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Urbanization in sub-Saharan Africa: Declining rates of chronic and recurrent infection and their possible role in the origins of non-communicable diseases

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Abstract

Background—Non-communicable diseases (NCDs), such as atherosclerosis and cancers, are a leading cause of death worldwide. An important, yet poorly explained epidemiological feature of NCDs is their low incidence in under developed areas of low-income countries and rising rates in urban areas.

Methods—With the goal of better understanding how urbanization increases the incidence of NCDs we provide an overview of the urbanization process in sub-Saharan Africa, discuss gene expression differences between rural and urban populations, and review the current NCD determinant model. We conclude by identifying research priorities.

Results—Declining rates of chronic and recurrent infection are the hallmark of urbanization in sub- Saharan Africa. Gene profiling studies show urbanization results in complex molecular changes, with almost one-third of the peripheral blood leukocyte transcriptome altered. The current NCD determinant model could be improved by including a possible effect from declining rates of infection and expanding the spectrum of diseases that increase with urbanization.

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Conclusions—Urbanization in sub-Saharan Africa provides a unique opportunity to investigate the mechanism by which the environment influences disease epidemiology. Research priorities include: 1) studies to define the relationship between infection and risk factors for NCDs, 2) explaining the observed differences in the inflammatory response between rural and urban populations, and 3) identification of animal models that simulate the biological changes that occurs with urbanization. A better understanding of the biological changes that occur with urbanization could lead to new prevention and treatment strategies for some of the most common surgical diseases in high-income countries.

Keywords

Inflammation; non-communicable disease; urbanization; rural-urban transition; gene expression

INTRODUCTION

Urbanization is the most important demographic change during the past century, and is a major divergence from how humans have lived for the past several thousand years (1). In 2014, 54 per cent of the world's population resided in urban areas; a figure that is expected to increase to 66 percent by the year 2050 (2). The urbanization process is occurring most rapidly in sub-Saharan Africa[1] and Asia, with contributing factors being rapid economic development, population growth, agricultural instability, forced migration due to political instability, ecological disasters (e.g., floods and climate change), and greater social and education opportunities in cities (2–4).

Urbanization in low-income countries represents an important inflection point in the epidemiology of disease, with infectious diseases predominating in rural areas and urban populations taking on a profile of NCDs (5–8). This epidemiological transition is also evident at the global level where NCDs have been rapidly increasing over the past 40 years (9, 10). NCDs are now the leading cause of death in lower-middle, upper middle, and high-income countries[2]. Of the 56 million global deaths in 2012, 68% were due to NCDs, principally cardiovascular diseases, cancer, and respiratory diseases (11). Even in low-income countries where infectious diseases have been the dominant public health problem, NCDs are rising rapidly and are projected to exceed communicable, maternal, perinatal, and nutritional diseases as the most common causes of death by 2030.

Many important questions remain about the factors that contribute to the development of NCDs and how best to combat this growing epidemic. A better understanding of the biological changes that occur with urbanization, particularly their underlying molecular

[1]Sub-Saharan Africa refers to the geographic area of the African continent that lies south of the Sahara. There are 42 countries located on the sub-Saharan African mainland, in addition to six island nations (Madagascar, Seychelles, Comoros, Cape Verde, and Sao Tome and Principe). This grouping is used the World Bank, World Health Organization and United Nations because these countries have similar levels of levels of economic development.

[2]The World Bank classifies countries according to four income groupings. Income is measured using gross national income (GNI) per capita, in U.S. dollars, converted from local currency using the *World Bank Atlas* method. Classifications as of July 2016 are as follows:
Low-income countries (LICs) = US$1,025 or less in 2015
Middle-income countries (MICs) are subdivided: Lower-middle-income = US$1,026 to US$4,0355
Upper-middle-income (UMICs) = US$4,036 to US$12,475
High-income countries (HICs) = US$12,476 or more

mechanisms, could provide insight into the pathophysiology of NCDs and ultimately lead to novel prevention and treatment strategies. With this goal in mind, we provide an overview of urbanization in sub-Saharan Africa and its impact on health, discuss recent gene profiling studies from rural and urban populations living in low-income countries, review the current NCD determinant model, and outline research priorities for better understanding the biological changes that occur with urbanization. These topics were selected to fill gaps in the NCD literature and to inform surgeons of the many opportunities that exist to investigate the etiology of NCDs, many of which are surgical conditions.

URBANIZATION IN SUB-SAHARAN AFRICA: ITS IMPACT ON HEALTH

The tremendous differences that exist between some rural and urban areas of sub-Saharan Africa (Figure 1) provide a unique opportunity to study the effects of urbanization. As is true for most low-income countries, rural and urban areas of sub-Saharan Africa differ markedly in their physical and social environment, and in their access to health and other social services (1). Important differences can also exist in food availability, eating habits and lifestyle. Infrastructure is typically better in urban compared to rural areas, meaning individuals living in cities have greater chance of having access to clean water, waste disposal and electricity. Cities are nevertheless heterogeneous environments, with levels of services varying by country, region and even within the same city (6). An important example is the urban slum, where crowding and poverty can increase transmission of infectious diseases, perhaps resembling the rural environment.

Varying rates of infection is perhaps the most striking difference that exists between rural and urban areas of sub-Sahara Africa. For all practical purposes the rural environment of some sub-Saharan African countries approximate the situation described by Omran as “The Age of Pestilence and Famine”—a pre-modern pattern of health and disease where the major determinants of death are epidemics, famines, and war (5, 12). The effects of these high infection rates are best observed in children. In some settings, under-five mortality rates exceed 200 per 1000 live births, with diarrheal disease being a leading cause of death because of poor sanitation (13). Growth failure and stunting are common findings in many rural populations of sub-Saharan Africa, with children falling off of the growth curve within several months of birth. Growth failure occurs more commonly during the rainy season and correlates with repeated episodes of infections (Figure 2). Once thought to be solely due to inadequate caloric intake, undernutrition is now attributed, in part to, a disorder of the small intestine known as environmental enteropathy (14). Instead of the long finger-shaped villi observed in the small bowel of healthy children living in high-income countries, individuals affected by environmental enteropathy display shortened, broad villi with hyper-cellularity of the lamina propria (15). These histological features are associated with decreased absorption and increased gastrointestinal permeability (16) – factors that enhance malnutrition and worsen diarrheal diseases. Plasma concentrations of endotoxin and anti-endotoxin antibodies are also elevated in these individuals, and relate to both growth failure and the severity of the enteropathy. These children also have evidence of chronic immune stimulation demonstrated by elevated numbers of white blood cells and increased concentrations of plasma C-reactive protein (17).

