HEALTH IN TRANSITION

Translating developmental origins
of health and disease science to
improve future health in Africa

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HOW ENVIRONMENTAL EXPOSURES EARLY IN LIFE MIGHT INFLUENCE PHENOTYPES OF NON-COMMUNICABLE DISEASES IN AFRICA

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Chronic non-communicable diseases, such as diabetes, cancer, cardiovascular and chronic respiratory diseases are leading causes of death and disability in the world – accounting for over 60 per cent of the nearly 60 million deaths in 2008.⁴ Importantly, 80 per cent of non-communicable disease deaths occur in low- and middle-income countries.⁵ Although Africa still has a high burden of infectious

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- 4 WHO. 2020. Cardiovascular Diseases. *Health Topics*. [<https://bit.ly/35mrVTy>].
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diseases, the non-communicable disease epidemic is rising rapidly; it is projected that, by 2030, non-communicable diseases will account for 46 per cent of all deaths in the region.⁶ For example, although diabetes was considered a rare disease in Africa until about a century ago, it now affects up to a third of the population in some countries; the prevalence of diabetes and hypertension will have increased by nearly 80 per cent, and deaths from ischemic heart disease doubled between 2008 and 2030. This chapter discusses how environmental exposures early in life might influence phenotypes of non-communicable diseases in Africa.

Introduction

Our knowledge of non-communicable diseases in Africa is severely limited, but evidence to date suggests there are important differences between African and Western settings. The limited data available indicate that non-communicable diseases such as type 2 diabetes mellitus and hypertension occur in younger people in Africa, with the largest number of those affected aged 30-59 years old, compared to Europe where most people with diabetes are over 60 years old. Additionally, in high-income countries, these disorders are classically associated with obesity. Africans appear to be more likely to develop diabetes for the same level of body mass index and lower, than Caucasians. South Asians are also known to develop diabetes at low levels of body mass index; a presentation thought to be related to the disproportionately central distribution of fat. Thus, while only seven per cent of deaths caused by hypertension occur in people under 60 years in high-income countries, in Africa, 25 per cent of deaths occur in individuals under this age.⁷ This high burden on the economically productive population in Africa will perpetuate

increasing challenge in developing countries. *Transactions of The Royal Society of Tropical Medicine and Hygiene*, 99(5):321-324. [https://doi.org/10.1016/j.trstmh.2005.02.001].

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the vicious cycle of poverty and, if left unattended, non-communicable diseases will threaten the gains (in life expectancy and socioeconomic developments) that have been achieved in combating infectious diseases.⁸

Traditional risk factors for non-communicable diseases

The rise of non-communicable disease in low- and middle-income countries has been mainly attributed to increased life expectancy and urbanisation or globalisation, with associated changes in lifestyle behaviours (such as unhealthy diets, physical inactivity, smoking and excessive alcohol consumption).⁹ Sub-Saharan Africa, in particular, is experiencing one of the most rapid increases in urbanisation, with urban populations growing at an average annual rate of 4.5 per cent.¹⁰ These traditional risk factors such as smoking, obesity, high salt intake, sedentary lifestyle and pollution will have the same adverse health effects in Africa as they have in the developed Western countries. However, there are limited data on the distribution of these risk factors and how strongly they are associated with non-communicable diseases in sub-Saharan Africa. Recent studies suggest that the prevalence of these potential non-communicable disease risk factors is increasing in many sub-Saharan Africa countries.¹¹ Rates of risk factors

