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## Helminth infections and micronutrients in children

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## Summary

Infections with intestinal worms (named 'soil-transmitted helminths') and micronutrient deficiencies are two major global health problems, especially in children. Both conditions are strongly related to poverty and often go unnoticed. Still, growth and general health can be considerably impaired by either condition. This thesis set out to examine possible interrelationships between intestinal worm infections and micronutrients in children. The approach consisted of analyzing research data from observational and experimental studies. **Chapter one** provides background information about intestinal worm infections and micronutrient status in children, as well as possible mechanisms underlying their interrelationships.

Firstly, a systematic review and meta-analysis were performed of existing studies addressing both worm infections and micronutrients (**chapter two**). Deworming studies in which micronutrients were measured as outcome and micronutrient supplementation or fortification trials in which worm (re)infection was assessed were searched, but also studies estimating associations between worm infections and micronutrients were included. Data were combined from these studies in meta-analyses, providing pooled estimates for the associations under study. The results showed that on the basis of the existing literature, worm infection was significantly and negatively associated with vitamin A but not with iron. Conversely, deworming resulted in an increase in iron status but not in vitamin A status changes. Iron supplementation did not have a significant effect on worm infection, but multi-micronutrient consumption tended to reduce the risk of worm infection. Research on worm infections and micronutrients other than iron or vitamin A was scarce.

In **chapter three**, associations were explored between three species of intestinal worms and several markers of micronutrient status in Vietnamese children. In this study population, the three types of worms most often studied (*Ascaris lumbricoides*, *Trichuris trichiura* and hookworm) were all prevalent. Concentrations of blood hemoglobin, plasma ferritin (iron), plasma retinol (vitamin A), plasma zinc and urinary iodine were measured and compared between children with single or multiple worm infections and uninfected children. Infections with the roundworm *Ascaris* were associated with vitamin A deficiency. This association was intensity-dependent: the heavier the infection with *Ascaris*, the lower the plasma vitamin A concentrations. Two other types of worm, *Trichuris* and hookworm, were associated with lower blood hemoglobin concentration but not plasma ferritin, a marker of iron status. Zinc deficiency occurred less often in children infected with *Trichuris* than in uninfected children. The results described in this chapter show that associations between

intestinal worm infections and micronutrients are species-specific and can be intensity-dependent.

Associations between height, zinc and intestinal worm infection were analyzed in **chapter four**. To this end, data were combined from two large epidemiological studies in Cuba and Cambodia. Zinc is known to be an essential nutrient for many biological processes, including growth. Indeed, in both populations, zinc was associated with height. In Cuba, worm infection was associated with height, but not with zinc. In Cambodia, a weak association between zinc and worm infection was found. These differences could be due to the fact that zinc was measured in different body compartments (in hair in Cuba and in plasma in Cambodia). The prevalences of both stunting and zinc deficiency were much higher in Cambodia than in Cuba.

**Chapter five** describes inflammatory markers in worm infected and uninfected children in Cuba and Cambodia. Markers of systemic (acute phase) inflammation C-reactive protein and alpha-1-acid glycoprotein (CRP and AGP) were measured in blood. In addition, a marker of local intestinal inflammation (calprotectin) was measured in stool samples. None of these inflammation markers were significantly associated with intestinal worm infection. While CRP and AGP are often used as general markers of any infection, intestinal worms are known to be able to suppress host immune responses. In both populations, an elevated concentration of CRP occurred less often in worm infected children. This finding is in line with descriptions by previous studies of the immunosuppressive capacities of worms. An elevated CRP level is a strong predictor of cardiovascular disease. Hence, the question whether worm infections are able to modify cardiovascular risk merits further investigation.

**Chapter six** shows the results of a cluster-randomized trial in Cambodia, wherein children were given micronutrient-fortified rice or placebo (regular white rice) within their daily school meals. Surprisingly, the children who received micronutrient-fortified rice became infected with hookworm (the locally predominant intestinal worm infection) more often than children in the placebo group. This held true for all three types of fortified rice which were studied. However, this effect was only seen in schools where the prevalence of hookworm exceeded 15% at baseline. These results are alarming, as micronutrient fortification of foods is considered very safe and is being increasingly implemented in countries where both micronutrient deficiencies and intestinal worm infections occur frequently.

Lastly, in **chapter seven** the findings of chapter two to six are integrated and discussed. The results of the research described in this thesis have shown that intestinal worm infections are associated with micronutrient status in children, and that these associations differ per worm species and per micronutrient. This information can be helpful in designing the most effective strategies to combat micronutrient deficiencies and worm infections in children in countries where both conditions are prevalent. To further our understanding of the interrelationships between intestinal worms and micronutrients, studies should address the possible mechanisms underlying these relationships. In particular, it is important and urgent to investigate how micronutrient-fortified rice could have increased hookworm infection risk in the Cambodian trial.