

Study of Evolutionary and Developmental Factors on Hypertension

Birth Weight & Blood Pressure

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ABSTRACT

Blood pressure is determined by numerous evolutionary and developmental factors. Adaptation to a hot tropical climate shaped physiological mechanisms to favor salt retention. Populations differ to the extent of being heat adapted, and some groups show a higher frequency of hypertensive alleles than others. Furthermore, growth and development of individuals provides understanding of how pre-natal and post-natal conditions can impact blood pressure and chances of developing hypertension. Epigenetic studies, the thrifty phenotype hypothesis, and allometric concepts give further insight into the possibilities of what can occur during one's early life. Specifically previous studies have associated intra-uterine-growth-retardation (IUGR) with low birth weight.

The relationship between low birth weight and hypertension was studied using the National Health and Nutritional Examination Survey (NHANES) conducted during 2007-2008. It was found, using SPSS, that 14.6% of African Americans had low birth weight, and only 2.7% of those with low birth weight developed hypertension. Caucasians had the lowest frequency of low birth weight with 6.7%, and Mexicans had 7.6%. However both of these groups did not have any frequency of low birth weight individuals with hypertension. Furthermore, it was found that African Americans had greater odds of developing hypertension than Caucasians or Mexicans. These studies show that low birth weight is not a significant factor in determining hypertension, which is contrary to previous studies.

CHAPTER 1: POPULATION DIFFERENCES IN BLOOD PRESSURE

Introduction

It is a major premise in human biology that variability in biological traits is a byproduct of evolutionary forces. In the words of Dobzhansky everything in biology makes sense in the eyes of evolution (Dobzhansky, 1964). Within this context I became interested in why some populations have a higher risk of hypertension than others. The answer lies in evolution and natural selection, which have shaped early human ancestors into modern day homo sapiens. Blood pressure in particular appears to have many evolutionary and adaptive roots. Hypertension, a modern day metabolic disorder, is a risk factor for numerous diseases such as heart attack, stroke, and much more. A major premise in biological anthropology is that variability in blood pressure and the high risk of hypertension among black populations is a byproduct of past adaptations to shortage of salt associated with hot tropical climates. As a result the sodium hypothesis (Gleiberman, 2009) has become the major paradigm that attempts to explain human diversity in blood pressure. Hence, in this chapter I will focus primarily on the developmental and evolutionary roots of variability of blood pressure.

Adaptation by Natural Selection

Heat adaptation

Ancestors of *Homo sapiens* all evolved under a similar hot wet climate that affected their adaptive mechanisms. Human adaptation to heat is crucial for survival because it helps maintain body and skin temperatures at an appropriate homeostatic level. The human body absorbs heat from a hot environment, which causes body and skin temperatures to rise. In order to maintain homeostasis, the body increases peripheral heat conductance by arteriole vasodilatation near the skin. Furthermore, the body increases sweat production. When the sweat evaporates from the skin the skin cools and thereby lowers the skin and body temperature. This physiological combination of vasodilatation and increased sweat rate allows the body to dissipate heat effectively. However, excessive sweating results in a significant loss of fluid and consequently salt that can cause numerous health problems such as low blood volume, which causes a drop in blood pressure with concomitant health consequences (Young & Young, 2007).

In order to compensate for the low blood volume resulting from low salt concentration the kidney will attempt to increase the absorption of water and salt. In view that the fact that humans have evolved in a tropical climate the leads to increased salt and fluid loss during sweating and low availability of salt humans have developed adaptive responses oriented at maximizing salt retention (Young & Young, 2007). As reviewed by Denton Africa has been characterized by a shortage of salt to the extent that prior to the 19th C salt was traded as a nutritional currency, and many of the tribal wars were related to access to the salt mines (Denton,). Given this background humans have been faced with a consequence of having

evolved from a tropical climate, which resulted in the increased risk of hypertension, which will be described below.

Hypertension Susceptibility

Human ancestors faced a changing environment and climate between the early Miocene and Pliocene. The landscape between these time periods was significantly changed due to increasing aridness of the land and a cooler climate. The rainforests and abundant canopies of the Miocene was vastly reduced by the Pliocene and replaced by woodlands and savannahs. Smaller primates adapted to such changes by staying in the canopies, while larger primates dwelled on forest floors and the growing savannah. (deMenocal,)

The savannah was a hot, dry, sun exposed landscape that greatly impacted human evolution by selecting for numerous traits. 3-4 million years ago marks a time period when a hominid first developed the ability to walk on two legs (deMenocal,). Bi-pedalism first developed in the extinct hominid *Australopithecus afarensis*, which eventually gave rise to the genus *Homo*. This type of locomotion allowed for less body surface area to be exposed to the sun (Frisancho, 2006).

2.8, 1.7 and 1 million years ago is associated with the beginning of increasing dryness of the land (i.e. aridification) that further compounded the climatic stress and to survive under such conditions humans had to develop adaptive traits fit for a savannah environment. As the land become hotter and dryer, sweat rate increased in order to dissipate heat, however as a consequence large amounts of salt were also lost. Therefore traits for hairlessness were selected for in order to facilitate evaporative sweat loss (Yablonski,). The transition of the African landscape, from rainforests and woodland to an open savannah is directly related to the evolution

of *Homo sapiens*. The increasing aridification changed the landscape and ultimately selected for modern day *Homo sapiens*. As illustrated in figure 1, hominid evolution occurs in a landscape that changed through time from woodland to grassland. Specifically, the transition from Australopithecines to *Homo habilis* to *Homo erectus* and eventually to *Homo sapiens* is characterized by periods of extreme dryness.

Once Anatomically modern *Homo sapiens* evolved they began to migrate out of Africa between 30,000 and 100,000 years ago. They spread north throughout Europe and east towards Asia. Their new environments presented them with cooler climates. As a result populations in these new environments had to adapt and overtime became more focused on the conservation and production of heat. This relationship between different environments and heat adaptation will be elaborated in the next section involving genetics (Young *et al.*, 2005). Theoretically, one would expect that given the circumstances under which human evolved, specific genetic traits suited for coping with a tropical climate would have developed, which will be discussed, in the next section.

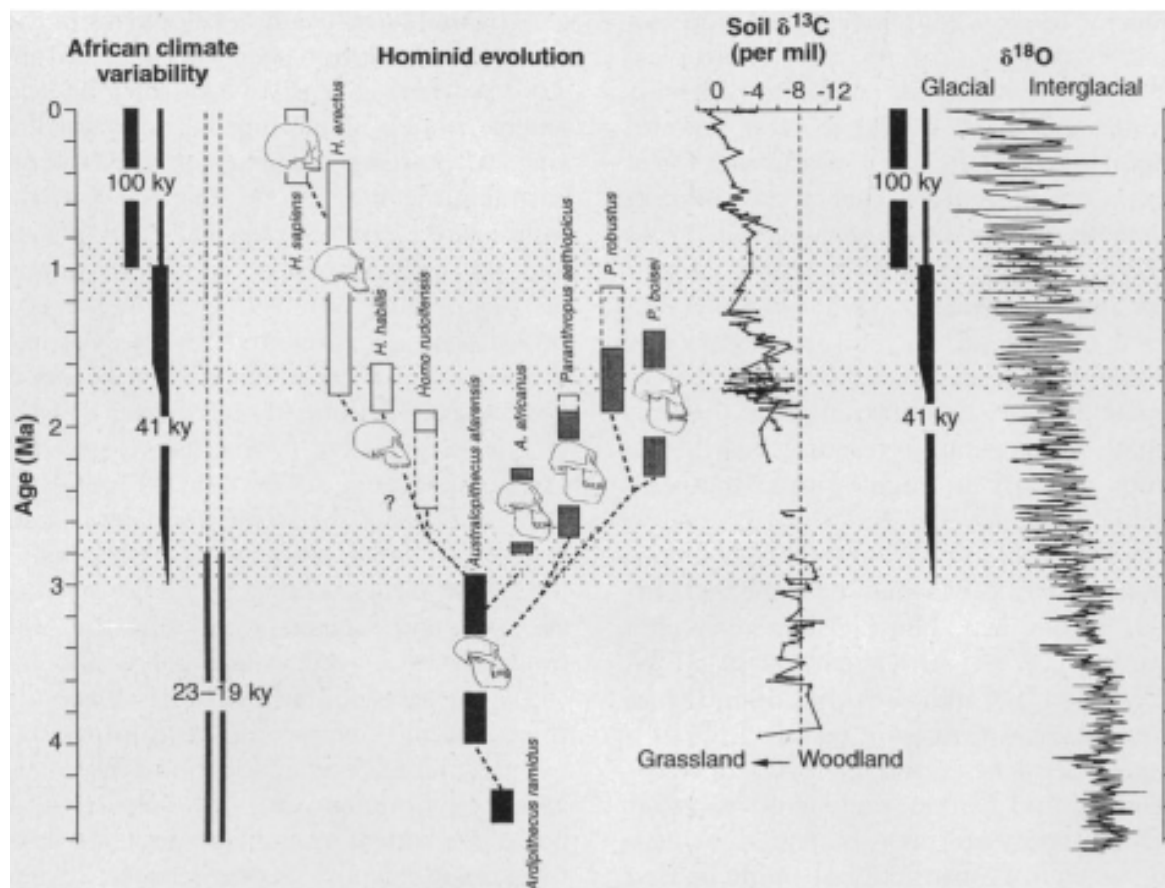


Figure 1: Progression of Hominid Evolution into genus Homo. There are three periods of increased aridity: 2.8, 1.7 and 1 million years ago. The landscape changed from woodland to grassland (savannah). Genus Homo evolved and the new emerging savannah selected for Homo sapiens. (Adapted from deMenocal)

Genetic Evidence of Hypertension Susceptibility

Introduction

Homo sapiens and non-human primates share common ancestors and certain physiological traits. When fed a high salt diet, chimpanzees exhibit an increase in mean systolic blood pressure, indicating salt sensitivity (Denton *et al.*, 1995). This increase in blood pressure

is very similar to humans, where a high salt diet triggers vasopressin secretion and activation of the Renin-Angiotensinogen-Aldosterone system (R-A-A), which reactivates salt absorption and water retention by the kidney, which brings blood pressure to a normal level . Further similarities between humans and chimps can be analyzed through genetic studies.