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- 9 BeLue et al., 2009; Madu et al., 2003; Dalal, S., Beunza, J.J., Volmink, J., Adebamowo, C., Bajunirwe, F., Njelekela, M., Mozaffarian, D., Fawzi, W., Willett, W., Adami, H.O. & Holmes, M.D. 2011. Non-communicable diseases in sub-Saharan Africa: what we know now. *International Journal of Epidemiology*, 40(4):885-901. [https://doi.org/10.1093/ije/dyr050].
- 10 Maher, D., Smeeth, L. & Sekajugo, J. 2010. Health transition in Africa: practical policy proposals for primary care. *Bulletin of the WHO*, 88(12):943-948. [https://doi.org/10.2471%2FBLT.10.077891].
- 11 Dalal et al., 2011; Njelekela, M., Negishi, H., Nara, Y., Tomohiro, M., Kuga, S., Noguchi, T., Kanda, T., Yamori, M., Mashalla, Y., Jian Liu, L., Mtabaji, J., Ikeda, K. & Yamori, Y. 2011. Cardiovascular risk factors in Tanzania: a revisit. *Acta Tropica*, 79(3):231-239. [https://doi.org/10.1016/s0001-706x(01)00134-6]; Echouffo-Tcheugui, J.B. & Kengne, A.P. 2011. Chronic non-communicable diseases in Cameroon - burden, determinants and current policies. *Global Health*, 7(1):44.

among countries, urban-rural location and sub-populations variate considerably. While these variations may reflect the varying speed at which the communities are undergoing the epidemiological transition, they may also result from differences in study design and measurement techniques, generally not standardised in sub-Saharan Africa because of the limited amount of research on non-communicable diseases. However, it is vital though that we know the relative importance of these traditional risk factors, as well as other drivers that may have unique importance in the region, to inform control strategies and further research.

Potential contribution of genetics to risk for non-communicable diseases

Urbanisation or globalisation and associated behavioural risk factors (such as reduced food quality or increased food quantity and reduced physical activity) may not explain the epidemic of non-communicable diseases in Africa fully; other factors might contribute to the apparent increase in susceptibility. For example, the effects of these environmental factors in mediating the development of non-communicable diseases will be modulated by genetic susceptibility. Understanding the contribution of genetics is particularly important in sub-Saharan Africa because, as a region where first humans evolved, it harbours high genetic diversity and lower linkage disequilibrium (the tendency for groups of genes to be inherited together).¹² Thus, differences have been observed in the distribution of genetic

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polymorphisms coding for susceptibility to communicable diseases (such as malaria, HIV, tuberculosis) and non-communicable diseases (such as breast and prostate cancer) in people of African ancestry compared to those of European descent.¹³ Recently, there have been major advances in identifying regions of the human genome that affect resistance or susceptibility to common conditions like heart disease, cancer and diabetes, using new scientific approaches such as genome-wide association analysis. For example, polymorphisms of genes associated with type 2 diabetes in the Caucasian population (e.g., of the TCF7L2 gene) have also been found in West African families.¹⁴ Moreover, most type 2 diabetes risk alleles appear to share a pattern of decreasing frequencies along with human migration from Africa, with, for example, genetic risk being consistently higher for individuals in the African populations than in the Asian ones.¹⁵ Therefore, studying the inter-

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action between environmental factors and genes in sub-Saharan Africa is likely to yield significant opportunities for scientific discovery.¹⁶

The impact of developmental origins of health and disease (DOHaD) on manifestations of non-communicable diseases in Africa

A better understanding of non-communicable diseases in sub-Saharan Africa will also require exploration of other environmental factors that may have unique importance in the region. In particular, there is compelling epidemiological and experimental evidence that early life exposures or insults play an important role in determining susceptibility to chronic degenerative diseases in adulthood. For example, many studies have shown strong associations between maternal undernutrition during pregnancy (reflected in a small size at birth) and substantially increased risk of adulthood obesity, type 2 diabetes, hypertension, coronary heart disease, as well as behavioural and neuroendocrine disorders.¹⁷ These relationships are independent of classical risk factors in adulthood, such as smoking, weight, social class, excess alcohol intake or sedentariness, which additive to the effects of birth weight.¹⁸ These observations led to the DOHaD concept, which proposes that early-life environments (periconceptional, fetal and early postnatal) have long-lasting influences in offspring to later health and disease susceptibility.¹⁹

Although initial studies linking low birth weight and later disease came from Europe and North America, the impact of ‘fetal programming’ is likely to be far greater in developing countries, where maternal and fetal malnutrition are common (approximately 95 per cent of all growth-retarded babies are born in

populations, compared to other diseases. *PLoS Genetics*, 8(4):e1002621. [<https://doi.org/10.1371/journal.pgen.1002621>].

