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

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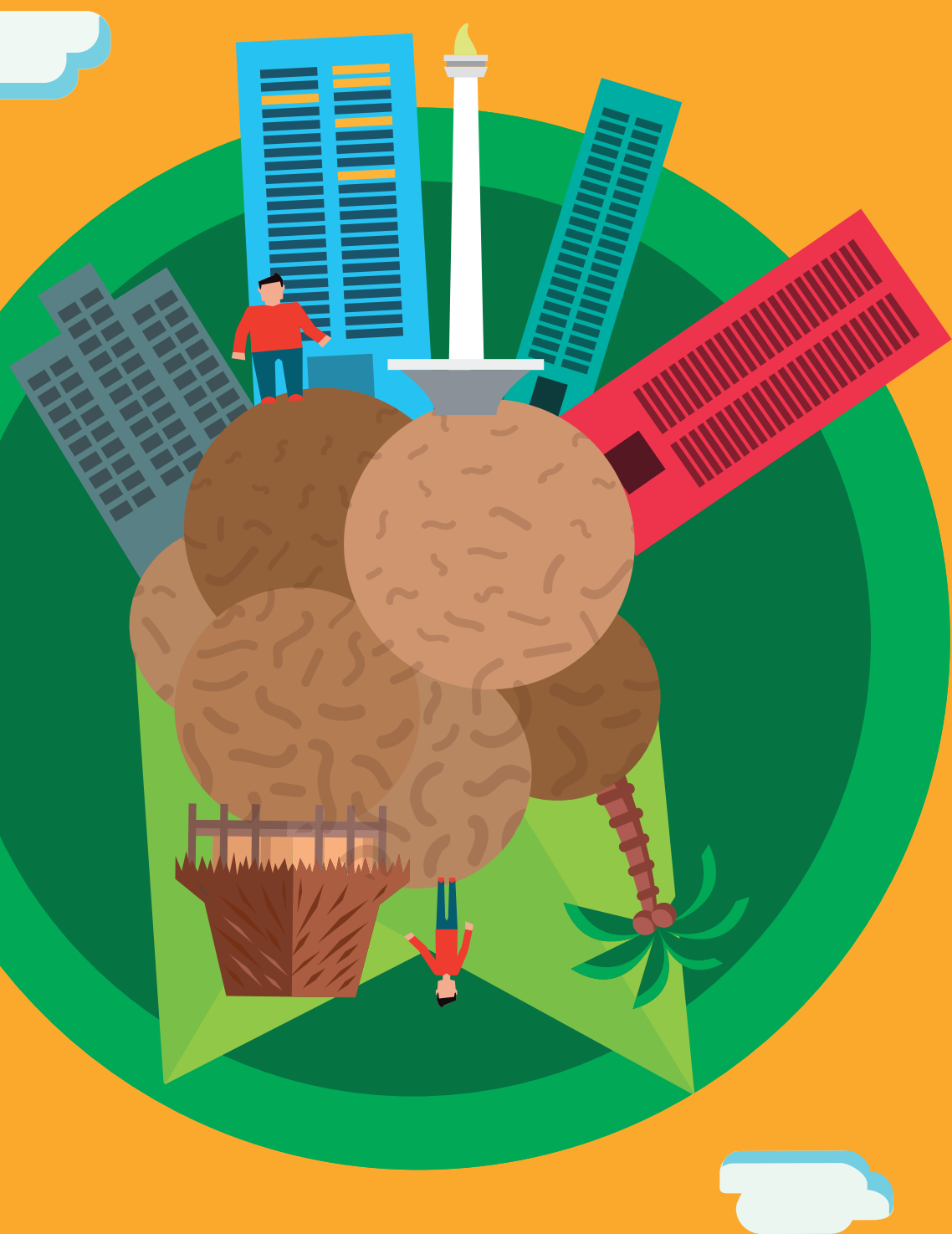


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Chapter 1

GENERAL INTRODUCTION

Adapted from:

A. Challenges in diabetes management in Indonesia: a literature review

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B. Helminths, hygiene hypothesis and type 2 diabetes

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EPIDEMIOLOGICAL TRANSITION: THE SITUATION IN INDONESIA

There has been an alarming increase in the worldwide burden of type 2 diabetes (T2D) [1], especially in low and middle-income countries (LMIC),[2] including Indonesia. As the fourth world's most populous country, Indonesia is currently undergoing an epidemiological transition. In 2014, 77% of total mortality was estimated to be attributed to non-communicable diseases (NCD), of which diabetes was the third highest after cardiovascular disease (CVD) and cancer.[3] This number considerably increased from the previous report in 2010, of which 63% of all deaths were attributed to NCDs. It is important to note, that whereas the percentage of mortality attributed to CVD and cancer were relatively constant, the diabetes-attributable death has doubled from 3% to 6%[3]. However, a marked geographical variation in disease patterns exists, which is exemplified by the high prevalence of infectious diseases in rural area, but of NCDs, including T2D, in urban areas.

