

A Critical Evaluation of the Fetal Origins Hypothesis and Its Implications for Developing Countries

Historic and Early Life Origins of Hypertension in Africans¹

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ABSTRACT Cardiovascular disease (CVD) causes 12.4 million deaths annually, most (9.6 million) occurring in developing countries. Hypertension, the most common CVD, arises within the context of obesity, but the underlying mechanisms remain obscure. Obesity and salt intake are two important risk factors for hypertension and are the focus of this paper. Traditional African populations show a low prevalence of hypertension, but hypertension is more common in migrant African populations in the West than in other ethnic groups. One explanation is genetic, but no causative gene has been confidently identified. Nongenetic susceptibilities such as fetal programming are an alternative explanation. Hypothetically, fetal programming induced by transient stimuli permanently alters fetal structure and function at the cellular, organ and whole-body levels. Birth weight is inversely related to blood pressure and hypertension risk, suggesting that susceptibility to hypertension risk factors such as obesity and salt sensitivity are themselves programmed. In support of this hypothesis, obesity (especially central obesity) is also inversely related to size at birth. Likewise, salt sensitivity might derive from undernutrition in utero, reducing the nephron number and resetting the pressure-natriuresis curve rightward. However, no robust human data or evidence of enhanced salt sensitivity among African-origin populations exist. In the United States, blacks have a greater prevalence of low birth weight than whites, suggesting that the higher prevalence of hypertension among blacks is related to fetal programming. Nevertheless, we need to be scrupulous in ascribing risk to the myriad other confounders of this relationship, including environmental and behavioral correlates of ethnicity, before concluding that excess risk of hypertension in Africans is programmed in utero. *J. Nutr.* 134: 211–216, 2004.

KEY WORDS: • *hypertension* • *fetal programming* • *salt sensitivity* • *Africans*

The development of chronic noncommunicable diseases (CNCD)³ in epidemic proportions characterizes populations undergoing the nutrition and epidemiologic transitions (1–3). Cardiovascular disease (CVD) accounts for the lion's share of prevalent CNCD and causes 12.4 million deaths annually; the majority (9.6 million) of these deaths occur in developing countries (4). Hypertension is the most common CVD. Its prevalence ranges from 0 to 40% across populations (5). It contributes ~6% of all deaths, defining the disease as a major health problem globally.

The prevalence of CVD is not homogeneous; it arises within the context of obesity and varies widely across populations (6–10). Obesity represents a sustained positive energy balance, and direct causal risk factors include energy-dense diets rich in oils, fats and simple sugars as well as reduction in physical activity. The mechanistic links between obesity and hypertension are still incompletely appreciated, although several hypotheses do exist; these include endothelial dysfunction, insulin resistance and deranged renal body fluid control (11,12).

The question therefore arises, that if the primary candidate in a hypothetical chain of causation of CVD is obesity, what are its root causes? In the broadest sense, obesity can be viewed as the price of social evolution. The development of agriculture ~10,000 y ago created a surplus of food. The industrial revolution ~300 y ago accelerated a process of dietary evolution wherein dietary patterns shifted from predominantly plant based toward increasing incorporation of animal and processed foods. More recently, globalization has accelerated these dietary and lifestyle shifts, particularly in the developing world, where the nutrition transition is taking place at a faster pace, putting these populations at greater risk of obesity and its comorbidities (1–3,13,14). Whereas wide population access to increased amounts of energy-dense foods drives the energy intake side of the energy budget equation, incorporation of

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³ Abbreviations used: CNCD, chronic noncommunicable disease; CVD, cardiovascular disease; RAAS, renin angiotensin aldosterone system.

labor-saving technologies into daily living promotes physical inactivity. Thus, the obesity epidemic arises in modern technological societies in which the requirement for physical work is greatly diminished and access to food is essentially unlimited. Under these circumstances, a large proportion of the population will develop obesity.