Angiotensinogen (AGT) and epithelial sodium gamma subunit (ENaC γ) are two genes that are common to both species. These genes contain two alleles that increase susceptibility to hypertension, AGT A-6G and ENaC γ A-173G, respectively. Because these genes are present in both humans and chimpanzees, and that the chimpanzees did not evolve in the savannah landscape, AGT and ENaC γ must be ancestral genes. Aridification and evolution in the savannah selected for the genus homo and various hypertension alleles in different genes in order to compensate for the thermoregulatory demanding environment. Such alleles of genes are called derived and include AGT-217A, GNB3, ADRB2, and ENaCa. (Young & Young, 2007)

One of the most important researched genes has been AGT because of its immediate impact on the R-A-A system. Therefore I will limit my discussion of genetic influences of hypertension to AGT. This gene has several variants that can affect expression of angiotensinogen and ultimately blood pressure.

Single Nucleotide Polymorphism (SNP) & Angiotensinogen Gene

In molecular genetics DNA sequences are usually defined in terms of nucleotides. Specifically a nucleotide is composed of nitrogenous bases such as Arginine (A), Guanine (G), Cytocine (C), and Thymine (T). Within a population differences among individuals is usually defined in terms of the different sequences of the above bases. Thus, an SNP can be defined as a single nucleotide difference within a gene. This single difference allows expression of various

alleles associated with the locus in a gene. In relation to hypertension, the AGT gene possesses various SNP's, however I will focus on two alleles: AGT-6A and AGT-6G. The AGT-6A variant is more frequent amongst African populations vs. non-African populations. Furthermore A(-6) exhibits 20% more expression than the G(-6) variants (Lalouel, 1997). Therefore it is highly probable that increased expression of AGT through the A (-6) variant can increase blood pressure. (Nakajima *et al.*, 2004)

The AGT A(-6) variant is also correlated to latitude, with more frequency towards low latitudes, and lower frequencies toward higher latitudes. As described before, Homo Sapiens migrated Africa and had to adapt to new environments that they encountered. It is possible that the A(-6) variant was selected for in hotter climates where a higher blood pressure would be beneficial. As populations live further away from the equator in colder climates, there may be selection against A (-6) because high blood pressure may be detrimental. Figure 2 shows the correlation between heat-adapted alleles such as AGT A (-6) and latitude (Young & Young, 2007). From this research it can be inferred that climate has contributed to the variability in the SNP sequences associated with variation of blood pressure. One way to test the possibility whether variability in blood pressure is related to genetic or socioeconomic factors is to study a population of African ancestry living under relatively good socioeconomic conditions. With this purpose in view I will summarize the studies done by Dr. Frisancho conducted in the lowlands of Bolivia.

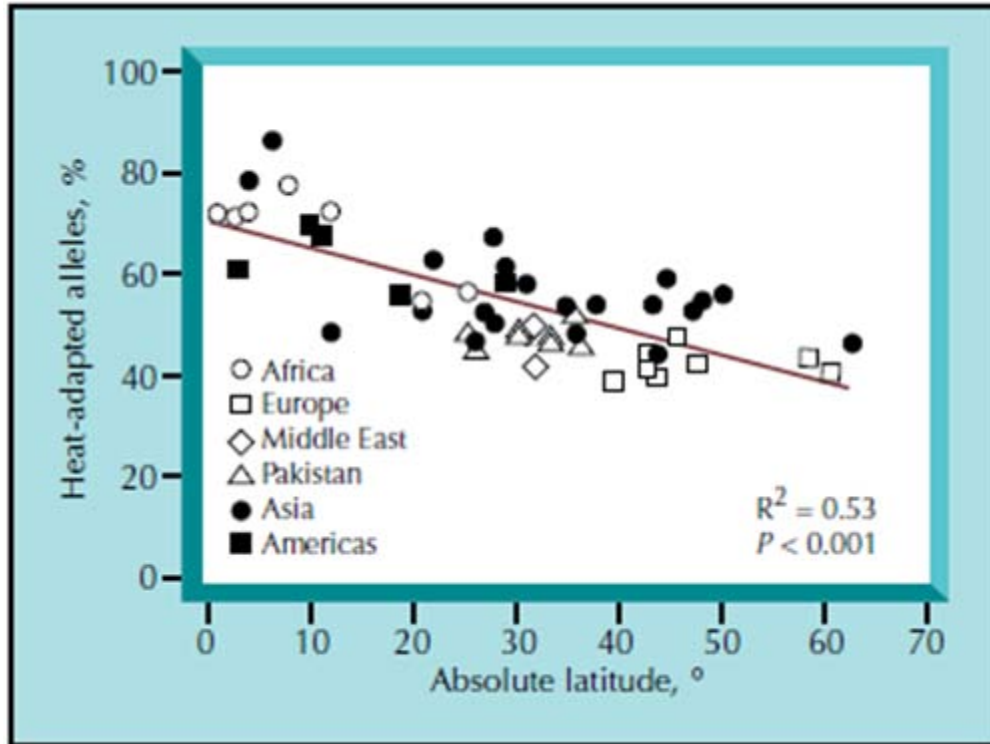


Figure 2: Study by Young and colleagues analyzing data from CEPH. As absolute latitude decreases, percent of heat adapted alleles increased. (Adapted from: Young & Young, 2007)

Population Study: Village of Chicaloma in Bolivia

People of African descent are more likely to have higher blood pressure based on genetic information. However environmental factors could also play a role. In order to have a better understanding of how genetics and race/ethnicity are related a population study can be analyzed. Dr. Frisancho studied a population in a village of Chicaloma in Bolivia. The study included 159 villagers, with 79 blacks and 80 non-blacks. Within this population the Bolivian blacks, as inferred from various economic indexes, enjoyed a better economic status than the native Bolivians that lived in the same community. Within this context the African Bolivians differed from the African Americans in the US, in that they are usually associated with a low SES

compared to non-blacks. This study found that the frequency of hypertension (150 mmHg/ 100 mmHg) among the Blacks in Chicaloma was only 7%, which is lower than those observed in African American, which was 30%, but it is higher than the non-blacks living in the same village, which had only 1.3%. Furthermore, the age associated increase in blood pressure was higher among the Bolivian blacks than in the non-blacks living in the same village. Therefore, it has been inferred that while the frequency of hypertension did not reach the levels observed in US populations, the Bolivian blacks have a tendency toward higher blood pressure, suggesting that there is a genetic propensity for hypertension among blacks, which is likely to be expressed under conditions of poor socioeconomic or stressful conditions. Another factor that contributes to the susceptibility to hypertension has also been discussed in terms of growth and development and Epigenetics, which will be dealt in the next section.

Growth and Development

Introduction

The rest of this chapter will be focused on human growth and development and its relationship to hypertension. I will focus primarily on the pre-natal environment and how various stimuli can potentially affect the growth and development of the fetus. Furthermore, I will specifically address the issue of low birth weight and its relationship with hypertension. Table 1 lists the ways newborns are classified. It is important to note that low birth weight babies are defined as weighing less than 2500 gm or 5.5 lbs. Furthermore pre-mature babies tend to have lower birth weights. The following sub-categories provide various perspectives on how the pre-natal environment can impact a fetus and hypertension.

Table 1: Classification of Newborns by Gestational Age and Birth Weight*

Gestational Length	
Pre-term / pre-mature	< 37 weeks
Term/ Full-term	>37 weeks to 39.9 weeks
Post-term	> 40 weeks
Birth Weight	
Low Birth Weight	<2500 gm; <5.5 lb
Average Birth Weight	2501 gm to 3500 gm; 5.51 lb to 7.70 lb
Large Birth Weight	>3500 gm to 4540 gm; 7.71 lb to 9.98 lb
Very Large Birth Weight	>4,540 gm; > 10 lb

Epigenetics

Epigenetics is the study of changes in gene expression that are not related to changes in actual nucleotide sequences. The way genes are expressed affects the phenotype of traits in the organism, such as blood pressure. Therefore any changes that occur that change genetic expression can ultimately produce a different phenotype than normal. Environmental triggers cause these changes, which modify genes and ultimately their expression. (Kuzawa & Sweet, 2009).

Epigenetic modifications to genes occur on chromatin, several complexes of numerous DNA wound around histone proteins. Methylation, the process of adding an extra methyl group, can cause the silencing of a gene. This can either occur directly on DNA or histones. Methylation of DNA promoter regions usually occur in locations of DNA a large amount of cytosine and guanine. Methylation of histones tightens the DNA around histones and prevents

gene expression. However, acetylation can reverse this process and loosen the chromatin. (Kuzawa & Sweet, 2009)

Epigenetic modifications on chromatin first occur during cell division and differentiation during an embryo’s development. This allows for different cell types to express different genes and ultimately create a broad range of various cell types. The issue of epigenetics and its correlation with hypertension is that a mother’s uterus serves as a prenatal environment that directly impacts the fetus. “Environmental triggers” such as low nutrition can cause silencing of genes that can ultimately impact the health of the fetus. Gene silencing can have a great effect on different cell lineages during fetal development as seen in Figure 3. Various tissues or organs may be affected and could cause problems such as hypertension later on in life. (Kuzawa, 2009)

