



RESEARCH ARTICLE

REVISED Low lung function in the developing world is analogous to stunting: a review of the evidence [version 2; peer review: 2 approved]

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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 just 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 genetic, 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 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, with malnutrition at the center of non-achievement of growth potential, susceptibility to infectious diseases and intrauterine programming for metabolic syndrome. This

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counter the idea of redefining the normal for lung function measurements, since observed inter-ethnic variations are likely a mix of natural genetic differences as well as differences in nurture such that reduced lung function reflects early life adversities.

Keywords

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



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REVISED Amendments from Version 1

In this version the manuscript was revised according to reviewer's comments on modification of the abstract to better reflect the manuscript, a more balanced review of literature, addition of missing references where necessary. Our choice of the words 'analogous' has been explained to some extent. We explained the interaction of ethnicity with socio-economic factors and its effect on lung function.

Any further responses from the reviewers can be found at the end of the article

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 particular¹⁻⁶. 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.

While the development of ethnic and geographical reference equations for lung volumes may incorporate differences in body habitus, the validity of these equations would rely heavily on assumptions regarding the reference population being 'healthy'⁷. Adverse socio-economic and environmental factors prevalent in the developing world obscure the definition of a phenotypically '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 Median⁸, 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 a roadmap for common interventions for both conditions. In this case, the idea of both stunting (as an outcome of growth faltering conditions) and poor lung function were examined as analogous processes, based on the hypothesis that both conditions appeared to be steeped in similar origins, had similar intermediate indicators and culminated in an elevated risk of similar outcomes.

The intersecting pathways culminating in growth faltering and poor lung function signal towards the pathological origins of poor lung function. 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 29th 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.

We identified relevant articles using the search terms grouped according to risk factors, such as maternal nutrition and anthropometry, nutrition, anthropometry, environmental factors, sanitation, genetic and epigenetic factors.

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

Outcomes of interest

The following outcomes of interest were included and assessed:

- Lung function as measured by spirometry (e.g. FEV1, FVC, PEF, FEF 25–75 and FEV1/FVC)
- Airway resistance as measured by R5, X5, R20, X20 and similar derivatives
- Respiratory infections
- 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. The heterogeneity in outcomes of the studies included in the review necessitated a narrative review, and to the extent possible, this review follows PRISMA guidelines.

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 FVC⁹.

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 population¹⁰. 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 Manila¹¹.

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 nations^{12,13}. The use of reference equations that are generated primarily in order to account for genetic heterogeneity, for developing world populations experiencing large variations in developmental conditions, could obscure the true prevalence of reduced lung function. Epigenetic mechanisms that may persist for generations make it even more difficult to fully exclude environmental effects on development.

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 life¹⁴. 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 pattern¹⁵. Here stunting differs from restrictive lung growth in that except for its contribution to a long term chronic inflammatory state, its effects may be reversible to an extent if addressed during the first 1000 days of life, whereas the consequences of restrictive lung growth persist throughout the life course¹⁶.

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*)¹⁵.

As a sequel to intrauterine growth restriction (IUGR), stunting appears to mirror 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 diseases¹⁷.

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.

Examining the 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 mother¹⁸. 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 children¹⁹.

Similarly, a Peruvian study with data from 553 asthmatic children, reported an association between food insecurity and poorer Asthma control²⁰. Asian children in low SES environments, with indications of stunting, such as short stature and low BMI, had the highest FEV₁/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 FEV₁, result in a high FEV₁/FVC ratio. Therefore, stunting manifests with restrictive lung function, as low values of FVC with normal to high FEV₁/FVC ratio²¹.

One point of discord in the analogy between growth faltering and poor lung function is the varying extent to which both conditions could be governed by genetic factors.

A study examining differences in lung function between Asian and White school-children ages 6-11 in Leicester²², found differences in ethnicity to be significantly associated with lung function, after adjusting for socio-economic factors (which additionally determine access to nutrition and exposure to air pollution). While ethnic differences were seen to exist, these differences could not be attributed to clear anthropometric correlates. This was also observed in a study examining the differences in lung function in 112 young adults, where differences in anthropometric indicators did not explain ethnic differences in lung function²³. In the CARDIA cohort too, race and sex differences in lung function appeared to persist despite detailed adjustment for frame size²⁴. The mechanistic influences of ethnicity ('nature') are speculated to manifest through surrogate markers for height, such as proportions of leg length to body height, sitting height, or differences in inspiratory muscle strength or lung compliance²². It is also plausible to assume that the difficulty in untangling the effects of genetic and environmental influences could be attributable to the low-penetrance nature of genes which regulate lung development and function. The nature and extent of gene-environment interactions are intrinsic to the mode of action of many common, low-penetrance genes²⁵.