In 2015, the International Diabetes Federation reported that, whereas, 6.5% of Indonesian adults have diabetes, 17.9% of them also have impaired glucose tolerance (IGT), which is associated with a higher risk to develop T2D.[1] These numbers have substantially increased from previous study in 2007 which reported that the prevalence of diabetes and IGT was 5.7% and 10.2%, respectively.[4] Epidemiological studies of diabetes have indicated that the prevalence in Jakarta, the capital city of Indonesia, rose from 1.7% in 1982 to 5.7% in 1993, and then more than doubled to 12.8% in 2001.[5] A study in Ujung Pandang, a metropolitan center on Sulawesi island, also showed similar results.[5] Despite the paucity of data from rural areas, a study in Ende, Flores island, a rural area of Indonesia, found a much lower prevalence of T2D of 1.56%.[6] The results of these epidemiological studies in urban and rural area of Indonesia, which are in line with studies elsewhere on the association between rural-to-urban migration and increased risk of T2D and other CVD risk factors,[7-11] indicates the importance of expanding studies to outside of urban centers. Collecting information from rural areas, not only would help prepare the health system for emerging diseases but it will also enable the identification of important risk factors for CVD and therefore guiding interventions. One potentially important aspect of rural areas, where 40% of the Indonesian population lives,[3] is the possible effect helminth infections might have on glucose metabolism.[12]

Helminth infections affect approximately 1.4 billion people worldwide, of which a significant proportion are in Southeast Asia,[13] including Indonesia [14] For

example soil-transmitted helminths (STH), which despite a decrease in overall national prevalence from 47.2% to 24.6%, [13] are still very prevalent in most rural area of Indonesia, [15-17] and in some villages more than 80% of the population are infected with these parasites [15, 17], which in part is due to the tropical and moist climate. [18] Poor sanitation infrastructure and hygiene practises, as well as lack of adequate clean water resources, might also contribute. [19]

INVERSE ASSOCIATION BETWEEN HELMINTH INFECTIONS AND T2D

Worldwide, there is little overlap between the prevalence of soil-transmitted helminths and T2D (**Figure 1**), which is supported by a number of epidemiological studies in different populations reporting an inverse association between helminths and metabolic diseases. [20-24]. Interestingly, these studies consistently reported an inverse association between previous [22, 23] or current [20, 21] helminth infections and metabolic diseases, namely metabolic syndrome prevalence [22, 23], T2D prevalence [21, 23] and Insulin Resistance (IR), as assessed by homeostatic model assessment (HOMA)-IR [20].

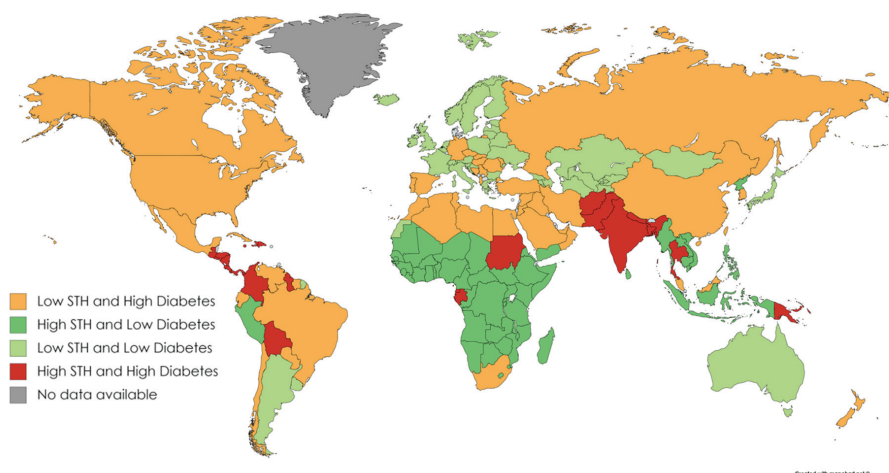


Figure 1. Worldwide prevalence of soil-transmitted helminths (STH) and diabetes. STH prevalence is defined as the estimated proportion of children (1-14 years of age) requiring preventive chemotherapy for STH per country, [14] of which in this figure, proportion of lower than 1/3 is considered low. The prevalence of diabetes in adults (20-79 years of age) per country, [1] of which in this figure prevalence of lower than 7% is considered as low).

