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# Health Disparities Among Indigenous Peoples: Exploring the Roles of Evolutionary and Developmental Mismatch on Cardiometabolic Health

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## Keywords

Indigenous health, evolutionary mismatch, developmental origins of health and disease, cardiometabolic disease, heart disease, diabetes

## Abstract

The health of Indigenous populations suffers compared with that of non-Indigenous neighbors in every country. Although health deficits have long been recognized, remedies are confounded by multifactorial causes, stemming from persistent social and epidemiological circumstances, including inequality, racism, and marginalization. In light of the global morbidity and mortality burden from heart disease, stroke, and diabetes, cardiometabolic health needs to be a target for building scientific understanding and designing health outreach and interventions among Indigenous populations. We first describe health disparities in cardiometabolic diseases and risk factors, focusing on Indigenous populations outside of high-income contexts that are experiencing rapid but heterogeneous lifestyle change. We then evaluate two evolutionary frameworks that can help improve our understanding of health disparities in these populations: (*a*) evolutionary mismatch, which emphasizes the role of recent lifestyle changes in light of past genetic adaptations, and (*b*) developmental mismatch, which emphasizes the long-term contribution of early-life environments to adult health and the role of within-lifetime environmental change.

## 1. INTRODUCTION

In popular discourse, Indigenous health is often portrayed in one of two ways. Relatively isolated groups of rural hunter-gatherers, such as the Hadza of Tanzania or the Tsimane slash-and-burn horticulturalists of Bolivia, are depicted as having low survival rates but living healthy, free from many degenerative diseases of aging, including heart disease, diabetes, and dementia. These groups are held as exemplars of what is possible without the excesses of modern, postindustrialized (hereafter Westernized[1]) sedentary lifestyles and diets, which are typically marked by a high intake of refined sugar and carbohydrates, saturated fats, and processed foods and a low intake of fiber and polyunsaturated fatty acids. As such, they have inspired an array of Paleo-ish fad remedies. In contrast, more urban-living Indigenous groups in high-income countries, such as the Diné and Puebloan groups of the American Southwest, and numerous aboriginal groups throughout Australia, Canada, and Micronesia display some of the highest incidence rates of obesity and type 2 diabetes mellitus (T2DM) ever reported. In popular discourse, genetics and recent transitions to contemporary lifestyles are often cited as principal causes. Of course, this dichotomous view of Indigenous health is overly simplistic: Linking subsistence lifestyles to the absence of noncommunicable diseases (NCDs) obscures the importance of rapid changes in the epidemiological landscape that many Indigenous populations currently experience. Furthermore, simply viewing "modernization" or "globalization" as monolithic and inevitable exogenous processes that create unchecked NCDs obscures incredible heterogeneity in these processes and sidesteps how systemic racism, exploitation, and marginalization interact with these factors to affect health.

Any comprehensive exploration of the complex factors affecting Indigenous health around the world is beyond the scope of a short article (see Anderson et al. 2016 and Valeggia & Snodgrass 2015 for broad reviews). Here, we focus on recent findings in one health domain—cardiometabolic diseases and their risk factors—because this group of health issues is a priority concern for many Indigenous communities today. We start by presenting a portrait of disparities in both cardiometabolic diseases (diabetes, heart disease, stroke) and risk factors (obesity, hypertension) in these groups. Although we touch on Indigenous health in high-income countries, where gaps in health and its social determinants compared with non-Indigenous health have increased over recent decades (Mitrou et al. 2014), our focus here is on Indigenous populations outside of this context. We focus specifically on Indigenous groups that have or had a largely rural, subsistence-based livelihood up until or through the past several decades but are now experiencing rapid changes in economy, culture, and health.

We then introduce several frameworks common to biological anthropology, but largely neglected from broader biomedical and public health discourse, that can improve understanding of these disparities in order to help reduce them: (*a*) evolutionary mismatch, which emphasizes the role of recent lifestyle change in light of past genetic adaptations; and (*b*) developmental origins of health and disease, which emphasize the long-term contribution of early-life environments to adult health, as well as developmental mismatch, which emphasizes the consequences of within-lifetime environmental change. We discuss the role of evolutionary mismatch and developmental processes in affecting the pace of cardiometabolic disease risks among Indigenous populations,

[1]This shorthand label suggests that these dietary and lifestyle changes originate in the West. The term Westernization is problematic because it gives primacy to a global causal process that centers on the West. The label suggests a sweeping culinary, capitalistic colonialism and cultural transformation. Alternatives such as "modernization" and "postindustrialization" and other catch-all terms are also problematic, but we use Westernization here because of its common usage in the literature.

## INDIGENOUS PEOPLES

Usually defined as "tribal peoples," the UN Permanent Forum on Indigenous Issues more formally describes Indigenous peoples as sharing seven characteristics: self-identified as Indigenous and accepted by the community as members; historical continuity with precolonial or presettler societies; strong link to territories and surrounding natural resources; distinct social, economic, or political systems; distinct language, culture, and beliefs; being from nondominant groups; shared resolve to maintain and reproduce aspects of their distinct identity. Other definitions also mention marginalization and geographic isolation. That being said, there is no universally accepted definition, nor is one always desirable (UN 2018). Article 33 of the Declaration on the Rights of Indigenous Peoples highlights self-identification as a key principle of indigeneity.

offer questions for future research, and explore areas for potential intervention. Cardiometabolic disease needs to be a primary target for surveillance and interventions in Indigenous populations, given its large increasing contribution to morbidity and mortality. We highlight ways that interdisciplinary biocultural anthropology can contribute to that target and improve Indigenous health in the twenty-first century.

