RESEARCH ARTICLE

Low lung function in the developing world is analogous to stunting: a review of the evidence [version 1; peer review: awaiting peer review]

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Abstract

Background: Low vital capacity, one of the consequences of restricted lung growth, is a strong predictor of cardiovascular mortality. Vital capacity is lower in the developing world than the developed world, even after adjusting for height, weight and gender. This difference is typically dismissed as ethnic variation, adjusted for by redefining normal. Whether this is a consequence of stunted lung growth, rather than genetically smaller lungs, has not been investigated in detail. Therefore, we sought to compare factors implicated in both stunting and lung development, particularly in the developing world.

Methods: We conducted a manual screen of articles identified through Google Scholar and assessed risk of bias. No language restrictions were applied, so long as there was an associated English abstract. We queried VizHub (Global Burden of Disease Visualization Tool) and Google Dataset search engines for disease burden and genome wide association studies. The scope of the article and the heterogeneity of the outcome measures reported required a narrative review of available evidence. To the extent possible, the review follows PRISMA reporting guidelines.

Results: Early life influences operate in synergism with environmental and nutritional factors to influence lung growth and development in children. Low lung function and stunting have common anthropometric, environmental and nutritional correlates originating during early development. Similar anthropometric correlates and shared chronic inflammatory pathways indicated that the two conditions were analogous.

Conclusion: The analogy between poor lung function and stunting is conspicuous in the developing world, where malnutrition lies at the center of non-achievement of growth potential, susceptibility to infectious diseases and intrauterine programming for metabolic syndrome. The common pathological mechanisms governing stunting and lung function deficits counter the idea of redefining the normal for lung function measurements.

Keywords
Stunting, malnutrition, low lung function, restrictive lung function, interventions for low lung function, population health, developing nations
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Introduction

Forced Vital Capacity normalized to height was found to be an independent indicator of cardiovascular risk in the Framingham Heart Study Cohort. A series of landmark studies since then have cemented the role of spirometry as a prognostic tool for non-communicable disease outcomes in general and cardiovascular disease outcomes in particular\(^1\text{–}^4\). This has allowed lung function to transcend its status as an indicator of respiratory disease severity to a predictor of all-cause and cause specific mortality.

Adverse socio-economic and environmental factors prevalent in the developing world obscure the definition of a phenotype ‘healthy’ population. Here, a non-invasive indicator such as lung function, influenced by perinatal growth conditions, growth faltering, repeated infections and malnutrition resulting in a chronic inflammatory state, reliably reflects health across the life course.

Defined as height-for-age more than two standard deviations below the WHO Child Growth Standards Median, stunting is an equally powerful proxy for similar exposures encountered early in the life course. As both lung function and early growth are strongly associated with and defined by linear growth, influenced by similar perinatal factors, and culminate in an elevated risk of non-communicable diseases sharing chronic inflammatory origins, the associations and intersections between poor lung function and stunting could reveal an analogy useful in designing common interventions for both conditions.

The analogous nature of restrictive lung function and stunting would imply that variations in lung function across communities might have pathological origins. Assumptions regarding the reference population being healthy are central to the generation of ‘normal’ spirometry values for a given population. These assumptions are violated in populations experiencing adverse developmental conditions leading to growth faltering and undiagnosed asymptomatic cardiometabolic disease. Therefore, this analogy merits detailed investigation.

Methods

We searched through Google Scholar and PubMed between June 2019-December 2019, with the last search performed on December 29\(^{\text{th}}\) 2019. The search was conducted in two main phases. A primary search was conducted to identify the main risk factors implicated in stunting, growth faltering and reduced lung function, using keywords such as “stunting”, “lung function”, “lung capacity”, “forced expiratory volume”, “forced vital capacity”, “lung development” and “growth faltering”. We also conducted a brief analysis of GBD 2017 data to describe the role of socioeconomic influences affecting both conditions.

After grouping risk factors, we identified relevant articles using the search terms given in Table 1.

Eligibility criteria for studies

Randomized controlled trials, cohort studies, case-control studies and cross-sectional studies in which participants were aged 0–25 years were included. In addition, the following inclusion criteria were used:

• English abstract available
• Human studies
• Participants of studies are children aged 0–25
• Published after 1990
• Papers contained original data and were full-length peer-reviewed

Studies with unclear methodologies were excluded.