Of importance, is that the growth failure resulting from undernutrition is not an isolated clinical finding, but rather occurs as part of a constellation of other systemic signs and symptoms (Figure 3). In addition to the growth failure and enteropathy (Figures 3a and b) mentioned above, several other subtle clinical differences are observed in this group of children. Diminished cognitive function (Fig. 3d) is arguably the most tragic, as it results in poorer performance in school; fewer years of completed schooling, and ultimately, lower economic productivity during adulthood (18, 19). Differences in pain behavior (Fig. 3b) have also been reported, especially by surgeons trained in high-income countries working in sub-Saharan Africa for the first time (20). This apparent higher pain tolerance is manifested as lower post-operative narcotic requirements, less tachycardia following injuries and less impressive physical exam findings when presenting with abdominal emergencies.

Not surprisingly, children living in these environments have impaired host immunity related to their poor nutrition and general debilitated state. From a surgical perspective, this impaired immune function is manifested by higher than expected post-operative wound infections and poorer outcomes following burns, injuries, and major operations (21). Further, children living in the poorest regions are at greater risk for developing poverty related surgical diseases. Cancrum oris (Figure 4a), a rapidly progressive polymicrobial gangrenous infection of the mouth of children aged 2–6 years living in Africa (22) is perhaps the best example. This condition was endemic in German and Japanese concentration camps during World War II (23), but has disappeared in high-income countries with improvements in hygiene and nutrition. Children living in the poorest areas also have a greater likelihood of developing abscesses, osteomyelitis, necrotizing soft tissue infections, and pyomyositis (Figures 4b–f).

For those children who survive this barrage of infectious diseases early in life, their immune systems are forever changed. This “immunological adaption” to chronic and recurrent infection has been aptly described by Greenwood and Whittle (24):

> “A peasant farmer is able to carry out a full day’s work in the fields and live a normal social life is considered a ‘healthy normal’ in many developing communities. However, by the medical standards of industrialized countries he would be considered far from healthy. He is likely to have had repeated attacks of acute malaria since early childhood and still have episodes of asymptomatic malaria parasitemia. He may well have schistosomiasis, although now this produces little in the way of symptoms, and he probably has two or three types of intestinal worms. He may have asymptomatic filariasis. In addition, he is likely to have passed through a period of malnutrition at the time of weaning which may have had permanent effects on the immune system. Such a ‘healthy’ normal shows immunological effects on the immunological changes that are not found among protected individuals in industrialized societies.”

It has long been appreciated that the population described above is at decreased risk for developing the NCDs commonly observed in high-income countries (25, 26). Importantly, these maladies were also rare or uncommon in the Western world a century ago (27). Further, when individuals move from low- to high-prevalence areas, the next and subsequent generations have a disease prevalence aligned with that of Western countries. Examples of

this phenomenon include the Japanese population that has settled in Hawaii (28), descendants of Pacific Islanders who immigrated to New Zealand (29), and African and Yemenite Jews who immigrated to Israel after the Second World War (30). Of note, these geographic variations also occur in the pediatric population (21), suggesting these differences are not solely due to aging.

In summary, a variety of environmental factors change with urbanization in sub-Saharan Africa, of which declining rates of infectious diseases may be the most prominent. Infection is also a leading cause of childhood deaths in rural areas, and thus is a strong evolutionary force in terms of natural selection. Chronic and recurrent infection is also intrinsically linked to nutritional status via its effect on the gut (i.e., environmental enteropathy). Underscoring the profound biological differences that exist in children living in the least developed areas, are the poorer outcomes of children with surgical diseases, the proclivity to develop poverty related surgical diseases, and the previously mentioned neurobiological phenotypes.

GENE EXPRESSION DIFFERENCES BETWEEN RURAL AND URBAN POPULATIONS

Several studies have profiled variations in gene expression within and between population groups where two or more lifestyles and ethnicities are present in the same country (31–33). In a study from southern Morocco, expression of over a third of the peripheral blood leukocyte transcriptome was shown to differ between adult residents of a rural area (Berber village) and the urban city of Agadir (31). Similar results were observed in a larger follow-up study from the same country (32), and in a comparison of Fijians living in a rural village and in the capital city of Suva (33). In all three studies, differences in genome-wide expression signatures were attributed to a combination of lifestyle, geography, and biotic factors. These broad changes in gene expression have been difficult to interpret, especially as they relate to specific risk factors for NCDs.

One evolving application of these rural-urban datasets is to test specific hypotheses regarding how individual genes or pathways change with urbanization. For example, the Moroccan dataset was used to show that the *NPC1* gene, which encodes Niemann-Pick C1 protein—the Ebola virus receptor, has a higher level of expression in rural versus urban Morocco (34). NPC1 is a transmembrane endosome protein responsible for the trafficking of intracellular cholesterol. Although the original purpose of this study was to better explain the rural-urban differences in the infectivity or the fatality rate of the Ebola virus, variations in the expression of several other cholesterol uptake genes (*NPC2 and LDLR*) were identified —suggesting urbanization alters the genes that control lipid metabolism. Of note, serum lipid levels were inversely correlated with high infection rates and inflammatory markers in an indigenous population of Bolivia Amazon (35).