## 2. CARDIOMETABOLIC HEALTH EPIDEMIOLOGY

Indigenous peoples, estimated at more than 476 million people or roughly 6% of the global population, live in all world regions (for a definition of Indigenous peoples, see the sidebar titled Indigenous Peoples). Most epidemiological data available on Indigenous peoples come from North America and Australia/New Zealand, although the vast majority of Indigenous peoples live in Asia, Latin America, and Africa (UN 2018) (**Figure 1**; see the sidebar titled Indigenous Cardiometabolic Health in High-Income Countries). Comprehensive data are lacking in many of these countries due to poor health data infrastructure. According to a 2016 survey attempting to compile readily available information, Indigenous peoples show worse health metrics than

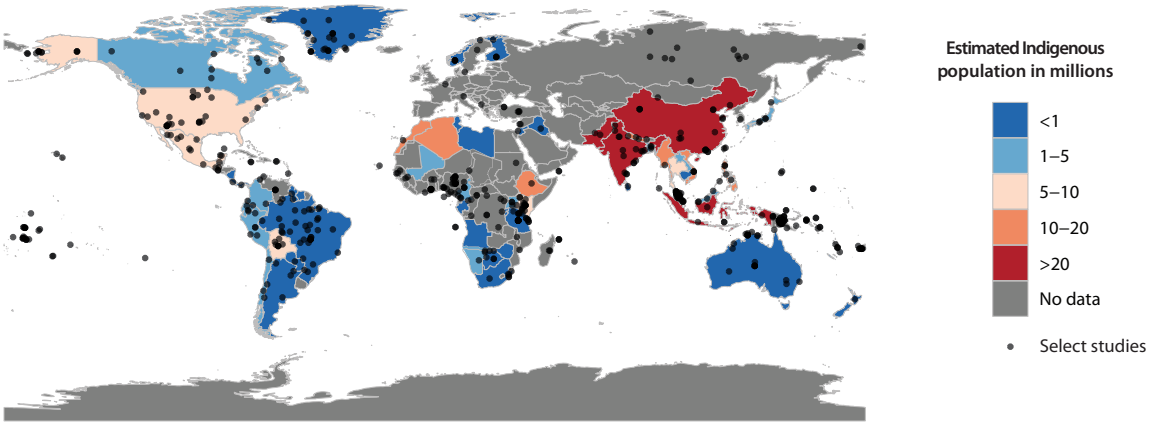


**Figure 1**

Indigenous populations in the world today. Estimates of current population (in millions) of Indigenous peoples by country. Black dots represent select studies appearing in **Figure 2**. Data from IWGIA (2022).

## INDIGENOUS CARDIOMETABOLIC HEALTH IN HIGH-INCOME COUNTRIES

American Indian and Alaskan Natives have up to 8 years lower life expectancy than do white peers, with death rates 1.2–3.6 times higher, especially among those <45 years (Espey et al. 2014), while life expectancy is 19 years lower among Aboriginal Australians than among non-Aboriginal peoples. While a sizable portion of the mortality differences is due to premature deaths from liver disease, accidents, and suicide, major reasons also include diabetes, heart disease, and obesity-related NCDs (Cobb et al. 2014, Harris et al. 2017, King et al. 2009). Risk factors such as greater prevalence of obesity, hypertension, and hypercholesterolemia contribute to greater cardiovascular and renal disease morbidity among many Indigenous populations living in high-income countries (Stoner et al. 2012). Indigenous populations with high prevalence of T2DM may also experience higher risks of complications, including nephropathy, end-stage renal disease, retinopathies, and cardiovascular disease. In these more urban contexts, worse health conditions among Indigenous peoples are linked to a long list of behavioral (or lifestyle) factors, such as tobacco use, alcoholism, poverty, lower educational attainment, discrimination, and less access and trust in health services (Curtis et al. 2010). Upstream from this level, colonization, land loss, disrupted livelihoods, loss of language and culture, and historical trauma are structural drivers of the poor nutrition, physical inactivity, substance abuse, and loss of community that are attributed as modifiable causes.

non-Indigenous benchmarks across 23 countries: lower life expectancy, higher infant and maternal mortality, and greater child and adult obesity (Anderson et al. 2016). For example, Indigenous groups in India, Panama, Kenya, and Cameroon have life expectancies that are 3, 8, 12, and 22 years lower than those of non-Indigenous groups in the same countries. While structural and institutional factors are sometimes mentioned in epidemiological studies, higher Indigenous morbidity and mortality are still often attributed to genetic or racial characteristics. However, race is a social construct with no biological basis, and while studies have uncovered genetic variants with unique impacts on complex traits in Indigenous groups (Asgari et al. 2020, Lea et al. 2023), large-scale health disparities between Indigenous and non-Indigenous groups are driven largely by systemic and structural factors rather than by subtle differences in allele frequencies. The importance of these contextual factors is not always considered. For example, in the largest study of stroke in Africa to date, Indigenous West Africans were found to experience higher hemorrhagic and lacunar strokes and hypertension relative to African Americans and Euro-Americans (Owolabi et al. 2017). Reasons have focused primarily on genetic risk factors (Akinyemi et al. 2021), or biological essentialist arguments that do not deal explicitly with environmental factors, the ways that stress embeds biologically, or genotype-by-environment interactions.

Throughout much of rural South America, sub-Saharan Africa, and Southeast Asia, many Indigenous peoples still practice traditional livelihoods, including farming, fishing, hunting, gathering, trading, or a mix of these and other activities that require physical activity for procurement and that jointly contribute nonprocessed foods to the diet. Among past and contemporary hunter-gatherers, cardiovascular risk factors and diseases appear to be rare (Eaton et al. 1988, Konner & Eaton 2023). Epidemiological surveys from the mid-twentieth century, such as those among Ju/'hoansi hunter-gatherers (Kaminer & Lutz 1960), Central African pygmies (Mann et al. 1962), Aboriginal Australians (Elphinstone 1971), South African Bantu (Becker 1946, Higginson & Pepler 1954, Laurie et al. 1960), Pacific Islanders (Maddocks 1961, Page et al. 1974), and other rural, subsistence-level populations with minimal exposure to market economies (Edington 1954, Lee 1971), support the notion that obesity, insulin resistance, hypertension, and other cardiometabolic risk factors are rare not just in hunter-gatherers, but in any subsistence-living group with non-Westernized lifestyles.