The risk factors for development of the most common CVD, hypertension, include obesity, salt intake, physical inactivity, alcohol intake and psychosocial stress (15). However, these risk factors account for less than half of the variance in prevalence within populations. Thus other factors must contribute to the variation in the relationship between obesity and disease outcome.

One such contributor to this variation in the cadence and intensity of the CVD epidemics is susceptibility to disease that is established in utero (16). The hypothesis of the early-life origins of adult disease proposes that fetal programming, although induced by a transient stimulus, causes permanent alterations in structure and function of the organism at the cellular, organ and whole-body levels, which can continue to act after birth (17,18). In utero programming is thought to cause changes in fetal body structure, physiology, metabolism and indeed genetic expression, affecting vulnerable developing organ systems, altering functional set points and reducing capacities. The absolute contribution of fetal programming to adult CVD is potentially great because intrauterine growth restriction affects some 30 million births per year, most of these occurring in developing countries: 75% in Asia, 20% in sub-Saharan Africa and 5% in Latin America and the Caribbean (19). If the subsequent environmental exposures exceed the reduced functional capacities of the programmed individual, child or adult pathology arises. Such environmental challenges can and do arise within the context of the nutrition transition when postnatal nutrition improves more rapidly than prenatal nutrition, increasing catch-up growth in weight and height. Catch-up growth is linked to risk for hypertension, diabetes and insulin resistance (20–23).

The prevalence of hypertension among populations of African origin living in the West is high, often higher than that among other ethnic groups living in the same countries (24–27). This higher prevalence of hypertension in blacks has fed speculation that genetic or other susceptibilities underlie these differences (28). The question posed in this paper is a variant of this; simply put, are populations of African origin exposed to greater intrauterine programming forces, leading to a higher prevalence of hypertension in adulthood? To answer this question it is prudent to 1) examine the epidemiology of hypertension among such populations, 2) identify the major risk factors for disease, 3) explore the mechanisms underlying these risk factors, and 4) examine the information available regarding intrauterine programming of these major risk factors.

Epidemiology of hypertension in populations of African origin

Ancestral African populations living traditional lives show lower mean blood pressure, little or no rise of blood pressure with age, and low prevalence of hypertension (29). However, within sub-Saharan Africa itself, there is substantial variation in hypertension prevalence, usually along internal demographic gradients going from pastoral through rural to urban (29–35). The forced migration out of Africa to the Americas >400 y ago gave rise to modern populations living contemporaneously in widely divergent environments, and this experiment of history affords an opportunity to identify genetic and environmental contributions to the development of the

epidemics of CVD in the more technologically based Western societies (36).

Within this ecological context, Cooper et al. (36) estimated the prevalence of hypertension in seven populations of African origin living in West Africa, the Caribbean and the United States and described a positive gradient in the prevalence rates from rural Africa to urban North America (Fig. 1). This rising prevalence of hypertension in these societies with increasing per capita gross domestic product was strongly related to mean BMI and salt intake, suggesting that adiposity and salt sensitivity are major risk factors for the development of hypertension (Figs. 2 and 3). These two risk factors, BMI and salt intake, accounted for ~70% of the variance in prevalence of hypertension across these populations. Obesity and salt intake are ubiquitous risk factors for hypertension worldwide (37–42).

Common risk factors for hypertension

It is remarkable that obesity and salt intake are such consistently demonstrated risk factors for hypertension worldwide (36–39). The other well-recognized risk factors are alcohol intake, inactivity and psychosocial stress. However, it is not yet feasible to measure psychosocial stress in a manner that allows comparisons across different populations and cultures. Physical activity can be measured with precision in the laboratory setting, but is hard to estimate accurately at the individual level in populations. Alcohol consumption is not a universal exposure. Thus, the major risk factors for the development of hypertension that are easily and precisely measured are obesity and high salt intake. This paper therefore focuses on obesity and salt intake and hypertension risk.

