THE HYPERTENSIVE OUTCOMES OF CHILDREN WITH LOW BIRTH WEIGHT IN UNDERDEVELOPED AND DEVELOPING COUNTRIES: A SYSTEMATIC LITERATURE REVIEW

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A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in Partial fulfillment of the requirements for the degree of Masters of Arts in the Department of Anthropology in the Graduate School

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ABSTRACT:

Anthony San Luis: The Hypertensive Outcomes of Fetal Growth-Restricted Children in Underdeveloped and Developing Countries: A Systematic Review.
(Under the direction of Dr. Fatimah Jackson)

Adult hypertension and Low birth weight (LBW) continues be an ongoing global concern. However, an increasing number of children in poor, low-income areas in underdeveloped and developing countries are exhibiting conditions characteristic of hypertension. Barker’s fetal origins framework hypothesizes that hypertension (and other cardiovascular and metabolic diseases) is a deleterious adaptation by the fetus as a result of restricted intrauterine growth stemming from maternal undernutrition that affect the functionality and structure of key organs responsible for blood pressure regulation while also remaining small resulting in LBW or being born small. This paper will systematically review contemporary literature that discuss hypertension and other associated risk factors as an outcome of LBW among children from underdeveloped and developing countries and will conclude with recommendations that attempt to assist future research efforts.
ACKNOWLEDGEMENTS

I would like to thank my committee for making this M.A. thesis possible. Their patience and superb guidance cannot be overstated as I finally complete this process. Their input and suggestions allowed me to significantly improve the numerous versions of this thesis leading up to completion. I am fully aware that I came here to this program with certain areas in need of improvement to succeed. I now feel like I will be leaving this institution with not only a stronger academic skillset but personal growth as well. For that, I am truly grateful for your contributions as they will never be forgotten.
# TABLE OF CONTENTS

LIST OF ABBREVIATIONS ........................................................................................................ vi

INTRODUCTION – Description of Problem ......................................................................................... 1

AIMS AND PURPOSES ............................................................................................................................ 6

Review of Relevant Literature: .............................................................................................................. 6

  Theoretical Framework: Fetal Origins as the Basis for Systematic Analysis .......................... 6

  Figure 1 - Effects of nutritional Interruptions during Prenatal Development ...................... 10

  Figure 2 - Alterations in Kidney Function during Nephrogenesis ................................. 12

  Previous Applications of Barker’s Framework in Retrospective Birth Cohort Studies ........... 14

  The Failures of Public Health Interventions in Developing Countries Endemic with LBW ....... 15

METHODS ............................................................................................................................................. 17

  Search Strategy of Literature Related to the Effects of LBW on Blood Pressure Regulation ...... 17

  Inclusion and Exclusion Criteria: ................................................................................................. 17

RESULTS ............................................................................................................................................... 19

  Figure 3: Flow Chart of the Article Selection Process ............................................................... 20

  Table 1 Characteristics of six studies selected for review (2009-2013) .................................. 20

DISCUSSION- Results of Systematic Literature Review ................................................................. 22

  The Effects of LBW on Blood Pressure in Latin American Children ...................................... 22
The Impacts of Being Born Small among South Asian Children......................................................... 25

Infectious Diseases Impact on Blood Pressure and LBW among African Children:....................... 26

CONCLUSION .................................................................................................................................. 28

Limitations: ....................................................................................................................................... 28

Future Challenges: ............................................................................................................................. 30

Recommendations............................................................................................................................... 33

Concluding Remarks: ......................................................................................................................... 34

REFERENCES.................................................................................................................................. 36
LIST OF FIGURES

Figure 1 - Effects of Nutritional Interruptions during Prenatal Development………………17
Figure 2 – Alterations to Kidney Functions during Nephrogenesis…………………………19
Figure 3 - Flow Chart of the Article Selection Process………………………………………25
Table 1 - Characteristics of six studies selected for review (2009-2013)…………………26
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVDs</td>
<td>Cardiovascular diseases</td>
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<tr>
<td>LBW</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>MeTs</td>
<td>Metabolic syndromes</td>
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<tr>
<td>NCDs</td>
<td>Non-communicable diseases</td>
</tr>
<tr>
<td>NHRC</td>
<td>The Nepal Health Research Council</td>
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<tr>
<td>WHO</td>
<td>The World Health Organization</td>
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INTRODUCTION – Description of Problem

In 1969, the United States Surgeon General William Stewart boldly declared it was “…time to close the book on infectious disease as a major health threat…smallpox, bubonic plague, and malaria were things of the past” (Armelagos et al. 2004). However, in under a half century, non-communicable diseases (NCDs) would eventually replace infectious diseases as the larger concern going forward mostly impacting those living in impoverished areas of Asia, Latin America, and Africa. In 2010, cardiovascular diseases (CVDs), metabolic syndromes (MeTs) and their associated risk factors (e.g., obesity, type-2 diabetes, hypertension, etc.) were tied to more than 17 million (30%) of deaths worldwide (Stuckler and Basu 2011). Furthermore, the World Health Organization has shown mortality rates linked with CVDs and MeTs in Asia, Africa, and Latin America now rival Western Europe and the United States (WHO 2008).

