Trends in Parasitology

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Opinion

Parasites and childhood stunting – a mechanistic interplay with nutrition, anaemia, gut health, microbiota, and epigenetics

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Globally, stunting affects approximately 149.2 million children under 5 years of age. The underlying aetiology and pathophysiological mechanisms leading to stunting remain elusive, and therefore few effective treatment and prevention strategies exist. Crucial evidence directly linking parasites to stunting is often lacking – in part due to the complex nature of stunting, as well as a lack of critical multidisciplinary research amongst key age groups. Here, based on available studies, we present potential mechanistic pathways by which parasitic infection of mother and/or infant may lead to childhood stunting. We highlight the need for future multidisciplinary longitudinal studies and clinical trials aimed at elucidating the most influential factors, and synergies therein, that can lead to stunting, and ultimately towards finding solutions to successfully mitigate against it.

Highlights

The mechanistic pathways by which parasites lead to stunting are likely multiple and context-specific, and dependent on parasite species, geographic location, and a myriad of other contextual factors.

The most well-recognised pathway to stunting is a 'vicious cycle' between deteriorating nutritional status and infection, which is evolving to encompass dysbiosis of the gut, local and systemic inflammation alongside energetic, hormonal, and metabolic consequences.

Anaemia is often presented as co-occurring alongside stunting. Despite this, anaemia of mother and/or child may be causative in the pathway leading to stunting.

The bidirectional relationship between intestinal parasites and the microbiota in early life, and their combined effects, could play a key role in stunting.

Epigenetic regulation of gene expression may link parasitic infections and poor gut health in early life to stunting.

Childhood stunting: not just a simple growth problem

Human height reflects a combination of an individual's **genotype** (see Glossary) and environmental factors which influence **phenotypic** expression of that genotype. An estimated 149.2 million children under the age of 5 were physically stunted in 2020, defined as falling at least –2 standard deviations below the height-for-age World Health Organization (WHO) Child Growth Standards median [1]. Stunting is a visible indicator of a deficient environment, the consequences of which include child morbidity, including an increased risk of long-term chronic diseases, and in severe cases even mortality (Box 1) [2]. Having been identified as a major global health priority, The World Health Assembly targets aim to reduce childhood stunting by 40% between 2010 and 2025. However, at current rates of progress, an estimated 127 million under-fives will be stunted by 2025, a reduction of only 26% [3]. Furthermore, progress has been interrupted, with an estimated 2.6 million additional children stunted as a result of the COVID-19 pandemic [4].

In the absence of disease, and when maternal nutrition and postnatal needs are met with little environmental constraints, children grow at a remarkably similar rate during the first few years of life, regardless of geographical location [5]. Interestingly, there is a clear geographical overlap between the communities suffering from high burdens of parasitic diseases and high rates of childhood stunting [6]. Parasites may be classified as macroparasites (encompassing parasitic protozoa, ectoparasites, and helminths) or microparasites (encompassing viruses and pathogenic bacteria) [7], although standard terminology often refers only to the former grouping. The WHO classifies a number of parasites as part of the 20 Neglected Tropical Diseases (NTDs), due to their disproportionate impact on impoverished societies in mainly tropical and subtropical regions [8].

Whilst the **typology** of stunting has not yet been fully deciphered, persistent and/or recurring parasitic infections are often proposed to play a key role [9], although to varying degrees depending

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Box 1. What is stunting?

Malnutrition refers to both over- and undernutrition (including micronutrient deficiencies). Classifying further, undernutrition describes stunting, wasting, and underweight (Figure I) [1]. Within each category, causes may be divided into endogenous and exogenous factors. For example, chronic food insecurity within low-income countries and conflict settings is a major exogenous risk factor, whilst parasitic infection represents an endogenous risk factor.

Stunting refers to both reduced physical growth and cognitive impairment, although the WHO definition focuses on the anthropometric aspect in which stunted children have a height-for-age that is 'more than 2 standard deviations below the WHO Child Growth Standards median' [1]. This classifies 149.2 million children under the age of 5 as stunted, although millions more suffer some degree of growth faltering despite not being classified as stunted by this arbitrary cut-off [79]. Furthermore, stunting, wasting, and underweight often coexist and interact, with repeated bouts of wasting having been shown to contribute to stunting [80]. These definitions are not all-encompassing, though, and children may classify as suffering from 'failure to thrive', which holds no universally accepted definition. Failure to thrive tends to refer to the situation in which a child falls below one or more weight centiles on the WHO growth chart, depending on birthweight, or when weight is below the second percentile of weight-for-age irrespective of birthweight [81].

The first 1000 days from conception to 2 years of age provide the foundations for optimal growth, and stunting is largely irreversible following this time frame [82]. Accompanying stunting is delayed and reduced development of organs and the immune system, and increased susceptibility to infections, resulting in greater child morbidity and mortality [2]. Short stature is a risk factor for rapid fat accumulation in adulthood, leading to overweight and obesity, which increases an individual's risk of noncommunicable diseases (e.g., diabetes and cardiovascular disease) [2]. Furthermore, due to a smaller pelvis, girls who grow up stunted are more likely to suffer from complicated pregnancies, difficult childbirth, and bear stunted children [83]. An estimated 20–30% of stunting occurs *in utero*, with maternal–foetal interactions leading to intrauterine growth restriction, and poor maternal health impacting lactation and early child nutrition [6]. Accompanying linear growth reductions is suboptimal neurocognitive development, leading to reduced educational attainment and intellectual capacity. Therefore, even before their second birthday, stunted children are likely to earn significantly less income in the future than their nonstunted counterparts, perpetuating the poverty cycle into future generations [6].