Rural-urban gene expression data has also been used to show that urbanization alters G protein-coupled receptor (GPCR) signaling. GPCRs are the largest single-family of the cell surface receptors and have a role in nearly every aspect of biology and health (36). The G protein family in humans includes 16 α subunits, five β subunits, and 12 δ subunits encoded by different genes (37). These subunits can be expressed in variable combinations to activate

different pathways. Using the Moroccan dataset, Bickler et al. (38) demonstrated that rural and urban populations express different G protein subunit genes, suggesting the possibility of environmentally specific pathway activation (Figure 5). Three genes controlling the phosphatidylinositol signaling pathway and one gene regulating cAMP (3'-5'-cyclic adenosine monophosphate) were altered by urbanization. Further, there was significantly increased expression of the ARRB1 gene in the rural population. This ubiquitously expressed gene encodes the β-arrestin 1 protein which has a role in modulating the sensitivity of GPCRs, and thus has the ability to dampen cellular responses to stimuli including hormones, neurotransmitters, and other sensory signals (39). Considered together, these preliminary findings suggest that urbanization alters signal transduction pathways, a fundamental mechanism by which intercellular communication occurs in multicellular organisms. Moreover, these studies illustrate the tremendous potential that exists for using molecular biological approaches to decipher the complex biological changes that occur during a transition from rural to urban environment.

MAIN DETERMINANTS OF NCDS: IMPROVING THE CURRENT MODEL

NCDs result from a complex interplay of genes, nutrition and the environment. The best summary of these complex interactions is, perhaps, the diagram provided by Jamison et al. in The Lancet Commission Report on Global Health 2035 (40). This report represents a culmination of economic thinking on global health development over the past 30 years, and thus reflects the current opinion on a broad spectrum of important global health problems. In the Commission Report, risk factors for NCDs are grouped into environmental and behavioral factors, which are potentially non-modifiable or modifiable. Non-modifiable risk factors include a person's age, genes, and fetal origins. Fetal origins refers to the long-term effects of the intrauterine environment, wherein critical events during development program the individual for non-communicable diseases later in life (41). While non-modifiable for the individual after birth, improvement in the health and nutrition of reproductive aged females could potentially mitigate the effects of this fetal programming. Modifiable factors include the physiological risk factors of obesity, hypertension, and adverse serum cholesterol concentrations among others. High blood pressure and abnormal serum cholesterol are classified as modifiable because they can be controlled using effective, low-cost drugs. Poor dietary quality (e.g., high-calorie processed foods and sugary sodas) and physical inactivity are both major, modifiable risk factors for obesity—itself a modifiable risk factor for other NCDs.

Based on our review of this topic, we suggest several modifications to the Jamison model. First, given the profound impact chronic and recurrent infections have on populations living in rural sub-Saharan Africa, and their declining rates with urbanization, we propose a role for diminishing infection in the origins of NCDs. The consideration here is that evolution has favored the selection of genotypes that are capable of a robust immune response. When chronic and recurrent infections diminish as a result of public health interventions (e.g., sewage disposal and clean water), the evolved phenotype is no longer well suited for the environment. In this conceptualization, the mechanisms that protect against pathogens in rural areas are the same as those that lead to NCDs in urban areas—albeit without the dampening effect from the chronic and recurrent infections. The concept that infection

protects against NCDs in rural environments aligns well with the hygiene hypothesis proposed by Strachan (42) over 25 years ago, and several other more recent derivations wherein health and disease is determined by the immune systems interactions with microbes and parasites in the natural environment and the human microbiome (43–45). Our second suggestion for improving the Jamison model is to expand the diseases included in the NCD list. As observed by Burkitt (27), adoption of a western lifestyle increases a broad spectrum of NCDs (Table 1). Thus, we have added atopic, autoimmune, and several gastrointestinal diseases to the Jamison list. The group of gastrointestinal diseases that increases with urbanization is of great importance to the field of surgery as it includes the majority of the surgical pathology (e.g., appendicitis, colon cancer, diverticulitis, and gallbladder disease) observed in high-income countries. Of these conditions, appendicitis is perhaps the best example. Appendicitis is the most common abdominal surgical emergency in high-income countries, but is rare in underdeveloped rural areas of low-income countries. Consider the epidemiology of childhood appendicitis. In the United States, the incidence of childhood appendicitis is 37.2 per 10,000 children aged 0–14 years per year (46). In comparison, the incidence of appendicitis in black children in Soweto, Johannesburg aged 0–14 years, is 1.1 per 10,000 (47). A similar incidence was reported from The Gambia where the incidence was 0.8 per 10,000 children aged 0–14 years, $1/24^{th}$ and $1/49^{th}$ the incidence of African American and Caucasian children in the USA, respectively (48). Reports from other centers in Africa suggest the incidence of appendicitis is rising with the adoption of Western lifestyles, further underscoring the importance of the rural-urban transition in this NCD (49–53).

Our working model for the relationships between risk factors and NCDs is presented in Figure 6. In this modification of the Jamison model, declining rates of chronic and recurrent infection are shown as a non-modifiable risk factor with potential effects on genes, fetal development, physiological risk factors and NCDs. The spectrum of NCDs has been expanded to include atopic, autoimmune, and gastrointestinal diseases, and “new biological markers” have been added to the physiological risk factors box. The last suggested modification is based on our belief that new measurable markers will be discovered, as the biology of the rural-urban transition becomes better understood.

FUTURE RESEARCH

We suggest the following research priorities.

1. Research to further define how urbanization impacts the epidemiology of disease

While we currently have broad impressions about how the transition from a rural to an urban environment impacts disease epidemiology, there is a need for more detailed population-based data. Recognizing that this data are extremely difficult and expensive to collect, it may be best to align this data collection with other ongoing epidemiological studies. One approach would be to expand the Global Burden of Disease (GBD) studies to collect more detailed data on rural and urban population. As an example, the 2013 Global Burden of Disease study stratified data into rural and urban populations, although this was done only for India and by cause of death (54). Ideally, future GBD studies would collect rural and

urban incidence data from additional countries, and perhaps even include the location in which a person lives as a risk factor for disease.