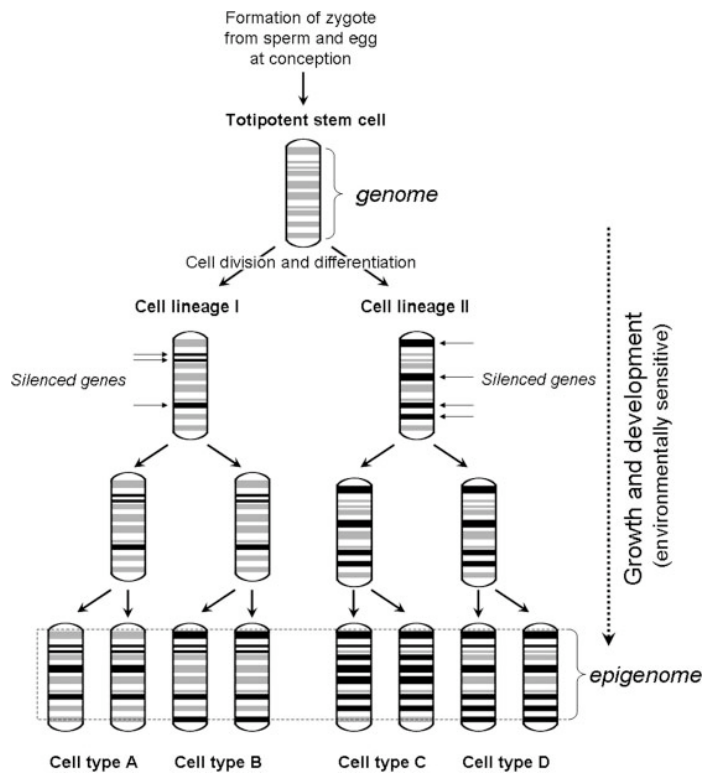


Figure 3: Schematization of Epigenetic modifications and outcomes. (Adapted from Kuzawa & Sweet, 2009)

The Thrifty Phenotype Hypothesis

Early studies by Barker, Hales observed a relationship between diabetes type 2 and birth weight. A fetus, like any other organism, adapts to its environment in order to survive. The mother's uterus is an environment that consists of numerous variables that could determine how the fetus adapts. The so-called "living conditions" of a uterus depends upon the mother's nutrition, socio-economic status, and genetic pre-dispositions. A uterus with limited nutrition can lead to fetal growth retardation and potential pre-mature pregnancy. Certain organs or tissues may not develop properly and this may alter their function. Barker and Hales viewed intra-uterine growth retardation (IUGR) and low birth weight as a short-term adaptation to the mother's fetus. However, once born this adaptation may be detrimental to life outside the fetus. Barker coined this phenomenon as the thrifty phenotype hypothesis. (Gluckman *et al.*, 2007)

When the fetus receives low levels of nutrients from the placenta, several physiological and metabolic changes occur in order to cope with the situation. The fetus immediately adapts by lowering its metabolism. This is accomplished by lowering two key growth-promoting hormones: insulin and insulin-like growth factor (IGF)-1. Insulin is released, by the beta cells of the islets of Langerhans in the Pancreas, in response to high glucose levels and increases glycogen production by the liver and muscles as well as increasing glucose uptake of adipose tissue. (IGF)-1 is a hormone that is released by the liver and affects almost all cells of the body by acting in a similar fashion to insulin. (Gluckman, 1995) Furthermore, the fetus reroutes blood flow to vital organs such as the brain and effectively retards growth in other parts of the body. (Gluckman *et al.*, 2007)

The fetus can also engage in a predictive adaptive response, which can be thought of, as preparing for future environments by assessing the current environment. An example of this

type of adaptation can be observed in newborn infants who develop sweat glands sometime after birth. The temperature of the environment determines the exact number of sweat glands. Infants in hotter climates develop more sweat glands than those in colder climates. This early determination of sweat glands is a “prediction” of what climate the infant most likely will experience through its life (Gluckman, 2005). Immediate and predictive adaptations can be cause for great concern because of the physiological damage that can occur and the potential health risks in the future.

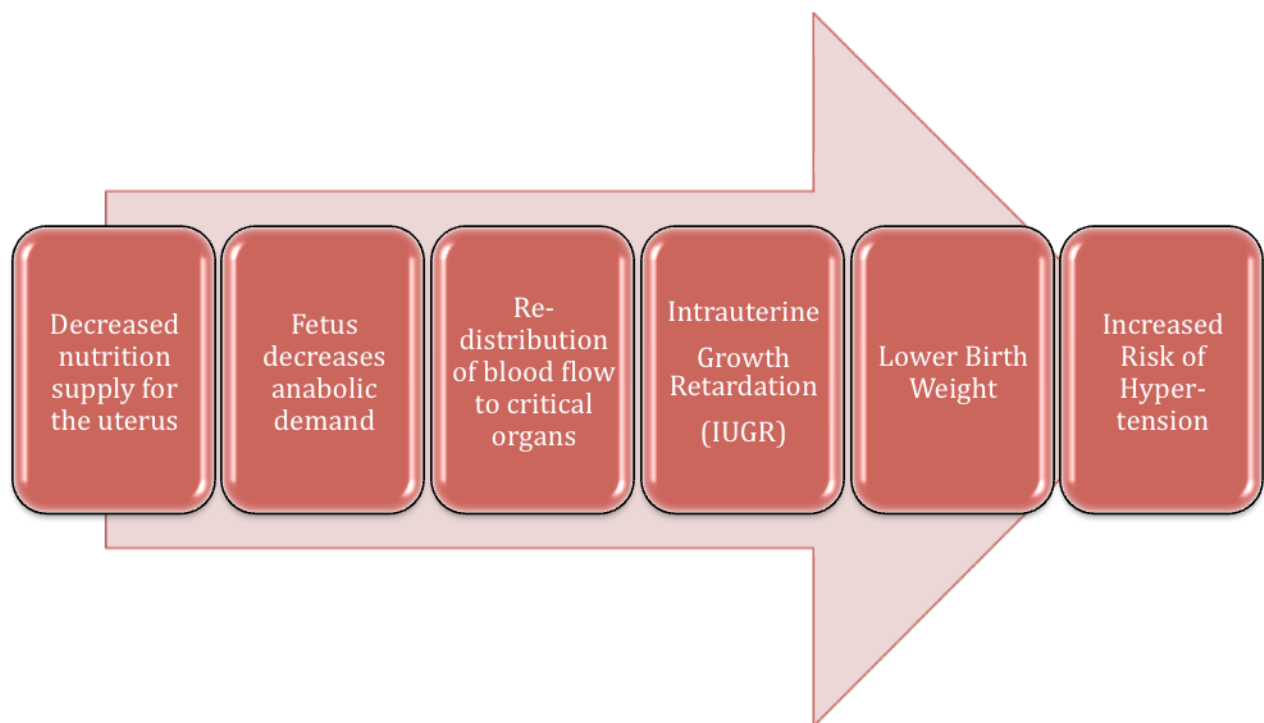


Figure 4: Schematization of Thrifty Phenotype and its relation to IUGR and hypertension.

(Adapted from Gluckman *et al.*, 2007)

Effects of Thrifty Phenotype on Fetal Kidney

The fetus is constantly growing and developing throughout pregnancy. Even after birth, humans continue to mature and change throughout life until death. The development of the renal system is crucial for determining blood pressure. Morphological formation of the actual kidney occurs during pregnancy, while kidney function develops during pregnancy and rapidly develops after birth and continues through adulthood. Any potential changes or damage to the anatomy of the kidney could potentially alter immediate and future functioning (Woods, 2000). Maternal malnutrition, toxins such as alcohol or smoking, and numerous other variables all risk growth retardation and kidney damage (Hoy *et al.*, 2005).

Nephrogenesis and organogenesis, the formation of the nephrons and organs respectively, occurs between the 6th and 36th weeks of gestation. After 36 weeks, approximately 1,000,000 nephrons fully develop in each kidney. It is important to note that babies born pre-mature (< 37 weeks) may be subject to incomplete nephrogenesis and organogenesis. Therefore pre-mature and possibly low birth babies would have fewer nephrons at birth. Furthermore, glomerular filtration rate (GFR) increases post-natally while sodium secretion decreases in order to facilitate tissue generation (Hoy *et al.*, 2005). As discussed previously, if the uterus lacks nutrients blood flow may be redirected to preserve vital organs like the brain. Less essential organs such as the kidneys are compromised and receive less blood flow and therefore have limited growth and development. This results in a decrease in total nephrons. Furthermore, the glomeruli become enlarged to compensate for this change. Recent studies by Woods hypothesizes that low maternal protein intake may have a negative effect on the fetus that could result in hypertension (Woods, 2000).

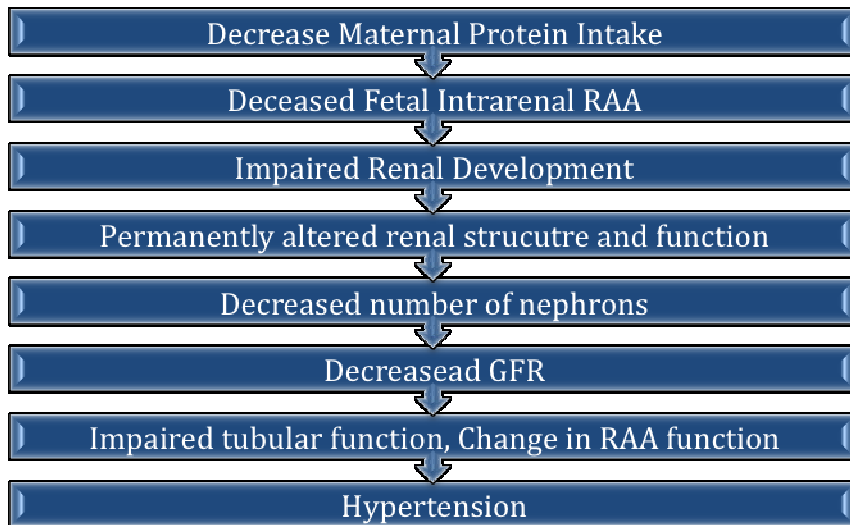


Figure 5: Schematization of maternal protein in hypertension. (Adapted from Woods)

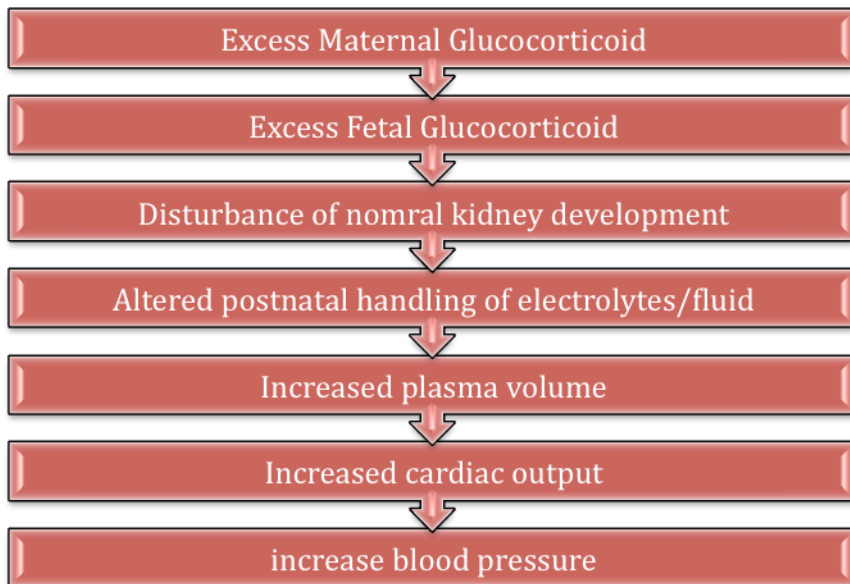


Figure 6: Schematization of Glucocorticoid relationship with hypertension. (Adapted from: Woods).