The association between previous helminth infections and metabolic diseases has been reported in China. Chen *et al.* used self-reported disease and medication history, cross-referenced with local government registry data, as a method to diagnose previous schistosome infections (PSI)[23]. The prevalence of both T2D and metabolic syndrome was significantly lower in the group with PSI compared to the non-PSI group (14.9% vs 25.4%, $P<0.0001$; 14.0% vs 35.0%, $P<0.0001$, respectively). In addition, PSI was associated with lower levels of body mass index (BMI), HOMA-IR, plasma fasting blood glucose, postprandial blood glucose, and glycated haemoglobin A1c (HbA1c)[23]. A different method of PSI diagnosis was used by Shen *et al.*, because schistosome-associated liver pathology can be present for years, therefore ultrasonography was performed to detect chronic schistosomal liver disease [22]. PSI was significantly associated with a lower prevalence of metabolic syndrome (18.28% in PSI group vs 34.01% in control group) and its components, including central obesity, hypertension, low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, and hyperglycaemia. [22]

The inverse association between current helminth infections and metabolic diseases was first reported in Chennai, India. Aravindhan *et al.* reported a significantly lower prevalence of lymphatic filariasis among diabetic subjects compared to pre-diabetic and non-diabetic subjects [24]. Furthermore, Hays *et al.* found that among 259 Australian Aboriginal adults, participants with a chronic *S. stercoralis* infection, as defined by serological testing, were 61% less likely to be diagnosed with T2D compared to those who were uninfected, after adjustment for age, blood pressure, triglycerides and BMI [21]. Furthermore, it was shown by a study in rural area of Indonesia that subjects with a current STH infection had a lower BMI and lower levels of HOMA-IR, indicating that infected subjects were more insulin sensitive compared to uninfected subjects [20]. A significant negative association was found between the number of helminth species a subject was infected with and HOMA-IR, even after adjustment for age, sex and BMI [20].

A recent meta-analysis showed that individuals with a previous or current helminth infection were 50% less likely to have an outcome of metabolic dysfunction (hyperglycaemia, T2D, metabolic syndrome or insulin resistance) compared to those uninfected (OR 0.50; 95% CI 0.38-0.66) [12]. However, cross-sectional studies provide no information on the causal relationship between helminths and metabolic diseases and therefore longitudinal studies are required.

MECHANISM BEHIND THE INVERSE ASSOCIATION BETWEEN HELMINTHS AND T2D

Adiposity and Adipose Tissue Inflammation

Insulin resistance, a decrease in insulin-stimulated glucose uptake, is a hallmark of T2D leading to hyperglycaemia. Whereas increased adiposity has been associated with an increased risk of developing IR and T2D[25], helminth infection has been commonly associated with a poor nutritional status and reduced adiposity,[20, 22, 23] suggesting that helminth-associated lower adiposity may contribute to the observed lower IR.[20] However, despite the abundance of evidence on the role of human adipose tissue on IR, which will be summarized below, no data are available on the effect of helminth infections on human adipose tissue.

Obesity-induced chronic low-grade inflammation seems to be a key feature in the development of IR, hence T2D [26-29]. Initiation of inflammation in obesity involves inflammation of visceral adipose tissue (VAT), and the release of free fatty acids (FFA) as well as liver inflammation (called non-alcoholic steatohepatitis (NASH)), which then promote systemic inflammation, reflected in increased levels of pro-inflammatory cytokines,[26] such as $\text{TNF-}\alpha$, [30, 31] that lead to an impairment in insulin signalling.[26] This will thereby affect glucose levels by leading to a reduced glucose uptake in skeletal muscles, increased hepatic gluconeogenesis, and an increase in circulating free fatty acids.[26]

Adipose tissue inflammation plays a prominent role in the development of obesity-induced inflammation [27], which is characterized by the accumulation of inflammatory cells in obese adipose tissue creating a pro-inflammatory milieu [32]. A number of studies have shown that there is a phenotypic switch [33-35] from anti-inflammatory alternatively activated macrophages (AAM or M2) in adipose tissue, which are activated by IL-4 and IL-13 and express anti-inflammatory IL-10 [32, 36], towards pro-inflammatory classically activated macrophages (CAM or M1), which secrete various pro-inflammatory mediators ($\text{TNF-}\alpha$, IL-6, IL-1 β , IL-12, IL-23) [32, 36]. This phenotypic switch is positively correlated with IR.[33-35]

