Review Article

Association of Soil-transmitted Helminth Infection and Micronutrient Malnutrition: A Narrative Review

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ABSTRACT

Micronutrient malnutrition, mainly iron, Vitamin A, and zinc, affects more than 2 billion people worldwide. One notable cause of this condition is an abnormal digestive function due to parasitic intestinal infections. Since infections with soil-transmitted helminths (STH) are observed in 24% of the world's population, it contributes to approximately 100 million malnutrition in children globally. The following parasites cause this: *Ascaris lumbricoides, Trichuris trichiura,* and hookworms *Ancylostoma duodenale* and *Necator americanus.* This narrative review aims to synthesize the existing literature on the epidemiology, pathogenesis, and clinical manifestations of micronutrient malnutrition—iron, Vitamin A, and zinc to explain its relationship with STH infections. Research journals and articles were retrieved from PubMed and Google Scholar. Search terms include "helminthiasis or STH infection or soil-transmitted helminth infection," "malnutrition or nutrition deficiency," "iron or ferritin or hemoglobin," "Vitamin A or retinol," and "zinc.". STH infections can cause micronutrient malnutrition. The existing relationship between STH and micronutrient malnutrition is a significant burden, mainly in children or pregnant women who reside in rural communities of developing countries. Iron deficiency is the most common micronutrient malnutrition manifested in infected populations, mainly in pregnant women. In contrast, Vitamin A deficiency occurs more often in children than in pregnant women. The least common of all micronutrient malnutrition occurring in STH-infected individuals is zinc deficiency. However, since only a few studies have conducted additional assessments for other possible contributing factors (e.g., diet intake, underlying genetic conditions), further research is needed to elucidate the complex interplay of other determinants and risk factors involved in this health scenario.

Key words: Soil-transmitted helminth, Micronutrient malnutrition, Iron deficiency, Vitamin A deficiency, Zinc deficiency.

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INTRODUCTION

More than 2 billion people worldwide are at risk of micronutrient malnutrition.[1] Iron, Vitamin A, and zinc deficiencies are mainly observed worldwide.[2] These three essential micronutrients primarily pose significant health issues. Iron deficiency affects 50% of the world's population.[3] It is defined as either plasma ferritin under 15 µg/L or hemoglobin below 115 g/L.[4] Usual symptoms manifested by the deficiency include dizziness, shortness of breath, weakness, and fatigue, commonly indicating anemia.[5] On the other hand, Vitamin A deficiency accounts for about 30% of children under five years of age.[6] It is described as plasma retinol under 0.70 µmol/L, and marginal Vitamin A status was determined as retinol below 1.05 µmol/L.[4] One of the early clinical indicators of this deficiency is night blindness. In severe cases, Vitamin A deficiency can cause damage to the cornea and retina, resulting in permanent blindness.[7] Zinc deficiency contributes to 20% of the world population

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and is considered a significant factor in the global disease burden.[8,9] It can be determined as <9.9 μmol/L plasma zinc.[4] Mental lethargy, weight loss, and delayed healing of wounds can be generally observed. Severe zinc deficiency cases may cause impotence, delayed sexual maturation, hypogonadism, and skin and eye lesions.[10] Micronutrient malnutrition is caused by combinations of factors, including a response to inflammation and genetic abnormality in nutrient metabolism. A notable cause is an inadequate intake due to an abnormal gastrointestinal function (poor appetite, malabsorption, blood loss) attributable to parasitic intestinal infections. This is developed from and is continuously maintained by the deeply rooted socioeconomic disparity.[11,12]

Globally, approximately 100 million people, particularly children, have experienced malnutrition and impaired growth due to soil-transmitted helminth infections.[13,14] Soil-transmitted helminthiases are infections caused by nematode worms transmitted to humans through fecally contaminated soil.[15] These comprise four main causative agents; *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm), and the hookworms (*Ancylostoma duodenale* and *Necator americanus*). STH infections are observed in 24% of the world's population. They are a significant contributor to neglected tropical diseases (NTD).[16,17]

In this same light, this narrative review will synthesize the current literature on the epidemiology, pathogenesis, and clinical manifestations of micronutrient malnutrition—iron, Vitamin A, and zinc, to describe its association with STH infections. The coverage of the information gathered will provide an insight into the current status of the before-mentioned public health issues. This review will widen scientific resources and expand national plans of actions for targetting micronutrient malnutrition and its morbidity and the WHO Strategic Plan of eliminating soil-transmitted helminth infections.