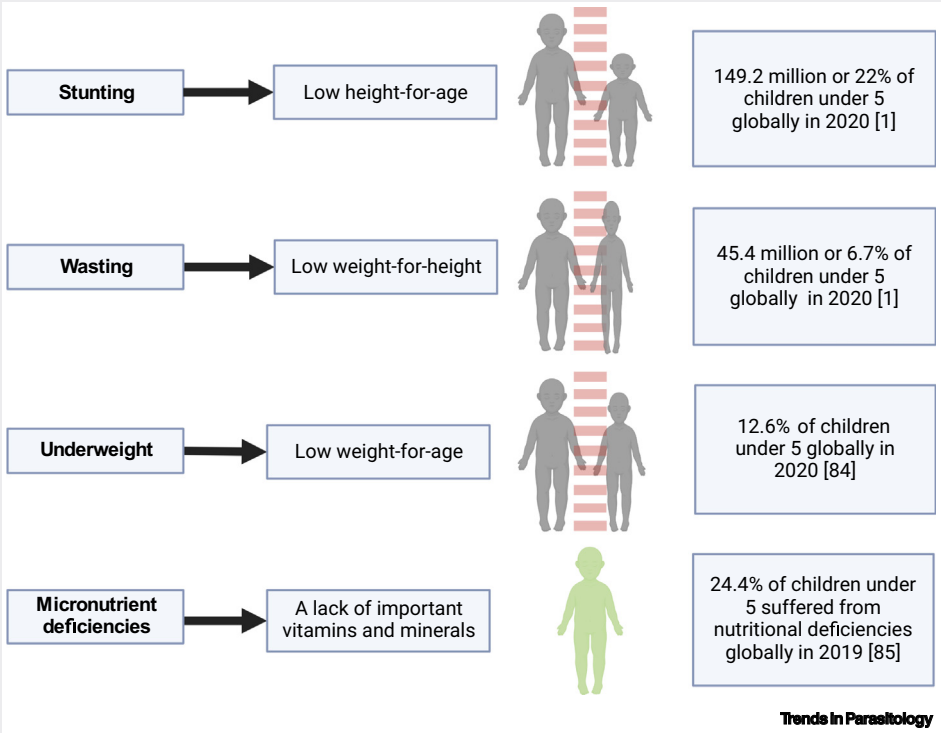


Figure I. Global prevalence of stunting, wasting, underweight (indicators of undernutrition), and micronutrient deficiencies in children under 5 years of age [1,84,85].

Glossary

Aetiology: the cause, set of causes, or manner of causation of a disease or condition.
Anaemia: a haemoglobin concentration below 110 g/l at sea level, in children under 5 years of age and pregnant women, and below 120 g/l at sea level, in nonpregnant women. This cut-off point depends on the age, gender, physiological status, smoking habits, and altitude at which the population being assessed lives.
Biomarker: a naturally occurring molecule, gene, or characteristic by which a particular pathological or physiological process, disease, etc. can be identified.
Cytokines: small and membrane-bound protein-based cell signalling molecules that aid cell-to-cell communication in immune responses and stimulate the movement of cells towards sites of inflammation, infection, and trauma.
Erythrophagocytosis: ingestion of red blood cells (RBCs) by polymorphonuclear leucocytes or macrophages.
Erythropoiesis: the production of red blood cells.
Genotype: the genetic constitution of an individual organism.
Haemolysis: the rupture or destruction of RBCs.
Phenotype (phenotypic): the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment.
Typology: a set of criteria used for classification.

on parasite species (including coinfections), timing, duration, infection intensity, and pathology. Potential mechanistic pathways could be linked via (but not limited to) malnutrition, environmental enteric dysfunction (EED), hormonal and metabolic derangement, immune changes, anaemia, altered microbiota, and changes in epigenetic signature of parents and child (Figure 1).

This opinion article therefore considers in detail the potential mechanisms by which parasitic infection of mother and/or baby may contribute to childhood stunting. We do not purport to ask here 'do parasites cause stunting?', nor quantify their contribution towards stunting, as has been the subject of recent empirical studies and reviews elsewhere [10]. Instead, our unique aim is to ask 'how could parasites cause stunting?' and hence consider potential pathways involved. In doing so, our objective is to add to our understanding of the mechanistic typology and/or processes behind the role of parasites in a stunted phenotype, and ultimately help to inspire future research aimed at treatment and/or prevention.

Parasites reduce host nutrient intake, which contributes to stunting (Figure 1, Key figure, pathway A)

It is well recognised that a chronic and/or reoccurring lack of sufficient, nutritious foods for mother and child in pre- and postnatal periods contributes to stunting [11]. Like many illnesses, parasitic infections may result in withdrawal of food from individuals who are overtly ill [12], or reduce appetite as a result of active abdominal pain and discomfort, the latter being common symptoms of parasitic gastrointestinal infection [13]. Parasites may also influence neuroendocrine control of appetite, for example, there is evidence that enteroendocrine cells 'sense' the presence of gastrointestinal parasites or their products in the gut and induce **cytokine** expansion. This subsequently alters taste receptor expression and release of satiety hormones [14]. Indeed, leptin, a major appetite suppressant has been found to be elevated in children infected with *Entamoeba histolytica*, *Strongyloides* spp., and *Giardia lamblia* [15]. Similarly, childhood *Trichuris trichiura* infection has been associated with below the recommended intake of protein, energy, iron, and riboflavin [16].

Parasites cause diarrhoea, which contributes to stunting (Figure 1, pathway B)

Protozoan and helminthic parasites are major causative agents of diarrhoeal illness (including bloody diarrhoea) in children. Diarrhoea, particularly when recurrent and/or severe, can impair absorption and digestion of macronutrients and micronutrients and increase catabolism of nutrient reserves, change intestinal enzyme activity, and damage the intestinal lining [17]. Diarrhoea has also been causally linked to stunting by directly reducing levels of the growth hormone insulin-like growth factor (IGF-1), as reported amongst Zimbabwean children [18]. Indeed, the Global Enteric Multicenter Study (GEMS) demonstrated significantly lower height-for-age z-scores (HAZ) in infants 2 months following a diarrhoea episode compared to age- and gender-matched controls [19]. Similarly, five or more diarrhoeal episodes in the first 2 years of life have been predicted to account for 25% of stunting [20]. However, parasite-induced diarrhoea alone may not be a sufficient mechanistic explanation for stunting. Other studies have reported that the incidence of diarrhoea has either little impact on linear height (interestingly, *Giardia* spp. infection has even been shown to be protective against enteropathogen-driven diarrhoea [21]), or alternatively, catch-up growth between diarrhoeal episodes may allow children to regain height after bouts of diarrhoea [22]. Indeed, birth cohort studies indicate that parasitic infection during the first 2 years of life impact linear height, even after controlling for diarrhoeal illness [23].

