-Brain Axis Signaling. *Infection and Immunity*, 89(9). <https://doi.org/10.1128/IAI.00059-21>
- Hoffman, D. J., Campos-Ponce, M., Taddei, C. R., & Doak, C. M. (2017). Microbiome, growth retardation and metabolism: are they related? *Http://Dx.Doi.Org/10.1080/03014460.2016.1267261*, 44(3), 201–207. <https://doi.org/10.1080/03014460.2016.1267261>

- Huey, S. L., Jiang, L., Fedarko, M. W., McDonald, D., Martino, C., Ali, F., Russell, D. G., Udipi, S. A., Thorat, A., Thakker, V., Ghugre, P., Potdar, R. D., Chopra, H., Rajagopalan, K., Haas, J. D., Finkelstein, J. L., Knight, R., & Mehta, S. (2020). Nutrition and the Gut Microbiota in 10- to 18-Month-Old Children Living in Urban Slums of Mumbai, India. *MSphere*, 5(5). <https://doi.org/10.1128/MSPHERE.00731-20>
- Huus, K. E., Rodriguez-Pozo, A., Kapel, N., Nestoret, A., Habib, A., Dede, M., Manges, A., Collard, J. M., Sansonetti, P., Vonaesch, P., Finlay, B. B., Andriatahirintsoa, E. J., Bastarud, A., Doria, M., Djorie, S. G., Etienne, A., Giles-Vernick, T., Gody, J. C., Godje, B. P., ... Wegener-Parfrey, L. (2020). Immunoglobulin recognition of fecal bacteria in stunted and non-stunted children: findings from the AfriBiota study. *Microbiome*, 8(1). <https://doi.org/10.1186/S40168-020-00890-1>
- Jahnke, J. R., Roach, J., Azcarate-Peril, M. A., & Thompson, A. L. (2021). Maternal precarity and HPA axis functioning shape infant gut microbiota and HPA axis development in humans. *PloS One*, 16(5). <https://doi.org/10.1371/JOURNAL.PONE.0251782>
- Kang, Y., Aguayo, V. M., Campbell, R. K., & West, K. P. (2018). Association between stunting and early childhood development among children aged 36-59 months in South Asia. *Maternal & Child Nutrition*, 14 Suppl 4(Suppl 4). <https://doi.org/10.1111/MCN.12684>
- Keunen, K., Van Elburg, R. M., Van Bel, F., & Benders, M. J. N. L. (2015). Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatric Research*, 77(1-2), 148–155. <https://doi.org/10.1038/PR.2014.171>
- Liégeois, F. J., & Morgan, A. T. (2012). Neural bases of childhood speech disorders: Lateralization and plasticity for speech functions during development. *Neuroscience & Biobehavioral Reviews*, 36(1), 439–458. <https://doi.org/10.1016/J.NEUBIOREV.2011.07.011>
- Liu, C., Yang, S. Y., Wang, L., & Zhou, F. (2022). The gut microbiome: implications for neurogenesis and neurological diseases. *Neural Regeneration Research*, 17(1), 53. <https://doi.org/10.4103/1673-5374.315227>
- Maiuolo, J., Gliozzi, M., Musolino, V., Carresi, C., Scarano, F., Nucera, S., Scicchitano, M., Oppedisano, F., Bosco, F., Ruga, S., Zito, M. C., Macri, R., Palma, E., Muscoli, C., & Mollace, V. (2021). The Contribution of Gut Microbiota–Brain Axis in the Development of Brain Disorders. *Frontiers in Neuroscience*, 15. <https://doi.org/10.3389/FNINS.2021.616883/FULL>
- Mustakim, M. R. D., Irwanto, Irawan, R., Irmawati, M., & Setyoboedi, B. (2022). Impact of Stunting on Development of Children between 1-3 Years of Age. *Ethiopian Journal of Health Sciences*, 32(3), 569–578. <https://doi.org/10.4314/ejhs.v32i3.13>
- Mutasa, K., Ntozini, R., Mbuya, M. N. N., Rukobo, S., Govha, M., Majo, F. D., Tavengwa, N., Smith, L. E., Caulfield, L., Swann, J. R., Stoltzfus, R. J., Moulton, L. H., Humphrey, J. H., Gough, E. K., & Prendergast, A. J. (2021). Biomarkers of environmental enteric dysfunction are not consistently associated with linear growth velocity in rural Zimbabwean infants. *The American Journal of Clinical Nutrition*, 113(5), 1185–1198. <https://doi.org/10.1093/AJCN/NQAA416>