2. Studies to define the relationship between chronic infection and risk factors for NCDs

Identifying the mechanisms by which the environment alters NCD risk factors is a formidable, yet inspiring challenge, as it offers an opportunity to better understand the biology of the most common diseases in high-income countries. Simultaneously it could provide important insight into the optimal treatment for childhood undernutrition in low-income countries—a major public health problem that is responsible for approximately 20% of child deaths worldwide. The therapeutic implications could be great. Basic biological principles could be gleaned from the type of gene expression studies we have discussed above. For example, one could feasibly decipher the molecular mechanisms responsible for the inverse relationship between low serum lipids levels and high infection rates observed in the indigenous population living in Bolivia (35). The rural-urban paradigm also provides an opportunity to investigate what role epigenetic mechanisms might have in modifying the risk of NCDs.

3. Research directed at understanding the outcome differences that exist in the inflammatory response between rural and urban populations

One of the most intriguing questions surrounding the rural-urban transition is: “Why are the consequences of inflammation so markedly different in the rural and urban environments?” In the rural environment, inflammation is an integral component of the immunological response to chronic and recurrent infections; while in the urban environment, chronic inflammation has an important role in the pathogenesis of NCDs—most notably atherosclerosis and autoimmune diseases. Whether epidemiological differences relate to the timing of infection, type of infection (e.g., viral, bacterial or parasitic), or to the magnitude of the infectious disease burden remains unclear. Regarding the latter, there must be inhibitory mechanisms within the inflammatory response allowing for a response that is “just right” (55). Too little, and the organism is overcome by infection and unable to repair damaged tissue. Too much, and an exaggerated inflammatory response can damage healthy tissue. In a broader sense, this “Goldilocks effect”, where the inflammatory response must carefully match the threat, sits at the nexus of every clinical problem in modern medicine and covers the entire spectrum of communicable and non-communicable diseases. A deeper understanding of the mechanisms that regulate the inflammatory response, especially in settings of high infectious disease burden, could provide important insight into a wide range of problems resulting from an excessive inflammation (e.g., autoimmune disease, sepsis, and multiple organ dysfunction syndrome in trauma patients). In this context, there is a need to develop improved tools to assess the inflammatory response in a variety of environments. Inflammation is currently assessed using single inflammatory markers or receptors, but this approach often fails to capture the complex interactions that can occur between genes, nutrition, and the environment. The rural-urban paradigm offers an important opportunity to rethink how inflammation and its consequences are measured. An evolving strategy in medicine is to use computational and mathematical modeling to answer complex biological questions (56, 57). This “systems biology approach” seems well suited for examining the biological effects of urbanization and how they intersect to determine health and disease.

The challenge for inflammation researchers is to adapt this this methodology to capture the multidimensional relationships that exist between nutrition, infection, metabolism, genetic predisposition, and the immune response.

4. Identification of animal models that simulate the biological changes that occur with urbanization

There is a critical need to develop an animal model that can be used to study the biological consequences of urbanization. An animal model could help untangle the complex interactions that occur between genetics, nutrition and infection, facilitate development of new biological markers, and ultimately serve as a preclinical model to test new NCD prevention strategies. The ideal animal model would replicate the nutritional and immune changes that occur in the rural environment, along with their associated neurobiological phenotypes. The urban component of the model would need to simulate the consequences of diminishing chronic and recurrent infections. If the model is properly designed, it could be used to better understand the pathophysiology of diseases at both ends of the socioeconomic development spectrum—child undernutrtion in rural areas, and NCDs in the urban population. A starting point for this research could be several animal models wherein growth failure has been shown to be associated with changes in the intestinal microbiome. Brown et al. (58) demonstrated that early-life consumption of a moderately malnourished diet, in combination with iterative oral exposure to commensal Bacteroidales species and Escherichia coli, remodels the murine small intestine to resemble features of environmental enteropathy in humans. More recently, impaired growth phenotypes have been replicated in mice by transplanting microbiota from undernourished Malawian and Bangladeshi children into young germ-free mice and feeding their representative diets (59, 60). Chickens fed a rye-based diet rather than the usual corn-based diet develop growth failure, enteropathy, increased intestinal permeability, bacterial overgrowth in the small bowel, and increased endotoxemia similar to that observed in under nourished children living in rural areas of low-income countries (61, 62). Rye contains a large amount of non-soluble polysaccharides, raising the question what affect a large amount of dietary fiber might have on the growth and development of children living in LMICs. Although mice have close genetic and physiological similarities to humans and many tools exist for manipulating its genome, the chicken is an intriguing experimental animal because of its rapid growth, and the extensive nutritional literature available because of the poultry’s industry keen interest in maximizing meat production.

CONCLUSIONS

Urbanization is occurring rapidly in sub-Saharan Africa with profound effects on disease epidemiology. In contrast to rural areas, where chronic and recurrent infections continue to be the dominant public health problem, urban populations have higher rates of NCDs—a profile similar to that observed in high-income countries. This epidemiological transition provides an exciting opportunity to investigate the mechanisms by which the environment shapes health and disease. A better understanding of the complex interactions that occur between genes, infection, and nutrition, along with their impact on the inflammatory

response, could provide important insight into the etiology for many common surgical and medical conditions encountered in high-income countries.