Parasites cause environmental enteric dysfunction, which contributes to stunting (Figure 1, pathway C)

Parasitic infection has been implicated in the **aetiology** of EED, which is an acquired, subclinical enteropathy of the small intestine (Box 2 and Figure 2) and may contribute to stunting [24]. Villous

Key figure

Overview of potential key pathways linking parasitic infection to childhood stunting

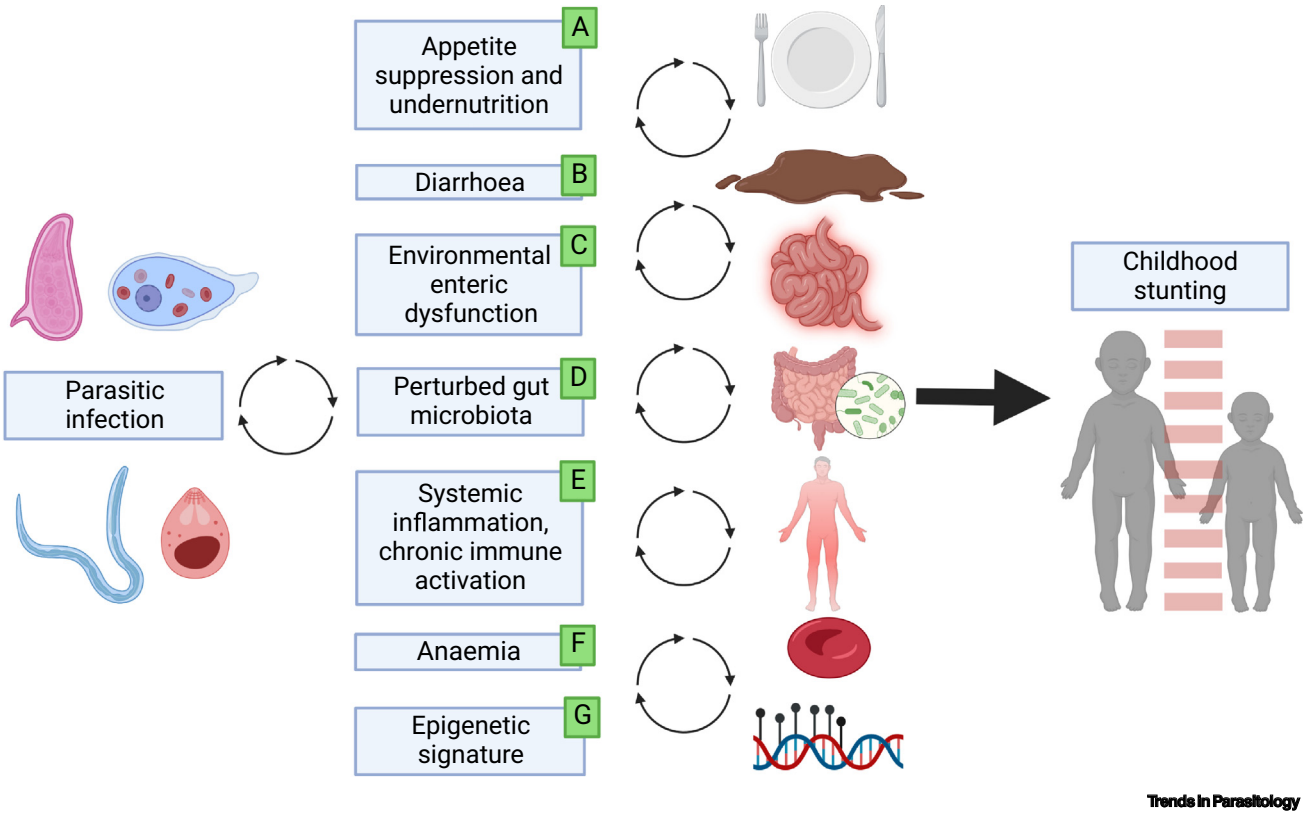


Figure 1. There is no singular, simple linear trajectory from parasite infection to stunting; there are many potential pathways and cycles at play. Pathways A–G are discussed in the text.

atrophy and crypt hyperplasia reduces the surface area of the small intestine, with fewer mature absorptive intestinal epithelial cells available for nutrient absorption and digestion. Therefore, EED likely contributes to exacerbation of undernutrition and/or micronutrient deficiencies [25]. Although direct evidence in humans is limited, associations between villous atrophy, infection (e.g., *G. lamblia* [26]) and stunting have been made in murine models. EED leads to depletion of catalytically active brush-border enzymes and nutrient transporters, providing a realistic route for parasites to limit absorption and digestion [27], although evidence for a direct association with subsequent stunting is lacking.

Parasites may increase gut permeability [28]; for example, *E. histolytica* can loosen tight junctions between intestinal epithelial cells by producing proteases [29]. Parasitic protozoa cause damage via attachment to, and invasion of the epithelium (e.g., *E. histolytica* [30]), and increasing enterocyte apoptosis (e.g., *G. lamblia* [31]). Further, undernourished, parasitized children may have insufficient or rate-limiting stores of essential nutrients to repair mucosal damage, thus exacerbating the effects of EED [32]. As a result of increased mucosal permeability, microbes and microbial-associated macromolecules may translocate into the lamina propria, causing an influx of inflammatory cells, activation of local intestinal inflammation, and a perpetual cycle of deteriorating barrier function,

Box 2. Environmental enteric dysfunction

A healthy intestine enables nutrient absorption and digestion and provides a barrier against invading pathogens. EED – or historically termed 'environmental sprue' or 'tropical enteropathy' – is an incompletely defined syndrome, although it is characterised by immune activation, gut mucosal inflammation, and altered intestinal architecture (see Figure 2 in main text). The consequences of this are not clear, although EED has frequently been associated with poor outcomes, such as stunting, wasting, and reduced vaccine efficacy [24]. The global distribution of EED is largely unknown, although epidemiological studies suggest that it is most prevalent in areas of poor access to clean water and sanitation [24]. A range of exposures have been implicated in the aetiology of EED, although causal attribution has proved challenging. These include (but are not limited to) chronic exposure to faecal pathogens, micronutrient deficiencies, and chemical toxicants (e.g., pesticides and aflatoxins) [86,87]. EED may result from a single factor or combination of factors; for example, malnutrition renders children more susceptible to repeated bouts of enteric infection, and together they may exacerbate EED [32]. There is no set of diagnostic criteria for EED, and the gold standard for diagnosis involves an invasive upper gastrointestinal endoscopy with biopsy, and microscope examination. More recently, biomarkers for EED have been identified relating to intestinal permeability, epithelial damage, and gut inflammation [24]. Diagnostics are important to better understand the condition, determine the associated negative outcomes, and ultimately develop interventions to effectively curb them.

