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Urbanization in Indonesia and its impact on non-communicable diseases: a clinical, epidemiological, and immunological study

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Chapter 1

GENERAL INTRODUCTION

URBANIZATION IN INDONESIA AND ITS RELATED CHANGES

Indonesia, a low-middle income country (LMIC) with the largest economic power in the Southeast Asian region,[1] has experienced rapid economic growth in the last two decades.[2] This socio-economic growth consequently accelerates urbanization in Indonesia, a phenomenon which is also observed in other developing countries.[3-5] In 2021, more than 57% of Indonesian population lived in urban areas, increasing from 30% in 1990, and projected to be around 67% in 2035.[6,7]

Urbanization is not only defined as migration of people from rural to urban areas, but also the changing status of previously rural areas that become more urban, along with the adoption of the urban lifestyles.[5] Urbanization is accompanied by significant changes in the social, environmental, and lifestyle aspects of human lives. Dietary pattern in urban population has shifted towards more fast and processed food with high-fat, high-calories, and less fiber containing diet.[8] Urban ecosystem also promotes sedentary behavior due to increased mechanization and digitalization, as well as reliance on transportation.[9] Meanwhile, increased exposure towards pollutions [10,11] with higher level of stress [12] are also often associated with urban environments. In addition, living in urban areas causes a relatively less exposure towards agricultural environments,[13] parasitic, including helminth infections,[14,15] and biodiversity.[16] All of these alterations related with urbanization could affect human microbiome,[17] the epigenome,[18] and the immune system,[19] and thus, potentially affect the disease prevalence and outcome (see conceptual framework in **Figure 1**).[20,21]

In relation to urbanization, the prevalence of infectious diseases in many LMICs has declined in the last few decades.[22] At the same time, the number of people with non-communicable diseases (NCD) such as obesity, diabetes, cardiovascular diseases, cancer, autoimmune diseases, and allergies has greatly increased.[23] This epidemiological transition is also observed in Indonesia. In 1990, the three leading causes for disability-adjusted life years were diarrheal diseases, lower respiratory tract infections, and tuberculosis. However, in 2016, these diseases were replaced by ischemic heart disease, cerebrovascular disease, and diabetes.[24] Moreover, Indonesia is currently experiencing a double burden of malnutrition, which is partly

related to urbanization. On the one hand, undernutrition and stunting are still quite prevalent with 21.6% of the children under five years of age diagnosed with stunting in 2022,[25] even though this prevalence has significantly decreased from 37.2% in 2013.[26] On the other hand, the prevalence of obesity, as manifestation of overnutrition, has almost doubled from 19.1% in 2007 to 35.4% in 2018.[27,28]

Similarly, this changing pattern of disease prevalence has also been seen for diabetes, which increased from 5.7% in 2007 to 10.9% in 2018.[27,28] Additionally, in term of allergic diseases, Indonesia previously had one of the lowest global prevalence of allergic rhinitis (AR), 5.2%, based on the report by The International Study of Asthma and Allergies in Childhood (ISAAC) in 1998.[29] However, this number has increased significantly to 23% according to a study in 2019.[30]

The expanding prevalence of NCDs in many LMICs, including Indonesia, is associated with high burden at the individual, societal, and economic levels. At the individual level, the burden consists of morbidity due to such diseases and the related complications, disability, decreased quality of life, and lastly mortality.[31,32] The social burden includes the support needed from family caregivers and other community members, such as people working in the nursing home and elderly housing.[33,34] Finally, the economic burden constitutes the direct and indirect costs of diseases. Direct costs comprise of the capital allocated for medicines and visits to health care services, while the indirect costs are related with absenteeism and loss of work productivity due to illness.[35,36]

Given the increasing burden of non-communicable diseases in Indonesia, and their complex association with urbanization, extensive research is needed to unravel the relationships to be able to design interventions. Although many studies related to urbanization and health have been conducted in Indonesia, majority of these previous studies have only used secondary data and were cross-sectional in nature.

