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

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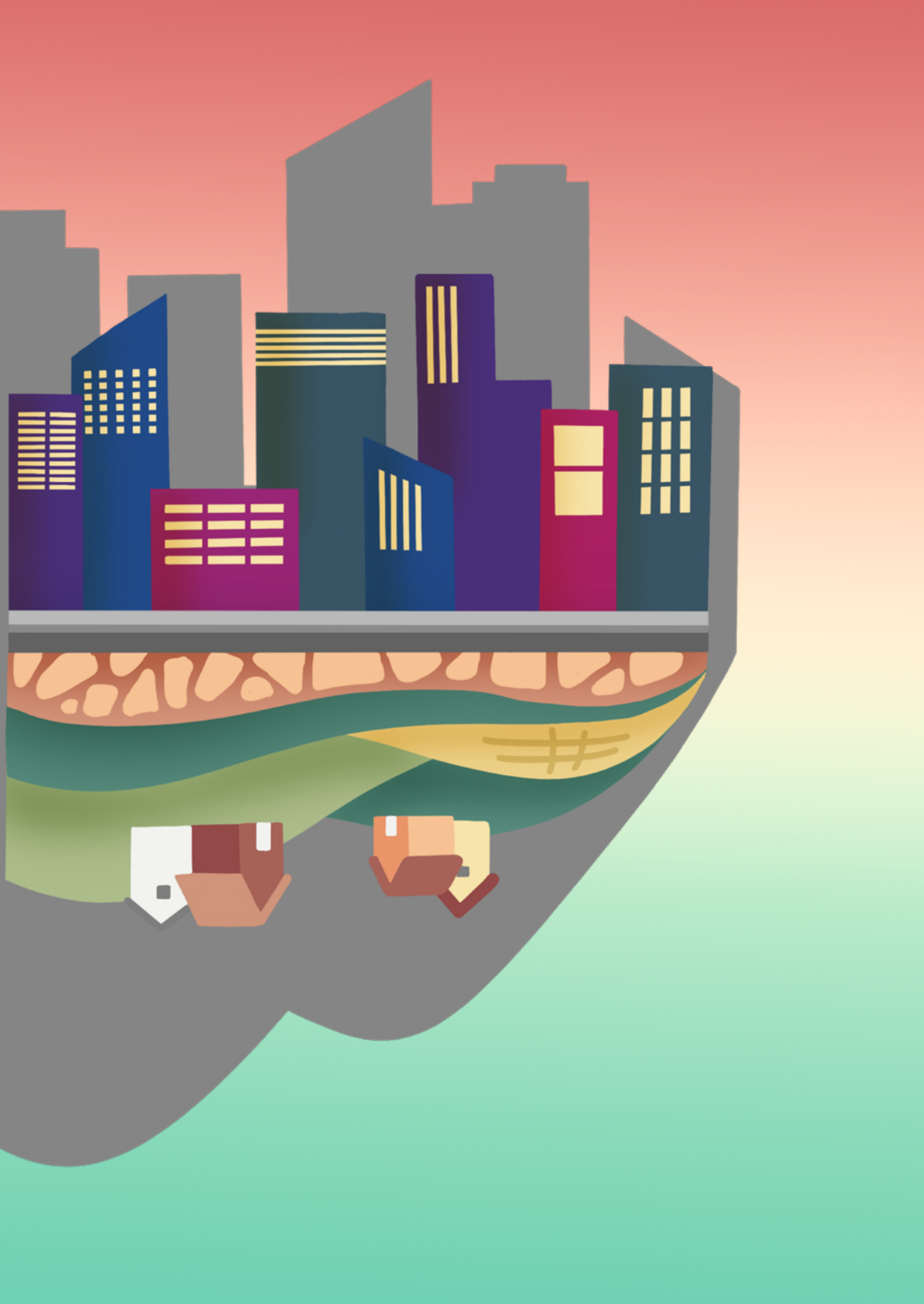