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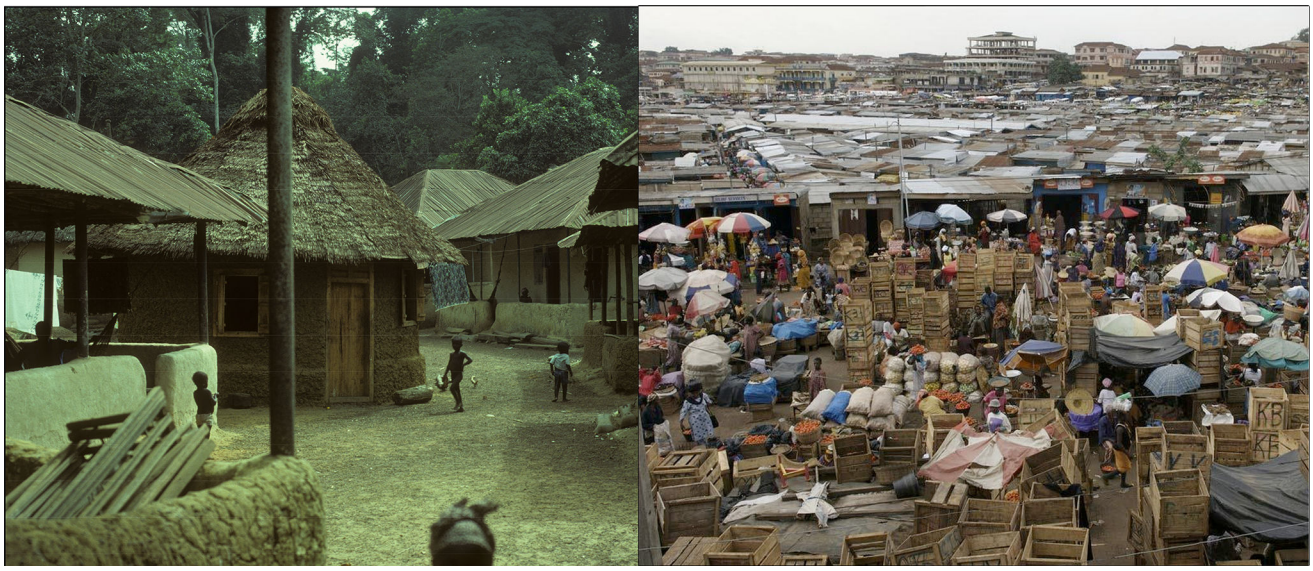

Figure 1.

Rural and urban areas of Sub-Saharan Africa. These contrasting environments offer a unique opportunity to better understand how the environment shapes human health. Infectious diseases predominate in the rural areas with the urban population taking on a Western profile of chronic metabolic diseases. Source: rural photo is the author's, urban photo: Jonathan Ernst/World Bank.

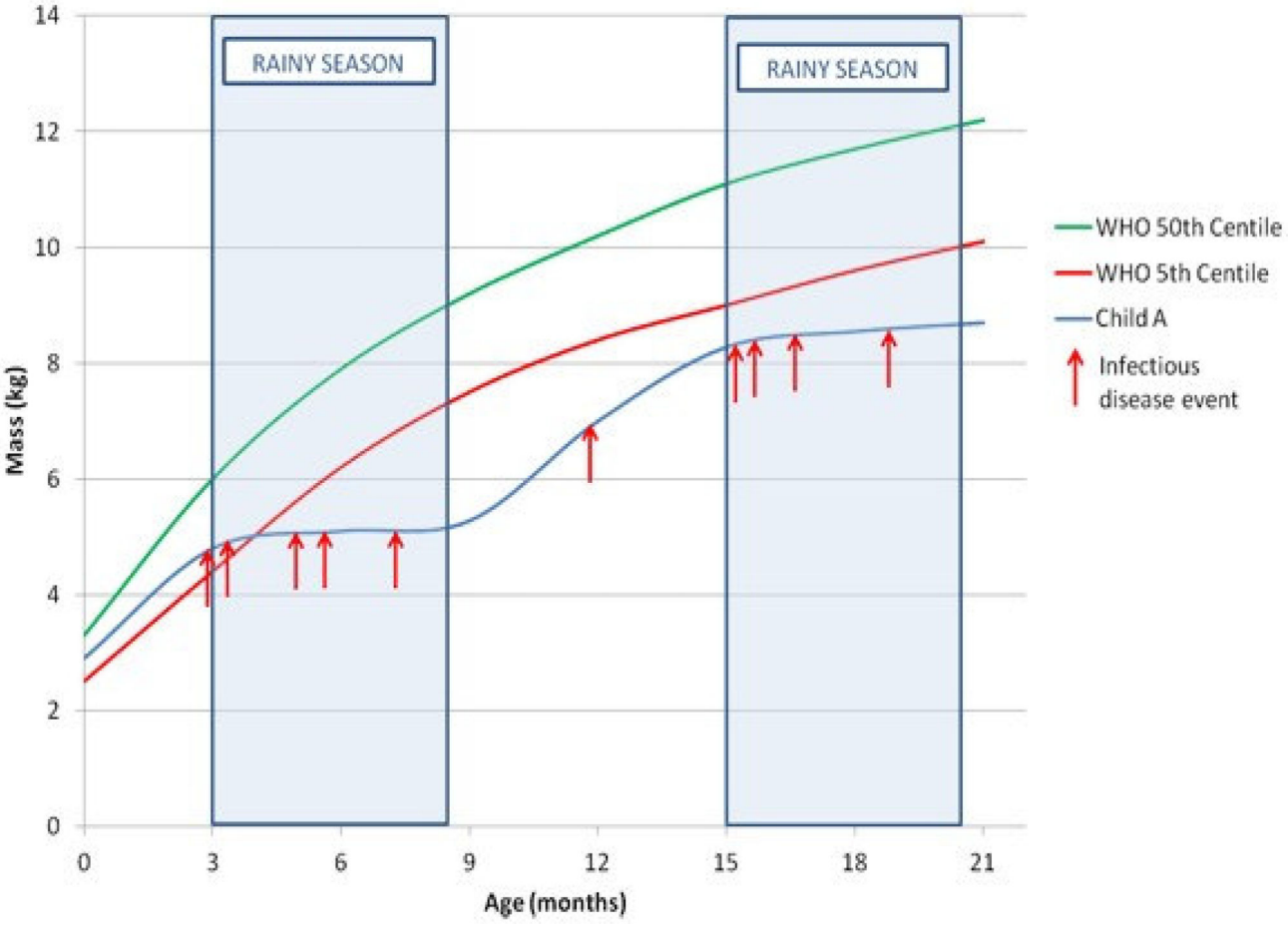

Figure 2.

Typical growth curve of a child living in a rural area of The Gambia (West Africa). Season of the year and infectious disease events affect growth. The rainy season presents an environment where food is scarce and infections are more common. Note the period of "catch-up-growth" following the first rainy season, but that the child never makes it back to even the WHO 5th Centile. Source: The London School of Hygiene and Tropical Medicine (63), adapted from McGregor (64).