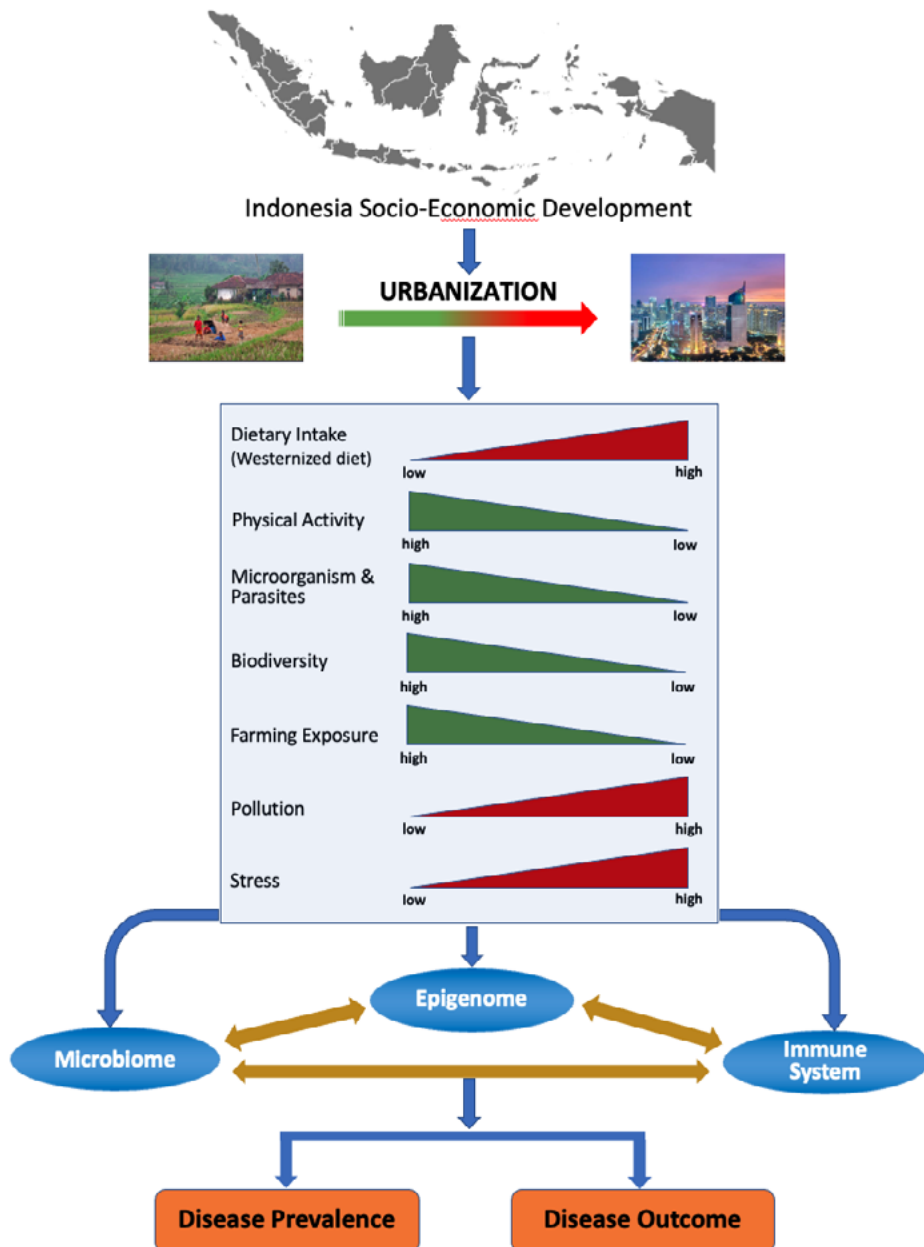


Figure 1. Conceptual Framework of Urbanization Related Changes and Its Effect on Health.

SCOPE AND AIM OF THE THESIS

The overall objective of this thesis is to evaluate the effects of urbanization on human health, focusing on metabolic health and allergy. In this thesis we combine clinical, epidemiological, and immunological approaches to unravel the relative contribution of urbanization and its associated sociodemographic, lifestyle, environmental, and clinical factors to human health and disease. For the clinical approach, a cluster-randomized clinical trial on anthelmintic treatment and an intervention study using short term high-fat high-calorie diet were conducted. This thesis also incorporates not only large scale secondary data for its epidemiological approach, but real world observation in the form of a prospective cohort study. In terms of immunology, mass cytometry has been utilized for in depth characterization of immune profiles associated with disease outcome.

Infection by soil-transmitted helminths (STH) is still highly prevalent in certain rural areas of Indonesia and is one of the prominent factors that distinguishes rural and urban areas. Thus, the first part of the thesis (**Chapter 2**) focuses on the effect of helminth infections and their treatment with albendazole on the metabolic-related hormones: free insulin-like growth factor (IGF)-1 and IGF binding protein (IGFBP)-3.

As the prevalence of NCDs are generally higher in urban compared to rural, we hypothesized that living in rural areas might be protective for developing metabolic diseases. Hence, in **Chapter 3**, we compare the differences in metabolic profiles between Indonesian rural and urban populations with same genetic background and a clinical intervention using short term high-fat high-calorie diet was undertaken to assess whether there are any differences in the metabolic and inflammatory responses between the two populations. In **Chapter 4**, the long-term effects of living in an urban area and adoption of associated lifestyles on the metabolic profiles (adiposity, insulin resistance, and adipokines) was evaluated in a prospective cohort study. Subsequently, **Chapter 5** describes the factors in urban and rural populations that associated with diabetes using a large scale secondary data from the 2018 Indonesian Basic Health Survey.

Aside from the relatively higher prevalence of allergic rhinitis (AR) in urban than rural population, previous studies also showed a relatively less severe clinical manifestation

of AR in rural compared to urban population.[37,38] Based on this, the immunological characteristics of Indonesian young adults, with and without allergic rhinitis, who originated from rural and urban areas, was studied in **Chapter 6**. High dimensional immunological data was generated using mass cytometry on peripheral blood and nasal mucosa to evaluate the association between clinical profiles and immune characteristics in these two populations. Lastly, **Chapter 7** summarizes and discusses our findings from previous chapters and provides directions for future research towards better understanding of the effect of urbanization on metabolic health and allergy.

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