METHODOLOGY

Literature Search

The search for articles and journals was conducted between February 1, 2021, and April 5, 2021, using PubMed and Google Scholar. The search terms used include the following: "helminthiasis or STH infection or soil-transmitted helminth infection," "malnutrition or nutrition deficiency," "iron or ferritin or hemoglobin," "Vitamin A or retinol," and "zinc."

Study Selection

Eligible journals were those published in English. Case reports were also included, provided that nutritional assessments of participants were reported. Narrative reviews and studies attributable to animals were excluded from the selection. No further exclusion criteria were applied due to the limited number of studies published in this field.

RESULTS AND DISCUSSION

Iron deficiency and STH infection

Epidemiology: Iron deficiency is currently the most globally common and prevalent nutritional problem concomitant with soil-transmitted helminth infection (Table 1). A majority of the studies have reported that pregnant women from rural communities primarily exhibit deficient iron levels with the co-occurrence of helminth infections. In 1994, a systematic review of studies about their nutrition and infections revealed that helminth infections were prevalent, and their iron status is generally poor. Furthermore, the severity of iron deficiency becomes progressive as women were examined later in their third trimester. However, the parasitic infection intensity did not vary significantly during points in their pregnancy.[18] Since then, additional studies have provided further documents on the detrimental effect of helminth infections on the iron status of pregnant women.[19-25]

Furthermore, schoolchildren from ages six to ten also carry the burden of this public health problem. A study of iron status in children living in endemic areas of STH noted that most affected children spend most of their time barefoot and have a high habitual frequency of sucking fingernails (Aini *et al*., 2007; Molla and Mamo, 2018). Also, most of the studies have emphasized that they belong to families with poor living conditions that have little access to clean water, poor hygiene practice, and improper diet.[4,13,26-32]

Pathogenesis: Soil-transmitted helminth infection as a risk factor for developing iron deficiency is recognized in 88% of the studies reviewed. Studies have identified hookworm infections to be the most significant contributor to iron malnutrition. In populations with a high prevalence of infection, hookworms were strongly associated with depleted iron stores.[27] Studies in Vietnamese, Cambodian, and Ethiopian children recognized hookworm infection intensity as a predictor of all three indicators of iron status (hemoglobin, ferritin, serum iron). When the decrease in iron was assessed specifically per STH species, the decrease was

Table 1: Association of STH infections and micronutrient malnutrition.

Micronutrient Malnutrition	Soil-Transmitted Helminthiases			
	Epidemiology	Pathogenesis		Clinical Manifestation
Iron deficiency	Bangladesh, Vietnam, Indonesia, Malaysia, Vietnam, Cambodia, Thailand, Nepal, Uganda, Kenya, Ethiopia, Nigeria, Peru, Mexico	Hookworms	Chronic bleeding from intestinal mucosa laceration	Iron deficiency anemia Impaired physical and cognitive growth and development in children (Trichuris dysentery syndrome) Risk for premature delivery, maternal morbidity, low infant birth weight in pregnant women
		A. lumbricoides	Reduced appetite due to parasitic adherence on the intestinal wall	
		T. trichiura	Lesions caused by constant defecation reflex in the cecum and ascending colon	
Vitamin A deficiency	Sri Lanka, Bangladesh, Indonesia, Vietnam, Kenya, Nigeria	*A. lumbricoides*	Expresses retinol-binding proteins that compete with the host's nutrient absorption in the jejunum	Xerophthalmia Diarrhea Risk for respiratory infections
		T. trichiura	Inhabitation of the ileocecal junction causes malabsorption	
Zinc deficiency	Nigeria, Cuba, Bangladesh, Cambodia, Vietnam, Malaysia	*A. lumbricoides*	Requires a zinc-dependent metalloproteinase which disrupts zinc absorption in hosts	Risk of malabsorption in other essential nutrients Chronic gastrointestinal abnormalities Diarrhea Dysentery Inflammation Anemia Poor appetite and rough skin Physical retardation Increased risk of contracting infectious and chronic diseases (e.g., measles, HIV, diabetes, cardiac diseases, cancer)
		T. trichiura	*No available information*	

significantly higher among hookworm infected children as the infection intensity increased.[4,26,30]

A similar pattern was seen in another study with the ferritin and hemoglobin concentrations of hookworm infected pregnant women.[18] In an earlier study, associations between hookworm infection and ferritin levels were only found, and not with hemoglobin. However, such contradiction was later on explained to be caused by the low-intensity infections in their study population.[19] In a systematic review for Nepali pregnant women, the association of heavy intensities of hookworm infection was later confirmed to cause lower hemoglobin levels than light intensity infections.[25]

Aside from hookworms, *A. lumbricoides* and *T. trichiura* were also investigated. An earlier study suggested that iron deficiency is common in *Trichuris* endemic areas.[33] However, there has not been enough evidence made to prove that single infections with either *A. lumbricoides* or *T. trichiura* are also responsible for decreasing iron. This is because the majority of the studies documented have co-infections with hookworms.