nutritional status, and chronic inflammation [33]. One study assessing **biomarkers** of intestinal inflammation found that children in the upper quartile for all biomarkers grew 1.08 cm less than children with the lowest biomarker levels over 6 months. Here, the authors attribute this inflammation to gastrointestinal infections [34]. Similarly, infants residing in São Tomé Island showed a small but significant association between the intestinal inflammatory biomarker faecal alpha-1 antitrypsin (A1AT), and current helminth infections, and A1AT levels and stunting [9]. Despite this, a breadth of evidence demonstrates the ability of helminths to attenuate and regulate some of the damaging effects of the inflammatory response towards intracellular bacteria and viruses. Helminths may encourage epithelial regeneration via interleukin-II production, thus helping to contain bacteria within the gut lumen [35]. Therefore, whilst evidence exists supporting the hypothesis that parasites contribute to EED, more data are required to better understand the complexity and relationships between parasites, intestinal integrity, and stunting.

Parasitic infections and the gut microbiota composition may interact to contribute to stunting (Figure 1, pathway D)

After the initial demonstration that malnourished children in Bangladesh with associated suboptimal growth have immature microbiota profiles compared to healthy children [36], recent studies have divulged potential characteristics of the 'stunted' or 'malnourished' microbiota. Examples include a greater proportion of immunoglobulin A-recognised bacteria [37], a greater proportion of 14 taxa including a *Veillonella* species, a *Streptococcus* species, and *Rothia mucilaginosa* (which were also positively correlated to inflammatory protein levels) [38], a lower microbiota diversity, and higher proportional abundance of *Enterobacteriaceae* [39].

The gut microbiota is also implicated in the manifestation of EED [28]; on the one hand, reduced gut epithelial surface area and increased inflammation in a state of EED creates a gut environment that likely supports different microbes than a healthy gut [24], while on the other hand, an immature microbiota may exacerbate EED [40] (Figure 2). Rural Malawian children with EED have increased *Megasphaera*, *Mitsuokella*, and *Sutterella* abundance and decreased *Succinivibrio*, *Klebsiella*, and *Clostridium_XI* abundance versus children with no EED [41], suggesting a potential altered metabolic capacity of the gut microbiota. Similarly, a recent study conducted in Madagascar and the Central African Republic showed that EED and stunting in children are associated with small intestinal bacterial overgrowth, higher relative abundance of *Fusobacterium*, *Megasphaera*, and *Collinsella*, and lower levels of butyrate-producing Clostridia in stool [42].

Associative studies are now accompanied by preclinical experiments inoculating mice with faeces from children with and without phenotypes of stunting and EED, providing evidence that