Historically, recorded incidence and mortality rates associated with NCDs accounted for a small percentage of total deaths. That all changed in 1920 where NCD-related deaths started to become clearer and more distinct end of World War II (Omran 1971). In Zimbabwe, for example, the probability of an individual having a cardiovascular event rose by 270% within a seven-year period in the early 1990’s; in Chile, within a ninety year period (1909-1999), the total death count from infectious disease was cut by more than half (1909 = 46.6% versus 1999 = 20.9%) while cardiovascular-related deaths have more than tripled (1909 = 14.8% versus 1999 = 53.2%) (Mefunda et al. 2006; McMichael 2001).
One of the most pervasive NCD’s, hypertension, is a significant contributor to premature deaths in Latin America, Asia, and Africa. Rates of hypertension have sharply risen in the last couple of decades tremendously contributing to the global burden of disease significantly (Chobanian et al. 2003). Health care professionals in developed countries have been successful in lowering morbidity and mortality as a result of early screenings and cost-effective medications, yet the increase in prevalence is still proving to too difficult to address. By definition, hypertension is the force against the arterial walls that is measured when blood pressure exceeds 140/90 mmHg or higher, making it one of the main risk factors of chronic renal failure and CVDs (Wright and Hammonds 1999). In countries in the midst of economic development or lack thereof, young children at various ages are showing signs of disease risk prior to adulthood. This is alarming because in general, people in poor, low-income countries mortality tends to occur at younger, economically productive age than their counterparts in developed countries (Stuckler and Basu 2011). This increasing death toll is attributed to outcomes of coronary heart disease and high blood pressure that have also parallel previous studies among Western European adults exposed to harmful maternal behavior (i.e., undernutrition and smoking) that have given birth to Low birth weight (LBW) offspring (see Osmond et al. 1993; Godfrey and Hanson 2010).

Children with LBW (≤2500g as per the WHO) in underdeveloped and developing countries are displaying symptoms of hypertension and other related conditions. The inverse relationship between hypertension and LBW has been illustrated in previous studies among adults (see Barker et al. 1989; Barker et al. 1989). UNICEF estimated there were more than 20 million LBW infants in 2004, while the World Health Organization currently estimate there are close to 30 million LBW infants (WHO 2013). Africa, Latin America, and Asia
have the highest concentration of LBW children with India alone accounting for close to 40% of the world’s total burden of LBW infants, where incidence is estimated to be 7837 per 1000 (UNICEF 2004). Another UNICEF report estimated the incidence of LBW among Brazilian children to be 361 per 1000, 169 per 1000 in Nepal, and 104 per 1000 in Nigeria (2004).

Various disciplines such as, genetics, or evolutionary biology have attempted to understand this rise in hypertension while others have tried to understand it as a product of demographic changes (see Ahmad et al. 2005; Jenkins 1976; Hall 2003). Abdul Omran’s description of not just hypertension but all NCDs is that they are linked to increases in life expectancy due to demographic transitions (1971). His third stage, the Age of Degenerative and Man-Made Diseases, occurs when mortality from infectious diseases continues to decline and approaches a low level of stability creating an environment for CVDs and MeTs, such as hypertension, to emerge and proliferate (Omran 1971). Additionally, transitions in nutritional patterns provide another facet for explaining describing rises in hypertension, especially in underdeveloped and developing countries among low-income, resource-poor populations.

Changes in behavior, such as physical activity, and more importantly, changes in diet lead to an increased consumption of nutritionally inadequate, calorically-dense foods abundant in carbohydrates and fats (Popkin 1993).

The fetal origins hypothesis is another view that attempts to understand adult hypertension as a result of behavior and environment. For the most part, applications of the fetal origins framework hypothesize that adult cardiovascular or metabolic outcomes are responses to fetal or neonatal exposures to stressors or stimuli (i.e., inadequate maternal nutrition, famine, smoking, etc.). David Barker (1993; 1995) posited that the origin of
hypertension can be traced back to early stages of human development. Functional changes to blood pressure regulating organs such as the kidneys and the vascular tree are outcomes determined by events occurring during fetal development (Barker 1993; Godfrey et al. 1994; Barker 1995; Osmond and Barker 2000). A 2000 observational study examined the relationship between ages of three and six years of age in developing countries (i.e., China, Guatemala, Chile, and Nigeria) (Law et al. 2000). Several other studies followed, producing several concepts that added to the collective knowledge that children of various ages groups who were born small were at risk of developing high blood pressure in their present environment is nutritionally adequate but also dissimilar to an exposure to adverse environmental conditions (i.e., maternal nutritional patterns) during the early stages of development (see Law et al. 2000; Adair et al. 2001; Adair and Cole 2003).

Adult hypertension can be viewed as a response stemming from environmental driver like maternal undernutrition producing inadequate growth marked by LBW (Barker et al. 1989). In another study, Barker identified a relationship between fetal growth patterns and high blood pressure in later life (1992). Barker’s work showed infants that were born small because of nutritional deprivation were more likely to become hypertensive as an adult (Barker 1992). As a result, he concluded hypertension is programmed by an adverse environment in utero (i.e., nutritional deficits, smoking and alcohol consumption), where impaired development in early and late gestation was likely to produce high systolic blood pressure. Conditions in developing and underdeveloped regions create an environment of nutritional deprivation that is driven by poor social conditions, infectious disease, and resource availability, resulting in hypertension in adulthood.
While Barker’s fetal origins hypothesis is used to describe and explain the factors that lead to adult hypertension among Western Europeans, its application to pediatric hypertension among the poorer populations in developing and underdeveloped countries is also appropriate. Within these countries’ impoverished settings, limited nutritional resources create adverse environments for hypertension precursors to develop and proliferate such as maternal undernutrition that produce LBW offspring with dysfunctions in physiological mechanisms responsible for blood pressure regulation. Children in Asia, Latin America, and Africa can be looked at as being exposed to harsher conditions with potentially more powerful determinants producing hypertensive conditions in childhood not found in adults from developed countries (Barker et al. 1989; Barker 1997; Gluckman and Hanson 2006).
AIMS AND PURPOSES

This systematic review will show that an increasing number of children who were born small in poor, low-income areas in developing and underdeveloped countries are exhibiting physiological conditions associated with hypertension. Hypertensive conditions such as microalbuminuria, the occurrence of albumin leaking into urine, and nocturnal dipping, the lack of blood pressure decreases that occur during normal sleep cycles have been found in LBW children in underdeveloped and undeveloped countries. Furthermore, children face an increased risk when born small in a country riddled with infectious diseases, namely areas in Africa with endemic mosquito-borne malaria that negatively influence maternal health and reduce birth size. This review will discuss the historical and current patterns of chronic diseases in order to show the epidemiological shifts and transitions leading to the global disease burden of hypertension are more prevalent among children in developing and undeveloped countries. This analysis will outline and review the various methods researchers use to assess the risk of hypertension among children in developing countries. Additionally, this paper will examine and discuss gaps and deficiencies in the field with recommendations for future research.