## 3. EVALUATING NCDs IN THE TWENTY-FIRST CENTURY

A skeptic might argue that the apparent absence of cardiometabolic diseases and risk factors in subsistence populations, based on the types of studies listed above, is an artifact of methodological constraints or a limited number of older adults. Some have argued that atherosclerosis has long been stalking the human condition. Computed tomography (CT) scans of mummies spanning 4,000 years in Egypt, Peru, the American Southwest, and Aleutian Islands show evidence of probable or definite calcific atherosclerosis and not just among well-fed elites (Thompson et al. 2013). First, it is difficult to discern from those studies whether such conditions would have been clinically salient, much less lethal. Second, sample sizes of adults at older ages, where risks are expected, are limited in many early studies. Third, if case fatality rates are high among those afflicted with heart disease and T2DM in the absence of health care, then brief cross-sectional surveys are unlikely to capture the short-lived cases, such as postmyocardial infarction survival. Even the axiomatic claim that Greenland Inuit were long free of atherosclerosis (e.g., Dyerberg et al. 1975) has been contested due to problematic mortality statistics (Bjerregaard et al. 2003). Last, most studies of cardiometabolic health in remote settings are of easy-to-measure but indirect risk factors such as blood pressure, anthropometrics, and blood lipid levels and not of direct diagnoses from measures requiring advanced technological sophistication, such as electrocardiogram (ECG) and CT, and they lack detailed information on causes of mortality.

Despite these practical concerns, converging evidence supports the early epidemiological surveys and suggests that hunter-gatherers, horticulturalists, and pastoralists living under relatively traditional conditions rarely experience atherosclerotic heart disease or T2DM. Even with some lifestyle change, groups may remain relatively protected. Lower mortality rates might be expected to increase NCDs simply because more adults are likely to survive well into their 70s, a time when morbidity and mortality from NCDs manifest. Tsimane horticulturalists have been in sporadic contact with non-Indigenous neighbors for more than a century, and more rapid changes have been occurring over the last four decades. Like other subsistence populations, they show a modal adult lifespan of ~65–75 years (Gurven & Kaplan 2007). Yet CT-based evaluations show very minimal coronary calcification, and ECGs show no evidence of past myocardial infarcts (Kaplan et al. 2017). Hypertension and hyperglycemia were also minimal, and adults over age 40 showed little to no increase in blood pressure with age (Gurven et al. 2012). These findings are noteworthy because Tsimane adults are not very lean, at least by the usual body mass index (BMI) definitions [e.g., 21% have BMIs between 25 and 30 kg/m$^2$, meeting the Centers for Disease Control and Prevention's definition of "overweight"].

## 4. LIFESTYLE CHANGE

While Indigenous cardiometabolic health has historically been favorable in subsistence-level contexts, current interactions with urbanization, globalization, and modernization are leading to changes in many key risk factors for cardiometabolic disease, such as diet, physical activity, pathogens, and exposure to Western, evidence-based medicine. Rather than viewing Indigenous health and well-being as static constants frozen in the ethnographic present, change is really the only constant. The pace and nature of lifestyle change, as well as its political, social, and institutional drivers, are different for every Indigenous population such that a one-size-fits-all approach to understanding or improving health will rarely be useful (see further discussion in the next section).

Lifestyle change has been recognized as a concern for Indigenous groups for some time. An older literature on the effects of "acculturation" to a Western lifestyle on health showed that immigrants exhibited worse cardiovascular health, especially blood pressure, in all world regions

(Steffen et al. 2006). Changes to BMI, cholesterol, and other risk factors only partly explain these differences (Teppala et al. 2010), suggesting that the "stress of cultural change" is also an important factor and that increased hypertension may mediate the relationship between acculturation and coronary artery disease (Diez Roux et al. 2005). Similarly, evidence suggests that hunter-gatherers, pastoralists, and horticulturalists show similar mean blood pressure levels and minimal blood pressure increases with age, while cash cropping, mechanized agriculture, and small industry are associated with higher mean systolic and diastolic pressure and higher rates of change with age (Waldron et al. 1982). Diverse subsistence livelihoods may thus be compatible with robust cardiometabolic health.

Many studies on the cardiometabolic health of Indigenous populations emphasize changes in diet, physical activity, and occupation. Whereas transition among the Turkana of northwest Kenya from a pastoral to an agricultural economy did not reveal differences in cardiometabolic health indicators, transition to a more urban lifestyle resulted in higher blood pressure, cholesterol, and blood glucose (Lea et al. 2020). Only in urban settings was higher socioeconomic status associated with worse cardiometabolic health (Lea et al. 2021). Groups with distinct histories and livelihoods may sometimes witness converging health patterns given similar experiences. For example, the Pehuenche and Atacameño of Chile have separate histories and had different traditional livelihoods in the past (agropastoralism and hunting-gathering, respectively), but uniform changes in diet, activity, environment, and lifestyle have resulted in similar high levels of multiple cardiovascular biomarkers (Fernández 2020). In these and other similar studies, psychological stress associated with cultural loss and cultural dissonance, discrimination, and breakdown of traditional social networks may be critical component beyond obvious lifestyle factors such as diet and physical activity; however, these are only rarely assessed or addressed in health evaluation.

## 5. A MOSAIC OF EXPERIENCES

While gaps in life expectancy, infant and maternal mortality, other health metrics, and the economic and social determinants of health are ubiquitous and large between Indigenous and non-Indigenous groups almost everywhere they have been studied (Anderson et al. 2016, Gracey & King 2009, King et al. 2009, Mitrou et al. 2014), appreciable differences have also been noted among Indigenous populations. **Figure 1** highlights Indigenous groups whose cardiometabolic health status has been studied in relation to the numbers of Indigenous groups in their home countries. Using this database of Indigenous health studies, we observe extreme variation in blood pressure and BMI among populations, and such variability is only weakly explained by subsistence type (**Figure 2*b*,*d***).[2] The main departure is that Indigenous people involved primarily in wage labor are heavier and show higher blood pressure. Experiences also vary by sex. On average, there appears to be greater global increase in systolic blood pressure among men and higher BMI among women (**Figure 2*a*,*c***).