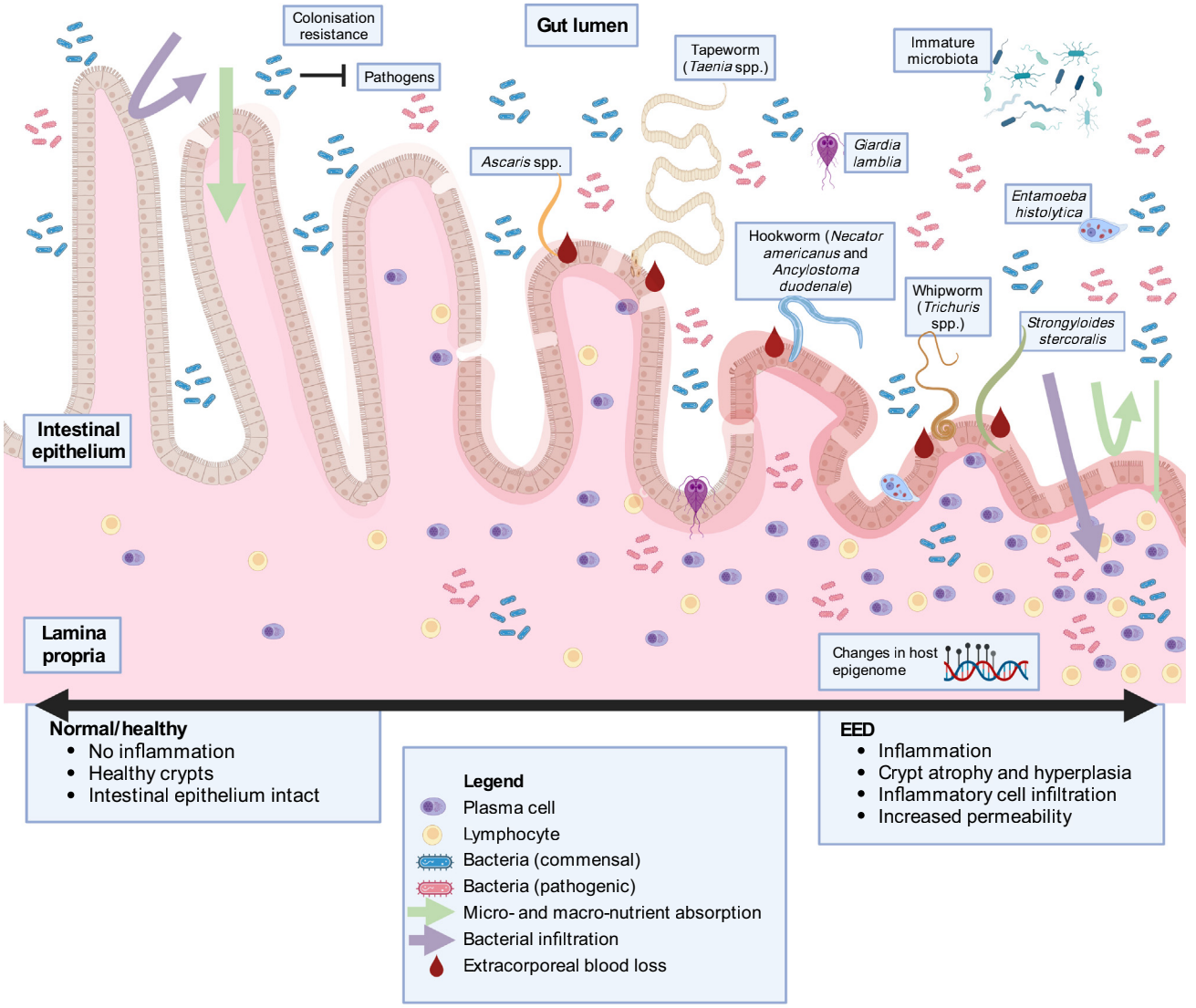


Figure 2. Proposed progression of environmental enteric dysfunction (EED) and microbiome changes in response to parasitic infection. The feeding behaviour of helminthic parasites in the gastrointestinal tract and invasion of the gut by protozoal parasites leads to damage of the intestinal epithelium. Chronic exposure to parasitic disease may result in inflammation, crypt hypertrophy, and increased intestinal permeability. Further, this ensuing damage may allow for bacteria to cross the intestinal epithelium, into the lamina propria, causing further infiltration of immune cells and subsequent inflammation. The resulting damage, characteristic of EED, may lead to reduced micronutrient and macronutrient absorption across the damaged and inflamed gut epithelium, exacerbating malnutrition. Furthermore, in the healthy gut, the microbiota provides colonisation resistance against invading pathogens. In a state of inflammation and EED in children, the composition of the microbiota is underdeveloped and less able to provide beneficial nutritional and immune support. All of this may impact gut epithelial and systemic changes in epigenetic regulation, affecting host gene expression and overall health. Figure not to scale.

the characteristics of the microbiota may be causal to these phenotypes [38,42]. This is unsurprising, considering the significant role of the gut microbiota in early child development, and its interactions with metabolism, the immune system, and protection against pathogens (Box 3). Based on this evidence, clinical trials are now evaluating whether prebiotic, probiotic and synbiotic treatments in early life can help to mitigate or prevent stunting by increasing the proportion of health-promoting bacteria in the gastrointestinal tract [43]. For example, a clinical trial administering a *Bifidobacterium infantis* strain to malnourished infants reported increased

Box 3. Gastrointestinal microbiota, early child development, and life-long health

The microbiota refers to the collection of microorganisms in a specific community. Of particular interest to human health is the composition of the gastrointestinal microbiota, which is dominated by bacteria. The gut microbiota plays important roles in human health, for example by breaking down fibres and other substrates from food, releasing energy and metabolites that become available to the host. In addition, the presence of commensal bacteria along the gastrointestinal tract makes it harder for pathogens to find a niche, a phenomenon known as 'colonisation resistance'. It is also widely accepted that the gut microbiota is critical for training and maintaining the human immune system and inflammatory responses, both locally in the gut and systemically [88]. The most readily available and most commonly used biological sample for gut microbiota studies is stool, despite the composition and metabolic capacity of the microbiota varying along the gastrointestinal tract. Defining microbiota 'signatures' belonging to specific diseases has been proven challenging, in part due to high interindividual variation in microbiota composition. However, differences in the gut microbiota composition between patients and controls have been reported for a wide range of disorders such as cancers, liver diseases, and obesity-related diseases.

The gut microbiota is established in early life, as microorganisms from the mother colonise the infant at birth. One of the main drivers of microbiota development is nutrition, with certain health-promoting microbes such as bifidobacteria thriving on complex sugars present in breast milk – human milk oligosaccharides. The timing of weaning and the types of complementary feeding will further influence the development of the microbiota. The first few years of life also represent a window for any other environmental influences, such as hygiene, medication (including antibiotic use), and enteropathogen infections with associated diarrhoea to influence microbiota maturation. After that time, the gut microbiota has reached a rather stable state and is less responsive to environmental influences or microbiota-directed therapeutics. Apart from its crucial role in colonising the infant at birth, the maternal microbiota has also been implicated in foetal programming during pregnancy, for example by providing metabolites that can enter circulation and reach the developing child through the placenta. Taken together, the perinatal period is crucial for the establishment of a healthy gut microbiota, and any environmental factors that alter the child or maternal microbiota may have long-term health consequences [89].

weight-for-age compared to placebo-treated infants [44]. The contribution of parasite infections to the microbiota immaturity observed in stunted children, the effect of microbiota-targeted interventions on susceptibility to parasite infection, and the co-occurrence and potential interactions between parasites, commensal microbes, and symptoms of EED in the aetiology of stunting are, however, yet to be fully elucidated (Figure 2).

Early studies noted co-occurrence of certain bacteria and intestinal parasites in malnourished children [45]. Because of their intercommunication with the host immune system, competition for nutrients, and overlapping habitat in the gastrointestinal tract, there are many potential interactions between intestinal bacteria and parasites [46]. Differences in helminth burden and associated host IgA responses between populations at risk for stunting has been proposed as an explanation for different proportions of IgA-targeted bacteria in these populations [37]. Similarly, higher proportional abundance of *Enterobacteriaceae* in children with severe acute malnutrition has been associated with low prevalence of *Giardia* spp. [39], potentially reflecting competition for resources [47]. However, as other studies found a positive association between *Enterobacteriaceae* and *G. lamblia* infection in mice [48], the relationship may be more complex [39]. A recent study in Thailand found increased relative abundance of *Akkermansia muciniphila* and *Bacteroides coprophilus*, and decreased *Bifidobacterium adolescentis* in the faecal microbiota of helminth-infected versus uninfected children [49]. In this population, with only a small number of stunted or wasted children, no significant association was found between helminth infection, microbiota diversity, and growth parameters [49]. In contrast, results from a mouse study suggested that changes in the gut microbiota composition associated with increased bile acid deconjugation may contribute to enhanced energy expenditure and reduced growth following early life *G. lamblia* infection [50]. Overall, suboptimal microbiota maturation may create an intestinal environment that is more susceptible to parasitic infection, while parasitic infection may in turn promote harmful and inhibit beneficial bacteria, potentially leading to a vicious cycle weakening the child's immune system and contributing to stunting (Figure 2). The importance of the relative timing of parasitic infections, deviations from healthy gut microbiota development, and symptoms of EED in modulating stunting

risk are to be elucidated. In general, there is a need for large longitudinal studies in populations vulnerable to stunting that assess microbiota development alongside comprehensive tracking of parasite burden and coinfections with other pathogens, as well as intervention studies (e.g., those involving deworming).