Review of Relevant Literature:

Theoretical Framework: Fetal Origins as the Basis for Systematic Analysis
The fetal origins hypothesis posits that the origins of NCDs, such as hypertension, in adults arise in response to being small at birth because of dissimilar nutritional environments experienced during early stages human development than environments experienced in adulthood. This framework further hypothesizes fetal undernutrition resulting from poor maternal diet nutrients transferred to the fetus, predisposing offspring to high blood pressure and other cardiovascular conditions (Fall 2013). Specifically, an individual is likely to physiologically respond to normal nutritional environments excessively after having experienced nutritional deficits during fetal development. Depending on the region, children are subjected to environmental conditions, such as maternal malaria influencing birth weight, thus increasing their risk of hypertension in childhood.

Before the arrival of agriculture, humans rarely developed hypertension because of shorter lifespans. The link between chronic, non-infectious disease and the environment was originally posited by James Neel’s Thrifty Genotype hypothesis. He proposed that evolutionary processes selected for metabolic changes in favor of the production of glucose-insulin. According to Neel, theoretically, early human genetics selected for metabolic thrift to efficiently maximize nutrients by storing excess calories as fat for survival purposes during periods of food scarcity was therefore, advantageous for early hunter and gatherer populations have shifted to become maladaptive in current contexts (Neel 1962; Adair and Prentice 2004).

Barker used Neel’s central idea of “thrift” as the backdrop of his fetal origins model. In what would be known as the Hertfordshire Cohort Study, Barker et al used evidence from ecological studies in the 1980’s to investigate a geographical correlation between living men and women born in Hertfordshire, U.K. during the 1930’s and the death rates from coronary
heart disease in various parts of England and Wales with infant mortality in the same areas sixty years earlier (Syddall et al. 2005). His landmark Hertfordshire Cohort study demonstrated a link between coronary heart disease and LBW in offspring who endured inadequate maternally supplied nutrition, maternal smoking and alcohol consumption (Barker and Osmond 1986). The Hertfordshire Cohort Study showed LBW was a product of the maternal behaviors exposing their offspring to future risk of cardiovascular conditions (Barker et al. 1989; Barker and Osmond 1986). Out of 7109 living men and women registered for the study, 6099 men and women that were small at birth and during infancy were recruited for this study using hospital records (Barker and Osmond 1986; Syddall et al. 2005). Out of this study, other investigations demonstrated the negative impact of adverse environments (e.g., maternal smoking, maternal undernutrition, and maternal alcohol consumption) that produce an increased risk of developing adult coronary heart disease, impaired glucose tolerance, ischemic heart disease, and hypertension (Barker and Osmond 1986; Barker et al. 1989; Hales et al. 1991; Barker et al. 1993; Barker 1995; Barker 1997). Overall, the studies yielded from the Hertfordshire Cohort Study were able to link cardiovascular outcomes later in life when exposed to harmful events experienced in utero and during infancy.

Furthermore, the fetal origins hypothesis depends on an individual’s predictive adaptive responses (PARs) during windows of developmental plasticity (when a system is most vulnerable to a stimulus). Developmental plasticity is a range of phenotypic characteristics and features that originate from a single genotype with the capability to express multiple phenotypic responses (LBW in Barkers model) to the environment (Gluckman et al. 2010). PARs often occur during windows of developmental plasticity (i.e.,
pre-embryonic, embryonic, fetal, and early postnatal stages) as projected responses to a range of future environmental conditions (Gluckman and Hanson 2006). The nature of a response is dependent on a confluence of factors, including type, intensity of a given environmental cue, the windows of plasticity, and chronological sequence of events. Responses by children born small are stimulated by the preservation of inadequate nutrient supply, thus programming the physiology of the kidneys and vascular structure to misinterpret appropriate caloric amounts as adversely abundant. When developing in such an environment, the fetus implements a tradeoff to ensure survival in order to best utilize the limited nutrients supply through adaptive programming that keeps the fetus small.

Also, the fetal origins hypothesis relies on the processes associated with prenatal growth. Reduced or inadequate maternal nutrition greatly decreases prenatal growth and overall growth potential because of a reduction in the size and quality of the intrauterine environment in which it develops. The embryonic period (or the first eight or nine weeks), while extremely critical, there are very little changes where there is little to no growth and the basic human form is established (Barker 1995). From this period onwards, the fetal period (starting at the nine to ten week mark) is where growth begins to take place (Barker 1995). In addition, restrictions on growth during the fetal period have dire effects on the development of organs at the cellular level. For example, cell growth and division becomes hindered as a result of a slowed production of insulin and growth hormone during critical windows of fetal development in the second and third trimesters (Barker 1999). This gestational period is impacted the most by maternal undernutrition, processes of growth are sensitive to perturbations in maternally supplied nutrients (Barker 1995). Between weeks ten to sixteen, most nutrient supply is dedicated to the brain and cranial development accounting
for close to half of the fetus’ size while the limbs and trunk develop soon thereafter (Fowden 2001). Figure 1 illustrates the normal curve of growth compared of body weight and the key organs affected during that period to demonstrate the windows of development that are influenced via intrauterine growth restriction.