Why are common risk factors common? Genes and hypertension

Obesity and high salt intake appear to be prime drivers of the epidemic of hypertension in all populations studied, globally. The consistency of these relationships raises a fundamental biological question: why are common risk factors common? Perhaps the most attractive hypothesis is the common

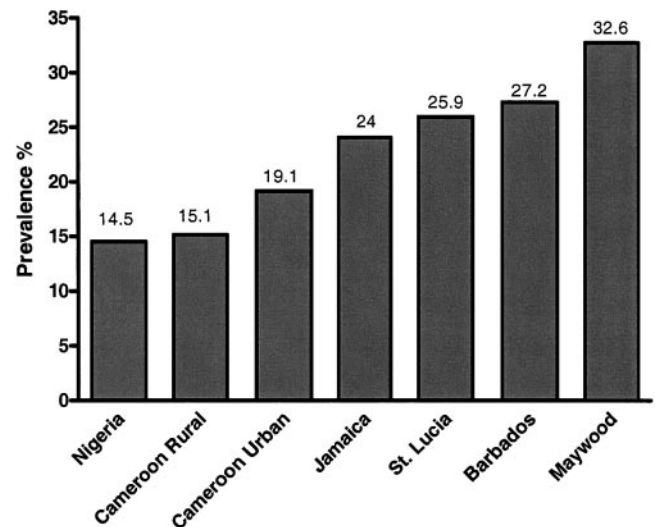


FIGURE 1 Age- and sex-adjusted prevalence of hypertension among seven populations of West African origin (age-adjusted to the total population): ICSHIB Study, 1995. Hypertension is defined as having blood pressure $\geq 140/90$ or taking antihypertensive medication.

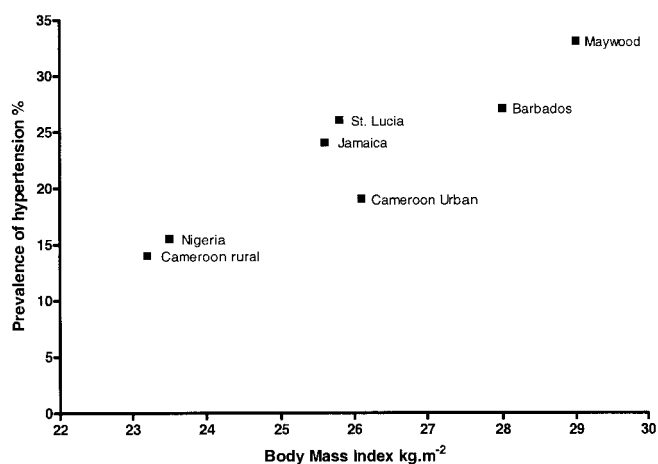


FIGURE 2 Prevalence of hypertension among seven populations of West African origin, by mean BMI: ICSHIB Study, 1995.

disease—common variant hypothesis (43). For hypertension the arguments would run as follows. Hypertension is a common disorder. “Common” implies that the disorder is prevalent within populations and that it is widespread across populations globally. High prevalence and widespread distribution could arise if susceptibility alleles for hypertension were prevalent in the founding population of modern human beings and became distributed globally with human dispersal.

The information available to date from genetic studies suggests that hypertension is a polygenic disorder with small contributions from multiple genes (43). Although no gene on this putative panel has yet been confidently identified, much promise attends the frenzy of research activity within the rubrics of gene discovery and candidate gene evaluation. Also, although there are population-specific genetic markers, there is thus far no evidence for aggregation of functional alleles that predispose specific ethnic groups to hypertension (44–46). We are thus unable to support the proposal that populations of African origin are genetically predisposed to developing hypertension. Before examining whether these populations harbor nongenetic susceptibilities to obesity and salt intake, a brief review of the mechanisms linking both to blood pressure is warranted.

How do salt intake and obesity affect regulatory mechanisms?