Epigenetic relationship with Thrifty Phenotype Hypothesis

During the maturation of a fetus, the epigenome develops based upon the intrauterine environment, as previously stated. Now this idea coupled with the thrifty phenotype hypothesis, it is possible to predict which new-borns will have a higher risk of developing hypertension and other metabolic diseases such as diabetes type II. In **Fig. 7** the relationship between epigenetics and thrifty phenotype is shown. A fetus acquires a specific epigenome, which ultimately effects how the fetus will develop physiologically. When a fetus adapts to a mal-nourished uterine environment, it is ultimately attempting to predict how the post-natal environment will be. All physiological changes that occur in a deprived pre-natal environment will ultimately help the newborn survive in a deprived environment. The same concept can be applied to a fetus that develops and adapts to a nutrient rich uterine environment; the fetus is predicting that the post-natal environment will also be nutrient rich. However, if a deprived adapted fetus lives in a nutrient rich environment post-natally, then the physiological changes that were made pre-natally are now considered detrimental to the individual. A mismatch of developmental and mature environments can cause an increased risk of hypertension. (Godfrey *et al.*, 2007)

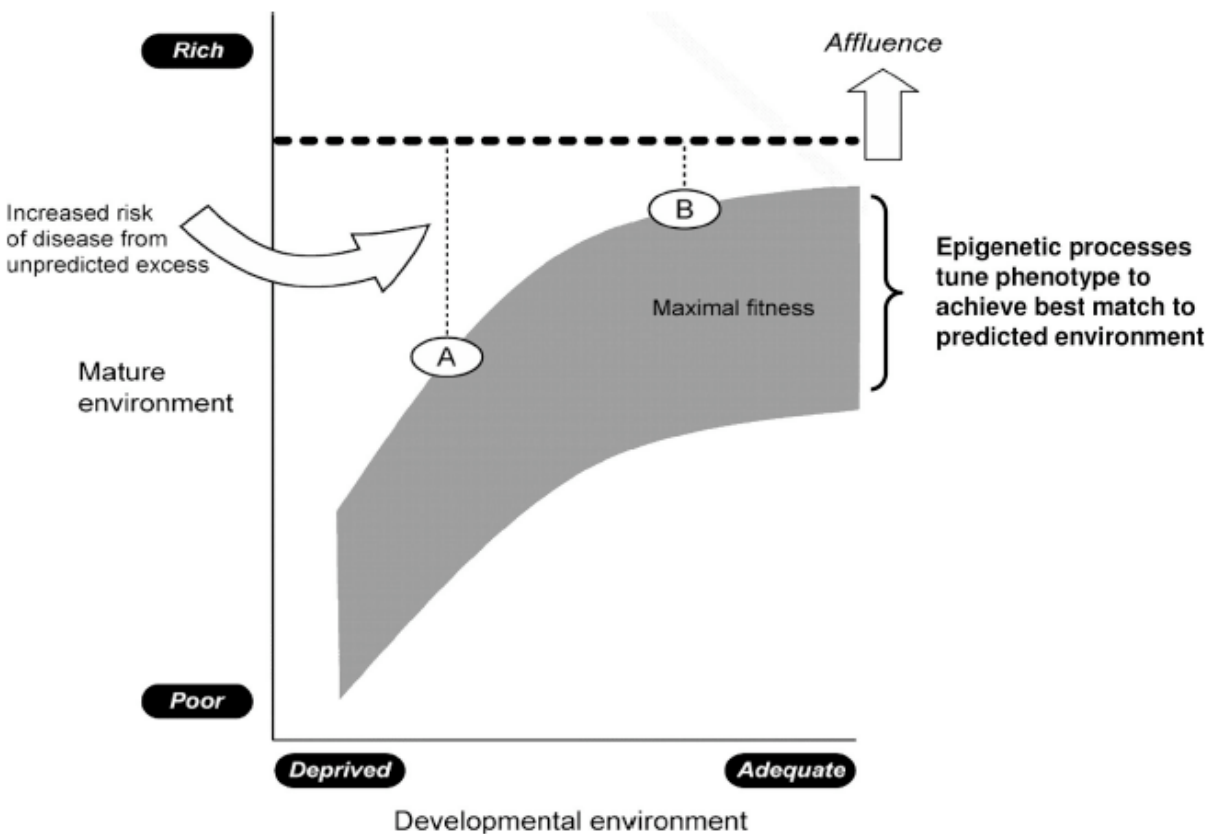


Figure 7: Individuals that are mismatched between developmental environment and mature environment have an increased risk of hypertension. Whereas if an individual is matched between the two environments the risk is low. (Adapted from: Gluckman *et al.*, 2007)

The degree to which a fetus is receptive to physiological change is called plasticity. Throughout the developmental period in the uterus the fetus is very malleable and can adapt to fit almost any circumstance. However, after birth and throughout life, plasticity decreases and any physiological changes become permanent. Furthermore, throughout one's life, exposure to various environmental factors increases. While the uterus provides a very sheltered and controlled environment through the placenta, the outside environment is much more variable and potentially dangerous. **Fig. 8** depicts how epigenetic changes ultimately influence phenotype.

Whether or not a metabolic disease occurs depends on matching the correct later environment. (Godfrey *et al.*, 2007). An example of the mismatch between prenatal and postnatal environmental can be inferred from the studies done on the survivors of the Dutch famine to be discussed next.

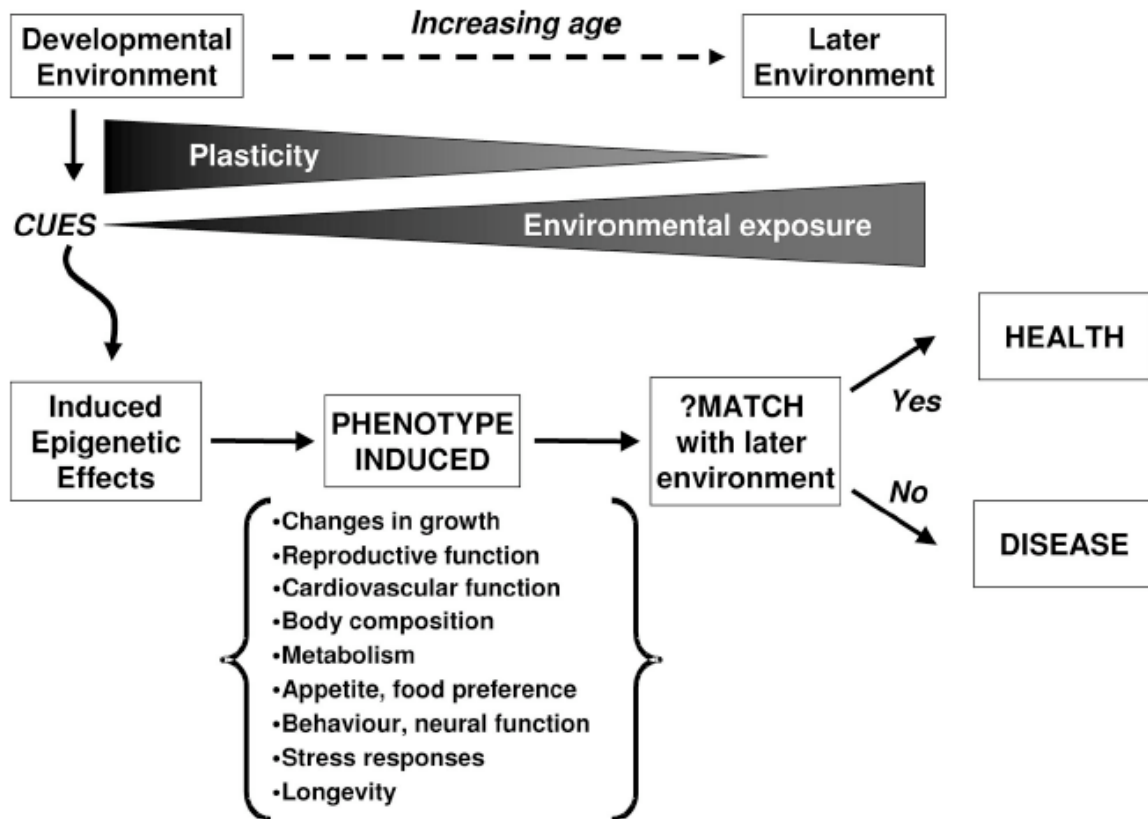


Figure 8. Physiological plasticity is greatest during childhood and developmental periods of life. It decreases during adult life, which could cause a problem if the individual is mismatched between development and adult environments. Epigenetics can play a role by expressing certain genes due to the developmental environment that may cause the individual to be more suited for a particular type of environment such as nutrient rich or nutrient depleted.