Overall, cardiometabolic health risks have increased over the past six decades (**Figure 2*a*,*c***). But as Indigenous populations have faced varied circumstances postcontact, longitudinal patterns of specific groups cluster in three categories: no appreciable changes (e.g., Hadza hunter-gatherers over four decades; Yanomamo horticulturalists and Fijian Melanesian fishers over two decades), gradual increases (e.g., Tsimane horticulturalists and Fulani pastoralists over 15 years), or rapid increases in cardiometabolic NCDs (e.g., Surui horticulturalists). In some rare cases,

[2] Although BMI is a crude, and sometimes misleading, measure of obesity (Hruschka & Hadley 2016), we use it here because it is widely available.

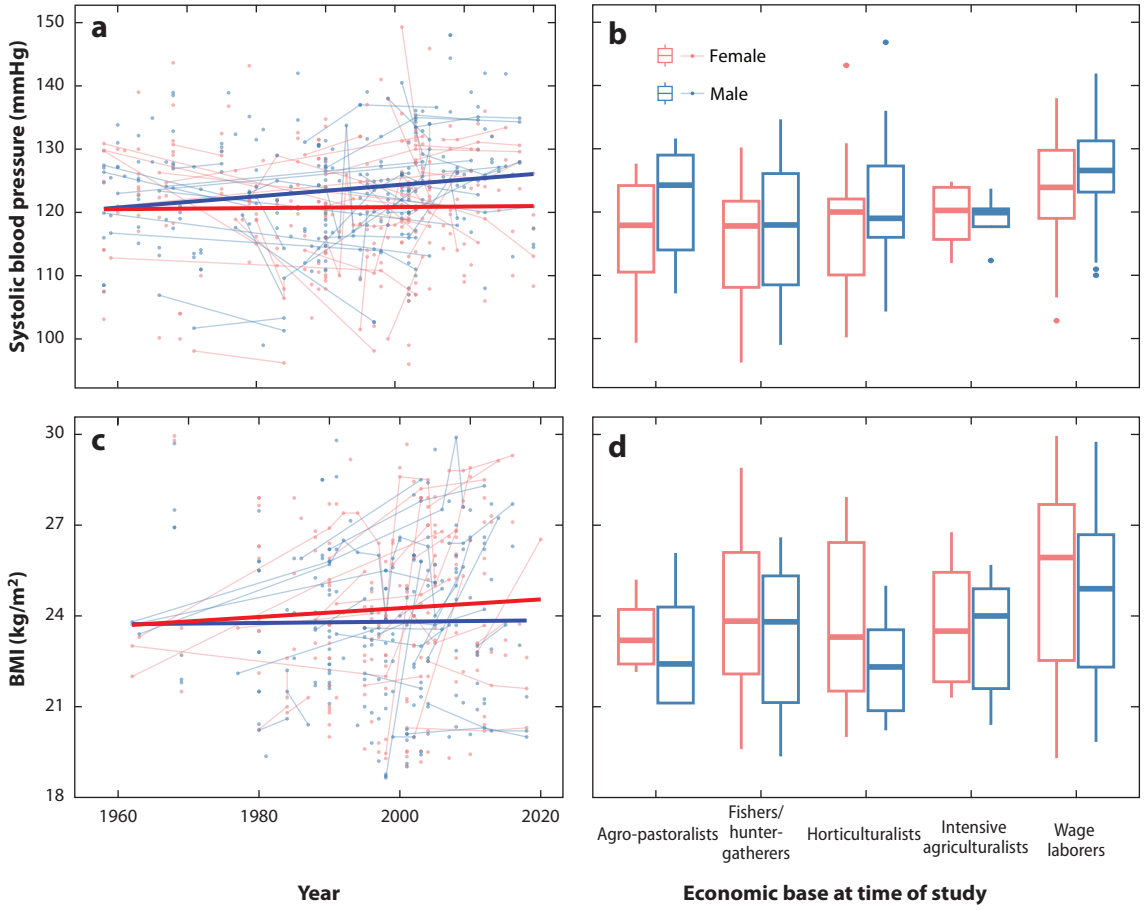


**Figure 2**

Systolic blood pressure (SBP) and body mass index (BMI) by ethnicity, study year, and subsistence type: adult SBP (mmHg) by (*a*) study year and (*b*) subsistence type; adult BMI (kg/m$^2$) by (*c*) study year and (*d*) subsistence type (for panels *b* and *d*: *red circles/lines*, females; *blue circles/lines*, males). Thin lines in panels *a* and *c* connect observations from the same Indigenous group. Bold lines are global ordinary least squares regression lines. For SBP, N = 106/322 unique Indigenous groups/samples. For BMI, N = 87/249.

cardiometabolic health indicators show improvement over time. Recognizing the extent to which the experiences of groups worldwide fall into each of these categories will require systematic surveys, with either repeated cross-sectional or longitudinal design combined with detailed ethnographic study. In general, the extent of epidemiological change seems to track the pace of acculturation, as increased contact with the dominant culture usually coincides with the adoption of cash cropping or wage labor jobs, consumption of calorie-dense, market-derived foods, and use of labor-saving devices (e.g., motorized transportation) that decrease physical activity levels. These patterns are confirmed in a recent regional meta-analysis of Indigenous Brazilians showing increases in obesity since 1990 and hypertension since 1960, in accordance with deforestation, changing livelihoods, and degree of urban living. Cardiometabolic health was much lower in urban areas compared with rural areas of more intact forest. However, cardiovascular mortality still increased substantially even in the more remote rural areas between 1998 and 2019 (due to low baseline) (Kramer et al. 2022).