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- 18 McMillen & Robinson, 2005.
- 19 Hales, C.N. & Barker, D.J. 1992. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia*, 35(7):595-601. [<https://doi.org/10.1007/bf00400248>].

developing countries).²⁰ Indeed, subsequent studies in China and India have supported this notion.²¹ This concept is also likely to be important in Africa where under-nutrition, particularly during pregnancy and in early childhood, remains common, yet coexists with the global obesity epidemic.²² In the Gambia, children who were born with low birth weight and retained the ‘lean, fit and frugal’ lifestyle of the rural areas tended to maintain normal cardiovascular and metabolic health into adulthood.²³ Those who migrated to urban areas (exposed to a diet of relative energy excess and reduced physical activity), had higher susceptibility to cardiometabolic disorders, consistent with the ‘thrifty phenotype’ hypothesis.²⁴

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Thus, the combination of adverse early life influences and a demographic shift towards urbanisation might explain, at least in part, the rapidly rising burden (and early age at onset) of non-communicable diseases in sub-Saharan Africa.²⁵ However, more data from different birth cohort studies in Africa are needed to address this question and inform interventions in pregnancy or early life to reduce long-term non-communicable diseases risk. It is also noteworthy that although most epidemiological evidence on DOHaD relates to malnutrition in early life, other insults associated with poverty (such as infections, use of biomass fuel) can have similar ‘programming effects’. It is also known that early-life psychological stress (either prenatally or in the early postnatal period) can impact on later health, in part by contributing to maladaptation of the stress-response system. Indeed, the fetus is normally protected from the relatively high maternal levels of glucocorticoids (stress hormones) by the enzyme 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2), highly expressed in the placenta, that breaks down active glucocorticoids into inert products. Maternal undernutrition reduces placental 11 β -HSD2, increasing the load of glucocorticoids reaching the fetus via placenta transfer.²⁶ Glucocorticoids might provide a common pathway through which diverse insults exert their programming effects.

Potential mechanisms through which early insults ‘programme’ disease

In the DOHaD concept, the developing fetus, if exposed to a hostile uterine environment (caused by insults such as poor nutrition, infections, chemicals, metabolite or hormonal perturbations), responds by developing adaptations (predictive adaptive responses), that not only foster its immediate survival, but that in a similar environment later in life.²⁷ However, if the individual grows up in

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an extra-uterine environment reversed to that experienced in utero, the ‘mismatch’ would predispose them to a higher risk of specific non-communicable diseases.²⁸ This risk is further exacerbated by postnatal risk factors, such as excessive weight gain, and by the ageing process itself.²⁹ Recent study findings have, for instance, shown that postnatal weight gain rather than birth weight, maybe more important in the developmental programming of later blood pressure, with fast-growing low birth weight children at particularly higher risk.³⁰

The mechanisms mediating the programming effects of diverse environmental insults, or how this memory is stored, are not fully understood, but a few have been postulated and are described below.

Change in organ size

It is thought that during periods of insult or stimuli (such as suboptimal nutritional or hormonal levels), the fetus’ immediate aim to survive, and preserve vital functions, occurs at the expense of other ‘less critical’ functions.³¹ For example, by diverting blood supply away from organs such as the kidneys alters their normal development and may lead to permanent changes in structure (too small organs)

tree.2005.08.001]; Hales, C.N. & Barker, D.J. 2001. The thrifty phenotype hypothesis. *British Medical Bulletin*, 60(1):5-20. [https://doi.org/10.1093/bmb/60.1.5].