Salt intake. Salt intake varies considerably across populations, from ~1 mmol Na/d among isolated populations living hunter-gatherer lifestyles to >250 mmol Na/d in populations living in highly industrialized societies (40–42). Precise estimates of lower reference nutrient intakes for sodium are not available, but approximations exist (47). The minimum daily intake required for physiological stability in salt and water balance can be assumed to be between 1 and 10 mmol Na/d, based on data on salt and blood pressure in remote populations, and there is a continuous positive relationship between salt intake and blood pressure across the range of dietary intake, from <1 mmol Na/d in Yanomami populations to >250 mmol Na/d in some industrialized populations (40–42,47).

Current understanding of the role of salt in the regulation of blood pressure emphasizes renal mechanisms that control salt and water balance (48). The final pathway for renal salt excretion is tubular rejection of salt and water, and both the

equilibrium set point and the dynamic response to perturbations of homeostasis of this function are controlled dually by humoral and neural mechanisms (49–51). The renin-angiotensin-aldosterone system (RAAS) operates to maintain body fluid balance through enhancing or decreasing renal salt and water reabsorption throughout the nephron (48,52). Both circulating and intrarenal RAAS play important roles. Renal sympathetic activity at tubular and vascular target locations is also a powerful mechanism controlling natriuresis, and the actions of the sympathetic nervous system are integrated with both intra renal and circulating RAAS (53,54). Guyton and coworkers were the first to hypothesize that higher equilibrium blood pressures can only be attained and defended if the renal pressure-natriuresis relationships are reset, such that salt and water balance are maintained at higher renal perfusion pressures (49–51).

Obesity. Obesity develops within the context of a sustained positive energy balance, due to a combination of reduction in activity related energy expenditure and increased dietary energy intake. Reduction of physical activity accompanies the assumption of increasingly technological lifestyles, whereas increased energy intake is associated simplistically with the consumption of energy-dense foods. However, appetite dysregulation appears to contribute also to adiposity; long-term inhibition of energy intake is supposedly modulated by leptin and insulin, two hormones that act centrally to close a feedback loop that maintains body weight (5). Nevertheless, the appetite control systems are asymmetric, with the prevention of weight loss being vigorously opposed in comparison with the prevention of weight gain. In fact, teleologically, the system seems set to favor the accumulation of a positive energy balance, which would have provided a survival advantage in past environments in which daily food insecurity was punctuated with famine. Short-term meal-to-meal regulation of dietary intake is under the control of several hormones, chief among them being ghrelin, PYY and CCK, gut hormones modulating meal-to-meal food intake, and NPY, AgRP and POMC/MSH, central nervous system modulators of appetite that are integrated with these gut hormones and other afferent inputs (56).

In relation to hypertension, adiposity modulates renal pressure-natriuresis, and thus blood pressure, via at least two mechanisms. Leptin, secreted in direct proportion to fat mass, acts centrally to increase sympathetic outflow to the kidney

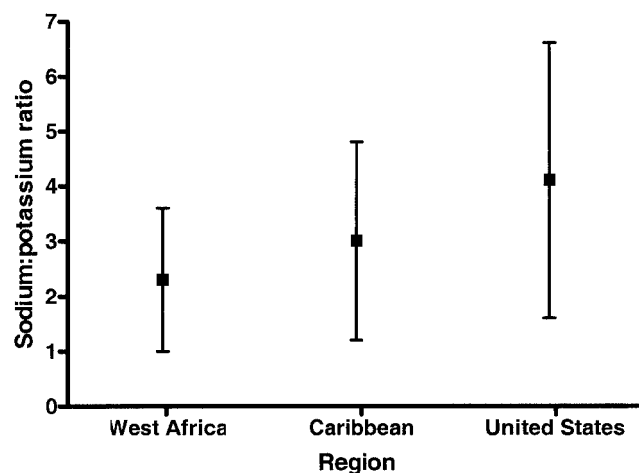


FIGURE 3 Urinary sodium:potassium ratio in persons of West African origin. Values are means \pm SD.