## 6. A MIX OF EVOLUTIONARY AND DEVELOPMENTAL MISMATCHES

The nascent field of evolutionary medicine has been deeply influenced by anthropological and ecological studies of ancestral environments, adaptation, and culture change. A basic premise is that, like all organisms, humans should be finely adapted to their local environments in ways that maximize biological fitness over evolutionary time. But environments change, not just because of rapid modernization and urbanization but whenever people migrate to new areas. Previous millennia saw changes in diet and pathogen exposure as people migrated globally, and in relation to plant and animal domestication some ~10 kya. The last several centuries have seen more rapid cultural and technological changes affecting many aspects of life. Through niche construction, people also build new environments. With environmental change, the potential for adaptive lag can occur on a variety of timescales, from hours, months, and years to generations and millennia (Kuzawa 2008). Evolutionary mismatch refers to failures of our genetic adaptations to respond to the magnitude of environmental change we experience in our modern lives. Specifically, the evolutionary mismatch hypothesis posits that genetic variants that were beneficial in past human environments may now instead be disease causing because they can become dysregulated under conditions that deviate strongly from those in which they were optimized by natural selection (Nesse & Williams 1994). If mismatches increase the likelihood of NCDs, then Indigenous groups that remained relatively unintegrated up until the last century but are now experiencing large mismatches over just a few generations would be most vulnerable.

Whereas evolutionary mismatch reflects the mismatch between our genes and the environment, developmental mismatch reflects a mismatch between our bodies and the environment due to a failure of phenotypic plasticity (i.e., flexible adaptive shifts) within our lifetimes. Development is a period of heightened environmental sensitivity, and challenging experiences early in life have long been known to increase lifelong risk of cardiometabolic disease (Cohen et al. 2010, Hoffman et al. 2017). The developmental origins of health and disease (DOHaD) hypothesis makes sense of these connections by positing that exposure to environmental factors during sensitive periods of development can permanently alter physiology in ways that predispose individuals to health issues later in life. Building on the DOHaD, several prominent hypotheses have since suggested that early-life conditions physiologically prime individuals for certain types of environments in adulthood, such that mismatch between early-life and adult environments could put individuals at an even greater risk for later-life health issues (Gluckman et al. 2019). While studies of transitioning populations have thus far come to mixed conclusions about the importance of within-lifetime mismatches in this context, they have emphasized that early-life experiences matter for health (McDade et al. 2010, Thayer et al. 2017, Urlacher et al. 2016, Wallace et al. 2019). Overall, however, developmental processes have received relatively little attention, and more work is urgently needed to understand when, why, and how early-life experiences shape adult cardiometabolic health in Indigenous groups.

### 6.1. Thriftiness

For Indigenous populations experiencing recent changes to their diet and lifestyle, the potential for evolutionary mismatch leading to compromised health may be especially great. The first proposal along these lines suggested that a "thrifty genotype" selected to increase efficient fat storage for use during lean periods of food shortage could lead to obesity, T2DM, and other features of metabolic syndrome under conditions of caloric excess (Neel 1962). Many scholars believed that such an evolutionary mismatch (though this term had not been proposed at the time) could explain the high prevalence of T2DM already observed by the 1970s in many Indigenous populations, including the Pimas, the Seminoles, and the Chamorros (West 1974). Despite much attention, the

evidence has been mixed for various aspects of the thrifty genotype hypothesis, including the idea that genetic variants associated with fat accumulation and T2DM have consistently undergone positive selection (e.g., Byars et al. 2017, Helgason et al. 2007, Southam et al. 2009). A few notable exceptions are the *ADCY3* variant, which greatly impacts both obesity and T2DM among Greenlandic Inuit; on average, one copy leads to 2 kg greater body mass and 2 cm greater waist circumference, whereas two copies lead to 15 kg and 17 cm increases, respectively (Grarup et al. 2018). Similarly, a study of Samoan Islanders identified a missense variant in the *CREBRF* gene, which shows evidence of past selection, predicts increased risk of obesity in modern Samoans, and, in functional experiments, appears to alter lipid biology and accumulation (Minster et al. 2016).

Similar in spirit to developmental mismatch, the thrifty phenotype hypothesis proposes that inadequate nutrition in utero shapes fetal (pancreatic) development in adaptive ways in preparation for a food-limited environment (Hales & Barker 2012). From conception to early childhood, periods of organ development and rapid growth are sensitive to nutritional and other stressors, with repercussions on the developing phenotype. If primed for an environment rife with food shortage, exposure to food abundance throughout life instead is argued to predispose the individual to obesity, insulin resistance, and T2DM (Barker et al. 1993). According to this view, if the later nutritional environment was instead food scarce (matching expectations), T2DM and other NCDs would not present as problems. An alternative view, however, is that compromised nutrition affects early development in ways that could increase health risks later in life, regardless of the degree of within-lifetime mismatch. Whether these early-life adjustments represent physiological adaptations to expected future environments or are instead just the best of a bad situation is still debated (Gluckman et al. 2019, Lea et al. 2018). Either way, NCD risks in adulthood may be higher in rural areas of low- and middle-income countries (LMICs) because of adverse childhoods marked by poverty, malnutrition, infections, and poor sanitation where childhood mortality is comparatively high (Mandy & Nyirenda 2018).