Population Study: The Dutch Famine

The Dutch famine occurred between 1944 and 1945 during World War II. Due to climate conditions and political turmoil people in the western Netherlands experienced a significant food shortage that ultimately impacted not only their lives but also the lives of future generations. Women who were pregnant in early, middle, and late stages of gestation gave birth to babies who were exposed indirectly to the famine through their mothers. Recent studies analyze the relationship between maternal nutrition during gestation and blood pressure of the offspring as adults (Painter *et al.*, 2005).

Studies found that there was a very small correlation between low birth weight due to the famine and increased blood pressure. More specifically, increased blood pressure of adults who were subjected to the famine during gestation was more strongly linked to the amount of protein to carbohydrate intake than total calories consumed by the mother. Low protein diets by mothers during the famine contributed strongly to the high blood pressure alter on in life for the offspring. Furthermore, protein intake was associated with the third trimester of gestation and not the first two. This means that it is possible that blood pressure determination could occur late in gestation; however more research must be conducted in order to validate this statement. (Painter *et al.*, 2005). As discussed below, another example of the mismatch can also occur as result of allometric growth of the kidney vs. body size.

Allometry and Growth of the Kidney

Blood pressure increases throughout life have physiological impacts on the kidney. In general throughout one's life, blood pressure generally increases for various reasons. As children grow into adolescents and ultimately into adults, body size increases linearly which causes a greater functional load on the kidneys. For example, the kidneys of a taller, larger teenager must filter more blood than a shorter, smaller child. Kidney weight on the other hand follows a sigmoidal growth pattern from childhood to early adulthood as seen in figure 9 (Perkkio,1985). The kidney rapidly grows in children and teenagers. Around the age of 20, growth plateaus and kidney weight is usually fixed for the remainder of one's life. Furthermore, blood pressure increases throughout childhood and adolescent growth in order to maintain renal homeostasis. Once adulthood is reached and linear growth between the body and kidney stops and blood pressure should be at an appropriate level to sustain renal homeostasis for the remainder of life. However, factors such as obesity, high salt diets, and alcohol consumption can alter body composition, kidney weight, and effectively blood pressure. (Weder, 2006)

There are several physiological milestones throughout an individual's life that impact blood pressure. The first milestone that the body undergoes occurs during a child's first year after birth when the systolic blood pressure may increase almost 20 mmHg. The next milestone, age of adrenarche, occurs at age seven and involves the maturation of the adrenal glands. During this age, children undergo a growth spurt that ultimately increases blood pressure. This is due to the linear relationship between blood pressure and height as previously discussed. The next milestone occurs during adolescence when children begin to sexually mature and have drastic

changes in body weight, height, as well as physiological mechanisms. Blood pressure is expected to increase almost 6 mmHg per year throughout adolescence. Periods of growth and development are important milestones in human life; however the timetables for growth have drastically changed, and continue to change into the future. Females specifically experience unique milestones because of their sex. For example, the age of menarche is when women begin their first ovulation cycle and potentially can have a period. Women over the past two hundred years are reaching menarche at younger and younger ages. This accelerated growth can cause numerous problems with blood pressure and renal activity. (Weder. 2006)

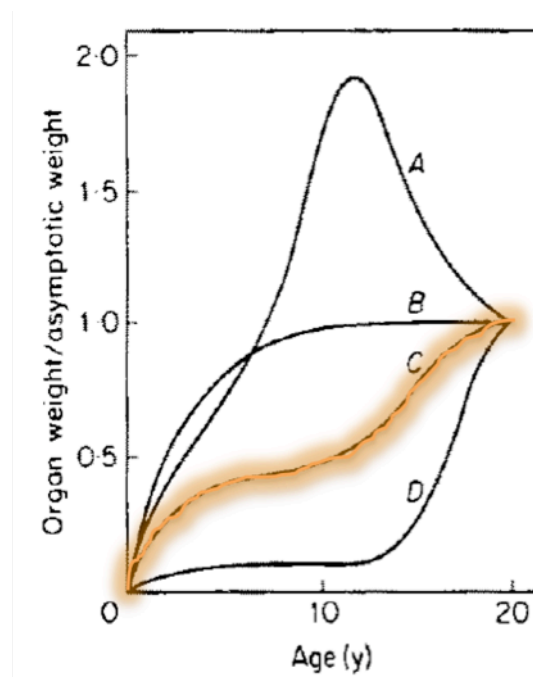


Figure 9: Growth curve C represents kidney growth throughout childhood, adolescence, and early adulthood. Around the age of 20, the kidney stops increasing in weight. (Adapted from: Perkkio, 1985)

Overview

As learned from epidemiological studies it's quite evident that variability in blood pressure is influenced by both genetic and environmental factors. All the evidence reviewed above support the conclusion that among African American, genetics plays an important role in the etiology of hypertension, specifically it's evident that there is susceptibility amongst African Americans which can be expressed under conditions of high environmental stress of poverty. Recent genetic studies have identified a cluster of alleles (AGT) that control blood pressure and such alleles appears to be more frequent amongst populations whose recent origins goes back to tropical climates or low latitudes. Recent studies indicate that the genetic control of blood pressure can be modified at the prenatal level as exemplified by epigenetic studies. Additionally, the evidence indicates that the risk of hypertension in some individuals and/or populations can be increased as a result of the mismatch between the prenatal and postnatal environment; so that individuals exposed to under nutrition and born with low birth weight are more susceptible to hypertension when they are exposed to better nutritional conditions than those who remain in under limited conditions. Similarly, the risk of hypertension can be increased as a result of the allometric effects concerned with the growth of the kidney and body size. The physiological pathways by which the above factors are expressed in the variability of blood pressure will be discussed in the next chapter.

CHAPTER 2: PHYSIOLOGY AND HORMONAL CONTROL OF BLOOD PRESSURE

Cardiovascular Physiology

The previous chapter detailed how blood pressure can vary between populations. It is also important to understand how blood pressure varies within the human body through physiological mechanisms. The purpose of the circulatory system is to distribute blood throughout the body. The main components of this system are the heart and blood vessels. The heart is comprised of four chambers: the right atrium, right ventricle, left atria and left ventricle. Blood vessels can be categorized by their function. Arteries and arterioles take blood away from the heart and carry almost always oxygenated blood, the exception being the pulmonary artery. Capillaries allow for simple diffusion of nutrients, oxygen, and waste products between the blood and tissue cells. Veins and venules take blood toward the heart and carry almost always deoxygenated blood, the exception being the pulmonary veins. The movement of blood creates pressure on the walls of the blood vessels. Blood pressure can be determined by many variables, which pertains to the study of hemodynamics.

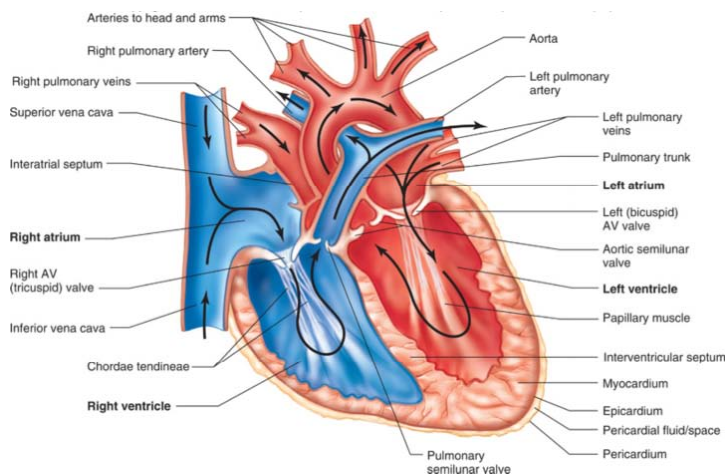


Figure 10: Image of the human heart and various structures. The arrows indicate blood flow through the heart. (Adapted from: Widamaier *et al.*, 2007)

Blood moving through the circulatory system creates pressure on the walls of blood vessels and in the heart. Hemodynamics specifically studies blood movement through three factors: blood flow, difference in blood pressure between two points, and resistance to flow by blood vessels. In short these factors can be simplified into Equation 1. Fluids usually move from high to low pressure, this movement ultimately will create flow. Resistance to flow can be due to multiple factors that can be summarized in the Equation 2. This shows how blood pressure can be manipulated by altering the variables that effect resistance.

$$F = \frac{\Delta P}{R}$$

Equation 1: F = flow, ΔP = change in pressure, R = resistance. (Adapted from: Widamaier, 2007)

$$R = \frac{8L\eta}{\pi r^4}$$

Equation 2: R = resistance, L = length of vessel, η = viscosity, r = radius of vessel. (Adapted from: Widamaier *et al.*, 2007)

Blood flow can start arbitrarily from any point in the circulatory system. For simplicity blood flow begins at when blood from the superior and inferior vena cava fills the right atrium. It then flows through the bicuspid valve and into the right ventricle. The right ventricle pumps the blood through the pulmonary semilunar valve and into pulmonary artery. Blood is then

oxygenated in the lungs via simple diffusion. Pulmonary veins then return blood into the left atrium. Blood flows through the tricuspid valve and into the left ventricle. The left ventricle pumps blood through the aortic semilunar valve and into the aorta. Blood flows in the following order: through the aorta, arteries, capillaries, venules, veins, venae cavae and back to the right atrium. The cardiac cycle specifies the importance of different phases during blood flow.