- Prendergast, A. J., & Humphrey, J. H. (2014). The stunting syndrome in developing countries. *Paediatrics and International Child Health*, 34(4), 250. <https://doi.org/10.1179/2046905514Y.0000000158>
- Sabra M, Ahmed, M.D., Hala H, Aboufaddan, M. D. . (2018). Risk Factors of Delayed Language Development among Preschool Children Attending Assiut University Hospitals. *The Medical Journal of Cairo University*, 86(9), 2279–2285. <https://doi.org/10.21608/MJCU.2018.57520>
- Sarubbo, F., Cavallucci, V., & Pani, G. (2022). The Influence of Gut Microbiota on Neurogenesis: Evidence and Hopes. *Cells*, 11(3). <https://doi.org/10.3390/CELLS11030382>
- Shrestha, M. L., Perry, K. E., Thapa, B., Adhikari, R. P., & Weissman, A. (2022). Malnutrition matters: Association of stunting and underweight with early childhood development indicators in Nepal. *Maternal & Child Nutrition*, 18(2). <https://doi.org/10.1111/MCN.13321>
- Soliman, A., De Sanctis, V., Alaaraj, N., Ahmed, S., Alyafei, F., Hamed, N., & Soliman, N. (2021). Early and Long-term Consequences of Nutritional Stunting: From Childhood to Adulthood. *Acta Bio-Medica: Atenei Parmensis*, 92(1). <https://doi.org/10.23750/ABM.V92I1.11346>
- Surono, I. S., Jalal, F., Bahri, S., Romulo, A., Kusumo, P. D., Manalu, E., Yusnita, & Venema, K. (2021). Differences in immune status and fecal SCFA between Indonesian stunted children and children with normal nutritional status. *PloS One*, 16(7). <https://doi.org/10.1371/JOURNAL.PONE.0254>

300

- Surono, I. S., Widiyanti, D., Kusumo, P. D., & Venema, K. (2021). Gut microbiota profile of Indonesian stunted children and children with normal nutritional status. *PLoS ONE*, *16*(1). <https://doi.org/10.1371/JOURNAL.PONE.0245399>
- Van Beekum, M., Berger, J., Van Geystelen, J., Hondru, G., Som, S. V., Theary, C., Laillou, A., Poirot, E., Bork, K. A., Wieringa, F. T., & Fortin, S. (2022). The associations between stunting and wasting at 12 months of age and developmental milestones delays in a cohort of Cambodian children. *Scientific Reports*, *12*(1). <https://doi.org/10.1038/S41598-022-22861-2>
- Vonaesch, P., Morien, E., Andrianonimiadana, L., Sanke, H., Mbecko, J. R., Huus, K. E., Naharimanananirina, T., Gondje, B. P., Nigatoloum, S. N., Vondo, S. S., Kaleb Kandou, J. E., Randremanana, R., Rakotondrainipiana, M., Mazel, F., Djorie, S. G., Gody, J. C., Finlay, B. B., Rubbo, P. A., Parfrey, L. W., ... Sansonetti, P. J. (2018). Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(36), E8489–E8498. <https://doi.org/10.1073/PNAS.1806573115>
- Vonaesch, P., Randremanana, R., Gody, J. C., Collard, J. M., Giles-Vernick, T., Doria, M., Vigan-Womas, I., Rubbo, P. A., Etienne, A., Andriatahirintsoa, E. J., Kapel, N., Brown, E., Huus, K. E., Duffy, D., Finlay, B. B., Hasan, M., Hunald, F. A., Robinson, A., Manirakiza, A., ... Gouandjika-Vassilache, I. (2018). Identifying the etiology and pathophysiology underlying stunting and environmental enteropathy: Study protocol of the AFRIBIOTA project. *BMC Pediatrics*, *18*(1). <https://doi.org/10.1186/S12887-018-1189-5>
- Xavier, R. J. (2020). Growth and the Microbiome — Integrating Global Health with Basic Science. *New England Journal of Medicine*, *383*(4), 391–393. <https://doi.org/10.1056/nejme2017496>
- Agnihotri, N., & Mohajeri, M. H. (2022). Involvement of Intestinal Microbiota in Adult Neurogenesis and the Expression of Brain-Derived Neurotrophic Factor. *International Journal of Molecular Sciences*, *23*(24). <https://doi.org/10.3390/ijms232415934>
- Ali, M., Khan, E., Khan, M. N., & Khan, A. U. (2021). Association of Malnutrition with Delayed Speech among Children 2-6 Years Undergoing Speech Therapy at Rehabilitation Center. *Journal of the Liaquat University of Medical and Health Sciences*, *20*(5), 324–328. <https://doi.org/10.22442/JLUMHS.2021.00834>