Some form of evolved thriftiness (be it on evolutionary or developmental timescales) is commonly invoked to explain the greater incidence of metabolic dysfunction in Indigenous populations throughout North America, Australia, and the Pacific Islands and the rapid rise of T2DM among New World Indigenous populations where it was previously absent. Arguments for the thriftiness-related adaptations hinge on assumptions about ancestral environments, namely that Indigenous lineages evolved in environments characterized by repeated feast–famine cycles. Thriftiness is thought to be advantageous in these food-limited contexts in ways that are more detrimental in food-rich settings: higher central adiposity with visceral fat stores, propensity for insulin resistance, and pancreatic β cell dysfunction affecting insulin secretory capacity. While these observations, and the selection pressures that are hypothesized to drive them, are by no means limited to Indigenous populations. For example, they have also been invoked to explain higher T2DM risks among South and East Asians (Shah & Kanaya 2014, Yabe et al. 2015). Nonetheless, Indigenous groups are thought to be especially susceptible given the relative recency and magnitude of lifestyle change.

### 6.2. Inflammation and Stress Dysregulation

While mismatch theories often focus on how lifestyle change is impacting cardiometabolic health, other biological systems are also vulnerable to mismatches between the evolutionary past and modern-day environments. For example, a long evolutionary history of diverse pathogens and other environmental stressors has favored genetic variants that foster resistance to infections and improve survival. These include genetic variants that promote inflammation, an initial multipronged, acute response to infection and injury. People from tropical regions exposed to a greater

pathogen burden may have evolved more inflammatory immune gene complexes than did people from dry or temperate areas (Pennington et al. 2009). Like thriftiness, a proneness to inflammation results in a mismatch when lethal pathogens are eliminated, as is the case everywhere the epidemiological transition from high infectious burden to high NCD burden has occurred, including high-income countries and urban regions throughout LMICs. While proinflammatory conditions have been linked to higher autoimmune disease risk (Brinkworth & Barreiro 2014), they also increase susceptibility to T2DM and atherosclerosis under more obesogenic conditions (Libby 2021). Repeated bouts of acute inflammation are common under infectious conditions such as in the tropics (Blackwell et al. 2016), whereas chronic sterile inflammation is due to obesity, cigarette smoking, and arthritis. Whether Indigenous populations are more prone to sterile inflammation (and inflamm-aging) under urban conditions because of evolutionary and/or developmental mismatch remains to be seen, though some Indigenous groups, such as those in Canada, do show higher risk of inflammatory health conditions (Hitchon et al. 2020). Under mismatch logic, some chronic infections (e.g., intestinal worms) that were common in past human environments and thus have coevolved with our immune systems could even help buffer against the adverse consequences of inflammation today (Gurven et al. 2016).

Mismatch can also occur over shorter timescales, such as over a single lifetime, when inputs are too much (e.g., salt, sugar, saturated fat), too little (e.g., breastfeeding, pathogen exposure), or too new (e.g., high heels, reading indoors, nicotine) for the ability of evolved reaction norms to reliably adjust physiology in ways that ensure healthy outcomes (Lieberman 2013). Each of these mismatches may be thought of as inducing physiological stress, which can be operationalized via cortisol excretion as a measure of hypothalamic-pituitary-adrenal (HPA) axis function. For example, Tsimane men with greater access to cash income had higher urinary cortisol compared with Tsimane men with no access, whereas those with greater political influence and community support had lower cortisol and experienced lower rates of respiratory infection (von Rueden et al. 2014). In a classic study in Samoa, a modernization gradient across islands was positively associated with prevalence of adult obesity, hypertension, and hyperlipidemia, with cortisol levels higher and more blunted in more Westernized contexts (Baker et al. 1986, Pearson et al. 1993). Cortisol levels did not differ among Turkana varying in lifestyle characteristics, however (Lea et al. 2021). Other studies also show no relationship between traditional status measures and cortisol levels (Fedurek et al. 2020), although more novel forms of wealth tend to associate with higher cortisol (Konečná & Urlacher 2017). One possibility is that when traditional social networks and redistribution patterns remain intact, people may retain resilient stress responses. High levels of cooperation may buffer the effects of incipient wealth inequality on health, as among the Agta (Page et al. 2023) and the Tsimane (Godoy et al. 2004).

This dysregulation of physiological systems that occurs with prolonged or poorly regulated stress responses has been called "allostatic load" (Seeman et al. 2001) and is usually viewed as a maladaptive consequence of novel stressors of prolonged duration. Chronic stressors that could impact HPA axis function among Indigenous populations include systemic racism, discrimination and other post-traumatic symptoms associated with colonization, cultural and livelihood loss, and adversity (Busse et al. 2017, Pascoe & Smart Richman 2009). Key characteristics of stressors that affect cortisol are a sense of uncontrollability and threats to social standing. Both of these may be common in the lived experiences of many Indigenous populations. When impaired, diurnal cortisol responses are blunted, leading to poorer responses to stressors (Miller et al. 2007) and greater susceptibility to depression and anxiety, as well as impaired glucose, insulin, and immune regulation. This combination can increase susceptibility to obesity, inflammation, and hypertension and indirectly to T2DM and heart disease via bidirectional feedback effects (Nijm & Jonasson 2009, Rutters et al. 2012).

As with thriftiness, there is also an intergenerational component to HPA axis dysregulation and maternal stress physiology: Cortisol dysregulation in pregnancy results in smaller preterm births, which itself is linked to greater cardiometabolic dysfunction in adulthood (Knop et al. 2018). Glucocorticoid exposure and HPA dysregulation are thus additional proximate mechanisms underlying DOHaD.

## 7. IDENTIFYING BIOLOGICAL LINKAGES BETWEEN MODERNIZATION AND HEALTH

While shifts toward Westernized diets, reduced physical activity, and disrupted cultural and social communities tend to increase risks of diabetes, heart disease, and related chronic diseases of aging, the pace of health changes varies widely, but the true extent has not been formally assessed, especially in a way that is comparable across populations. The specific functional form of the relationship between modernization and cardiometabolic health hinges on the content of what constitutes socioeconomic and cultural change (see **Figure 2**). Cardiometabolic health can decline linearly in an additive dose–response fashion or nonlinearly due to threshold effects or multifactorial changes operating at different speeds.