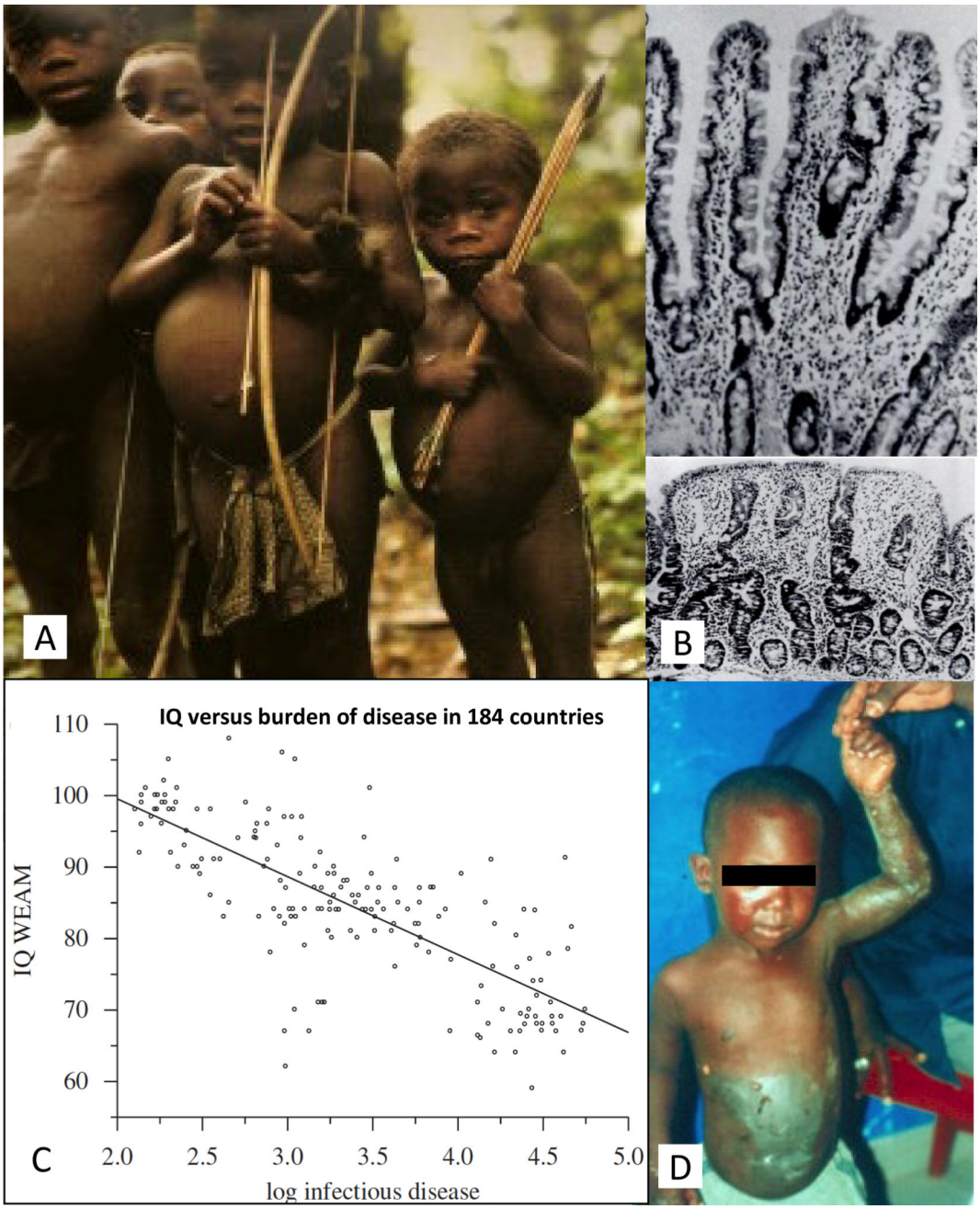

Figure 3.

Neurobiological phenotypes commonly observed in children living in rural areas of sub-Saharan Africa. A. Growth failure: Children from a remote area of The Congo showing signs of subclinical malnutrition (thin discolored hair, small upper arm circumference, protuberant abdomens). Photo by William Wheeler, MD (65); B. Environmental enteropathy: Blunted villi with inflammation of the lamina propria (lower panel), long narrow villi observed in children living in high-income country (upper panel). Adapted from Korpe and Petri (66); C. Cognitive deficits: Relationship between IQ and burden of infectious disease. Adapted from Eppig (19); D. Altered pain behavior: Un-medicated three-

year child with a scald burn illustrating minimal response to a typically very painful stimulus (author's photo).