In addition, an imbalance between pro- and anti-inflammatory adipokines may also contribute to the development of IR [37]. Leptin, a pro-inflammatory adipokine [37], can increase and suppress the production of circulating Th1 and Th2 type cytokines, respectively [38]. Other pro-inflammatory adipokines, such as resistin, $\text{TNF-}\alpha$, IL-6, IL-18, retinol-binding protein (RBP) 4, lipocalin 2, angiopoietin-like

protein (ANGPTL) 2, CC-chemokine ligand (CCL) 2, and CXC-chemokine ligand (CXCL) 5 have been reported to be upregulated in an obese state [37]. Adiponectin, an anti-inflammatory adipokine [39, 40], can stimulate the production of IL-10 by macrophages [41]. Recently, another anti-inflammatory adipokine, Sfrp5, was reported to have beneficial metabolic effects [39].

Aside from the adipose tissue, inflammation in other tissues, such as liver, skeletal muscle and the pancreas, might also contribute to the development of obesity-induced inflammation and therefore the development of IR. In obesity, the activation state, but not the number of Kupffer cells (KC), in the liver changes [42, 43] promoting the expression of inflammatory genes, [42] as well as the production of inflammatory mediators which leads to an increased IR in the liver. [43] Liver inflammation might also be initiated by the abdominal adipose tissue-associated increased secretion of pro-inflammatory cytokines into the portal circulation. [27] In contrast, skeletal muscles may not be the site where inflammation is initiated, but the target of inflammation-induced IR. [27] An increased expression of inflammatory markers within skeletal muscle was only reported among obese people with T2D, but not among obese people without T2D. [44] In the pancreatic islets of diabetics, increased levels of the pro-inflammatory cytokine IL-1 β have been found, [45] which is a master regulator of islet cell inflammation in T2D. [46] This pancreatic islet inflammation is a key step in the development of T2D, as the failure of beta cells to compensate IR will lead to the development of hyperglycaemia and T2D. [47]

Immunomodulatory Effects of helminths

Helminth has been shown to be a potent natural inducer of type 2 and regulatory responses. [48-51] As chronic low grade inflammation plays a key role in the development of IR and T2D, [29] helminth-associated immune responses may therefore dampen systemic inflammation, hence increasing insulin sensitivity. [52-54] Despite the possible main role of adiposity in mediating the helminths-associated protective effects in human, it has been reported that even after adjustment for adiposity, the association between helminth infections and lower IR is not completely attenuated [20], suggesting that other pathways, such as helminth-associated immunomodulatory effects, may be involved.

A number of experimental studies in mouse models have provided evidence for the beneficial effects of helminths and helminth-derived molecules on metabolic homeostasis, [55-60] and shed light on the immunomodulatory mechanisms that

could explain the link between helminths and T2D. Helminths influence metabolic homeostasis,[61-63] at least partly, by changing the immune cell composition in the adipose tissue. Whereas obesity-induced low-grade chronic inflammation is characterized by the accumulation of CD8⁺ T cells, CD4⁺ Th1 cells, CAMs, B cells and mast cells in the adipose tissue (AT), chronic helminth infections or helminth-derived molecules induce increased numbers of CD4⁺ Th2 cells, eosinophils, AAMs, Tregs and ILC2s, dampening the inflammation and improving glucose tolerance.

Although there is very little human data available that could explain the mechanism by which helminths may protect against T2D, it can be speculated that helminths suppress chronic inflammation associated with T2D by modulating the immune response. Recent population-based study has shown that community deworming program alleviates helminth-associated immune hyporesponsiveness,[64] however, the question whether this would lead to the development of inflammatory disorders, including T2D, in the future, remains unanswered.

Taken together, there is evidence that suggests living a more traditional lifestyle in a rural environment might confer a protective effect against the development of NCDs, including T2D. With the rapid pace of socioeconomic development and increased rate of urbanization, these relatively protective lifestyle and environment will progressively subside. In urban areas or urbanized communities, changes toward a more sedentary lifestyle and increased consumption of energy-dense food, will lead to a positive energy balance and increased adiposity, contributing to the increased burden of T2D.[65] It is also hypothesized that improved hygiene and sanitation in parallel with the current deworming programs, leading to a decreased exposure to helminth infections, which have been shown to have a protective metabolic effect,[12, 20-23] might also contribute to the increasing prevalence of T2D.[52-54] The proposed association between epidemiological transition, urbanization, insulin resistance, and helminth infections are schematically summarized in **Figure 2**.

