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Epidemiological transition in Indonesia : impact of helminths and urbanization on the development of Type 2 diabetes

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APPENDIX

SUMMARY

In the past few decades, there has been a substantial increase in the number of people with type 2 diabetes (T2D) worldwide, especially in low and middle income countries. In these countries, rapid socioeconomic developments and urbanization have led to changes in diet, lifestyle, and environmental factors. This in turn is associated with complex changes in disease pattern, evident from the increasing prevalence of non-communicable diseases, including T2D, as well as the reduction in communicable diseases. Despite the strong evidence that T2D is associated with increased risk of infectious diseases, and that the presence of infections will worsen the host glucose metabolism, recent evidence suggests that helminth infections might give protection against the development of T2D. In this thesis, we reported our investigations on the impact of helminth infections, in light of increasing urbanization, on the development of T2D in Indonesia.

Chapter 1

Here we discussed the increasing prevalence of non-communicable diseases, especially T2D, in Indonesia, which is largely attributed to the rapid pace of socioeconomic development and urbanization. As a result, there is great geographical variation where high prevalence of T2D is seen in urban areas but low prevalence in rural regions of the country. This might suggest that traditional living environments in rural areas might give a relative protection against the development of T2D. This protection against the development of T2D has been reported to be mainly related to the more physically active lifestyle and healthier traditional diet, however other environmental factors might play a role as well. Several epidemiological studies, conducted in different populations, suggest that helminth infections, which are still endemic in many rural areas of low and middle income countries, including Indonesia, might confer protection against the development of T2D.

Chapter 2

Here we described in detail our study protocol to investigate whether helminth infections have a direct effect on insulin resistance, a marker and strong predictor for the development of T2D. To achieve this, we designed a large-scale randomised population-based, household-clustered, double-blind placebo-controlled trial of anthelmintic treatment in an area endemic for soil-transmitted helminth (STH), on Flores Island, Indonesia. The 12-months anthelmintic treatment regimen consisted of four rounds of three monthly 400mg albendazole or matching placebo given

for three consecutive days under direct supervision. We performed clinical anthropometry measurements, as well blood, urine, and stool sample collections before and after the anthelmintic treatment to assess any changes in insulin resistance (and other metabolic parameters), as well as immune responses, after reduction in STH infection prevalence and intensity.

Chapter 3

This chapter reported the main outcomes of an intensive 12-months anthelmintic treatment. Our intensive treatment significantly reduced STH prevalence and intensity, but did not eliminate these infections. Importantly, anthelmintic treatment in helminth-infected subjects lead to a significant but slight increase in insulin resistance, providing the first causal evidence on the protective effect of helminths on insulin resistance, hence T2D. Furthermore, the increase in insulin resistance was mainly mediated by the increase in body mass index, suggesting the importance of human adipose tissue in helminth-associated beneficial metabolic effects.

Chapter 4

Here we provided additional evidence on the importance of human adipose tissue in helminth-associated beneficial metabolic effects. Anthelmintic treatment in helminth-infected subjects lead to significant changes in two hormones secreted by adipose tissue, namely leptin and adiponectin. We observed an increase in leptin to adiponectin ratio which may contribute to the increase in insulin resistance. While leptin has been associated with inflammation and insulin resistance, the converse has been reported for adiponectin. Thus, leptin to adiponectin ratio can be regarded as a marker of a balance between inflammation and anti-inflammation, and has, in some studies, been reported to be positively associated with insulin resistance.

Chapter 5

In order to assess the contribution of different living environments on the development of T2D, we compared the metabolic profiles between people living in rural and urban area with similar genetic background. People who moved from Flores island to Jakarta had a higher degree of insulin resistance, which was mainly due to the higher adipose tissue mass and leptin level. Increasing time spent in urban area was positively associated with higher adipose tissue mass. Next, to assess whether rural living environments protect against diet-induced insulin resistance, we compared the metabolic response on a high-fat high-calorie diet

(HFD) between rural and urban participants with the same amount of adipose tissue mass. Living in a rural area or having current helminth infection, did not protect against the induction of insulin resistance by short term HFD intervention.

Chapter 6

This chapter summarizes and discusses the main findings of this thesis. First, we have proven that helminth infections do have a causal effect on the development of insulin resistance. Thus, the currently on going deworming programs might accelerate the development of T2D, which advocates that the current deworming program should go hand in hand with efforts to monitor and prevent the development of obesity and T2D. Second, the effect of helminths on the development of T2D seems to be mainly explained by reduction of adipose tissue mass, as well as modulating secretion of adiponectin and leptin. Third, living in urban area is also associated with higher insulin resistance, hence a higher risk to develop T2D, which is mainly explained by a progressive increase in adipose tissue mass with increasing duration of time spent in an urban area. In addition, although it is not a major question in our study, the findings in our deworming trial suggests that the current World Health Organization deworming treatment regimen might need to be intensified to reach helminth elimination.