<table>
<thead>
<tr>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Effects on Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td>When maternal undernutrition occurs so early, there is a slowing down growth trajectory.</td>
<td>Interruptions in the fetal nutrient supply during the first critical window of growth.</td>
<td>Fetus is nearing complete development but is undernourished.</td>
<td>LBW</td>
</tr>
<tr>
<td>The decreased blood and nutrient supply is dedicated to brain, where the head comprises close to half the size of the fetus.</td>
<td>Fetus remains small in size to adapt to the reduced nutrient supply.</td>
<td>Functionality of renal system and vascular structure not functioning at optimal level because of deficiencies in structural integrity.</td>
<td>Renal system and vascular structure are overworked when exposed to normal nutritional intake.</td>
</tr>
<tr>
<td>Organ structure does not achieve scheduled development.</td>
<td>Fetus doesn’t not achieve mature growth and it born small.</td>
<td>Exhibiting conditions indicative of hypertension as early as infancy and as late as pre-adolescence.</td>
<td></td>
</tr>
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</table>

**Figure 1 - Effects of nutritional Interruptions during Prenatal Development**

Outcomes of restricted fetal growth also impede the normal functionality of organs responsible for blood pressure regulation. Blood pressure is determined by several factors such as arterial blood volume, the arterial compliance, cardiac output (heart rate and stroke volume, the blood flow into the arterial system), peripheral resistance, and aging (Levy et al.
The kidneys and vascular tree are particularly sensitive to IUGR which negatively impacts their role in managing blood pressure. Kidney dysfunction stems from aortic blood flow dedicated to the brain at the expense of trunk and limb development, thus implicating the underdevelopment of the organs located in that area of the body.

As a result, LBW children are born with kidney impairments negatively impacting the system’s ability to appropriately stabilize blood pressure. Kidney size is reduced and the components of the nephron, the so-called “building block” of the kidney never achieve mature development (Moritz et al. 2003). This effectively produces a corruption in nephrogenesis lowering nephrons and glomeruli to under-develop and delay the activation of the fetal renin-angiotensin system (Copstead and Banasik 2005; Godfrey 2006). Sodium and water is then retained while potassium is not, thereby leading to unstable fluid homeostasis and increasing vascular volume and blood pressure (Shier et al. 2004; Moritz et al 2003). Figure 1 details the processes of intrauterine growth restrictions impact on nephrogenesis that lead to hypertension.
Figure 2 - Alterations in Kidney Function during Nephrogenesis.

Dysfunction in the vascular tree plays a key role in the pathophysiology of hypertension. Hypertensive changes are reflected in all levels of the circulatory system, making all structures from large arteries to microcirculatory structures vulnerable due to IUGR (Thom 1997). The circulatory system is vulnerable to developing arteriosclerosis and coarctation, or narrowing of the aorta (Copstead and Banasik 2005). Elasticity arterial wall and the endothelium-dependent vasodilation are blood pressure regulating mechanisms found to be compromised in LBW infants (see Ligi et al. 2010).

Impairments in the vascular tree where the role of the vasodilation and vasoconstriction mechanisms to control or maintain blood pressure is another biomarker for hypertension in LBW infants. Dysfunction in the vascular structure is considered a pathophysiology of hypertension and has been observed in young children with LBW, implicating this as another consequence of fetal programming (Ojeida et al. 2008). Two separate studies by Martin et al. (2000 and 2000) found that “healthy” children with LBW developed insufficient arterial wall elasticity characterized by carotid stiffness mitigating the ability to carry out endothelium-dependent vasodilation while also finding insufficient vascular responses to acetylcholine in LBW infants within three months. Carotid stiffness also mitigates the supplementation of L-arginine needed to stabilize vascular function and decrease blood pressure (Gokce 2004). Also, children born small are unable to mediate certain vasoactive substances, namely, nitric oxide. Inability to mediate nitric oxide increases shear stress, acetylcholine, histamine, and ATP which in turn, increases glomerular filtrate rate and renal blood flow (Martin et al. 2000; Levy et al. 2006). LBW infants are at risk of developing endothelial dysfunction of regulatory roles of coronary arterioles ability to dilate and maintain homeostatic processes that mitigate cardiovascular inflammation (Esper et al.
Abnormalities in the endothelium-dependent nitric oxide pathway is programmed because of restricted intrauterine growth due to maternal undernutrition (Ojeida et al. 2008).

Normal functions in the renal system and the vascular tree are obviously critical for stable blood pressure. Reduction in nephron number and impairments in the structure of arterioles ability to regulate blood pressure demonstrate a complex multifaceted depiction of the cardiovascular outcomes of LBW. Importantly, these conditions found in LBW infants precede the development of hypertension or hypertensive conditions, implicating hypertension as a childhood outcome of fetal programming.

**Previous Applications of Barker’s Framework in Retrospective Birth Cohort Studies**

A robust body of literature of human studies have shown the long term cardiovascular outcomes on health in individuals who were exposed to famines (e.g., the Dutch Famine, the Leningrad Siege, and the Great Chinese Famine) during fetal and neonatal development (see Stamner et al 1997; Ravelli et al. 1999; Roseboom et al 1999; Roseboom et al 2000; Huang et al 2010). Offspring born from mothers who faced profound nutritional and caloric deficits during the second and third trimesters of gestation were at the greatest risk (Stein et al 2006; Wang et al 2012). Survivors were more likely to develop coronary heart disease, obesity, more atherogenic lipid profiles, microalbuminuria and high blood pressure (Roseboom et al. 2000; Roseboom et al. 2006; Stein et al. 2006; Koupil et al 2007; Li et al 2011; Chen et al. 2013).
The Failures of Public Health Interventions in Developing Countries Endemic with LBW

As LBW continues to be one of the biggest concerns in the developing and underdeveloped regions of the world. Global organizations such as the United Nations, the World Health Organization, and UNICEF have deemed LBW one of the top priorities to address going forward. The promotion and subsequent implementation of nutritional interventions have struggled largely because of earlier-than-expected mortality rates associated with an increase in chronic disease incidence (see Sharma et al. 1991; Dewey et al. 1999; Hales and Ozanne; Min et al. 2007; Sharma et al 2010; Raj and Kumar 2010).