28 Gluckman et al., 2008.

29 Hales & Barker, 2001; Vickers, M.H., Breier, B.H., Cutfield, W.S., Hofman, P.L. & Gluckman, P.D. 2000. Fetal origins of hyperphagia, obesity, and hypertension and postnatal amplification by hypercaloric nutrition. *American Journal of Physiology-Endocrinology And Metabolism*, 279(1):83-87. [https://doi.org/10.1152/ajpendo.2000.279.1.E83].

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31 Hoet, J.J. & Hanson, M.A. 1999. Intrauterine nutrition: its importance during critical periods for cardiovascular and endocrine development. *Journal of Physiology*, 514(6):617-627. [https://doi.org/10.1111%2Fj.1469-7793.1999.617ad.x].

and function (hormonal and metabolic).³² Indeed, at post-mortem, intrauterine growth retardation is associated with reduced nephron numbers per unit area of kidney among human stillborn infants.³³ Intrauterine growth retardation effectively reduces the long-term functional capacity of the kidney (the total number of nephrons in the kidney is set at birth).³⁴ The effects of early life insults on nephron number and kidney size have been demonstrated in several animal models, including nutritional restriction in sheep and rats, and placental insufficiency in rabbits and rats.³⁵ The small kidneys with a reduced number of nephrons will have reduced hemodynamic and excretory functional capacity (important for blood pressure regulation) and increase the risk of hypertension.³⁶ Similar changes in the size or number of beta-cell islets in the pancreas or skeletal muscle would compromise their function (insulin secretion and glucose disposal, respectively), and contribute to increased risk of diabetes in individuals who suffered insults early in life. In rats,

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- 33 Hinchliffe et al., 1992.
- 34 Ojeda, N.B., Grigore, D. & Alexander, B.T. 2008. Developmental programming of hypertension: insight from animal models of nutritional manipulation. *Hypertension*, 52(1):44-50. [<https://doi.org/10.1161/HYPERTENSIONAHA.107.092890>]; Brennan, K.A., Olson, D.M. & Symonds, M.E. 2006. Maternal nutrient restriction alters renal development and blood pressure regulation of the offspring. *Proceedings of the Nutrition Society*, 65(1):116-124. [<https://doi.org/10.1079/pns2005484>].
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- 36 Langley-Evans, S.C. 2007. Fetal programming of cardiovascular function through exposure to maternal undernutrition. *Proceedings of the Nutrition Society*, 60(4):505-513. [<https://doi.org/10.1079/pns2001111>].

for example, exposure to severe starvation leads to poor development of pancreatic beta-cell mass and function, which persists into adulthood.³⁷ Similarly, poor intrauterine nutritional conditions have been shown to influence the development of skeletal mass and increase the risk of insulin resistance in later life.³⁸

Altered gene expression

Another mechanism through which early exposures might mediate their long-term effects involves epigenetics.³⁹ Epigenetic modifications, which include deoxyribonucleic acid (DNA) methylation, histone marks and non-coding ribonucleic acids, regulate gene expression independent of changing the DNA sequence and are important to normal development and differentiation.⁴⁰ DNA methylation, for example, is vital to cell differentiation, carcinogenesis and genomic imprinting.⁴¹ Several studies in animal models and humans have shown that prenatal insults such as undernutrition can change methylation levels and expression of genes in biological pathways involved in growth and metabolic function, including pancreatic beta cell functioning and insulin signalling.⁴² The offspring of mothers who were pregnant during historical famines, such as the Dutch Hunger in the winter of 1944-1945 or the Great Chinese Famine have increased risk of non-communicable diseases (including type 2 diabetes) and reduced methylation at regulatory regions for the insulin-like growth factor 2, a hormone critical to

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38 Gluckman et al., 2008.

39 Ibid.

40 Martin-Gronert, M.S. & Ozanne, S.E. 2012. Mechanisms underlying the developmental origins of disease. *Reviews in Endocrine and Metabolic Disorders*, 13(2):85-92. [<https://doi.org/10.1007/s11154-012-9210-z>].

41 Jaenisch, R. & Bird, A. 2003. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. *Nature Genetics*, 33(Supplement):245. [<https://doi.org/10.1038/ng1089>].