- Carabotti, M., Scirocco, A., Maselli, M. A., & Severi, C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Annals of Gastroenterology: Quarterly Publication of the Hellenic Society of Gastroenterology*, *28*(2), 203. <https://doi.org/10.22442/JLUMHS.2021.00834>
- Chen, R. Y., Kung, V. L., Das, S., Hossain, M. S., Hibberd, M. C., Guruge, J., Mahfuz, M., Begum, S. M. K. N., Rahman, M. M., Fahim, S. M., Gazi, M. A., Haque, R., Sarker, S. A., Mazumder, R. N., Di Luccia, B., Ahsan, K., Kennedy, E., Santiago-Borges, J., Rodionov, D. A., ... Gordon, J. I. (2020). Duodenal Microbiota in Stunted Undernourished Children with Enteropathy. *The New England Journal of Medicine*, *383*(4), 321–333. <https://doi.org/10.1056/NEJMJA1916004>
- Collard, J. M., Andrianonimiadana, L., Habib, A., Rakotondrainipiana, M., Andriantsalama, P., Randriamparany, R., Rabenandrasana, M. A. N., Weill, F. X., Sauvonnnet, N., Randremanana, R. V., Guillemot, V., Vonaesch, P., & Sansonetti, P. J. (2022). High prevalence of small intestine bacteria overgrowth and asymptomatic carriage of enteric pathogens in stunted children in Antananarivo, Madagascar. *PLoS Neglected Tropical Diseases*, *16*(5). <https://doi.org/10.1371/JOURNAL.PNTD.0009849>
- Dinh, D. M., Ramadass, B., Kattula, D., Sarkar, R., Braunstein, P., Tai, A., Wanke, C. A., Hassoun, S., Kane, A. V., Naumova, E. N., Kang, G., & Ward, H. D. (2016). Longitudinal analysis of the intestinal microbiota in persistently stunted young children in south India. *PLoS ONE*, *11*(5). <https://doi.org/10.1371/JOURNAL.PONE.0155405>
- Eslick, C. J., Krüger, E., & Kritzinger, A. (2022). Exploring swallowing, feeding and communication characteristics of toddlers with severe acute malnutrition. *The South African Journal of Communication Disorders = Die Suid-Afrikaanse Tydskrif Vir Kommunikasieafwykings*, *69*(1), e1–e10. <https://doi.org/10.4102/SAJCD.V69I1.874>
- Fadila, S. (2017). *Correlation of Stunting With Developmental Delays on Children Age Under 24 Months in Growth and Development Division of Dr. Soetomo General Hospital Surabaya 2018 (Analytical Observational Research)* [Airlangga]. <https://repository.unair.ac.id/107530/2/2>. ABSTRAK.pdf
- Gizaw, Z., Yalew, A. W., Bitew, B. D., Lee, J., & Bisesi, M. (2022). Stunting among children aged 24-59 months and associations with sanitation,

- enteric infections, and environmental enteric dysfunction in rural northwest Ethiopia. *Scientific Reports*, 12(1). <https://doi.org/10.1038/S41598-022-23981-5>
- Gough, E. K., Stephens, D. A., Moodie, E. E. M., Prendergast, A. J., Stoltzfus, R. J., Humphrey, J. H., & Manges, A. R. (2015). Linear growth faltering in infants is associated with *Acidaminococcus* sp. and community-level changes in the gut microbiota. *Microbiome*, 3(1). <https://doi.org/10.1186/S40168-015-0089-2>
- Hennessey, C., Keogh, C. E., Barboza, M., Brust-Mascher, I., Knotts, T. A., Sladek, J. A., Pusceddu, M. M., Stokes, P., Rabasa, G., Honeycutt, M., Walsh, O., Nichols, R., Reardon, C., & Gareau, M. G. (2021). Neonatal Enteropathogenic *Escherichia coli* Infection Disrupts Microbiota-Gut-Brain Axis Signaling. *Infection and Immunity*, 89(9). <https://doi.org/10.1128/IAI.00059-21>
- Hoffman, D. J., Campos-Ponce, M., Taddei, C. R., & Doak, C. M. (2017). Microbiome, growth retardation and metabolism: are they related? *Http://Dx.Doi.Org/10.1080/03014460.2016.1267261*, 44(3), 201–207. <https://doi.org/10.1080/03014460.2016.1267261>