Encouraging catchup growth was one intervention that examined nutritional programming in children born small in developing countries (Fewtrell et al. 2001). However, evidence shows promoting weight gain in the first two years of childhood exacerbates cardiovascular risk by increasing high blood pressure, coronary heart disease, obesity, etc. among adolescents and adults (Victora and Barros 2001; Adair and Cole 2003). Among Western European adults, longitudinal and prospective cohort studies showed children who gained too much weight in the first two years of life have the same risks of cardiovascular diseases in later life, and developing earlier in some cases (Eriksson et al. 1993; Ong et al.2000). However, Adair and Cole (2002) showed the same pattern in a developing country where high blood pressure among Filipino adolescent boys was identified after experiencing catch-up growth during infancy. Chinese children also showed a similar relationship between acute postnatal weight gain and hypertension risk in childhood (Bowers et al. 2011). Acute growth in a short period of time overburdens organs (i.e., kidneys and vascular structure) by exceeding their functional tolerance. While such growth patterns produce linear
physical growth, at the same time, organs responsible for blood pressure regulation are forced to work beyond normal functioning capacity to adapt to these rapid changes.
METHODS

Search Strategy of Literature Related to the Effects of LBW on Blood Pressure Regulation

PUBMED, Google Scholar, and the UNC-CH library’s online databases were used for article selection. The aim of this review was to provide and demonstrate the contemporary relevance when Barker’s fetal origin hypothesis was applied to investigating hypertensive children with LBW in underdeveloped and developing countries. To achieve this, articles were selected from 2009 and later. Search terms “developmental,” “programming,” “blood pressure,” “LBW,” “hypertension,” “low income countries,” and “children” led to articles from all three databases. A search of review articles led to other chosen articles. This systematic review utilized a total of seven articles.

Inclusion and Exclusion Criteria:

To be eligible for inclusion, a study had to satisfy the following criteria: it must be an original report investigating the relationship of the impact of LBW on the blood pressure of children; it must have a publication date after January 2009; it must be a study concerning Asia, Africa, or Latin America; and it must only use children as subjects. Articles were excluded for the following reasons:

- The paper was a review or commentary article.
- There were no measurements of birth weight.
- The subjects were 18 years old or older.
• The abstract or title did not contain explicit information on birth weight, hypertension, and blood pressure.

• It had a publication date prior to January 2009.
RESULTS

All three databases yielded a total of 23,791 articles. Terms such as “developmental,” “programming,” “blood pressure,” “LBW,” and “hypertension” were used to filter results. Additional filtering for journal articles published after January 2009 was implemented for observing the current relevancy of the topic. To further reduce the selected articles, the term “children” was added and resulted in a decrease to 3041 articles. This was further reduced after adding “low income countries” to the search, resulting in 977 articles. A journal articles only filter was used to reduce and subsequently exclude abstracts, conference presentations, dissertations, and non-academic articles (i.e. newspaper, magazines, etc.). A manual search of the references and citations in a number of review publications was used to obtain additional original research articles. In total, fifteen articles were selected that reported the association between birth weight and risk of high blood pressure and hypertension among children.

A final total of six articles were selected for this systematic review. For the following reasons, eight articles were excluded from the 15 that were deemed appropriate for this systematic review:

- A collaborative study about metabolic disorders from birth cohorts in India and Canada (n=1).
- A comparative study measuring blood pressure of children who are underweight and normal weight without any data on birth weight (n=1).
- Subjects were from Northern Europe or the United States (n=3).
• Measured hypertension and blood pressure in adults who were exposed to severely deficient nutritional environments such as famine (n=2).
• Measured intergenerational influence on birth weight but not blood pressure (n=1).
• Study only focused on weight gain during early childhood (n= 1).

![Flow Chart of the Article Selection Process](image)

**Figure 3: Flow Chart of the Article Selection Process**

<table>
<thead>
<tr>
<th>Table 1 Characteristics of six studies selected for review (2009-2013)</th>
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<td><strong>Author</strong></td>
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<tr>
<td>Winder et al. 2010</td>
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<td>Pereira et al. 2010</td>
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<td>Stewart et al. 2010</td>
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<td>Salgado et al.</td>
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<td>Author</td>
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<tr>
<td>Ayoola et al. 2013</td>
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<tr>
<td>Salgado et al. 2009</td>
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DISCUSSION - Results of Systematic Literature Review

All studies reviewed relied on LBW as a determining factor identifying elevated blood pressure and its associated outcomes. The results of the systematic review indicate there are a number of effects present in children with LBW. Not only is LBW a programmed effect, but it further confirms its effects on the circulatory and renal systems in children and comes with additional susceptibilities to other conditions that predictably intensify future risk. Depending on the environmental or regional context, the presence of underpinning stressors, such as placental shape and size along with maternal malaria, increase the probability of being small at birth and subsequently engender elevated blood pressure in early life.

The Effects of LBW on Blood Pressure in Latin American Children

Three studies investigated the association between LBW and blood pressure in Latin American children. Similarities among Brazilian children of prepubertal age illustrated an inverse relationship between birth weight and blood pressure. However, studies differed in their proposed effect of LBW on Brazilian children. Pereira et al. (2009) studied the effects of LBW on blood pressure. Salgado et al. (2009) differed in their investigation from a temporal perspective on ambulatory blood pressure, and in another study, Salagado et al. (2009) examined microalbuminuria by examining albumin levels via urinalysis.
Pereira and colleagues study of children 5-8 years old in Jundiai City, Brazil also found blood pressure is inversely related to LBW. Their findings additionally suggest underprivileged areas of Brazil qualify as an adverse environments impacting maternal health, thus programming children to be born small. Elevated arterial blood pressure was found among the children studied, putting children at higher risk of becoming hypertensive earlier than young adulthood (Pereira et al. 2010).