Outcomes of interest

The following outcomes of interest were included and assessed:

• Lung function as measured by spirometry (e.g. FEV\(_1\), FVC, PEF, FEF\(_{25–75}\) and FEV\(_1/FVC\))
• Airway resistance as measured by R\(_5\), X\(_5\), R\(_{20}\), X\(_{20}\) and similar derivatives
• Respiratory infections

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<table>
<thead>
<tr>
<th>Table 1. Search terms.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sections</strong></td>
</tr>
<tr>
<td>Maternal nutrition and anthropometry</td>
</tr>
<tr>
<td>Nutrition</td>
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<tr>
<td>Anthropometry</td>
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<td>Environmental factors</td>
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<td>Sanitation</td>
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<td>Genetic</td>
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<td>Epigenetic factors</td>
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• Respiratory mortality
• Chronic obstructive pulmonary disease (COPD)
• Stunting
• Related comorbidities

Synthesis of results
Studies meeting the inclusion criteria were grouped according to the risk factors identified during the primary search. Risk factors included intrauterine growth restriction, malnutrition, sanitation, air pollution, cigarette smoking, genetic and epigenetic factors. Subsequent searches were then performed to examine the relationship between each set of risk factors with both stunting and lung function.

Evidence from community-based studies and mechanistic studies were then examined together to identify the interrelationships between stunting and lung function and organized into sections according to chief risk factors implicated in both conditions. Consequently, the results were summarized in a narrative form.

Results
Higher burden of stunting and low lung function in the developing world indicates the role of socioeconomic influences
Evidence of reduced lung function in the developing world emerged from the Prospective Rural Urban Epidemiological Study (PURE), which investigated global variation in lung function in healthy populations by region. Compared with North American or Europe, FEV1 adjusted for age, height and sex, was 31.3% lower in south Asia, 24.2% lower in Southeast Asia, 12.8% lower in East Asia, 20.9% lower in Sub-Saharan Africa, 5.7% lower in South America, and 11.2% lower in the Middle East. Similar and larger differences existed for FVC8.

While it is conceivable that low lung function in apparently healthy communities in developing nations represents a healthy but genetically smaller lung than western populations, this should not be assumed given the high rates of chronic respiratory and cardiovascular disease mortality.

The prevalence of reduced FVC was strongly associated with education level and biomass index in a study assessing the prevalence of reduced FVC and associated risk factors in the African population7. In the Burden of Lung Disease study, the prevalence of a restrictive spirometry varied widely by site and gender, affecting as few as 4.2% of males in Sydney to as many as 48.7% of females in Manila10.

Indeed, across Burden of Obstructive Lung Disease (BOLD) study sites, with NHANES III as the reference data, Restrictive Lung Function (RLF), defined as Forced Vital Capacity<80% of predicted, was extremely common in the developing world, but less so in affluent nations11,12. Despite the existence of a clear socioeconomic dependent pattern, the use of different reference equations for populations experiencing large variations in developmental conditions could obscure the true prevalence of reduced lung function.

Stunting was estimated to affect 21% of children under 5 years of age globally, more than half of whom live in Asia and a third in Africa. It is distinguished from other nutritional disorders that affect the life course, in that it is irreversible if not addressed within the first 1000 days. Even if catch-up growth does occur, it predisposes the individual to an elevated risk of metabolic dysfunction in later life13. The human capital loss resulting from stunting is likely to overwhelm health systems of developing nations, ill-equipped to rehabilitate the 39.6 and 96.8 million affected children in low-income and low-middle-income countries, respectively. In comparison, 2.1 million children are affected in high-income countries. This is because indicators of stunting such as low per capita income, household food insecurity, repeated infections due to substandard sanitation and unsafe water, and poor maternal health and birth outcomes, follow a socio economic dependent pattern14. Here stunting differs from restrictive lung growth in that except for its contribution to a chronic inflammatory state, it is reversible if addressed during the first 1000 days of life, whereas the consequences of restrictive lung growth persist throughout the life course.

An analysis of the GBD 2017 data, showed a relationship between Socio-Demographic Index (a development metric used by the Global Burden of Disease Study), and deaths due to respiratory tract infections, stunting, wasting, preterm birth, diarrhea, suggesting that both disease, and risk factors implicated in both conditions followed a socio economic dependent pattern (see Extended data)8.