Parasites can cause chronic immune activation and systemic inflammation which contributes to stunting (Figure 1, pathway E)

Parasitic infection may directly – and via local gut inflammation as a result of EED, induce systemic inflammation and immune activation, sustained via the adaptive immune response [51], potentially leading to stunting (Figure 3). Immune activation is both energetically and metabolically costly and this may directly (or indirectly via reduced IGF-1) divert calories and nutrients away from other physiological processes such as linear growth, in an energetic trade-off [18,52]. In Amazonian children, an increased antiparasite adaptive immune response (total IgE level) was associated with growth reductions [53].

Parasites may deplete amino acids by using them up, or via increased requirement by the immune system during infection. Essential amino acids are critical for nucleic acid and hormone (e.g., IGF-1) biosynthesis and cellular replication, and in turn, child growth [32,54]. Parasites may utilise host amino acids; for example, *Giardia intestinalis* directly consumes arginine as an energy source [55]. Furthermore, amino acids are also important for intestinal barrier function, with scarcity potentially exacerbating the EED cycle by reducing intestinal injury repair. Low serum glutamine and arginine concentrations were associated with impaired barrier function and reduced linear growth in Brazilian children [32].

Parasitic infection can cause dysregulation of growth factors which are important for prenatal and postnatal growth. Immune activation upregulates acute-phase proteins, which inhibit IGF-1 in the liver, leading to growth hormone (GH) resistance and inhibition of longitudinal bone growth via effects on the growth plate, potentially reducing linear growth [56]. *Cryptosporidium* spp. infection

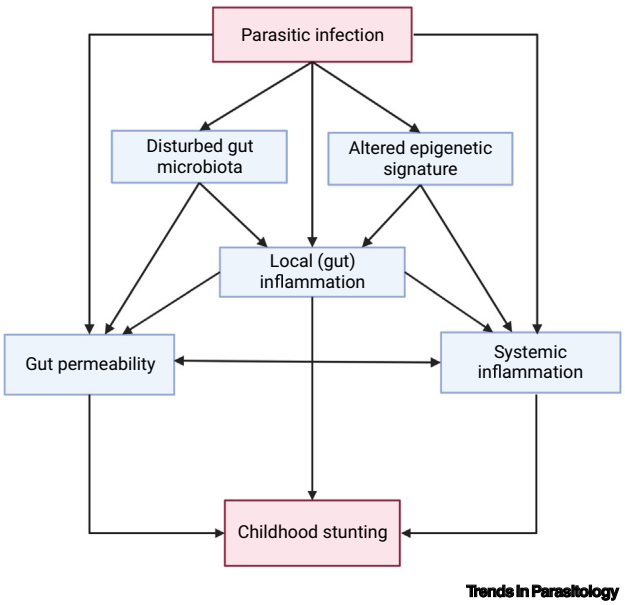


Figure 3. Potential mechanistic pathways leading from parasitic infection to childhood stunting. Gastrointestinal parasitic infection may increase gut permeability, local (gut) inflammation, and systemic inflammation directly. Parasites not residing in the gastrointestinal tract may cause systemic inflammation directly via activation of the immune response. Changes in the gut microbiome and epigenetic signature of the host may also be implicated in the pathway to stunting, via the gut and/or systemic inflammatory response. Gut permeability and inflammation (associated with environmental enteric dysfunction) and systemic inflammation may be causative in the pathway to stunting.

was indirectly associated with lower length-for-age through increased systemic inflammation and reduced plasma IGF-1 concentrations in Malawian infants [57]. Spanning these theories, a Gambian infant study found that three commonly assessed EED and immune markers (representing permeability, microbial translocation, and inflammatory response), together as a mechanism, predicted up to 55% of growth faltering [58]. Overall, EED and subsequent inflammation resulting from parasitic infection together may be an underappreciated contributor to stunting.

Parasites can cause anaemia, which contributes to stunting (Figure 1, pathway F)