Cardiac Cycle and Systoles

The cardiac cycle involves two phases, diastole and systole, that explain how blood is moves through the heart. Diastole represents ventricular relaxation and filling of blood while systole represents ventricular contraction and ejection of blood. Pressure changes throughout the cycle and can be measured accordingly. Diastole begins with isovolumetric ventricular relaxation, when all valves are closed and there is no blood movement in the heart. As the venae cavae returns blood into the right atrium, the pressure in the right atrium increases and becomes greater than the pressure in the right ventricle. This pressure difference opens the tricuspid valve and allows blood to flow into the right ventricle. Simultaneously the same scenario occurs with the left side of the heart. The pulmonary veins return blood to the left atrium, which increases pressure in that chamber and makes it greater than the pressure in the left ventricle. This pressure difference opens the bicuspid valve and allows blood to flow into the left ventricle. As a result of these mechanisms, both ventricles are filled. There comes a point when the building pressure in the right and left ventricles equals pulmonary artery and aortic pressure respectively. This closes all valves, ends diastole, and marks the beginning of systole. Systole begins with isometric ventricular contraction where all the valves are closed in the heart. The ventricles then begin to contract simultaneously which increases pressures inside the ventricles and makes it

greater than the pressure in the aorta and the pulmonary artery. This pressure difference pumps deoxygenated blood from the right ventricle into the pulmonary artery and oxygenated blood from the left ventricle into the aorta. As blood is lost from the ventricles, pressure decreases. When pressure in the ventricles is lower than the artery pressures, the semilunar valves are shut closed. All valves are closed once again which marks the beginning of diastole and the end of systole. Systole tends to produce a greater pressure than diastole. This is due to the greater force at which the ventricles pump blood, which occurs during systole. The cardiovascular system provides the framework for which blood can interact with the vessels in order to create pressure. Mainly the renal system and its various hormones control how this blood pressure is regulated.

Renal Physiology

The Kidneys play a crucial role in maintaining a homeostatic blood pressure as well as many other important functions such as filtering the blood. The kidney is comprised of an outer section called the renal medulla and an inner section called the renal cortex. The renal pelvis is connected to the ureter, which ultimately leads to the bladder. The functional unit of the kidney is the nephron and is located within the medulla and cortex. There are over one millions nephrons in each kidney and only two types: the juxtamedullary nephron and the cortical nephron. Each nephron is comprised of a renal corpuscle, the site of blood filtration. A schematic of the nephorn is shown in **Fig. 11**. The corpuscle can be divided into the glomerulus, a ball of capillaries, and Bowman's capsule, which surrounds the glomerulus and contains bowman's space. An afferent arteriole feeds into the glomerular capillaries and an efferent arteriole takes blood away. Blood is filtered through bowman's space via bulk flow and into the proximal tubule. Blood then flows down and up the loop of henle, through the distal tubule and

into the collecting duct. Throughout this process mineral and nutrients are reabsorbed or secreted. The collecting duct transports the resulting urine into the bladder where it is stored and later expelled.

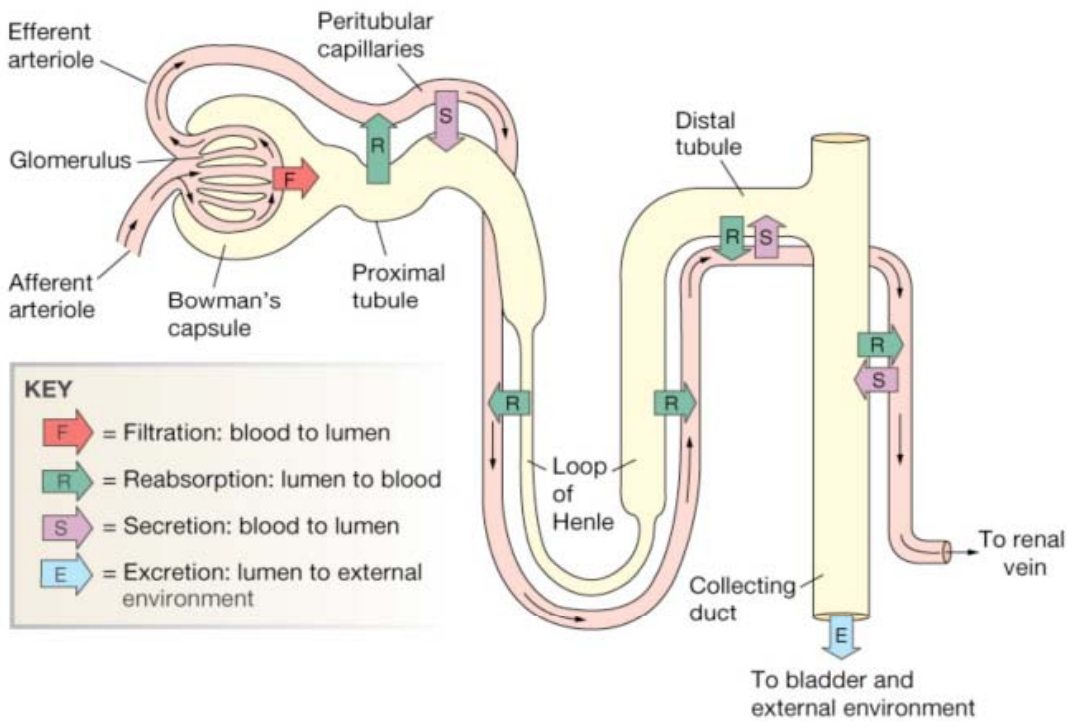


Figure 11: Schematic of nephron. Filtrate can either be reabsorbed or secreted by tubules. Any filtrate that remains will be excreted. (Adapted from: Silverthorn, 2007)

Regulation of Salt and Water

As filtrate passes through the nephron, salt is actively reabsorbed while water passively reabsorbed. These processes of reabsorption can be controlled by certain physiological

mechanisms. Antidiuretic hormone (ADH) also known as vasopressin, and Aldosterone are two key hormones involved in water and salt reabsorption respectively.

ADH

ADH is a peptide hormone released by the posterior pituitary gland located in the brain. ADH ultimately increases water reabsorption by the kidney. When osmolarity increases in the blood (increase salt concentration), ADH is secreted and acts on the collecting duct. ADH binds to an external receptor and triggers a secondary messenger system, which ultimately increases the number of aquaporins. Aquaporins are water channels located on the filtrate side of the collecting duct; ADH creates more of these channels, therefore water reabsorption increases. The purpose of this mechanism is to decrease osmolarity by diluting the blood. The secondary purpose is to increase blood pressure. More water in the blood means more force being exerted on the blood vessel walls, therefore blood pressure increases. See **Fig. 12** below for a summary of this process.

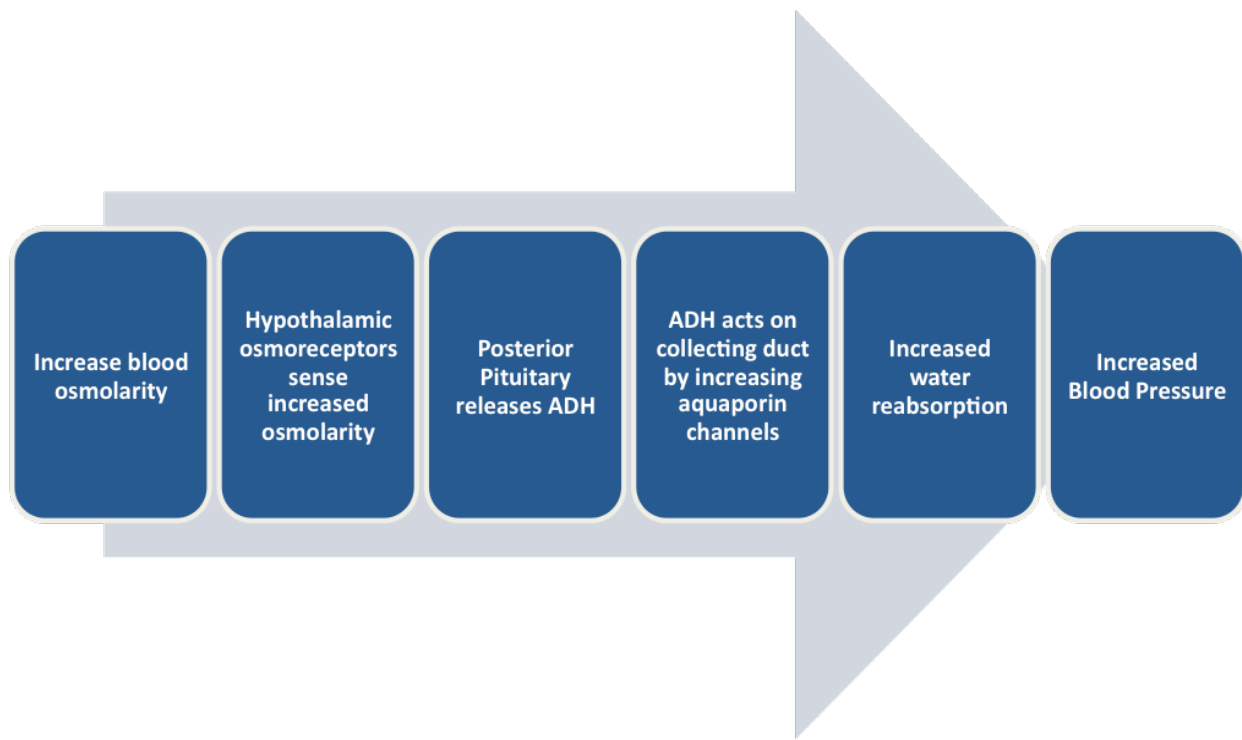


Figure 12: Schematization of physiological process involving ADH/ vasopressin. (Adapted from: Widamaier *et al.*, 2007)

Aldosterone

The steroid hormone Aldosterone is secreted by the adrenal cortex and is involved in a broader physiological process called the R-A-A (Renin – Angiotensin -Aldosterone) system. Aldosterone ultimately increases sodium (Na^+) reabsorption by the kidney. The R-A-A system, see **Fig. 13**, can be triggered by numerous stimuli. Increased sympathetic renal nerve stimulation, decreased blood pressure, and decreased NaCl concentration at the macula densa, all contribute to the activation of renal juxtaglomerular cells which ultimately release the enzyme renin. Once renin is secreted into the blood, it cleaves the pro-hormone angiotensinogen (originally secreted by the Liver) into Angiotensin I. Angiotensin I is then cleaved by

angiotensin converting enzyme (ACE) into Angiotensin II. Angiotensin II then triggers the adrenal cortex to secrete Aldosterone.