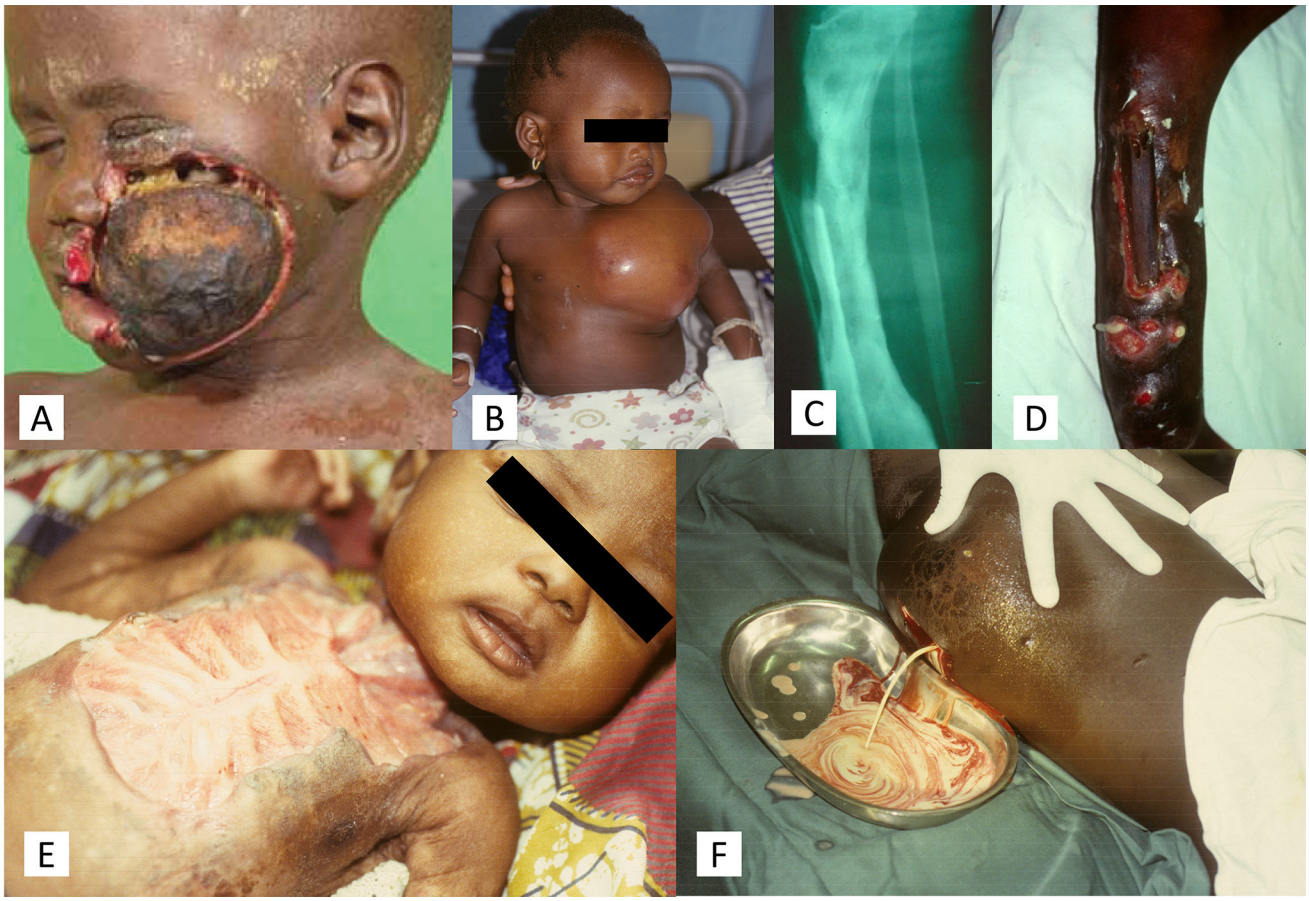

Figure 4.

Examples of poverty related surgical diseases occurring in children living in the poorest regions of sub-Saharan Africa. A: Cancrum oris or “Noma” – a rapidly progressive polymicrobial gangrenous infection of the mouth that affects children aged 2–6 years of age in poorest countries of Africa. Source: Legbo and Ameh (67); B: Breast abscess. C and D: Chronic osteomyelitis of the tibia and fibula showing radiological findings and protruding bone. E. Necrotizing soft tissue infection. F: Tropical pyomyositis—collection of pus being drained from a child’s quadriceps muscle. While access to health care contributes to the severity of these conditions, their higher incidence in the poorest areas of sub-Saharan Africa suggests an environmental effect—most likely resulting from the complex interactions that occur between chronic infection and nutrition. Photos B-F are the author’s.

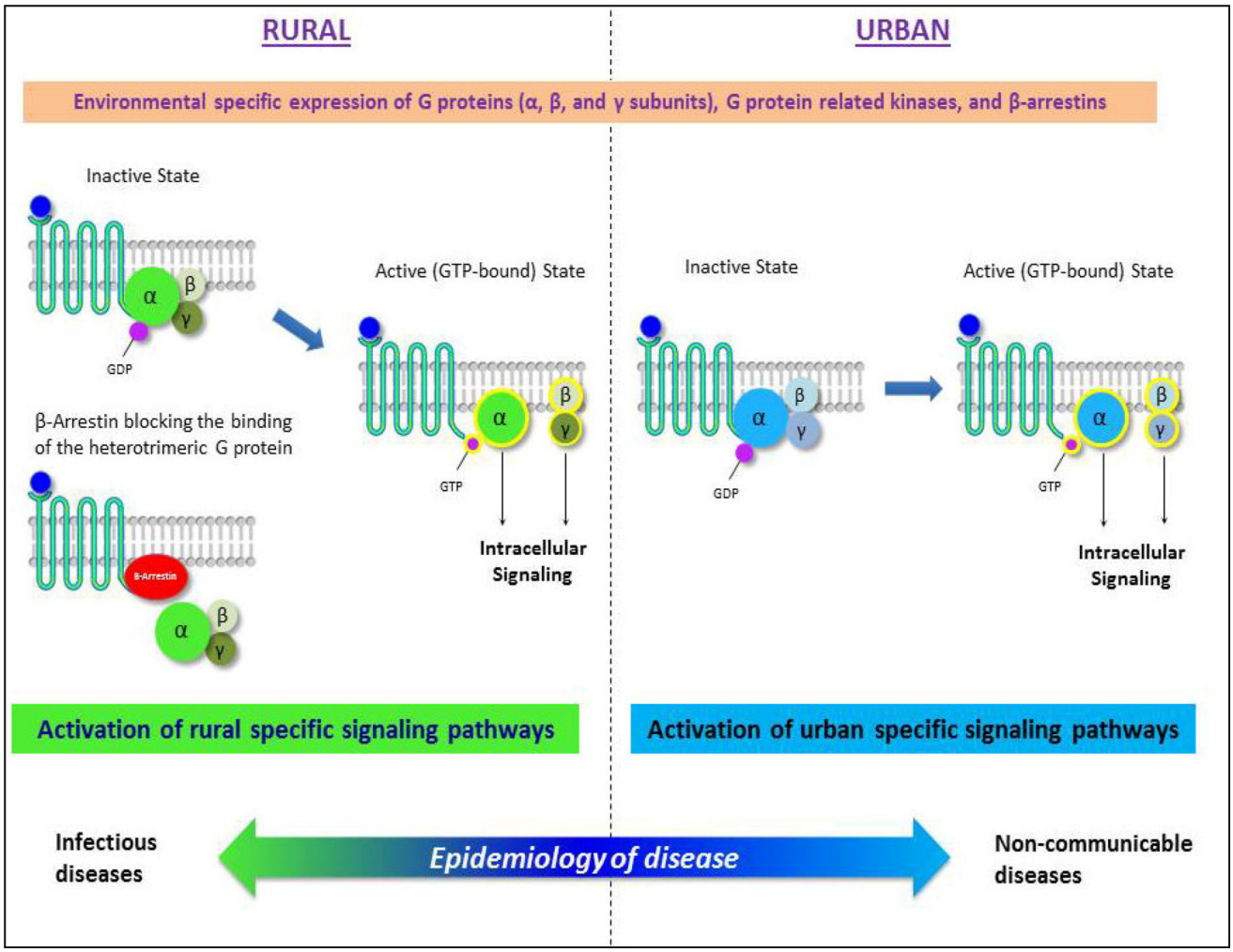

Figure 5.