Regardless of the terms used (e.g., modernization, delocalization), sustained health inequalities affecting Indigenous peoples invoke political economic forces and colonization history, distal factors higher up in the causal chain.[3] In practice, regional studies usually create their own internal scales for assessing the degree of modernization, and comparative studies often rely on crude comparisons of traditional, transitional, and modern. One promising move forward to facilitate comparative work is a proximate determinants approach (sensu Bongaarts 1978) (**Figure 3**). The variegated and complex mix of experiences with modernization must ultimately manifest as changes in diet (including alcohol, cigarettes, and processed foods), physical activity, pathogen exposure, pharmaceutical intervention via health care access, psychosocial stress, and other direct features of our exposome that we know can get under the skin to affect biology (Trumble & Finch 2019). A proximate determinants approach makes no assumptions about which of these features are in sync, which is an important question in itself, and could help facilitate systematic comparisons of exposure–health relationships within and among Indigenous populations.

While complex notions of perceived stress and objective political, social, or ecological stressors are also measurable and important to well-being, their interpretation in relation to health requires an understanding of local context—the bread and butter of ethnography. Market integration, nonlocal language use, formal schooling, proximity to roads, urban industry, land use change and degradation, resettlement schemes, access to smartphones—all of these are modernizing influences, but how they impact individual lives through changing attitudes, values, and behavior requires deliberate study (Dressler 1999, McDade & Nyberg 2010). Unlike diet, physical activity, or pathogen exposure, these aspects of socioenvironmental change likely affect the molecular and cellular processes that determine health via more complex pathways. Ethnography can help identify the many constraints shaping lifestyle behaviors, beyond limited finances and education, in order to help identify locally relevant paths connecting stress or behavior to health, and ultimately to help design locally relevant and meaningful interventions. Furthermore, the valence and meaning ascribed to cultural loss, colonization, and inequality can help contextualize effects on stress and HPA axis function on health more broadly.

[3] Dressler (1999), remarking on prior work by Pelto, rightly critiques reliance on the term and concept of "modernization," given its emphasis on unidirectional change toward a Western industrial system. The term delocalization instead reflects increasing reliance on sources outside the local community for production, energy use, and information.

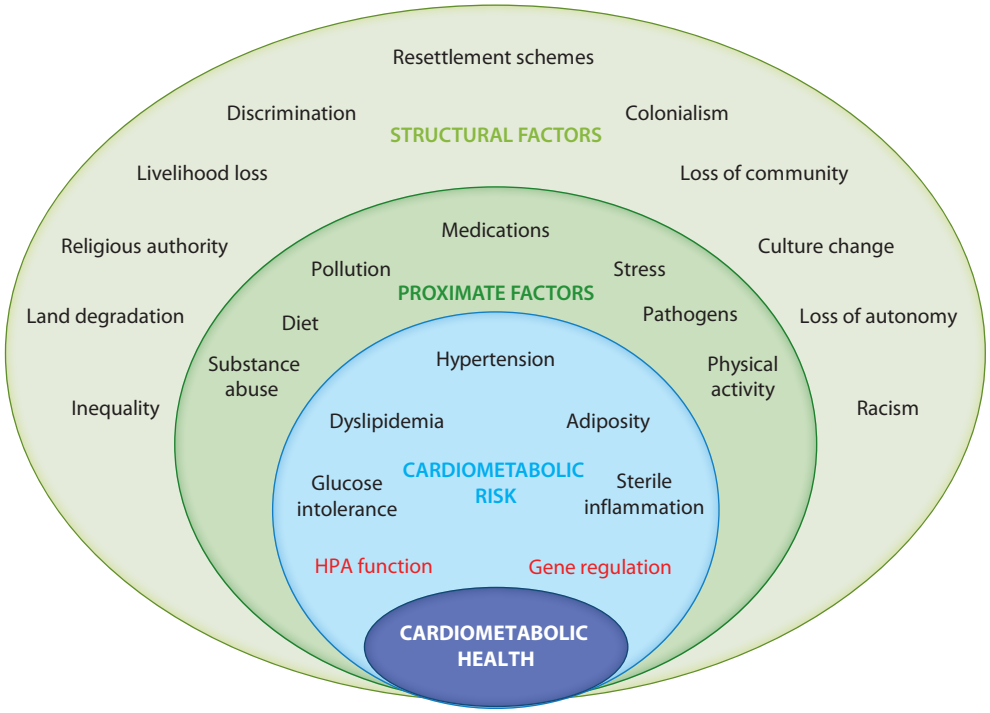


**Figure 3**

Modernization and cardiometabolic health. Outer layer shows most distal factors, such as colonialism, resettlement schemes, and loss of autonomy, affecting Indigenous populations. These distal factors affect diet, pathogen exposure, and other more direct behaviors that can result in the health symptoms, such as adiposity and hypertension, that harm cardiometabolic health. Hypothalamic-pituitary-adrenal (HPA) axis function, gene regulation, and epigenetics are examples of biological pathways by which stressors from the outer layers express impacts on the inner layers. (*Red text*) More indirect biological mechanisms; (*black text*) cardiometabolic risk factors; (*green circles*) factors affecting health; (*blue circles*) health outcomes.