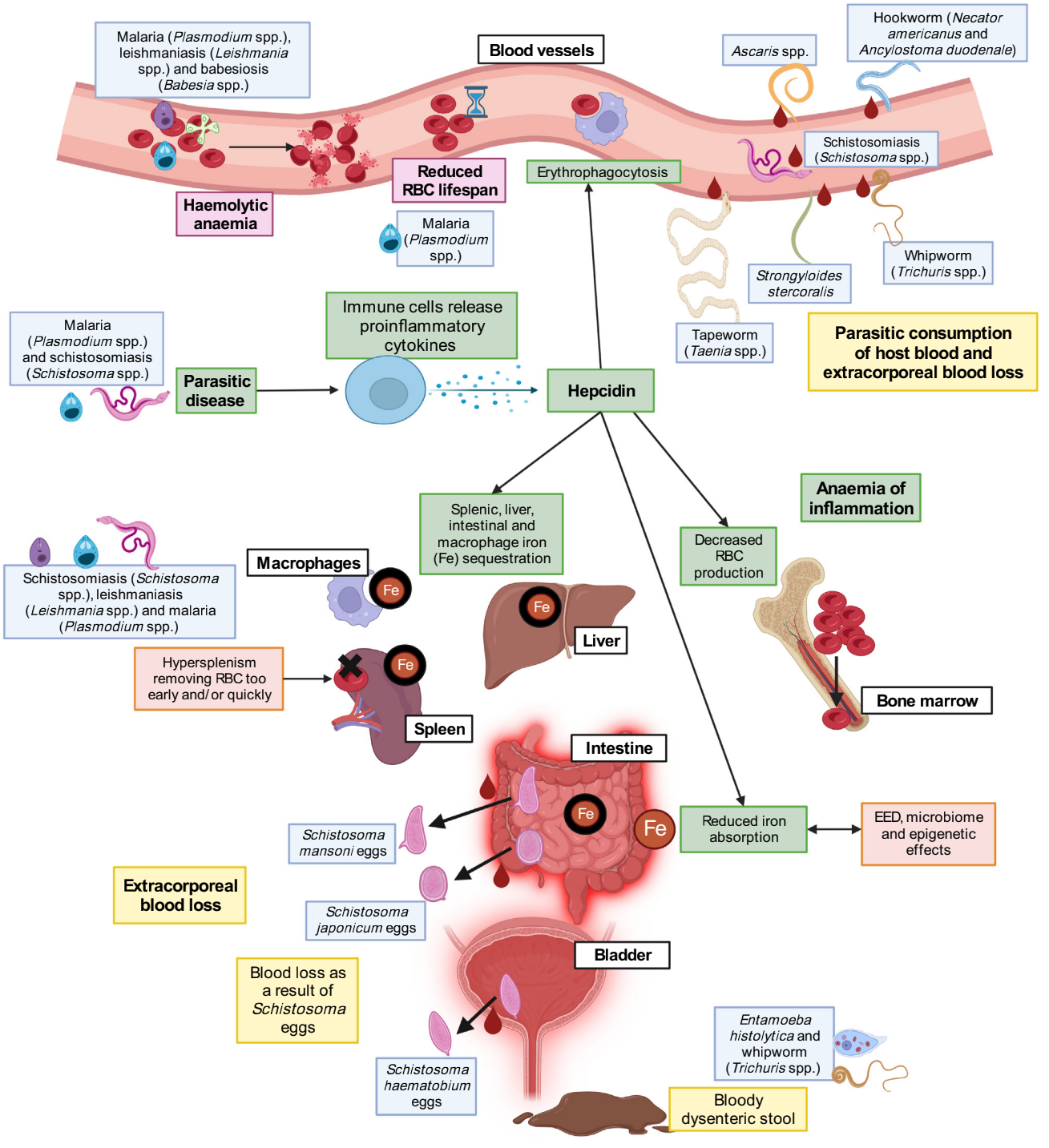
Anaemia and stunting often coexist [59], although it is difficult to distinguish cause and coexistence between these two conditions since they hold similar underlying determinants (e.g., malnutrition) indicative of a deficient environment. Anaemia may directly limit child growth via reduced oxygen-dependent cellular energy metabolism, imposing hypoxic conditions on cells. In mice, hypoxia contributes to embryonic growth retardation via interference with the IGF-1 system [60]. There is also ample evidence for helminths and parasitic protozoa, including parasitic protozoa residing in the blood (such as those causing malaria, leishmaniasis, and babesiosis), as risk factors for **anaemia** (Figure 4) [61–64]. Importantly, at least for malaria, there is evidence that infection increases stunting risk, although the exact mechanism remains elusive [65]. Indeed, in terms of a dynamic interplay, there is evidence that well-nourished children are less vulnerable to the adverse effects of parasite-induced iron loss, and, further, parasites are less able to establish in healthy non-anaemic hosts [16]. Furthermore, parasite-induced anaemia may be most critical in relation to the child's first 1000 days of life. Whilst exclusive breastfeeding has been shown to reduce the risk of child stunting [66], parasites may directly or indirectly reduce the quality or quantity of breastfeeding. For instance, parasite-induced maternal anaemia may reduce energy levels, leading to decreased exclusive breastfeeding and a lower weaning age [67]. Further, maternal anaemia may reduce quantity and nutritional status (e.g., protein content) of milk, as demonstrated in parasitised ruminants [68].

Parasites can alter epigenetic regulation which contributes to stunting (Figure 1, pathway G)

In recent years, evidence has accumulated for a role of DNA methylation (Box 4) in regulating childhood growth. For example, epigenetic signatures are associated with birth weight across studies [69]. Although there is much heterogeneity between study designs, a systematic review found some evidence for links between childhood growth outcomes, diet, socioeconomic position, and DNA methylation, with potential effects into adulthood [70]. In fact, evidence supports a role for DNA methylation in mediating the effects of exposure to malnutrition during gestation on growth and life-long metabolic health [71].

A recent pig study has shown that malnutrition, along with disrupted body growth and an altered gut microbiota composition, leads to changes in gene expression related to energy balance, cell growth, oxidative stress, and the immune response along the gastrointestinal tract [72]. Similarly to EED, epigenetics has thereby been put forward as a potential mechanism linking poor gut health in early childhood to stunting, although empirical research into this area remains lacking [40,73] (Figure 2).

Studies demonstrating the influence of parasitic infections on host epigenetic regulation relating to inflammation and the immune response are, however, accumulating [74]. Epigenetic states may confer susceptibility or resistance to parasite infection, while manipulation of host epigenetic regulation of gene expression by parasites may be an important pathway for host immune system evasion [75]. Active *Schistosoma haematobium* and *Ascaris lumbricoides* infection induces a specific DNA methylation signature in human primary immune cells, derived from tuberculosis-



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Box 4. Epigenetics, early child development, and life-long health

Whereas genetics refers to an organism's genetic sequence, epigenetics concerns characteristics in or on the DNA that can influence gene expression but do not involve the genetic sequence. The genome is essentially stable over an individual's lifespan and identical between cells in the body, while the epigenome largely drives differences between cells and tissues and can change in response to signals from the environment. Epigenetic regulation alters whether and how genes are expressed, for example through chemical modifications of the DNA or DNA-associated proteins – histones – that modify the three-dimensional structure of chromatin, or through noncoding RNAs which are involved in transcriptional and post-transcriptional regulation. The most well-understood epigenetic signal is DNA methylation – the addition of a methyl group to a cytosine nucleobase. Genomic locations that can be methylated are known as CpG (cytosine–phosphate–guanine) sites. DNA methylation in promoter regions is usually associated with a decrease in gene expression through blocking access to transcription factors.