# Chapter 7

## SUMMARIZING DISCUSSION

This thesis presents several clinical, epidemiological, and immunological aspects of urbanization in Indonesia in the context of metabolic health and allergic diseases. To this end, studies have been done in rural and urban areas of Indonesia. A cluster-randomized placebo-controlled clinical trial of anthelmintic treatment was conducted in an Indonesian rural population living in a soil-transmitted helminth (STH)-endemic area (**Chapter 2**) to assess how chronic helminth infections in rural areas affect metabolic health. A short-term high-fat high-calorie diet intervention was performed in both urban and rural Indonesian adults to evaluate how lifelong residence in an urban versus rural area responds to a strong metabolic perturbation (**Chapter 3**). The question of how metabolic health changes over increasing years of residence in an urban area, was also addressed in Chapter 3 examining the metabolic health of individuals who had moved from rural areas to reside for varying lengths of time in an urban area. Looking at the same question prospectively, a cohort study evaluated the effect of living in an urban area on the metabolic profiles in young Indonesian adults of urban- and rural-origin (**Chapter 4**). At the national level, secondary data from a large Indonesian Basic Health survey conducted in 2018 assessed the determinant factors for diabetes in urban and rural populations of Indonesia (**Chapter 5**). Lastly, the application of mass cytometry to evaluate the differences in the systemic and nasal mucosal immune profiles between individuals with and without allergic rhinitis in urban and rural areas, made a dive into how cellular immune responses might be affected by urbanization (**Chapter 6**).

## SUMMARY OF MAIN FINDINGS

One characteristic that distinguishes urban and rural populations is the exposure to parasitic infections, in particular, soil-transmitted helminths. In **Chapter 2**, we showed that in adults, STH infection was associated with lower levels of serum free IGF-1, a metabolic hormone essential for human anabolic functions.[1] The lower adiposity (BMI) and fasting insulin levels observed in STH-infected subjects, partially mediated the lower free IGF-1 levels found, in agreement with previous reports.[2,3] Interestingly, there is an inverse correlation between the number of different helminth infections with the levels of free IGF-1. This might suggest a possible impact of higher infection burden on BMI and fasting insulin levels,[4] thereby resulting in further lowering of the free IGF-1 levels.

Anthelmintic treatment with albendazole increased the levels of free IGF-1, although not specifically in STH-infected subjects.[1] This indicates that albendazole treatment might have broader effects than its action on STH. Albendazole might affect the gut microbiome[5] and the intestinal protozoa,[6] potentially affecting the levels of free IGF-1.[7]

Based on the outcome on the clinical trials that show increasing adiposity following anthelmintic treatment,[8] the question arises as to what are the long-term metabolic effect of helminth eradication in rural areas endemic for STH. While the absorption of nutrients would be expected to be improved, thus lowering the risk of undernutrition and stunting in children,[9,10] the increasing adiposity and body mass index and their adverse impact on metabolic health also need to be considered for preparing appropriate policies. Furthermore, in the context of urbanization, rural people often migrate to urban areas and adopt urban lifestyles. The effect of these urbanization-related changes on the metabolic health of such rural populations, with or without previous helminth infection, is another important question that requires further research. We need to understand the precise changes that occur upon urbanization, in order to create a knowledge base to devise approaches for mitigation of any adverse impact of urbanization on health.



Our study described in **Chapter 3** attempted to answer the question of how migration to an urban area affects metabolic health. Indonesians with similar genetic backgrounds living in urban and rural environments were compared. We observed higher adiposity indices (body mass index and waist circumference), whole-body insulin resistance (IR), and leptin levels in the urban compared to rural subjects. Interestingly, in the individuals living in an urban area, the time spent in an urban environment was positively associated with increasing body mass index (BMI) and waist circumference (WC).[11] This suggests that a higher degree of acculturation in terms of urban lifestyle, could lead to a positive energy balance, hence increasing adiposity over time.[12]

We also showed that past or current exposure to STH, as assessed by total IgE, albeit relatively small, could contribute to the differences in adiposity, whole-body IR, and leptin levels between individuals living in urban and rural areas. However, living in rural areas or having STH infections, could not protect against increasing IR induced by short-term high-fat diet (HFD) intervention. Nevertheless, increased liver inflammation, as assessed by cholesteryl ester transfer protein (CETP) level,[13] was observed after HFD intervention, in subjects living in urban, but not in rural areas. This might be explained by the higher pre-HFD intervention CETP levels in the individuals living in rural areas, thus precluding further increase. As CETP plays an important role in lipoprotein metabolism,[14] the effect of this relatively high CETP levels in individuals living in rural areas on the long-term risk of developing metabolic diseases, such as metabolic syndrome and dyslipidemia, warrants further studies. An important question is also what causes the higher CETP levels in those living in rural areas.

In **Chapter 3**, we only investigated short-term HFD as an urban-associated lifestyle that could influence metabolic health, in this case IR. Nonetheless, in real life, urbanization is associated with long-term adaptation to urban lifestyle and environmental exposures. Thus, the acute induction of IR by short-term HFD intervention in individuals living in urban and rural areas might not truly reflect the metabolic health effects of urbanization. This we attempted to address in **Chapter 4**.