As a sequel to intrauterine growth restriction (IUGR), stunting mirrors the pathology of restrictive lung function. When accompanied by rapid weight gain during infancy and later childhood it is an intermediate predictor of risk of metabolic dysfunction during adulthood. Early manifestations such as low birth weight, short stature and a high Cormic index (upper to lower body segment ratio) too are common to restrictive lung function and stunting. Once the foundation of altered metabolic programming is laid during the perinatal period, continued exposure to adverse environmental conditions result in a heightened inflammatory state and predispose individuals to a high risk of chronic metabolic diseases.

This exacerbation of disrupted metabolic programming during development has been a major mechanism influencing epidemiological transitions in the developing world, where populations traditionally experiencing high rates of IUGR, malnutrition and stunting are now confronted with an increasing prevalence of chronic metabolic diseases. It is important to note that nations in different stages of epidemiological transition would exert opposing effects on the association between SDI and deaths due to chronic diseases.

This is observed in the moderately high, positive correlation between SDI and Ischemic Heart Disease (GBD 2017). This association would likely grow and stabilize in future, as most nations
would tend to a lower epidemiological transition level (ETL). The interplay between socioeconomic status and variations in ETL across populations/communities needs to guide the design of interventions for both stunting and restrictive lung function.

Common mediators of stunting and low lung function: interplay of ethnicity, environment and access
In the arid regions of rural Tanzania, stunting mediated growth retardation was associated with cultivated land size, gender and age of the child, duration of breastfeeding, household size, use of iodized salt, the distance to a water source, literacy status and BMI of the mother\textsuperscript{15}. Stunting influenced deviations from predicted lung function values among 208 stunted and 365 non-stunted children in Tibet. These differences were compatible with the effects of retarded growth and lung maturation characteristic among stunted children\textsuperscript{16}.

Similarly, a Peruvian study with data from 553 asthmatic children, reported an association between food insecurity and poorer Asthma control\textsuperscript{17}. Asian children in low SES environments, with indications of stunting, such as short stature and low BMI, had the highest FEV\textsubscript{1}/FVC ratio on average. This is because exposures implicated in stunting result in reduced lung growth and low FVC values, and due to their limited and indirect effect on FEV\textsubscript{1}, result in a high FEV\textsubscript{1}/FVC ratio. Therefore, stunting manifests with restrictive lung function, as low values of FVC with normal to high FEV\textsubscript{1}/FVC ratio\textsuperscript{18}.

Chronologically, IUGR results in smaller organs and low birth weight infants with a higher susceptibility to diarrheal and lower respiratory tract infections. Both these intermediates lead to repeated growth faltering and reinfections, which are implicated in stunting. While these narratives confirm the existence of a common socio economic dependent pattern in stunting and restricted lung growth, evidence indicating causality is needed\textsuperscript{19–22}.

IUGR: The cornerstone for stunting and low lung function
The foundation for compromised (‘brain sparing’) organ growth and metabolic dysfunction is laid during the perinatal period. According to the fetal origins hypothesis the fetus adapts itself in response to variations in nutrient and oxygen supply and its development is closely regulated by complex interactions between maternal nutritional status, endocrine and metabolic signals and placental development\textsuperscript{23}. ‘Size at birth’ and related derivatives such as small for gestational age (‘SGA’) reflect metabolic and anthropometric programming in the intrauterine environment (see Figure 1).

IUGR results in metabolic reprogramming during periods of rapid cell proliferation and differentiation. In later life, exposure to IUGR works synergistically with ante-natal factors such as malnutrition and infections during early life, to result in a compounded risk of stunting. Maternal anthropometric indicators of IUGR, such as short maternal stature, low body mass index and poor weight gain during pregnancy contribute to a higher risk of SGA and stunting in the child\textsuperscript{24–29}.

It is well documented that the timing of undernutrition determines the pattern of growth retardation. Babies with large heads are speculated to have grown more rapidly during early gestation such that their higher demand for nutrients during later gestation remains unmet\textsuperscript{30}. Early undernutrition results in small but normally proportioned animals, while later undernutrition results in selective organ damage. Babies who have experienced undernutrition in later gestation therefore have small lungs for their bodies\textsuperscript{31}.

Besides other consequences of disparate nutrient supply, thymus growth impairment during late gestation disrupts the differentiation of specific thymus-derived helper lymphocytes (Th) from Th2 to Th1, leading to exaggerated IgE responses and hyper responsive airways in later life\textsuperscript{32,33}. This explains the

![Figure 1. Intrauterine growth restriction contributes to both low lung function and stunting.](image-url)
association linking larger head circumference and increased serum IgE concentrations to the development of asthma in later life, while low birth weight is known to be associated with reduced FEV and FVC\textsuperscript{30,34,35}.