Another path forward to better understand the biological connections between modernization and Indigenous health is to merge modern omics techniques with hypotheses about evolutionary and developmental mismatch. Tackling the developmental origins of disease could involve studies of epigenetic gene regulatory marks (e.g., DNA methylation, chromatin accessibility) that are thought to embed early-life experiences into long-term physiology (Hertzman 2012, Hertzman & Boyce 2010). Identifying the genes that are (or are not) sensitive to specific early-life exposures could help us determine which have the strongest biological effects, whether diverse exposures target common or distinct pathways, and which effects are stable versus attenuated over time. For understanding evolutionary mismatch, omics integration could focus on taking the study of genotype-by-environment interactions more seriously (Lea et al. 2023). Evolutionary mismatch is inherently a mismatch of genotypes to the environment, but relatively little attention has been given to the details of the genetics. Greater attention to biological ancestry will permit more precision medicine, given the role of ancestral selection pressures in shaping many genes involved in complex health traits (e.g., Nédélec et al. 2016). Ancestry alone will likely not be instructive for illuminating mismatch without some understanding of the specific genetic adaptations to diet, pathogens, and the like. A good example is variants in the *APOL1* gene, where certain variants confer resistance to trypanosomes that are widespread across areas of Africa. Among African Americans, however, those same variants increase the risk of kidney disease

## COLLABORATIVE APPROACHES

Broader population representation in biomedical and epidemiological research is critical for reducing health disparities but, moving forward, requires that we simultaneously acknowledge and learn from past mistakes and abuses. Stemming from statements to improve Indigenous representation in genomics, Claw and colleagues (2018) provide six ethical principles to guide research: understand community sovereignty and research regulations, engage and collaborate, build cultural competencies, improve transparency, build local research capacity, and disseminate research in accessible formats. The common thread behind these principles is the importance of building trustful and long-term relationships based on principles of dynamic consent, reciprocity, beneficence, and sovereignty. In our own experience, building trusting relationships takes deliberate effort and time (typically years) but is essential to do before engaging in research. Whenever possible, collaborating with local and Indigenous scientists is ideal. Sharing ideas with local experts at all stages is critical, especially if attempting interventions. Capacity enhancement, such as training health promoters, nurses, and physicians, is another way to help ensure that research and community support reinforce each other. Working jointly with Indigenous populations to better understand, integrate, and prioritize Indigenous values in the explicit planning, monitoring, and assessment of research impact leads to more ethical, collaborative, and cost-effective research (Tsey et al. 2016). While data sharing is an important value necessary for open science, Indigenous sovereignty takes precedence, with data ownership and profit sharing benefiting tribes whose data are used by others.

(Friedman & Pollak 2020). Similarly, the *APOE4* allele that is detrimental for atherosclerosis and Alzheimer's disease in many urban Westernized populations shows survival and fertility advantages in more rural contexts, especially where pathogen burden is high (Oriá et al. 2010, Trumble et al. 2023). There may be many more of these variants that provide fitness advantages in the environments in which they evolved but promote health issues under more novel conditions; however, most genomic work has focused on white, European, high-income contexts (Sirugo et al. 2019), which is insufficient for understanding genetic effects on disease in other ancestries or environments. For example, one-fourth of genome-wide association studies (GWAS)-identified variants related to obesity, diabetes, and blood lipid levels had substantially different effect sizes in those of non-European ancestry (Carlson et al. 2013). As novel conditions appear to affect groups and individuals within groups differently, a fuller understanding of gene-by-environment effects among Indigenous populations could help move practitioners away from one-size-fits-all solutions in medicine and public health.

## 8. CONCLUSIONS AND APPLICATIONS

This review argues that the study of Indigenous cardiometabolic health with a biocultural anthropological lens—incorporating perspectives and methods from developmental and evolutionary mismatch, biology, genomics, and ethnography—can help uncover new insights into the mechanisms underlying the variable pace of changing health. Greater cross talk and multidisciplinary collaborations among different areas of anthropology, epidemiology, biology, and medicine are necessary to make new advances with translation potential for workable interventions—all done in an ethical, collaborative way with Indigenous partners (see the sidebar titled Collaborative Approaches). We focus our discussions on cardiometabolic disease but note that the general principles and paths for moving forward should apply to other NCDs impacted by environmental and lifestyle factors, such as autoimmune diseases and Alzheimer's and related dementias.

That globalizing forces are leading to rapid shifts in lifestyles and exposomes among most Indigenous populations is a ripe opportunity to unpack NCD susceptibilities and resistance,

not just to point out health disparities but to help tailor interventions toward resolving them (see Sanson-Fisher et al. 2006 for a discussion of descriptive versus intervention studies of Indigenous health). Better epidemiological surveillance, however, will still be essential, especially to help monitor progress. For many countries, where surveillance data do exist for Indigenous people, they are often aggregated among large numbers of ethnic groups whose needs may differ because of differences in culture, lifestyle, and other relevant dimensions. More training of local health workers within specific communities can help with systematic monitoring of health conditions.

Certain interventions will be more practical than others. To date, clinical interventions to improve NCD outcomes among Indigenous peoples are sparse, but those targeting Indigenous communities typically focus on behavioral change, including education or group sessions in person or via mobile platforms (Umaefulam et al. 2022). While offering a good start, these suffer from being of short duration and limited sustainability, and they do not always easily scale up. A return to more traditional ways of life may be desirable for some but not for everyone, and it may not be feasible even if desired. Some degree of lifestyle change may be unavoidable due to land loss, insecure tenure rights, and territorial degradation from climate change and population pressure. While each of the proximate determinants of modernization can be addressed as separate targets for intervention, more distal structural causes may require nested policy change. In many rural contexts, infectious disease and preadult survival are still major priorities, leaving few resources and attention for NCDs. Primary health care transformation will be needed to prevent or further delay NCD onset and to improve management and care, especially for T2DM, hypertension, and obesity.

Here, we have argued that new theoretical approaches are needed to help make sense of the variable health trajectories that Indigenous peoples experience and to improve prevention and treatment strategies. While standard clinical approaches usually assume similar health outcomes given common exposures and experiences, this one-size-fits-all approach is not well-suited for improving health for Indigenous peoples given complex evolutionary histories and current situations. We believe that anthropologists and ethnographers are well-poised to document heterogeneity in collaboration with these groups in ways that can lead to localized biological understanding as well as interventions. The relatively scarce attention given to Indigenous health and biomedical studies in nonurban settings in general is a pervasive bias that obstructs progress toward health equity (Gurven & Lieberman 2020). Frameworks common to biocultural anthropology have the potential to contribute new insights, especially about how the exposome gets under the skin to impact biology and health.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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