Our prospective cohort study described in **Chapter 4**, confirmed overall better metabolic profiles in Indonesian young adults with lifelong residence in rural areas who had just recently migrated to an urban area in comparison to their urban counterparts. The better metabolic health was reflected in lower mean BMI and proportion of overweight/obese subjects, as well as lower whole-body IR and leptin/ adiponectin (L/A) ratio. Despite these findings at baseline, after 1-year of living in an urban area, these rural subjects experienced almost double the increase in BMI and three times higher increase of L/A ratio, compared to subjects residing their whole life in urban areas.[15] These findings, once again, suggest that living in a rural area does not protect individuals from adverse alterations in their metabolic profile upon urbanization, and might even result in more unfavorable changes.

In the same study, we revealed the role of fat intake as the major driver of the increase in BMI for both groups originating from rural and urban areas. In addition, although the rural group consumed almost twice as much protein compared to the urban group, this could not explain the enhanced gain in BMI of the rural subjects. Furthermore, the incorporation of physical activity, another important factor related to urbanization, could also not explain the differences in the BMI increase between the two groups after one year. This implies the possible role of changes in other factors, among others, epigenetics[16] and/or gut microbiome.[17]

Previous studies have shown the association between BMI and L/A ratio with whole-body IR.[18-20] Interestingly, despite significant changes in BMI and L/A ratio found in our study after one year, no changes in HOMA-IR was observed. The preserved pancreatic beta-cell function in young adults[21] and relatively short follow-up period might explain this finding. A previous longitudinal study with follow-up time of more than twenty years that reported greater adherence to Westernized diet, characterized by high-fat high calories, refined carbohydrates, and processed foods, to be associated with higher risk of metabolic syndrome and IR.[22] Thus, a longer prospective cohort study is needed to understand more clearly the effect of urbanization, and most important factors associated with it, on metabolic profiles, especially IR.



Our studies in chapters 3 and 4, similarly observed relatively better metabolic profiles in rural compared to urban Indonesians. Difference in the dietary intake pattern was also seen between these two populations. Diabetes as a metabolic-related disease, is increasing in prevalence in Indonesia, alongside rapidly growing socio-economic development and urbanization. Hence, in **Chapter 5**, we assessed the differences in the association between lifestyle, as well as clinical factors, with diabetes prevalence in the Indonesian urban and rural populations using secondary data from the 2018 Indonesian Basic Health Survey.

Our results confirm that the rural population has a more healthy metabolic profile than the urban population in Indonesia. Nevertheless, there were no differences in the prevalence of diabetes between rural and urban populations. Strikingly, the majority of individuals with diabetes were undiagnosed and untreated, in particular in the rural population. 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 the two populations.

When considering immunological changes related to urbanization, **Chapter 6** focused on allergic rhinitis and its relationship to local and peripheral immune responses. We found that individuals with allergic rhinitis (AR) from urban areas in Indonesia had stronger inflammatory immune responses in the nasal mucosa compared to their rural counterparts, as shown by the upregulation of several immune cells known to play an important role in the AR pathogenesis, such as: basophils, mast cells, CD4 Th2, and pathogenic Th2A cells.[23-25] Moreover, these immune cells were positively correlated with the severity of activity disturbances due to AR symptoms, only in urban but not in rural subjects. Interestingly, systemic immune profiles in rural AR subjects 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 as reported previously,[26-28] and might dampen the expression of severe debilitating symptoms. Although these findings still need further confirmation by functional studies, they might explain the reports of less severe AR seen in populations living in rural areas.[29,30]

## DIRECTIONS FOR FUTURE RESEARCH

### Study of the adipose tissue

Although our studies provide us with information regarding the effects of urbanization on the metabolic health, the observed findings were mostly obtained from measurements in the peripheral blood due to ease of accessibility. It is important to note that BMI and waist circumference, consistently showed higher adiposity profiles in Indonesians living in urban rather than rural areas. Moreover, the findings of leptin, adiponectin, and L/A ratio are interlinked with adipose tissue as the major source of these adipokines. Thus, direct evaluation of the adipose tissue should be incorporated in future studies. Previous studies have utilized minimally invasive procedures under local anesthesia, such as 14G needle aspiration [31] or small liposuction cannula,[32] to obtain the subcutaneous adipose tissue (SAT) samples. For the visceral adipose tissue (VAT), samples could be obtained from patients with obesity that undergo bariatric procedures.[33] Alternatively, elective abdominal surgery can be the source for SAT and VAT samples both for obese and lean patients.[32,34] From these adipose tissue samples, studies on the immune cells and the gene expression of adipokines, cytokines, or chemokines can be performed and correlated with the findings from systemic compartment.[31-34]