(48,57). Renal sympathetic nerve activity at the tubular as well as vascular levels increases sodium reabsorption. Adiposity also upregulates the RAAS (48). Together, these mechanisms effectively reset the renal pressure natriuresis mechanism toward the right and thus raise equilibrium blood pressure. Therefore, there is a cogent hypothesis that explains how adiposity and salt intake can combine to elevate blood pressure and, at the population level, raise blood pressure with age along with the prevalence of hypertension.

New risk factor for hypertension: Intrauterine modification of underlying susceptibilities

The hypothesis of the early-life origins of disease rests on the demonstration of a consistent relationship between body size and proportions at birth and risk for CNCD, and posits a process whereby the programming of fetal metabolism and physiology has carryover effects into postnatal life that increase the risk of developing several diseases, including CVD, in adulthood (16). Body size and proportions at birth are direct results of the cadence and rate of fetal growth. Fetal growth itself is largely regulated by placentally mediated nutrient flow, which is in turn determined by maternal body mass and composition, as well as by the pattern of dietary intake during pregnancy. Fetal undernutrition results in catabolism and in faltering growth if the catabolism is prolonged. The timing of undernutrition determines which organs are primarily affected. Specific impairment occurs in those organs most rapidly developing at the point of insult. Adaptation to the intrauterine insult secures a redistribution of blood flow from organs in less critical stages of development, or lower down on a teleological priority listing, to organs higher up the priority scale. This salvages vital organs such as the brain at the expense of the abdominal organs and skeletal muscle. Fetal undernutrition occurs in a setting of maternal undernutrition (17,18). Maternal undernutrition is associated with upregulation of the maternal HPA axis, leading to increased cortisol production (58–60). Access of maternal cortisol to the fetus is simultaneously enhanced by changes in placental cortisol receptors, which are downregulated (11- β -hydroxy steroid dehydrogenase) enhancing entry into the fetal circulation (58–60). In addition, fetal HPA axis sensitivity is centrally enhanced. Increased fetal exposure to cortisol causes accelerated ontogeny through the process of accelerated differentiation (61). This results at birth, for example, in a reduced number of nephrons (62), a reduced pancreatic B-cell mass and shifts in the balance of hepatic enzymes that affect carbohydrate metabolism, promoting gluconeogenesis at the expense of glycolysis (64,65).

With respect to hypertension, a large number of studies from both developed and developing countries show an inverse relationship between birth weight and blood pressure (66–71). Populations of African origin, including ancestral populations, clearly share this risk (68–71). The relationships between blood pressure and other newborn anthropometric indexes, such as ponderal index or head circumference, are weaker and less consistent than that with birth weight. Maternal markers of increased susceptibility to adult disease in offspring (i.e., fetal programming) are primarily nutritional and include prepregnancy weight, weight gain in pregnancy, body composition in pregnancy, the pattern of macronutrient intake and micronutrient status (16). What mediates these associations between materno-fetal relationships and hypertension in later life? The thesis of the present argument is that causal risk factors for hypertension are themselves programmed. Thus, because obesity and salt intake are associated

with the development of hypertension, it is important to explore whether obesity and salt sensitivity themselves might also be programmed in utero.

Programming of obesity. The propensity to develop obesity as well as to deposit fat centrally, leading to the development of syndrome X, appears to be modulated in association with body size and proportions at birth (72,73). In addition, the pattern of BMI change in early infancy predicts later obesity (74). For example, the age at which BMI rebounds from its first minimum after birth is predictive of later obesity (74).