Nocturnal dipping is another risk factor for future cardiovascular events commonly found in hypertensive adults (Clement et al. 2003; Fagard 2009). Nocturnal dipping increases susceptibility to cardiovascular or metabolic diseases a lot earlier in adulthood, possibly as early as late adolescence (Salgado et al. 2009). In the first study of its kind for investigating this outcome among children, Salgado et al. studied Brazilian children with LBW between the ages of 8-11. Studying ambulatory blood pressure, they found a causal relationship, 24-hour, daytime, and nighttime systolic blood pressures were higher in children with LBW compared to children with normal birth weight (Salgado et al. 2009). Nocturnal dipping was present, failing to a lower, more stable rate during normal rhythms of nighttime sleep, when blood pressure and heart rates should lower for normal recovery purposes. However it remains to be seen, if pubertal changes can alleviate this condition through growth and hormone changes.

In a separate study, Salgado et al. found children with LBW and elevated blood pressure were associated with the presence of microalbuminuria, the loss of albumin (2009). Once preterm children were excluded, albumin excretion remained high among the children who comprised the LBW group (Salgado et al. 2009). Kidney functionality plays a significant role in blood pressure regulation and microalbuminuria is identified as a
‘progression promoter’ of renal disease disrupting influences metabolic function (Vasarhelyi et al. 2000). Even low levels of microalbuminuria are associated with increased risk of cardiovascular and metabolic diseases and are particularly harmful for hypertensive adults where serum albumin keeps colloid osmotic pressure in blood (Høstmark et al. 2005).

This conflicts with a previous study by Genovesi et al. in 2011 that investigated microalbuminuria among Indian children and did not find any statistical significance of urinary abnormalities in children with high blood pressure. This difference may be due to specific factors that Salgado et al. measured among the Brazilian children that Genovesi et al. did not measure in Indian children. Salgado et al. included children with family history of hypertension (Genovesi et al. did not) as a potential intergenerational programming effect (2009). The findings presented in this portion of the systematic review conflict with a previous study in Pelotas, Brazil that shows once confounders have been taken into account, LBW is no longer a significant predictor of high blood pressure in adolescence (Menezes et al 2006).

Overall, the findings presented by Pereira et al. and Salgado et al. are especially important to the study of high blood pressure among children in low-income populations. Kidney malfunctions found in one population and not others exemplifies the need for further investigation.

The studies used in this analysis are geographically spaced far apart with Jundiaí City approximately 895 kilometers southeast of Goiânia in order to illustrate the overall health concerns among Brazilian children as a whole. Like any large country with high population density, Brazil has many isolated areas where children are likely experiencing metabolic and cardiovascular conditions resulting from nutritionally inadequate environments encroaching on windows of developmental plasticity that program the mechanisms responsible for blood
pressure management. Further study is needed in the rural and urban areas of Brazil to address the likely health concerns of younger Brazilian populations.

**The Impacts of Being Born Small among South Asian Children**

South Asia as a whole is experiencing an upward trend in hypertension prevalence (Sharma 2008). Within India, there is considerable variability in socioeconomic status within inter-geographical regions that do not share the same sense of advancement that is enjoyed by high-income populations in metropolitan areas. Socioeconomically-depressed areas have endured a high prevalence of high blood pressure in adults and children (Das et al 2004, Gupta 1997, and Gupta et al. 1995). Numerous studies indicate this trend will continue among Indian children and adolescents as a result of catch up growth program (Genovesi et al. 2011; Sharma et al 2010; Raj and Kumar 2010; Sharma et al. 1991).

Winder et al. examined the outcomes of placental size and shape resulting in LBW and elevated blood pressure in prepubertal children (2011). During critical periods of fetal development, placental surface is highly sensitive to various environmental stressors that directly program the function of blood pressure regulating systems. Low placental weight is a predictor of higher systolic blood pressure and LBW (Thornburg 2010; Barker and Thornburg 2013). Winder et al. found placental surface area has a programming effect on children’s systolic blood pressure, where differences in placental surface area were positively associated with systolic blood pressure between boys and girls. Higher systolic blood pressure was associated with smaller placental surface area in boys (2011). Additionally, this study also demonstrated the effects of placental shape when a larger difference between breadth and length, creating a more oval-shape, impacted systolic blood pressure in girls more than in
boys and also found higher systolic blood pressure in girls born small with larger placental surface areas (Winder et al 2011).

Nepal is another South Asian country struggling with hypertension. Nepal is endemic with isolated populations experiencing a wide range of health issues, as it is one of the poorest countries in the world with stagnant economic progress; it is experiencing high rates of CVDs (NHRC 2010). The Nepal Health Research Council (NHRC) performed a survey that found almost a third of its adult participants had some type of NCD (2010). While mortality and morbidity rates among adults have been documented by this survey, Nepalese children are emerging as an at-risk group for hypertension.

Stewart et al. examined cardiovascular and metabolic risk among Nepalese children. In one of the first pediatric studies performed in Nepal, Stewart et al. identified a similar inverse relationship between LBW and blood pressure among the children (6-8 years old) studied that were born small (2010). Folic acid was given to the mothers in this study in a previous supplementation program to reduce preterm birth (Scholl and Johnson 2000; Das 2003). As a result, the authors caution that folic acid could confound the results due to an observation that demonstrated that maternal folic acid supplementation reduced microalbuminuria but not blood pressure (Stewart et al. 2010). Further studies are needed to ascertain a clearer depiction of the effects of LBW on children’s blood pressure absent of such interventions.

**Infectious Diseases Impact on Blood Pressure and LBW among African Children:**

Many parts of sub-Saharan Africa are experiencing rises in non-communicable diseases. While African birth rates and crude death rates remain high, the rise of non-
communicable disease is afflicting younger populations as a result of deficiencies in maternal health due to infectious diseases. It has been posited that infectious diseases impose great limitations on human development as a result of trade-offs occurring when immune systems are forced to ward off infection at the expense of growth (Ewald 1994). Endemic malaria carrying mosquito-vectors plays a prominent role in producing offspring with LBW in Sub-Saharan African countries. Expecting mothers in areas rife with malaria are likely to have smaller children due to preterm delivery (Menendez et al. 2000).