**Study of the microbiome**

Numerous studies have shown the differences in the gut microbiome between urban and rural populations, which could be influenced by many factors.[35-39] Moreover, certain gut microbiota composition and functionality were associated with metabolic markers. *Prevotella* genus was enriched in individuals with high consumption of vegetables[40] and a shift towards Bacteroides dominance was seen upon adaptation of Westernized diet,[41] while *Faecallibacterium* genus was positively correlated with the duration of exercise habits.[42] Gut microbiota dysbiosis and a lower relative abundance of short-chain fatty acid (SCFA) producing bacteria from *Prevotella, Faecallibacterioum, Roseburia, Bifidobacterium,* and *Ruminococcus genera*, were reported in patients with obesity and type 2 diabetes (T2D) compared to healthy subjects.[43,44] These SCFAs were known to have essential role for maintaining intestinal integrity, energy homeostasis and body weight regulation, improving insulin sensitivity, and anti-inflammatory properties.[45] In addition, several interventions taking into consideration urbanization-related factors, such as dietary modification and exercise training, showed significant alteration in the gut microbiome that correlated well with changes in metabolic and inflammatory parameters.[46-48] Hence, assessment of gut microbiome, with the focus on the presence of gut dysbiosis and health-promoting bacteria, as well as their association with changes in the adiposity profiles, dietary intake, and physical activity, is essential in studies evaluating the effect of urbanization on human metabolic homeostasis.

In addition, the differences of nasal microbiome between urban and rural populations have been observed,[49,50] and many studies have found that microbiome differs significantly in the airway of patients with allergic diseases, such as AR and asthma. [51-53] Since there is significant interaction between microbiome and host immune system in the nose,[54,55] further studies incorporating the evaluation of these two aspects in the urban and rural populations will provide better understanding of the impact of urbanization on allergy, especially AR.

**Epigenetic studies**

Although individuals might have a genetic predisposition to certain cardiometabolic diseases,[56,57] the rapidly increasing prevalence of non-communicable diseases (NCDs) points to the importance of environmental, social, and behavioral determinants of health. Furthermore, significant interplay between genetic and environmental factors, which can result in the modifications of gene expression patterns without changing the DNA sequence, known as epigenetic changes, has been observed, and linked to the pathogenesis of NCDs.[58] Previous studies reported a negative association between DNA methylation levels in leptin (LEP) gene and BMI,[59,60] whereas DNA methylation levels in the adiponectin (ADIPOQ) gene were positively associated with BMI.[59] Urbanization is inseparable from environmental and social alteration that could potentially induce epigenetic changes. Obesogenic diet could induce alteration in DNA methylation of pro-opiomelanocortin (POMC) gene in the arcuate nucleus of hypothalamus, an important gene for regulating satiety and energy homeostasis. This gene has been shown to be associated with raised leptin and insulin levels and the development of obesity.[61] Altogether, further studies that incorporate measurements of DNA methylation levels as a representative of epigenetic changes, such as in the LEP and ADIPOQ genes from blood and adipose tissue, are needed. Such changes can then be correlated with the changes in metabolic profiles, dietary intake, physical activity, and adipokines, to provide a better understanding of the complex interaction between urbanization, epigenetic changes, and NCDs.

**Immunological studies**

Although we have included immunological evaluations in this thesis to assess differences between urban and rural AR, a lot more needs to be done. The functional assays and antigen/allergen specificity of the effector cells that were observed to be upregulated in either urban or rural AR, as well as the measurements of cytokines and chemokines in the nasal mucosa, will provide more comprehensive information to understand the differences between urban and rural AR individuals.

Furthermore, the fact that the pathogenesis of cardiometabolic diseases, such as T2D and atherosclerotic cardiovascular diseases, are closely related with systemic and vascular inflammation,[62,63] justifies the assessment of the immune system in such studies in Indonesia. In addition, it would be even more important to identify the immunological changes before the onset of these diseases. As the increasing prevalence of NCDs occurs concurrently and could be attributed to rapid urbanization,[64] the study on the effect of urbanization and its associated factors on the immune system and metabolic homeostasis is essential. For example, we need to identify specific subsets of T cells, dendritic cells, macrophages or other immune cells present in the peripheral blood and tissues, such as adipose tissue, with their functional capacities, and associate them with changes in metabolic profiles, dietary intake, and adipokines upon urbanization.