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growth and development.⁴³ Other studies also found undernutrition in utero to alter methylation rates of important enzymes (11 β -HSD2) and hormonal receptor sites (glucocorticoid receptors), changes that perturb hormone homeostasis and can lead to adult disease.⁴⁴ Changes in non-coding ribonucleic acid and histone modifications at genes of key transcription factors such as the PPARs, Hnf4 α and Pdx1, critical to normal tissue and organ development (adipose tissue, the pancreas, liver), cellular differentiation and metabolism, have also been associated with aberrance and susceptibility to type 2 diabetes.⁴⁵

Non-human experiments have demonstrated that exposure to malnutrition in one generation can affect a range of outcomes in two subsequent generations.⁴⁶ It is thought that such transgenerational inheritance is mediated by epigenetic changes. However, with decades between generations and complex life histories, evidence of transgenerational inheritance in humans has been inconsistent. That said, many observational studies of multigenerational birthweights have found positive associations between maternal and offspring birthweights.⁴⁷ However, it is complex to quantify a causal relationship as it is confounded by shared genetic and environmental factors. Moreover, few studies have rigorously examined harder outcomes such as the occurrence of disease, beyond birth weight in subsequent generations.

Exposure of the developing fetus or infant to stressors, as mentioned above, has also been shown to alter the function of the hypothalamic-pituitary-adrenal axis, resulting in permanent overactivity.⁴⁸ The mechanisms that lead to the altered

43 Heijmans et al., 2008.

44 Drake, A.J., McPherson, R.C., Godfrey, K.M., Cooper, C., Lillycrop, K.A., Hanson, M.A., Meehan, R.R., Seckl, J.R., Reynolds, R.M. 2012. An unbalanced maternal diet in pregnancy associates with offspring epigenetic changes in genes controlling glucocorticoid action and foetal growth. *Clinical Endocrinology*, 77(6):808-815. [<https://doi.org/10.1111/j.1365-2265.2012.04453.x>].

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hypothalamic-pituitary-adrenal axis are not clearly understood but are thought to include tissue-specific changes in the expression of the glucocorticoid receptor.⁴⁹ For example, studies in rodents have shown that exposure to insults in early life induces permanent downregulation of glucocorticoid receptor expression in the hippocampus and pituitary gland, resulting in attenuation of negative feedback by glucocorticoids at these centres, and therefore increased adrenocorticotropin production and stimulation of the adrenal gland.⁵⁰ Since the hypothalamic-

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pituitary-adrenal axis is responsible for regulating the development and function of several homeostatic systems and organs (including those involved in the regulation of blood pressure and glucose metabolism), disturbances in this system may play an important role in mediating effects that lead to fetal programming. Disruption in its development by stressors in early life not only severely affects its function, but also those of systems it regulates, leading to permanent changes in fetal physiology and behaviour.⁵¹ These changes, in turn, predispose the individuals to a plethora of cardiometabolic, neurological and neuroendocrine derangements in adulthood.⁵² The hypothalamus is also involved in appetite regulation, and animal studies have shown that obesity or undernutrition during pregnancy can programme the

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hypothalamic circuitry to influence eating behaviour and lead to later obesity and metabolic disease.⁵³

Why is this evidence important?

We must have a proper understanding of non-communicable diseases in Africa, to avoid the danger of assuming that these disorders will have similar phenotypes or approaches to prevention and treatment as those described in Western societies. For example, if obesity is currently not a major risk factor for diabetes or hypertension in Africa, prevention efforts to tackle these conditions might require going beyond simple calorie intake. Similarly, there might be implications for treatment of diabetes – is metformin, whose benefit is highest in obese people with insulin resistance, the best treatment for all phenotypes of diabetes in Africa where a significant proportion present without overweight or obesity?

Careful epidemiological and clinical studies, coupled with recent advances in technology including genomics and bioinformatics, offer vast opportunities to improve our understanding, and therefore prevention and treatment of non-communicable diseases in Africa.

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