Maternal malaria significantly impacts the size of offspring and blood pressure within the first year of life (Ayoola et al. 2011; 2013). Southwest Nigeria typically experiences year round instances of malaria. Ayoola et al. (2013) found within one year, infants from mothers with malaria have hypertension and increased systolic blood pressure. The results of this study highlight several long-term challenges that impede the success of future preventative efforts. For one, the impact of maternal malaria during the prenatal and gestational stages implicates an intergenerational effect that limits fetal and postnatal growth. Second, this study indicates the potential for populations in other areas where infectious diseases persist to experience a dual-burden risk of infectious and non-infectious diseases at various points in their lifecycles. Third, it is difficult to prioritize long-term health versus short-term survival, where it becomes a challenge for policy makers to navigate such an environment knowing there are long-term risks for a portion of the population who are able to survive through early bouts of malaria.
CONCLUSION

Limitations:

There are some limitations to this systematic review. One limitation is the repeated use of studies from Brazil. Similarly, past studies have measured the effect of birth weight among children in developing countries, which can reduce the novelty of this systematic literature review (see Adair et al. 2013; Martorell et al. 2009). Another limitation is the lack of diversity in the populations studied with groups from only four countries reviewed. This is because many other countries often focus on changes in blood pressure as an outcome of weight gain in early life in those born small, while this study focused on blood pressure in children who remained small throughout childhood.

An additional limitation is the small number of studies using human subjects. The majority of the literature on this topic derives from animal models that can control for potential confounders in a laboratory setting where programming effects can be observed with a short period of time (see Ozanne et al 1997). The challenge in observing the effects of early adverse environment among human subjects stems from measurement or design issues such as time-efficiency, attrition or relocation; therefore, only six articles found in the database search results fit the selection criteria.

Another limitation is being unable to generate a clear assessment of placental size and shape across all populations. The overreliance on birth weight as a measure of nutritional sufficiency becomes problematic because of inherent cultural and nutritional differences
across all populations that engender varying degrees of growth. For example, limitations on nutritional resources resulting from urbanization and sociocultural practices (i.e., stratification via the caste system) are region-specific stimuli that impact placental shape and birth weight (Das et al. 2005). Therefore, it has been suggested that a supply and demand model applied to maternally supplied nutrients and fetal demand would potentially reconcile the issues stemming from the overreliance on crude birth weight. A supply and demand model focusing on growth potential as its basis would account for factors beyond LBW to include not just maternal nutrient supply, but fetal nutritional demand, birth outcome, etc. The confounding variable in birth weight is growth potential and trajectory. If babies who were born small had the growth potential of normal weight babies, then birth weight as an index would be appropriate in predicting the probability that they would develop a non-communicable disease as an adult. Similarly, individuals born big from taller or naturally more robust mothers and have unmet growth potential are still exposed to the same disease risks of as an adult (Kuzawa 2004).

Modifications in birth weight assessment could accurately predict the risk of disease when comparing 1) small babies are born to tall mothers and 2) small babies born to malnourished mothers. For instance, people who have a high potential for fetal growth (high demand) but are born to poorly nourished mothers (low supply) are going to be at the greatest risk of disease; also, a baby who is considered small can still be a product of a nutritionally sound mother who is coincidentally small in stature (i.e. sitting maternal height) (Kuzawa 2004). Incorporating this model along with measurements of maternal health status, birth length, and body mass index can help further determine overall risk in infants of
undeveloped or developing regions who tend to be smaller in overall size than infants in more developed countries.

**Future Challenges:**

It will be difficult to alleviate these health concerns moving forward. Populations that continue to bear small children are susceptible to the ill-effects of the changes of rapid economic advancement, whereby goods such as nutritional products are mobilized throughout the world (Hunealt et al. 2012). Pinpointing the mechanism affecting human health and subsequent generations is extremely difficult in the face of rapid global changes. Underdeveloped and developing countries trying to keep pace with economic advancement and development create negative impacts on the cardiovascular and metabolic systems of their populations because of rapid changes in subsistence patterns. Presumably, there are broader, long-term economic effects from these early mortality and morbidity hypertension rates. The relationship hypertension and LBW infants and premature deaths negatively effects potential economic growth in these regions. An estimated 40% of deaths attributed to NCDs afflict those of working ages, which impacts the future sustainability of the workforce in poor, low-income countries (WHO 2009; Stuckler and Suhrcke 2011). In Brazil, for instance, premature death from heart disease and its associated risk factors, like hypertension, will have cost close to an estimated $49 billion in national income by 2015 (Matsudo et al. 2010). The early loss of primary wage earners in these countries can potentially set in motion a series of reactionary behaviors or actions, such as reduced education in favor of early employment to garner immediate income or changes in preferred diet towards more economic but nutritionally inadequate food choices.
During this process, transitions in nutrition and activity patterns directly impact pediatric populations in the areas examined, populations in underdeveloped and developing countries are now living longer and becoming more sedentary with easy access to an abundance of obesogenic food. On top of these changes at the population level, there are challenges that limit future success due to institutional instability.

Public health efforts to address the rise not just hypertension but all CVDs and MeTs have come up short, garnering merely short-term success or none at all. Children with LBW cannot avoid elevated blood pressure risk by increasing caloric intake. The implication of catch-up growth is a detriment to the long-term health of children as adults (Hales and Ozanne 2002). Conflicts exist on the efficacy of nutritional interventions that encourage weight gain among children born small. While others found cardio-protective effects and socioeconomic gains (i.e., improvements in schooling achievements) for weight gain in five birth cohort studies in five developing countries (Brazil, Guatemala, India, the Philippines, and South Africa) along with gains in height and improved schooling outcomes (Adair et al. 2013).