These in turn may work in tandem with developmental mediators such as the intra uterine growth environment and early life exposures. Part of the residual variability could be attributed to unmeasured determinants, which are likely to be both genetic and epigenetic. It must however be noted that ethnicity is a complex imperfect socio-political construct and can be a poor surrogate of genetics, as argued elegantly by Quanjer *et al.*²⁶

In this context, while attained lung function may be considered a phenotypic expression of both genetic endowment and childhood environment, stunting primarily appears to be a consequence of deprivation and inequality encountered during development. Disruptions in environmental factors such as maternal nutritional status, feeding practices, hygiene and sanitation, frequency of infections and access to healthcare are the major determinants of the risk of stunting²⁷.

IUGR is an interesting intersection point for the purpose of this study that is environment driven, highly prevalent in developing nations, results in smaller organs and low birth weight infants with a higher susceptibility to diarrheal and lower respiratory tract infections. This sequence, which may even persist beyond a single generation since maternal size is in itself a limiting point for fetal growth, leads to repeated growth faltering and reinfections, which are implicated in stunting²⁸⁻³¹. IUGR, as a consequence of maternal loss of growth potential, may be considered a point of convergence in the pathways for poor lung development and stunting, for which we have more data than either of the two alone.

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 development³². '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 child³³⁻³⁸.

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 unmet³⁹. 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 bodies⁴⁰.

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^{41,42}. This explains the 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^{39,43,44}.

A study conducted by Todisco *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

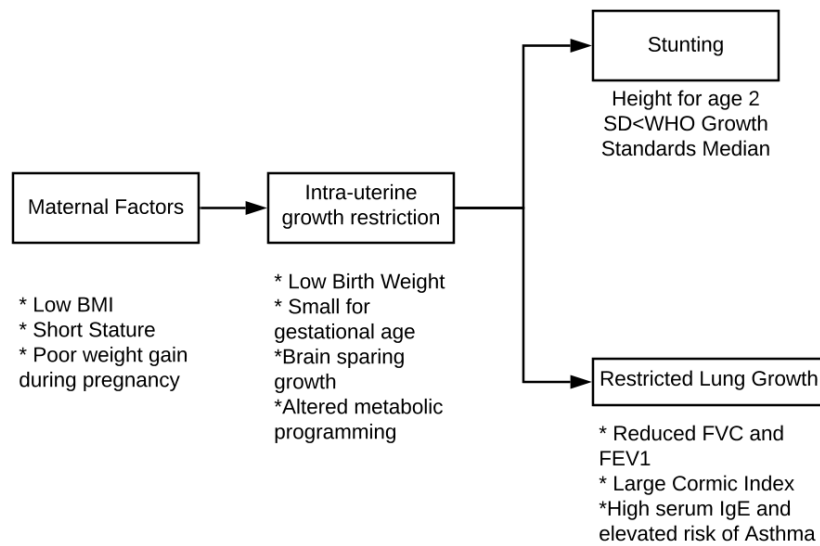


Figure 1. Intrauterine growth restriction contributes to both low lung function and stunting.

pre-term birth category compared to matched siblings delivered at term, indicating that lung function deficit at birth persists into early adolescence⁴⁵. 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 factors⁴⁶ interfering with healthy lung development. Maternal hypertension and pre-eclampsia, often implicated in pre term birth and low birth weight infants can be indirectly implicated in contributing to low lung function during childhood^{47,48}.

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 hyperoxia⁴⁹. 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. The effects of IUGR and growth faltering in utero, when sustained through malnutrition and frequent infections leads to stunting as an outcome. This is an interesting point of convergence in the pathophysiology of both conditions.

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 FEV₁ and FVC⁵⁰. 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 cohort⁵¹. 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 FVC⁵². 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 lung⁵³.

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 Africa⁵⁴) 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

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 obstruction²¹. Analogous adaptations characterized by shorter limbs and sitting height are observed in both stunting and restrictive lung function⁵⁵. The positive association between age at peak adiposity and higher FVC, FEV₁ and FEF₂₅₋₇₅ implies that IUGR, followed by rapid weight gain during childhood results in poor lung function⁵⁶. 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 function⁵⁷.

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 association⁵⁸⁻⁶³. In the PIAMA birth cohort⁶¹ (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 12⁶⁴.

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^{19,65,66}. 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 $\leq 2.5 \mu\text{m}$; PM_{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*⁶⁷. Low birth weight is also an independent risk factor for stunting, particularly in developing nations with both high air pollution and malnutrition contributing to IUGR⁶⁸.