Conceptual model showing environmentally specific G protein-coupled receptor (GPCR) signaling with activation of different pathways in rural and urban environments. The model is based on the general principles of GPCR signaling presented by Oldham and Hamm (68), with the effects derived from gene expression data from a rural and urban population living in Morocco(31). The heterotrimeric proteins (α, β, and δ subunits), which are associated with the seven membrane-spanning region in the unstimulated state, dissociates into the α, β, and δ subunits upon cell stimulation. Because the expression of the α, β, and δ subunit genes vary between the rural and urban population (shown with different shades of blue and green), different pathways are activated in the rural and urban environments. In the rural population, increased expression of β-arrestin 1 protein (red) decreases the binding of the heterotrimeric protein to the seven membrane-spanning region, thus dampening down the entire signaling process. Source: Bickler et al, 2016 (38).

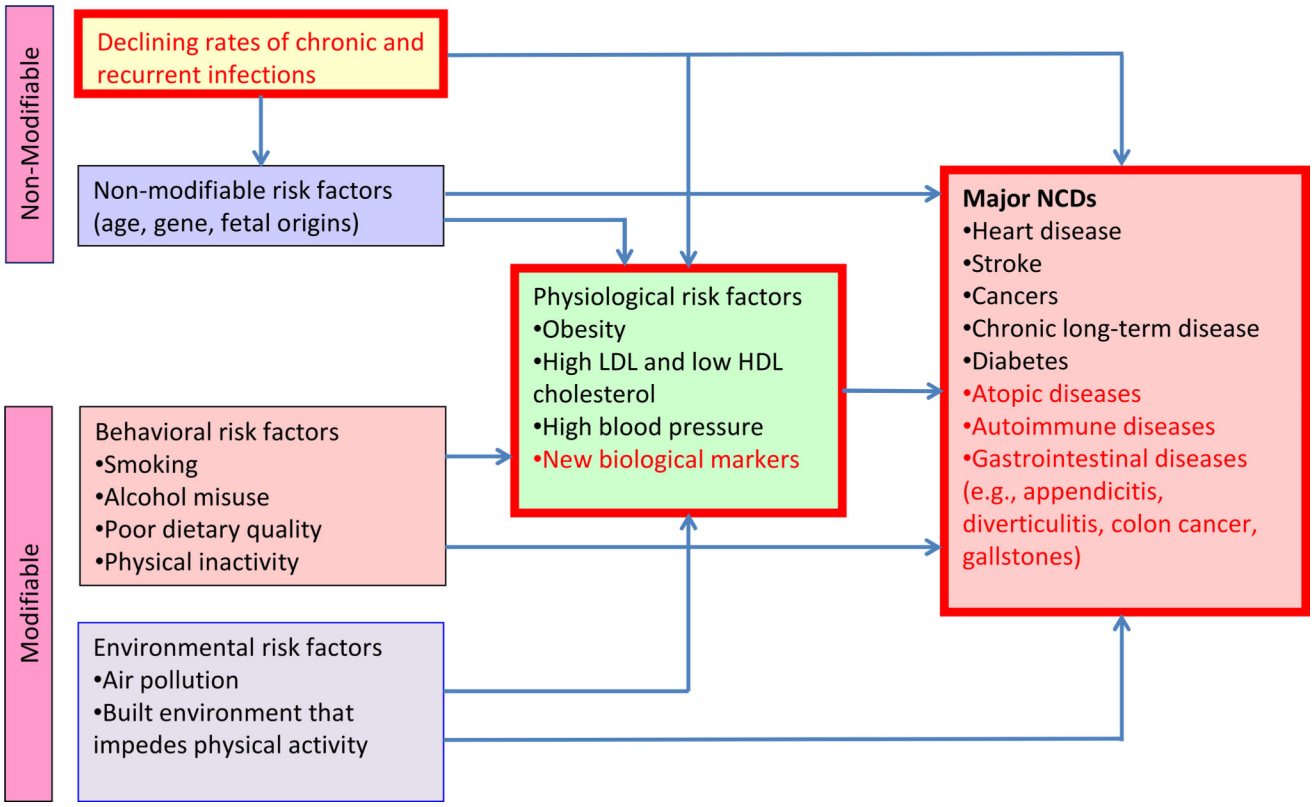

Figure 6.

Relationships between key risk factors and NCDs. Model is based on Figure 15 in Jamison et al. (40). Red font and boxes outlined in red show modifications to the Jamison model. Declining rates of chronic and recurrent infection are included as a risk factor for NCDs. Atopic, autoimmune, and gastrointestinal diseases such as appendicitis, diverticulitis, colon cancer and gallstones are now included in the list of NCDs. NCD=non-communicable disease. LDL=low-density lipoprotein. HDL=high-density lipoprotein.

Table 1

Non-communicable diseases that increase with urbanization. Adapted from Burkitt (25, 27).

Diseases characteristic of modern western civilization (25,27)		
Atherosclerosis	Inflammatory bowel disease	Obesity
Stroke	Appendicitis	Asthma
Essential hypertension	Irritable bowel syndrome	Varicose veins
Diabetes	Gastroesophageal reflux	Pulmonary embolism
Gallstones	Hiatal hernia	Autoimmune disease
Colorectal cancer	Hemorrhoids	Constipation
Diverticular disease		