One study of iron absorption in 284 children revealed that of all those infected with at least one of the following: *A. lumbricoides*, *T. trichiura*, and hookworm, –61% had iron deficiency.[27] Another study from Ethiopian school children revealed that co-infections of *A. lumbricoides* and hookworms were generally associated with an

increased risk of iron depletion.[34] In some reports, the significant decrease in hemoglobin levels of infected schoolchildren was mainly attributed to hookworms, compared to the less than ten percent attributed to *A. lumbricoides*.[35] Moreover, there has also been a study that denied the association of *A. lumbricoides* to serum hemoglobin and ferritin levels. Instead, association with hookworm infections was emphasized.[27]

A study conducted to assess the association of *T. trichiura* in iron deficiency found out that there were no significant differences in hemoglobin concentration despite a varying intensity of infection.[28] In contrast, studies on the co-infection of hookworm and *T. trichiura* have successfully described an associated decrease in iron levels in pregnant women. Therefore, the association of *Trichuris* infection intensity with iron deficiency is strengthened when accompanied by hookworm infections.[20,24,36] One study has considered checking another known risk factor for iron deficiency prevalent in STH endemic areas. The dietary assessment of school-age children revealed that even those with a high daily intake of iron were infected with *T. trichiura* and still manifested malnutrition.[28]

Several pieces of evidence have linked the mechanism of infection with helminths to the development of iron deficiency. Reports from several studies have shown that hookworm infections cause chronic bleeding from the intestinal mucosa's mechanical laceration. These species ingest blood for their nutrition and cause enzymatic damage, leading to a significant iron depletion.[30] Despite the lack of direct reports of clinical cases, there are still reports hypothesizing the mechanism of *A. lumbricoides* and *T. trichiura* infections and their association with iron deficiency. *A. lumbricoides* eggs enter the host's body and mature into larvae at the small intestine, resulting in adult worms' residence for up to 1 to 2 years.[37] With their capacity to adhere in the intestinal wall, they are believed to indirectly affect the host's iron status with low hemoglobin levels due to reduced appetite.[34] *T. trichiura* starts with egg-containing larvae moving into the intestinal villi to grow and mature. As the adult worms reside in the cecum and ascending colon, such obstruction can cause constant defecation reflex that will result in lesions with intestinal bleeding that depletes the body's iron stores.[31,38-41]

Clinical Manifestations: Approximately 76% of STH with presenting iron deficiency ultimately manifest anemia (Table 1). Iron deficiency anemia (IDA) is triggered by lowering hemoglobin levels and serum ferritin due to impaired red blood cell synthesis even at low intensities of hookworm infections.[18,36] In children, IDA from infections is associated with impaired growth or stunting and essentially contributes to reduced cognitive functions.[4,30,42] Furthermore, infected pregnant women that develop IDA appear to be at risk with premature delivery, maternal morbidity, and infants' low birth weight.[43] Aside from anemia, iron deficiency can also imply a severe form of trichuriasis—Trichuris Dysentery Syndrome (TDS). Such a condition causes growth deficits both physically and cognitively, which are irreversible despite anthelmintic treatments or iron supplementation.[36]

Vitamin A deficiency and STH infection

Epidemiology: The distribution of STH-associated Vitamin A deficiency occurs in populations that are parallel with iron deficiency (Table 1). Rural communities from Asia and Africa remain to be a significant concern. The WHO has addressed that school-aged children are at a greater risk of STH with moderate or severe Vitamin A deficiency.[44] A majority of the clinical reports documented are of preschool-aged children from ages 3 to 4 and school-aged children from ages 5 to 11 (Ayogu *et al*., 2018).[4,13,26,29,45-47] Based on the findings, cases of Vitamin A deficiency from STH infection also occur in pregnant women, although they are less prevalent than iron deficiency as only a few have been reported.[29,44,48]