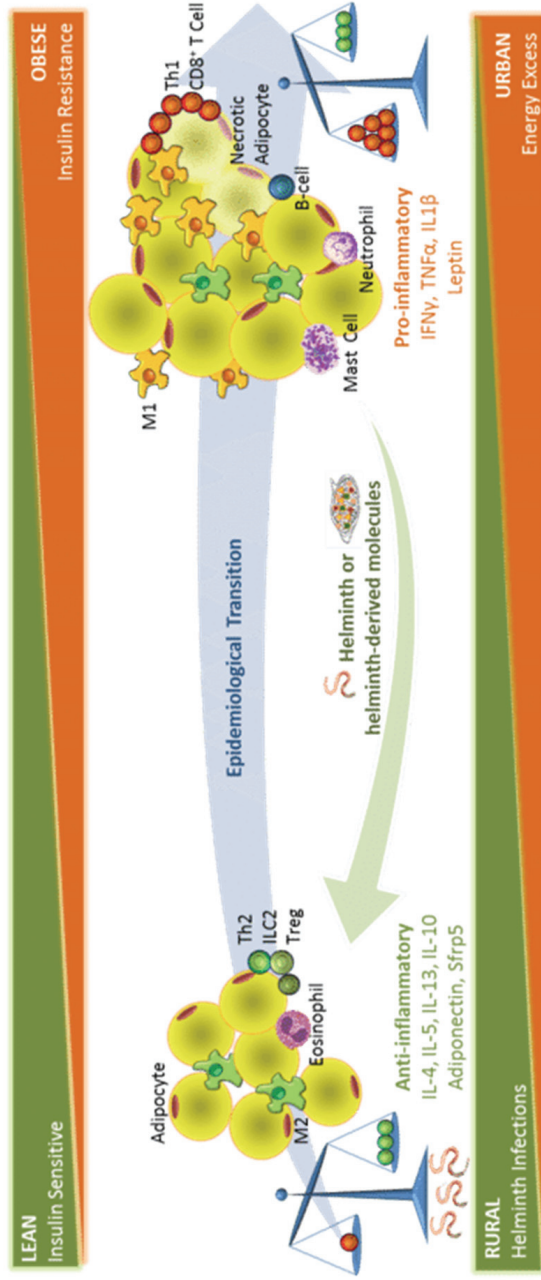


Figure 2. Epidemiological Transition, Insulin Resistance, and Helminth Infections. Along with epidemiological transition, the prevalence of obesity is higher and exposure to helminth infections is lower in urban areas compared to rural areas. With obesity, the immune cell composition in the adipose tissue shifts towards a pro-inflammatory profile associated with insulin resistance. Helminths or helminth-derived molecules are thought to prevent and/or reverse this shift by inducing an anti-inflammatory immune cell environment, which is associated with insulin sensitivity.

SCOPE AND AIMS OF THE THESIS

The main objective of this thesis is to improve understanding of the role of helminth infections in the development of IR, hence T2D, in the light of increasing urbanization in Indonesia. We aimed to unravel the causal effect of helminth infections on human metabolic homeostasis by assessing how anthelmintic treatment (deworming) could affect IR and other metabolic parameters. Our large scale cluster randomized controlled trial (RCT) was performed in a rural area of Indonesia, which is an area endemic for STH, and has been previously reported to have a low prevalence of IR and T2D. We also assessed the role of adiposity and adipokines in mediating the effect of helminths on IR. Next, we also aimed to assess the different metabolic profile between populations living in rural and urban area, and to study the relative protective effect of rural environment on the development of IR by performing a short-term high-fat diet intervention study.

The first part of this thesis addresses the following question:

What is the effect of anthelmintic treatment (deworming) on host metabolic homeostasis?

Chapter 2 describes the design of an RCT to answer the question whether anthelmintic treatment will affect host metabolic homeostasis by performing a household-clustered randomized double-blinded placebo-controlled anthelmintic trial in an area endemic for STH in Indonesia.

Chapter 3 describes the outcomes of this RCT on STH prevalence, Th2 responses, adiposity, and IR

Chapter 4 describes the outcome of this RCT on adipokines and how this mediates the changes in IR

The second part of this thesis we focus on the following question:

What are the differences in metabolic profiles between populations in rural and urban areas?

Chapter 5 describes the different metabolic profile of subjects with the same genetic background living in rural and urban areas. It also describes their responses to a short-term high fat diet intervention.

Chapter 6 summarizes our findings and provide directions for future research to understand the link between helminth infections, urbanization, adiposity, and insulin resistance.

Author Details

A. Challenges in diabetes management in Indonesia: a literature review

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B. Helminths, hygiene hypothesis and type 2 diabetes

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