A study conducted by Todisco \textit{et al.} compared the lung function of former pre-term and full-term children at 12.5 years of age and found higher rates of low lung function in the pre-term birth category compared to matched siblings delivered at term, indicating that lung function deficit at birth persists into early adolescence. This is because birth offsets one of the first and most profound gene environment interactions where the delivery of oxygen via the placenta is transferred to the lung, a process that is adversely affected by preterm birth. Evidence from expression profiling studies suggests that it is after the expression of developmental genes that genes involved in oxygen transport, genes coding for antioxidant species and genes involved in host defense are expressed, signaling a strong dependence on a developmentally mature and functional lung, which in preterm births is usually compromised. Additionally, supplemental oxygen therapy for preterm neonates not only causes inadvertent oxidative damage but also results in a highly simplified alveolar epithelium because of aberrant immune response. This aberrant response additionally suppresses angiogenic factors\textsuperscript{36} interfering with healthy lung development. Maternal hypertension and pre-eclampsia, often implicated in preterm birth and low birth weight infants can be indirectly implicated in contributing to low lung function during childhood\textsuperscript{37,38}.

In addition to direct effects such as a higher risk of preterm birth, compromised organ growth and stunting IUGR also exacerbates the adverse consequences of preterm delivery and postnatal hyperoxia. Preterm birth renders growth-restricted infants vulnerable to infections, leading to growth faltering, triggering a cycle of infection and undernutrition, hindering the attainment of maximum growth potential. IUGR directly results in brain sparing growth and restrictive lung growth but appears to set the foundation for stunting. This, when sustained through malnutrition and frequent infections leads to stunting as an outcome.

**Malnutrition and anthropometry: Manifestations of stunting and low lung function**

Nutritional insults throughout the life course initiate and sustain the pathophysiology of both stunting and restrictive lung growth. The Avon Longitudinal Study of Parents and Children reported positive associations between maternal intake of zinc and childhood FEV\textsubscript{1} and FVC\textsuperscript{39}. FVC was found to be higher in children who were breastfed for 6 months or longer as compared to children breastfed between 2 to 4 months, among 4464 children embedded in a population-based prospective cohort\textsuperscript{40}. Postnatal vitamins A, E and D supplementation was observed to have the greatest effect on alveolar development and capillary growth, which are critical determinants of FVC\textsuperscript{41}. In growth restricted infants, as alveolar numbers continue to increase after birth, postnatal nutrition interventions may influence growth and affect the size of the adult lung\textsuperscript{42}.

Like restrictive lung function, growth faltering in stunting is compounded by suboptimal breastfeeding in the first months of life, a poor and unbalanced diet and/or insufficient vitamin and/or micronutrient intake and frequent infections during early childhood. In the Maternal and Child Undernutrition Group (a review of cohort studies from five low- and middle-income countries – including Brazil, Guatemala, India, Philippines and South Africa\textsuperscript{43}) SGA at birth and stunting were linked with short adult stature, reduced lean mass, which are also phenotypic correlates of low lung function.

**Manifestations in body composition and altered metabolic programming**

Indeed, similar phenotypic adaptations conspicuous in anthropometry and body composition support the analogy between stunting and restricted lung growth (see Figure 2). For instance, stunted growth has disproportionate effects on FVC as

![Figure 2. Stunting and restrictive lung function (FVC <80% of predicted) - anthropometric correlates.](image-url)
compared to FEV₁. This is because exposures implicated in stunting result in reduced lung growth and low FVC values, and due to their limited and indirect effect on FEV₁, result in a high FEV₁/FVC ratio. Therefore, stunting manifests with low values of FVC—indicating smaller lungs, as opposed to a smaller FEV₁/FVC ratio, characteristic of airway obstruction\textsuperscript{41}. Analogous adaptations characterized by shorter limbs and sitting height are observed in both stunting and restrictive lung function\textsuperscript{44}. The positive association between age at peak adiposity and higher FVC, FEV₁ and FEF\textsubscript{25-75} implies that IUGR, followed by rapid weight gain during childhood results in poor lung function\textsuperscript{45}. Besides being shorter, stunted children have shorter leg length, resulting in a longer sitting-height-to-stature ratio, which is known to influence population level differences in lung function\textsuperscript{46}.