Once Aldosterone is in the blood it travels to the kidney where it affects the collecting duct and distal tubules. Aldosterone is lipid soluble so it passes through the cell membranes and effects RNA transcription at the nucleus. New sodium potassium pumps are produced as well as sodium and potassium channels. Furthermore, existing pumps and channels are up regulated (more active). Ultimately more Na^+ is reabsorbed and more K^+ is secreted. Because of the higher sodium concentration in the blood, water follows and therefore blood pressure increases. It should also be noted that Angiotensin II is a powerful vasoconstrictor and helps to increase blood pressure. How blood pressure increases and decreases is very important to the understanding of why certain populations may have hypertension. Measurement of blood pressure is crucial to provide an accurate reading for health care professionals to determine whether someone is hypertensive or not.

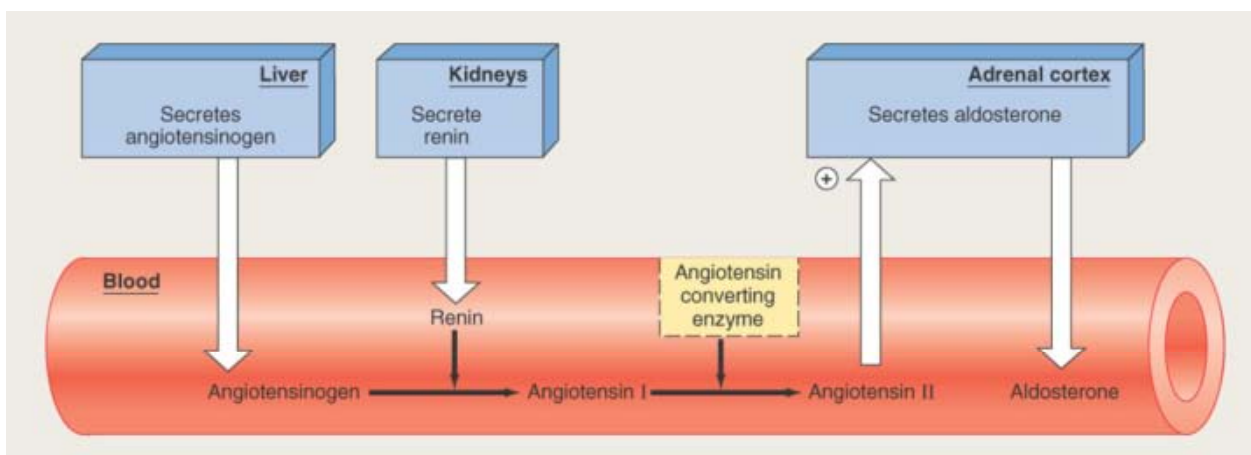


Figure 13: Schematization of RAA system. (Adapted from: Widamaier *et al.*, 2007)

Measurement of Blood Pressure

Blood pressure can be measured through direct (invasive) or indirect (noninvasive) procedures, however the indirect methods are most common in the medical field. Indirect measurements include palpatory, flush, auscultatory, ultrasonic, and oscillometric methods. All of these methods however use a cuff to assist measurement. The cuff is inflatable and applies counter pressure on an artery (usually in the arm or leg). The cuff pressure starts at a level greater than systolic blood pressure and is then decreased gradually by deflating the cuff (at a rate of 3mmHg/s). When measuring a person's blood pressure, body location and position are crucial factors to ensure accuracy of the reading. The optimal location would be the left upper arm around the bicep, because it is at the same height as the left ventricle. Furthermore, this allows one to read the blood pressure that the heart is producing and not pressure produced by gravity. For example, if blood pressure is measured at the foot then the reading will be higher than normal because of the weight of the blood above the foot, which contributes to added pressure. Body orientation can change blood pressure readings depending on if the person is supine (laying down on their back) or standing up. Blood pressure is usually higher overall when the person is lying down, and is lower when standing up.

Palpatory Method

The palpatory method can only detect the systolic blood pressure and is primarily used when all other indirect methods fail or are not available. A patient's radial pulse is palpated while the blood pressure cuff is inflated. The cuff should be continuously inflated until the pulse disappears. Once this occurs, inflation to continue until the final cuff pressure is approximately 30 mmHg over the cuff pressure reading at which the pulse disappeared. Then deflation should

slowly occur until the pulse reappears. The cuff pressure at which this occurs is considered to be the systolic blood pressure.

Auscultatory Method

The Auscultatory method can measure systolic diastolic and mean blood pressure and is the most commonly used method by health care professionals. This method is shown below in **Fig. 14**. Korotkoff first created this method and used a stethoscope and a blood pressure cuff. He stated that during cuff deflation the first sound one hears is considered to be the systolic pressure and the point of sound disappearance is considered to be the diastolic pressure. In addition to the previously explained cuff procedure, when using this method, the head of the stethoscope should be placed gently against the palpated brachial artery; this allows one to hear Korotkoff sounds. This method is most widely used by hospitals and doctors because it provides an accurate measurement of blood pressure and can be readily implemented if other superior technological instruments fail such as automatic blood pressure readers.

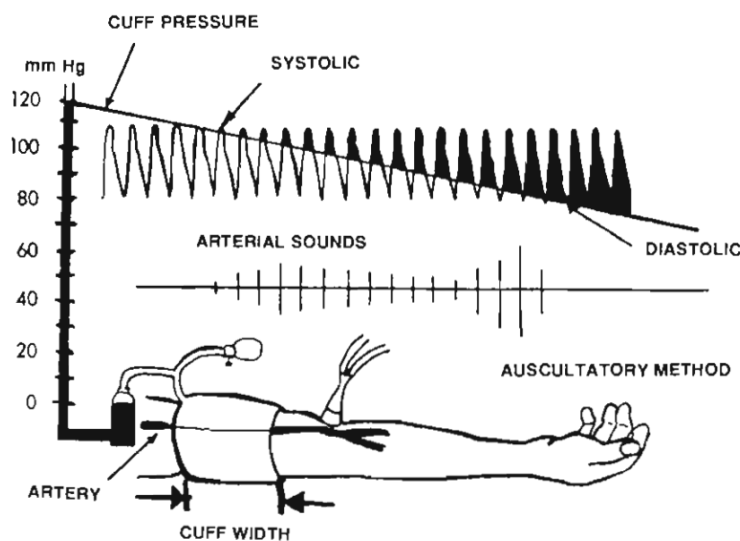


Figure 14: Schematic of Auscultatory method. (Adapted from: O'Brien and O'Malley, 1991).

Overview

The physiological mechanisms of blood pressure are primarily controlled by the cardiovascular and renal systems. The genesis of blood pressure is due to the contraction of the ventricles in the heart and the pushing of blood against the vessel walls. Variables such as viscosity of the blood and general morphological size of the vessels (shown above in Equation 2) can have a significant impact on blood pressure. Hormones associated with the renal system account for the regulating homeostatic levels of blood pressure. An increase or decrease in osmolarity in the blood can initiate a physiological reaction to correct for such changes. ADH (vasopressin) is released in the event of a decrease in water concentration in the blood, and acts to adjust these levels back to normal. Aldosterone, part of the R-A-A system, is released in the event of low sodium levels in the blood, and acts to increase reabsorption to compensate for the loss. Blood pressure changes can be measured by several methods, two of which are the Palpatory and Auscultatory. It is quite evident that there are physiological and hormonal factors that contribute to variability of blood pressure among individuals; an important question is what other factors contribute to population differences in the frequency of hypertension. With this purpose in view, the next chapter will review the issues of the pre-natal environment and race/ethnicity.

CHAPTER 3: STUDY OF LOW BIRTH WEIGHT, RACE/ETHNICITY, & HYPERTENSION

Birth Weight & Hypertension

Introduction

Previous investigations based on the association of low birth weight and post-natal environment have postulated that differences in the pre-natal environment leading to variability in birth weight can be associated with differences in the risk of acquiring the metabolic syndrome, which includes a cluster of chronic diseases such as hypertension, diabetes type II, and high cholesterol. Specifically these studies have postulated that low birth weight may be an important factor that contributes to the increased risk of hypertension among adults. With this purpose in view, I have analyzed the anthropometric and cardiovascular data sets from the National Health and Nutritional Examination Survey (NHANES) conducted during 2007-2008.

Methods

NHANES 2007-2008 data was collected across the United States and used several different questionnaires for various purposes. The SPSS computer program was used for analysis purposes. Because NHANES uses cluster sampling, some populations may be over-sampled or under-sampled; therefore I specifically used the complex samples version of the SPSS program. Complex samples utilizes different weights that correlate the data to represent the entire United States population and thereby corrects for over/under sampling.

Results

Table 1 shows that 6.7% of Caucasians had low birth weight (birth weight < 5,5 lbs)., 14.6% of African Americans had low birth weight and 7.6% of Mexican Americans were of low

birth weight. Among African Americans only 2.7% of those born with low birth weight had hypertension while among both Caucasians and Mexicans no one of those born with low birth weight had hypertension.

A logistic regression was attempted between birth weight and hypertension with a race/ethnicity variable, however it did not work. The sample size of birth weight was too small and there was too much missing data. However, from the crosstabs analysis, African Americans were the only population to have low birth weight and hypertension. There could be some kind of relationship between birth weight and hypertension, however more complete data is needed.

Discussion and Health Implications

Contrary to previous assumptions the present study demonstrates that only a small percentage (2.7%) of African Americans ended up having high blood pressure. cases present are found in low birth weight African Americans. The implication of this finding is that IUGR or fetal programming accounts for a small proportion of individual's with high blood pressure. This interpretation that IUGR is not a major factor contributing to high blood pressure is supported by the finding that no Whites or Mexicans with low birth weight were hypertensive

Low birth weight, due to improper nourishment during pregnancy can be caused by numerous factors. The mother's socio-economic status could play a role, specifically the mother's access to proper nutrition. The term socioeconomic refers to an individual's ethnicity/race coupled with their fiscal standing within society. Census information states that African American households on average have the lowest mean income at \$30,134. Caucasians ranked the second highest with \$48,977 while Hispanics were second lowest with \$34,241. It is evident that African Americans on average have a low socioeconomic status.