Low birth weight was higher among women who delivered in facilities where PM_{2.5} concentrations were above the median (i.e., $>12.0 \mu\text{g}/\text{m}^3$) compared with women delivering at facilities with average PM_{2.5} levels $<6.3 \mu\text{g}/\text{m}^3$. In China, the country with the largest range of PM_{2.5} exposure levels, both preterm birth and LBW were significantly higher among women with estimated exposure to at least $36.5 \mu\text{g}/\text{m}^3$ of PM_{2.5} compared with women in the lowest quartile of exposure ($<12.5 \mu\text{g}/\text{m}^3$)⁶⁹. The ENVIRONAGE birth cohort too reported an association between *in utero* PM 2.5 exposure and placental mitochondrial DNA methylation in 381 mother-newborn pairs⁷⁰.

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 PM₁₀ during the first trimester of pregnancy was found to be associated with a lower peak expiratory flow

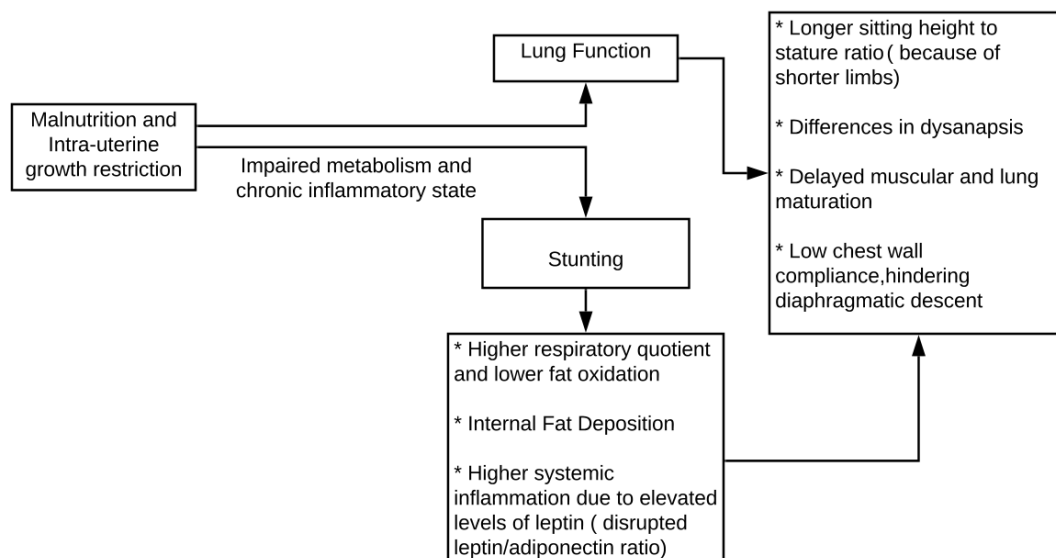


Figure 2. Stunting and restrictive lung function (FVC <80% of predicted) - anthropometric correlates.

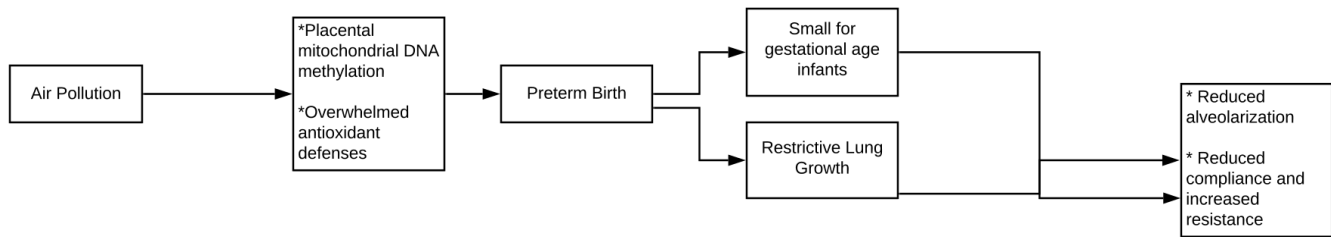


Figure 3. The role of air pollution in stunting and RLLF.

volume between ages 6–11 years⁷¹. A 90 mL lower FEV₁ at 5 years was observed in the Krakow birth cohort, comprising 176 exposed children of non-smoking mothers⁷², while a 60mL reduction in FEV₁ was found in Swedish children exposed to higher concentrations of PM₁₀ 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 (R₅–R₂₀) at age 16⁷³.

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 observed⁷⁴. 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 lung were observed⁷⁵.