With the exception of obese children exhibiting a reduction in static lung volume with degree of obesity, there exists a phase of transition from a positive to inverse association\textsuperscript{47-52}. In the PIAMA birth cohort\textsuperscript{50} (n=1288, at 12 years), high BMI and waist circumference were found to be associated with higher FVC, particularly in females. Girls with higher waist circumference and BMI at ages 8 and 12 had significantly higher FVC at age 12 than girls with normal BMI at both ages, suggesting that the inverse relationship between high BMI, waist circumference and FVC-FEV1 develops after age 12\textsuperscript{53}.

The effect of stunted height on lung function growth is further compounded by maturational delays, particularly during the onset of adolescent growth spurt in stature. During puberty, dysynaptic growth appears to be more conspicuous in stunted children as compared to normal children, as stunted children are not only shorter but also more likely to exhibit delayed increment in muscular strength and lung maturation\textsuperscript{54,55}. However, while the phenotypic correlates of stunting recede due to rapid catch up growth during early childhood, indicators of restrictive lung function persist late into the life course.

Air quality and environmental toxicants

Inhalation of fine particles (particulate matter with diameter ≤2.5 μm; PM\textsubscript{2.5}) can induce oxidative stress and inflammation, and may contribute to onset of preterm labor and other adverse perinatal outcomes. This triggers a chain of events leading to SGA infants with poorly developed lungs (see Figure 3). Exposure to environmental toxicants is another factor common to the origin of both low lung function and stunting. It impacts health through both inhalation and trans-placental transmission in utero\textsuperscript{56}. Low birth weight is also an independent risk factor for stunting, particularly in developing nations with both high air pollution and malnutrition contributing to IUGR.

Low birth weight was higher among women who delivered in facilities where PM\textsubscript{2.5} concentrations were above the median (i.e., >12.0 μg/m\textsuperscript{3}) compared with women delivering at facilities with average PM\textsubscript{2.5} levels <6.3 μg/m\textsuperscript{3}. In China, the country with the largest range of PM\textsubscript{2.5} exposure levels, both preterm birth and LBW were significantly higher among women with estimated exposure to at least 36.5 μg/m\textsuperscript{3} of PM\textsubscript{2.5} compared with women in the lowest quartile of exposure (<12.5 μg/m\textsuperscript{3})\textsuperscript{57}. The ENVIRONAGE birth cohort too reported an association between in utero PM 2.5 exposure and placental mitochondrial DNA methylation in 381 mother-newborn pairs\textsuperscript{58}.

In addition to mechanisms operating through pre-term birth, exposure to air pollution also directly affects lung function growth. In a Californian study in 232 asthmatic children, fetal exposure to PM\textsubscript{2.5} during the first trimester of pregnancy was found to be associated with a lower peak expiratory flow volume between ages 6–11 years\textsuperscript{59}. A 90 mL lower FEV₁ at 5 years was observed in the Krakow birth cohort, comprising 176 exposed children of non-smoking mothers\textsuperscript{60}, while a 60mL reduction in FEV₁ was found in Swedish children exposed to higher concentrations of PM\textsubscript{2.5} during the first year of life. These children were likely to have FEV₁ and FVC less than the lower limit of normal at age 16. Children of the same cohort exhibited higher peripheral airway resistance from impulse oscillometry (R\textsubscript{S}-R\textsubscript{L}) at age 16\textsuperscript{61}.

In non-cigarette smoking women with lifelong biomass exposure, a direct link between childhood exposure to PM and an increased susceptibility to adult respiratory disease (including COPD) was observed\textsuperscript{62}. In experimental studies conducted on mice with either pre or postnatal exposure to traffic-related PM, significant alteration of alveolar structure and changes in the elastic properties of the lungs were observed\textsuperscript{63}.

Newborns exposed to PM\textsubscript{10} in utero exhibited a higher oxygen demand, indicated by higher minute ventilations and tidal flows. These changes were similar to those in premature infants with broncho-pulmonary dysplasia, infants with smoking mothers and in animal models of pre-natal nicotine exposure and were also indicative of increased airway resistance (smaller

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**Figure 3.** The role of air pollution in stunting and RLLF.
airways), decreased compliance (smaller/stiffer airways) and disruption of factors that directly influence control of breathing.