Many metabolic disorders such as diabetes and hypertension are linked to a socioeconomic gradient; with those in low standing are at a greater risk for developing say hypertension. Furthermore, many of these metabolic disorders can be traced to the type of dietary intake. High quality foods such as whole wheat breads lean meat, and fresh fruits and vegetables are most often consumed by people with a high socioeconomic background. Low quality foods such as refined grains/sugar and fatty meats are most often consumed by people with low socioeconomic backgrounds. Factors such as education and accessibility to nutritious foods are key to understanding why this pattern of behavior occurs. High quality food is more expensive and harder to find in low socioeconomic neighborhoods. Most supermarkets are located closer to “richer” areas and are harder to access by the lower classes (Darmon & Drewnowski, 2008).

Pregnant women living in a low socioeconomic neighborhood have a greater tendency to consume low quality food that can ultimately impact the fetus. The mother’s diet determines the nutrients available for the fetus; therefore as mentioned previously, a lack of nutrients during pregnancy can cause IUGR. One study claimed that African-American women consumed only 19% and 37% of the daily-recommended servings of fresh fruits and vegetables respectively. IUGR and maternal diet are most likely associated in some manner. Further longitudinal studies should be conducted researching maternal diet and status of hypertension of offspring later in life.

It is known that a consistent diet that includes fruits and vegetables can protect against hypertension. This information can help to resolve an interesting observation in the data; only low birth weight African American babies developed hypertension and none of the Caucasian low birth weight babies. Although the low birth weight white babies were born as potentially

IUGR, they did not develop hypertension due to possibly being born into a high socioeconomic family. Therefore, eating nutrient rich high quality food could have offset the risk for developing hypertension. On the other hand, African American low birth weight babies may have been born into low SES neighborhoods and may have grew up on a low quality energy dense diet that helped them to develop hypertension (Henry *et al.*, 2006).

Race/Ethnicity & Hypertension

Results

Using an SPSS Complex Samples logistic regression analysis, I was able to find a statistically significant relationship between race/ethnicity and hypertension. Table 2 shows the relationship as having a p value = 0.03, which is statistically significant (p value < 0.05). The odds ratio between Mexican Americans and Caucasians was 1.662 while between African American and Mexican Americans was 2.093. This means that the association of race/ethnicity and hypertension was greater between Mexican Americans and African Americans.

Discussion

Blood pressure can be affected by many factors that include genetics, natural selection, socio-economic status, etc. Previous studies have shown that ancestry contributes to variability in blood pressure. Some populations have been selected for by different variables that influence their present day state. For example certain hypertensive alleles such as AGT 6-A are more common in specific populations such as Africa. This allele expresses angiotensinogen, which is part of the RAA system described in the second chapter. These adaptations were beneficial in the hot African climate, where prolonged sweating can lead to a loss in electrolytes such as sodium, and ultimately lower blood pressure. Therefore it is probable that current day African

American have higher blood pressure due to their physiological and genetic ancestral adaptations. This claim is supported by the data analysis.

It is commonly reasoned in the medical field that African Americans are more likely to develop hypertension when compared to Caucasians. The data analysis supports the statement that one's race/ethnicity can determine the chance of that person being hypertensive or not. According to Table 2, there was a higher chance of African Americans having hypertension compared to Mexican Americans and Caucasian Americans. Furthermore, the odds ratio of the logistic regression shows that the relationship between race/ethnicity and hypertension is best seen between African American and Mexican American populations.

Overview

In summary, despite all the environmental factors that reduce birth weight the present study demonstrates that intra-uterine-growth-retardation is not a major factor that contributes to hypertension amongst African Americans. However, the fact that nearly 35% of African American blacks are known to have high blood pressure in the United States is probably related to other factors influencing either the pre-natal or post-natal environment may contribute to this high incidence. The mal-nourished pre-natal environment could be a consequence of socio-economic factors that affect the mother. It is also known through studies that African American have a lower house-hold income than Whites and other populations, as well as a insufficient access to high quality food. These factors can potentially negatively affect a pregnant mother's capability to provide proper nourishment for the fetus. Race/ethnicity was significantly linked to hypertension, with African-Americans having the greatest odds to have hypertension compared

to Mexicans or Caucasians. Evolutionary and genetic factors contribute to this finding due as previously stated.

Table 2. Frequency of Birth Weight among Caucasian, African Americans, and Mexican Americans (derived using cross tabs analysis and SPSS).

Race/ Ethnicity	Total Sample Size (# of people)	Percent with Low Birth Weight (<5.5 lbs)	Percent with Average Birth Weight (5.51-7.7 lbs)	Percent with Large Birth Weight (7.71-9.98 lbs)	Percent with Very Large Birth Weight (>10 lbs)
Caucasian	394	6.7 %	52.5%	38.6%	2.2%
African American	336	14.6%	58.1%	25.2%	2.1%
Mexican American	329	7.6%	57.9%	31.2%	3.4%

Table 3. Frequency of Low Birth Weight among Caucasian, African Americans, and Mexican Americans (derived using cross tabs analysis and SPSS).

Race/ Ethnicity	Total Sample Size (# of people)	Percent with Low Birth Weight (<5.5 lbs)	Percentage of Low Birth Weights with Hypertension
Caucasian	394	6.7 %	0%
African American	336	14.6%	2.7%
Mexican American	329	7.6%	0%

Table 4. Chance/ Odds of developing hypertension among Caucasian, African Americans, and Mexican Americans (derived using logistic regression analysis and SPSS).

Race/Ethnicity Comparisons	Odds Ratio	Significance (p-value)
Caucasian vs. Mexican	1.662	0.03
African American vs. Mexican	2.093	0.03

CHAPTER 4: SYNTHESIS

Introduction

The origin of hypertension stems from a multitude of factors ranging from adaptation and genetics to growth and development. An understanding of the factors that contribute to the variability of blood pressure is of paramount importance to studies of health and human diversity.

Genetic and Evolutionary Roots

Human evolution provides insight into how a hot tropical climate shaped our evolution and physiological mechanisms to favor salt retention and high blood pressure. Further evidence from genetic studies shows how certain populations of human, specifically those of African descent, have a higher frequency of hypertensive alleles. One such allele, AGT (6-A) affects Angiotensinogen, a prohormone that is directly involved in the Renin-Angiotensin-Aldosterone axis. These physiological mechanisms account for an increase in blood pressure; therefore the AGT (6-A) allele is hypertensive in nature. Furthermore latitude has a direct correlation with hypertensive alleles, proving that various populations have adapted to different selective pressures in their respective environments. The importance of genetic influence on hypertension was further supported by studies done by Dr. Frisancho in Bolivia. However, other factors involving growth and development must be analyzed as well.

Growth and Development

The condition of the pre-natal environment is crucial to the potential development of hypertension later on in life. Epigenetics has provided insight of environmental factors can affect DNA. A poor pre-natal environment according to this view can alter the way a fetus is genetically and metabolically programmed. This concept is further explained by the thrifty phenotype hypothesis. A fetus that is exposed to a low nutrient environment can adapt by altering certain physiological mechanisms. For example, blood can be re-routed to focus on major organs like the brain or heart. This can cause certain organs and tissues to not receive enough nutrients for adequate growth that can result in intra-uterine growth retardation (IUGR) and ultimately low birth weight. However, IUGR can impact an individual's life more so if they are born into a mismatched environment that is not similar to the pre-natal environment. In other words, the pre-natal efficiency that helped the fetus to survive under conditions of under nutrition becomes detrimental when the conditions are good. The concept of low birth weight being linked to hypertension was exemplified in the Dutch famine study, that show those conceived during the famine were of low birth weight but during adulthood had higher risk of hypertension. Growth and development from childhood to adulthood brings about dramatic changes in an individual's body. Certain periods of growth result in an increase in body and kidney size. However the kidney follows a sigmoidal growth pattern, which indicates its growth ultimately, lags behind the body. As a consequence of this mismatch the small kidney cannot keep up with the large body size and blood pressure increase throughout one's lifetime. Furthermore, physiological milestones such as the age of adrenarche and menarche can drastically change blood pressure of individuals. The physiological mechanisms behind blood

pressure are crucial for better understanding of how exactly blood pressure is generated and regulated by the body.

Physiological and Hormonal Control

Blood pressure is generated by the contraction of the ventricles, two muscular chambers of the heart, and by the pushing of blood against the walls of blood vessels. Many factors such as viscosity, and length of the vessel can impact the resistance of blood pressure and ultimately the flow of blood itself. Systolic blood pressure is generated by the contraction of the ventricles and the pumping of blood out of the heart and into the pulmonary artery and aorta. Diastolic blood pressure is generated by the relaxation of the ventricles and blood filling the ventricles; this tends to be lower than systolic because lack of contraction. The normal systolic to diastolic blood pressure reading is 120/80. Hypertension is defined by having a reading of 140/90. The actual control and regulation of blood pressure is done by the renal system through a series of hormones. ADH (vasopressin) allows for the increase of blood pressure due to water loss. The R-A-A system and ultimately Aldosterone allows for the increase of blood pressure due to salt loss. The concepts of physiological mechanisms coupled with the understanding of the variability of blood pressure in different populations provides a solid foundation from which further studies can be conducted. In my study, I was interested in the effect of low birth weight on hypertension, and the effect of race/ethnicity on hypertension.

Present Research

In view of the fact that several studies indicated that intra-uterine growth retardation may be an important factor that contributes to the high blood pressure of African Americans. In the present research I analyzed the anthropometric and blood pressure data of the fourth Nutrition

and Health Examination Survey of the US conducted 2007-2008. Analysis of the data, (using SPSS), indicate that 14.6% of African Americans had low birth weight (birth weight less than <5.5lbs) of those with low birth weight only 2.7 percent are hypertensive. This finding indicates that negative pre-natal environment inferred from the low birth weights plays a small role in the high frequency of hypertension found amongst African Americans.

In terms of race/ethnicity the data analysis indicates that African Americans for some reason have a higher chance of developing hypertension in adulthood than Caucasians or Mexican Americans. Hypertension has many variables ranging from genetics to growth and development. No one factor can fully predict whether someone will have hypertension or not. It is instead important to analyze all of the factors when assessing the variability of blood pressure amongst different populations.

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