- Huey, S. L., Jiang, L., Fedarko, M. W., McDonald, D., Martino, C., Ali, F., Russell, D. G., Udipi, S. A., Thorat, A., Thakker, V., Ghugre, P., Potdar, R. D., Chopra, H., Rajagopalan, K., Haas, J. D., Finkelstein, J. L., Knight, R., & Mehta, S. (2020). Nutrition and the Gut Microbiota in 10- to 18-Month-Old Children Living in Urban Slums of Mumbai, India. *MSphere*, 5(5). <https://doi.org/10.1128/MSPHERE.00731-20>
- Huus, K. E., Rodriguez-Pozo, A., Kapel, N., Nestoret, A., Habib, A., Dede, M., Manges, A., Collard, J. M., Sansonetti, P., Vonaesch, P., Finlay, B. B., Andriatahirintsoa, E. J., Bastarand, A., Doria, M., Djorie, S. G., Etienne, A., Giles-Vernick, T., Gody, J. C., Godje, B. P., ... Wegener-Parfrey, L. (2020). Immunoglobulin recognition of fecal bacteria in stunted and non-stunted children: findings from the AfriBiota study. *Microbiome*, 8(1). <https://doi.org/10.1186/S40168-020-00890-1>
- Jahnke, J. R., Roach, J., Azcarate-Peril, M. A., & Thompson, A. L. (2021). Maternal precarity and HPA axis functioning shape infant gut microbiota and HPA axis development in humans. *PloS One*, 16(5). <https://doi.org/10.1371/JOURNAL.PONE.0251782>
- Kang, Y., Aguayo, V. M., Campbell, R. K., & West, K. P. (2018). Association between stunting and early childhood development among children aged 36-59 months in South Asia. *Maternal & Child Nutrition*, 14 Suppl 4(Suppl 4). <https://doi.org/10.1111/MCN.12684>
- Keunen, K., Van Elburg, R. M., Van Bel, F., & Benders, M. J. N. L. (2015). Impact of nutrition on brain development and its neuroprotective implications following preterm birth. *Pediatric Research*, 77(1–2), 148–155. <https://doi.org/10.1038/PR.2014.171>
- Liégeois, F. J., & Morgan, A. T. (2012). Neural bases of childhood speech disorders: Lateralization and plasticity for speech functions during development. *Neuroscience & Biobehavioral Reviews*, 36(1), 439–458. <https://doi.org/10.1016/J.NEUBIOREV.2011.07.011>
- Liu, C., Yang, S. Y., Wang, L., & Zhou, F. (2022). The gut microbiome: implications for neurogenesis and neurological diseases. *Neural Regeneration Research*, 17(1), 53. <https://doi.org/10.4103/1673-5374.315227>
- Maiuolo, J., Gliozzi, M., Musolino, V., Carresi, C., Scarano, F., Nucera, S., Scicchitano, M., Oppedisano, F., Bosco, F., Ruga, S., Zito, M. C., Macri, R., Palma, E., Muscoli, C., & Mollace, V. (2021). The Contribution of Gut Microbiota–Brain Axis in the Development of Brain Disorders. *Frontiers in Neuroscience*, 15. <https://doi.org/10.3389/FNINS.2021.616883/FULL>
- Mustakim, M. R. D., Irawanto, Irawan, R., Irmawati, M., & Setyo-boedi, B. (2022). Impact of Stunting on Development of Children between 1-3 Years of Age. *Ethiopian Journal of Health Sciences*, 32(3), 569–578. <https://doi.org/10.4314/ejhs.v32i3.13>
- Mutasa, K., Ntozini, R., Mbuya, M. N. N., Rukobo, S., Govha, M., Majo, F. D., Tavengwa, N., Smith, L. E., Caulfield, L., Swann, J. R., Stoltzfus, R. J., Moulton, L. H., Humphrey, J. H., Gough, E. K., & Prendergast, A. J. (2021). Biomarkers of environmental enteric dysfunction are not consistently associated with linear growth velocity in rural Zimbabwean infants. *The American Journal of Clinical Nutrition*, 113(5), 1185–1198. <https://doi.org/10.1093/AJCN/NQAA416>
- Prendergast, A. J., & Humphrey, J. H. (2014). The stunting syndrome in developing countries. *Paediatrics and International Child Health*, 34(4), 250. <https://doi.org/10.1179/2046905514Y.0000000158>
- Sabra M, Ahmed, M.D., Hala H, Aboufaddan, M. D. . (2018). Risk Factors of Delayed Language Development among Preschool Children

- Attending Assiut University Hospitals. *The Medical Journal of Cairo University*, 86(9), 2279–2285.
