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

Kurniawan, F.

Appendix

ENGLISH SUMMARY
NEDERLANDSE SAMENVATTING
CURRICULUM VITAE
LIST OF PUBLICATIONS
ACKNOWLEDGEMENTS

SUMMARY

In many low-middle income countries, including Indonesia, socio-economic development goes hand in hand with rapid urbanization. Urbanization, the process of migration of people from rural to urban areas, as well as the process of transforming rural into an urban population, leads to alterations in the social, environmental, and lifestyle aspects of human lives. This causes an epidemiological transition of disease profiles, a decreasing prevalence of infectious disease on the one hand, but increasing prevalence of non-communicable diseases (NCDs) on the other. Studies have suggested that urbanization could also potentially affect disease outcome. In this thesis, we report the impact of urbanization in Indonesia on non-communicable diseases, in particular metabolic diseases and allergies.

Chapter 1

In this chapter, we described the potential social, environmental, and lifestyle changes associated with urbanization, such as dietary intake, physical activity and sedentary behavior, exposure towards microorganisms and parasites, biodiversity, farming, pollution, as well as social stress. These alterations could influence the human microbiome, epigenome, and immune system. Thus, potentially affect the disease prevalence and outcome. The increasing prevalence of NCDs and potentially worse outcomes related to urbanization causes significant burden on the health system. Therefore, more research is needed. Due to the multidimensionality of urbanization, studies incorporating many aspects of scientific investigation are important to evaluate the effect of urbanization on NCDs. In this thesis, we used different approaches to address the influence of urbanization on metabolic and allergic diseases. We conducted intervention studies, a prospective cohort study, and used a large dataset from Indonesian national health survey, but also incorporated an in depth immunological study, to evaluate the impact of urbanization on specific health outcomes.

Chapter 2

This chapter described the effect of soil-transmitted helminths (STH), a common feature of rural areas, on the serum levels of free IGF-1, a metabolic hormone, essential for

human anabolic functions. Serum samples were analyzed from a cluster-randomized double-blind placebo-controlled trial of albendazole treatment in an area endemic for STH. We observed lower levels of serum free IGF-1 in STH-infected subjects, which was partially mediated by the lower BMI and fasting insulin levels. Interestingly, with increasing number of different helminth infections, often also associated with higher burden of these parasitic infections, a further lowering of free IGF-1 levels was seen. Furthermore, the levels of this metabolic hormone were increased after four rounds of three-monthly albendazole (400 mg) treatment for three consecutive days, although not exclusively in STH-infected subjects. The metabolic parameter changes associated with STH and albendazole treatment warrant further research on the long term impact of deworming on metabolic health of rural populations living in STH-endemic areas.

Chapter 3

In this chapter we assessed the contribution of the living environment on metabolic profile. We compared people living in rural areas and their counterparts, who were individuals with similar genetic background that had migrated to an urban area, in terms of metabolic health and metabolic response. We found higher adiposity indexes (BMI and waist circumference), whole-body insulin resistance (IR), and leptin levels in residents of urban compared to rural areas. Increasing time spent in the urban area was positively correlated with higher adipose tissue mass, indicating a higher degree of acculturation in terms of urban lifestyle, which can lead to a positive energy balance, hence increasing adiposity over time. Additionally, acute intervention with a 5-days high-fat diet (HFD), induced a similar increase of whole-body IR in both groups living in urban and rural areas, as well as in rural subjects with and without helminth infection. These results show that living in rural areas or having current STH infection, was not protective against the induction of IR after short-term HFD intervention.

Chapter 4

Here we investigated the metabolic profiles of Indonesian young adults starting their university studies in an urban area. Metabolic parameters were compared between students originating from a rural area who had recently migrated to the urban center, and their counterparts originating from urban areas. We observed an overall better

metabolic profiles, reflected as lower BMI, whole-body IR, and leptin/adiponectin (L/A) ratio in those who originated from rural compared to those from urban areas. Moreover, after 1-year of living in an urban area, the rural subjects experienced almost double the increase in BMI and three times higher increase in L/A ratio, compared to subjects residing their whole life in urban area. Once again, we found that previously living in rural areas does not protect individuals from the negative changes in metabolic profiles upon migration to an urban area and adoption of urban lifestyle.

Chapter 5

Using large-scale nationally representative data of the 2018 Indonesian Basic Health Survey, we reported the differences in lifestyle and clinical factors and their association with diabetes in populations of urban and rural Indonesia. Here, we confirmed that Indonesian rural population has healthier lifestyle and metabolic profiles compared to their urban counterparts. Nevertheless, the prevalence of diabetes was similar between the two populations. Strikingly, the majority of individuals with diabetes were undiagnosed and untreated, particularly in the rural areas. Additionally, despite the better metabolic profiles in the rural population, there were no differences in the associations of lifestyle and clinical factors with the prevalence of diabetes between urban and rural populations. These findings indicate that living in a rural environment does not protect against metabolic disease, such as diabetes, in the Indonesian population.

Chapter 6

Urbanization could potentially affect disease prevalence and outcome. In this chapter we described how the immune system might contribute to the differences in clinical manifestation of allergic rhinitis (AR) between urban and rural populations in Indonesia. We observed that urban Indonesian young adults with AR have stronger inflammatory immune responses in the nasal mucosa compared to their rural counterparts, as shown by the upregulation of basophils, mast cells, CD4 Th2, and pathogenic Th2A cells. These immune cells showed positive correlation with the severity of activity disturbances due to AR, only in subjects from urban but not from rural areas. Additionally, systemic immune profiles in AR subjects from rural areas,

showed a skewing towards more regulatory state with the upregulation of CD163+ dendritic cells, regulatory T cells, and non-classical monocytes which are known to have anti-inflammatory and tolerogenic properties, and might dampen the expression of severe debilitating symptoms. These findings might explain the reports of less severe AR manifestation observed in populations living in rural areas, although further confirmation by functional studies are needed.

Chapter 7

This chapter summarized and discussed the main findings of this thesis. By incorporating multiple aspect of different scientific areas in our studies, we provided a better understanding of how urbanization could impact non-communicable diseases, in particular metabolic diseases and allergic rhinitis, in Indonesian population. First, we confirmed that helminth infections and anthelmintic treatment could influence metabolic health through their effect on metabolic hormones, although long term implications warrant further research. Second, our studies showed that Indonesian rural population generally have more favorable metabolic profiles compared to their urban counterparts, as shown by the lower adiposity indices, proportion of overweight/obesity, proportion of dyslipidemia, whole-body IR, and L/A ratio levels. Third, living in rural areas does not protect individuals from the negative consequences of urbanization and adoption of urban lifestyles on the metabolic health, even it might result in more unfavorable changes. Lastly, contrary to the finding related with metabolic health, rural living might associate with less severe clinical manifestation of allergic disease, as indicated in the findings of the systemic and nasal mucosal immune profiles. Altogether, urbanization could have major impacts on human health, although more research is needed to gain a more comprehensive understanding of the pathogenesis, and this thesis can be a valuable foundation for further studies. Additionally, healthcare and health-associated policies should take into consideration our reported impacts of urbanization on human health to improve overall health of the Indonesian population.