Air pollution induced oxidative stress and localized or systemic inflammation in the mother could affect permeability of the blood-air barrier, leading to an increase in fetal breathing movements and reduced alveolarisation. Reduced alveolarisation could also be a result of systemic inflammation, which disrupts placental blood flow and affects the nutrient transfer to the fetus, influencing intrauterine growth and future lung function.

Post birth, pre-term or small for gestational age children in developing nations traditionally experiencing the effects of intergenerational malnutrition, are also more likely to be exposed to a higher level of ambient PM 2.5 both in utero and during early childhood, and exhibit higher risk for anthropometric failure, even after accounting for various confounding characteristics.

Maternal smoking and tobacco consumption

*In utero* exposure to nicotine remains the single, most important and potentially preventable insult to the developing lung. It is a major cause of sudden infant death, LBW, preterm delivery and IUGR. In 2015, out of 933 million daily smokers, 5.4% were women, while 72.5% of pregnant women who smoke, were daily smokers throughout their pregnancies and around 2% of women smoking throughout their pregnancies resided in South East Asia and Africa.

In addition to IUGR and low birth weight, maternal smoking was found to increase the risk of COPD in offspring by 1.7, and in terms of airflow limitation was equivalent to 10 years of personal smoking by the offspring. The effect of smoking on lung function may transcend generations, as Grand-maternal smoking not only increases the risk of maternal asthma, but also raises the risk of asthma in her offspring even if the mother herself does not smoke.

Gender is an effect modifier in the association between *in utero/postnatal* exposure to secondhand smoke, with a stronger association in males than in females. *In utero/postnatal* exposure to second hand smoke results in a 64.6% odds of reduced FVC in males and a 21.6% odds of reduced FVC in females.

The immediate effects of tobacco exposure are difficult detect because children exposed to tobacco smoke do not necessarily manifest reduced lung function or increased propensity for respiratory morbidity possibly owing to differences in maternal and fetal susceptibility. It is also difficult to distinguish between the effects of pre and postnatal tobacco exposure because women who smoke during pregnancy continue to do so after childbirth.

However, it is clear that multiple inflammatory insults from tobacco exposure reduce airway caliber and disrupt fetal immune responses inducing prematurity and low birth weight, resulting in growth restricted infants. As IUGR and size at birth predict risk of stunting and restrictive lung function, controlling maternal smoking may influence both outcomes substantially (see Figure 4).

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**Figure 4. In utero nicotine exposure, RLLF and Stunting**

- Reduced Lung Growth
- *Reduced alveolar capacity*
- *Lower capillary density*
- *Abnormal airway branching*
- *Increase in airway smooth muscle proliferation*
- *Collagen deposition resulting in low FEV1*
- *Reactive airways*

- Stunting
- *Sub-optimal development of fetus*
- *Increased oxidative stress*
- *Reduced nutrient and oxygen flow to fetus*
The impoverished gut

Stunted children inhabit unhygienic settings and live in conditions of acute deprivation where environmental enteric dysfunction (EED) is prevalent\(^1\). EED is a result of sustained and frequent low inoculum exposure to a wide range of pathogens, mostly through contaminated food and water. The resulting low grade infection causes both systemic and gut inflammation leading to intestinal leakiness, heightened permeability, nutrient malabsorption and disrupted immunomodulation\(^2\).\(^3\). Frequent infections, vaccine failures and chemotherapy lead to a disruption in the homeostasis of the gut microbiota, a phenomenon referred to as dysbiosis.

The gut microbial community possesses enzymatic machinery for assimilating a variety of dietary nutrients leading to the release of multi-functional metabolites in the host. EED compromises gut integrity and when coupled with immaturity and dysbiosis of the gut microbiome, hampers nutrient assimilation\(^4\).\(^5\).\(^6\). This leads to a pattern of growth faltering and recurrent infections leading to a decline in length-for-age Z scores, particularly among children between 18–24 months of age.

Although the mature gastrointestinal tract and the respiratory tract (RT) have different environments and functions, they have the same embryonic origin and therefore share structural similarities. Thus, similar mechanisms operating bi-directionally along the gut-lung axis allow GI microbiota to play a key role in immune adaptation and initiation at other distal mucosal sites such as the lung.

This cross-talk along the gut-lung axis happens during early development, possibly during the first two years of life, which are critical to the stabilization of an individual’s microbiome. This hypothesis is supported by the existence of a strong correlation between low microbial diversity in the gut during early infancy and an asthmatic phenotype in childhood and the simultaneous manifestation of both respiratory and GI disease symptoms during adulthood\(^7\).\(^8\).\(^9\).\(^10\).\(^11\).