<https://doi.org/10.21608/MJCU.2018.57520>
- Sarubbo, F., Cavallucci, V., & Pani, G. (2022). The Influence of Gut Microbiota on Neurogenesis: Evidence and Hopes. *Cells*, 11(3).
<https://doi.org/10.3390/CELLS11030382>
- Shrestha, M. L., Perry, K. E., Thapa, B., Adhikari, R. P., & Weissman, A. (2022). Malnutrition matters: Association of stunting and underweight with early childhood development indicators in Nepal. *Maternal & Child Nutrition*, 18(2). <https://doi.org/10.1111/MCN.13321>
- Soliman, A., De Sanctis, V., Alaaraj, N., Ahmed, S., Alyafei, F., Hamed, N., & Soliman, N. (2021). Early and Long-term Consequences of Nutritional Stunting: From Childhood to Adulthood. *Acta Bio-Medica: Atenei Parmensis*, 92(1).
<https://doi.org/10.23750/ABM.V92I1.11346>
- Surono, I. S., Jalal, F., Bahri, S., Romulo, A., Kusumo, P. D., Manalu, E., Yusnita, & Venema, K. (2021). Differences in immune status and fecal SCFA between Indonesian stunted children and children with normal nutritional status. *PLoS One*, 16(7).
<https://doi.org/10.1371/JOURNAL.PONE.0254300>
- Surono, I. S., Widiyanti, D., Kusumo, P. D., & Venema, K. (2021). Gut microbiota profile of Indonesian stunted children and children with normal nutritional status. *PLoS ONE*, 16(1).
<https://doi.org/10.1371/JOURNAL.PONE.0245399>
- Van Beekum, M., Berger, J., Van Geystelen, J., Hondru, G., Som, S. V., Theary, C., Laillou, A., Poirot, E., Bork, K. A., Wieringa, F. T., & Fortin, S. (2022). The associations between stunting and wasting at 12 months of age and developmental milestones delays in a cohort of Cambodian children. *Scientific Reports*, 12(1).
<https://doi.org/10.1038/S41598-022-22861-2>
- Vonaesch, P., Morien, E., Andrianonimiadana, L., Sanke, H., Mbecko, J. R., Huus, K. E., Naharimanananirina, T., Gondje, B. P., Nigatoloum, S. N., Vondo, S. S., Kaleb Kandou, J. E., Randremanana, R., Rakotondrainipiana, M., Mazel, F., Djorie, S. G., Gody, J. C., Finlay, B. B., Rubbo, P. A., Parfrey, L. W., ... Sansonetti, P. J. (2018). Stunted childhood growth is associated with decompartmentalization of the gastrointestinal tract and overgrowth of oropharyngeal taxa. *Proceedings of the National Academy of Sciences of the United States of America*, 115(36), E8489–E8498.
<https://doi.org/10.1073/PNAS.1806573115>
- Vonaesch, P., Randremanana, R., Gody, J. C., Collard, J. M., Giles-Vernick, T., Doria, M., Vigan-Womas, I., Rubbo, P. A., Etienne, A., Andriatahirintsoa, E. J., Kapel, N., Brown, E., Huus, K. E., Duffy, D., Finlay, B. B., Hasan, M., Hunald, F. A., Robinson, A., Manirakiza, A., ... Gouandjika-Vassilache, I. (2018). Identifying the etiology and pathophysiology underlying stunting and environmental enteropathy: Study protocol of the AFRIBIOTA project. *BMC Pediatrics*, 18(1).
<https://doi.org/10.1186/S12887-018-1189-5>
- Xavier, R. J. (2020). Growth and the Microbiome — Integrating Global Health with Basic Science. *New England Journal of Medicine*, 383(4), 391–393. <https://doi.org/10.1056/nejme2017496>