Newborns exposed to PM₁₀ *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 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^{76,77}.

Post birth, pre-term or small for gestational age children in developing nations traditionally experiencing the effects of inter-generational 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 IUGR⁷⁸. 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^{79,80}.

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 offspring⁸¹. 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 females⁸².

The immediate effects of tobacco exposure are difficult to 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 susceptibility⁸³. 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 infants⁸⁴. 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).

The impoverished gut

Stunted children inhabit unhygienic settings and live in conditions of acute deprivation where environmental enteric dysfunction (EED) is prevalent⁸⁵. 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^{86,87}. Frequent infections, vaccine failures and chemotherapy lead to a disruption in the homeostasis of the gut microbiota, a phenomenon referred to as dysbiosis⁸⁸.

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 assimilation⁸⁹⁻⁹¹. 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 lung⁹².

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 adulthood⁹²⁻⁹⁴. An asthmatic phenotype during childhood was seen to be associated with an elevated risk of COPD⁹⁵ and lower values of FEV1,FVC during adulthood (when compared to control groups without asthma during childhood)⁹⁶. These associations offer subtle insights into the role of gut microbiota in influencing long term adult lung function, via other indirect influences.

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 vaccines⁹⁷. 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.

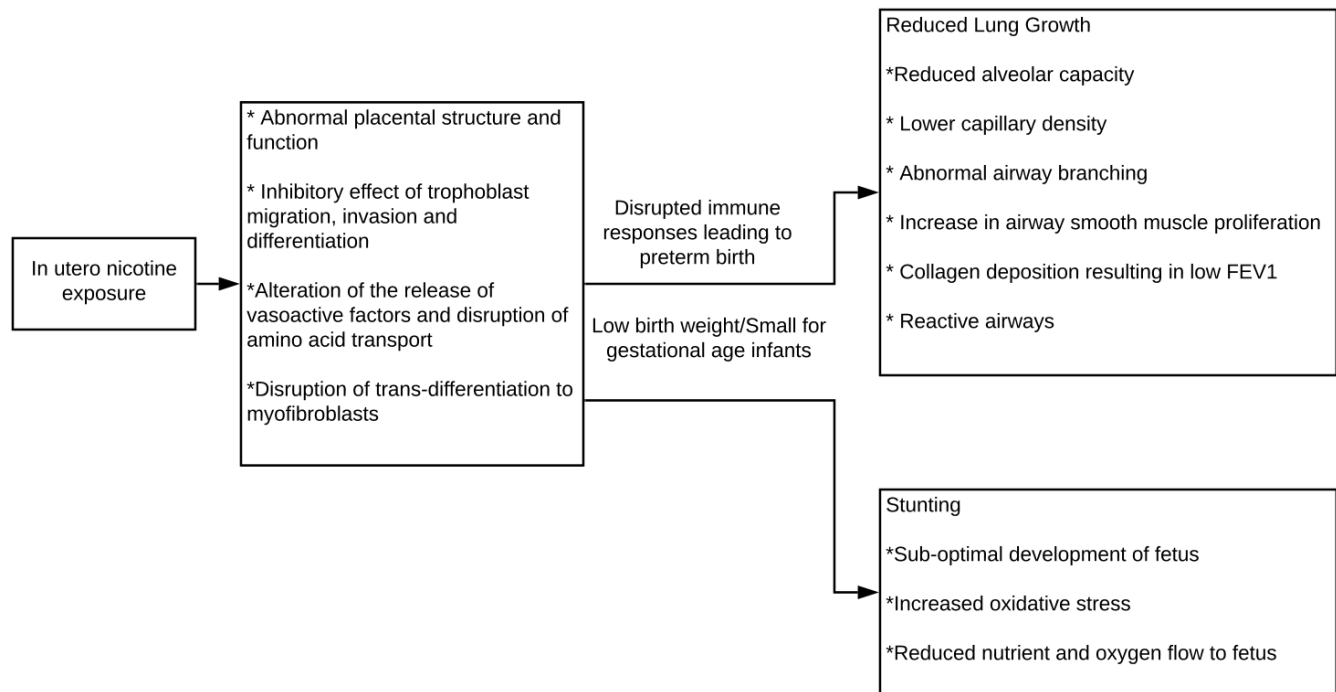


Figure 4. In utero nicotine exposure, RLLF and Stunting^{78,81-83,98}.