Pathogenesis: STH is a notable cause of Vitamin A deficiency. Recent studies suggested that infection from any species of STH can be associated with a greater prevalence of Vitamin A deficiency even after controlling other known risk factors such as diets that may affect the assessments.[13,44] However, there are yet to be documented reports for hookworm infections and Vitamin A deficiency. Of all the studies that examined the worldwide prevalence of STH infections and Vitamin A deficiency, results showed that malnutrition is more commonly affiliated with trichuriasis and ascariasis.[45]

In children of both preschool and school ages, lower serum Vitamin A concentrations were noted on all *Trichuris* infected subjects. The decrease was significant despite having a majority of low-intensity infections for *T. trichiura* only. On the other hand, lower serum levels of Vitamin A were only reported for *A. lumbricoides* when there are multiple infections with other species.[29,45,47] Even so, another study remonstrated this claim. Assessments showed that even *Ascaris* single infections exhibit association with lower retinol concentrations. Furthermore, there is an intensity-dependent relationship between Vitamin A deficiency and *Ascaris* infection.

The association becomes more potent as the severity of infection increases.[4] It has been noted by some studies that STH-associated infections can cause a transient decrease of serum retinol concentrations credited to an acute-phase response.[49,50] Nonetheless, deficit Vitamin A levels in infected hosts are more commonly attributed to the inhabitation of helminths in the intestine. In the jejunum, Vitamin A absorption from the diet starts after its emulsification with fatty acids and bile salts.[4] As *A. lumbricoides* mature in the small intestine and *T. trichiura* in the ileocecal junction, their adult worms interfere with the nutrient absorption.[46] The helminths compete for Vitamin A in the gut and lead to general malabsorption. *A. lumbricoides*, in particular, have been reported to express various retinol-binding proteins, dehydrogenases, and retinoic acid receptors for their growth and development.[36,44]

Clinical Manifestations: Xerophthalmia is three times more prevalent in *A. lumbricoides* infected children with Vitamin A deficiency.[36] In 2009, the World Health Organization estimated that over 5 million school-age children with Vitamin A deficiency had developed this severe complication that causes an abnormal dryness of the cornea and conjunctiva of the eye which can be accompanied by inflammation and can, later on, lead to blindness.[4,26,36,44,51,52] Furthermore, Vitamin A deficiency from STH infection often cause impaired mucosal barriers and reduced macrophages, NK cells, and neutrophils due to parasitic infestation of the intestine, leading to diarrhea and respiratory infections.[51,53,54]

Zinc deficiency and STH infection

Epidemiology: There are significantly fewer documented reports about STH-associated zinc deficiency compared to the previously discussed micronutrients. Studies are pooled from low and middle- income countries as demonstrated in Table 1. Members of rural communities with poor access to sanitation and hygiene continue to be the primary concern in this public health issue. The prevalence of STH infection and zinc deficiency is comparably more common in young children of school age rather than pregnant women.[4,8,29,47,55]

Pathogenesis: Much like the other micronutrient deficiencies, a significant association between zinc and STH-linked infections can be observed. Only *Trichuris* and *Ascaris* infections have been successfully correlated to zinc deficiency. A study from Bangladesh has reported that zinc deficiency was highly prevalent in children infected with *T. trichiura*.[55] This was supported later by another study that presented lower mean serum zinc detected in *T. trichiura* infected Vietnamese and Nigerian children.[4,47] Associations of zinc deficiency with *Ascaris* infections were also significantly identified in children and pregnant women.[4,29,55]

Contrastingly, a study reported that any species of STH had no association with the rate of zinc deficiency in pregnant women.[56] They claimed that the lower levels of zinc in women were caused by their pregnancy and not by helminth infection. The rate of zinc deficiency was two-fold higher than non-pregnant women. Even so, the absence of association may be attributed to the intensity of the infections in their study population. This is because most of the infected women in their study had light infections only. This was supported by a study that explains how the severity of nutritional deficiency in infected hosts depends significantly on the intensity of infection.[57] Several reports have also concluded that reduced uptake of zinc results from increasing worm infection intensity.[8,47,58]

Although documented clinical cases on zinc deficiency and STH infection are still significantly lacking, efforts have been made to describe the mechanism of the helminths during infection. Studies have shown that *A. lumbricoides* tend to feed on the host's tissues and severely consume zinc during serious infections in children since STH requires a zinc-dependent metalloproteinase for their function. Overall, this phenomenon impairs and neutralizes the immune system for the maturation of the parasitic ovum inside the jejunum.[4,29,58] Another study has noted that zinc deficit reduces infection resistance by interfering with T cells to produce interleukin-4, vital in infection control for STH.[29] There is yet to be available information that explains the underlying mechanisms of other STH species in zinc depletion.