In the urbanization and AR study, we confirmed the importance of immunological evaluation not only in the systemic compartment but also at the effector site. With regards to metabolic homeostasis, the evaluation of the immune system in adipose tissue, intestinal tract, and endothelial layer would complement and add valuable information apart from the systemic immune profiles. As an example, it will allow the study of macrophages, immune cells that are absent in the peripheral blood, but have shown to play a key role in metabolic homeostasis.[65,66]



**Studies of social aspects**

Urbanization could greatly impact human social factors. Living in an urban area can be associated with higher levels of chronic stress due to factors like noise, pollution, crowding, and social pressures.[67] Prolonged stress might cause a disruption in the metabolic homeostasis.[68] Moreover, urbanization often leads to changes in social structures and support networks.[69] These changes could potentially affect dietary choices,[70] physical activity,[71] and the prevalence of social isolation or psychological stress,[72] all of which might influence metabolic health. All of our studies described in this thesis focus more on the biological (environmental and behavioral) aspects of urbanization, thus lacking the social aspects. Collaboration with social scientist is needed to examine more deeply the impact of these social aspects of urbanization on metabolic health and the biological pathways involved.

### Longitudinal study: longer follow-up time

Our prospective cohort study with 1-year follow-up has provided us with valuable information on the unfavorable effects of urbanization on metabolic profiles, especially in individuals from rural areas who migrate to urban centers. Nevertheless, this one-year period is too short as most rural people who migrate to urban areas will stay for longer periods or even become permanent residents. Hence, a longitudinal study with longer follow-up period that incorporates suitable tools to assess dietary intake, physical activity, and psychological stress, as well as the evaluation of changes in microbiome, epigenetics, and the immune system, will be the ideal set up to obtain better understanding of the cumulative effects of urbanization over time, on metabolic health. Similar design should also be applied to studies on allergic diseases. However, such studies are very expensive and need strong financial commitment.

### The urban wealthy versus the urban slum resident

The concept of rural and urban areas date as far back as classical Roman times and have acquired particular environmental, cultural, and social associations.[73] However, this dichotomy has been considered inadequate in many disciplines, due to several reasons: heterogeneity within categories, multidimensionality, changing dynamics, and interconnectedness with blurred boundaries.[73,74] Even within one urban setting, there can be some areas with high socio-economic status/SES (urban wealthy) and others with low SES (urban slum), which associate with different microbiome[75] and immune profiles.[76] Several urbanicity scales have been developed to quantify urbanization as a continuous variable, which can outperform the rural-urban dichotomy in terms of association with health.[77-79] It would be beneficial to adopt these urbanicity indexes in Indonesia and correlate it with the effects on metabolic health.

## DIRECTIONS FOR FUTURE HEALTHCARE POLICY

Although the members of rural populations pose a relatively healthier metabolic profile, our studies observed that living in rural areas does not protect the inhabitants from the deleterious metabolic changes when adopting urban lifestyle. Thus, in terms of health policy, appropriate and adequate education and knowledge have to be provided to prevent and monitor the development of NCDs, such as obesity and T2D.

Additionally, urbanization is not only related with negative impacts towards human health. There are many beneficial effects of urbanization, such as decreased burden of infectious diseases due to improved hygiene and sanitation, better access to health care facilities, and improved knowledge regarding health due to better education. This notion was supported by one of our study results using secondary data from the 2018 Indonesian National Health Survey showing a twice higher diagnosed diabetes in urban compared to rural populations. However, the prevalence of undiagnosed and untreated diabetes in Indonesia is still high and the number has not yet declined compared to the data reported in 2007. This problem requires special attention from all related stakeholders. It is important to develop locally or nationally, practical and sensitive diagnostic tools to detect the presence of NCDs, such as T2D, especially applicable to many resource-limited rural areas of Indonesia. Moreover, improvement of health care access and facilities, especially in many rural areas, is needed to better diagnose NCDs at an early stage to prevent further complications and to provide higher quality treatment.



As urbanization is unavoidable, it is essential to create an urban environment that can support good health, which is in line with the United Nations Sustainable Development Goals (SDG) 11: Sustainable Cities and Communities. Since urbanization is closely related to economic growth, creating adequate employment opportunities could lead to increased household incomes. Higher income levels can positively influence health by providing individuals and families with better access to nutritious food, healthcare, and improved living conditions. Providing enhanced transportation infrastructure in the urban environment can be another way to optimize positive urbanization impact on human health. Efficient transportation can increase accessibility to healthcare facilities, reduce air pollution by promoting the use of public transport, and encourage physical activity through active transportation options, like walking or cycling. Additionally, the establishment of recreational facilities, such as parks, sports complexes, and fitness centers, could promote physical activity and encourage a healthier lifestyle, reducing the risk of chronic diseases associated with sedentary behavior.

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