EED further amplifies the effects of growth faltering and poor lung development in the developing world by reducing the efficacy of oral vaccines, possibly even leading to vaccine failure (see Figure 5). Among Bangladeshi infants, EED was linked to the reduced efficacy of oral polio and rotavirus vaccines\(^12\). Barriers to nutrient absorption and disrupted immunomodulation thus affect both growth and lung development. Although the gut–lung axis is only beginning to be understood, emerging evidence indicates that there is potential for manipulation of the gut microbiota in the treatment of lung diseases.

The effect of gut microbiome on nutrient assimilation is relevant to the implementation of oral vaccination and nutrition programs in the developing world where EED is rampant.

**Genetic and molecular modulators of perinatal lung maturation**

The genetic and epigenetic correlates of both conditions largely appear to encode physiological responses to early nutritional and environmental insults.

Around 50 genes for lung function and 13 genes influencing the indicators of stunting were identified, and seen to influence similar early developmental pathways and nutrient absorption. Of these, three genes—\(FGF21\) (cellular proliferation, survival, migration, and differentiation), \(FUT2\) (cell-cell interaction, interaction with intestinal microbiota) and \(IGF1/IGF2\) (growth promotion, 2DG transport and glycogen synthesis in osteoblasts)—were found to be common to both conditions (see Table 2). The individual effect sizes of these genetic and epigenetic

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**Figure 5.** How the impoverished gut mediates stunting and low lung function.
<table>
<thead>
<tr>
<th>Gene (Stunting)</th>
<th>Gene (Lung Function)</th>
<th>Function</th>
<th>B (SE)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGF-1</td>
<td>FGF21</td>
<td>Development and differentiation of many types of lung cells, including airway basal cells, club cells, alveolar epithelial cells, and fibroblasts.</td>
<td>0.41</td>
<td>-1.9E-13</td>
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<tr>
<td></td>
<td>FGF21</td>
<td>Decreased protein intake, increased carbohydrate intake, increased fat intake, and marginally decreased protein intake.</td>
<td>-2.12 (0.21)</td>
<td>1.4E-06</td>
</tr>
<tr>
<td></td>
<td>BMP6</td>
<td>Calcium ion binding and epithelial growth factor receptor binding and signaling, regulating chondrocyte differentiation</td>
<td>2.89 (6.2)</td>
<td>1.4E-06</td>
</tr>
<tr>
<td></td>
<td>EFEMP1</td>
<td>Encoded ligand for transforming growth factor-β signaling, promoting cell proliferation and migration</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>FUT2</td>
<td>Generating the H-type antigen in saliva and on digestive and respiratory epithelia</td>
<td>1.41</td>
<td>1.4E-06</td>
</tr>
<tr>
<td></td>
<td>HSD17B1</td>
<td>Long-chain fatty acids elongation cycle</td>
<td>-1.15 (4.2)</td>
<td>3.0E-05</td>
</tr>
<tr>
<td></td>
<td>PRDM1</td>
<td>Nucleic acid binding and methyltransferase activity</td>
<td>2.28 (6.5)</td>
<td>4.0E-05</td>
</tr>
<tr>
<td></td>
<td>WWOX</td>
<td>Regulation of a wide variety of cellular functions, such as protein degradation, transcription and RNA splicing</td>
<td>17.1 (4.1)</td>
<td>2.0E-05</td>
</tr>
<tr>
<td></td>
<td>KCN2</td>
<td>Hydroxide activity, hydrolyzing O-glycosyl compounds</td>
<td>23.3 (5.6)</td>
<td>3.7E-05</td>
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<tr>
<td></td>
<td>LCT</td>
<td>Embryonic development, cell growth, differentiation, and signaling</td>
<td>27.34</td>
<td>2.1E-08</td>
</tr>
<tr>
<td></td>
<td>FAM13A</td>
<td>May bind zinc and other divalent cations, and recruit them to vesicular organelles</td>
<td>-19.94 (3.919)</td>
<td>3.6E-07</td>
</tr>
<tr>
<td></td>
<td>TMEM163</td>
<td>Myeloid differentiation factor 7 (MAFF), regulator of hematopoiesis</td>
<td>18.63</td>
<td>1.0E-06</td>
</tr>
<tr>
<td></td>
<td>PTEN</td>
<td>Tyrosine phosphatase activity</td>
<td>1.29</td>
<td>1.4E-06</td>
</tr>
<tr>
<td></td>
<td>CREM84,85</td>
<td>Transcriptional regulation, constitutive and alternative pre-mRNA splicing</td>
<td>1.29</td>
<td>3.0E-07</td>
</tr>
<tr>
<td></td>
<td>NTN5/SEC1P</td>
<td>Decreased fat intake, increased carbohydrate intake, and marginally decreased protein intake</td>
<td>2.42</td>
<td>2.14E-09</td>
</tr>
<tr>
<td></td>
<td>FGF1/IGF-2</td>
<td>Decreased in birth weight and gain, increased birth weight gain, and increased body mass index</td>
<td>1.18</td>
<td>5.22E-22</td>
</tr>
<tr>
<td></td>
<td>BMP6</td>
<td>Calcium ion binding and epithelial growth factor receptor binding and signaling, regulating chondrocyte differentiation</td>
<td>-0.11 (0.02)</td>
<td>7.9E-09</td>
</tr>
<tr>
<td></td>
<td>IGF1/IGF-2</td>
<td>Decreased in birth weight and gain, increased birth weight gain, and increased body mass index</td>
<td>1.27</td>
<td>8.0E-14</td>
</tr>
<tr>
<td></td>
<td>FGF21</td>
<td>Development and differentiation of many types of lung cells, including airway basal cells, club cells, alveolar epithelial cells, and fibroblasts.</td>
<td>1.27</td>
<td>7.9E-11</td>
</tr>
<tr>
<td></td>
<td>NCAM1</td>
<td>Decreased carbohydrate intake, increased protein intake, and marginally decreased fat intake</td>
<td>2.42</td>
<td>2.14E-09</td>
</tr>
<tr>
<td></td>
<td>FGF1/IGF-2</td>
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<td>Decreased carbohydrate intake, increased protein intake, and marginally decreased fat intake</td>
<td>2.42</td>
<td>2.14E-09</td>
</tr>
</tbody>
</table>