Clinical Manifestations: The increased worm burden can further aggravate the risk of malabsorption in other essential nutrients (iron and Vitamin A) and eventually present chronic gastrointestinal abnormalities.[47,58] STH infection in relationship with zinc deficiency causes diarrhea, dysentery, inflammation, and anemia based on the intensity of infection present on the host's body.[4,29,51,56,58,59] Due to the altered metabolism pathways in the gut, metal homeostasis becomes unregulated and manifests physical retardation in infected children.[60] A cross-sectional study conducted in Ede-Oballa showed that school-aged children with this deficiency manifest stunting, thinness, and underweight.[47,61] Moreover, poor appetite and rough skin also occur. If it remains untreated, a severe implication of this deficiency is an increased risk of

contracting infectious and chronic diseases such as measles, HIV, impaired neurogenesis, diabetes, cardiac diseases, and cancer.[59]

CONCLUSION AND RECOMMENDATIONS

From the extensive review, it can be concluded that STH infections can cause micronutrient malnutrition. The database on epidemiology reveals that the existing relationship between STH and micronutrient malnutrition is a significant burden in a specified population, contributing mainly to children or pregnant women who reside in rural communities of developing countries (e.g., Asia, Africa). The bottom line of this issue is the unresolved problem of poverty—leading these nations to have little access to clean water, practice poor hygiene, and proper diet. Such factors are significant contributors to the prevalence of infections with malnutrition since the pathogenesis of STH begins with the ingestion of infective eggs and into their maturation in the intestine.

Iron deficiency is the most common micronutrient malnutrition manifested in infected populations, mainly in pregnant women. The resulting serum iron levels become deficient due to chronic intestinal bleeding from the worm inhabitation. In contrast, Vitamin A deficiency occurs more often in children than in pregnant women. Low Vitamin A levels are caused by malabsorption due to competing parasites in the gut. Lastly, although with the least number of reports, zinc deficiency can be caused by the gastrointestinal tract's impaired assimilation and immune functions as parasites feed on the hosts' tissues. Eventually, the emerging micronutrient deficiencies manifest through anemia, impaired physical and cognitive growth in children, premature delivery and maternal morbidity in pregnant women, and increased susceptibility to infections and chronic diseases (e.g., measles and HIV).

This narrative review provides an essential framework that will be useful for planning public health administrations of rural communities in endemic populations. Health strategies such as deworming programs (only after the first trimester in pregnant women) and vitamin supplementation for the targeted demographics will alleviate the burden of STH-associated micronutrient malnutrition. Such band-aid solutions must also be accompanied by interventions, including investing in infrastructure development required for a clean and safe water source, adequate sanitation facilities, and information education on water, sanitation, and hygiene in affected communities to help address the root cause of the problem.

Since only a few of the studies have conducted additional assessments for other possible contributing factors (e.g., diet intake), further research is needed to elucidate the complex interplay of other determinants and risk factors that may also be involved in this health scenario.

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Authors' Contributions

This review paper was designed, coordinated, and directed by DUM together with SRC. The gathering of the data and literature search was conducted by AJYA, ARB, SRC, JDF, DUM, SMS, RMB, ARB, and SRC have written the abstract, providing a concise summary of the dissertation. The introduction was accomplished by AJYA, SRC, SMS, and RMB, giving an overview of the paper. In contrast, JDF and DUM constructed the methodology section. The results were analyzed by AJYA, ARB, SRC, JDF, DUM, and SMS. Furthermore, JDF and DUM discussed the significance of the findings, including the conclusion and recommendations. All authors have read and approved the final paper.

CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ABBREVIATIONS

STH: Soil-transmitted Helminth; **WHO:** World Health Organization; **NTD:** Neglected Tropical Diseases; **HIV:** Human Immunodeficiency Virus; **IDA:**

Iron Deficiency Anemia; **TDS:** Trichuris Dysentery Syndrome; **NK Cells:** Natural Killer Cells.

SUMMARY

This review deals with the comprehensive literature on the correlation of soil-transmitted helminth infections with micronutrient malnutrition of iron, vitamin A, and zinc.

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