Aging and lifespan increases are one aspect of modernization that aligns with certain aspects of Omran’s third transition. Aging and blood pressure are positively related to one another, and populations are at greater risk as they continue to shift their activities towards sedentary lifestyles. Acculturation of the “Western” lifestyle has given a high-reward in the interim providing access to seemingly vast food resources as a result of increased income; at the same time, this type of excess living puts populations at high-risk future of becoming hypertensive due to a perceived excess in food over the long term (Popkin 1993; Angeli et al.
2013). More and more, underdeveloped and developing countries willingly participate in these promising efforts under the guise it will provide socioeconomic benefits.

The political-economic climate in the countries studied in this review is another challenge. The intersection of health policy makers and private sectors have garnered negative attention for prioritizing profitability at the expense of those in need of proper medical care. Vitamin A supplementation programs in India come to mind, where proponents claim the program is one way to prevent night blindness and other diseases associated with vitamin A deficiencies (Sommer 2008; Rotondi and Khobzi 2010). However, opponents of universal vitamin A supplementation argue there is no longer a need for such a program because these conditions are no longer a looming concern, and any effort to continue supplementation is to behoove private companies and policy makers only for profit, thus marginalizing those who are in the most need (Latham 2010; Gopalan 2010; Kapil 2004).

The dilemma of the dual-burden disease risk is another obstacle that impedes many efforts to combat LBW. Infectious diseases produce outcomes that are difficult to address since many of these conditions surface during the early stages of postnatal development. The challenge is prioritizing the treatment and prevention of NCDs over that of infectious diseases especially in countries with limited resources to effectively prioritize one disease over another. Another obstacle is the difficulty of creating and executing a successful long term strategy for addressing the hypertensive outcomes associated with LBW. However, it is critical to remain focused on short-term survival because of the substantially higher mortality rates associated with infectious diseases while NCDs can be somewhat mitigated by through modifications in diet and physical activity. Unfortunately, the health concerns exist now, and
any intervention, if successful, will not be felt for many generations, at a rate which conflicts with the instantaneous and streamlined production of results that is often demanded.

**Recommendations**

All too often, many attempts to address NCDs focus on the healing or treatment once the disease has been acquired as opposed to prevention. The cultural and geographical landscape paired with the intergenerational aspect presents a difficult challenge, highlighting the importance of focusing on future generations. A long-term intergenerational strategy pinpoints at-risk mothers likely to have LBW offspring. An emphasis on maternal and postnatal nutrition, stressing the quality of diet eliminates issues encountered by other interventions such as rapid weight gain or increased caloric intake during early childhood. To address the long-term nature of high blood pressure increasing among children, the World Health Organization has proposed a life-cycle approach (2003). This approach focuses on the improvement of health between successive generations, ensuring optimal pregnancy outcomes through systematic nutritional improvements through education and access to healthy food helping young women throughout the various stages leading up to pregnancy and giving birth (WHO 2003).

In addition, a reframing of the problem is needed to develop a deeper understanding of the cultural and societal elements reinforcing hypertensive mechanisms. This requires a collaborative effort between global institutions and local public health sectors to develop and implement a strategy that utilizes all available resources. By building a social network within specific populations, one can bring in the previous traditions of social medicine that appeal to any group’s cultural norms (Stuckler and Siegel 2011). The broad, large-scale approach to
nutritional interventions needs to be scrapped in favor of one that is more focused to “personalize” efforts at the local level. Genuine efforts to remain culturally appropriate will help produce and sustain effective participation rates among at-risk mothers.

A plastic definition of growth and fitness should be applied wherever LBW is prevalent in a group. As mentioned before, adjustments in birth weight need to be made when studying populations in developing countries (Kuzawa 2004). Based on the different outcomes associated with LBW in different countries, it is difficult to have one uniformed definition that determines what it is to be healthy. Before populations can develop the same characteristics that are used to measure “healthy” individuals, an evolving, flexible definition is needed.

Furthermore, collaborative efforts would entail the sharing of relevant data, the development of uniformed definitions, and the involvement of multiple disciplines. The details of the specific outcomes associated with elevated blood pressure in children will come into greater focus with a broader theoretical and methodological base.

Concluding Remarks:

This paper explored several different mechanisms that influence the development of hypertension among children who were born small. Studies included in this paper add to our knowledge that the physiological systems responsible for blood pressure regulation in small children produce several other harmful conditions indicative of hypertension. LBW isn’t solely responsible for elevated blood pressure in children. Rather, LBW is a predictor of harmful conditions that increase the risk and predictability of circulatory diseases prior to adolescence. This paper illustrated that the presence of microalbuminuria, maternal malaria
(or other infectious diseases), and nocturnal dipping are all specific facets of hypertension and cardiovascular risk that need to be considered going forward in populations where LBW is rampant.

From the information presented and discussed, it is unfortunate but not at all difficult to take a fatalist perspective. Unfortunately, it appears this global pattern will continue to persist for some time. Populations in these countries run the risk of cycling back into the first stage of Omran’s demographic transition. The economic impact of these patterns have far-reaching effects that compromise overall economic progress, because children exhibiting signs of cardiovascular and metabolic impairments won’t be given the opportunity to contribute. Future population growth is impeded or rendered stationary in large part due to rises in mortality rates among young adults, where consistent replacement fertility will not be sustained among the economically reproductive age groups.

Beyond measurements of blood pressure, other methods that measure the features of hypertensive risk need to be considered, such as a uniformed inclusion of procedures like urinalysis and blood tests. Overall, this systematic review provides the need for more research in underdeveloped and developing countries among pediatric populations with LBW. Additional research will encourage the predictability of mortality and morbidity in populations that have the possibility of encountering the same health problems found in Barker’s work in Northern European populations.
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