Establishment, maintenance, and modification of epigenetic factors play a critical role in human development, health, and disease and are increasingly regarded as therapeutic targets. A specific set of CpG sites whose DNA methylation levels are highly correlated with age is known as the 'epigenetic clock'. Evidence is accumulating to support slow 'epigenetic ageing', linked to lifestyle factors such as nutrition, body mass index, and physical activity, as a biomarker of health. Similarly, early life environmental factors such as stress, drug exposure, infections, and diet are thought to affect the long-term risk of metabolic-, neurological-, and age-related disorders through DNA methylation, a phenomenon known as 'epigenetic programming'. Epigenetics is tightly linked to nutrition and metabolism, with micronutrients such as B vitamins acting as methyl donors and cofactors.

Some have proposed that maternal and paternal epigenetic marks may be directly heritable and could be responsible for transgenerational maintenance of metabolic phenotypes. Although epigenetic modifications are largely preserved across mitotic cell division, most epigenetic marks are erased in germline cell chromatin. Therefore, although some genes do remain methylated across meiosis, true transgenerational epigenetic inheritance remains controversial in humans. Despite this, perinatal establishment of epigenetic marks can be mediated by parental factors that are themselves under epigenetic control. Taken together, the perinatal period is a critical window for the establishment of epigenetic marks, and any environmental factors that alter the child or parental epigenic marks may have long-term health consequences [90].

exposed children that is suggested to mediate the disruption to immune functioning following helminth infection [76].

Infection during pregnancy may affect offspring immune functioning through epigenetic mechanisms, as suggested by murine studies showing that chronic schistosomiasis during pregnancy was associated with disruption to T-cell differentiation and decreased histone acetylation at the interleukin-4 promoter in offspring [77]. In a human study in Latin America, exposure to maternal *Trypanosoma cruzi* infection during gestation was linked to differential methylation of genetic loci involved in haematopoietic cell differentiation and immune functioning in the umbilical cord. The authors suggest that even without direct exposure to the parasite, newborns from *T. cruzi*-infected mothers may have long-term alterations in immune functioning through epigenetic programming [78]. Although no difference in birthweight was found between maternally exposed

Figure 4. Proposed mechanisms by which parasites may cause and/or contribute to anaemia. Certain parasite species (blue boxes) may contribute to anaemia of the host via several mechanisms. Firstly, parasites may contribute to anaemia via consumption of host blood and/or extracorporeal blood loss (yellow boxes). Helminths inhabit blood vessels and/or feed directly on red blood cells (RBCs) within host vessels. This causes loss of blood directly to the parasite, and extracorporeal blood loss at the feeding site due to epithelial damage, and secretion of anticoagulases allowing for continued bleeding at the site. Further, spined *Schistosoma* eggs penetrate host tissues, through the intestinal walls into the faeces (*Schistosoma mansoni* and *Schistosoma japonicum*) or bladder into the urine (*Schistosoma haematobium*), rupturing blood vessels and causing extracorporeal blood loss. Additionally, certain parasites are known to cause blood loss as a result of bloody diarrhoea, proposed to be a consequence of mucosal damage and inflammation. Secondly, certain parasites may infect RBCs, causing destruction via autoimmune **haemolysis** (haemolytic anaemia), and reductions in RBC lifespan (purple boxes). Thirdly, parasitic disease may induce a proinflammatory response (green boxes). This is characterised by proinflammatory cytokine (particularly tumour necrosis factor-alpha and interleukin-6) production and upregulation of the protein hepcidin. Hepcidin causes **erythrophagocytosis** of RBCs, decreased RBC production in bone marrow, and sequestration of bioavailable iron (Fe) to storage forms (trapping the iron) in the spleen, liver, and in macrophages, causing a decrease in intestinal absorption of iron. Iron is also trapped in intestinal epithelial cells and may be lost during normal cell turnover. This leads to a decreased iron bioavailability to meet the needs of **erythropoiesis**, leading to anaemia. Environmental enteric dysfunction (EED), the microbiota, and epigenetic effects can further influence intestinal iron absorption. Finally, hypersplenism, or an overactive spleen resulting from parasitic infection, may remove RBCs too quickly and/or early, leading to anaemia (orange box). Figure not to scale.

and non-exposed babies, alterations in immune functioning in early life are likely to affect child growth and development.

To our knowledge, there are no studies to date investigating the interaction between parasitic infections and host epigenetic regulation in the context of early life malnutrition and stunting. Considering the evidence for parasitic manipulation of host epigenetics related to immune functioning, and the fact that early life immune functioning is crucial for healthy development, this is worth investigating. Furthermore, epigenetic regulation is involved in a wide range of physiological systems, including nutrition and metabolism, and is thought to mediate intergenerational effects of environmental exposures (Box 4) that may be worth studying in relation to parental parasite infections and growth in early life.

Concluding remarks

Childhood stunting is an intractable problem, and to improve our chances of reaching the World Health Assembly targets we must understand and address the aetiology. Parasites are among a number of enteropathogens which may contribute, to varying degrees, to childhood stunting. Here, we present mechanistic pathways from parasitic infection to stunting, via malnutrition, alongside EED and its potential influence on the immune, metabolic, and hormonal systems. Further, we have implicated anaemia, the microbiome, and epigenetics. Due to heterogeneous evidence from the literature, and potential interactions between both direct and indirect factors, there is difficulty establishing causality. More evidence is required (see Outstanding questions), preferably from longitudinal studies, to capture this complexity.

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Declaration of interests

The authors declare no competing interests.

Outstanding questions

Which parasite species are most likely to influence stunting outcomes – and should therefore be prioritised in future studies?

Are stunting outcomes influenced by helminth-associated immune modulation?

To what extent does anaemia cause stunting, or are anaemia and stunting two related conditions with similar determinants?

Within the first 1000 days of life, is there a critical period when parasitic infection may influence stunting?

How do parasites and commensal microbes interact along the length of the gastrointestinal tract to potentially contribute to stunting, and what does that mean for our interpretation of the majority of human studies in this field performed on stool samples?

What is the effect of parasitic infections on epigenetic alterations in various tissues and cell types in the gut and beyond, which might be relevant to stunting in the host?

What might be the potential contribution of maternal parasitic infections to stunting in children, and how may the maternal microbiota and epigenome mediate that relationship?

Now that international guidelines recommend anthelmintic treatment of pregnant women and children from 2 years of age, could multicountry randomised controlled trials provide evidence for potential associations between helminth infection and stunting?

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