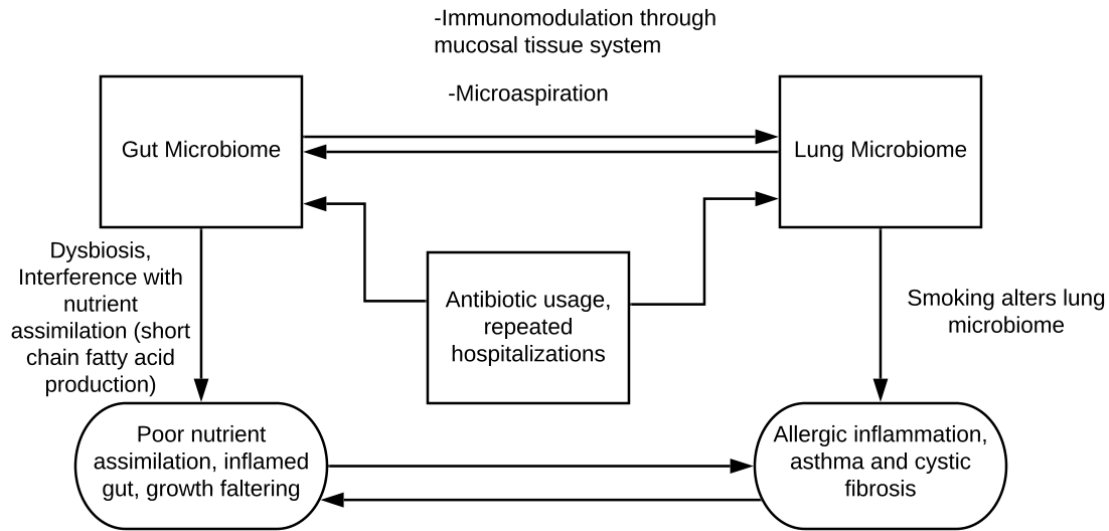


Figure 5. How the impoverished gut may mediate stunting and low lung function.

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 1). The individual effect sizes of these genetic and epigenetic modulators is small (known SNPs for FVC account for only 14.3% of variation in heritability).

The genes common to both forced vital capacity and stunting were found to be largely associated with early development (*IGF1*, *BMP6*), morphogenesis (*IGF1*) and nutritional insults due to recurrent GI infections (*BMP6*, *FUT2*). (See Table 1)

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 activity⁹⁹. 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.

Table 1. Genes implicated in stunting and low lung function. (Lung function¹⁰⁰⁻¹⁰⁵, stunting¹⁰⁶⁻¹⁰⁹).

Gene (Lung Function) (FEV/FVC, FVC)	P Value	Function	Gene (Stunting)	P Value	Function
IGF-1	2.19E-13	Development and differentiation of many types of lung cells, including airway basal cells, club cells, alveolar epithelial cells, and fibroblasts.	IGF1/IGF-2	5.22E-22	IGFs are involved in the proliferation, differentiation and apoptosis of fetal cells in vitro and the IGF serum concentration is closely correlated with fetal growth and length.
FGF21	-	Inhibits pulmonary fibrosis through activating Nrf-2 pathway, subsequently suppressing oxidative stress, inhibiting ECM deposition and pulmonary fibrogenesis	FGF21	7.9E-09	Decreased protein intake, increased carbohydrate intake, and decreased fat intake after adjusting for body mass index
FUT2	0.00	Generating the H-type antigen in saliva and on digestive and respiratory epithelia	FUT2	8.00E-14	Involved in histo-blood group antigen production, Diarrhea by one year of age
BMP6	1.45E-06	Encoded ligand for transforming growth factor,ERK signalling	NTN5/SEC1P	7.00E-11	Diarrhea by one year of age
EFEMP1	1.45E-06	Calcium ion binding and epidermal growth factor receptor binding,cell adhesion and migration. May function as a negative regulator of chondrocyte differentiation	CREM84,85	6.05E-09	Susceptibility to susceptibility to E. histolytica disease
HSD17B12	3.70E-05	Long-chain fatty acids elongation cycle	H6PD	3.19E-07	carbohydrate binding and glucose-6-phosphate dehydrogenase activity
PRDM11	4.80E-05	Nucleic acid binding and methyltransferase activity	RSRC1-SHOX2	2.14E-09	Transcriptional regulation, constitutive and alternative pre-mRNA splicing
WWOX	2.04E-05	Regulation of a wide variety of cellular functions, such as protein degradation, transcription and RNA splicing	PPP2R2A	4.29E-05	Negative control of cell growth and division,protein serine/threonine phosphatase activity
KCNJ2	3.73E-05	Probably participates in establishing action potential waveform and excitability of neuronal and muscle tissues,	FTO	1.42E-08	Total percentage of carbohydrate intake,childhood obesity ,
LCT	2.18E-08	Hydrolase activity, hydrolyzing O-glycosyl compounds and lactase activity	TANK	1.00E-05	Decreased fat intake, increased carbohydrate intake, and marginally decreased protein intake
FGF10	1.49E-06	Embryonic development, cell growth, morphogenesis, tissue repair	FADS1, FAD2, FADS3	4.20E-09	Breast milk fatty acid composition,regulating immunity and inflammation
TMEM163	3.60E-07	May bind zinc and other divalent cations and recruit them to vesicular organelles	RBP4	-	Retinol Binding Protein 4, specific transport protein for vitamin A in the circulation
FAM13A	2.90E-03	putative role in signal transduction, Signaling by GPCR and Signaling by Rho GTPases	TMEM18	2.03E-04	vesicle transport in exocrine cells and Sertoli cells

