APPENDIX

SUMMARY

There has been a global increase in prevalence of allergic diseases. This is particularly so in developed and in urban centres of developing countries. An inverse geographical pattern is seen when one considers helminth infections. Exposure to helminth infections has been minimal in developed countries and is being controlled in urban centres of developing countries due to improvement in sanitation and education as well as improved medical care. At the same time, in rural areas of developing countries helminth infections are still highly prevalent.

Interestingly, both helminth infection and allergens are potent inducers of Th2 responses that lead to high levels of IgE, eosinophils, as well as the secretion of Th2 cytokines such as IL-4, IL-5, IL-9 and IL-13. Despite the similar immunological profiles associated with both helminth and allergies, several epidemiological studies have failed to show a consistent relationship between helminth infections and allergies. The role of socio-economic status (SES) which can be intertwined with presence or absence of helminth infections, has been examined in relation to development of allergic disorders in several studies. The results are gain conflicting.

In both developed and developing countries, a strong correlation is observed between allergen-specific IgE and symptoms of allergy among urban populations of high SES. However, in developing countries, in rural populations or urban populations with low SES, helminth-induced IgE cross-reactivity and regulatory networks may prevent the translation of allergen-specific IgE into skin reactivity or allergic symptoms.

In addition, the isolation and characterization of allergen components, as well as their production by recombinant techniques, has led to significant progress in allergy diagnosis. Component-resolved diagnostics (CRD) allow the detection of specific IgE against individual allergen molecules instead of against allergen extracts comprised of mixtures of allergen molecules, which are commonly used in SPT and conventional specific IgE testing. The CRD method has been widely used in developed countries, but less used in non-affluent areas where helminth infections are highly prevalent.

The studies presented in this thesis shed light on the relationship between helminth infection, SES and atopic disorders in a developing country (Indonesia) where large differences in life-style, environmental exposure and SES are seen.

Chapter 1

This chapter presents the associations found between helminth infections and atopic disorders from previous studies. It also discusses how helminth infection can lead to IgE cross-reactivity with allergens and how this IgE has poor biological activity. In addition, it describes important information regarding the use of new diagnostic methods using CRD for allergic disorders in countries where helminth infections are highly prevalent.

Chapters 2 and 4

Recent studies indicate that helminth infection is one of the environmental factors that, together with socio-economic status (SES), contribute to the development of allergies. In Chapters 2 and 4 we examined differences in prevalence of allergic outcomes in rural and semi-urban areas of Indonesia on Flores Island and in children of high and low SES families from an urban centre. Higher prevalence of skin reactivity to house dust mite (HDM) was found in the semi-urban area that seemed to be due to higher level of education (as part of the SES indicators) and a lower degree of helminth infections compared to the rural area. When considering children from the same urban centre but belonging to families with different socio-economic status, we found that whereas specific IgE to HDM increased the risk of being skin prick test positive and that a positive SPT to HDM was then associated with increased risk of wheezing in children of high SES, this was not the case in children of low SES families. Taken together, these results highlight that environmental as well as socio-economic factors should be considered by clinicians and researchers working on prevention, diagnosis and treatment of atopic disorders in low-to-middle income countries. More research is needed to evaluate the possible risk and protective factors in more detail as well as to pinpoint elements of SES that matter in the development of atopic disorders.

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Chapter 3

Here we provide a study protocol of a household randomized placebo-controlled trial in Flores Island to answer the question whether helminth infections play a role in the development of atopic disorders. This chapter describes in detail the overview of the study population in a semi-urban and a rural area of Flores Island, Indonesia, which is used in chapters 4, 5 and 6.

Chapter 5

This chapter reports the malarial parasitemia and allergy outcomes of a 2-years duration randomized trial. Our two-year placebo controlled deworming trial shows a trend that deworming increases skin reactivity to any allergen. We found a significant increase in SPT reactivity to cockroach after 21 months of anthelmintic treatment. In addition, we also found that repeated three-monthly treatment with albendazole reduces but does not eliminate helminth infection. These findings suggest that longer intensive anthelmintic treatment, possibly a combination of drugs, or drugs and environmental control, is needed for future studies to achieve helminth elimination.

Chapter 6

The study presented here, regarding the profile of IgE antibodies using a biochip array and plasma from a helminth-endemic area, provides evidence that there is strong IgE reactivity to some of the natural allergen components from pollen which carry cross-reactive carbohydrate determinants (CCDs). This reactivity is probably helminth-induced. Our study also found

unexpectedly high reactivity to recombinant venom allergens (bee, common wasp and paper wasp) in children from a helminth-endemic area, but the origin of this sensitization still needs to be elucidated. We provide evidence of cross-reactivity between IgE to allergens and CCD markers, suggesting that using natural and recombinant allergens on the microarray might help to better differentiate between primary sensitization that is biologically relevant and cross-reactivity for diagnosis of atopic disorders in helminth-endemic low-to-middle income countries. Further research into helminths and IgE should focus on refining and preparing new diagnostic methods for the developing world where allergies are increasing but the diagnosis is hampered by the lack of knowledge on locally important allergen sources and the complexity of the specificities and characteristics of IgE antibodies.

Chapter 7

This chapter summarizes and discusses the main findings of the thesis. Taken together, we have demonstrated the association between atopic disorders and helminth infection and SES, as well as provided evidence that two years of deworming has a minimal impact on allergy outcomes. We characterized IgE antibody profiles in a helminth-endemic area and we showed that high levels of IgE do not translate to skin prick test reactivity or clinical symptoms of allergy.