Programming of salt sensitivity. An intuitively attractive hypothesis claims that undernutrition in utero results in reduction in nephron number (62). Further, reduced nephron number effectively resets the pressure natriuresis curve rightward when the individual is exposed to salt intakes typically encountered in Western lifestyles (75,76). However, although there are animal data that support the hypothesized relationship between birth weight and nephron number, there are no robust human data. In addition, few data relating nephron number to salt sensitivity in humans exist. In summary, therefore, maternal size before and during pregnancy and dietary intakes are directly related to fetal growth and birth weight. Smaller size at birth is related to higher blood pressure and risk of hypertension, and this increase in risk is probably mediated through programmed susceptibility to adiposity and its physiological effects, and less well demonstrated, programming of blood pressure sensitivity to salt intake.

Is there any evidence that populations of African origin are more programmed to develop hypertension?

Genetic. To date there are no data to suggest that populations of African origin possess an aggregation of genetic variants that predispose individuals to develop hypertension (45,46). On the contrary, the few genetic signals detected to date are not population specific, consistent with the common disease–common variant hypothesis (43,77–79).

Obesity. Africans seem no more or less susceptible to obesity than other populations, given environmental exposures. Thus, there are no data to indicate that at any calibration of the energy budget equation, any combination of energy intake and expenditure, Africans will secure a greater positive energy balance.

Salt sensitivity. Surprisingly, there is no single definition of salt sensitivity nor any accepted measurement technique to assess the magnitude of this physiological variable, despite decades of research and despite the obvious importance of salt and water balance to blood pressure homeostasis. We therefore can make no cogent assertion regarding whether salt sensitivity is enhanced among populations of African origin.

Are there markers of greater fetal programming among Africans?

One way of examining this question is the rather prosaic approach of comparing anthropometric markers of fetal growth retardation, birth weight, placental weight, body circumferences and the like. If one accepts this as the primary measure of fetal programming of hypertension, then there are several populations with lower values for birth anthropometry—and, by inference, greater intensity of fetal programming—than those of ancestral populations in West Africa, the origin of the vast majority of forced migrants whose descendants are now living in the West. In the United States, where there are data comparing birth outcomes such as mean birth weight and low

birth weight rates, the prevalence of low birth weight among blacks is 2.3-fold higher than that seen among whites (80,81). Faced with this observation, one might propose that the higher prevalence of hypertension, diabetes and stroke among this group might be related to presumed greater fetal growth retardation. Nevertheless, we would need to be scrupulous in ascribing risk to the myriad other confounders of this possible relationship, including environmental and behavioral correlates of ethnicity.

Likewise, if one assumes that fetal programming can and does take place in the absence of alterations in newborn weight and proportions, and might be marked by maternal characteristics such as maternal weight prepregnancy and during pregnancy as well as maternal dietary intake of energy, protein and micronutrients, then again, there are lighter, thinner women consuming less food in other populations. Thus, susceptibilities related to maternal and fetal exposures are not systematically greater among populations of African origin. However, the commonly reported greater burden of obesity among populations of African origin compared with other ethnic groups in the West suggests that programmed susceptibilities to obesity and salt intake might be exploited by environmental exposures that exceed their metabolic and physiological competences, thus resulting in greater prevalence of hypertension.

All available epidemiological evidence points to a combination of ill-defined underlying susceptibilities coupled with environmental exposures to salt and obesogenic influences as the primary drivers of hypertension. The large variation in prevalence rates of hypertension among populations worldwide can, and probably do, hide an infinitely varying combination of underlying susceptibilities and environmental exposures. Ultimately, answering definitively the question of whether Africans or any other populations are more programmed to develop hypertension will require the availability of research data collected in such a fashion as to allow direct comparisons across populations in relation to susceptibility factors and environmental exposure variables. Thus, in the absence of such data, we cannot state with confidence that populations of African origin are either more susceptible or more exposed to influences that affect the development of hypertension. Perhaps the most germane question, however, is not whether any population has greater underlying susceptibility to the development of hypertension. Far more important in the population management strategies to control hypertension are the questions regarding remediable susceptibilities and correctable exposures.

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