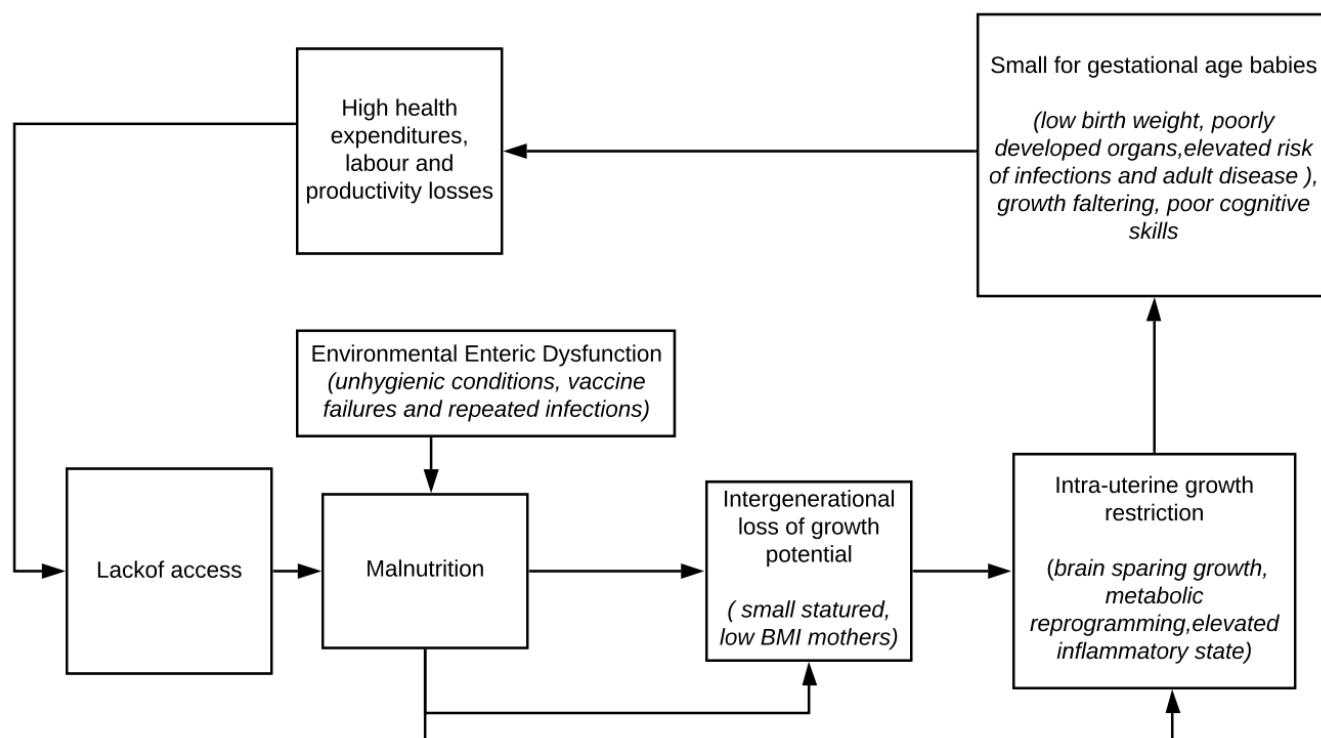


Figure 6. Intergenerational effects of malnutrition and inequality.

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 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

Figshare: Review Data (GBD).csv. <https://doi.org/10.6084/m9.figshare.12278129>¹⁰.

This file contains the collated data used to examine the relationship between SDI, risk factors and diseases (in the section “Higher burden of stunting and low lung function in the developing world indicates the role of socioeconomic influences”). Data were originally obtained from the GBD visualization tool, originally available at <https://vizhub.healthdata.org/gbd-compare>¹⁵.