**Table 2.** Genes implicated in stunting and low lung function. (Lung function: FEV1/FVC, stunting: BMI.)
modulators is small (known SNPs for FVC account for only 14.3% of variation in heritability).

We observed that the genes common to both forced vital capacity and stunting were largely associated with early development, morphogenesis and malnutrition. While the small heritability of associated genes did not lend much support to the analogy, identification of unique SNPs with high heritability may be useful in paving the way for community profiling and the mapping of appropriate interventions to communities.

**Conclusion**

While IUGR is central to the pathophysiology of both stunting and compromised lung growth, malnutrition, mediated by several complex factors, appears to be the true point of convergence (see Figure 6). Although malnutrition may manifest in several ways, WHO maintains that the path to prevention remains identical across populations. Major preventive measures may include: adequate maternal nutrition ranging from the perinatal period to lactation, optimal breast feeding during the first two years of life, healthy childhood nutrition, sanitation and safe physical activity. In addition to multi-sectoral collaborations, design of appropriate interventions, embedding NCD impact evaluation into maternal and child health programs is crucial to addressing rapid epidemiological transitions in the developing world.

Our inability to maintain stringent inclusion criteria of human randomized controlled trials in areas of nutrition, vaccination, tobacco cessation and environmental health across populations in developing nations is representative of the absence of necessary research to guide interventions in this area. This necessitated a narrative review design to present an updated perspective and not to directly guide clinical practice.

The correlation between Socio Demographic Index and indicators of both chronic and infectious diseases reflects the need to understand heterogeneity in lung function and linear growth patterns in the context of socioeconomic variations that determine nutritional and environmental exposures, access to sanitary living conditions and inter-generational patterns of growth faltering. Identifying highly heritable genetic variants, which could potentially mediate response to interventions, might serve as genetic signatures unique to communities. These inputs could assist in tailoring interventions for communities by capturing meaningful environmental influences in addition to ethnic differences.

Creation of proxy scores for communities incorporating epidemiological transition levels, heritability of traits associated with disease, responses to existing programs and, metabolic health and growth trajectories could aid in mapping communities to appropriate health interventions. Further research is needed in utilizing existing data sources, assigning weights to individual

**Figure 6. Intergenerational effects of malnutrition and inequality.**
components and generating comprehensive scores useful for community profiling.

**Data availability**

**Underlying data**

All data underlying the results are available as part of the article and no additional source data are required.

**Extended data**


**References**