Extended data are available under the terms of the [Creative Commons Attribution 4.0 International license](https://creativecommons.org/licenses/by/4.0/) (CC-BY 4.0).

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Open Peer Review

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Reviewer Report 16 December 2020

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Ashutosh Nath Aggarwal 

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, Punjab and Haryana, India

This revision has tried to address most of my concerns, and is much improved in both content and direction. I consider some residual differences in opinion to be an essential part of the scientific thought process which should not lessen the merit of the current manuscript. I have no additional comments to offer.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of chronic respiratory disorders, Pulmonary function testing, health outcomes research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 August 2020

<https://doi.org/10.21956/wellcomeopenres.17471.r39560>

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Ashutosh Nath Aggarwal 

Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, Punjab and Haryana, India

General:

- The manuscript attempts to visualize the differences in lung function across various ethnic groups from a different perspective, one that is slowly being recognized as perhaps being of some importance. However, the overall handling of the issue and its presentation leave much to be desired. In their zeal to increase the width of discussion (and trying to evaluate variables that may or may not be even remotely connected with the problem at hand), the authors compromise a lot on the depth of their discussion. The manuscript essentially tries to identify factors associated with perinatal and childhood stunting (and related conditions), on which extensive literature is available. The manuscript also explores literature (to a limited extent) to try and identify if some of these factors also correlate with diminished pulmonary function, and tries to build a viewpoint that the two appear analogous. I personally am not comfortable with this translation from 'association' to 'analogy'. For instance, tobacco smoking is known to be associated with several developmental, inflammatory, infective, metabolic, degenerative and malignant disorders, but one cannot conclude that all these hundreds of health conditions are analogous to each other just because they share one risk factor, one among the several that is associated with each clinical scenario. In addition, the entire presentation attempts to build a concept of causality, and we all understand the perils of extrapolating associations to causality.
- The manuscript, although being close to a systematic review (as claimed by authors), presents only one side of the viewpoint, a viewpoint that authors have probably pre-conceived to be correct. I cannot figure out how during their review of evidence they did not come across or discuss even a single study that is contrary to this viewpoint. Although I partly agree with this stated viewpoint, but even as a lay person I can raise several objections. For instance, women across the globe have poorer lung function than men. Does that imply that all women are 'stunted' (based on their lower height, weight, chest circumference, etc.) and hence exhibit a lower vital capacity? In India, north Indians are generally taller and less stocky than south Indians and show better lung function. Would it mean that south Indians are uniformly less privileged, and hence 'more stunted', than north Indians in this country? It seems too simplistic and naïve to conclude that poor lung function in certain populations is almost completely related to poor lung growth, which in turn is almost completely related to malnutrition, poor socio-economic status, etc. For instance, a study from the UK concluded that chest dimensions did not explain the substantial effect of ethnicity (whites vs. Asians) on pulmonary function in children aged 6-11 years (Whittaker *et al.*, 2005¹). Similarly, a study on college students aged 18-23 years in the UK recruited 112 subjects of two ethnicities with similar parental socio-economic environment and birth weight, yet their difference in FVC was 0.81 L after adjustment for gender, age, anthropometry and social variables (Saad *et al.*, 2017²). There are more such studies that seem to fulfil the authors' eligibility criteria but are neither cited nor discussed. I don't feel that it is so simple (as the authors' make it out to be) to untangle the influences from deprivation and genetics on pulmonary function.

Abstract:

- The abstract is a well-written summary but seems totally disconnected to the manuscript. The background here is quite different from what is presented as the Introduction in the

main text. The methods too are different with respect to databases and datasets queried for literature search. There is no mention of following PRISMA guidelines in the manuscript.

Introduction:

- The authors state certain facts with certainty and draw conclusions right away. For instance, ... "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" ..., and ... "analogous nature of restrictive lung function and stunting would imply" ..., etc. I believe these are actually the research questions here that they are trying to explore. A proper justification and statement regarding need for this research would be welcome.

Methods:

- A proper search strategy is lacking, and the keywords provided are too general. I am sure any bibliographic search would have returned tonnes of citations, and I am not sure how the authors sifted through for relevant publications. I am also not sure how the search terms stated in table 1 could have been used to identify relevant articles, since these appear too restrictive in the single phrases that they employ. Yet a large body of evidence is provided. For instance, the genetic studies listed in table 2 could not have been derived from the search string "stunting AND low lung function AND genetic NOT animal NOT cystic fibrosis". Studies with unclear methodology were excluded, but there is no explanation how this was determined. Overall, the section is nowhere close to what PRISMA guidelines advocate.

Results:

- A major drawback of the manuscript is that it tries to fit a narrative review in an original article format. This may have been possible if this were a systematic review, but clearly that is not the case. So the Results section is basically a summary of some articles considered important by the authors, expression of authors' perceptions about the evidence, and conclusions on potential pathways even without sufficient evidence. There is no Discussion section. A lot of statements do not actually stem from published data reported by the authors, but are rather thoughts or hypotheses. Overall, this seems straight out of an informal literature review for a thesis/dissertation, rather than the Results section of an original research article. I would expect slightly better focus, and a better review of strength and weakness of data, before jumping to interpretation.
- Some studies are not referenced in the bibliography (Todisco et al on page 6, column 1).
- The section on impoverished gut seems totally out of context in this article as it does not provide any evidence correlating abnormalities in gut microbiota to poor lung function. Asthmatic phenotype cannot be equated with poor lung function.
- In the section on genetic modulators I am not clear how the conclusion, that genes common to both FVC and stunting were associated with early development, morphogenesis and malnutrition, was arrived at.

Conclusions:

- At this stage, the conclusions seem largely conjectural and not completely borne out by

data presented (and not presented). Most of this section seems superfluous and largely irrelevant to the present discussion. It should be crisp and to the point.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology of chronic respiratory disorders, Pulmonary function testing, health outcomes research

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 07 Nov 2020

Anurag Agrawal, Institute of Genomics and Integrative Biology, Delhi, Delhi, India

1. "Issue - translation from 'association' to 'analogy'" **Main Response – Explanation for describing this as an analogy has been added. The abstract has been modified slightly to represent the content of the manuscript better.**

2. "The manuscript, although being close to a systematic review (as claimed by authors), presents only one side of the viewpoint" - **A detailed explanation for why we could not conduct a systematic review on the subject has been presented both in the abstract and listed as a limitation. Attempts for a balanced literature review were made, other references were added.**

3. It seems too simplistic and naïve to conclude that poor lung function in certain populations is almost completely related to poor lung growth, which in turn is almost completely related to malnutrition, poor socio-economic status, etc. , impossible to untangle the influences from deprivation and genetics on pulmonary function. **Response: There are points in the manuscript where differences between the nature of both conditions were described - these differences have been explained in greater detail. The role of genetics has also been described in greater detail. Both studies and others similar to them have been included in the 'interplay of ethnicity and access' section of the manuscript.**

4. Abstract: The background here is quite different from what is presented as the Introduction in the main text. The methods too are different with respect to databases and datasets queried for literature search. There is no mention of following PRISMA guidelines in the manuscript. **Response: The abstract has been modified to reflect the contents of the manuscript better. PRISMA guidelines have been followed to the extent possible and reported in the methods section.**

5. Authors state certain facts with certainty and draw conclusions right away. A proper justification and statement regarding the need for this research would be welcome. **Any conclusive statements about the hypothesis have been removed from the beginning of the manuscript.**

6. A proper search strategy is lacking, and the keywords provided are too general.. Overall, the section is nowhere close to what PRISMA guidelines advocate. **Response: Methods re-written, results modified accordingly, new references added**

7. A major drawback of the manuscript is that it tries to fit a narrative review in an original article format. There is no Discussion section. A lot of statements do not actually stem from published data reported by the authors, but are rather thoughts or hypotheses.

Response: Additional references provided.

- Some studies are not referenced in the bibliography (Todisco et al on page 6, column 1).

Response: Additional references provided.

- The section on impoverished gut seems totally out of context in this article as it does not provide any evidence correlating abnormalities in gut microbiota to poor lung function.

Response: Additional references provided.

- Asthmatic phenotype cannot be equated with poor lung function. - **Correction made.**

In the section on genetic modulators I am not clear how the conclusion, that genes

common to both FVC and stunting were associated with early development, morphogenesis and malnutrition, was arrived at. **Response: Additional explanation provided.**

Competing Interests: No competing interests were disclosed.

Reviewer Report 10 July 2020

<https://doi.org/10.21956/wellcomeopenres.17471.r39246>

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Vishal Bansal 

Department of Physiology, Vallabhbhai Patel Chest Institute, New Delhi, Delhi, India

The authors have touched upon a clinically relevant topic i.e. impact of stunting on lung function in developing world.

They have critically reviewed the available literature in a crisp and appropriate manner.

Though they have focused mainly on IUGR and malnutrition with brief mention of obesity; it would add to value of the manuscript if more literature is added on the correlation between obesity and stunting.

References

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardio-respiratory physiology, Cardio-pulmonary rehabilitation.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
